Original paper

Permanent prostate brachytherapy extracapsular radiation dose distributions: analysis of a multi-institutional database

Gregory S. Merrick, MD[1], Wayne M. Butler, PhD[1], Peter Grimm, DO[2], Mallory Morris, BS[1], Jonathan H. Lief, PhD[1], Abbey Bennett, BS[1], Ryan Fiano, BS, MPH[1]

[1]Schiffler Cancer Center & Wheeling Jesuit University, Wheeling WV, [2]Prostate Cancer Center of Seattle, Seattle, Washington, USA

Abstract

Purpose: Periprostatic brachytherapy doses impact biochemical control. In this study, we evaluate extracapsular volumetric dosimetry following permanent prostate brachytherapy in patients entered in a multi-institutional community database.

Material and methods: In the database, 4547 patients underwent brachytherapy (3094 – ^{125}I, 1437 – ^{103}Pd and 16 – ^{131}Cs). Using the originally determined prostate volume, a 5 mm, 3-dimensional peri-prostatic anulus was constructed around the prostate (except for a 2 mm posterior margin), and evaluated in its entirety and in 90° segments. Prostate dosimetric parameters consisted of a V_{100} and D_{90} while the annular dosimetry was reported as a V_{100}.

Results: The intraprostatic V_{100} and D_{90} for ^{103}Pd, and ^{125}I were statistically comparable when stratified by isotope and/or monotherapy vs. boost. The overall mean V_{100} for the periprostatic annulus was 62.8%. The mean V_{100} at the base (51.6%) was substantially less than the apex (73.5%) and midgland (65.9%). In addition, for all patients, the anterior V_{100} (45.7%) was less than the lateral (68.8%) and the posterior (75.0%). The geometric V_{100} annular differences were consistent when evaluated by isotope. Overall, the V_{100} was higher in the ^{125}I cohort.

Conclusions: The optimal extracapsular brachytherapy dose and radial extent remains unknown, but will prove increasingly important with reductions and/or elimination of supplemental external beam radiation therapy. The large multi-institutional community database demonstrates periprostatic annular doses that are not as robust as those in selected high volume brachytherapy centers, and may be inadequate for optimal biochemical control following monotherapeutic brachytherapy, especially in higher risk patients.

Purpose

Permanent prostate brachytherapy represents a highly efficacious treatment for clinically localized prostate cancer with a defined relationship between dosimetric quality, biochemical outcome and complications [1,2]. Previous studies have demonstrated that long-term cancer control is related to intra-prostatic radiation dose and periprostatic treatment margins [3-6]. However, treatment margins can vary markedly between patients with comparable intra-prostatic dose distributions [5]. Because brachytherapy dose decreases by as much as 20 Gy per millimeter at the periphery of the target volume, as many as 50% of patients with a pre-treatment prostate specific antigen (PSA) < 10 ng/mL manifest extracapsular extension (EPE), and the radial extent of EPE is usually in the range of 2-5 mm [7-9], periprostatic treatment margins accomplished by either monotherapeutic brachytherapy and/or the addition of supplemental external beam radiation therapy (XRT) are necessary to ensure geographic coverage of potential sites of EPE.

Currently, there is interest in minimizing and/or eliminating supplemental XRT in patients with higher risk disease [10]. A reduction/elimination of supplemental XRT will mandate adequate brachytherapy periprostatic treatment margins to address possible EPE and to maximize long term cancer control. At the present time, there is no consensus regarding the extent of periprostatic margins or the dose necessary to sterilize EPE, even among brachytherapy experts [11]. Previously in the Pro-Qura database (Pro-Qura, Seattle, WA, USA), we have documented substantial differences in overall intraprostatic sector dosimetric quality [12]. In the current Pro-Qura evaluation, we evaluate extracapsular dose distributions in patients implanted with permanent prostate brachytherapy. Hopefully, analysis of the Pro-Qura database and other multi-institutional studies will illustrate po-

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Address for correspondence: Gregory S. Merrick, MD, Schiffler Cancer Center, 1 Medical Park, Wheeling, WV 26003, USA, phone: +1 304 243-3490, fax: +1 304 243-5047, ✉ e-mail: gmerrick@urologicresearchinstitute.org
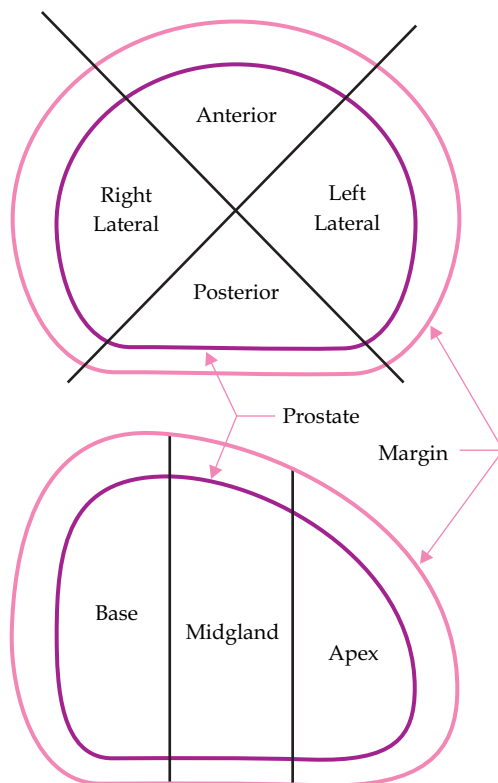
tential population-based inadequacies and help establish national standards of care.

Material and methods

From August 1999 to December 2008, 4547 post-implant computed tomography (CT) scans in the Pro-Qura database were available for analysis. The CT scans originated from 129 Pro-Qura participating brachytherapists. Patients implanted at the authors institutions are not part of the Pro-Qura database. The original post-implant prostate dosimetry was reported in terms of a V_{100} (the percentage of the prostate volume covered by the prescription dose) and D_{90} (the maximum dose covering 90% of the prostate volume). All implants were pre-planned. Post implant CT was performed at a median of 30 days following brachytherapy.

The Pro-Qura technique for post-implant dosimetric analysis has been described in detail [13]. In this study, using the Pro-Qura defined post-implant prostate volume, a 5 mm, 3-dimensional periprostatic annulus was constructed around the prostate gland (except posteriorly where a 2 mm margin was used), and evaluated in its entirety and in separate sectors to include the anterior, posterior, inferior and right/left apical aspects. Dose to the periprostatic annulus was defined in terms of an annular V_{100}. Figure 1 is an il-

lustration of the periprostatic annulus and the individual segments.

Of the 4547 patients, 3094 (68.0%) were implanted with ^{125}I, 1437 (31.6%) with ^{103}Pd and 16 (0.4%) with ^{131}Cs. For ^{125}I, 84.3% of patients underwent monotherapy (144-145 Gy) and 15.7% a boost (110 Gy) for ^{103}Pd, 67.4% of patients underwent monotherapy (125 Gy) and 32.6% a boost (90-100 Gy). For ^{131}Cs, 62.5% of patients underwent monotherapy (115 Gy) and 37.5% a boost (84 Gy). Because of small patient numbers, ^{131}Cs patients were not included in the analysis of periprostatic treatment margins, but were included in Table 1 for completeness.

Statistical analysis was performed using Predictive Analytics Software (PASW), Statistics Version 17.0 (SPSS Inc., Chicago, IL, USA). The means for continuous variables were compared using independent-samples t-tests, and one-way analysis of variance and chi-square tests were used to compare distributions within categorical variables. Probabilities of deviation from the null hypothesis of no significant differences were marked if statistically significant, $p < 5\%$.

Results

Treatment and summary dosimetric data for the 4547 patients in the study population are summarized in Table 1. There was no statistically significant difference in prostate V_{100} or D_{90} when stratified by isotope or monotherapy vs. boost. In addition, there was no difference in prostate size or number of implanted seeds when stratified by isotope. However, for both ^{125}I and ^{103}Pd, prostate glands were statistically larger and more seeds were implanted in the monotherapy vs. the boost cohorts.

Table 2 summarizes the mean margin sector analysis for V_{100} for the 4547 evaluated patients. For all sectors, the mean V_{100} was 62.8%. The V_{100} at the base (51.6%) was less than the apex (73.5%) and the midgland (65.9%). In addition, for the group as a whole, the anterior V_{100} (45.7%) was less than the lateral (68.8%) and the posterior (75.0%) V_{100}. Tables 3 and 4 describe the mean margin sector volumes, and V_{100} for ^{125}I and ^{103}Pd. The V_{100} for ^{125}I was greater than the V_{100} for ^{103}Pd both overall, and when evaluated by apex/midgland/base and anterior/lateral/posterior sectors.

Discussion

Despite favorable long term biochemical control rates in patients treated with permanent prostate brachytherapy, the definition of a technically adequate implant including periprostatic dose distributions remains somewhat unclear [14,15]. However, data suggests that permanent cancer control is related to intraprostatic radiation dose and periprostatic treatment margins [3-6].

Since extracapsular treatment margins can vary substantially in patients with high quality intraprostatic brachytherapy [5], analysis of annular brachytherapy doses will become mandatory as supplemental XRT is phased out of higher risk brachytherapy protocols. Periprostatic doses are attainable via either a brachytherapy approach that includes generous periprostatic treatment margins and/or the addition of XRT [3,4,11].

Fig. 1. Transverse (top) and sagittal (bottom) schematic of the prostate and its annular margin. The base, midgland, and apex were each divided into 4 transverse sectors producing 12 prostate and 12 annular sectors. The prostate was auto-margined by 5 mm in all directions except posterior, where the margin was 2 mm

Table 1. Treatment and summary dosimetric data for the 4547 patients in the study population stratified by radionuclide and implant type

| | Implant type | ^{125}I | | | ^{103}Pd | | | ^{131}Cs | | |
| | | $n = 3094$ | | | $n = 1437$ | | | $n = 16$ | | |
		Mean	± SD	$p*$	Mean	± SD	$p*$	Mean	± SD	$p*$
Monotherapy or boost (%)	mono	84.3	%		67.4	%		62.5	%	
	boost	15.7	%		32.6	%		37.5	%	
Prostate volume (cm^3)	mono	37.7	10.3	< 0.001	33.9	10.2	< 0.001	33.8	6.6	0.125
	boost	35.8	10.1		31.4	9.5		28.5	5.4	
Seed strength (U)	mono	0.40	0.04	< 0.001	1.92	0.15	< 0.001	1.83	0.20	0.001
	boost	0.33	0.03		1.49	0.17		1.49	0.03	
Number of seeds	mono	100	19	< 0.001	97	19	< 0.001	99	19	0.077
	boost	92	18		92	19		83	10	
Total strength (U)	mono	40.0	7.2	< 0.001	186	40	< 0.001	179	24	< 0.001
	boost	29.9	5.6		136	31		124	15	
Specific strength (U/cm^3)	mono	1.10	0.21	< 0.001	5.72	1.11	< 0.001	5.40	0.87	0.029
	boost	0.87	0.17		4.54	1.00		4.43	0.59	
Prostate V_{100} (% Vol)	mono	91.3	7.3	0.250	89.0	8.0	0.570	94.2	4.3	0.531
	boost	90.9	8.5		88.7	8.9		92.6	5.3	
Prostate D_{90} (% Rx)	mono	106	14	0.371	102	16	0.508	115	20	0.495
	boost	106	15		102	15		109	16	

*Independent samples t-test. There was no significant difference between monotherapy or boost treatments for the percentage dosimetric parameters V_{100} and D_{90}

Table 2. Mean margin sector volumes and V_{100} for the 4531 patients analyzed

	Anterior	Left and right lateral		Posterior	All
Apex	Anterior apex	Left apex	Right apex	Posterior apex	All apex
Volume (cm^3)	1.69 ± 0.6	1.86 ± 0.5	1.84 ± 0.45	0.71 ± 0.3	6.09 ± 1.4
V_{100} (%)	59.8 ± 29	78.1 ± 22	80.3 ± 21	77.8 ± 25	73.5 ± 19
Midgland	Anterior midgland	Left midgland	Right midgland	Posterior midgland	All midgland
Volume (cm^3)	2.36 ± 0.6	2.39 ± 0.5	2.39 ± 0.5	0.65 ± 0.3	7.80 ± 1.6
V_{100} (%)	48.1 ± 28	70.7 ± 24	72.7 ± 23	90.0 ± 18	65.9 ± 19
Base	Anterior base	Left base	Right base	Posterior base	All base
Volume (cm^3)	2.18 ± 0.6	2.38 ± 0.5	2.38 ± 0.5	0.79 ± 0.4	7.73 ± 1.8
V_{100} (%)	33.2 ± 23	57.7 ± 24	59.6 ± 23	62.7 ± 28	51.6 ± 17
All	All anterior	All lateral		All posterior	All sectors
Volume (cm^3)	6.23 ± 1.6	13.2 ± 2.7		2.15 ± 0.7	21.6 ± 4.5
V_{100} (%)	45.7 ± 21	68.8 ± 15		75.0 ± 18	62.8 ± 14

*Independent samples t-test. There was no significant difference between monotherapy or boost treatments for the percentage dosimetric parameters V_{100} and D_{90}

Data suggests that periprostatic dose impacts the likelihood of treatment success [5,6,9,16]. Choi *et al.* demonstrated that the anterior treatment margin in low risk prostate cancer patients was statistically significant in predicting biochemical outcome [5]. In a more sophisticated study, Crook *et al.* using magnetic resonance imaging (MRI) defined prostate contours reported dosimetric coverage of the prostate gland with 2-, 3-, and 5-mm margins in patients biochemically controlled and in those with biopsy proven recurrence [16]. The mean D_{90} and V_{100} were statistically lower in the 2-, 3-, and 5-mm expansions in patients with biopsy proven local failure. Among patients without and with local recurrence, the mean V_{100} in the 5 mm-group were 77.4% and 72.4% ($p = 0.045$). Merrick *et al.* reported an annular V_{100} of 95.1% in a series of ^{125}I and ^{103}Pd patients [6]. In that study, margin status did not correlate with biochemical control, probably as a result of robust intraprostatic and annular dosimetry. In the current Pro-Qura study, the overall annular V_{100} was 62.8% for all evaluated patients (65.2% for ^{125}I and 57.6% for ^{103}Pd), which compared to the

Table 3. Mean margin sector volumes and V_{100} for the 3094 [125]Iodine patients analyzed

	Anterior	Left and right lateral		Posterior	All
Apex	Anterior apex	Left apex	Right apex	Posterior apex	All apex
Volume (cm³)	1.74 ± 0.6	1.90 ± 0.5	1.88 ± 0.5	0.72 ± 0.3	6.23 ± 1.4
V_{100} (%)	65.7 ± 28	81.6 ± 20	84.5 ± 18	81.0 ± 23	77.8 ± 17
Midgland	Anterior midgland	Left midgland	Right midgland	Posterior midgland	All midgland
Volume (cm³)	2.43 ± 0.6	2.45 ± 0.5	2.45 ± 0.5	0.67 ± 0.3	8.00 ± 1.6
V_{100} (%)	52.0 ± 28	72.5 ± 24	75.2 ± 22	92.0 ± 16	68.6 ± 20
Base	Anterior base	Left base	Right base	Posterior base	All base
Volume (cm³)	2.23 ± 0.6	2.44 ± 0.5	2.44 ± 0.5	0.82 ± 0.4	7.92 ± 1.8
V_{100} (%)	34.1 ± 23	57.8 ± 24	60.2 ± 24	63.76 ± 28	52.2 ± 18
All	All anterior	All lateral		All posterior	All sectors
Volume (cm³)	6.41 ± 1.7	13.6 ± 2.7		2.20 ± 0.8	22.2 ± 4.5
V_{100} (%)	49.0 ± 21	70.8 ± 15		77.1 ± 17	65.2 ± 14

Table 4. Mean margin sector volumes and V_{100} for the 1,437 [103]Palladium: patients analyzed

	Anterior	Left and right lateral		Posterior	All
Apex	Anterior apex	Left apex	Right apex	Posterior apex	All apex
Volume (cm³)	1.57 ± 0.5	1.77 ± 0.4	1.74 ± 0.4	0.70 ± 0.3	5.78 ± 1.3
V_{100} (%)	47.2 ± 29	70.5 ± 24	70.9 ± 23	70.7 ± 27	64.1 ± 20
Midgland	Anterior midgland	Left midgland	Right midgland	Posterior midgland	All midgland
Volume (cm³)	2.21 ± 0.5	2.27 ± 0.5	2.27 ± 0.5	0.61 ± 0.2	7.36 ± 1.6
V_{100} (%)	39.7 ± 26	66.6 ± 23	67.0 ± 23	85.6 ± 21	60.0 ± 18
Base	Anterior base	Left base	Right base	Posterior base	All base
Volume (cm³)	2.06 ± 0.5	2.26 ± 0.5	2.26 ± 0.5	0.73 ± 0.3	7.31 ± 1.7
V_{100} (%)	31.5 ± 22	57.6 ± 22	58.4 ± 22	60.3 ± 29	50.4 ± 16
All	All anterior	All lateral		All posterior	All sectors
Volume (cm³)	5.85 ± 1.3	12.6 ± 2.6		2.04 ± 0.7	20.5 ± 4.3
V_{100} (%)	38.4 ± 19	64.4 ± 15		70.5 ± 19	57.6 ± 13

above mentioned results from high volume brachytherapy centers are probably inadequate for monotherapeutic approaches, especially those with higher risk disease. Previously, it has been reported that ^{125}I resulted in higher annular doses compared to [103]Pd [6], but did not result in biochemical control differences.

Although the radiation dose needed to sterilize periprostatic disease is unknown, the dose to control extraprostatic disease is probably significantly less than the threshold intraprostatic doses, because the ratio of extraprostatic to intraprostatic cancer is in the range of 0.4% [17]. Eventually, predictive modeling and improved imaging may enable prostate brachytherapists to tailor treatment margins on a case by case basis [18,19]. Until these technologies become available, a 3-5 mm periprostatic treatment margin appears prudent [6,9,16].

A strength of our analysis is the diverse representation of a large number of community brachytherapy practices with post-implant dosimetry performed with a consistent and highly reproducible technique. However, a limitation of the study is that once stored in the Pro-Qura database, the individual brachytherapist responsible for the CT scan is no longer identifiable and as such a learning curve analysis for margin assessment was not possible. Most importantly, there are limitations to the Pro-Qura post-implant dosimetric technique. Because the Pro-Qura technique uses the pre-implant TRUS determined prostate volume, it is highly probable that the actual annular doses are less than what is reported in this study. In addition, due to the rapid dose fall off at the periphery of the target volume, annular dose distributions are very sensitive to contouring errors. In the current study, this variable has been minimized [8]. Finally, Pro-Qura was established as a preplanning and dosimetry service, and does not have access to outcomes including biochemical control and/or complications. This eliminates our ability to establish a dose response curve for the annular dose necessary to secure long-term biochemical control.

Conclusions

The optimal extracapsular brachytherapy dose and radial extent remains unknown, but will prove increasingly important with reductions and/or elimination of supple-

mental external beam radiation therapy. The Pro-Qura database demonstrates periprostatic annular doses that are not as robust as those in selected high volume brachytherapy centers, and may be inadequate for optimal biochemical control following monotherapeutic brachytherapy, especially in higher risk patients.

Conflict of interest

Peter Grimm is an owner of Pro-Qura.

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