

## Evaluation of dosimetry and excess seeds in permanent brachytherapy using a modified hybrid method: a single-institution experience

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(Received 9 March 2012; revised 29 November 2012; accepted 29 November 2012)

Permanent prostate brachytherapy is frequently performed worldwide, and many studies have demonstrated its favorable outcomes. Implant seeds used in this procedure contain a precise amount of radionuclide and are completely sealed. Because these seeds are not manufactured in Japan, they are expensive (6300 yen per seed) and therefore need careful management as a radioisotope. The proper implantation technique requires considerable procedure time, good dosimetric outcomes and simple radioactive isotope management. To evaluate the modified hybrid interactive technique based on these considerations, we assessed 313 patients who underwent hybrid interactive brachytherapy without additional external beam radiotherapy. We evaluated the duration of the procedure, dosimetric factors and the total number of excess seeds. The dosimetric results from computed tomography on Day 30 of follow-up were: 172 Gy (range 130–194 Gy) for pD90, 97.8% (83.5–100%) for pV100, 54.6% (27.5–82.4%) for pV150, 164 Gy (120–220 Gy) for uD90, 194 Gy (126–245 Gy) for uD30, 210 Gy (156–290 Gy) for uD5, 0.02 ml (0–1.2 ml) for rV100 and 0 ml (0–0.2 ml) for rV150. The number of excess seeds was determined by subtracting the number of implanted seeds from the expected number of seeds calculated from previously proposed nomograms. As per our method, nine excess seeds were used for two patients, whereas using the nomograms, the number of excess seeds was approximately eight per patient. Our modified hybrid interactive technique reduced the number of excess seeds while maintaining treatment quality.

**Keywords:** prostate cancer; excess seeds; I-125; hybrid interactive brachytherapy

### INTRODUCTION

Permanent prostate brachytherapy (PPB) has evolved over the last 20 years. This procedure is now recognized as an established treatment for localized prostate cancer with projected long-term outcomes comparable with radical prostatectomy and external beam radiotherapy [1–3]. Many hospitals currently perform PPB with an interactive planning technique (IP) [4–13]. According to the American Brachytherapy Society (ABS) and the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO), IP is an intraoperative stepwise refinement of treatment plans using computerized dose calculations derived from image-based needle position feedback [14–16].

As IP techniques have spread, pre-plan volume studies have been avoided, and the number of required seeds needed for PPB now tends to be calculated by nomograms [9–12]. However, seed placement techniques used at different institutions may yield significantly different numbers of seeds. Consequently, calculation of the required number of seeds based solely on nomogram data in the absence of institution-specific modifications has resulted in the use of more than 10 excess seeds in prior studies [13, 17]. Because excess seeds are not only wasteful for the patient but also a form of radionuclide waste, this is a serious problem. Radiation oncologists should calculate the appropriate number of seeds needed for each PPB patient and reduce the excess.

It is well known that the conventional hybrid technique and the preplanning technique both reduce excess seeds. However, studies that compare the number of excess seeds based on the implanting method are scarce. Therefore, in this study we evaluated our modified hybrid interactive technique in terms of procedure efficacy and the reduction of excess seeds.

## PATIENTS AND METHODS

From April 2005 to June 2010, 352 patients underwent PPB with I-125. To simplify the study, we evaluated 313 patients treated with our hybrid interactive technique without performing external radiation therapy.

### Patient characteristics

A total of 147 low-risk and 166 intermediate-risk patients were enrolled. Intermediate-risk patients with Gleason scores 4 + 3 were excluded because they were treated by a combination therapy of both PPB and external beam radiotherapy (EBRT). Median follow-up time was 45 months (Table 1).

### Characteristics of the modified hybrid interactive technique

We used the modified hybrid interactive technique proposed by Grado [18, 19] and Shanahan *et al.* [6, 20]. We performed a pre-plan volume study 3–4 weeks before implantation. To minimize patient discomfort, we did not use a urethral catheter or rectal enema. When we did not

have a clear-contour prostate image, we inserted a suction tube to remove rectal gas or feces. In the pre-plan volume study, we defined the clinical target volume (CTV) as the prostate plus a 3-mm margin. Patients were treated with loose I-125 radioactive seeds with an activity of 0.33 mCi per source. Our prescription dose for the CTV, which was equivalent to the PTV, was 145 Gy. We used a modified peripheral loading pattern. The dosimetric constraints were as follows: prostate V150 limitation of 20–60%; prostate V100 >95%; maximum urethral dose  $\leq$ 218 Gy; rectal V150 (rV150) of 0 cm<sup>3</sup>. We ordered the number of seeds from the supplier (Nihon Mediphysics Co., Ltd, Tokyo, Japan) on the basis of the results of the preplanning technique.

During seed implantation, we initially made a quick intraoperative pre-plan (IOPre). In contrast to the conventional hybrid method, 8–10 needles were inserted inside the prostate capsule by the urologist during the intraoperative preplanning. All the needles were advanced superiorly to the base of the prostate to reduce its movement. We took special care to achieve clarity in axial and sagittal ultrasound images, and using more than 10 needles can cause artifacts that reduce image quality. It was necessary to recapture prostate images and modify the plan because of the changes in prostate shape. We referred to this procedure as interactive plan 1 (IP1).

We then inserted the remaining needles using an axial ultrasound view, beginning with the most anterior and second rows. Our treatment planning system, InterPlant ver. 3.4 (ELEKTA, Stockholm, Sweden), has a built in optical encoder in the probe stepping mechanism that permits real-time spatial registering of ultrasound images against the position of the probe and template, thereby providing instant operator feedback on the probe position relative to the prostate. Dose distribution was updated dynamically as per actual seed position as the seeds were deposited. Motion of the prostate during placement and changes in its size and shape due to edema were allowed for by manual adjustment of the plan in accordance with the real-time shape. We referred to this minor adjustment plan as interactive plan 2 (IP2) (Fig. 1). Undesirable seed positions, such as outside the prostate or too close to the rectum (Figs 1a and b), were adjusted to the appropriate seed position using needle tract implantation (Figs 1c and d). At the end of the procedure, we verified seed position with fluoroscopy. Fluoroscopy was used during the procedure only if seed migration was suspected or if the needle tip position was uncertain.

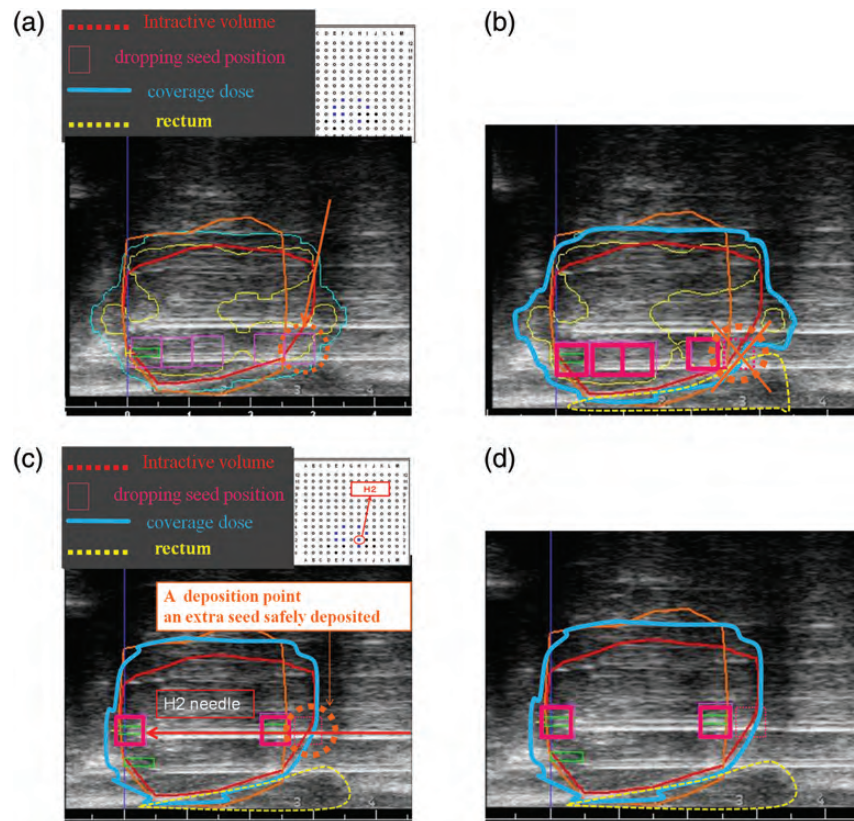
### Dosimetric and short-term results

We performed computed tomography (CT) examinations at 30 days after treatment (Day 30 CT) and analyzed dosimetric parameters that included prostate D90 (pD90), prostate V100 (pV100), prostate V150 (pV150), urethral D90 (uD90) and urethral D30 (uD30). Clinical follow-up was

**Table 1.** Patient characteristics

Factor	Number or range
Age (median)	45–80 (69)
i-PSA (median) ng/ml	1.6–19.7 (6.8)
<10	213
10–20	100
Gleason score	
6	162
3 + 4	133
Prostate volume (ml)	
<20	143
20–30	118
>30	52
Risk classification	
Low	147
Intermediate	166

i-PSA = initial(before definite diagnosis) prostate specific antigen.



**Fig. 1.** Interactive procedure and real time dose coverage; interactive plan<sub>2</sub> (IP<sub>2</sub>). Swelling prostate and adjust the seed position to the real implanted position. IP<sub>2</sub> could modify the excess seed in swelling prostate and adjust the seed position by the real implanted position. (a) According to the changing size and shape of prostate, IP<sub>1</sub> showed impossible seed position (outside the prostate and too close to the rectum). The seed might turn to be an excess seed. (b) Deletion of excess seed. (c) Search for other needle in which the seed could be deposited safely. (d) Changing plan by additional seed, and no extra seed.

started from the day of implantation. All patients were followed up at 2 weeks, 4 weeks, 2 months, 3 months and every 3 months thereafter.

### Calculation of potential excess seeds

Using these techniques, we implanted 19 357 seeds in 313 patients resulting in only 9 excess seeds in 2 patients. The number of seeds per patient ranged from 35–100 seeds (median 60 seeds). The number of potential excess seeds was calculated according to our proposed nomogram as well as the Mt. Sinai look-up table and Anderson nomogram [9].

## RESULTS

### Time of procedure

Previous studies have reported the time for the PPB procedure separately from the time for planning [6, 22–24]. In this study, however, the procedure time was inclusive of the planning time. Using our modified hybrid interactive technique, the median procedure time was 54 min (range 35–75

min). The preplan technique required significant time to set the prostate position to match the pre-plan. Despite multiple planning states (IOpre, IP1 and IP2), the overall time for the hybrid interactive technique in our study was not longer than that in other studies (Table 2). During the IOpre, we inserted peripheral needles to shorten the treatment time by preventing prostate movement.

### Dosimetric outcomes and results

The dosimetric results from Day 30 CT were as follows: 172 Gy (range 130–194 Gy) for pD90, 97.8% (range 83.5–100%) for pV100, 54.6% (range 27.5–82.4%) for pV150, 164 Gy (range 120–220 Gy) for uD90, 194 Gy (range 126–245 Gy) for uD30, 210 Gy (range 156–290 Gy) for uD5, 0.02 ml (range 0–1.2 ml) for rV100 and 0 ml (range 0–0.2 ml) for rV150. The results were acceptable for our treatment protocol. Our prescription dose was 145 Gy to the CTV. At the time of the pre-plan volume study, pD90 was 172 Gy (range 153–185 Gy).

**Table 2** Summary of studies of preplan and interactive techniques

	procedurtime(min)	D90 (Gy)	V100 (%)	V150 (%)	uD90 (Gy)	uD30 (Gy)	uD5 (Gy)	rV100 (ml)	rV150 (ml)
Preplan	Gewanter (21)	153	80	NA	NA	NA	NA	NA	NA
	Shanahan (6)	122	86	51	NA	NA	NA	NA	NA
IOpre	Gewanter (21)	150	83	NA	NA	NA	NA	NA	NA
	Wilkinson (24)	40	NA	NA	NA	NA	NA	NA	NA
	Kaplan (23)	104	NA	NA	NA	NA	NA	NA	NA
Interactive	Zelfsky (7)	NA	96	67	NA	NA	NA	NA	NA
	Beyer (22)	57	94	49	NA	NA	NA	NA	NA
	Beauieu institution 1	174	99	75	NA	NA	NA	NA	NA
	Beauieu institution 2	167	100	73	NA	NA	NA	NA	NA
Hybrid interactive	Shanahan 6	45	94	42	NA	NA	NA	NA	NA
	Our study	54	97	55	164	194	210	0.02	0

Adverse events are shown in Table 3. Acute GU toxicity above grade 2 was seen in 1% of patients. Urinary retention that required temporary catheterization occurred in 4 out of 313 patients. Late GU toxicity above grade 3 was seen in one patient who underwent TURP. Late GI toxicity of grade 2 with rectal hemorrhage occurred in two cases, which were successfully treated by steroid enema.

Six patients developed prostate-specific antigen (PSA) failure according to the Phoenix definition (nadir plus 2) with a median follow-up of 45 months. Out of these six patients, the PSA increase in five turned out to be PSA bounces. Only one patient began hormone therapy. None of the patients experienced clinical local recurrence or metastasis.

**Excess seeds**

We utilized 19 357 seeds for treating 313 patients with our hybrid interactive technique and had only nine excess seeds in two patients. Considering the actual numbers of seeds used with the proposed nomograms, we were able to conserve 2485 seeds. Thus, the number of excess seeds was approximately eight per patient using the proposed nomogram. In this single-institution study we were able to save 1 565 500 yen. The data showed we could conserve more than 10 seeds in approximately 20% of the cases and more than five seeds in 45% of the cases. The estimated number of seeds proved to be insufficient in 3–4% of patients (Fig. 2).

**DISCUSSION**

Minimal invasiveness, high efficacy and low cost are all important criteria for the ideal implantation technique. This requires reasonable procedure time, good dosimetric outcomes and simple radioactive isotope management. In addition to reducing excess seeds, a pre-plan volume study is important for assessing patient-specific anatomical variations such as pubic arch shape, presence of median lobe hypertrophy and the configuration of vessels around the prostate. Accurate three-dimensional information (size, shape and volume) enables us to verify the dose coverage from the ultrasound template and to order the appropriate number of seeds in a cost-efficient manner. In addition, because prolonged procedural time causes prostate swelling, shorter procedure duration contributes to improved dosimetric results. The hybrid interactive technique reduces this duration and helps maintain good dosimetric outcomes similar to our results [6, 20]. It is necessary to compare the number of excess seeds between the pre-planning method and that of our study; however, there is currently no such published data from Japan.

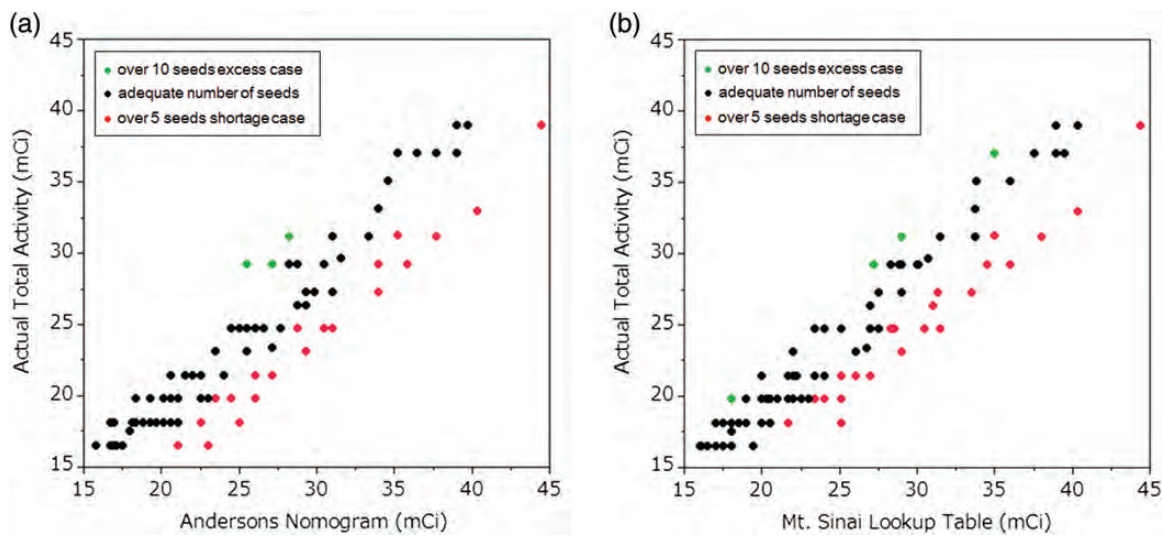
Nomogram-based seed ordering often leads to an excess or insufficient number of seeds. Because the nomogram determines the number of seeds on the basis of prostate volume only, the use of 10 or more seeds has been reported

**Table 3.** Adverse events (a) Acute adverse events

CTCAE vers. 4	Frequency	Retention	Pain	Incontinence	Hematuria	Proctitis	Rectal hemorrhage
1	222 (71%)	14 (4.5%)	3 (1%)	6 (2%)	1 (0.3%)	43 (4%)	7 (2%)
2	0	4 (1.2%)	0	2 (0.6%)	1 (0.3%)	0	0
3	0	0	0	0	0	0	0

(b) Late adverse events							
CTCAE vers. 4	Frequency	Retention	Pain	Incontinence	Hematuria	Proctitis	Rectal hemorrhage
1	15 (4.7%)	8 (2.5%)	17 (5.4%)	6 (2%)	1 (0.3%)	1 (0.3%)	4 (1.3%)
2	0	2 (0.6%)	0	2 (0.1%)	1 (0.3%)	0	2 (0.1%)
3	0	1 (0.3%)	0	0	0	0	0



**Fig. 2.** Comparison of proposed Nomogram to our actual seed ordering. (a) Mt. Sinai Lookup Table. We were able to conserve over 10 seeds in 22% of cases, over 5 seeds in 46% cases, while the estimated number of seeds proved to be insufficient in 4% of patients. (b) Anderson Nomogram.  $d \text{ avg} = (AP + RL + SI)/3$ ;  $d \text{ avg} \pm 3 \text{ cm}$ : Actual total activity =  $5.709 \times d \text{ avg}^2$ ;  $d \text{ avg} > 3 \text{ cm}$ : Actual total activity =  $1.524 \times d \text{ avg}^2$ . AP; antero-posterior, RL; right-left, SI; superior-inferior. We were able to conserve over 10 seeds in 20% of cases, over 5 seeds in 43% cases, while the estimated number of seeds proved to be insufficient in 3% of patients.

[13, 17]. We believe it is necessary for institution-specific nomograms to be established if the interactive method is to be successfully applied. As per our estimation, using the Anderson nomogram or Mt. Sinai look-up table, more than five excess seeds would be ordered for 40–50% of patients, and insufficient seeds would be used in 3–4% of patients.

Smaller prostate size and unusual shape (i.e. more flat than round) can be the causes of nomogram mismatch in Japanese patients [26–28]. We believe that preplanning prior to seed implantation contributed to our appropriate estimation of the number of seeds because it provided shape as well as volume information for the prostate. In addition, in our hybrid technique, it was important to use IP1 and IP2, thereby allowing us to treat patients with small prostates. Consequently, we avoided wastage due to redundant seeds.

Several institutions have used excess seeds with variously weakened activity to improve interactive planning. We tried using such an approach in one case, but the storage of excess seeds with different degrees of weakened activity was troublesome. From a risk-management standpoint, a complicated storage procedure may cause greater misuse or loss of radioactive nuclides.

Several limitations of our modified hybrid method should be considered. First, based on overseas studies, a disadvantage of our pre-plan volume study may be the extra cost required to use the operating room with the treatment planning system [22]. Second, we think it is necessary to observe these patients for a longer period and to accumulate a greater number of cases. Consequently, this technique requires further studies conducted at multiple institutions before its merits can be validated.

In conclusion, our hybrid interactive technique reduced the number of excess seeds used for PPB while maintaining the efficacy of the procedure and the quality of the related dosimetric parameters.

### ACKNOWLEDGEMENTS

No financial support was provided by any institute/funding body. The authors wish to express their appreciation to Professor Thomas G. Shanahan for his support and insightful comments regarding this study.

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