FIVE-YEAR CLINICAL RESULTS AND REVIEW OF PHYSICS OF PROSTATIC IMPLANTATION WITH Au-198 SEEDS AND EXTERNAL IRRADIATION IN THE MANAGEMENT OF LOCALIZED ADENOCARCINOMA

A Thesis

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by
Md. Ali Haider Rashidee
M.B.B.S., University of Dhaka, Bangladesh, 1984
D.M.R.T., University of Dhaka, Bangladesh, 1991
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Dedicated to

cancer patients

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ABSTRACT

Purpose: To analyze, the outcome of treatment of localized prostatic adenocarcinoma using transperineal implantation of radioactive ^{198}Au seeds and external irradiation, and radiation safety.

Material and Methods: One hundred and forty patients, from March, '88 to March, '95, with clinically localized prostatic adenocarcinoma (stage T1-T3), were treated definitively with transperineal implantation of ^{198}Au seeds, with an aim of 30 Gy minimum peripheral dose followed by external irradiation, to a minimum prostatic dose of 65 to 75 Gy. Stages were T1, in 27%; T2, 59.3%; and T3, 13.6%. Gleason scores were, 2 to 4, in 21.1%; 5 and 6, 57.2%; and 7 to 9, 21.7%. Pre-treatment PSA were 0 to 4 ng/ml, in 32%; 4.1 to 10, 34%; 10.1 to 20, 25.4%; 20.1 to 40, 5.8% and >40, 2.9%. Mean follow-up time is 35 months.

Results: Stage and Gleason score correlated with pre-treatment PSA, with $p < 0.0001$ and $= 0.002$ respectively. Only biochemical failure occurred with 5.7% patients, 5.8% failed locally and 8.4 %, locally and/or distantly. 9.2% patients experienced grade III (RTOG equivalent) genitourinary complications including 6.4% from incontinence. 1.4% patients experienced grade III gastrointestinal complications. Of the potent and partially potent patients, 45% experienced impotency in one year. Implantation exposures to extremities averaged 36, 26 and 15 mR/case, for three urologists. The radiation oncologist, received 100 mrem to body and 290 mrem to extremity from 203 implantations.

Conclusion: Disease free survival and local recurrence rates are comparable to published results of external irradiation and external irradiation and/or implantation series. Acute and late morbidity of treatment are roughly equivalent to external irradiation but showed a lower incidence of major gastrointestinal morbidity. Exposure to personnel was minimal. This technique offers a reasonable treatment for localized prostate cancer from a clinical viewpoint and radiation safety concern.

INTRODUCTION

Prostate cancer is the most common cancer among American men and is only second to lung cancer as a cause of cancer death. Prostate cancer causes almost 3% of all deaths in men older than 55 years of age in the United States. The incidence and mortality rates have continued to rise and no reduction has been projected for several years to come (4). For the year 1994 the projected incidence was about 200,000 and mortality about 40,000 cases.

In the midst of all the controversies on the optimal treatment of prostate cancer including no and deferred treatment, surgery and radiation therapy have established their role in the management of prostate cancer. Patients of relatively younger age, (mean age of treatment ranging from 60-64 years) of better general health and with well to moderately differentiated very localized and small tumors (T1 to T2b, a small fraction of the total number of prostate cancer patients) present with the optimal criteria for surgical procedures (18). This leaves much room for offering optimal treatment opportunities with definitive irradiation to older patients with localized carcinoma, their risk of having extracapsular disease, existing comorbidities and to those who refuse surgery. Comparison of treatment outcomes from different modalities is very difficult because of the widely varying patient and tumor characteristics in different studies employing different modalities of treatment.

Since the beginning, radiotherapy has come a long way having megavoltage external beam irradiation set as a definitive treatment modality for prostate cancer.

Though external beam radiotherapy offers reasonable disease control, it has a substantial risk of serious late sequelae associated with it. With the dose delivered to the prostate, external irradiation has been associated with significant incidence of small bowel injury, urethral stricture and radiation proctitis requiring medical management (25). In more recent series namely Radiation Therapy Oncology Group (RTOG), Patterns of Care Study (PCS) and Fox Chase Cancer Center studies, lesser incidence of genitourinary and gastrointestinal complications are being reported (18). Brachytherapy has the conceptual advantage of delivering high dose in a small volume. ^{198}Au, ^{125}I, ^{103}Pd and ^{192}Ir have all been employed alone or in combination with external beam irradiation, to deliver high dose to the prostate

In 1988, a study was undertaken under the joint auspices of Mary Bird Perkins Cancer Center (MBPCC) and the Department of Urology, Our Lady of the Lake Regional Medical Center (OLOL), Baton Rouge, Louisiana to definitively treat clinically localized adenocarcinoma of the prostate with transperineal implantation with ^{198}Au seeds implanted under transrectal ultrasonic guidance in combination with external beam irradiation. The implantation aims at achieving 30 Gray (Gy) minimum peripheral dose (mPD) to the prostate to be followed by about 45 Gy of external irradiation totaling to about 70 Gy of mPD to the prostate. The externally delivered amount of dose was delivered depending upon the comorbidities and risk factors for nodal involvement. External beam irradiation fields varied from limited (10x10 cm.) to pelvic (14x16 cm).

The use of ^{198}Au was pioneered by the works of Flocks *et al.* at the University of Iowa Medical School in 1952 (13). Presently, ^{198}Au is not much favored as a radionuclide of choice for implantation in radiation therapy, primarily because of it's 412 KeV gamma emission which is considered to pose a radiation protection problem for the involved personnel. Two other issues has been mentioned too; short shelf life and the significant inhomogeniety of the seed activity (9). On the other hand, it has many characteristics which may make it an excellent choice as an implantable radioisotope. To find out the efficacy of the adopted treatment modality, a five-year study was undertaken. This consisted of detailed collection and analysis of data, 5-year clinical results and review the radiotherapeutic physics conditions relative to the clinical condition. A final goal was to be able to be able to compare the studied modality with other modalities of treating localized adenocarcinoma of the prostate.

The broad objectives of this study are to;

(a) assess acute and late morbidity

(b) assess local control and distant disease free survival

(c) assess biochemical (Prostate Specific Antigen) progression free survival

(d) compare with current published experience with surgery, external irradiation alone or in combination with implantation and implantation alone and

(e) assess the adequacy of radiation protection measures.

LITERATURE REVIEW

Historical overview: Radiation therapy of the prostate began with brachytherapy dating back to the first decade of the century. According to Flentje and Wannenmacher (12), Paschkis and Tittinger in 1910 and Pasteau in 1911 reported of treating prostate cancer with ^{226}Ra loaded needles. Young (1917, 1922) was able to apply dosimetric calculations for the implants and in 1934 Widman started offering palliative treatment with external irradiation in the orthovoltage range (12). All these efforts resulted in many associated complications instead of good clinical results. The interest in prostate radiotherapy was waned by the work of Huggins and Hodges in 1941 (21), who claimed that hormone therapy could control prostate cancer. Hormone therapy was later found to be reliable in inducing temporary remission and pain relief in advanced disease but not curing the disease. With the advent of megavoltage radiotherapy with ^{60}Co and medical linear accelerators in the early 1960s, interest in curative irradiation for prostate cancer revived. Early results by Budharaja and Anderson in England (5) and Del Regato in the United States (11) provided the impetus for subsequent larger clinical trials with external beam radiotherapy.

Contemporary Literature Review: With the advent of medical linear accelerators in the megavoltage range, external irradiation became very successful in treating prostatic adenocarcinoma, optimized by the works of Bagshaw and associates at Stanford University as cited by Catalona (9). Surgery is also a mainstay of treating prostate cancer. Thus at present radical prostatectomy, nerve sparing radical

prostatectomy and external beam radiotherapy are the most established treatment modalities. In the 1950s and 1960s many investigators were enthusiastic about brachytherapy with a view to reduce the complications experienced with external irradiation. In 1952 Flocks *et al.* pioneered surgical implantation of the prostate with ^{198}Au in colloidal form (13). This approach was later improved by Carlton and Hudgins (7) using freehand retropubic surgical implants of solid ^{198}Au seeds. In 1977 Whitmore *et al.* (42) from Memorial Sloan-Kettering Cancer Center reported the use of freehand surgical implantation of prostate with ^{125}I seeds as the sole modality of treatment. In 1977 Court and Chassagne introduced an afterloading technique using ^{192}Ir which has been further developed by Syed *et al.* (37). Non-invasive imaging and computer based dosimetry has contributed to the state of the art advancements with the advent of transperineal implantation under transrectal ultrasonic guidance, reported by Holm *et al.* in 1983 (19), and conformal therapy by remote afterloading technique reported by Porter *et al.* in 1988 (31). ^{103}Pd was introduced as an implantable isotope in 1988. The transperineal implantation technique has been further developed by Blasko and associates and they are monitoring the outcomes from several regional institutions that are treating early, well differentiated disease with implants alone and advanced and moderate to poorly differentiated disease with a combination of implantation and external beam (18).

In the Baylor series, Scardino *et al.* (33) combined ^{198}Au (30Gy) implant and external irradiation (45Gy) for different stages of prostatic adenocarcinoma after pelvic lymphadenectomy and reported 5-year 83% overall and 46% no evidence of disease

(NED) for A2 tumors to 85% overall and 51% NED for C1 tumors (9). Historically, prostate brachytherapy had never proved to be very successful, but the quest goes on.

In March, 1988 percutenous transperineal prostatic implantation of ^{198}Au seeds under transrectal ultrasonic guidance in combination with external irradiation was started at Mary Bird Perkins Cancer Center and Department of Urology, Our Lady of the Lake, Regional Medical Center, as a modality of treating localized prostatic adenocarcinoma. The study took into consideration the experience of other institutions treating localized prostate cancer by this modality and the radiobiological and physical characteristics of the radioisotope ^{198}Au, and megavoltage external beam irradiation.

METHODS AND MATERIALS

Patient Characteristics:

Patients: Patients were selected jointly by the urologists and the radiation oncologist, who took into consideration the stage, degree of differentiation of the neoplastic tissue, pretreatment PSA level, prostate volume, existing comorbidities, performance status and life expectancy of the patients. Patients' choice was one of the criteria for choice of therapy, making this study, essentially non-randomized. All the patients signed an informed consent form. One hundred and forty patients treated consecutively over a period of five years (extending from March, 1988 to March, 1993), have been chosen for evaluation of the treatment outcome. The urology, radiation oncology and physics records of the patients were reviewed and entered in a code sheet for the purpose of statistical computations. All these patients had histologically confirmed adenocarcinoma of the prostate confined to the prostate and periprostatic tissue (Stages T1-T3). Three patients with surgically staged nodal involvement, three patients treated for recurrence following surgery and ten patients who have had hormone therapy at some time prior to or during irradiation, have been excluded from this study. Patients having higher degrees of obstructive symptoms, too large prostatic volumes (> 60 cc.) and too large defects from Transurethral Resection of Prostate (TURP) were not selected for this treatment modality. Too large prostatic volume presents two problems, namely, interference in implantation from the pubic arch, and susceptibility of implantation quality, since more seeds are required. Too

T3 Tumor extends through the prostatic capsule**

T3a Unilateral extracapsular extension

T3b Bilateral extracapsular extension

T3c Tumor invading the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles

T4a Tumor invades any of: bladder neck, external sphincter, rectum

T4b Tumor invades levator muscles and / or is fixed to pelvic wall

*Note: Invasion into prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

**Note: Tumor found in one or both lobes by needle biopsy; but not palpable or visible by imaging is classified "T1c".

Table 1 : Gleason score and Stage distribution.

Gleason Score	T1a	T1b	T1c	T2a	T2b	T2c	T3a	T3b	T3c	Total
2 - 4	7	2	6	3	5	2	1	0	3	29
5 - 6	2	3	13	27	12	14	3	1	4	79
7 - 9	0	0	4	8	7	4	2	0	5	30
Not available		1				1				2
Total	9	6	23	38	24	21	6	1	12	140

Pretreatment Prostate Specific Antigen level: Prostate Specific Antigen (PSA) is a glycoprotein and an antigen weighing approximately 35,000 Daltons produced usually by the prostate acinar cells, was identified by Wang and associates in 1979. PSA level rises in benign enlargement, inflammation, infarction, surgical or digital manipulation and development of cancer of the prostate. Serum PSA has

replaced prostatic acid phosphatase as a diagnostic, predictive and prognostic tool for having better sensitivity and specificity as a tumor marker. Pretreatment serum PSA levels of 138 patients were available. Baseline and follow-up PSA levels were determined with serum drawn before digital examination. Thirty-two percent patients had 0 - 4.0.; 34%, 4.1-10; 25.4%, 10.1 - 20; 5.8%, 20.1- 40 and 2.9% , > 40 ng/ml. pretreatment serum PSA levels. All were assessed by the Hybritech Tandem-R immunoenzymatic assay, normal level being 0-4 ng/ml. Four patients had PSA level assessed by the Yang Pros-Check polyclonal assay, normal limit being 0-2.5 ng/ml. These four levels were converted to equivalent Hybritec Tandem-R levels, made possible by the fact that both the procedures essentially measure the same analyte (20). Table 2 shows the means of the pretreatment PSA levels for different stages and Gleason score groups. The pretreatment PSA levels were correlated to the stages of the disease, Gleason scores and prostate volumes.

Table 2: Distribution of pre-treatment PSA levels for different stages and Gleason score groups.

Clinical Stages	Number of Observations.	Mean PSA (ng/ml.) ± Standard Error
T1	36	6.1 ± 1.2
T2	83	9.2 ± 1.0
T3	19	17.2 ± 2.8
Gleason Scores	Number of observations.	Mean PSA (ng/ml.) ± Standard Error
2-4	27	5.3 ± 1.0
5-6	79	9.4 ± 1.0
7-9	30	13.0 ± 2.2

Methodology:

Radiation Therapy: Radiation therapy was administered with transperineal prostate implantation with ^{198}Au seeds followed by external beam irradiation in about three weeks. Initially, an ultrasound (US) prostate volume study was done using a 7 megahertz (MHz) Bruel and Kjaer axial transrectal ultrasound, with 5 mm. apart cross sectional images, with the patient in lithotomy position and a catheter in the urethra. For hand calculation, prostate volume is calculated using the following dimensions; cranio-caudal x transverse x thickness (at maxima, determined from the US study) x 0.5, a factor used for correcting for the ellipsoidal configuration of the prostate. This formula closely approaches the volume calculation formula for an ellipsoid ($\pi/6$ length x breadth x thickness at maxima at mutually perpendicular planes). Then a CT was done with a catheter in the urethra, which better delineates the base of the prostate while the US shows the apical region better. The catheter marks the position of the urethra as it traverses the prostate. Computer calculation from the CT was matched with initial calculation to confirm true prostate volume. Then conformal plan with ^{198}Au seeds was done by the radiation oncologist, by distributing the seeds of uniform activity for each case in the prostate volume at different coordinates. The plans aimed at achieving 30 Gy of minimum peripheral dose (mPD) to the prostate. 'Minimum Peripheral Dose' is generally accepted as the dose of greatest clinical significance surrounding the target volume as shown by the isodose distribution. On the other hand 'Matched Peripheral Dose' (MPD) is defined as the dose for which the computed contour volume 'matches' the ellipsoidal volume inferred from mutually perpendicular dimensions (length, breadth

and thickness) measured for the implanted prostate volume. Except in the unlikely event that both the target volume and the same volume isodose contour are ellipsoidal, the target will project beyond the dose contour in some regions and recede within it in others. So the minimum peripheral dose is actually few percent lower than the matched peripheral dose. Usually the seeds were fewer at the center of the gland and more at the periphery and were placed at a minimum distance of 1 cm. measured from one seed's center to adjacent seed center, patterned to avoid acute urethritis, urethral necrosis and incontinence. The ^{198}Au component of the seeds were 2.2 mm. long, diameter of 0.5 mm., encapsulated in a 0.15 mm. thick platinum envelope. The overall seed length is 2.5 mm. with an outer diameter of 0.8 mm. (28). The pre-implant plans were run in a Capintec 'Cap- Plan' 2D radiation therapy planning computer to depict the dose distribution in and around the prostate. Seed coordinates were adjusted to achieve the optimal conformal plan as necessary.

The implants were done under general or spinal anesthesia. The urologist and the radiation oncologist, after visualizing the target volume with a loaded needle inserted under template guidance to place the seeds in the predetermined coordinates, completed the implant by 'real time' transrectal ultrasound imaging. The duplication of seed placement in the planned transverse planes were crucial for planned dose distribution. Superimposition of the template points on the ultrasound picture, ensured the reproduction of the conformal plan configuration. Sharp needles were used so as not to displace the prostate each time a needle was introduced for seed insertion. Needles were inserted past the planes of interest and then retracted to the planes of interest to

avoid misplacement due to tenting effect. After implant, the pelvis were x-rayed for seed count and for the record. Then the patients were moved to the post-anesthesia care unit for about three to four hours to be moved to a designated suite. Most of the patients had no surgical morbidity and left for home having been informed of the appropriate radiation protection measures.

After about two weeks, the patients came in for CT scans of the implanted volume for assessment of dose distribution. The seed distribution depicted by 2 mm. CT scans were used to reconstruct the dosimetry in the planning computer for qualitative analysis of the dose distribution over the target volume. Most (46.8%) of the patients received 30 Gy mPD. Twenty-three percent patients, 25 Gy; 24.8%, 20 Gy. and 5.7%, 15 Gy mPD to the entire gland. In cases with lower mPD, parts of the glands were covered by higher isodose lines. External irradiation dose was delivered to the prostate, periprostatic tissue and regional lymph nodes. External beams of 15 and 18 MV energy from different accelerators were used as convenient for patient features and scheduling. Except for two patients, all were treated by four field box technique, antero-posterior (AP), postero-anterior (PA) and right and left lateral fields, usually 200 cGy per fraction, five days a week. Effective field sizes for external field dimensions were 11.5 (41.7%), 11.6-14.5 (18.7%) and $\geq$ 14.6 cm^2 (14x16 cm., 39.6%). The dimensions of external irradiation fields were dictated by the stages, Gleason scores and pretreatment PSA levels which corroborate with the possibilities of nodal involvement. Comorbidities, if any, also dictated the size of the external field. The mean pelvic dose was 45 Gy. Highest mPD prostate, implant plus external irradiation,

were 6501 to 7000 cGy in 60.7%, and 7001 to 7500 cGy in 21.4% of the patients, ranging from 6000 cGy to 8040 cGy. Underdosage assessed in the CT based post-implant dosimetry characterized by lower mPD from the implants, were compensated by external beam irradiation by modulating the amount of dose and blocking the desired areas of the target volume with customized cerrobend blocks. In most underdosed cases the bases of the prostate were most likely to receive lesser dose than the rest. The AP and PA fields were more conveniently employed to deliver the extra compensatory dose to the bases by blocking the remainder of the gland.

Radiobiology and Physics: ^{198}Au has the advantage of higher dose rate constant. Moderate to high grade adenocarcinomas with shorter tumor doubling time can be taken better care of by implanting with ^{198}Au seeds for having a dose rate constant of 2.03 cGy hr^{-1} mCi^{-1}, derived from the ^{198}Au dose rate constant of 0.0548 $mGy.m^2.h^{-1}.GBq^{-1}$ cited by Sommerkamp (35), compared to the dose rate constants of 1.08 and 0.95 cGy hr^{-1} mCi^{-1} of ^{125}I and ^{103}Pd seeds respectively (14). Temporary ^{192}Ir implants deliver dose with a dose rate of 4.55 cGy hr^{-1} mCi^{-1}(14). Amount of dose per cell cycle is more crucial than the total dose, though for slow-growing tumors, cell killing by ^{125}I and ^{103}Pd increase by 3 and 5-6 log respectively, ^{198}Au remaining the same as with rapidly growing tumor (24). As for sequencing, all except three patients were treated with the implantation first followed by the external irradiation. ^{198}Au dissipates almost all of it's energy over a short period of time for having a short half life of 2.69 days, the effective treatment time being in the order of 14-21 days depending on the tumor potential doubling time (24), there is almost no dose

overlapping as external irradiation is started in about three weeks unlike the pre-implantations with ^{125}I or ^{103}Pd. Post-implant planning permitted manipulation of external irradiation, dose and site, that could correct for dose inhomogeneity that may have occurred, as stated before. Combination of external irradiation with interstitial ^{198}Au implant made the dose distribution even more homogeneous. Treatment with implants only or implantation following external irradiation, does not permit institution of any compensatory measure if the implantation quality is compromised. Also, suboptimal placement of seeds, is less likely to distort the distribution and leave a undertreated spot, because of the 412 KeV gammas which have a half value layer (HVL) of water amounting to 7.0 cm. and the situation is not the same with implants with ^{125}I and ^{103}Pd having HVL (water) of 2.0 and 1.6 cm. respectively (15). One analysis, with a mean seed deviation from pre-plan, 3.01 mm; median, 3.16 mm in the central $x\,y$ plane revealed a range of variation in the target area from -8% to +15% for ^{125}I and -9% to +18% for ^{103}Pd implants (10). With time, seeds may drift making the dose even more inhomogeneous specially in slowly decaying ^{103}Pd (half life-17 days) and ^{125}I (half life-60 days) which take much more time than ^{198}Au to deposit the biologically effective dose.

The sources were ordered, received, surveyed and calibrated by physics personnel. With today's fast and timely shipping facilities, the short shelf life is not actually disadvantageous. Catalona (9) opined that ^{198}Au seeds are inhomogeneous in activity. To look at the homogeneity of the seed radioactivity, the measured activities for all the seeds calibrated in the year 1989 and 1990 were accounted for. The ratios, of

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the minimum measured activity over maximum measured activity in a batch, ranged from 0.73_6 to 0.98_3. Presently, since many seeds (mean number of $42.5_3 \pm 1.0_2$ with a range of 17 to 83 seeds in this study) of low level activity (mean activity of $1.2_5 \pm 0.0_2$ mCi) are used, significant inhomogeniety may not result from the inhomogeniety of the seed activity. In the early days of retropubic ^{198}Au implantation, 4-8 seeds of higher activity (4-6 mCi each) were used and inhomogeniety of the seeds could be accounted for a inhomogeneous dose distribution for obvious reasons. For the implants, the supplier mentioned activity was used in planning when accepted for implantation, the criteria of acceptance being average measured activity to be within ± 10% of supplier's average activity. Seeds were unacceptable only once.

The seeds were carried to the hospital, sterilized, and loaded in the needles according to the planned logistics by the physics personnel with proper precautionary measures. In the operation room (OR), the loaded needles were kept in rectangular lead boxes called to reduce exposure to personnel. During implants physics personnel kept written accounts of the seeds implanted. An AP film was taken after the implantions for seed count and record. The OR was monitored for radiation levels by a physics staff and all personnel and machines going out of the OR were monitored for stray seeds. After implantation a clearing survey of the OR was done. Unused sources were put back in the laboratory for decaying. Radiation monitoring was done in the recovery ward where a bedside shield was used to reduce exposure to other patients and personnel. The suite and the collected urine were monitored for expelled sources. Two patients had

chest x-ray done in an endeavor to locate lost seeds, the results being negative. Some pertinent data are summarized in table 3.

Table 3 : Mean seed activity, number of seeds implanted, seed loss in urine, number at simulation, actual loss, and days stayed at hospital for implantation.

	Cases reviewed	Minimum	Maximum	Mean ± Standard error of mean
Seed Activity (mCi)	140	0.96	1.86	$1.2_5 \pm 0.0_2$
Number of seeds implanted	140	17	83	$42.5_3 \pm 1.0_2$
Seeds recovered from urine	137	0	8	$0.6_3 \pm 0.1_2$
Seeds at simulation CT	130	19	79	$42.2_7 \pm 1.0_2$
Number of seeds lost	130	0	8	$1.0_5 \pm 0.1_5$
Days of Hospital Stay	96	2	4	$2.2_2 \pm 0.0_6$

Patients were not allowed to move out of the recovery suite. Visitors, excluding pregnant women and person below the age of 18 years, were allowed to visit the patient for a limited amount of time. Visitors were not allowed to get closer than 2 meters from the patient. Patients were dischargeable from radiation monitoring only when the survey read below 5 mR/hr at one meter from the pelvis of the patient. Housekeeping was done by nurses, not the regular housekeepers and at discharge the suite was cleared for use only after a radiation survey. Urine, linen and trash were monitored for expelled seeds. Cautionary radioactive signs were posted wherever radioactivity was present. The patient chart was labeled showing radioactivity symbol, number of seeds and their activity. All personnel involved were monitored by TLD body and ring badges as required.

Follow-up: Most of the patients were seen in intervals ranging from 3 months to 1 year, at MBPCC and Urology at OLOL by the urologists and the oncologist. For

follow-up physical examination, DRE, urinalysis, PSA and PAP (excluded in the later part of the study for having lesser specificity and sensitivity than those of PSA) were done routinely. DRE combined with PSA determination has high positive predictive value. Investigations such as US, CT or MRI of the pelvis, biopsy or whole body bone scan were done as necessary. Thirteen patients received hormonal therapy for biochemical failure, defined as having a continuos increase of PSA levels after initial fall following radiation therapy, and local and distant failures.

Statistics: Personal Computer / SAS software was used for the statistical analysis. The local recurrence rate and distant metastasis rates were calculated by the Kaplan-Meier product limit estimates of survivorship. To find out the correlations of stage, Gleason score and volume to pretreatment PSA levels, Pearson correlation procedure was run by the SAS software.

RESULTS AND DISCUSSION

Relation of stage, volume and Gleason grade to pretreatment PSA level: It may be asserted that the stage and volume are directly related to the pretreatment PSA level, the relation being significant with volume ($p = 0.0002$) and stage ($p < 0.0001$). Gleason score was found to be significantly related to ($p = 0.002$) pretreatment PSA level. The relation of volume to pretreatment PSA level is not much emphasized because the ratio of the volume of the cancerous tissue and the prostatic volume is not ascertained in the current methodology of defining the disease extent. Same type of correlations of statistical significance has been reported by other authors.

PSA follow-up profile: The PSA profile of the patients, were studied individually. For most patients, post treatment PSA levels did normalize (≤ 4.0 ng/ml) within 2-4 months post RT, even in some of those with much higher levels of initial PSA. Tables 4 and 5 show the profile of biochemical failures. In Table 4, the patients who had PSA level ≤ 4 ng/ml. of serum have not been accounted for, because they already had normal levels of pretreatment PSA.

Table 4: Time taken for the PSA levels to fall to normal range (≤ 4.0 ng/ml.) following radiation therapy.

Initial PSA (ng/ml)	Time (months) to Normalize				Never Normalized	Biochemical Failures
	2-4	5-8	9-12	> 1 yr.		
≤ 4						3
4.1-10	38	4	2		1	3
> 10	25	10	4	4	2	9

Three patients failed biochemically despite having ≤ 4.0 ng/ml pre-treatment PSA levels. Two patients out of 44 in the 4.1-10 ng/ml range and 7 patients out of 43 with ≥ 10 ng/ml pretreatment PSA levels were characterized by an increase in post-treatment PSA levels after fall to normal levels. In three patients PSA never reached normal levels.

Elevation of PSA following treatment with irradiation has become a major concern. There is no unanimous limit of PSA concentration, in excess to which a biochemical failure could be assigned. Zagars *et al.* (44) found 1.2 ng/ml, on the normal scale of 0-4.0 ng/ml, as the PSA level associated with long term disease-free survival Stamey *et al.* (36). have reported approximately 20% cure rate in patients with clinical stages A to D1 prostate cancer characterized by indefinitely persistent low levels of PSA with a mean of 1.7 ng/ml at a mean follow-up of 9 years with external irradiation, but they emphasized that though elevated levels and increasing PSA concentrations with time strongly suggest failure of radiation therapy to cure prostate cancer, positive biopsies are the best evidence for failure. From their point of view, long term survival or cure from prostate cancer in patients is a remote possibility, but it may be emphasized that these patients are not to be surgically managed and complications play a vital role in making the choice of treatment modality rather than the possibility of long term disease-free survival or cure in patients who are more likely to die of intercurrent disease. Patients having increase of PSA after initial fall were carefully assessed for biochemical failure and usually underwent thorough investigation including prostate biopsy. Though regular biopsies can be done in an outpatient setting, those were not

done unless warranted for having elevated PSA or suspicious or palpable nodule at DRE, a combination of which have higher positive predictive value. Hormone therapy was instituted to control the recurred cases. Thirteen patients out of 140, (9.3%) underwent bilateral orchiectomy, leuprolide or flutamide therapy and all of them are doing well so far. Characteristics of the progressors are listed in Table 5.

Table 5 : The characteristics of the progressors .

	Stag	Gleason Score	Initial PSA	Dose mPD	Biopsy (G. Score)	PSA at recur.	Metastatic work-up	Time to recur.	Progression
1	T1b	6	5.0	65	not done	4.1	not done	~3.5 yr.	Biochemical
2	T1c	2	1.9	70	not done	5.3	not done	~5 yr.	Biochemical
3	T2b	9	13.4	72	not done	4.7	not done	~1 yr.	Biochemical
4	T2a	7	3.9	64	negative	7.3	not done	~6 yr.	Biochemical
5	T2a	6	5.1	65	negative	140.5	negative	~1 1/2 yr.	Biochemical
6	T3c	6	31.5	80.4	Altered Ca. / DRE neg.	8.9	not done	never normalized	Biochemical
7	T2a	7	14.0	65	not done	6.5	not done	~1 yr.	Biochemical
8	T2b	6	19.2	70	negative / DRE neg.	12.8	not done	~3 yr.	Biochemical
9	T2a	6	26.6	71	positive/ DRE neg.	7.5	not done	~3 yr.	Local
10	T2b	8	6.2	65	positive (8)	5.0	not done	~5 yr.	Local
11	T3c	7	14.7	70	positive (7) /DRE pos.	12.6	not done	~3 yr.	Local
12	T2c	High grade	23.0	70-75	High grade / DRE pos.	5.0	not done	~ 2 yr.	Local
13	T1c	7	42.3	65	positive	11.9	not done	never normalized	Local
14	T3c	7	45.4	70.4	DRE neg.	30.0	pos. Scan	~1.5 yr.	Distant
15	T3a	5	21.2	71	not done	normal	pos. node & B. Scan	~2 yr.	Distant
16	T2a	5	0.3	76	large lumpy prostate	>100.0	positive B. Scan	~4.5 yr.	Local and Distant

Five patients died of intercurrent disease in 1-2 years without having follow-up PSA levels done and one patient moved out of state. Two patients had suspicious palpable nodule and positive finding of carcinoma at TURP after about 2 years post RT, but they did have normal PSA levels at multiple follow-ups. They did not get further therapy and are doing well at this time. Despite having normal PSA levels at follow-ups, one other patient had positive para-aortic nodes discovered at biopsy for right leg edema two years post RT. Overall 11.2% patients had an increase in PSA levels.

Clinical Results: Making a comparison with other results is very difficult though necessary. The age of the patients in different series vary and so does their general health. Surgical patients of much lower mean age at treatment, usually have very small well to moderately well differentiated tumors, whereas the radiatherapeutically treated patients of higher mean age at treatment are more likely to have poorly differentiated tumors with accompanying poorer prognosis. The surgical patients undergo pathological staging while others do not (18). These crucial factors demand much awareness while making comparisons.

Mean follow-up time (from the beginning of treatment) for all the patients is 35 months, ranging from a minimum of 9 months to a maximum of 80 months. Follow-up was 1 year in 22 patients, 2 years in 43 , 3 years in 33, 4 years in 21 and 5 to 7 years in 20 patients. A patient was considered free of disease, when the results of a physical and rectal examination, serum PSA level of ≤ 4 ng/ml. and prostate biopsy and / or bone scan were negative. Out of 140 patients, 27 died of intercurrent disease with out

evidence of disease progression. One patient died of prostate cancer. Six patients have evidence of disease progression with increased PSA levels only.

Local failure: Local failure was defined by positive biopsy with increase in PSA levels, in the presence or absence of positive DRE findings. Five patients are biopsy ± DRE positive with increased PSA level, at this time. Five-year survival free of local failure, for stage T1 is 96.7%; T2, 95.2% and T3, 81.8%, overall for all the stages being 94.2%.

Local and distant failures: Two patients have distant metastasis and one, local failure and distant metastasis. For stage T1, five-year survival free of disease is 96.8%; T2, 93.7%, and T3, 69.2%. Overall disease free survival is 91.6%. These data are summarized in Table 6.

Table 6: Five-year local and distant failure rates.

Stage	Local failure rate	Local and distant failure rate
T1	3.2%	3.2%
T2	4.8%	6.3%
T3	19.2%	30.8%
T1, T2, and T3	5.8%	8.4%

Many researchers have reported five-year results for treatment with other modalities. Table 7 summarizes different aspects of treatment failures reported by some authors. The treatment results from the above described treatment modality compare to many other modalities of treatment, as shown in Table 7.

Table 7: Comparison of 5-year results from different treatment modalities.

Five-year Results	Middleton *et al.* (28) #	Hanks *et al.* (17)*	Walsh *et al.* (41)	Paulson *et al.* (29)*	Blasko *et al.* (2)*	Syed *et al.* (38)*	Blasko *et al.* (2)*	This series *
Method	RP	XRT	RP	XRT RP	Implant	^{192}Ir + XRT	Imp. + XRT	^{198}Au + XRT
Number	153	104	586	56 45	291	200	160	140
Any recurrence$	10%	15%	11%	41% 14%	5%	15%	14%	8.4%
Local recurrence $	7%	4%	4%	0% 0%	4%	4.5%	7%	5.8%
Mortality @	3%	4%	3%	NS	0%	NS	0%	0.7%
Overall survival	94%#	87%	93%	NS	100%	84%	100%	99.3%
PSA elevation	NS	NS	10%	NS	11%	NS	20%	11%

Middleton, Hanks ,Walsh and Paulson *et al.* series of T1B, T2, N0, M0 prostate cancer. Blasko *et al.* and Syed *et al.* - A2-C tumors

Absolute, with lost patients eliminated , * Actuarial analysis, @ cause specific mortality, $ 5-year rate, RP Radical prostatectomy, XRT External radiotherapy, Imp. Implants, NS Not stated.

The earlier radical prostatectomy and external beam radiation therapy series did not report of the rate of the biochemical failures, which is more commonly done today as PSA has become a dependable tumor marker for diagnostic, predictive and prognostic purposes.

Treatment related morbidities: As the patients reach 70 years of age their probability of dying from intercurrent disease outruns the probability of dying from cancer of the prostate (22). Quality of life becomes equally important as the probabilities of overall or disease-free survivals. For the purpose of comparison, the complications in this study have been graded in equivalence with the Radiation Therapy

Oncology Group (RTOG) 75-06 and 77-06 protocols' (24) morbidity grading criteria stated as the following;

Grade 1	Minor symptoms requiring no treatment
Grade 2	Symptoms responding to simple outpatient management, life-style (performance status) not affected
Grade 3	Distressing symptoms altering patient's life-style (performance status); hospitalization for diagnosis or minor surgical intervention (such as urethral dilation) may be required
Grade 4	Major surgical intervention(such as laparotomy, colostomy, cystectomy) or prolonged hospitalization required
Grade 5	Fatal complications

Mortality due to treatment is rare in patients treated with radiation therapy. Surgery has been reported to have an associated mortality rate of about 0.5-2.0% depending on the skill of the surgeon and patient care quality of the facilities.

Acute complications: Acute minor genitourinary complications including mild-moderate degree of irritative and obstructive urinary symptoms, incontinence and hematuria occurred in most (84.9%) patients. Minor gastrointestinal complications defined as diarrhea controllable with medications, mild passage of mucus, hematocchezia, tenesmus, abdominal cramps, increased bowel frequency and urgency and anorectal pain occurred in 69.9% of the patients. These complications were mostly self limiting and not severe and equivalent to Grade 1 and 2 complications on the RTOG scale described above.

Acute major genitourinary complications comprised of severe or recurrent urinary tract infection - UTI (0), urinary retention requiring multiple self catheterization (4), indwelling catheterization (2) or TURP (9) and severe hematuria requiring transfusion (1), and occurred with 16 (11.4%) patients; of these, one patient had TURP before RT. One patient suffered from intermittent hematuria requiring transfusion. All these treatment related morbidities are Grade 3 equivalent of the RTOG 75-06 and 77-06 protocols. See summary in Table 8.

Table 8 : Listing of patients with acute major genitourinary complications who did not require TURP for relief of symptoms.

Pt. #	Imp. + Ext. mPD (Gy)	Ext. F.S. (cm)	Complications
1	30+46=76	10x10	Urinary retention , multiple self-catheterizations
2	30+44=74	12x12	U. retention requiring indwelling catheterizations
3	20+50=70	14x16	U. Retention requiring multiple self-catheterizations
4	30+44=74	14x16	U. Retention requiring multiple self-catheterizations
5	25+46=71	12x11	Intermittent hematuria requiring transfusions
6	20+44=64	12x14	U. Retention requiring multiple self-catheterizations
7	30+40=70	14x16	Outlet obstruction, indwelling catheterization

Nine patients (6.4%) listed in Table 9, underwent TURP mostly for bladder outlet obstruction leading to retention. Single cases of severe dysuria, bladder spasm and recurrent UTI had to undergo TURP following the irradiation closely. Five patients out of these 16, had moderate degree of obstructive and irritative symptoms before radiation therapy. No other surgery like salvage prostatectomy, diversion procedures or artificial sphincters (RTOG Grade 4 equivalent) were required.

Table 9: Listing of patients who underwent TURP for relief from obstructive complications.

Pt. #	Imp. + Ext. mPD (Gy.)	Ext. F. Size (cm.)	Reasons and time to TURP
1	30+46=76	11x11	Bladder outlet obstruction, following RT
2	30+44=74	13x12.5	Bladder spasm, immediately after RT
3	25+46=71	13x15	Recurrent UTIs , in 3 months post RT
4	30+40=70	11x12	Urinary retention, immediately
5	25+42=67	12x12.5	Obstructive symptoms and in three months
6	20+46=66	11x14	Severe dysuria, TURP in three months
7	25+44=69	14x16	Bladder outlet obstruction, within three months
8	20+46=66	14x16	U. retention, immediately
9	30+40=70	13x16	U. Retention, bladder spasm & TURP in 2 months

.

Acute major gastrointestinal complications were defined as having severe diarrhea or tenesmus requiring narcotics or more than three days break in treatment, hematocchezia requiring transfusion, multiple episodes of fecal incontinence which are equivalent to RTOG Grade 3 complications. None of the patients developed any of these or other major complications (RTOG Grade 4 equivalent).

Late complications: Late minor genitourinary complications defined same as acute minor complications and equivalent to RTOG Grade 3 complications, occurred with 10 (7%) patients; urge and stress incontinence in 7 (5%), gravity or total incontinence in 2 (1.4 %), dribbling in 3 (2%) and stricture in 1 (0.7%). Five of these patients (38.5%) have had TURP within four months prior to RT. The complications are listed in Table 10 and Table 11 shows a comparison with the results of some other series.

Table 10: Listing of patients experiencing urinary incontinence over different periods of time.

MR #	Imp. + Ext. mPD(Gy)	Ext. Field Size (cm)	Complications
1	30+44=74	11x11	Moderate incontinence & mild proctitis for 4 years
2	30+40=70	12x12.5	Urinary dribbling until death 3 years post RT
3	35+40=75	11x11	Has significant urinary incontinence
4	20+44=64	9x9	Slight urge incontinence for ~ 3 years
5	20+44=64	9x9	Stress & gravity incontinence up to 3 yr. Mild dribbling now. Did not want artificial sphincter.
6	20+44=64	11x11	Severe hesitancy due to stricture, TURP done
7	25+44=69	13x14	Slight urinary dribbling till death 3 yr. post RT
8	25+44=69	11x11	Slight urge incontinence for 4 yr. post RT
9	25+36=61	11x11	Frequency and mild dribbling , 3 $^{1}/_{2}$ yr. post RT
10	15+50=65	13x16	Slight stress incontinence, TURP 1 $^{1}/_{2}$ yr. post RT
11	25+42=67	12x12.5	Urge and stress incontinence, recovered now
12	30+40=70	12x16	Urgency and urge incontinence for 2 years post RT
13	30+40=70	14x16	Moderate incontinence for two years post RT

Table 11: Comparison of rate of incontinence with different modalities of treatment.

Incontinence	Surgery*	External*	$^{125}I/^{103}Pd$ plus Ext.^	$^{125}I/^{103}Pd$ `	This study
Stress	40%	5%	6%	6.8%	5%
Gravity/Total	13%	2%	3%	Overall	1.4%

* Talcott J. A. (39) ^ Ragde (32), ` Blasko, Grimm, Ragde (2).

Late minor gastrointestinal complications (RTOG Grade 3 equivalent) were experienced by two patients (1.4%) who had fairly frequent diarrhea and mild to occasional bouts of diarrhea by 4 (2.8%) patients, the rates being lower than other modalities. Fairly frequent diarrhea is usually seen in 4% and 21% of RP and externally irradiated patients respectively (35). Implants with ^{125}I and ^{103}Pd had 3% incidence of proctitis and External irradiation plus ^{125}I or ^{103}Pd had 10 % proctitis and 1% fistula (30) These findings are summarized in Table 12.

Table 12: Listing of late minor gastrointestinal complications.

MR #	Implant + Ext.(Gy)	Ext. F. S. (cm)	Complications
1	30+44=74	11x11	Moderate proctitis, no hematocchezzia
2	30+40=70	12x14	Moderate proctitis for $2^1/_2$ yr. now resolved
3	30+40=70	11x11	Mild diarrhea for $3^1/_2$ yr. but now resolved
4	30+40=70	11x11	Occasional bouts of diarrhea for 3 yr.
5	25+44=69	11x11	Occasional bouts of diarrhea for 2 yr. resolved now
6	15+50=65	14x16	Bouts of diarrhea

Late major genitourinary complications defined as having severe decrease in bladder capacity requiring urinary diversion, severe hematuria requiring multiple transfusions, severe urinary incontinence not resolved with surgery, urethro-rectal and vesico-urethral fistula, which are equivalent to RTOG Grade 4 morbidities. No patient in this study suffered any major genitourinary complication.

Surgery and external beam radiation therapy are associated with 20-40% and 3-5% major genitourinary complications respectively. Blasko *et al.* (2) reported of late cystitis/urethritis (7%), superficial urethral necrosis (SUN-3%), hematuria (1%), stricture (2%) and incontinence (6%) in patients treated with ^{125}I implants only. With external plus ^{125}I implants, they reported a lesser rate for urinary complications but a higher rate of rectal complications; 4% cystitis/urethritis, 4% SUN, 4% incontinence, 6% proctitis and <1% of urethro-rectal fistula.

Major gastrointestinal complications were defined as having severe proctitis or proctosigmioditis sometimes requiring colostomy, severe rectal bleeding requiring

transfusion, and rectovesical fistula (RTOG Grade 4 equivalent). None of the patients in this study experienced any of these major gastrointestinal complications.

Surgery and external irradiation usually entails 2 to 10% and 3 to 8% complications respectively. Ragde (32) reported 3% proctitis a with implants only, 10% suffered from proctitis and 1% fistula in patients treated with external irradiation followed by ^{103}Pd / ^{125}I implants in a series of 122 patients. Boileau and associates (3) reported very mild and limited degree of complications in most patients treated with staging lymphadenectomy, retropubic implantation of the prostate with ^{198}Au in combination with external irradiation. Carey *et al.* (6) also reported mild and short-lived complications in patients treated with gold seed implantation and external radiotherapy. Syed and Puthawala (38), treating localized prostatic adenocarcinoma with temporary implant of ^{192}I and external irradiation reported reduction of moderate to severe rectal and urinary complications from 11% in the first (series 1) to 4% in the second series (in series 2), by modifying the source distribution and reducing the total dose in those patients who underwent TURP prior to RT. Overall, it would not be an overstatement to say that the early and late complications in patients treated with ^{198}Au and external radiotherapy are less than all other modalities of treating prostate cancer in general. The rate of incontinence is about the same with most other modalities. Loening (25), reported of lower rate of both genitourinary and gastrointestinal complications in patients (stages A2-D1) treated with ^{198}Au implants (70-150 Gy) often supplemented with 20-30 Gy of external irradiation. This is important to recognize that

lower complications rates are a special advantage for the old age patient population treated for prostatic carcinoma.

Prevalence and worsening of potency: In this study, 29% of the patients were impotent at presentation and there was no information on 16.4% of the patients. Half of the remaining 54.6% were already having a mild degree of impotence. In one year following RT, 46% of the potent and mildly impotent patients experienced deterioration to impotency. This figure is acceptable considering the age and potency profile in the study.

In surgically treated patients, impotence occurs with a wide range of variation from 20% to 70% depending on the skill of the surgeons, patients' age and mode of surgery. Nerve sparing radical prostatectomy has good prospect of continued potency for relatively younger potent patients with very small tumors. Walsh and Schlegel reported 74% preservation of potency and also reported a correlation with the time of diagnosis as cited by Hanks (18). External beam alone causes impotence in about 40% patients of older age groups as compared with those undergoing surgery. The multi-instituitional study by. Talcott J. A. reported 77% post-surgical impotence rate while the external beam series had 41% impotence rate (39).

External beam therapy causes about 40% impotence rate. Blasko *et al.* (2) doing ^{125}I or ^{103}Pd Implants and external beam radiation therapy and implants reported post radiation therapy deterioration to impotency in 15% under the age of 70 and 50% over the age of 70, there being no significant difference between the two modalities.

With ^{192}Ir and external beam therapy, Syed *et al.* (37) reported a 25% occurrence of impotence in their series with 50% prevalence of impotency prior to treatment.

Complications in patients over the age of 70 years is probably the most important criterion for judging a treatment's efficacy. Because as patients reach the age of 70 years, their probability of dying with intercurrent disease increases and so quality of life becomes more important than any other factor. A positive biopsy or a palpable abnormality may not signify future clinical recurrence or decrease the life span or quality of life of the host (22). Routine post-irradiation biopsies were not done, unless indicated by palpable prostate or rise of PSA which would dictate a change in treatment approach.

Radiation protection of personnel involved in the brachytherapy procedures: Records of the Physics Department at MBPCC, of counting, calibration, loading and unloading and handling of sealed sources namely ^{192}Ir, ^{137}Cs, ^{103}Pd and ^{198}Au, showed that transperineal ^{198}Au implants comprise about one third of all the brachytherapy procedures. Number of personnel doing these tasks in rotation are shown in Table 13 for the years 1990 to 1993. Table 14 shows the number of implants, both ^{198}Au and ^{103}Pd done over the years, 1988 to 1993. Table 15 shows the number of implants done by the urologists.

Table 13 : Number of physics personnel rotating for different source handling tasks, including the implants. (Source: Task calendar, Physics Implants Records).

Year and # of personnel	1990=7	1991=8	1992=9	1993 = 10
Number of cases in total	88	108	98	72
Gold Implants (# and %)	35 (39.8)	36 (33.3)	34 (34.7)	18 (25.3)

Table 14: Number of prostate implants, from 1988 to 1993. (Source: Physics implant records).

Year	Number of ^{198}Au implants	Number of ^{103} Pd implants	Total
1988	26		26
1989	21	1	22
1990	35	4	39
1991	36	8	44
1992	34	12	46
1993	18	5	23

Since, between 7 to 10 physics personnel rotated to do the source handling for the implants or other brachytherapy procedures, their individual exposure becomes very low from these procedures (see Table 13). Exposure to hand and wrist during ^{198}Au seed counting and calibration averaged 17mR per case. Personnel exposure during needle loading and implantation procedure by the needle loader and implanting urologist averaged 19.8 mR/case (43).

Five year review of personnel monitoring data reveals the following highest ring and body badge readings (source: TLD dose reports, Landauer Inc. / OLOL and Physics records) tabulated in Table 15. The urologists for being in close proximity to the loaded needles and the radiation oncologist, for being the only one doing all the implantations, had the highest exposure risk. These doses recorded are exclusively from ^{198}Au, ^{103}Pd and other interstitial implants.

Table 15: Number of ^{198}Au and ^{103}Pd implants done by different urologists.

1988-1993	Dr. A		Dr. B		Dr. C		Dr. D	
Implants	^{198}Au	^{103}Pd	^{198}Au	^{103}Pd	^{198}Au	^{103}Pd/^{125}I	^{198}Au	^{103}Pd
Number	64	10	54	6	40	13/1	13	0

Table 16 shows the doses received by different personnel from the beginning of the implants to the end of 1993. These doses are in addition to the doses received from other sources. The doses received from doing the implants, recorded as cumulative dose, show averages of 37, 25.6 and 16.5 mR/case for different urologists, assuming the ^{103}Pd implant dose contribution to the dedicated TLD dosimetry to be minimal because of the soft 21 KeV x-rays from ^{103}Pd.

Table 16 : Review of TLD dose reports showing doses to the personnel who received the most exposure from the implants, including the radiation oncologist. (Source: Radiation Dosimetry report, OLOL. reported by Landauer Inc.).

	TLD	1991		'92		'93		Cumulative u to 12/93	Inception date	# ^{198}Au imp. up t 12/93
		Dee	Shallo	D	S	D	S			
Control			M M	90	90 270		M M	Deep/Shallow Shallow		
Urologists:	Body	20	20	30	30	30	30	160/160	4/88	64
	Ring		460		530		460	2370	10/88	
B	Body	M	M	M	M			90/90	1/88	54
	Ring		140		400			1380	10/88	
C	Body	10	10	10	10	M	M	30/30	4/88	40
	Ring		160		110		140	660	10/88	
Radiation Oncologist	Body	10	10	60	60	M	M	100/100	4/88	> 201
	Ring		140		170		60	290	9/88	
Highest (ring badge)	Body	M	M	30	30	M	M	30/30	9/88	
	Ring		380		670		430	2860	9/88	

For all personnel the exposure ranged from minimal to 60 mrem/yr. (deep) and minimal to 60 mrem/yr. (shallow) for body badges and minimal to 670 mrem/yr. (shallow) for ring badges. The person receiving the highest body deep dose is one of the urologists, amounting to 160 mrem so far (shaded ellipse in Table 16). The person

receiving the highest ring badge dose amounting to 2860 mrem (shaded ellipse in Table 16) from '88 to '93 received the dose from doing most of the loadings of the needles only and participating in no other brachytherapy procedures. In one incidence on 4/19/93, having left the ring badge near the loaded needles while scrubbing, the same person exposed the ring badge to some extent too.

The maximum permissible dose (MPD) limit for the whole body is 0.05 Sievert (Sv) or 5 roentgen equivalent man (rem) a year provided the limit on lifetime total effective dose is not exceeded. This amount is the total effective dose, which includes dose from both external and internal exposures. The MPD for extremities limits to 0.50 Sv (50 rem) shallow dose equivalent, a year. These limits have been set with worst case lifetime risks of fatal probabilistic effects caused by radiation exposure to occupationally exposed personnel. With the current safety measures, the exposures to the urologist, oncologist and others are well below the set limits and is not in conflict with the ALARA principle. Carlton (8) reported that one radiotherapist in his center, after performing more than 100 ^{198}Au implantations in a year, received 6360 millirem to the hands and 340 millirem to the whole body. Fewer ^{198}Au seeds of higher activities and placement by hand in the retropubic method caused a higher exposure to the hands. The perineal approach is altogether different and radiation exposure experienced by the participating personnel, is minimal and certainly not in conflict with the ALARA principle.

Exposures, as documented for the years 1993 and 1994, in adjacent surgery room at chest level, about one foot away from the wall across the seed loading table

ranged from a minimum of 0.5 mR/hr to a maximum of 2.2 mR/hr, mean being 1.3 mR/hr). maximum permissible exposure rate for unrestricted area being 2.0 mR/hr (Table 17). Xetex meters placed on the wall measured higher; 3, 6.1 and 9.4 mR/hr (shaded ellipses in Table 17). The room was occupied 22% of time on average (43).

Table 17: Exposure rates (mR/hr) recorded by Xetex integrating exposure meter in the adjoining operation room (OR # 5) through the years 1993 and 1994. (Source: Physics Records, Brachytherapy Implants Radiation Safety book 60.222).

Date	Exposure rate	Date	Exposure rate	Date	Exposurerate
2/8/93	1.4	2/10/93	2.1	2/22/93	0.6
3/1/93	1.1	3/5/93	1.3	4/12/93	0.6
4/19/93	3.0	4/21/93	1.0	4/26/93	0.8
5/24/93	0.8	10/4/93	2.0	10/8/93	9.3
10/18/93	2.2	11/8/93	1.2	1/3/94	0.9
1/31/94	1.4	2/20/94	1.4	2/22/94	1.2
4/4/94	6.1	5/9/94	0.5	7/11/94	1.9
8/1/94	1.0	9/8/94	1.7	10/10/9	1.8

The operation room (OR), post-anesthesia care unit and suite were surveyed during and after each implant procedure (Figure 1 and Table 18). Survey result review show that exposure is minimal when the seeds are in the needles. When the seeds are inside the patient the exposure to the personnel varies with a range of 2-6 mR/hr as seen in a patient with highest activity (73 mCi.) in '92. After implantation the patient remains in the OR only for a short while, moving onto the post anesthesia care unit. The bedside activity recorded was 40 mR/hr and 12 mR/hr at 1 meter from the patient. The nearest patient lies at a distance of about 3 meters from the patient with the implant. The nurse's station readings ranged from background to a maximum of 0.2 mR/hr.

Table 18: Survey results showing exposures at different points for a patient with highest implanted activity and highest exposure rate by bedside at post anesthesia room. (Source: MBPCC Brachytherapy Implants Radiation Safety, book 60.222).

OR. SURVEY	Loaded	Exposure	Needles in	Exposure	Recovery	Exposure
4.26.93	Needles	mR/hr	Patient	mR/hr	Room	mR/hr
	Sites # 1	0.6	Sites # 1	2	Bedside	40
	2	0.3	2	2	1 meter	12
Seeds in OR:78	3	0.1	3	6	Head	1
	4	0.2	4	5	Nurse's	0.1
# of Seeds	5	0.4	5	2	Station	
implanted:73	O.Room #5: 2.1 mR in 2.5 hours.					
1.0 mCi/seed	Autoclave: Cleared					
	O. Room: Cleared			Survey Meter : Ludlum M3 # 59402		
Signed	Yes			Calibration due:7.15.93		

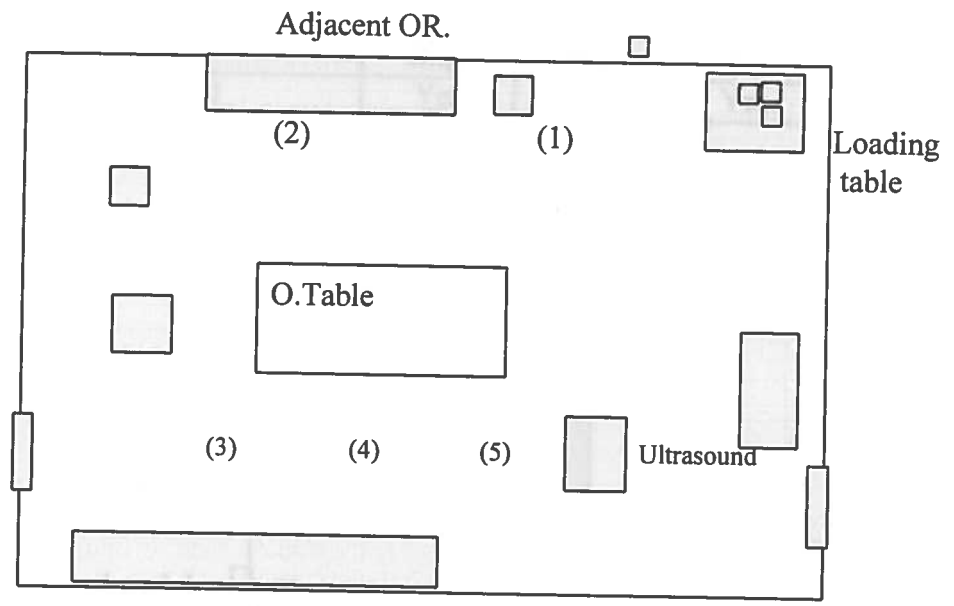

Figure 1: Schematic diagram of the Operation Room showing the survey positions.

The patient and the suite were also surveyed. One patient, having the highest bedside exposure rate of 15 mR/hr at 1 meter in the suite, stayed for four days until the

exposure rate dropped to 5.3 mR/hr on the fourth post operative day as shown in Table 19. Figure 2 shows the points in the suite where radiation surveys were performed.

Table 19: Exposures at different points in the suite. (Highest recorded for a patient implanted with 80 seeds (1.12 mCi/seed) with a total of 89.6 mCi activity dated 9/24/90-MBPCC Brachytherapy Implantation Radiation Safety record book 60.221).

SUITE SURVEY	Day 1	Day 2	Day 3	Day 4	Post Discharge
Site # 1 = Anteroom	0.5 mR/hr	0.4 mR/hr			
2 = 2 ft. from source	20	19	18	12	Background
3 = 3 ft. from source	15	8.5	7.5	5.3	Bkg.
4 = 6 ft from source	3	2.5	2.0	1.0	Bkg.
5 = Outside closed door	0.1	0.1	0.1	Bkg.	Bkg.
6 = Hallway	Bkg.	Bkg.	Bkg.	Bkg.	Bkg.
7 = Sofa	7.0	7.0	6.0	5.0	Bkg.
Bath room	Bkg.	0.9	0.7	0.5	Bkg.
Urine	Bkg.	Bkg.	Bkg.	Bkg.	Bkg.
Linen	Bkg.	Bkg.	Bkg.	Bkg.	Bkg.
Trash	Bkg.	Bkg.	Bkg.	Bkg.	Bkg.
Signed	Yes	Yes	Yes	Yes	Yes

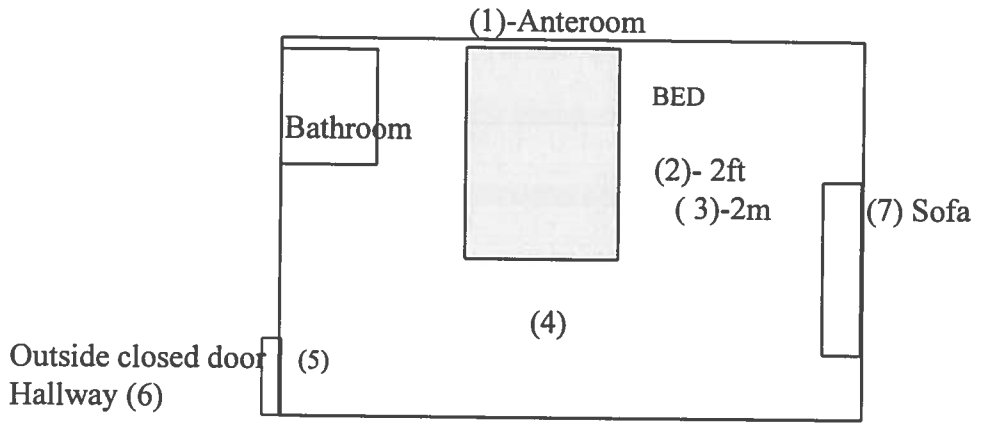

Figure 2: The Suite layout schematic showing the layout of the suite used, different objects in the suite and the numbered exposure measurement points.

Most of the patients were discharged on the second post operative day. Besides the suite, linen, urine and trash were invariably monitored for expelled seeds. At discharge, the suite was surveyed for clearing for next use. The allowable limit for patients containing radiopharmaceuticals or permanent implants at discharge is 50 microSievert (5 mrem) per hour at one meter as per Louisiana radiation protection regulation 33:XV.725 (26). The maximum decayed activity allowable within a patient having a ^{198}Au permanent implant at discharge is 23 mCi. (34). The average stay for the patients in the hospital was found to be 2.2 days.

CONCLUSION

Compared to published results, disease free survival and local recurrence rates are comparable to external beam irradiation and other implants plus external beam series. As with other series, pre-treatment PSA level and Gleason score is a strong predictor of disease progression. Early and late toxicities of treatment are equal to or lower than external beam irradiation and implants alone or in combination with external beam. The incidence of gastrointestinal complications are markedly lower than most of the other series. With achievement of more precise seed implantation, ensuring 30 Gy mPD in most if not all cases, further improvement may be expected. Radiation protection was adequate for having proper design and maintenance of safety protocols. Exposure from the implant procedure experienced by personnel was minimal. This can be concluded that this technique offers a reasonable alternative therapy for clinically localized prostate cancer in selected group of patients because it offers reasonable disease control and lower rate of treatment related morbidity in general.

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VITA

Md. Ali Haider Rashidee was born on April 05, 1958, in Dhaka, Bangladesh. He attended the Mirzapur Cadet College, Tangail, Bangladesh, and graduated in December, 1976. He obtained his Bachelor of Medicine and Bachelor of Surgery from the University of Dhaka, Bangladesh. He practiced Medicine for six years and then joined the Institute of Postgraduate Medicine and Research, to earn his Diploma In Medical Radiotherapy from the University of Dhaka in July, 1991. He entered the graduate school in Spring, 1992 and received a graduate research assistantship in August, 1992 in the Nuclear Science Center at Louisiana State university. From Fall, 1993, his assistantship duties and clinical training were centered at Mary Bird Perkins Cancer Center, Baton Rouge, Louisiana. He is currently a candidate for the degree of Master of Science in Nuclear science and Engineering, Medical Radiation Science option.

MASTER'S EXAMINATION AND THESIS REPORT

Candidate: Md. Ali Haider Rashidee

Major Field: Nuclear Science and Engineering

Title of Thesis: Five-Year Clinical Results and Review of Physics of Prostatic Implantation with Au-198 Seeds and External Irradiation in the Management of Localized Adenocarcinoma

Approved:

Oscar Hidalgo S.
Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Edward D. Lomenick

Sheldon Lam

Date of Examination:

April 6, 1995