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## The Observed Variance Between Predicted and Measured Radiation Dose in Breast and Prostate Patients Utilizing an in-vivo Dosimeter

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### Abstract

**Purpose**—Report the results of using a permanently implantable dosimeter in radiation therapy: determine specific adverse events, degree of migration, and acquire dose measurements during treatment to determine difference between expected and measured dose.

**Methods and Materials**—DVS (Dose Verification System) is a wireless, permanently implantable MOSFET dosimeter using a bidirectional antenna for power and data transfer. The study cohort includes 36 breast (33 received 2 devices) and 29 prostate (21 received 2 devices) cancer patients. A total of 1783 and 1749 daily dose measurements were obtained on breast and prostate patients, respectively. The measurements were compared to the planned expected dose. Bi-weekly CT scans were obtained to evaluate migration and NCI CTCv3 used to evaluate adverse events.

**Results**—Only grade I/II adverse events of pain and bleeding were noted. There were only four instances of dosimeter migration of >5mm due to known factors. A deviation of  $\geq 7\%$  in cumulative dose was noted in 7 of 36 (19%) for breast cancer patients. In prostate cancer patients, a  $\geq 7\%$  deviation was noted in 6 of 29 (21%) and 8 of 19 (42%) during initial and boost irradiation,

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**Conflict of Interest Statement:** The following participants are associated with Sicel Technologies, Inc., the manufacturer of the implantable dosimeter used in the study: Charles W. Scarantino, MD, PhD, is a co-founder of the company, medical director for the company, and member of the Board of Directors; Gloria P. Beyer, Ph.D., is an officer of the company; Robert D. Black, PhD, was an officer of the company during the study and a consultant for the company at the time of data analysis; Natasha Bolick is an employee of the company.

The study analyzes the data obtained from a FDA approved study protocol. The data used and presented in this research was collected, monitored, and managed in accordance with the FDA's adopted ICH Guideline for Good Clinical Practice and 21 CFR Parts 50, 54, 56, and 812 and 45 CFR Parts 160 and 164.

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respectively. The two patterns of dose deviation were random and systematic. Some causes for these differences could involve organ movement, patient movement and/or treatment plan considerations.

**Conclusions**—The DVS was not associated with significant adverse events or migration. The dosimeter can measure dose *in situ* on a daily basis. The accuracy and utility of the DVS complements current IGRT and IMRT techniques.

### Keywords

Implantable dosimeter; *in-situ* radiation; dosimetry prostate and breast cancer

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## Introduction

One of the most important tenets in oncology is to minimize toxicity and maximize malignant cell kill. The desire to hold to this tenet has been particularly important in radiation therapy because of the long term effects of radiation on normal tissue. Recent technological advances (including 3-D conformal therapy, intensity modulated radiation therapy [IMRT]) have allowed more complex and conformal treatment plans in order to deliver higher doses to smaller target volumes and avoid critical structures. In so doing, steep dose gradients are created making target coverage and dose delivery important. Several important factors including target motion and deformation, patient alignment and treatment delivery can alter the position of the target (1). Ultimately, the identification of an anatomical target and verification of the delivered dose become paramount to the physician as the nexus for improved therapeutic outcome.

Image guided radiation therapy techniques allow for more precise identification of the target volume. IGRT can reduce patient positioning errors due to daily setup variations and organ movement (2). Interfractional movement has been studied in bladder (3), rectum (4), gynecological (5) and prostate (6,7,8) while intrafractional movement has been investigated in lung (9), liver (10) pancreas (11) and prostate (12,13,14). Although there is general agreement on the importance of IGRT particularly when involving IMRT, there does appear to be uncertainty regarding the features and approaches of competing IGRT systems. In order to verify the validity of these techniques and be assured of achieving improved therapeutic ratio, knowing the dose delivered to the target would be beneficial. Errors in delivery of radiation and the efficacy of the IGRT positioning system can be known by performing direct dose measurements.

Reports of dose measurements are, except for a few cases, limited to work in phantoms or by measuring entrance and exit dose, the latter of which is not used extensively for IMRT because of its complexity. Regardless of the *ex vivo* technique used, the true *in-situ* dose delivered to the target volume in the patient has not been directly verified. The ability to monitor the delivered dose *in situ* at the target tissue(s) (15) introduces the next phase in radiation oncology that of dose guided radiation therapy (DGRT).

A previous report (16) introduced the first implantable dosimeter capable of measuring the radiation dose *in-situ*. The accuracy, safety and functionality of the device as well as the results of the pilot study have been reported (16).

This report contains the results of the clinical implementation of the DVS dosimeter from a pivotal study in breast and prostate patients and breast cancer patients from the initial pilot study. Based on the results of these studies, the implantable dosimeter has been cleared by the United States Food and Drug Administration (FDA) for use in breast and prostate cancer patients.

## Methods and Materials

### a) Study Design

The current analysis is based on an FDA approved pivotal and pilot study protocols, conducted at four institutions including Rex Cancer Center, Duke University School of Medicine, Wake Forest University School of Medicine and the Texas Cancer Clinic. The Institutional Review Board (IRB) of each institution approved the study. The nature of the procedure was explained and consent was obtained from each patient prior to insertion of the device. The primary objective of the study was to evaluate the safety (migration and frequency of adverse events) of the device after implantation and secondarily its ability to measure the delivered dose at the site of implantation. FDA study guidelines did not permit alterations of treatment parameters or methodology.

### b) DVS Dosimeter

The Dose Verification System (DVS<sup>®</sup>, Sixel Technologies Inc., Morrisville, NC) is a wireless dosimeter designed to be permanently implanted *in vivo* to record the actual dose to the target on a daily basis. The structure and technical aspects of the dosimeter system have been previously described (16,19). In summary, the DVS is a wireless MOSFET based dosimeter designed to be permanently implanted *in situ* at the tumor volume and provides a method for verifying the actual dose to the target on a daily basis. A portable telemetric readout system couples to the dosimeter antenna powering the dosimeter and permitting data transfer. Accuracy of the dosimeter used for the patient clinical trial was validated and found to be within the manufacturer specification of 5% ( $2\sigma$ ) for these dosimeters (17). The active area of the MOSFET was  $690\mu\text{m} \times 15\mu\text{m}$  and can be considered a point detector. The DVS modulates the magnetic field generated by the reader to transmit the measured dose data.

The device characteristics, *in vitro* calibration methodology, and test results have been previously reported (16-19). The dosimeters used in the clinical trials were individually calibrated to perform within 5% ( $2\sigma$ ) up to 80Gy and had a capsule size of 27 mm  $\times$  3.1 mm. *In vitro* testing found minimal day to day variation with reproducibility of  $\pm 2\%$  (17). Another *in vitro* study included a heterogeneous phantom and different positions of the dosimeter in the isodose configuration showing a performance within  $\pm 5\%$  when compared to the predicted dose from the planning system (16). Currently the DVS is commercially available in a smaller capsule size (20 mm  $\times$  2.1 mm) with lot calibration with an accuracy of  $<5.5\%$  ( $2\sigma$ ) up to 20 Gy and  $<6.5\%$  ( $2\sigma$ ) up to 74 Gy). Phantom testing has verified the accuracy and performance of the new dosimeter for different irradiation conditions (18)

### c) Study Population

The study population included 36 breast (30 from pivotal and 6 from pilot studies) and 29 prostate cancer patients. All patients were required to have biopsy proven malignancy (resectable or unresectable) and to be candidates for definitive radiation therapy. It was recommended but not required that each patient be implanted with two dosimeters - one associated with the malignant tissue and a second associated with the normal tissue being irradiated. Additional criteria included a prothrombin time of 10.2 to 12.2s and a partial thromboplastin time of 24 to 36s.

### d) Breast Implantation

Two DVS devices were implanted; one in the tumor bed and, if possible, one in the opposite side of the same breast, either at the time of lumpectomy or in the radiation therapy department using local anesthesia and CT guidance. When implanted at the time of lumpectomy, the device was placed in a polyethylene mesh and sutured in the tumor bed. A second dosimeter was then

placed in the normal tissue of the opposite quadrant with a specially designed trochar. To provide appropriate build up and comfort, it was recommended that the DVS dosimeter be implanted  $\geq 3$  cm from the skin surface in the breast cancer patients.

#### e) Prostate Implantation

DVS dosimeters were inserted in the prostate either under monitored anesthesia care (MAC) or with a local anesthetic, using a transperineal approach. One device was placed at or inside the prostate capsule and defined as the Gross Tumor Volume (GTV). The second device was placed on the opposite side of the prostate 0.5 to 2.0 cm lateral to the prostate capsule but within the treatment volume and designated as normal tissue.

#### f) Simulation and Dosimetry

After implantation, simulation was generally delayed for at least 3-5 days to allow the dosimeter to become anchored in the tissue. All patients underwent computed tomography (CT) simulation in the treatment position. Once the DVS implant was identified, 1- 3 mm slices were obtained through the device beginning 2 cm cephalad and continuing to 2 cm caudal to the dosimeter. Sensor migration could lead to a discrepancy between measured and expected dose values; therefore the specific CT protocol was repeated every 2 weeks during treatment to determine any degree of migration. Migration of the device was evaluated by an independent board certified radiologist. Migration was defined as a change in the device location of greater than 5 mm from the initial CT, not attributable to patient movement or tumor shrinkage. The protocol required re-planning which established a new predicted dose, but did not allow for the implementation of a new treatment plan.

Standard treatment planning procedures were followed. The three main planning characteristics – heterogeneity correction, type of planning system and daily localization were not stipulated in the protocol. However, the planning details for the prostate patients have been reported (30). The active area of the dosimeter was obtained by using CT scout views and digitally reconstructed radiographs. The position of the MOSFET dosimeter within a specific isodose line was identified and designated in the treatment plan via a point of interest, to obtain the expected radiation dose. The only requirements for the delivery of radiation were that the patients receive at least 4 weeks of treatment and daily fractionated photon irradiation in the range of 150-250 cGy per fraction. The DVS was interrogated before and after each fraction of radiation to obtain the dose delivered to the sensor. The measured results were recorded and compared with the expected dose of radiation.

#### g) Clinical endpoints

This report represents the results of 36 breast patients and 29 prostate cancer patients. Thirty-three breast patients had 2 dosimeters inserted and 21 prostate patients had 2 dosimeters inserted. In each case, daily measured dose values were compared with expected plan values. Patients were evaluated at the time of insertion of the DVS and each week for adverse events attributable to the implanted dosimeter. All data was collected and referred to the Duke Clinical Research Center for independent registration and evaluation.

#### h) Statistics

A data point is defined as a single reading from any one dosimeter. Accordingly, the results presented for breast patients represents 1783 data points (during photon beam only) and for prostate patients, 1749 data points.

Cumulative percent difference is the percent difference between cumulative planned and measured doses. The cumulative measured dose was an accrual of daily fractional radiation

dose measurements to the tumor or normal tissue site as obtained by the DVS dosimeter while the cumulative planned dose was the total prescribed dose to the MOSFET position. The percent difference between cumulative measured and planned doses was calculated for each dosimeter at tumor or normal tissue locations for each patient in the study.

Fractional dose difference (or fractional percent difference) was calculated for each patient as the difference between the daily fractional planned dose and the daily dose measurement obtained by the DVS dosimeter. The daily fractional planned dose was obtained from the treatment plan based on the patient's prescribed treatment and the MOSFET location. The numbers of fractional percent differences greater than or equal to 5 and 7% were counted (not mutually exclusive) for each patient. Those values were then divided by the total number of fractions for each patient, giving the percent frequency at which fractional dose differences greater than or equal to 5 and 7% occurred per patient.

## Results

### a) Safety

The primary objective of this study was to determine the safety of the device following implantation. Safety is defined as the degree of migration of the device following implantation and any associated adverse events. The National Cancer Institute Common Toxicity Criteria v3 (20) were utilized to evaluate adverse events. There were a total of 119 dosimeters inserted.

The most common adverse events associated with implantation of the device in the prostate patients were pain and bleeding as noted in Table 1. They were reported to be mild to moderate by patients and surgeons. All events were considered within the range of expected discomfort associated with the surgical procedure. Six of the eight events resolved within 24 hours and two by 23 days. There was one instance of migration of 6 mm attributed to the simulation being done immediately following the implant and not allowing sufficient time for the normal process of retention to occur.

The 5 adverse events associated with breast implantation were directly attributable to the device. All events resolved within 24 hours. There were two instances of post surgical adverse events. One event was related to improper placement of the device and the second to a retained suture. There were three episodes of migration. One case was attributed to the shallow placement of the device (noted above), a second due to soft tissue displacement associated with evolving post operative changes and a third, noted as movement of 8 mm by serial CT scans, indicated conformational differences led to an apparent shift of the dosimeter with respect to the appointed landmarks.

### b) In vivo dose measurements

**Breast Patients**—All patients were treated with tangential fields to the entire breast. The data represents dose measurements during photon irradiation. No electron measurements are reported at this time. All patients had a device placed in the tumor bed; three did not have a device implanted in the normal tissue.

The distribution of observed differences between measured and predicted doses of all daily fractions are shown in Fig. 1. The majority of measurements (1111 or 62%) were within 5% of the expected dose, however, 38% of the fractions differed from the expected by  $\geq 5\%$  and 19% differed by  $\geq 7\%$ .

Figure 2 depicts the cumulative percent difference in each patient including the tumor and normal sites. There are 13 patients (36%) who had a  $\geq 5\%$  cumulative percent difference in at least one site. There was  $\geq 7\%$  difference in cumulative dose in 7 of the 36 (19%) patients and

one patient with  $\geq 14\%$  difference. Fig.3 is a histogram of the cumulative percent error which graphically displays the tendency toward the delivery of higher doses than expected in the breast group as a whole.

**Prostate patients**—A total of 50 devices were implanted in 29 patients; 21 patients received 2 dosimeters and 8 patients received one. A total of 1749 data points were obtained - 1308 data points during treatment of the primary field and 441 data points during delivery of the boost or reduced field. The distribution of observed differences between measured and predicted doses of all daily fractions during large field are shown in Fig.4. A total of 33% of the fractions differed from expected dose by  $\geq 5\%$  and 19% by  $\geq 7\%$  and some  $\geq 20\%$ . The cumulative percent difference between the observed and measured doses for each patient is shown in Fig.5. Thirty-one percent (9/29 patients) had a  $\geq 5\%$  absolute difference and 21% (6/29 patients) demonstrated a  $\geq 7\%$  absolute difference during large field radiation.

Figure 6 shows the frequency distribution during the boost field when field sizes were reduced and treatment margins of 1.0 to 1.5 cm were frequently employed. A total of 51% of fractions differed from expected dose by  $\geq 5\%$  and 35% differed by  $\geq 7\%$ . Figure 7 shows the cumulative percent difference for prostate boost treatment only. A total of 19 patients received reduced field (boost) irradiation; 15 patients or 79% had values that differed by  $\geq 5\%$  and 8 patients or 42% had  $\geq 7\%$  difference from expected. It is also important to note that in all but one case, the dosimeter was within the treatment isodose line. A summary of the percent variation of the data on all the patients is presented in Table 2.

### c) Patterns of Dose Differences

Figures 8a,b,c illustrate two patterns of dose measurements observed in several prostate patients. In each case the expected (blue) and measured (red) doses are shown for each day.

Fig. 8a illustrates what would be considered an acceptable result (i.e. dose measurements within the 5% acceptable range). The expected dose in this patient was 187.0 cGy on the majority of days this was delivered. Of note is the change in expected dose on days 29 and 34 which corresponded to a change from large field to boost field and the recognition of the change by the dosimeter. The cumulative dose measurement in this patient was +1.40% of expected.

Fig. 8b is representative of a systematic pattern of dose deviations. In this case the expected dose is 200.0 cGy which increased due to field change on day 34. The measured dose is consistently or systematically low throughout the course of treatment and followed the change in expected dose during the boost field treatment. The cumulative dose delivered was -11.64% of expected.

Fig. 8c demonstrates a random or inconsistent pattern in dose deviations. Although random measurements  $\geq 7\%$  of expected are noted on days 3, 14, 20 and 22, there was little effect on the cumulative dose which was -0.54% of expected.

## Discussion

As this report represents the initial presentation of complete data from the pivotal study, specific observations related to variability in measured versus expected dose and the relevance to current radiotherapeutic practice will be emphasized:

### a) The pivotal study verified the safety of the implanted device

There were only Grade 1 (minimal) and moderate adverse events associated with the implanted device, and the Grade 1 events occurred primarily at the time of the insertion of the device. The

incidence of migration was low, occurring in only 4 of 119 implanted devices and could be explained.

#### **b) Approximately 20% of all patients had $\geq 7\%$ difference in cumulative dose delivered**

The variability of *daily* readings occurred sporadically during treatment in most patients. The percent frequency of  $\geq 7\%$  variability was 19, 19 and 35% in the breast, prostate (large field) and prostate (boost) respectively. The degree of variability during daily treatment did not translate into as high a percent of patients with cumulative dose difference which was 19, 21 and 42%. Although the degree of variability was similar in both the breast and prostate patients (19 and 21% respectively) the cause(s) may be different since one would not expect the same degree of uncontrollable organ movement to occur in breast (due to breathing) as in prostate. In breast patients, set up and movement of the patient would predominate. The major variation from expected dose is seen in prostate patients during treatment of reduced fields (most treated with IMRT), where tight margins were employed. In combination with organ movement, this could result in significant variation in delivered dose. Additional measurements and comparisons with phantoms would help evaluate the main causes for the discrepancy and would be of additional interest. However, the goal of the study was to summarize the initial findings on a large patient population and indicate how the dosimeter can help alert that something in the treatment delivery is not going as planned. This information can help physicians review the treatment plan, patient setup and equipment functionality to evaluate and possibly find the cause of the discrepancy.

Previous reports of in-vivo dose measurements included dosimeters placed daily in the anal-rectal lumen which limited the number of measurements made. The results of those studies showed discrepancies of 7% with diodes (21) and 5.8% with thermoluminescent dosimeters (22) between the measured and predicted dose and 6.5%  $\pm$  21.6 with an ion chamber (23). The latter increased to  $> 30\%$  if the probe was related to posterior dose gradient. The current study noted a higher percent of dose differences than were reported by others (21,22,23). The primary differences were that the previous studies utilized a small number of observations, rigid systems and placement of the measuring devices in lumens. In contrast, the DVS dosimeter, placed in-situ and more reflective of the daily clinical processes of a patient receiving radiation therapy and therefore subject to the same influences affecting patient preparation, set up and organ movement. The current show the importance of verifying the actual dose delivered to the target during irradiation of malignant and normal tissue.

#### **c) The variability in readings can occur in a random or systematic fashion**

Two types of discrepancies were encountered in this study: random and systematic. Random variability refers to an inconsistent pattern of higher or lower than expected dose measurements. Systematic variability refers to dose measurements that are consistently lower or higher than expected and generally observed in the first 3-5 fractions.

Potential cause(s) for systematic variation particularly during large field irradiation include patient set up, treatment planning error, and use of heterogeneity correction factors in the treatment plan and/or tight margins. During reduced field irradiation with IMRT, variation is most likely related to organ movement, deformity, patient set up or inconsistent preparation of bowel or bladder in the case of prostate patients. The systematic pattern was also noted by Kupelian et al (24) in their initial report on real-time monitoring of the prostate during external radiotherapy. Others also noted shifts (25) and organ deformity of the prostate (26) More recently Yue et al, (27) utilizing a 4DCT scanning system, noted the potential for intrafractional motion during irradiation of both whole and partial breast irradiation.

Organ movement and deformity are events that can be inconsistent and not easily controlled or anticipated during a course of treatment but can be suggested with evidence of the final dose delivered. One of the major advantages of DVS is early detection of any dose deviation. Therefore the ability to address and correct for the cause of the discrepancy is important. Accordingly, specific guidelines have been proposed as a means of determining potential causes for the discrepancies. The guidelines are divided into three broad categories including a) evaluate the treatment plan including dose value and scaling, heterogeneity correction factors, dose gradient, b) evaluate the patient setup including patient position, SSD and separation, patient preparation and treatment margins and c) verify equipment function including linac output and report and verify transfer data.

The DVS addresses the concept of individualized therapy that is aligned with IGRT/IMRT as well as dose guided and adaptive radiotherapy. The implantable dosimeter is designed to measure the dose delivered to the target(s), verify treatment plans, ensure the delivery of the dose necessary to maximize tumor control, and minimize side effects and alert the physician to the observed difference in dose.

#### d. Dose variation and IGRT techniques

The DVS compliments IGRT by acting as a fiducial marker as well as a dosimeter, thereby verifying the accuracy of IGRT. There were 18 patients in the prostate group reported by Beyer et al (30) in whom IGRT methods were incorporated (2U/S, 3 CBCT/13MV imaging and fiducial markers). No clear relationship was correlated between predicted and measured dose and IGRT method. The small number of patients precludes any definitive reason for the lack of correlation, although it may be related to IGRT techniques (28.29) organ or patient movement. However the consistency in results across diverse institutions with different techniques and treatment planning systems indicates that this may represent the norm.

The importance of consistency and accuracy in delivering dose is embodied in the concept of dose response curves (sigmoid) which describe the relationship between dose, tumor control and outcome as well as dose and complications from radiation. The literature is replete with good objective data on dose response to radiation of malignant tissue obtained from tissue culture and animal studies. Clinically, dose response curves have been suggested for tumors of the larynx (31,32), Hodgkin's lymphoma (33) and breast (34) which have relied on clinical response or local control rates and not objective measurement of dose delivered. The dose response curve for an individual site can be steep and a 7% or greater difference in cumulative dose delivered can be significant. Hanks et al (35) and more recently Eade et al (36) reported on dose response in prostate. Eade (36) described the dose groups as <70Gy, 70-74.9 Gy, 75-79.9 Gy and  $\geq 80$  Gy. The 5 year estimates for freedom from biochemical failure for the four dose groups were 70%, 81%, 83%, and 89% respectively. The results indicate a steep dose response curve and pertinent to the current study a difference in cumulative dose  $\geq 7\%$  could move the patient down on the dose response curve to a less favorable outcome, e.g. a patient assigned to receive 80.0Gy receiving  $>7\%$  less dose or <75Gy, would have a 6% less chance for biochemical control.

Clinically, the dose response curves generated are by inference or the absence of *in situ* data on dose delivered. Variability between predicted and measured dose does occur and must be considered when interpreting dose response curves without associated *in situ* data. In addition, dose measurements made *in situ* should help to identify more definitive and effective dose limits to maximize tumor control and minimize normal tissue toxicity.



## Conclusions

The implantation of the DVS dosimeter caused 8% of patient to experience GrI level of either pain, which lasted one day, or bleeding, which resolved within 30 minutes post implantation. Dose measurements showed that when using large radiation treatment fields, the cumulative dose difference between delivered and planned was 20%, which increased to 42% with cone-down fields. The discrepancy is most likely due to tight field margins, organ movement and deformity. Specific patterns of variability can be recognized early and addressed in order to allow a consistent delivery of a tumoricidal dose to the malignant tissue while minimizing the dose to normal tissue. The variability between measured and predictive dose observed in this pivotal trial of DVS reflects the importance and need for true *in vivo* dosimetry.

The ability of DVS to be both a fiducial marker and *in situ* dosimeter allows it a central role in discerning and verifying the complex interactions of IMRT and IGRT. The future application for *in situ* dosimetry is in adaptive radiotherapy and dose guided radiotherapy where dose alterations can be identified and adjusted on line in real time.

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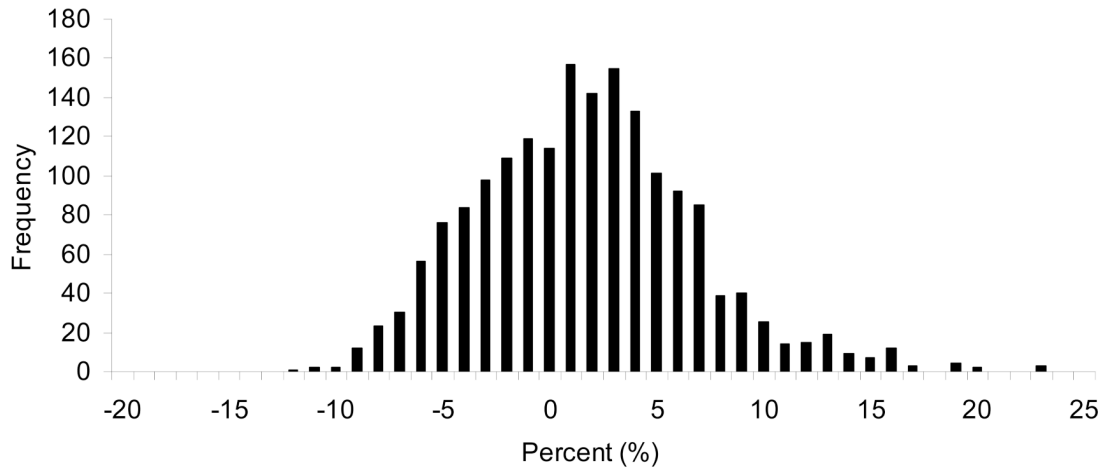
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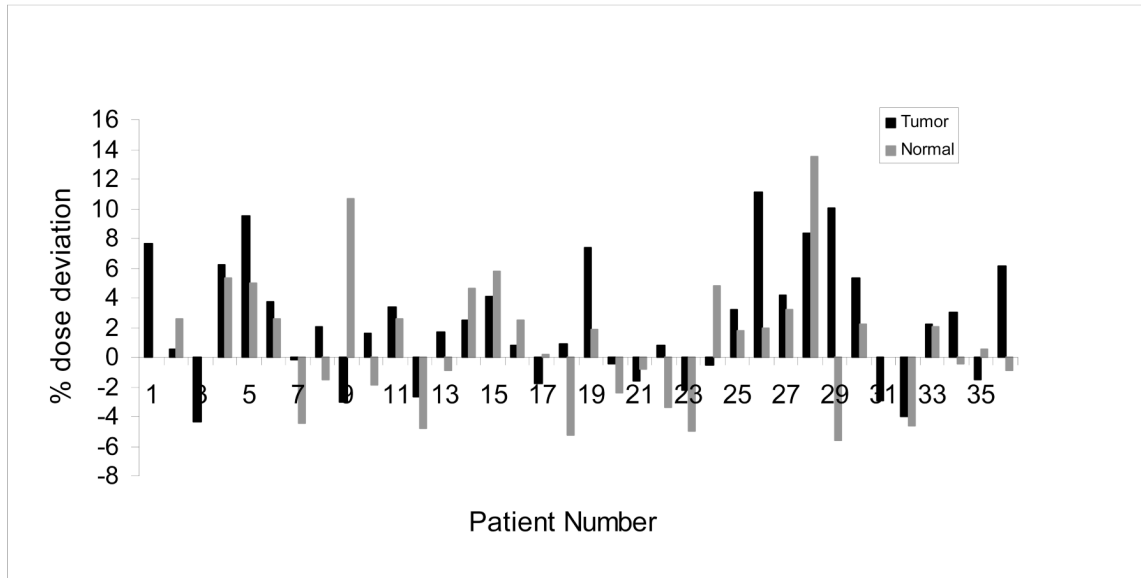
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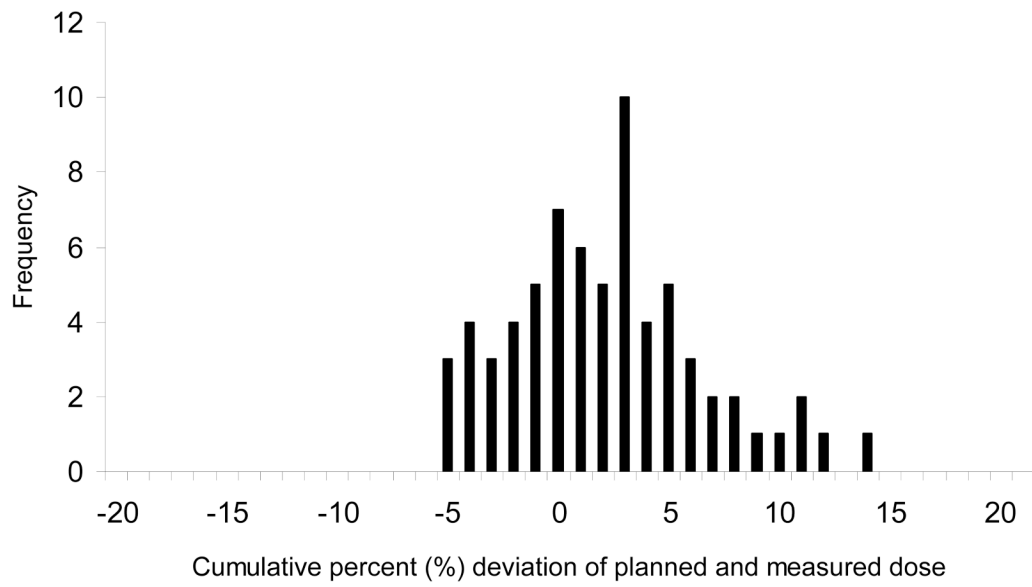
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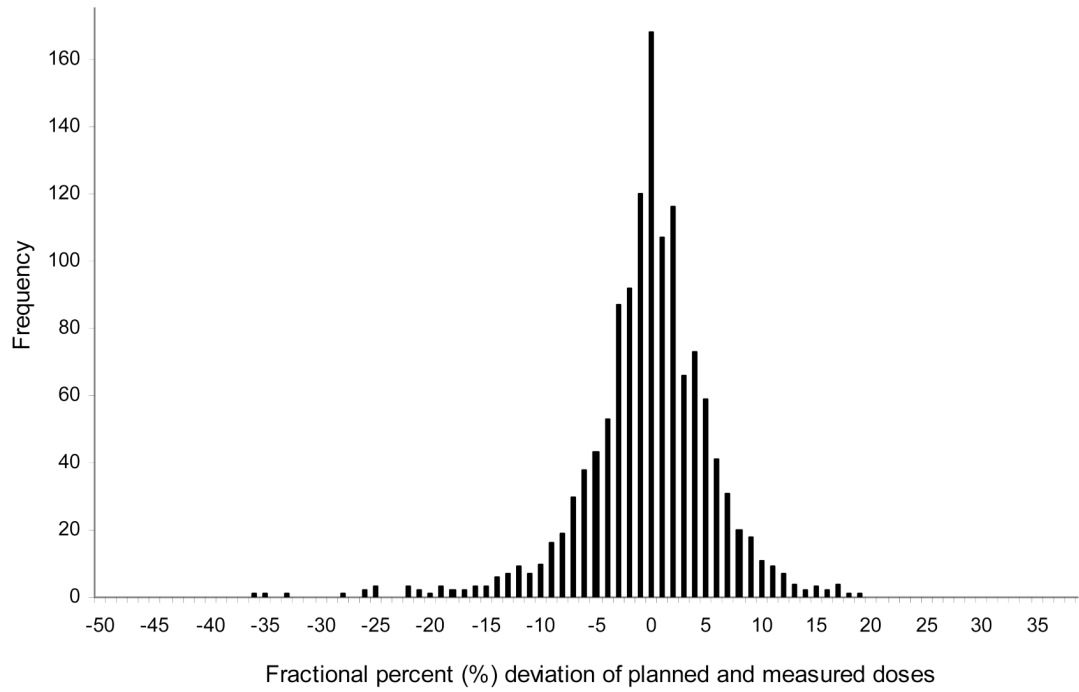
**Fig.1.**  
The frequency of the percent difference between planned and measured daily dose in the breast cancer patients during whole breast irradiation.



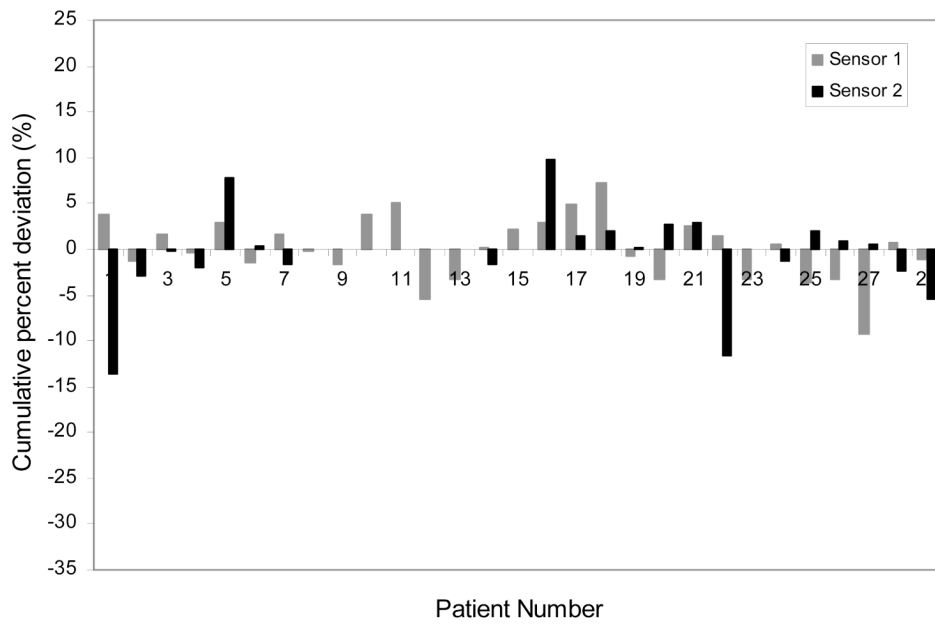
**Fig.2.**  
The cumulative percent difference between measured and planned dose from the dosimeters implanted in the tumor bed and normal tissue of each patient.



**Fig.3.** Frequency of cumulative percent difference between measured and planned dose of all breast cancer patients.

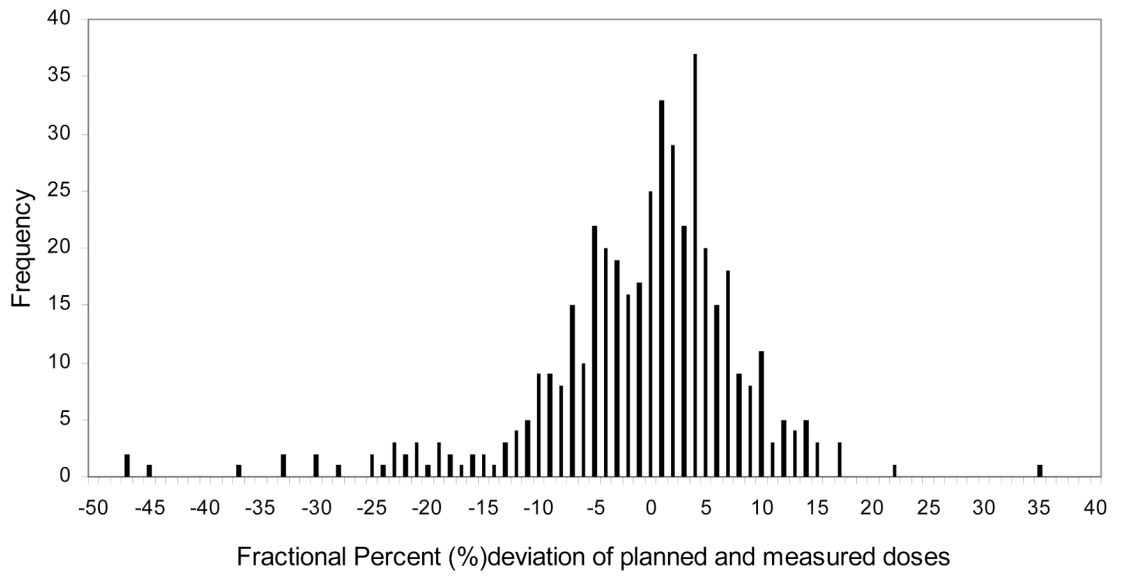


**Fig.4.** The frequency of the percent difference between planned and measured daily doses during large field irradiation in all prostate patients

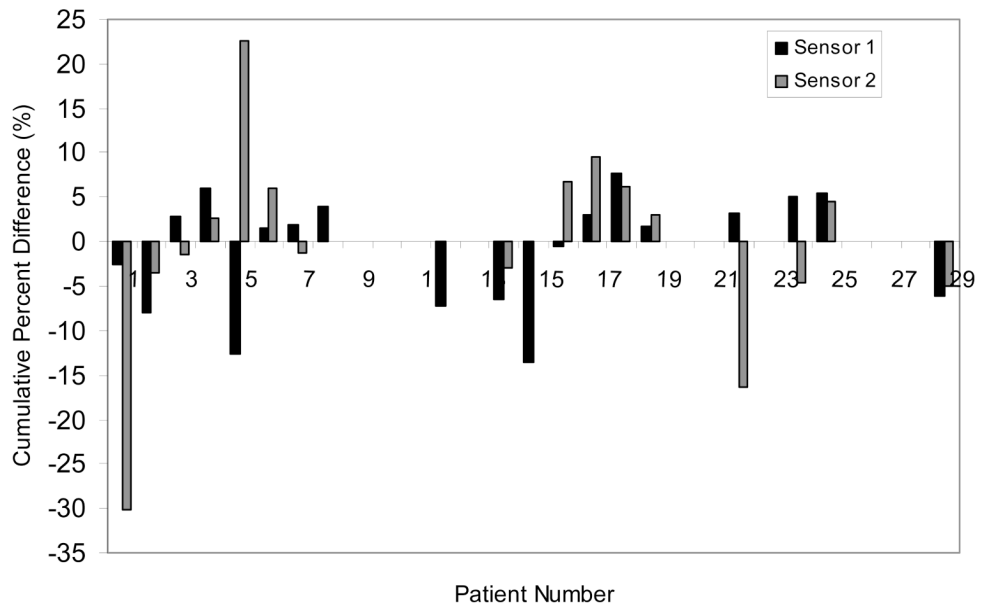


**Fig.5.** The cumulative percent difference between measured and planned dose during large field irradiation in all the prostate patients.





**Fig. 6.**  
The frequency of the percent difference between planned and measured daily doses during boost irradiation in all the prostate patients.



**Fig. 7.** The cumulative percent difference between measured and planned dose during boost field irradiation in all prostate patients.

Fig. 8a

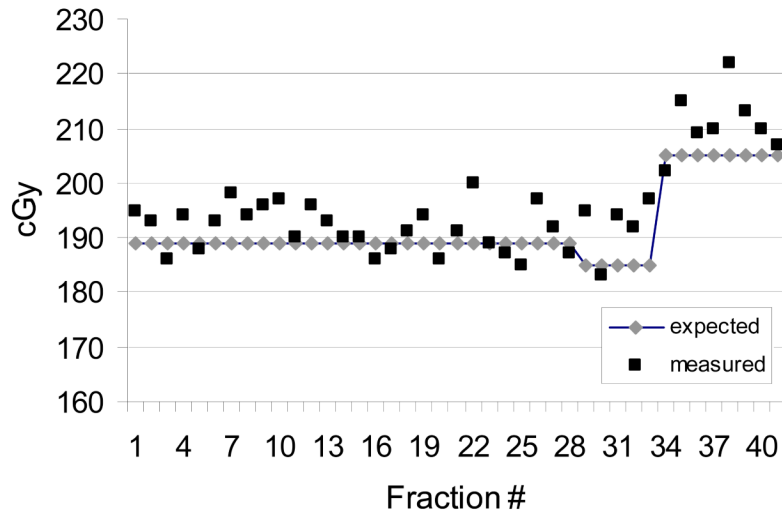


Fig. 8b

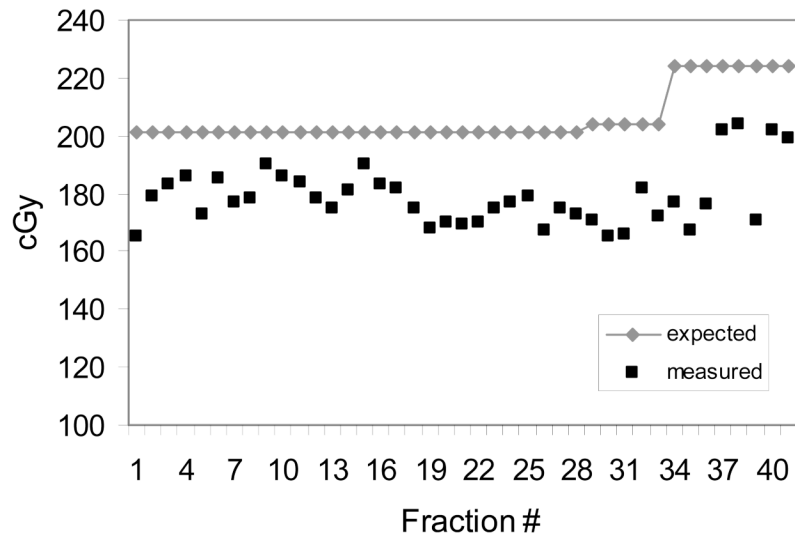
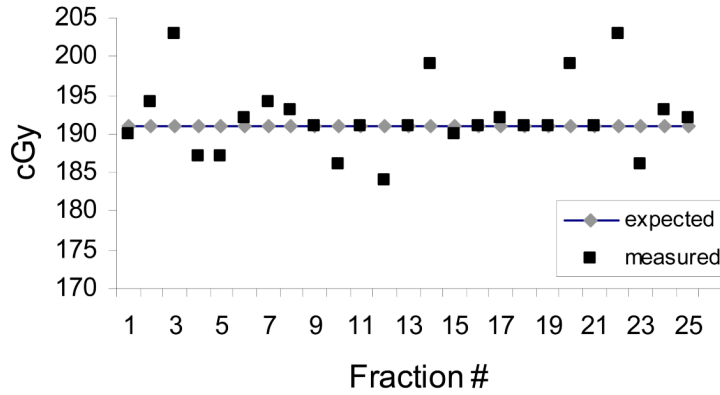


Fig. 8c



**Fig. 8.** The predominant patterns of daily dose measurements observed with the implanted dosimeter. (a) An acceptable pattern where the measured dose differs < 5% from the planned dose. (b) Systematic pattern: where the measured dose is consistently higher or lower than the planned dose. The systematic pattern usually results in a cumulative dose difference greater than 7%. (c) Random pattern: when there is no definite pattern in measured dose, rather the measurements may vary from higher than expected (day 3) or lower (day 12). The random pattern usually will not result in a cumulative dose difference of greater than 5%.

Table 1

**Safety Analysis**

Site	Adverse Events*				
	Pain		Bleeding		Migration > 5 mm
	# Patients	Grade	# Patients	Grade	
	<b>Prostate</b>				
Surgical	2	1	3	1	1
Non-surgical	3	1	0		
	<b>Breast</b>				
Surgical	2	1	1	1	
Non-surgical	2	2			3

\* NCI/CTOG CTCv3

Grade (Gr) 1 = minimal; 2 = moderate

Surgical – as reported by surgeon

Non-surgical – as reported by patient

**Table 2**  
**Summary of Percent Difference Between Expected and Measured Dose**

Site	Fractional Percent <sup>*</sup>		Cumulative Percent <sup>+</sup>	
	> 5%	> 7%	> 5%	> 7%
<b>Breast</b>	38	19	36 (13/36)	19 (7/36)
<b>Prostate</b>				
Large Field	33	19	31 (9/29)	21 (6/29)
Boost	51	35	79 (15/19)	42 (8/19)

<sup>+</sup> Cumulative numbers are taken as percent of patients.

<sup>\*</sup> Fractional numbers are taken as percent of fractions.

Total number of fractions for breast patients was 1783.

Total number of fractions for prostate was 1749 (large field = 1308, boost = 441).