

Literature Review

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Review on the feasibility of using PRESAGE[®] dosimeter in various radiotherapy techniques

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Abstract

The emergence of advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), brachytherapy, conformal radiotherapy, magnetic resonance-guided radiotherapy (MRgRT), stereotactic synchrotron radiotherapy (SSRT) and microbeam radiotherapy (MRT), has increased the importance of the verification of volumetric dose distribution. The verification of dose distribution is usually done by 2D films and 3D gel dosimeters, but PRESAGE[®] due to its affordability, reproducibility, precision, accuracy, unique dosimetric and physical properties is considered as an effective candidate in providing 3D dose data. PRESAGE[®] is insensitive to oxygen contamination, machinable and can be molded to a variety of shapes and sizes. It is absorbing rather than scattering light which facilitates high-accuracy readout by optical computed tomography (OP-CT). This review focuses on the feasibility of using PRESAGE[®] in various complicated radiotherapy techniques by comparing its measured doses with 2D films and treatment planning system (TPS) calculated doses.

Introduction

The introduction of advanced radiotherapy techniques has escalated the significance of validating 3D dose distribution specified by steep dose gradients and complicated shapes. Among various other dosimeters such as polymer and Fricke gels, required for 3D dosimetry, PRESAGE[®] (Heuris Pharma LLC, Skillman, NJ, USA) due to its dosimetric and physical properties is chosen in 3D dosimetry to give volumetric dose information.¹ PRESAGE is a radiochromic 3D dosimeter that was first fabricated in 2006.² It is basically a plastic material which is composed of leuco dye and an optically clear, solid polyurethane matrix with free radical initiators. Halogens and leucomalachite green (LMG) are commonly used as radical initiators and leuco dye, respectively. Fabrication details of PRESAGE[®] are documented in previously published studies and also in US Patent Application Publication No. 2007/0020793A1.^{3–5}

When radiation beam is administered to PRESAGE[®], oxidation of LMG in malachite green occurs due to the production of free radicals by radical initiators and local optical density (OD) of the dosimeter changes.⁶ In the literature presented by Adamovics et al., the change in OD is directly proportional to the amount of radiation dose delivered and can be determined for cuvettes by spectrophotometer and for larger volumetric dosimeter by optical computed tomography (OP-CT) scanners.⁷

PRESAGE[®] possesses numerous significant advantages over other polymer and Fricke gel dosimeters. Presence of polyurethane matrix enables the PRESAGE[®] dosimeter to retain its solid shape and insensitivity to atmospheric oxygen.⁸ This eliminates the need of any supporting chamber. Furthermore, it has also become convenient to fabricate PRESAGE[®] into various shapes by using different molds. Bache et al. have interpreted the possibility of molding PRESAGE[®] into different shapes and producing regions of various densities in their investigation.⁹ The spontaneous polymerisation of PRESAGE[®] is not affected by the temperature below 80°C.¹⁰ Various investigations by Guo et al., Sakhalkar et al. and Wang et al. have described the dosimetric properties of PRESAGE[®] dosimeters and mentioned its suitability as a relative dosimeter in clinical applications. According to these studies, the dosimeter response remained linear till 100 Gy dose, insignificant dependence of photon beam on dose rates varying from 100 to 600 cGy/min.^{11–17}

This study is intended to review previous work on the feasibility of PRESAGE[®] dosimeter in various radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), brachytherapy, 3D conformal partial radiotherapy, magnetic resonance-guided radiotherapy (MRgRT) and stereotactic radiotherapy (SRT). For this purpose, dose distribution measured by PRESAGE[®] was verified by comparing it with external beam therapy (EBT) film measured and treatment planning system (TPS) calculated dose distribution. Isodose line profiles, dose volume histograms (DVHs) and gamma maps were used as tools for evaluating the performance of PRESAGE[®] dosimeter in various radiation treatment techniques.

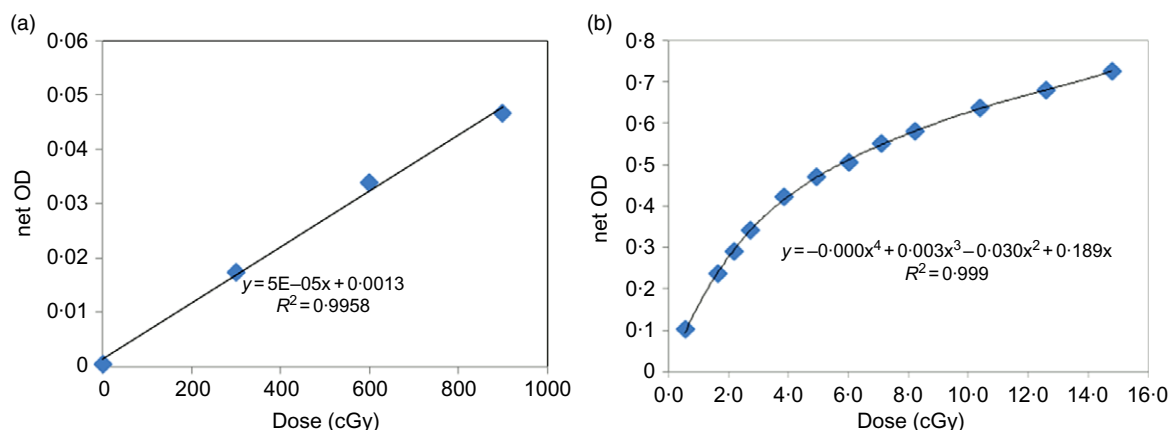


Figure 1. OD to dose curve for PRESAGE (a); OD to dose curve for EBT2 film (b).

Dosimetric Verification Using GAFCHROMIC EBT Film

The purpose of including independent dose measurement by EBT film is to resolve discrepancies between PRESAGE[®] measured and TPS calculated doses. In radiotherapy, EBT films are mainly used for the verification of dose distribution.¹⁸ Gafchromic EBT films play a tremendous role in verifying and assuring the quality of treatment plans.¹⁹ There is a large number of publications on the properties of EBT films like their homogeneity, dose response, post-colouration behaviour, absorption spectra, sensitivity to light, temporal stability, directional independence and convenience of self-developing.^{20–30}

Linearity in dose response of PRESAGE dosimeter

Dose response linearity of PRESAGE[®] dosimeter has been confirmed in the previously published studies.^{31–33} In accordance with the investigation by Iqbal et al., breast-shaped anthropomorphic PRESAGE[®] dosimeter with EBT2 films inserted was irradiated with 6 MV beam with the 5-field IMRT plan. PRESAGE[®] had Z_{eff} and physical density of 7.6 and 1.07 g/cm³, respectively. It was scanned with Duke mid-sized optical scanner dedicated for RPC (Duke University, Durham, NC, USA).²¹ OP-CT scans of PRESAGE[®] did not give rise to any variation in the OD of the PRESAGE[®]. In Figure 1, the radiochromic response was found linear showing sensitivity of 0.0059 OD change for a path length of 1 mm. PRESAGE[®] dosimeter showed a coefficient of variation of 1.0%. EBT2 had 0.75% coefficient of variation.²³

Further studies by Iqbal et al. on brachytherapy, there appeared an uncertainty of 0.8% in OD, estimated for breast-shaped PRESAGE[®] dosimeter and 0.7% for EBT2 film. A Strut-Adjusted Volume Implant (SAVI) device was used for irradiating the PRESAGE[®] dosimeter. While calibrating PRESAGE[®], radiation dose was delivered to the small volumes from the same batch of breast-shaped PRESAGE[®] with an intent to detect errors when comparing dose distribution.^{34,35} The volume effect uncertainty of PRESAGE[®] necessitates the utilisation of normalisation as to compare dose distribution of PRESAGE[®] with Oncentra TPS and EBT2 film.³⁶

For the two film planes, the maximum dose difference between PRESAGE[®] and Oncentra TPS was 4.5% and between Oncentra TPS and EBT2 film was 2.42%. Further, mean percentage differences of skin dose between PRESAGE[®] and Oncentra TPS were 3.54 and 2.85% for films 1 and 2, respectively. At various chosen number of points, mean percentage differences between

Oncentra and EBT2 film were 0.97 and 0.53% for films 1 and 2, respectively (Figure 2).

In 3D conformal radiotherapy, radio-chromic response of an EBT2 film was linear with sensitivity of 0.0057 OD variation for a path length of 1 mm. The uncertainty in the net OD was 1.8% in case of EBT2 films with a reference dose of 3 Gy. The sources of errors responsible for introducing uncertainty in OD have been discussed in detail in the literature [3-field]. In the case of PRESAGE[®], there was an uncertainty of 0.8% for the same reference dose. The power of dose–response linearity of PRESAGE[®] did not cause any limitation on the data analysis.³⁷

According to the exploration of Gye Won Choi in MRgRT, dose response curve of EBT3 film illustrated the difference of less than 2% in net OD between the two cases of 0 magnetic field and when adjusted to 1.5 T.³⁸ The performance of PRESAGE[®] was evaluated by establishing EBT3 film as a standard. PRESAGE[®] curve displayed under dose response of 9% in the presence of 1.5 T magnetic field. The dose response of PRESAGE[®] dosimeter showed linearity when used as a relative dosimeter indicating that magnetic field effects would not disturb its dosimetry in this case.

Verification of PRESAGE[®] Dosimeter in IMRT

Gamma analysis

Gamma analysis is a well-established verification tool required to compare the agreement between the measured and computed dose distributions.³⁹ This analysis is essential in evaluating the performance of radiotherapy clinics to deliver the prescribed doses. For research purposes, gamma maps can do an assessment of the efficiency of new dosimeters against standard dosimeters or treatment plans.

Mark Oldham et al. delivered 11-field IMRT plan to the cylindrical PRESAGE[®] of 16 cm in diameter and 11 cm in height. PRESAGE[®] measured dose distributions were compared with EBT and Eclipse TPS (Varian Medical Systems, Palo Alto, CA, USA) calculated distributions. Isodose line profiles, gamma maps and DVHs were employed to evaluate the agreement among three dose distributions.⁴⁰ A good agreement was found with a maximum difference of 3% among them at all points excluding within 3 mm outer ring due to edge artefacts. Gamma pass ratio was 96% between the Eclipse and PRESAGE[®] measured dose distributions. Guo et al. evaluated the functionality of PRESAGE for 5-field

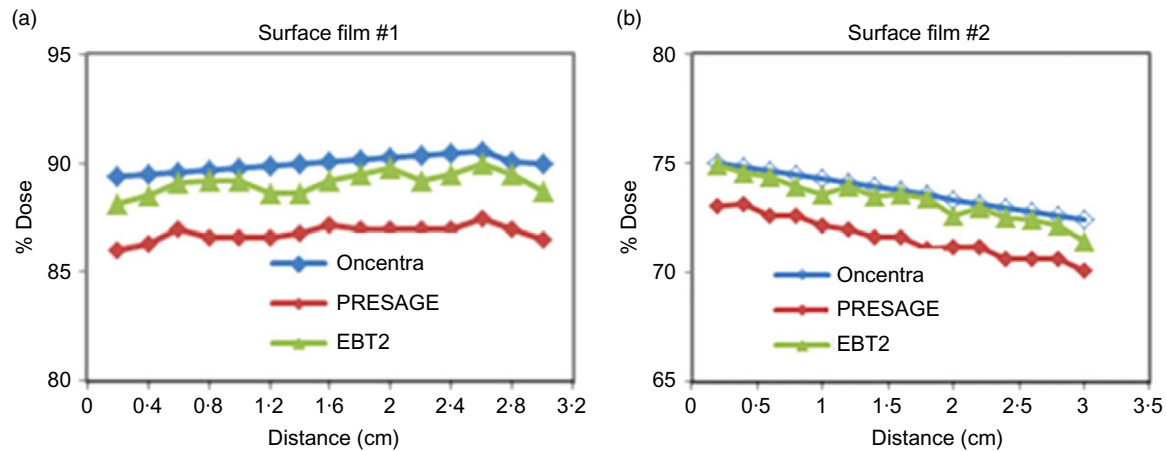


Figure 2. (a) Comparison of the calculated and measured point skin doses for PRESAGE, Oncentra Brachy Planning TPS (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) and EBT2 film for film 1. (b) Comparison of the calculated and measured point skin doses for PRESAGE, Oncentra Brachy Planning TPS and EBT2 film for surface film 2.

radiotherapy by comparing the agreement among the Eclipse TPS calculated, PRESAGE[®] and EBT film measured dose distributions. The gamma criteria of 4% dose difference and 4 mm distance to agreement (DTA) appeared. Owing to the presence of edge artefacts, the outer layer comprising 10% of the radius of PRESAGE[®] dosimeter was not included.⁴¹ From the investigation by Oldham et al., gamma criteria of 3%/3 mm occurred with a pass rate of 96% for Eclipse TPS versus PRESAGE[®] dosimeter without considering edge artefacts in 11-field IMRT. Even taking into account the region of edge artefact, PRESAGE[®] dosimetric characteristics showed similarity with that of film dosimeters. The gamma pass rates for PRESAGE[®] versus Eclipse and EBT film versus Eclipse were 91.4 and 94%, respectively.⁴² Sakhalkar et al. achieved a good agreement among EBT film, PRESAGE[®] and Eclipse TPS with passing rate of more than 98% using head and neck phantom in IMRT. This analysis had a gamma criteria of 4%/3 mm by excluding 4 mm outer rim of the PRESAGE[®] due to edge artefacts.⁴³ Thomas and Newton et al. achieved a gamma criteria of 3%/3 mm with 97.9% passing rate for PRESAGE[®] versus TPS in 4-field IMRT.⁴⁴ Moutsatsos et al. employed PRESAGE[®] dosimeter for verifying dose distribution generated in helical tomotherapy using small fields for head and neck treatment plans. A comparison was made among TPS calculated, PRESAGE[®] and film measured dosimetry results. Gamma index pass rates were achieved more than 90% and uncertainties remained within 2%.⁴⁵

Iqbal et al., for 2D axial gamma comparison, determined the pass rates of 91.2, 90.6 and 88.4% for EBT2 versus Pinnacle, PRESAGE[®] versus Pinnacle and EBT2 versus PRESAGE[®], respectively, in breast IMRT.²³ In all comparisons, failures were found near the dosimeter periphery in the 8 mm outer layer of the PRESAGE[®]. In this area, PRESAGE[®] measured doses are possibly imprecise owing to edge artefacts, and Pinnacle determined doses are likely to be erroneous due to complexity in modelling the buildup region. Without this 8 mm outer layer, gamma pass rates increase to 95% for PRESAGE[®] versus Pinnacle comparison (Figure 3).

DVH analysis

From studies by Iqbal et al., in 5-field breast IMRT plan, DVHs of the planning target volume (PTV) determined by PRESAGE[®] were

different from that calculated by the Pinnacle TPS (Philips Radiation Oncology Systems, Fitchburg, WI, USA).²³ In addition to this, a slightly less homogeneity was observed in PRESAGE[®] determined DVH than that calculated by Pinnacle TPS. This is due to aberrations occurring at the edges of the breast-shaped PRESAGE[®]. A maximum dose difference of 5% for the PTV DVH was seen at 5 and 95% of the fractional volume. For PTV 1 mm, PTV 3 mm and PTV 5 mm, sub-volume DVHs showed a maximum dose difference of 3, 2 and 1%, respectively. DVH of the breast-shaped PRESAGE showed a deviation from Pinnacle calculated DVH occurring between 0.5 and 3 Gy dose. Edge artefacts are responsible for this discrepancy because the breast region of interest encircles the whole PRESAGE.

Comparison between isodose line profiles of PRESAGE, TPS and EBT film

In IMRT by Iqbal et al., Pinnacle TPS computed, PRESAGE[®] and EBT2 film measured line dose distribution gave a good agreement among them with a maximum dose difference of 5% which occurs at the periphery of the breast.²³ However, it is complicated to investigate about the dose distribution of which dosimeter (PRESAGE[®] and EBT) correlates more with Pinnacle calculated distribution. Moreover, within 80% of the central field width, a maximum difference of 2% was produced among three line dose distributions. PRESAGE[®] and EBT2 film measured dose distributions are related to two independent deliveries of the same radiotherapy plan. Line profiles are presented in Figure 4.

PRESAGE Dosimeter in Brachytherapy

Verification through dose profiles

In 2010, Pierquet et al. determined a satisfactory agreement between PRESAGE[®] measured and Eclipse calculated isodose line profiles in brachytherapy. PRESAGE[®] dosimeter with Z_{eff} of 8.1 was irradiated with 7 Gy dose at 1.5 cm from the centre of the source, and line dose distributions were obtained along the transverse axis from the planes. Edge artefacts were present in the ± 3 mm region from the source centre, but on the whole measured and calculated dose distributed agreed well with each other in the region between 5 and 20 mm from the source centre.⁴⁶ In the studies by Iqbal et al. in 2018, for taking measurements

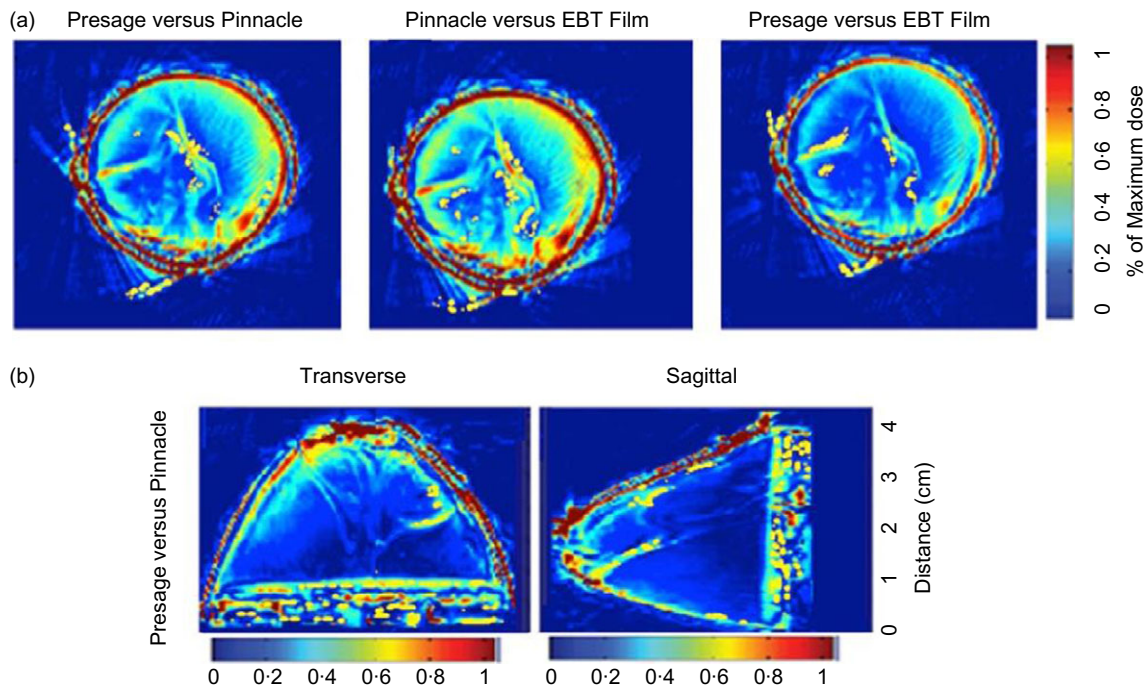


Figure 3. Gamma maps (a) ($\pm 3\%/3$ mm) between Pinnacle, EBT2 and PRESAGE for a region of PTV 5 mm on film plane; (b) ($\pm 3\%/3$ mm) in the transverse and sagittal planes for PTV 5 mm intersecting film plane.

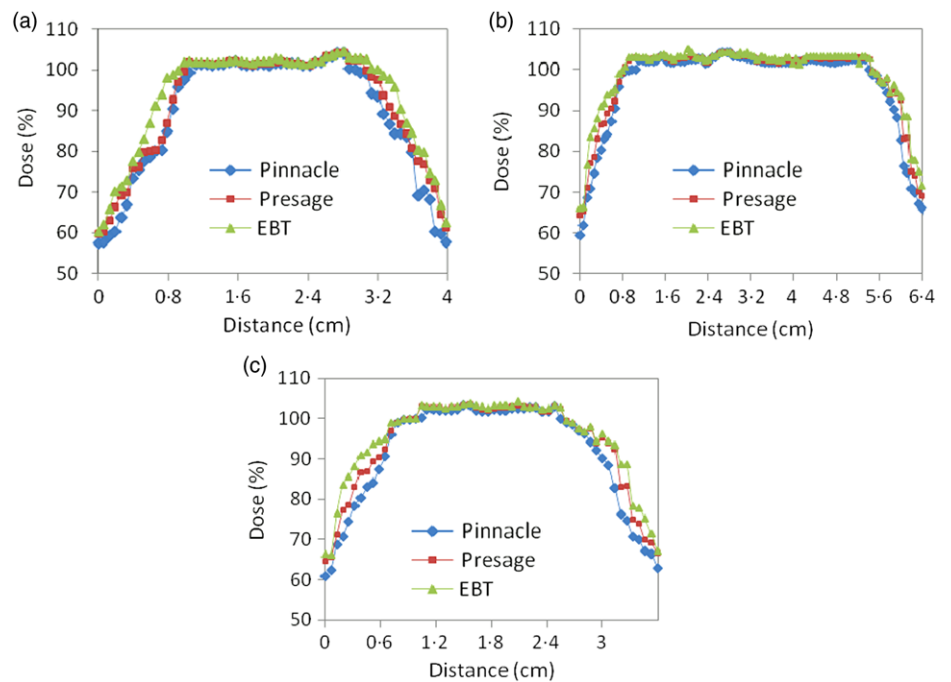


Figure 4. Line profiles of Pinnacle, PRESAGE and EBT2 film dose distributions from axial slices.

of isodose profiles, PRESAGE[®] was cut at its central long axis and EBT2 film pieces were inserted between the two halves of the PRESAGE. The maximum dose difference in dose profiles was 2.48% between Oncentra TPS and PRESAGE[®] using both films. Between EBT2 film and Oncentra TPS, the maximum difference was 4.06%. The mean dose differences in the line plots of both films 1 and 2 were 2.25 and 1.80% between Oncentra and PRESAGE[®] and 3.31 and 2.82% between Oncentra and EBT2 film.³⁶

DVH of PTV and normal tissue

Iqbal et al. in their studies showed a DVH comparison between Oncentra TPS and PRESAGE[®] which showed a maximum percentage difference of 4%. This difference occurred because of the reflection artefacts as described in previous studies.¹¹ The PTV_EVAL V90 and V95 of breast-shaped PRESAGE[®] and Oncentra were 97, 96.59% and 99.6, 98.95%, respectively.

The dose distribution determined by the PRESAGE[®] varied from Oncentra calculated dose distribution particularly near the edges of the dosimeter due to edge artefacts in the PRESAGE[®] dose distribution. By considering DVH curve of PTV_OPT, PRESAGE[®], measured dose distribution was found insignificantly less homogeneous than Oncentra calculated dose distribution because of the presence of small regions of relatively under and over lying closer to the dosimeter edges. A maximum dose difference of 4% appeared at the lower and upper volume ends. From the DVHs of 1, 3 and 5 mm sub-volumes of the normal breast tissue, the maximum dose difference of 3.2, 2.5 and 1.5% occurred between the PRESAGE[®] and Oncentra treatment plans.

3D Conformal Radiotherapy

In 3D conformal therapy, Guo et al. verified the cylindrical-shaped PRESAGE[®] dosimeter by comparing its dose distribution with EBT film measured and Eclipse TPS calculated dose distribution. PRESAGE[®] dosimeter had a Z_{eff} of 8.3, physical density of 1.07 g/cm³ and a OP-CT number of 200, and it was irradiated with 6 MV beam from Varian 21EX linac with a prescription dose of 15 Gy. All distributions were normalised at treatment plan isocentre found centrally in the high-dose region. There found a good agreement among all the three dose distributions with a maximum dose difference of 4%. However, under dosage was noticed at the periphery of the PRESAGE[®] due to edge artefacts.¹¹

Further in 2017, Iqbal et al. analysed the comparison of gamma pass rates between Pinnacle calculated and PRESAGE[®] measured dose distribution, and it was 97.4% in 3-field partial radiotherapy. An axial 2D gamma map comparisons of EBT2 versus Pinnacle and EBT2 versus PRESAGE[®] were 95.3 and 97.6%, respectively. About 95.3% pass rate can be increased up to 96%, if the outer boundary of 3 mm is eliminated.

From the investigations by Iqbal et al., in this treatment modality, independent 2D line dose measurements using EBT2 films in two selected levels simplified resolving any dose difference between PRESAGE[®] and Pinnacle.³⁷ A good correlation was found among Pinnacle, PRESAGE[®] and EBT2 film measured dose distribution showing maximum difference of 1.5% (Figure 5).

DVHs comparison between PRESAGE and Pinnacle TPS

DVH curve of the PRESAGE[®] PTV showed less homogeneous dose distribution than Pinnacle calculated dose distribution with a maximum dose difference of 2.2%. Furthermore, gross tumor volume (GTV) and clinical target volume (CTV) manifested 0.8 and 1.5% dose difference. This difference again happened due to edge artefacts similar to that in other treatment techniques (IMRT and brachytherapy) (Figure 6).

Edge artefacts

Dose distribution measurements with PRESAGE[®]/OP-CT often undergo deterioration due to edge artefacts. This effect has been reported in detail in the literature by Doran et al.⁴⁷ The sensitivity of PRESAGE[®] is highly affected by any mismatch in the refractive indices between the matching fluid and the dosimeter such that the mismatch of only 0.3% can produce the edge artefact of several millimeters. In the studies involving PRESAGE[®]/OP-CT dosimetry, edge artefacts regions have been excluded which extend from the outer 3 to 8 mm rim of the PRESAGE dosimeter.^{48,49}

Magnetic Resonance Imaging-Guided Radiotherapy

In radiation therapy techniques, which are guided by magnetic resonance imaging, there occurs an alteration in the delivered dose distribution in the presence of strong magnetic field created during magnetic resonance (MR) imaging. In this treatment mode, electron return effect (ERE) becomes more pronounced as it is responsible for the loss of electronic equilibrium and enhancement of dose in the original medium near the interface. This phenomenon is shown to cause major clinical concerns which are presented in detail by Raaijmakers et al.^{50,51}

Dosimeters response in magnetic field

For the measurement of dose distribution in magnetic field, the response of various dosimeters was investigated. Meijnsing et al. determined that by changing the strength of magnetic field from 0 to 1.2 T, the response of farmer-type ionisation chamber varies by 10–15%.⁵² Conventional 2D dosimeters like thermo luminescent dosimeters (TLDs), optically stimulated luminescent dosimeters OSLD and EBT3 film were not affected by magnetic field, but dosimetric results with PRESAGE showed an under dose response.^{53–57}

Validity of PRESAGE dosimeter in MRgRT

Gye Won Choi demonstrated the viability of employing PRESAGE[®] dosimeters in MRgRT. In this treatment modality, PRESAGE[®] cuvettes (1 cm x 1 cm x 4 cm) were irradiated with 1, 4, 7 and 10 k MU by adjusting magnetic field to 1.5 T. From the studies by Mathic et al., magnetic field did not produce any considerable effect on the EBT3 film response, so it was chosen as the standard for the verification of the PRESAGE[®] dosimeter in this modality.⁵³ EBT3 and the PRESAGE[®] measured dose distributions when compared with each other showed a gamma criteria of 5%/3 mm. Despite the modifications in dose distributions caused by ERE, there observed still a satisfactory agreement between EBT3 and PRESAGE[®] measured doses with passing rate of more than 90%.³⁸

In the radiotherapy techniques currently in use, all the differences among the EBT, PRESAGE measured and TPS calculated doses were found within the tolerance limits of $\pm 5\%$ specified by ICRU and also in the literature.^{54–56}

PRESAGE[®] in Proton Beam Therapy

Zhao et al. determined the dosimetric characteristics of PRESAGE[®] dosimeter in proton beam therapy. They compared PRESAGE[®] measured dose profiles with that of ion chamber (IC) in water phantom. PRESAGE[®] showed a linearity in dose response to proton beam.⁵⁷ Mitchell Carroll et al. studied on the feasibility of PRESAGE[®] dosimeter in measuring dose distribution generated by proton beam using anthropomorphic head phantom. A comparison of low linear energy transfer-dependent PRESAGE[®] measured dose distribution was made with EBT2, radiochromic film, TLD measured and TPS calculated dose distribution. Digital multi-camera optical surveillance system was implemented to read out PRESAGE[®] dosimetric distribution. Isodose line profiles of PRESAGE[®] depicted an agreement within 3 and 4 mm in the coronal and sagittal planes, respectively. Beam doses measured by radiochromic film manifested agreement to 2 mm in both the given planes. Gamma pass ratio of 95% was achieved between

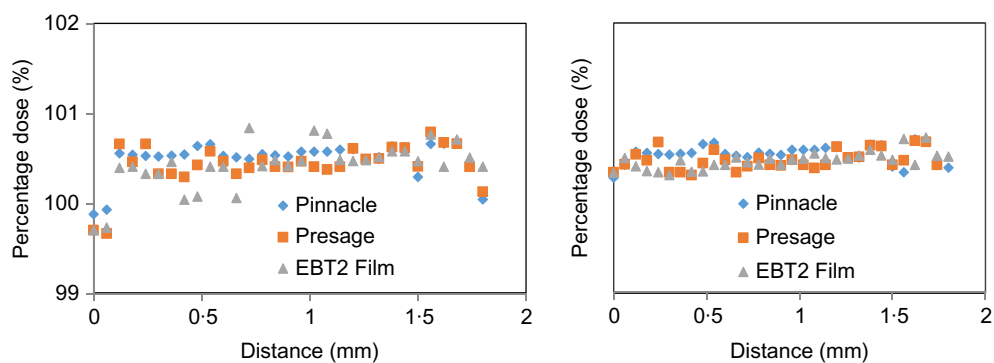


Figure 5. Line profiles of the Pinnacle3, PRESAGE® and EBT2 film dose distributions of axial slice.

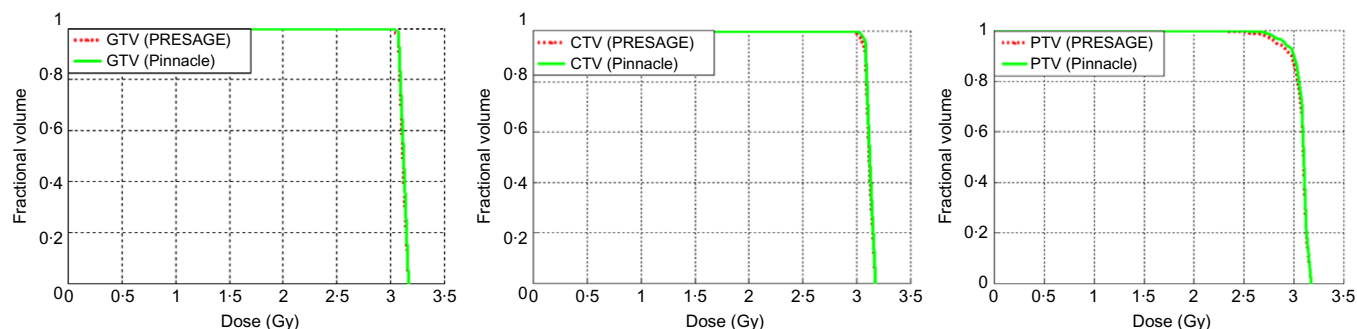


Figure 6. GTV, CTV and PTV DVH comparison between the PRESAGE® and Pinnacle3 Planning dose distributions.

TPS computed and PRESAGE® measured doses with gamma criteria of 5%/3 mm and 5%/4 mm in both planes.⁵⁸

PRESAGE® Dosimetry in Stereotactic Synchrotron Radiotherapy

Through investigations by Alqathami et al. and Gorjiara et al., it was determined that minor changes in the chemical composition of PRESAGE® can alter its dosimetric properties to become radiologically equivalent to water with an energy range appropriate for kV and MV dosimetry.^{59,60} Jackson et al. and Brady et al. have documented that water equivalent PRESAGE® is capable of verifying 3D dose distribution in IMRT, volumetric modulated arc therapy and external beam gated treatments with 6 MV beam.^{61,62} It is reported in the literature by Gagliardi et al. that water-equivalent PRESAGE® is well suited for high-resolution 3D imaging of synchrotron-generated micro beams in stereotactic synchrotron radiotherapy (SSRT).⁶³

Gagliardi et al. have investigated in their other exploration about the validation of the radiological response of water equivalent PRESAGE in 3D dosimetry for synchrotron X-ray photon energies. PRESAGE® was shaped into cylindrical rods with 70 mm in length and 43 mm in width. They compared PRESAGE measured dose data with GAFCHROMIC EBT3, IC and Monte Carlo (MC) GEANT4 (Version 9.4.6) calculated data. PRESAGE® measured percentage depth dose (PDD) profiles and IC measured profiles agreed with each other within 2% for 6 and 18 MV beams showing an under response at the entrance of the PRESAGE® due to the affects given in the literature.⁶⁴ IC measured and MC calculated PDD profiles showed an agreement within 1% with PRESAGE® measured profiles above 5 mm depth using 10 × 10 mm field size. There was an agreement between MC data and PRESAGE® measured data within 2% below 5 mm depth

(buildup region). PRESAGE® showed an inability to measure field penumbra, but PRESAGE® possesses the potential to determine dose profiles which were calculated by MC model and verified by EBT3 films in SSRT and microbeam radiotherapy (MRT).⁶³

Conclusion

PRESAGE® dosimetric results were found comparable to the Gafchromic EBT film measured and TPS calculated results as evaluated by DVHs, Isodose line profiles and Gamma map analysis. These results revealed that PRESAGE® can reliably be used in verifying volumetric dose distribution data in highly advanced and complicated radiotherapy techniques. From the comparison of anthropomorphic breast-shaped PRESAGE® measured dose distribution with EBT2 film measured and TPS calculated doses, it was confirmed that PRESAGE® can be fabricated into anthropomorphic shapes for validating breast IMRT, brachytherapy and 3D partial breast radiotherapy. PRESAGE® dosimeter should be fabricated into other anthropomorphic shapes for assuring the quality of radiotherapy plans of other tumour sites.

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