RESEARCH ARTICLE

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Dosimetric Comparison of Isodose Surface Volume and Total Reference Air Kerma (TRAK) based Volume in Cervical Cancer Brachytherapy

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Abstract

Objective: We aim to compare TRAK & TPS based isodose volumes in cervical cancer brachytherapy and assess the feasibility, accuracy and potential future implications of TRAK in this regard and as a newer emerging tool to assess treatment intensity in cervical cancer brachytherapy. **Methods:** one hundred patients with histologically proven squamous cell carcinoma of cervix uteri were assessed for brachytherapy (after completion of external radiation) and prospectively enrolled for the study. 60 Gy, 75 Gy, and 85 Gy isodose volumes were obtained from the TPS (VTPS) for 50, 25 & 25 patients with Manchester, Fletcher & interstitial implant respectively, receiving various fractionation schedules by Ir^{192} HDR remote after-loading system. Using the formula V_{pred}=4965(TRAK/dref)3/2+170(TRAK/dref)-1.5 the TRAK based isodose surface volumes (V_{pred}) were derived. Reference doses (dref) were calculated based on accumulated EBRT and brachytherapy doses. The two sets of volume were compared with respect to applicator type, standard, and optimised plan. Surrogate point A dose was also correlated. **Result:** VTPS – V_{pred} were 5.24 ± 2.7%, all volumes being predicted within 10%. Correlation of TRAK vs VTPS60/ VTPS75/ VTPS85 showed R2 of 0.994, 0.987 and 0.971 respectively. There was no significant difference in predicted volumes with respect to applicator type. The surrogate point A showed mean volume and standard deviation of 7.44 ± 13.4%, 17.63 ± 16.38 and 3.5 ± 0.95 for Manchester optimised, Fletcher optimised and standard plans respectively. TRAK with point A (R2=0.5632), bladder (R^2=0.2015) and rectal doses (R^2=0.121) yielded no correlation. **Conclusion:** Volumes calculated by TRAK correlate with TPS obtained volumes significantly and the formula predicting isodose surface volumes within 10% accuracy for ICBT applications and not for pure interstitial implants. However, TRAK fails to correlate with surrogate point A, bladder and rectal doses hence has questionable utility as a marker for biological response & treatment intensity.

Keywords: Cervix- TRAK- Isodose volume- Brachytherapy

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Introduction

Historically, the reporting in cervical cancer brachytherapy has been underwhelming [1] especially, total reference air Kerma (TRAK) which being completely a physical entity can be a potential surrogate for biological response. This was previously proposed by few authors by incorporating it into a simple mathematical formula to estimate isodose surface volumes. This has allowed centres who lack a treatment planning system (TPS) or have upgraded/changed their TPS but have TRAK data, to easily and accurately generate 60 Gy, 75 Gy and 85 Gy isodose surface volumes using these simple formulas.

Our objective in this study is to not only compare TRAK calculated volumes to isodose surface volumes estimated by TPS in cervical cancer brachytherapy using these formulae but also to analyse and validate their accuracy, feasibility, reproducibility and applicability in daily clinical practise. Further we intend to assess potential future implications of TRAK as a newer emerging tool to assess treatment intensity by studying the respective volume changes when applied in intracavitary and interstitial implant settings. We have also assessed role of TRAK based isodose volume calculations for the first time with interstitial implants, and have analysed in depth of its utility in various applicator configurations and plan optimisations schedules.

Materials and Methods

One hundred patients were prospectively enrolled in this study, each patient being histologically proven case

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of squamous cell carcinoma of cervix uteri, all patients underwent external beam radiotherapy to a dose of 45Gy in 25 fractions over 5 weeks via 4 field 3D conformal technique with concurrent weekly chemotherapy.

Seventy-five patients underwent intracavitary brachytherapy (50 with Manchester type of applicator and 25 patients with fletcher suit) based on availability of applicators. 31 patients received 4 fractions of 6Gy each at 2 fractions per week while 44 patients received 3 fractions of 7Gy each based on physician preferences.

Twenty-five patients underwent interstitial brachytherapy as per indications of which 8 received 4 fractions of 6Gy each and 17 received 3 fractions of 7Gy each, twice weekly and were at physician's discretion. The 60Gy, 75Gy and 85Gy isodose curves depicted as V60 GyTPS, V75 GyTPS and V85 GyTPS respectively were obtained from treatment planning system for 50 patients with Manchester type of applicator, 25 patients with Fletcher Suit applicator and 25 patients with interstitial implant, receiving various fractionation schedules by Ir192 HDR remote after loading brachytherapy system. (Table 1).

Using the formula $V_{pred}=4965(TRAK/d_{ref})^{3/2}+170(TRAK/d_{ref})-1.5$, the TRAK based isodose surface volumes (V_{pred}) were derived. The reference doses (d_{ref}) were calculated based on accumulated EBRT and brachytherapy doses. The two sets of volume were compared with respect to applicator type and standard vs optimised plans. Scatter plots for both isodose based and TRAK based volumes were plotted to find the regression. The surrogate point A was also correlated.

Results

The V60 Gy_{pred}, V60 Gy_{TPS}, V75 Gy_{pred}, V75 Gy_{TPS}, V85 Gy_{pred} and V85 Gy_{TPS} Mean ± SD of TPS and predicted volumes for 75 ICBT applications were 196.73 ± 36.29, 210.6 ± 38.86 (R^2 = 0.9949), 92.0 ± 16.85, 97.37 ± 18.24 (R^2 = 0.9879), 68.15 ± 12.41, and 70.94 ± 13.39 (R^2 = 0.9719) respectively with the overall R^2 value of 0.9987 (Table 1) showing excellent regression (Figure 1).

Also it was observed that as we move closer to the sources i.e. V85 Gy isodose volume, there was poorer regression compared to larger isodose volume i.e. V60Gy with respect to assumptions made by the formula for predicting isodose volumes utilizing TRAK that the sources are point source and their relative positions in the applicator are negligible when compared to 1-meter distance at which TRAK is calculated. Similarly, The V60 Gy_{pred}, V60 Gy_{TPS}, V75 Gy_{pred}, V75 Gy_{TPS}, V85 Gy_{pred} and V85 Gy_{TPS} Mean ± SD of TPS and predicted volumes for 25 ISBT applications were 133.1 ± 45.49, 162.86 ± 53.29 (R^2 = 0.9781), 62.3 ± 21.3, 78.91 ± 26.6 (R^2 = 0.8982), 46.3 ± 15.86, 53.43 ± 21.22 (R^2 = 0.9998) respectively (Table 1) with the overall R^2 value of 0.9883 (Figure 2).

As shown in the scatter plot (Figure 3), though the overall R^2 value was 0.9907 for the combined IC-IS applications, the individual volumes didn't show good regression as they are two heterogeneous groups with an unequal proportions of patients in each group. On subgroup analysis between standard plan vs. optimised plan among 75 ICBT applications, it was found that the standard plan TPS derived isodose volumes had complete regression with the TRAK based predicted isodose

Table 1. Volumetric Comparison of All Data –ICBT, ISBT and Combined

Isodose volume ICBT	Mean volume (cm^3)	SD	R^2 Value	
V60 Gy_{pred}	196.73	±36.29	R^2 = 0.9949	
V60 Gy_{TPS}	210.6	±38.86		
V75 Gy_{pred}	92	±16.85	R^2 = 0.9879	R^2 = 0.9987
V75 Gy_{TPS}	97.37	±18.24		
V85 Gy_{pred}	68.15	±12.41	R^2 = 0.9719	
V85 Gy_{TPS}	70.94	±13.39		
Isodose volume ISBT	Mean volume (cm^3)	SD	R2 Value	
V60 Gy_{pred}	133.1	± 45.49	R^2 = 0.9781	
V60 Gy_{TPS}	162.86	± 53.29		
V75 Gy_{pred}	62.3	± 21.3	R^2 = 0.8982	R^2 = 0.9883
V75 Gy_{TPS}	78.91	± 26.6		
V85 Gy_{pred}	46.3	± 15.86	R^2 = 0.9998	
V85 Gy_{TPS}	53.43	± 21.22		
Combined IC-IS	Mean volume (cm^3)	SD	R2 Value	
V60 Gy_{pred}	179.5	± 54.41	R^2 = 0.7547	
V60 Gy_{TPS}	203.62	± 44.6		
V75 Gy_{pred}	98.01	± 27.49	R^2 = 0.0641	R^2 = 0.9907
V75 Gy_{TPS}	90.94	± 24.31		
V85 Gy_{pred}	64.96	± 15.09	R^2 = 0.869	
V85 Gy_{TPS}	69.67	± 15.12		

$V60Gy_{pred}$, $V75Gy_{pred}$, $V85Gy_{pred}$, respective isodose volumes predicted using the proposed formula; $V60Gy_{TPS}$, $V75Gy_{TPS}$, $V85Gy_{TPS}$, respective isodose volumes obtained from treatment planning system; R^2, respective regression values.

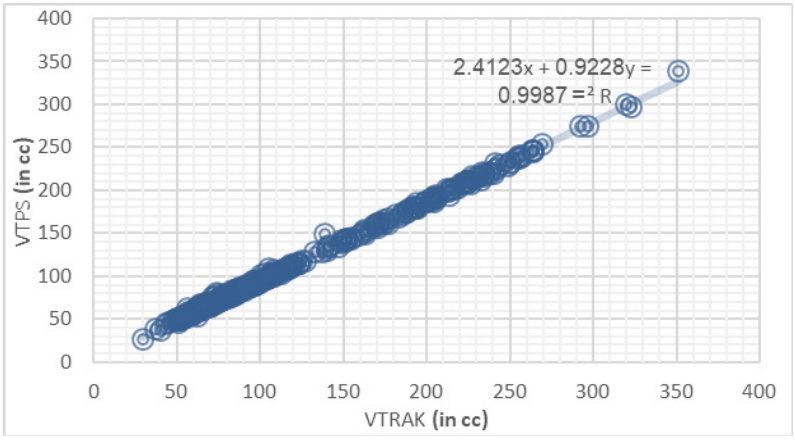

Figure 1. Scatter Plot Depicting Regression between TPS Obtained Isodose Volumes (VTPS) with TRAK based Predicted Isodose Volumes (VTRAK) for 75 ICBT Applications.

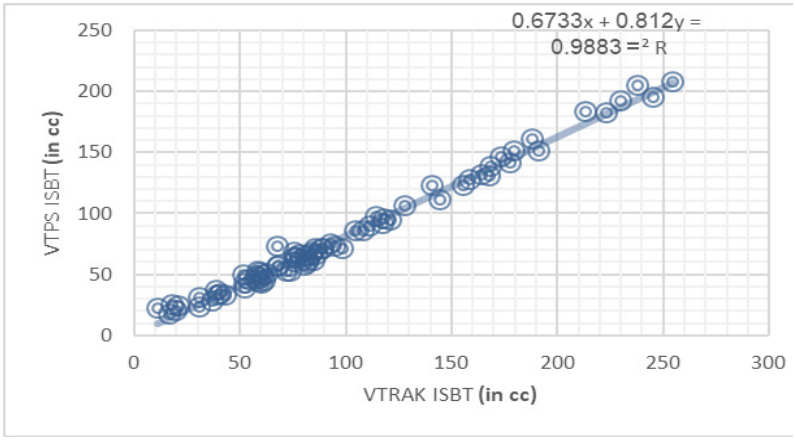

Figure 2. Scatter Plot Depicting Regression between TPS Obtained Isodose Volumes (VTPS ISBT) with TRAK based Predicted Isdose Volumes (VTRK ISBT) for 25 ISBT Applications.

volumes (Figure 4). Whereas the optimised plans volumes showed a good regression ($R^2 = 0.9982$) (Figure 5).

The percentage difference between V60 Gypred & V60 GyTPS (Mean ± SD) were all within 10% even with the subgroups i.e. different applicator and whether optimised or standard plan except in ISBT applications where the volume difference exceeded 10% meaning the proposed formula to predict various isodose volumes from TRAK is not valid in ISBT applications. But the overall volume difference was still less than 10% as the ISBT dataset was 3 times the ISBT dataset. When TPS obtained isodose volumes were plotted against TRAK/d_{ref} there was good regression with R^2 value of 0.9636 (Figure 6). The once highlighted in red being ISBT application volumes.

The mean ± SD delivered point A doses for both types of applicators for optimised plans didn't differ significantly

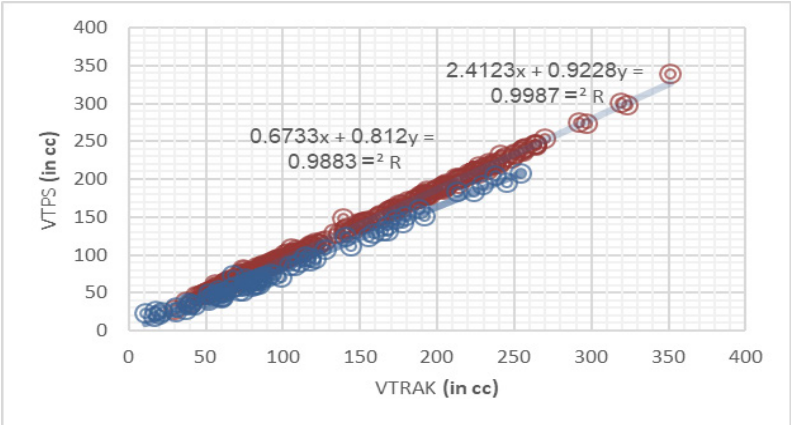

Figure 3. Scatter Plot Depicting Regression between TPS Obtained Isodose Volumes (VTPS) with TRAK based Predicted Isodose Volumes (VTRAK).

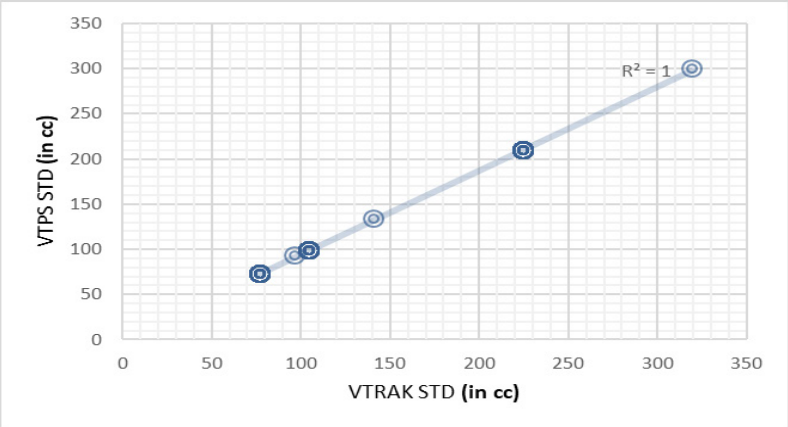

Figure 4. Scatter Plot Depicting Regression between TPS Obtained Isodose Volumes (VTPS STD) with TRAK based Predicted Isodose Volumes (VTRAK STD) for Standard Plan.

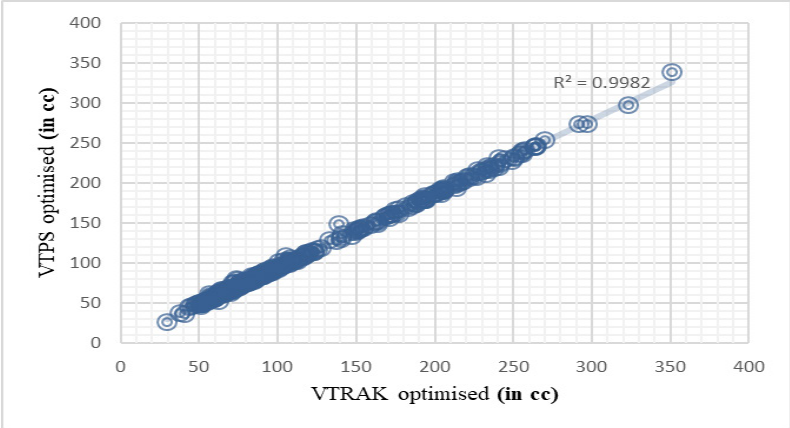

Figure 5. Scatter Plot Depicting Regression between TPS Obtained Isodose Volumes (VTPS optimised) with TRAK based Predicted Isodose Volumes (VTRAK optimised) for Optimised Plan.

nor did the 2cc bladder and rectum doses, but the surrogate point A predicted was 5-10% higher than the delivered dose for Manchester type of applicator and 10-20% for fletcher suit. Whereas for the standard plan it was only 3.5% higher (Table 2). In ISBT the mean surrogate point A doses were much lower compared to the prescription doses meaning the lower intensity of treatment with the mean EQD2 being 65.16 Gy. ISBT Mean CTV volume = 87.16cc range (45.1-142.5cc). The mean D100 & D90 values for the 25 ISBT applications are depicted in Table 3. There was no linear correlation between TRAK and point A ($R^2 = 0.5632$) (Figure 7) as well as between TRAK and D_{2cc} of bladder ($R^2 = 0.2015$) (Figure 8) & rectum ($R^2 = 0.121$) (Figure 9). The surrogate point A EQD2 had linear regression with VTPS 75 Gy (Figure 10).

Discussion

Even though centres across the globe do routinely record the parameters recommended in the latest GEC-ESTRO [2]. However, the total reference air kerma (TRAK) which is one such simple physical parameter which is ignored and under reported. Previously few authors have incorporated TRAK in different mathematically

Table 2. IC & IS Dosimetric Parameters

	fractionation	Point A dose (mean ± SD)	D2cc bladder (mean ± SD)	D2cc rectum (mean ± SD)	Surrogate point A	Diff (Gy) point A vs. surrogate point A	Diff % point A vs. surrogate point A
Manchester Optimized	6x4(19)	5.34 ± 0.69	4.73 ± 0.66	3.88 ± 0.79	5.56 ± 0.66	-0.21 ± 0.67	-5.12 ± 12.73
	7x3(31)	5.9 ± 0.74	5.29 ± 0.86	4.4 ± 0.74	6.44 ± 0.78	-0.53 ± 0.68	-9.92 ± 12.77
Fletcher Optimized	6x4(12)	5.24 ± 0.62	4.64 ± 0.66	3.77 ± 0.71	6.1 ± 0.56	-0.86 ± 0.51	-17.5 ± 12.71
	7x3(13)	5.3 ± 0.97	5.37 ± 0.83	4.12 ± 0.95	6.01 ± 0.87	-0.71 ± 0.94	-15.59 ± 18.95
Standard	7X3(39)	6.99	6.99	6.99	7.35 ± 0.06	0.36 ± 0.06	3.5 ± 0.95
ISBT n=8	6x4	NA	3.78 ± 1.19	3.77 ± 0.68	4.05 ± 1.12		
n=17	7x3		4.42 ± 1.07	4.68 ± 0.54	5.49 ± 1.17		

D_{2cc}, dose to 2cc of respective organ volume.

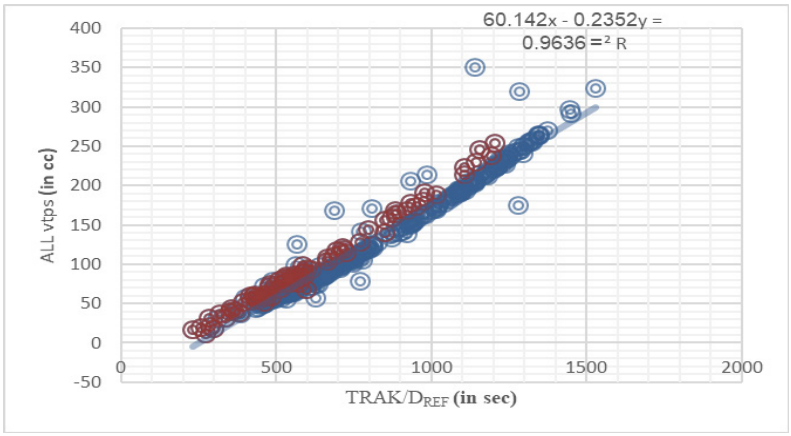

Figure 6. Scatter Plot Depicting Regression between TRAK/d_{ref} with all TPS Obtained Isodose Volumes (ALL VTPS).

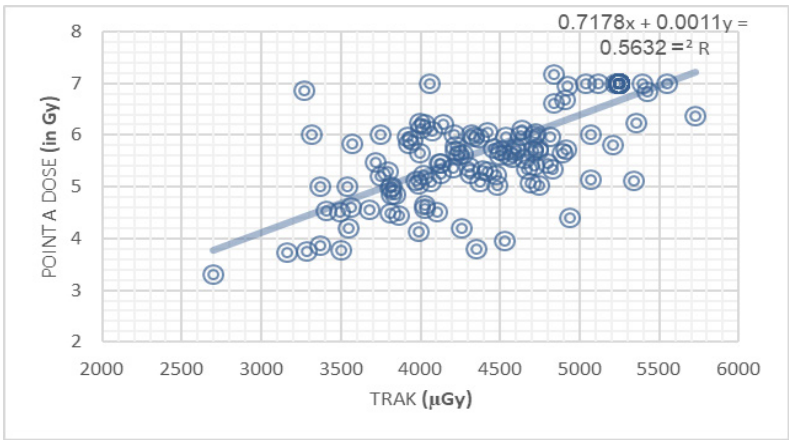

Figure 7. Scatter Plot Depicting Regression between TRAK with Point A Dose.

formulae, described further in the discussion and proposed that it could hold potential to be a surrogate marker of biological response [3] have used the Manchester method of intracavitary brachytherapy where TRAK was calculated and tabulated as a function of the prescription of the standard Manchester source configurations. They predicted that for traditional Manchester geometries, depending on the source distributions, there could be a random error of ± 3% in estimates of reference isodose volumes. Their expression was quite simple, with V, the volume enclosed by the isodose surface, being estimated as 160 (K/D) 3/2 ml, where K is the TRAK in mGy, and D is the isodose surface in Gy.

Table 3. ISBT Dosimetric Parameters

ISBT	D_{100}Gy Mean ± SD	D_{90}Gy Mean ± SD	CTV Mean Vol in cc
n=8 6x4	3.08 ± 0.78	5.45 ± 0.86	80.21
n=17 7x3	3.74 ± 0.77	6.58 ± 0.99	90.44

D_{100}, dose to 100% of volume; D_{90}, dose to 90% of volume; CTV, clinical target volume.

Eisbruch [4] analysed over 200 implants from more than 100 patients and found the same relationship characterized ICBT dose–volume histograms for

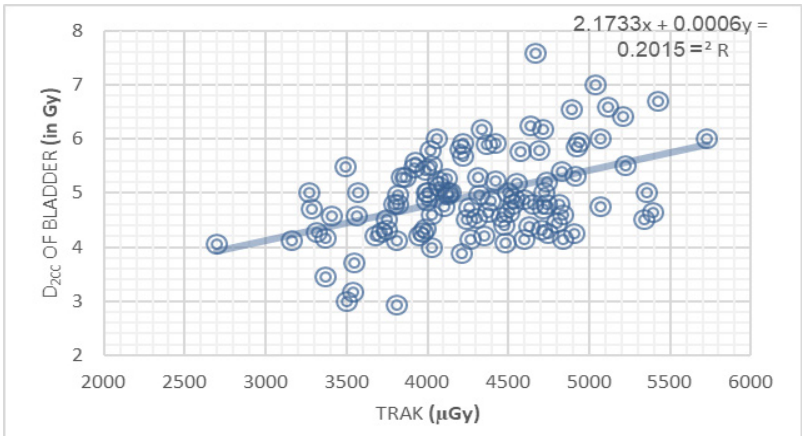

Figure 8. Scatter Plot Depicting Regression between TRAK and D_{2cc} of Bladder.

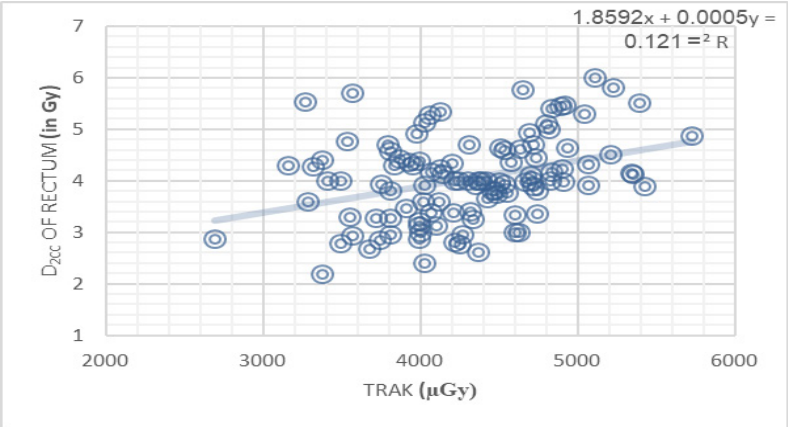

Figure 9. Scatter Plot Depicting Regression between TRAK and D_{2cc} of Rectum.

Table 4. Sub Group Volumes

Isodose volume	Mean volume (cm^3)	SD	R^2 Value	Combined R^2
V60 Gy_{pred} std	190.97	± 39.98	$R^2 = 1$	$R^2 = 1$
V60 Gy_{TPS} std	204.58	± 42.93		
V75 Gy_{pred} std	89.29	± 18.67	$R^2 = 1$	
V75 Gy_{TPS} std	94.34	± 20.19		
V85 Gy_{pred} std	66.03	± 13.77	$R^2 = 1$	
V85 Gy_{TPS} std	68.51	± 14.81		
V60 Gy_{pred} optimized	212.54	± 14.28	$R^2 = 0.9944$	$R^2 = 0.9982$
V60 Gy_{TPS} optimized	227.14	± 14.97		
V75 Gy_{pred} optimized	99.45	± 5.55	$R^2 = 0.9867$	
V75 Gy_{TPS} optimized	105.67	± 5.72		
V85 Gy_{pred} optimized	73.97	± 3.17	$R^2 = 0.9693$	
V85 Gy_{TPS} optimized	77.6	± 3.09		

$V60Gy_{pred}$ std, $V75Gy_{pred}$std, $V85Gy_{pred}$ std, respective isodose volumes predicted using the proposed formula for standard applications. $V60Gy_{TPS}$ optimised, $V75Gy_{TPS}$ optimised, $V85Gy_{TPS}$ optimised, respective isodose volumes obtained from treatment planning system for optimised plans. R^2, respective regression values.

Fletcher-Suit geometries, tandem, and cylindrical implants. They used the curve-fitting techniques and proposed that the volume encompassed by each isodose level could be predicted by a modified power-law function of the mgRaEq-hour/dose ratio. Their relation of volume estimates was therefore, V = [104.8-8.103 (M/D) + 0.437 (M/D) 2] (M/D) 1.635 ml, M/D being mgRaEq-hour/cGy. They observed that volume estimates with their model were accurate within ±10% in 95% of the cases when M/D was 0.8.

Deshpande [5] used the Fletcher-Suit applicator with a Selectron-LDR remote after loading device to derive the relation between ICRU reference volume, TRAK and dose levels. Of all patients treated, they selected 12 cases

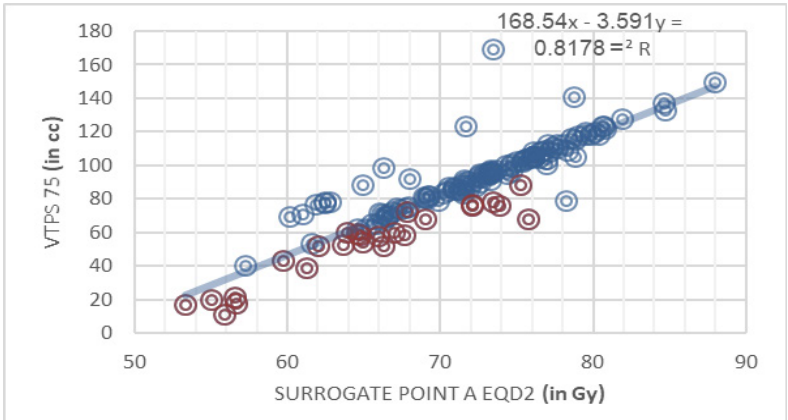

Figure 10. Scatter Plot Depicting Regression between Surrogate Point A EQD2 with VTPS 75Gy.

on the basis of satisfactory geometry representing various combinations of tandem and colpostat to derive the above relation. Their expression was very similar to that of Wilkinson and Ramachandran, with V = 156 (K/D) 1.55 ml. They observed that the percentage variation between actual and the estimated 25 Gy ICRU reference volume ranged from -2% to -9%.

Nkiwane [6] demonstrated that V60 Gy, V75 Gy, and V85 Gy isodose surface volumes can be accurately estimated from total reference air kerma (TRAK) in cervix cancer MRI-guided brachytherapy (BT). Predicted volumes $V_{pred} = 4965 (TRAK/d_{ref}) 3/2 + 170 (TRAK/d_{ref}) - 1.5$ gave the best fit to VTPS. The difference between VTPS and predicted volumes was 0.0% ± 2.3%. All volumes were predicted within 10%. The prediction was valid for (1) high-dose rate and pulsed dose rate, (2) intracavitary vs. intracavitary/interstitial applicators, and (3) tandem-ring, tandem-ovoid, and mould. Point A*14 TRAK was converted to total EQD2 and showed high correlation with V75 Gy. Concluded that TRAK derived isodose surface volumes may become a tool for assessment of treatment intensity. Furthermore, surrogate Point A doses can be applied for both intracavitary and intracavitary/interstitial BT and can be used to compare treatments across fractionation schedules.

The emphasis of our current study was thus to ascertain the feasibility, accuracy and potential future implications of TRAK in this regard and as a newer emerging tool to assess treatment intensity in cervical cancer brachytherapy. In our study we observed that the volume correlations were accurate within 10% irrespective of applicator type and across various fractionation schedules and the proposed TRAK based formula ($V_{pred} = 4965 (TRAK/d_{ref}) 3/2 + 170 (TRAK/d_{ref}) - 1.5$) is very much reproducible to obtain isodose volumes in cervical cancer brachytherapy, be it intracavitary or IC+IS hybrid applications. Especially at resource constrained centres in some lower & middle income countries who lack dedicated TPS or have upgraded their TPS and they want to retrieve TRAK data, presumably also in some high volumes centres because of its easy of calculation. but these calculations failed for pure interstitial implants as there are multiple sources/dwell positions and since these formulae and calculations are based on the approximation that there is a single point source at the centre and all dose deposited by it is accumulated inside the respective isodose volume.

What we also observed in intracavitary applications was that the volumes predicted in standard plans were lower compared to optimized plans (Table 4), since TRAK is a fair estimate of the amount of dose deposited in the respective isodose volumes. The former suggests lower intensity of treatment. On the contrary, in interstitial implants the mean surrogate point A were much lower compared to the prescription doses meaning the lower intensity of treatment. Long-term clinical follow up of these patients may help to explore whether these reduced intensity treatments will or not affect local disease control and pattern of recurrences in cervical cancer, which we very well intend to do. Hence in this era of image guided brachytherapy as we are moving from point based to volume based planning, TRAK may prove if not pivotal but certainly a surrogate marker to assess treatment intensity as well as compare with historic data.

TRAK with point A (R^2=0.5632), bladder (R^2=0.2015) and rectal doses (R^2=0.121) yielded no correlation which questions its utility as a predictor of biological response. Further long-term follow-up studies are crucial in order to answer these controversies.

In conclusion, volumes calculated by TRAK correlate with TPS obtained volumes significantly and the formula predicting isodose surface volumes within 10% accuracy for ICBT applications and not for pure interstitial implants. However, TRAK fails to correlate with surrogate point A, bladder and rectal doses hence has questionable utility as a marker for biological response & treatment intensity.

Author Contribution Statement

Naveen T (creation, manuscript, data analysis); Vishal Malavade, Corresponding author (manuscript, data analysis); Uday Krishna A S (creation, manuscript, data analysis); Sathiyan Saminathan (creation, data analysis); Tanvir Pasha (data analysis); Lokesh Vishwanath (creation, manuscript, data analysis)

Acknowledgements

General

we would like to express our heartfelt gratitude towards Prof Keshav sir for explaining us the concepts of deriving reference doses, our colleagues of radiation oncology & radiation physics for their constant support, suggestions and valuable inputs. We also are in debt to our patients and friends without whom this study couldn't have been possible. It was part of an approved student thesis.

Approval

The study was approved by the scientific committee in the letter dated - KMIO/MEC/028/05JANUARY2018.

Ethical Declaration

institutional Medical Ethics Committee approval was sought in the letter dated - KMIO/MEC/028/05JANUARY2018. (Attached)

Conflict of Interest

No Conflict of interest.

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