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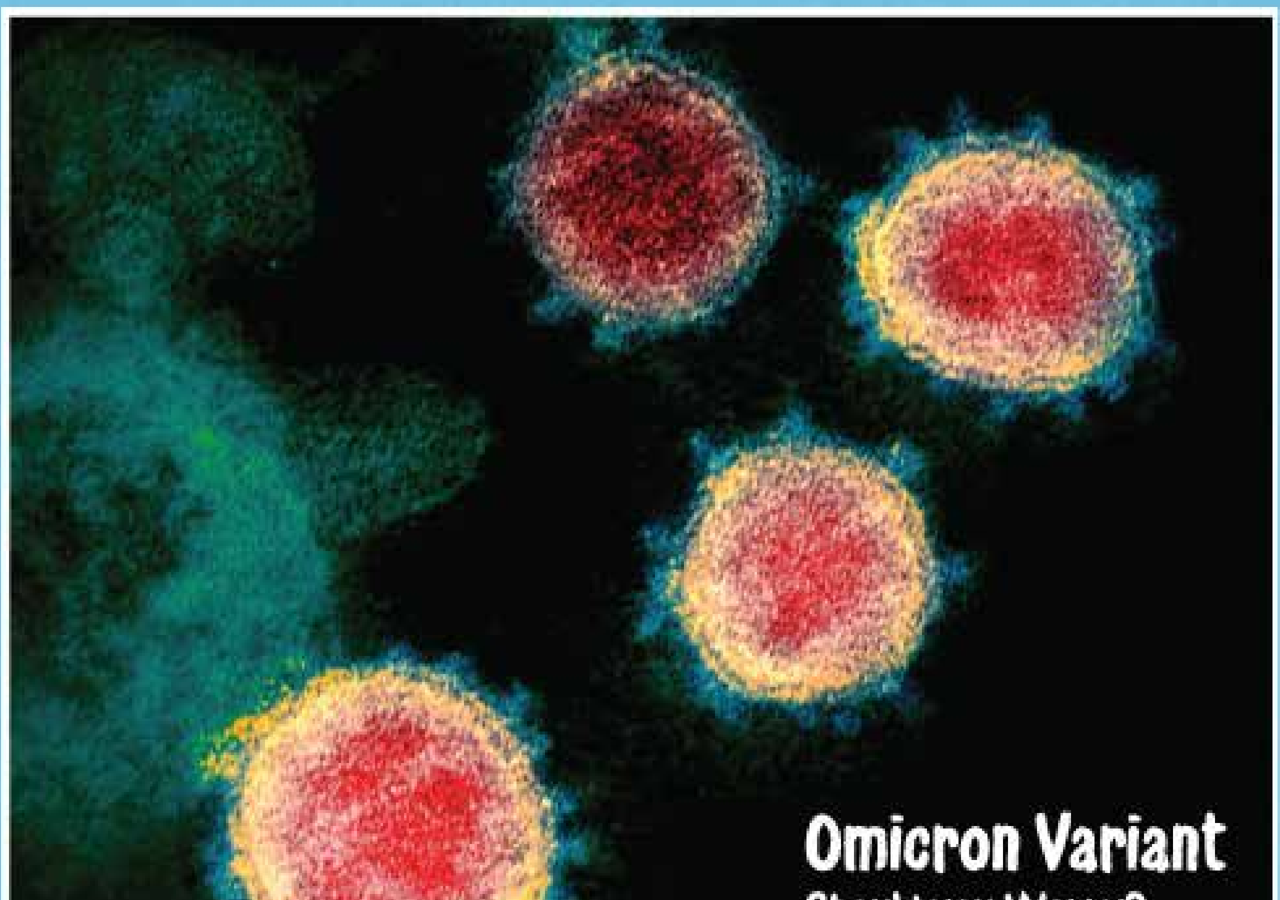

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Image–Guided Brachytherapy a Comparison Between ^{192}Ir and ^{60}Co Sources in Carcinoma Uterine Cervix

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Abstract

Introduction: Combination of external beam radiotherapy (EBRT) and High Dose Rate (HDR) brachytherapy (BT) with concurrent chemotherapy (Cisplatin 40mg/m^2/weekly) is the standard treatment of approach for the carcinoma of uterine cervix. In this study for image based HDR brachytherapy of intracavitary both ^{192}Ir and ^{60}Co sources were used for dosimetry and the dose distribution compared between point doses and volume doses as per the recommendation of ICRU89 and GEC–ESTRO on 3D image based planning. The dosimetry and clinical outcome will decide decision–making on choice of radionuclide for HDR brachytherapy of cervix in addition to economic reason.

Materials and Methods: The Study conducted for 27 patients of cancer cervix stage IIB or IIIB with vaginal involvement limited to the upper third of vagina. All patients underwent concurrent chemoradiation Cisplatin 40mg/m^2 weekly throughout EBRT by 3D conformal therapy 46Gy in 23# followed by two fractions of HDR brachytherapy with 9Gy/1Fr. Post implants 3mm slice selection of pelvic CT scans performed with ring applicator in place followed by T2 weighted paracorpal or paracoronal section of MRI imaging. The solid ring applicator (AL13017000) from library used for applicator reconstruction. Initially all plan calculated with TG–43 formalism using ^{192}Ir radionuclide (Varian, GammaMed HDR Plus source) and then modelled ^{60}Co radionuclide (Eckert & Ziegler BEBIG GmbH, Co0. A86) used for dose computation. ICRU89 recommended points and volumes of targets and OARs evaluated and compared.

Results: The study concludes that ^{60}Co based point–A, B_{ICRU} and R_{ICRU} doses showed a comparable result with that of ^{192}Ir HDR source based dosimetry. The volume based criterion for the target such as GTV, CTV_{HR}, CTV_{IR} for D_{90}, D_{98}, $V_{150\%}$ and $V_{200\%}$ are all within 5% dose level comparing two sources.

Conclusion: ^{60}Co a viable alternate to ^{192}Ir by taking into consideration frequency of source exchange and cost reserve with comparable dosimetry.

Keywords: Image–guided , ^{192}Ir, ^{60}Co, Carcinoma cervix, HDR Brachytherapy, Treatment planning

Introduction

According to GLOBOCAN 2020, carcinoma of uterine cervix is the eighth most commonly diagnosed cancer in world constituting about 3.1% of worldwide cancer incidence and 3.4% of mortality rate(1). Combination of external beam radiotherapy (EBRT) and High Dose Rate (HDR) brachytherapy (BT) with concurrent chemotherapy (Cisplatin 40mg/m^2/Weekly) is the standard treatment of approach for the carcinoma of uterine cervix. BT, being a highly conformal form of radiation technique to the tumour, while limiting the dose to surrounding normal tissue which will give ideal clinical outcomes and toxicities.

International Commission on Radiation units and Measurements (ICRU) report 38 recommend point–based dosimetry for HDR brachytherapy without the benefit of time–dependent volumetric imaging. The target approach recommended, referring to the clinical tumour presentation at diagnosis and reporting 60Gy reference volume covering this target(2). Due to tumour growth pattern, change in volume during radio–chemotherapy and topography of Organs at Risk (OAR), adaptive planning is essential in current scenario. With the use of modern imaging modalities like computed tomography (CT) and

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Magnetic Resonance Imaging (MRI), the dosimetry for HDR brachytherapy moved from point to volume–based computation and evaluation. There is accumulating evidence for the use of MR image–based brachytherapy with improved outcomes and hence it is considered as the preferred method when available[3,4]. For the boost treatment of the tumor, a special CTV–T terminology used and specifically defined for the time of brachytherapy after initial radio–chemotherapy. The high–risk CTV–T ($CTV–T_{HR}$), an adaptive CTV–T, includes the residual tumor, the cervix, and residual adjacent pathologic tissue. A second CTV, the intermediate–risk CTV–T ($CTV–T_{IR}$), includes the initial tumor extent and the $CTV–T_{HR}$ with a margin[5].

Similarly, the radioactive materials used for treatment were also seen a shift from traditionally used ^{192}Ir in HDR brachytherapy after loader unit to ^{60}Co source. However, significant difference lies between economical versus clinical requirements. ^{60}Co with enhanced specific activity has allowed the design of miniaturized sources that are equal to ^{192}Ir sources. Applicators are same in shape and diameter (Except in shielded applicators), application techniques are similar for both sources. The source operation time limited to one half life for ^{60}Co and required to exchange source in 2–3 year interval in light of increasing treatment times and 3–4 months for ^{192}Ir. The higher photon energy of ^{60}Co might cause higher risk to distant organs is difficult to access. The pros and cons have to be weighed up in every individual case. The decision for choice of proper radioactive material for clinics depends on various factors like workload, financial implication and clinical outcome. Within the treatment volume, both sources give similar dose distributions, thus existing optimizations and inverse planning tools give similar results. Outside of the treated volume, dose comparisons in peripheral organs at risk show opposite behaviour (^{192}Ir doses > ^{60}Co doses) at shorter distances from the treated volume in contrast to the behaviour at larger distances (^{192}Ir doses < ^{60}Co doses), as presented in the study of Venselaar et al[6].

In this study gynecologic working group formed by the Groupe European de Curietherapie and European Society for Therapeutic Radiology and Oncology (GEC–ESTRO) on –3dimensional (3D) image–based treatment planning in cervical cancer BT[7,8] protocol adopted using ^{192}Ir and ^{60}Co radioactive sources. Both point doses and volume doses of target and OARs analysed to view the dosimetric pattern and clinical impact in making decision for choosing the proper radioactive source for clinical use. The results of this study will be helpful in selecting appropriate radioactive source for HDR BT taking into consideration half–life, logistic advantages, cost, source exchange and disposal.

Materials and Methods

The Study conducted for 27 patients of cancer cervix stage IIB or IIIB with vaginal involvement limited to the upper third of vagina. All patients underwent external beam radiation by 3D conformal therapy of 46Gy in 23#, 2Gy/# followed by two fractions of HDR brachytherapy with 9Gy/#. The patient's assessment done after completion of 30Gy or completing EBRT. All patients received concurrent chemotherapy with Cisplatin 40mg/m^2/Weekly. A fixed bladder protocol followed with catheterization using Foley's and bulb pushed with 7cc of normal saline for point as well as volume dosimetric evaluation. The catheter pulled down to rest at the trigone of bladder and fixed catheter to inner thigh by micropore for reproducibility. Rectal retractor used to push the rectum away high dose region along with adequate vaginal packing to stabilize applicator geometry. Post implant pelvic CT scans done with the applicator in place for treatment planning. A 3mm slice selection made for the pelvic CT followed by Magnetic Resonance Imaging (MRI) with the applicator in place for the first fraction. T2 weighted images obtained in the paracorpal or paracoronal sections. The MRI images were co–registered with the planning CT using the uterine tandem as the reference and the target volumes were delineated. The volumes of organs–at–risk viz., the bladder, rectum and target volumes as shown in the figure 1, delineated on each CT slice using MRI registered images. The solid ring applicator (AL13017000) from digital library used for applicator reconstruction. Initially all plan in HDR brachytherapy calculated using TG–43 formalism using ^{192}Irsource. These patients were planned with HDR ^{60}Co source to check and estimate the difference in the dosimetry pattern.

Pre–treatment evaluation

Pre–treatment evaluation for all patients include history, general physical examination and complete systemic examination including gynaecological examination (per–speculum, per–vaginal and per–rectal examination). Clinical staging of the patients done according to FIGO staging and patients with FIGO stage IIB and IIIB with vaginal involvement limited to the upper one–third included in the study.

Criteria

Inclusion

- Patients with histologically confirmed carcinoma cervix with FIGO stage IIB or IIB with vaginal involvement limited to the upper third
- Patients assessed for fitness for radical treatment

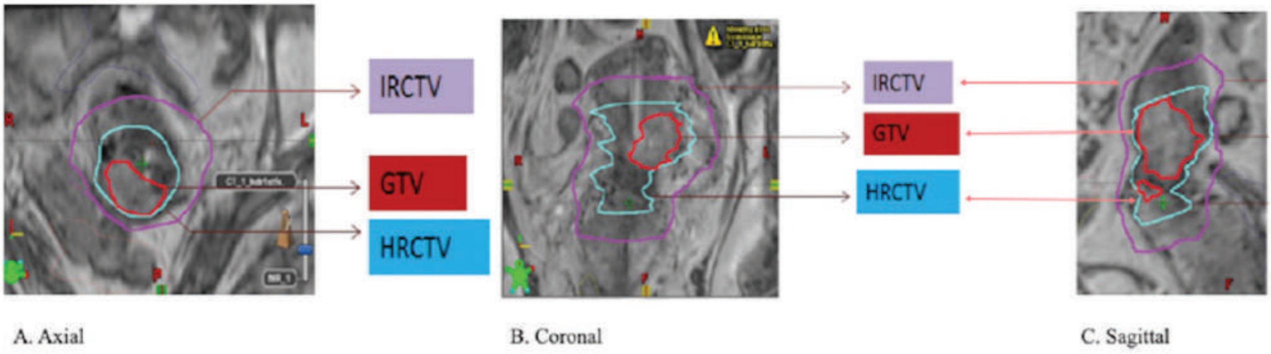


Figure 1: Delineation of targets – GTV, HR–CTV, IR–CTV on MRI

Exclusion

- – Patients with earlier distortion of local anatomy such as 3rd degree perineal tears, rectal prolapse
- – Patients with anatomic abnormalities of vagina and uterus.

Radionuclide model and dose calculation algorithm

The Varian Medical Systems, GammaMed HDR Plus source (GM12000680) and Eckert & Ziegler BEBIG GmbH, Co0.A86 source used for this study. The Physical dimension of length 4.52mm and 0.9mm in diameter with active core of 3.5 mm in length and 0.7 mm in diameter taken in to account for Gamma Med HDR Plus source and the Monte Carlo (MC) code GEANT4 modelled Co0. A86 source composed of central cylindrical active core made of metallic ^{60}Co, 3.5 mm in length and with a diameter of 0.5 mm. A cylindrical stainless steel capsule of 0.15mm thick covered over with an external diameter of 1mm. The difference in physical properties of these two sources shown in table 1. The ^{60}Co source modelled in Varian Medical Systems, Palo Alto, CA, Treatment Planning software version 10.0. The dose calculation formalism for brachytherapy sources based on American Association of Physicists in Medicine (AAPM) Task Group No. 43 (TG–43) protocol. Both 2D (cylindrically symmetric line source) and 1D (point source) data used for dose calculation in both the sources wherein, different 2D dose–rate equation parameters viz., Air–kerma strength, Dose–rate constant, Geometry function, Radial dose function, Anisotropy function taken into calculation.

Treatment Modality

Each brachytherapy delivered 9Gy/# with interval of one week between fractions. The Ring and Tandem applicator set of 60º (AL13017000) made of titanium, which were CT and MR compatible used for each application and Varian GammaMed plus iX HDR unit for treatment with ^{192}Ir radioactive source.

Parameters	Varian Medical Systems, GammaMed HDR Plus ^{192}Ir source	Eckert & Ziegler BEBIG GmbH, Co0.A86 HDR ^{60}Co source
Half–life (days)	73.83	1923.5
Gamma Energy Range (keV)	110.4–1378.2	1173.2–1332.5
Air–kerma rate constant (μGy m^2 h^{-1} MBq^{-1})	0.1091	0.3059
Specific activity (GBq mg^{-1})	341.0	41.91

Table 1: Physical Properties of radionuclides

Dosimetric evaluation and Assessment

The 3D dose calculated using ^{192}Ir Gammamed plus source with an aim to meet prescribed dose to point A, either geometric, graphical or manual optimization technique. If prescribed dose encloses CTV_{HR} then plan approved for treatment. Without alteration the same plan calculated with ^{60}Co source without changing the dwell positions and dose difference between the two compared and analysed. The cumulative dose volume histograms (cDVH) used for comparison due to complex dose heterogeneity.

Dose parameters

2D dose parameters (ICRU Reference points)

- – Point A: Left and Right
- – ICRU recto–vaginal point
- – ICRU bladder point dose

3D dose parameters (GEC–ESTRO recommendations)

- – $D_{0.1CC}$, D_{2CC} for bladder, rectum and sigmoid
- – D_{90}, D_{100} for GTV_B
- – D_{90}, D_{98} for CTV_{HR}

– D_{90}, D_{98} for CTV_{IR}

– $V_{100\%}$, $V_{150\%}$, $V_{200\%}$ for assessment of high dose volumes.

Statistical Approach

All the data analysed statistically by statistical analysis for windows (version 21.0, IBM Corp., Armonk, NY, USA). Mean with standard deviation of normal distribution of continuous data presented. Paired data compared using paired t–test to study the difference in mean between the group. A statistical significance of p ≤0.05 considered significant.

Results

Table 2 illustrates the quantitative analysis of simple comparison of point–dose calculated using ^{192}Ir and ^{60}Co sources for a typical HDR carcinoma cervix treatment, with Intrauterine tandem and ring applicator, with same loading of two sources, prescribed to point A. The table depicts the effect of the inherent differentiation between two isotopes on the resulting dose point. Either side of the point A showed a variation of –4.33% difference in the mean values with respect to ^{192}Ir plan, whereas point B showed difference of –8.8%. Consistently lower doses delivered from the applicators, including distant portions of bladder by up to 3.4% and rectum by 1.9% compared to ^{192}Ir plans in similar loading pattern.

The mean volume of all three targets were 9.48cc (GTV), 26.17cc (CTV_{HR}) and 94.16cc (CTV_{IR}). From table 3, it is clear that various volume parameters analysed, there were statistically significant differences ($p<0.01$) in all volume parameters for CTV_{HR} between ^{192}Ir and ^{60}Co plans with relatively lower doses for ^{60}Co plans. The mean value of $V_{150\%}$ and $V_{200\%}$ showed almost comparable value between the plans for CTV_{HR} but the value of $V_{150\%}$ and $V_{200\%}$ showed statistically significant result for CTV_{IR}. There was statistically significant difference for the CTV_{HR} and CTV_{IR} of D_{90} and D_{98} as shown in the box and whisker plot of figure 2. However, GTV mean dose(Gy) and CTV_{HR} mean dose(Gy) both showed no significant difference with p=0.423 and p=0.29 respectively.

The Organs at Risk (OARs) associated with cervix are bladder, rectum and sigmoid and as per GEC–ESTRO and ICRU89 recommendations, D_{2cc} and $D_{0.1cc}$ of all these organs studied. All the values are statistically significant as shown in the figure 3, but the rectum mean max dose(Gy) reflects statistical insignificant results with p=0.845. From figure 4, the rectum D_{2cc}, $D_{0.1cc}$ and ICRU rectal reference point compared and D_{2cc} showed decrease of %6.77 to ICRU rectal point as against increase of %18.4 with respect ICRU rectal point for ^{60}Co radionuclide. If we see with ^{192}Ir radionuclide, similar percentage decrease comparable to ^{60}Co whereas, 25.04% increase in dose compared to ICRU rectal point using ^{192}Ir. Similarly, bladder doses were compared and showed 24%, 62% increase in

	Mean	Std. Deviation	Correlation	Paired Differences				Sig. (2–tailed)	p–value (significance)
				Mean	Std. Deviation	95% Confidence Interval of the Difference			
						Lower	Upper		
AL(Gy)_^{192}Ir	9.00	.00	.310	.388	.026	.378	.398	.000	p<0.01 (S)
AL(Gy)_^{60}Co	8.61	.03							
AR(Gy)_^{192}Ir	9.00	.00	.079	.388	.027	.377	.398	.000	p<0.01 (S)
AR(Gy)_^{60}Co	8.61	.03							
BL(Gy)_^{192}Ir	2.25	.16	.999	.189	.015	.183	.195	.000	p<0.01 (S)
BL(Gy)_^{60}Co	2.06	.15							
BR(Gy)_^{192}Ir	2.27	.18	.999	.192	.016	.186	.199	.000	p<0.01 (S)
BR(Gy)_^{60}Co	2.08	.17							
B_ICRU(%)_^{192}Ir	56.39	20.38	.999	1.924	1.272	1.421	2.427	.000	p<0.01 (S)
B_ICRU(%)_^{60}Co	54.47	19.40							
R_ICRU(%)_^{192}Ir	62.93	16.41	.999	1.199	.597	.963	1.435	.000	p<0.01 (S)
R_ICRU(%)_^{60}Co	61.73	16.29							

AL – Point A Left, AR – Point A Right, BL – Point B Left, BR – Point B Right, B–ICRU – Bladder ICRU point, R–ICRU – Rectum ICRU point

Table 2: Comparison of point doses using ^{192}Ir and ^{60}Co sources

	Mean	Std. Dev.	Correlation	Paired Differences				Sig. (2–tailed)	p–value (Significance)
				Mean	Std. Dev.	95% Confidence Interval of the Difference			
						Lower	Upper		
BL_Min(Gy)_Ir192	1.21	0.41	.151	–.232	1.701	–.905	.441	.485	p=0.485 (NS)
BL_Min(Gy)_Co60	1.44	1.71							
BL_Max(Gy)_Ir192	14.77	6.21	.999	.113	0.247	.015	.211	.025	p=0.025 (S)
BL_Max(Gy)_Co60	14.66	6.28							
BL_MeanDose(Gy)_Ir192	3.33	0.97	.998	.146	0.071	.118	.175	.000	P<0.01 (S)
BL_MeanDose(Gy)_Co60	3.18	0.93							
Rec_Min(Gy)_Ir192	0.65	0.27	.997	.022	0.027	.012	.033	.000	P<0.01 (S)
Rec_Min(Gy)_Co60	0.63	0.26							
Rec_Max(Gy)_Ir192	9.29	4.47	.999	.009	0.233	–.083	.101	.845	p=0.845 (S)
Rec_Max(Gy)_Co60	9.28	4.53							
Rec_MeanDose(Gy)_Ir192	2.52	0.78	.999	.070	0.033	.057	.083	.000	P<0.01 (S)
Rec_MeanDose(Gy)_Co60	2.45	0.77							
Sig_Min(Gy)_Ir192	1.13	0.34	.997	.085	0.029	.073	.096	.000	P<0.01 (S)
Sig_Min(Gy)_Co60	1.04	0.32							
Sig_Max(Gy)_Ir192	11.13	5.69	.999	.117	0.303	–.003	.237	.055	p=0.055 (S)
Sig_Max(Gy)_Co60	11.01	5.87							
Sig_MeanDose(Gy)_Ir192	3.14	0.85	.999	.148	0.046	.130	.166	.000	P<0.01 (S)
Sig_MeanDose(Gy)_Co60	2.99	0.82							
GTV_Meandose(Gy)_Ir192	22.85	6.04	1.000	–.027	0.171	–.095	.041	.423	p=0.423 (NS)
GTV_Meandose(Gy)_Co60	22.88	6.12							
CTV_{HR}_Meandose(Gy)_Ir192	19.95	3.59	1.000	.037	0.082	.004	.069	.029	p=0.029 (S)
CTV_{HR}_Meandose(Gy)_Co60	19.91	3.63							
CTV_{IR}_Meandose(Gy)_Ir192	13.88	2.84	1.000	.133	0.041	.117	.149	.000	P<0.01 (S)
CTV_{IR}_Meandose(Gy)_Co60	13.75	2.86							

BL – Bladder, Rec. – Rectum, Sig. – Sigmoid ; GTV – Gross Tumour Volume, CTVHR – High Risk Clinical Target Volume, CTVIR – Intermediate Risk Clinical Target Volume.

Table 3: Minimum, Maximum, Mean doses of different targets and Organs at Risks comparing ^{192}Ir and ^{60}Co.

dose to D_{2cc} and $D_{0.1cc}$ as against ICRU bladder point. The trend is similar to both the radionuclides based planning. The mean sigmoid volume in this study were 37.80cc of which $D_{2.0cc}$ and $D_{0.1cc}$ showed difference of %3.80 and %2.79 with respect to ^{192}Ir based planning.

Discussion

The standard treatment modality for carcinoma cervix is EBRT and HDR brachytherapy with chemotherapy. HDR brachytherapy by remote after loading technique introduced by Henschke et al. and O'connell et al[9,10]. The standard radionuclide of choice for remote after loader brachytherapy unit is ^{192}Ir whose half–life is short. The produce of miniaturized ^{60}Co source for HDR brachytherapy, geometrical dimensions identical to that of ^{192}Ir, the use of this radionuclide is increasing worldwide due to long half–life and economically viable alternative. Its equivalence to ^{192}Ir sources demonstrated to physical data, source construction and dose distribution of a single source and clinically applied more complex dose distributions[11–13]. Despite that ^{192}Ir and ^{60}Co sources of same dimension and

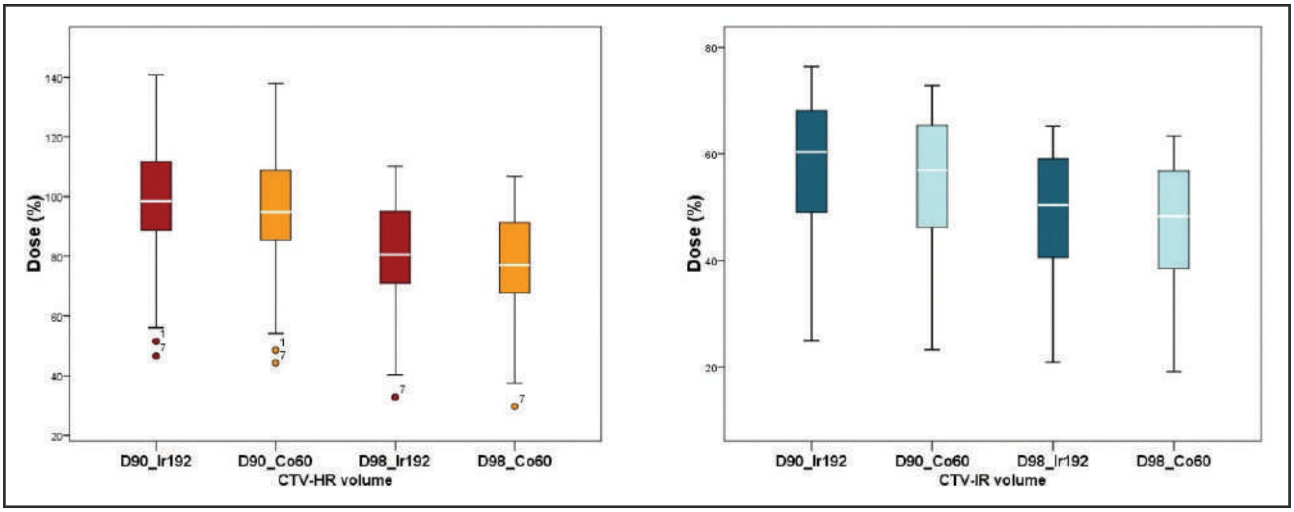


Figure 2: Box and Whisker plot comparing the difference in D90 and D98 of CTVHR and CTVIR planned with ^{192}Ir and ^{60}Co radioactive source

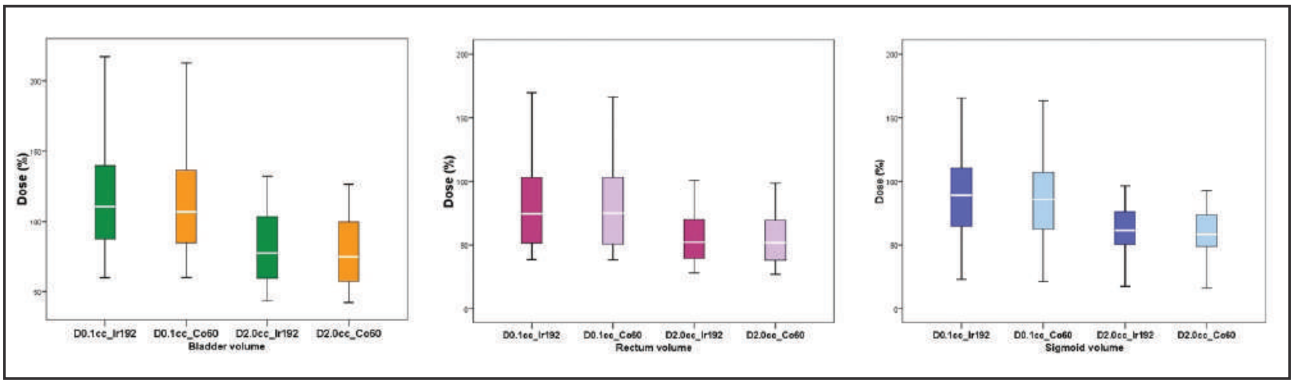


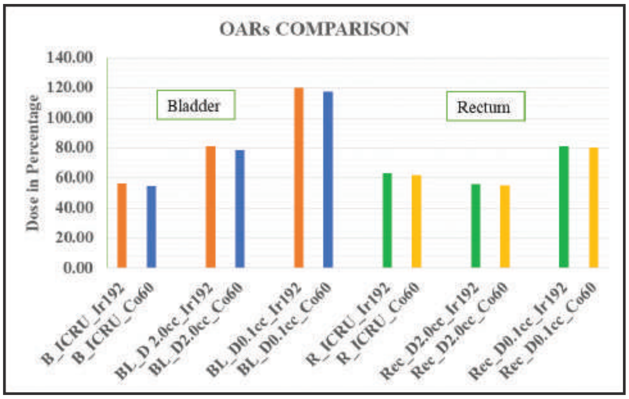
Figure 3: Box and Whisker plot comparing difference between D2cc and D0.1cc of Bladder, Rectum and Sigmoid with ^{192}Ir and ^{60}Co radioactive source

have different physical characteristics, they show similar dose distributions, as demonstrated in various studies. Several researches published their experience using ^{60}Co HDR brachytherapy in cervical cancer treatment with favourable result[14,15].

The applicator reconstruction is very important in MRI based intracavitary brachytherapy because it can lead to geometric and dosimetric uncertainties, as recommended by ICRU89, GEC–ESTRO and IBS (Indian Brachytherapy society)[16], the applicator reconstruction classified either by direct digitization or Library based digitization. In this study, all the applicators reconstructed by Library based digitization where solid applicator set is directly positioned into the images according to visible structures of applicators. These has reduced error to greater extend.

From the analysis of twenty–seven patients' treatment plans, using a 3D image–based approach, only small differences in dose distribution observed when using either ^{60}Co or ^{192}Ir isotopes. When treatment plans prescribed to Point A and identical loading patterns used, there was a small, but statistically significant. With reference to ICRU rectal and bladder point, mean difference of 3.4% and 1.9% noted between the two. Whereas in Park et al.[17] decrease of 1.14% and increase of 0.83% note when using ^{60}Co rather than ^{192}Ir. This work is not of particular clinical significance for modern treatment planning. Of more significance are the clinical treatment plans that were produced when optimisation of source dwells permitted, which is a standard practice for modern brachytherapy. The volume based evaluation of doses to organs are more relevant in the present context where bladder D_{2cc} showed a decrease of %3.3, $D_{0.1cc}$ showed 1.7% variation with respect to ^{192}Ir source which agreed well with Palmer et al[18].

The mean D_{90} of CTV_{HR} using ^{192}Ir is 95.69(%) ± 4.4 whereas for ^{60}Co it is 92.5 (%) ±3.9. Similarly, mean CTV_{IR} using ^{192}Ir and ^{60}Co were 56.67 (%) ± 2.9 and 58.84 (%) ± 2.8, these results were comparable to Gujar et al[19] where mean dose to CTV_{HR} for D_{90} was found 102.0 (%) ± 3.07 for ^{60}Co radionuclide based planning. Strohmaier et al[20] also concluded there to be insignificant clinical differences between the two isotopes based on analyses using ICRU point doses. It is apparent that the inherent differences between the two isotopes, which itself lead to



B_ICRU – Bladder ICRU point, R_ICRU – Rectum ICRU point
BL – Bladder, R – Rectum
D2.0cc – Dose received by 2.0cc of volume, D0.1cc – Dose received by 0.1cc of volume

Figure 4: Histogram comparing ICRU point, D2cc and D0.1cc of Bladder and Rectum

small differences in dose distribution, can be overcome by application of treatment planning optimisation techniques. The key physical parameters for ^{60}Co and ^{192}Ir HDR sources have been presented and analysed to deduce clinically relevant information for use in brachytherapy treatments. It is essential that this data is fully understood to mitigate the risk of any treatment error in moving from ^{192}Ir to ^{60}Co.

The irradiation time for each treatment using ^{60}Co will certainly increase over the time but actually it reduces the overall time compared to ^{192}Ir by taking into account setup time, ancillary services. The initial cost of radiation bunker for ^{60}Co will be higher than ^{192}Ir due to higher average gamma energy however this is insignificant when compared to longer operation cost due to long half–life. Monte Carlo simulations show that the distance beyond 20 cm from the source due to higher photon energy of ^{60}Co, the integral dose is higher compared to ^{192}Ir. Use of ^{60}Co source for HDR brachytherapy in patients is well–documented and showed 3years follow–up of the patients with low toxicity and acceptable clinical outcome[(21)]. Significant cost reserves be achieved with ^{60}Co due to need of source exchange every 2–3years compared to 4–5 months with ^{192}Ir .

Conclusion

The study concludes that ^{60}Co based point–A, B_{ICRU} and R_{ICRU} doses showed a comparable result with that of ^{192}Ir HDR source. The volume based criterion for the target such as GTV, CTV_{HR}, CTV_{IR} for D_{90}, D_{98}, $V_{150\%}$ and $V_{200\%}$ are all within 5% dose level comparing two sources. There are no pros and cons exits between the two with respect to intracavitary brachytherapy dosimetry. ^{60}Co can be used for HDR BT for carcinoma uterine cervix due to logistic advantage, longer half–life, infrequent source exchange and disposal.

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Nil

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