ORTHOGONAL VERSUS IMAGE GUIDED BRACHYTHERAPY IN CARCINOMA CERVIX: A COMPARITIVE DOSIMETRIC STUDY BASED ON THE RESPONSE TO EXTERNAL BEAM RADIATION.

A Dosimetric Observational Study

in partial fulfillment of the requirements for the award.

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IN RADIOTHERAPY

A DISSERTATION SUBMITTED TO
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CERTIFICATE

This is to certify that this dissertation titled, "**ORTHOGONAL VERSUS IMAGE GUIDED BRACHYTHERAPY IN CARCINOMA CERVIX: A COMPARITIVE DOSIMETRIC STUDY BASED ON THE RESPONSE TO EXTERNAL BEAM RADIATION."** is a bonafide record of the work done by **Dr.Krithikaa.S**, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of her postgraduate study for the degree of M.D. (Branch IX – Radiotherapy) from 2016-2018 under my direct guidance and supervision.

Date:
Place: Chennai

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I thank Mr.Sam Dev Kumar,our physist for his valuble contribution in the form of ideas,time and effort spared for this study.

My deep sense of thanks to the division of gynecological radiation oncology and the team of Anesthetist,OT staff,technitian ,technologists and Physists involved in the procedure..

I thank God and my parents for standing by my side and in helping me in making all my endevours coming true.

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ABSTRACT

TITLE: ORTHOGONAL VERSUS IMAGE GUIDED BRACHYTHERAPY IN CARCINOMA CERVIX: A COMPARITIVE DOSIMETRIC STUDY BASED ON THE RESPONSE TO EXTERNAL BEAM RADIATION

AIM

To compare conventional point A based brachytherapy planning and conformal planning in patients with differential response to EBRT and to analyse if Point A based planning is non-inferior to IGBT.

OBJECTIVES

Primary Objective:

To compare and analyse the variations in dose to target volume and OAR in orthogonal ICRU 38 recommendation based planning versus CT based volumetric planning in patients with differential response to EBRT and to identify the subgroup of patients in whom point A based planning may be non-inferior to IGBT.

Secondary Objective:

To identify the subgroup in which IGBT offers maximal benefit in terms of Target coverage and therapeutic ratio.

MATERIALOS AND METHOD

STUDY DESIGN:Prospective Dosimetric study

TYPE OF STUDY:Case series

STUDY PERIOD:March 2017-August 2017

NO OF PATIENTS:40(20 in Group A & 20 in Group B)

40 patients with carcinoma of the uterine cervix who underwent EBRT with or without chemotherapy were stratified to Group A (No residue) or Group B (Residual disease) based on the response to EBRT. At the time of first intracavitary application, both orthogonal point A based planning and CT based volumetric planning were done and variations in the dose to the Target volume(D90/D100/V100 & Dose to point A) and OAR(D0.1/1/2cc & ICRU Bladder and rectal points)were compared..

RESULTS:

In Group A,target coverage was achievable withj conventional planning methods ,however with image guided brachytherapy the dose to organ at risk could be reduced.In Group B,for adequate target coverage ,combined intracavitary and interstitial needle techniques were necessary and only image guided brachytherapy

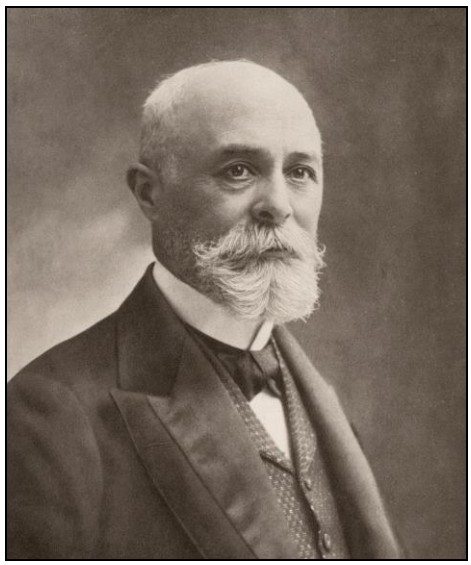
without needles couls not achieve this target coverage,thus,it was the choice of technique which was important in this group.

CONCLUSION:

From our observation, IGBT is essentially important to treat a larger target volume , in patients who have residue after initial chemo radiation for adequate target coverage,provided the choice of technique such as combined intracavitary and interstitial brachytherapy were utilized . IGBT also improves the therapeutic ratio in patients who do not have a central residue. In patients with good response after external beam radiation to pelvis, IGBT could be used to reduce the dose to the organ at risk thus improving the therapeutic ratio ,however without much difference with respect to target coverage in comparison to orthogonal planning.

EVOLUTION OF CERVICAL BRACHYTHERAPY

DISCOVERY OF RADIUM

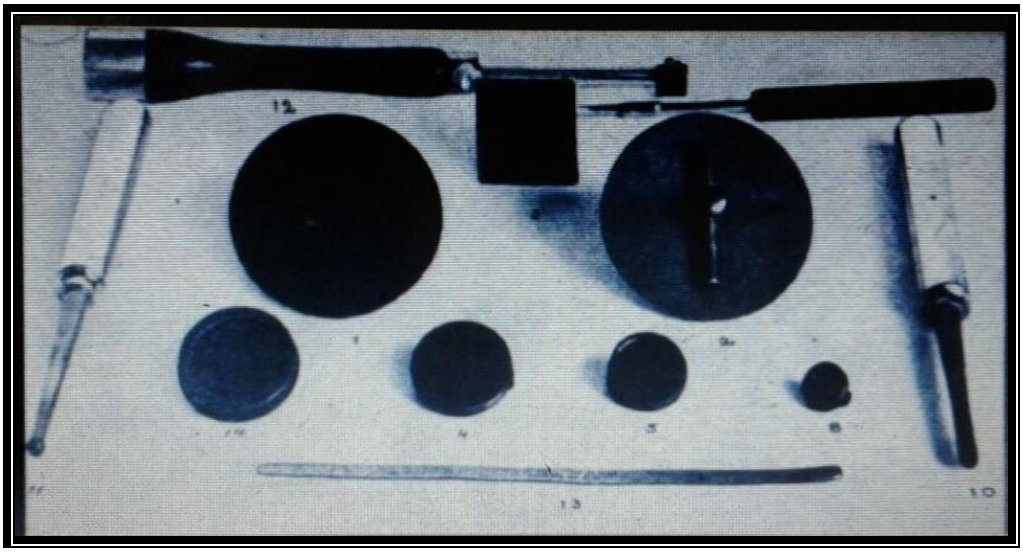


Sir Henri Becquerel

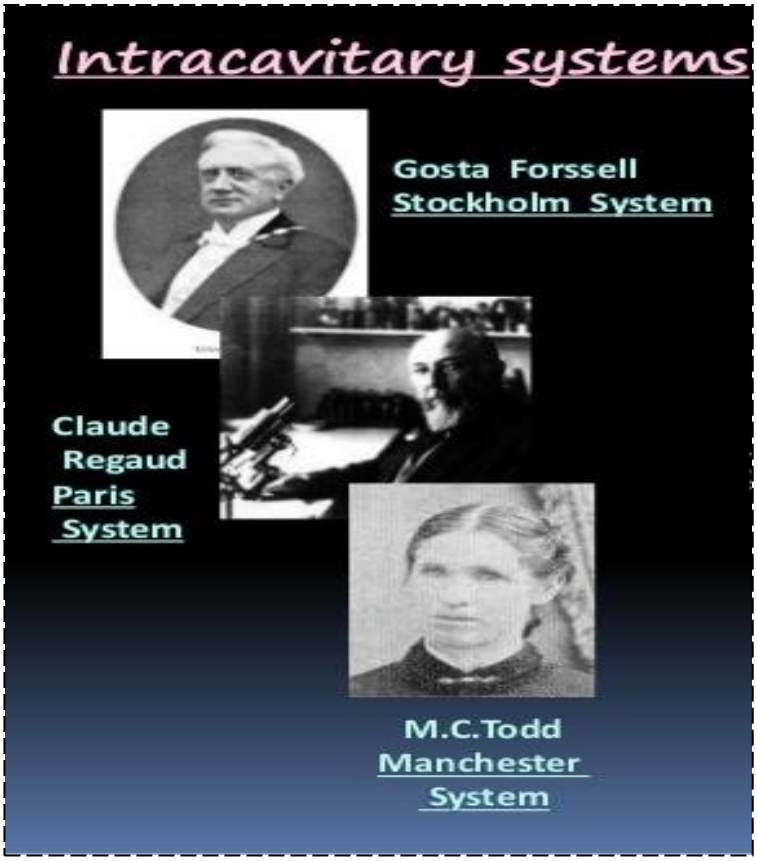
Madam Marie Curie & Pierie Curie

Brachytherapy as a treatment modality owes its existence to the discovery of radioactivity by Henrri Becquerel in 1896 and discovery of radium by Madam Marie Curie and Pierie curie in1898 in Paris,after which the therapeutic effects of radium was explored extensively.[1].After observing the effects of radium on successful treatment of several skin conditions such as lupus, lichen, eczema, psoriasis, naevus and dermatitis by Danlos and several other investigators in 1901,[2], the first reported successful brachytherapy application for malignancy was done in 1903 ,for basal cell carcinoma of skin at St. Petersburg , prompting its widespread use for skin cancers in Europe.[3].

RADIUM APPLICATORS

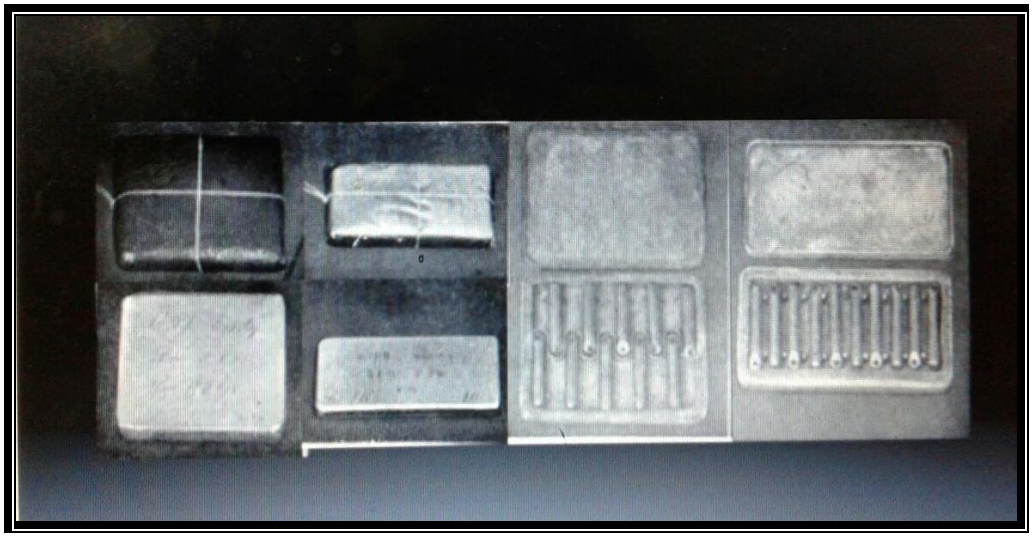


INTRACAVITARY SYSTEMS



The use of endocavitary treatment in cervical cancers dates back to 1904 when Wickham initiated carcinoma cervix treatment with radium [4],although, the dosimetry with regards to amount of radium to be used and the duration of application were empirical till 1914 due to lack of knowledge about the biological effects of radiation on the normal tissues and tumour and the understanding of dose distribution, when Stolkholm system was developed in 1914 by Gosta Forsell.

STOLKHOLM APPLICATORS



It consisted of Tandem or the intrauterine tube made of flexible rubber and vaginal box made of lead or gold, application reported in terms of milligram hours(product of amount of radium used and duration of application),with unequal loading of radium in uterus and vagina. A fractionated course of treatment over a period of one month, usually 2-3 applications each lasting for 20-30 hours

repeated 2-3 weekly to contribute a total prescribed dose of 6500-7100 milligram hours[5].

PARIS SYSTEM APPLICATORS

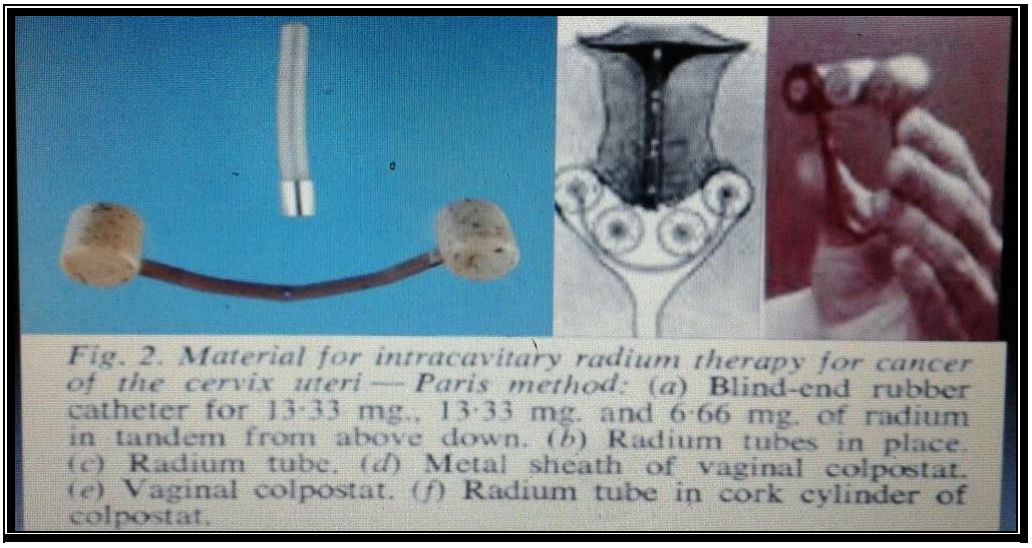


Fig. 2. Material for intracavitary radium therapy for cancer of the cervix uteri — Paris method: (*a*) Blind-end rubber catheter for 13·33 mg., 13·33 mg. and 6·66 mg. of radium in tandem from above down. (*b*) Radium tubes in place. (*c*) Radium tube. (*d*) Metal sheath of vaginal colpostat. (*e*) Vaginal colpostat. (*f*) Radium tube in cork cylinder of colpostat.

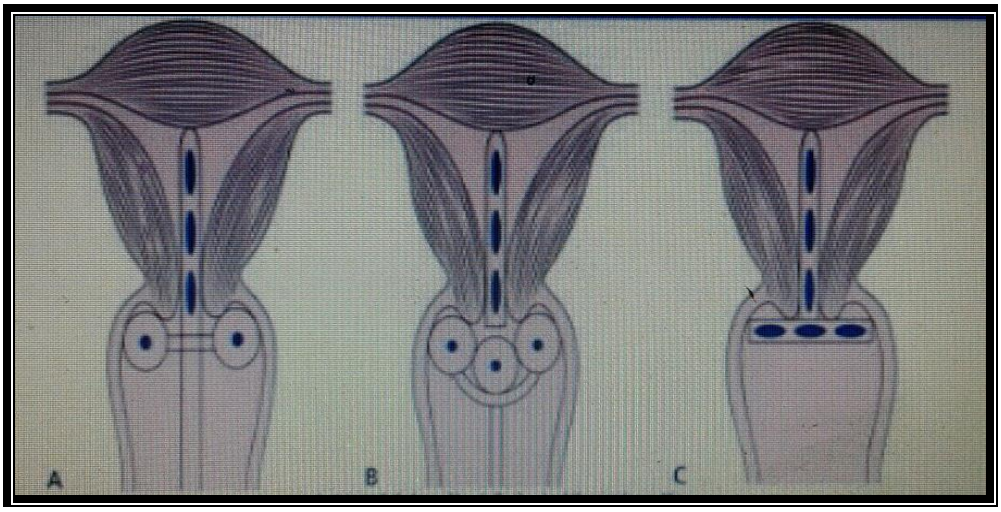
The Paris system of brachytherapy was developed in 1926 by Regaud ,which used semi flexible silk rubber intrauterine tube and vaginal cork colpostat. A dose of 7000-8000 milligram-hours delivered in a single fraction over a period of 5 days.Equal amounts of radium was used in uterus and vagina.The advantage of paris system over stolkholm system is that due to the vaginal colpostats the dose received by the parametrium was higher.[6]

The Manchester system was developed in 1930 by Todd and Meredith ,as a modification of the Stolkholm and Paris system using the source loading pattern of Paris system and fractionated dose delivery of Stolkholm system, dose calculated in Roentgen to various points in pelvic region where dose variation was not rapid.

MACHESTER SYSTEM APPLICATORS

The origin of Point A dates back to the Manchester system who defined the paracervical triangle where radiation necrosis occurs. Point A was defined as 2cm lateral to centre of uterine canal and 2cm superior to mucosa of lateral fornix ,the point in medial end of broad ligament where uterine artery crosses ureter.Point B defined to be 5cm from the midline and 2cm above the mucosa of lateral fornix,a measure of rate of lateral dose fall off and dose to the obturator nodes[7].

DIFFERENT INRACAVITARY SYSTEMS



A.Manchester system B.Paris system C.Stolkholm system

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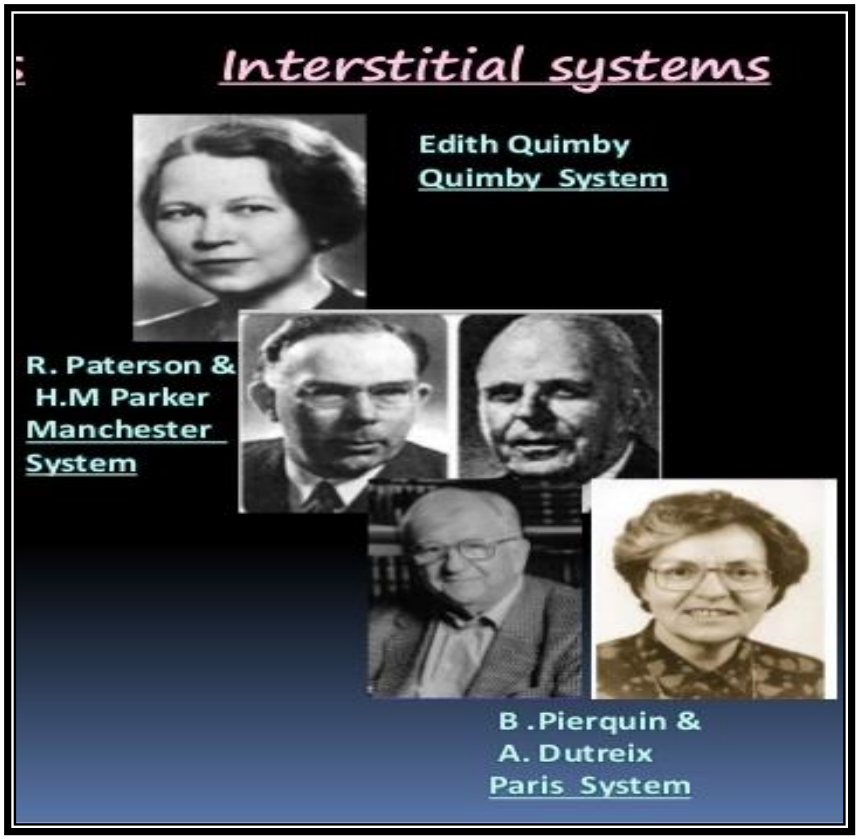
INTERSTITIAL IMPLANTATION SYSTEMS

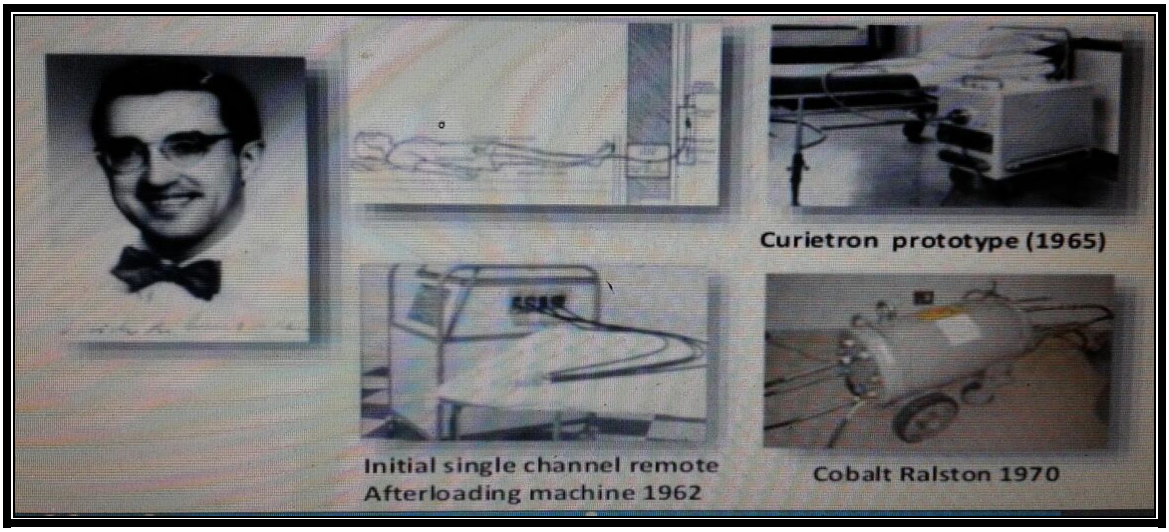
Meanwhile systems of interstitial implantation was also under evolution. Quimby system of interstitial implantation was developed in 1932 which used uniform distribution of activity in radium needles for defining planar and volume implant rules and tables to calculate the milligram-hours required to produce the required dose distribution[8].

PIONEERS IN INTERSTITIAL SYSTEM



Paterson and parker's work (Also known as Manchester system) on radium dose distribution was published in 1934[9], which used heavy peripheral loading of radium and then the memorial system which was a modification of the Quimby system with computer based calculations was introduced in 1964[10]. Later after the discovery of iridium 192 the Paris system of uniform radium wire loading was introduced following which the computer system was introduced[11].

DEVELOPMENT OF AFTERLOADING DEVICES

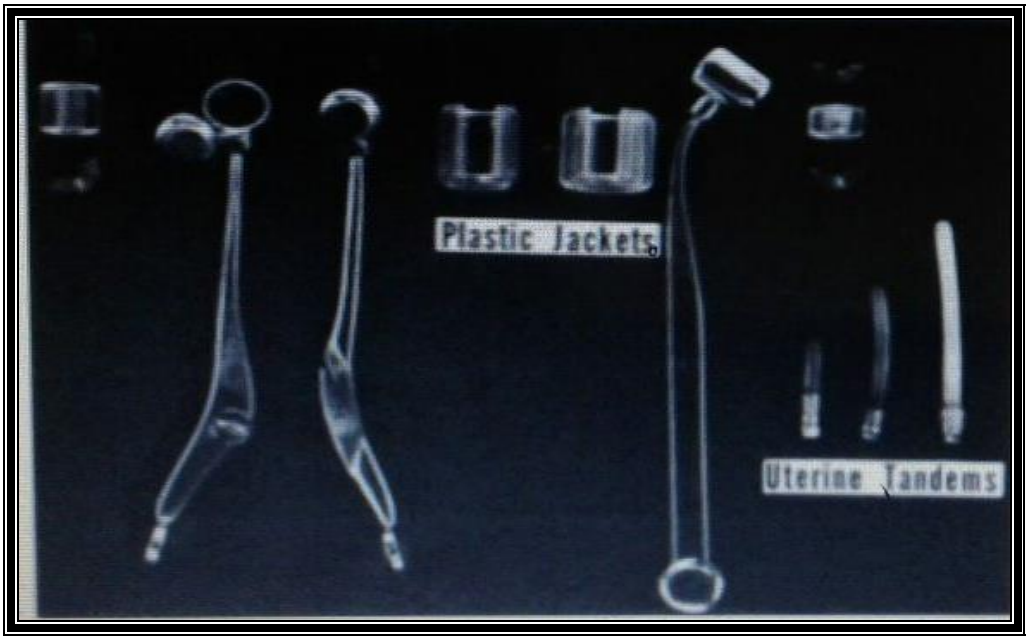


Dr.Henschke and his discovery of afterloadig devices

The development of nuclear reactors allowed the production of several other radionucleides. Dr.Henschke from MSKCC introduced gold-198 seeds in 1944 and subsequently cobalt-60 in 1948 and Iridium-192 in 1954.This led to the most revolutionary step in brachytherapy , the development of 'stepping source dosimetry system' using a single miniature Ir-192 source.[12] .With the introduction of afterloaading techniques, the potential hazards due to radiation exposure was eliminated.The development of afterloading techniques paved the way for further evolution of brachytherapy .

SWITCH FROM LDR TO HDR BRACHYTHERAPY

PRELOADED FLETCHER APPLICATORS



Since the introduction of radioactive isotopes at the beginning of the 20th century, LDR-ICBT has been almost exclusively employed in the treatment of uterine cervical cancer. This was not because LDR was considered superior to HDR, but simply because high-activity sources that were suitable for HDR treatment were unavailable. HDR sources were first applied to brachytherapy by Henscke and O'Connell (Henschke 1966; O'Connell 1965) in the early 1960s[12], and the interest in the use of HDR-ICBT has steadily grown worldwide during the past four decades. This is mainly because of the advantages of remotely afterloading HDR-ICBT compared with LDR-ICBT

.

The advantages include

1) short treatment time,

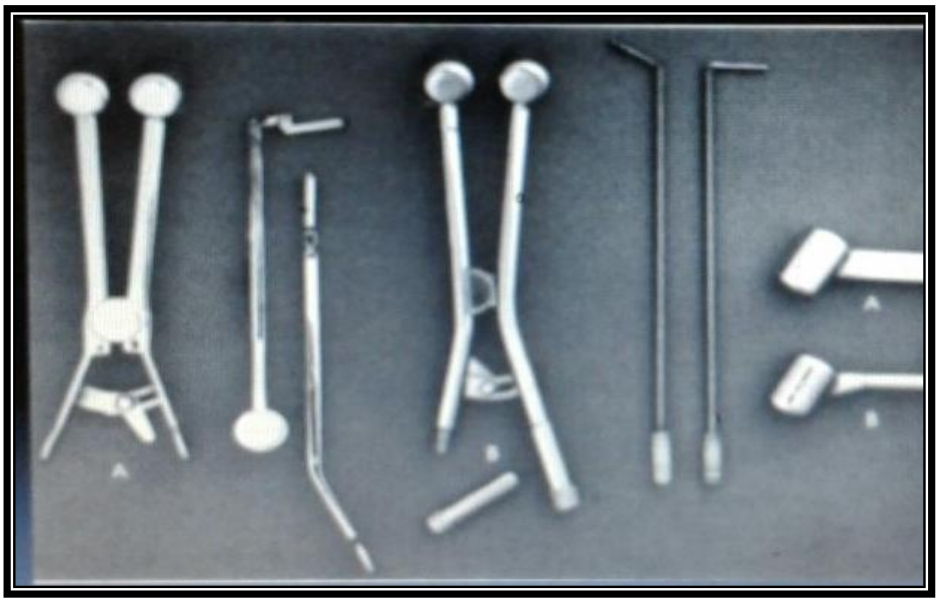
2) reduced radiation exposure of medical personnel,

3) no major anatomy changes during treatment,

4) no overnight nursing and resultant daycare-based treatment required,

5) use of a single-stepping source to allow optimisation of dose distribution by varying the dwell time at each dwell position

AFTERLOADED FLETCHER APPLICATORS



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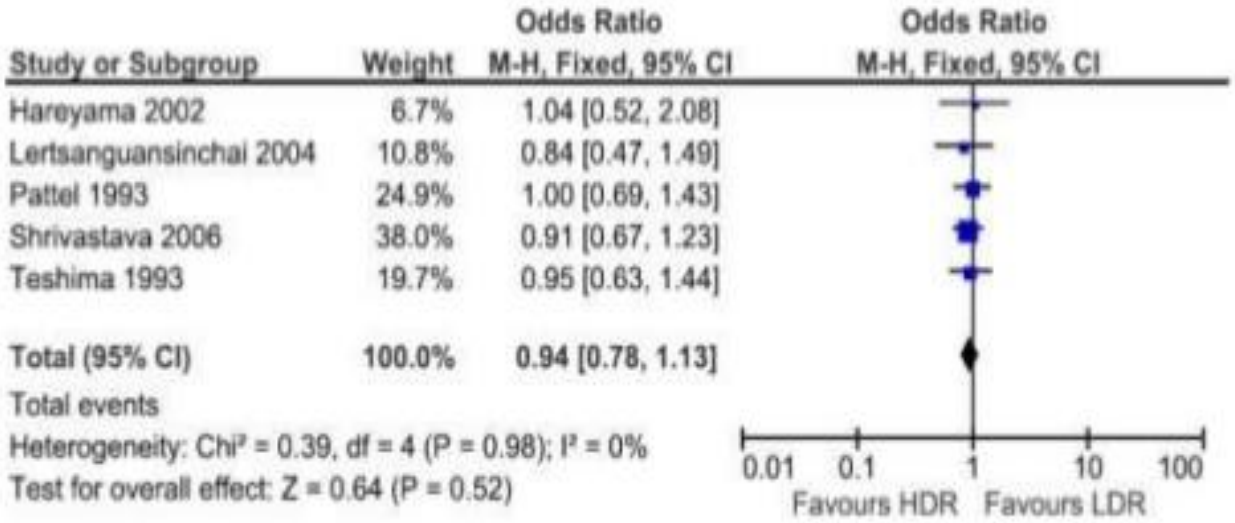
The Fletcher Suite Delchos applicator

The cochrane review done on LDR versus HDR brachytherapy showed that both the modalities were similar in outcomes ,however,due to some potential advantages of HDR-ICBT, such as rigid immobilization, outpatient treatment, patient convenience, accuracy of source and applicator positioning, individualized treatment with source optimisation and complete radiation protection for personnel,they suggest that HDR-ICBT may be preferred over LDR-ICBT. This review showed that HDR-ICBT was comparable with LDR-ICBT and there was no significant difference between HDR and LDR when considering Overall survival, Disease specific survival, relapse-free survival, local control rate, recurrence and metastasis and treatment related to complications for patients with clinical stages I, II and III. Therefore we recommend the use of HDR for all clinical stages of uterine cervix cancer.[13].

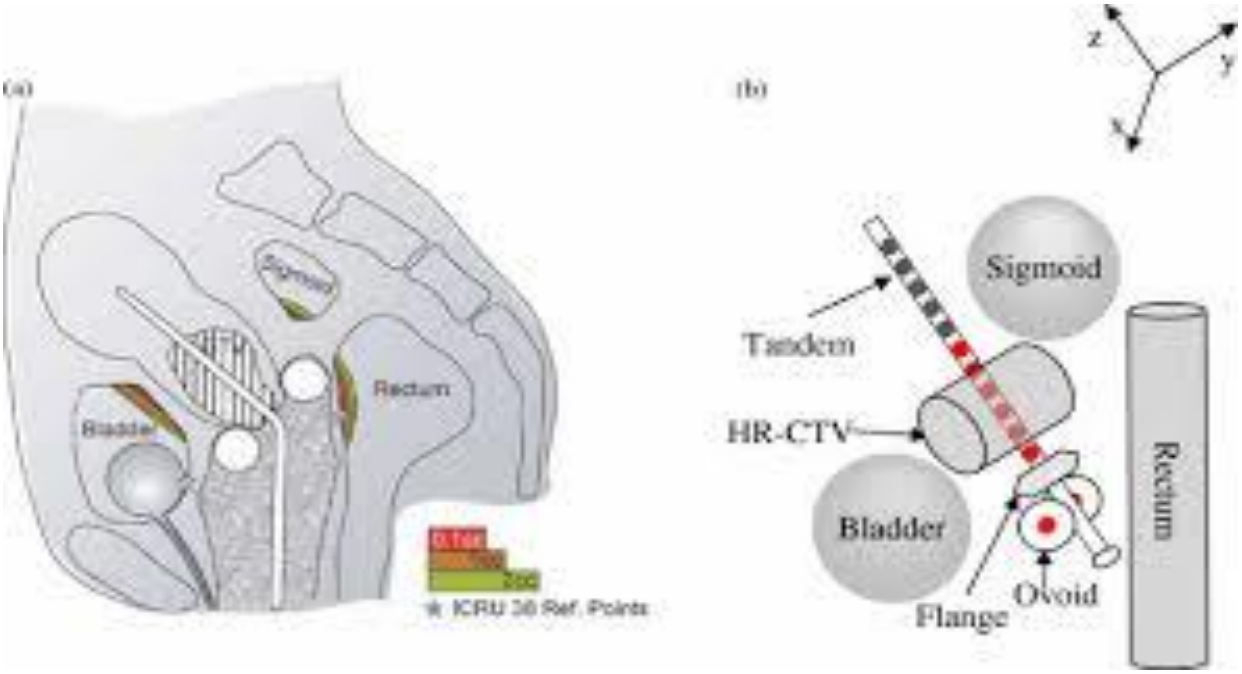
TRIALS COMPARING LDR AND HDR BRACHYTHERAPY



DEVELOPMENT OF IMAGE GUIDE BRACHYTHERAPY

Historically, treatment planning has been performed using 2-dimensional techniques with the dose prescribed to a modification of the classical Manchester system point A for target coverage and specified points for normal tissues on conventional radiographs. This technique follows a "one-size-fits-all" approach and does not allow for individualized dose distribution based on patient-specific factors. Three-dimensional IGBT allows a practitioner to modify dose distributions based on a patient's individual anatomy and tumor response, typically using CT and/or MRI.[14,15,16].

SCHEMATIC REPRESENTATION OF TARGETS IN ICRU 38 BASED PLANNING AND IMAGE GUIDED BRACHYTHERAPY



Several centers have compared 2-dimensional vs. 3-dimensional planning in dosimetric studies and have shown improved cervical tumor coverage and decreased dose to critical normal tissues with 3-dimensional planning.[17] One study from the University of Alabama, Birmingham, revealed that prescription to point A allowed for excellent GTV coverage for earlier stage tumors, but overestimated tumor coverage in more locally advanced cases (IB1 98.5%, IB2 89.5%, IIB 79.5%, and IIIB 59.5%).[18]. Other prospective studies from MD Anderson, Korea and Vienna have shown that standard specified normal tissue points (defined by ICRU 38) can underestimate the dose to the OAR.[19]. These studies have also helped to obtain valuable correlative data on normal tissue dose and long-term toxicity to better define appropriate and clinically relevant normal tissue constraints with modern IGBT .

UNIVERSITY OF ALABAMA,BRIMINGHAM

	IB1	IB2	IIB	IIIB
TARGET COVERAGE	98.5%	89.5%	79.5%	59.5%

Other potential advantages of 3-dimensional-based planning include

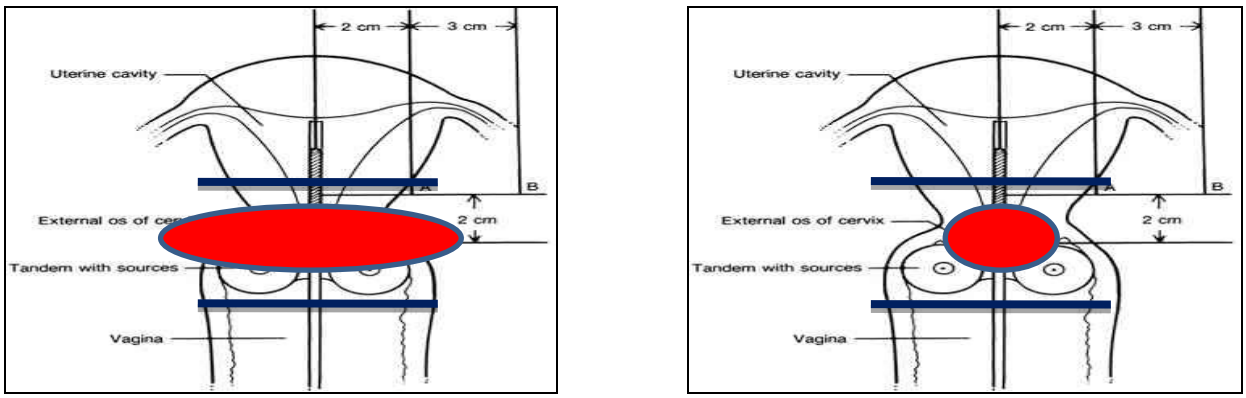
(1) verification of tandem placement in the uterine cavity and decreasing the risk of treating a patient with a uterine perforation;

(2) a better understanding of the doses delivered to other normal tissues at risk, especially the small bowel, and the potential to spare dose to these organs

(3) the ability to use more combined intracavitary/interstitial techniques (Vienna applicator) for locally advanced disease to achieve better coverage of gross disease while sparing normal tissue; and

(4) optimized target coverage and normal tissue dose with adaptive replanning based on tumor response.[20,21]

POINT A BASED PLAN-TUMOUR COVERAGE

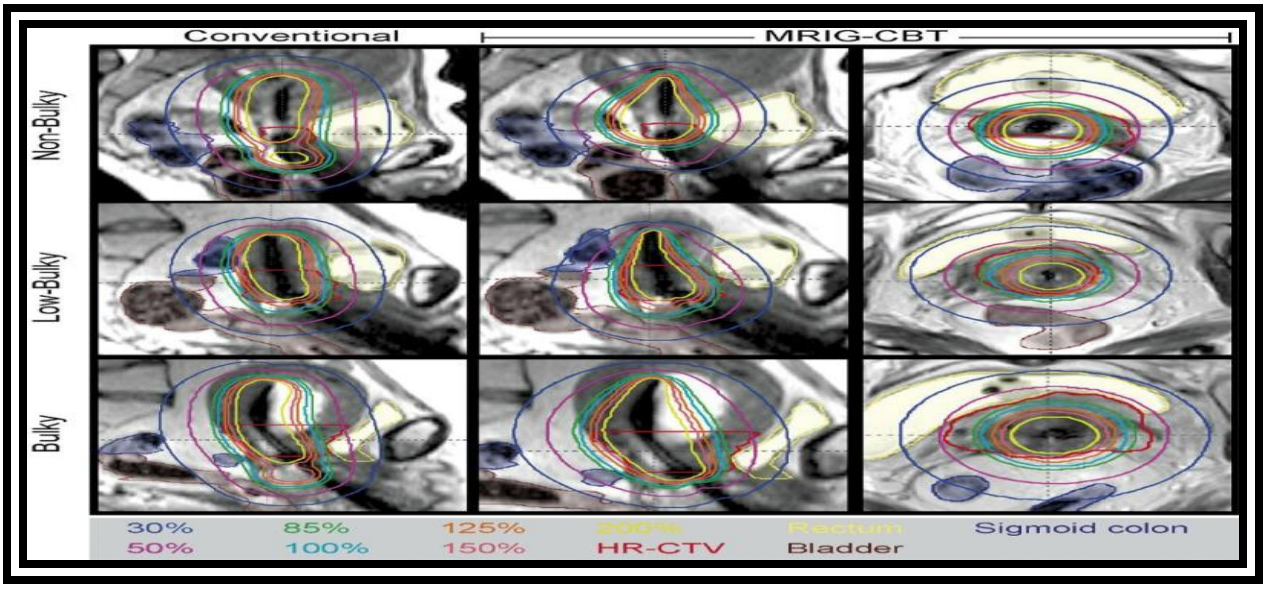


Undercoverage of large volume tumour in point A based planning.

Planning studies have shown that MRI-based IGBT significantly improves target coverage (particularly in larger tumors > 31 cc) and reduces OAR dose compared to standard planning to point A [22, 23].

The Vienna group reported their series of MRI-planned brachytherapy patients (treated from 2001-2003) compared to conventional brachytherapy prescribed to point A (treated from 1998-2000) [24]. They showed an increase in the mean D90, which was 81 Gy during the first period and 90 Gy during the second period ($p = 0.0007$). Overall survival (OS) at 3 years was increased for tumors > 5 cm from 28% in the first period to 58% in the second period ($p = 0.003$). For tumors 2-5 cm, there was no significant difference. Therefore, the increased dose delivered has greater benefits in bulkier tumors but there will still be benefits of IGBT over conventional brachytherapy (CBT) in smaller tumors such as lower doses to OAR. The grade 3 or 4 late morbidity rate at 3 years was 10% in the first period and 2% in the second period.

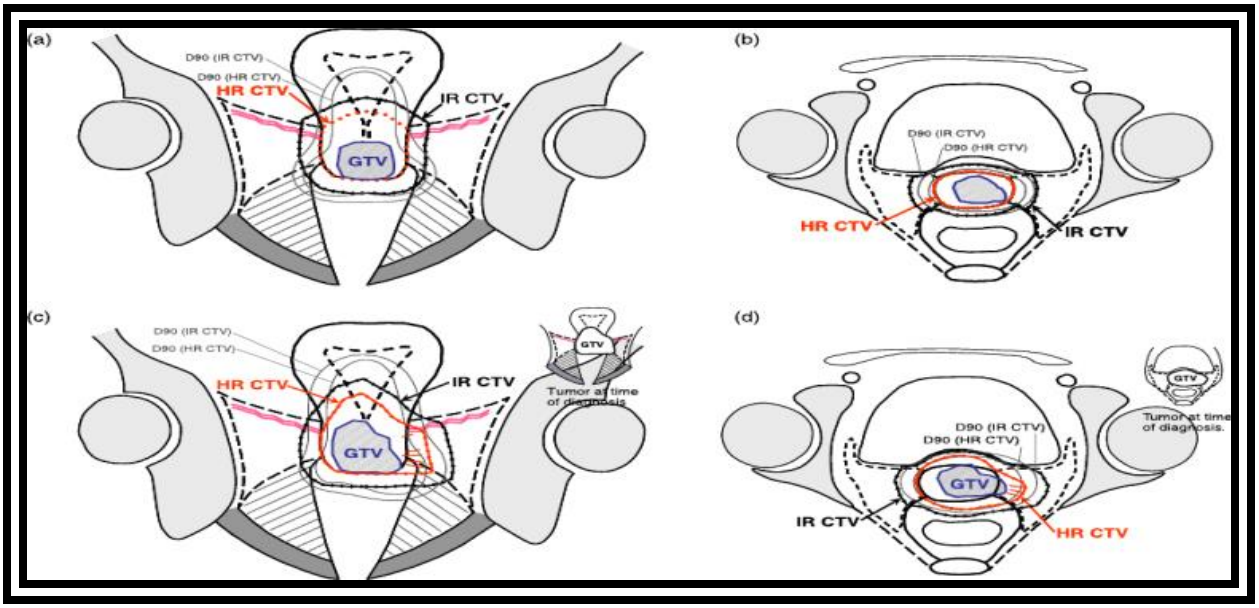
BENEFITS OF IMAGE GUIDED BRACHYTHERAPY



The shape of the isodose curve modified based on the residual disease

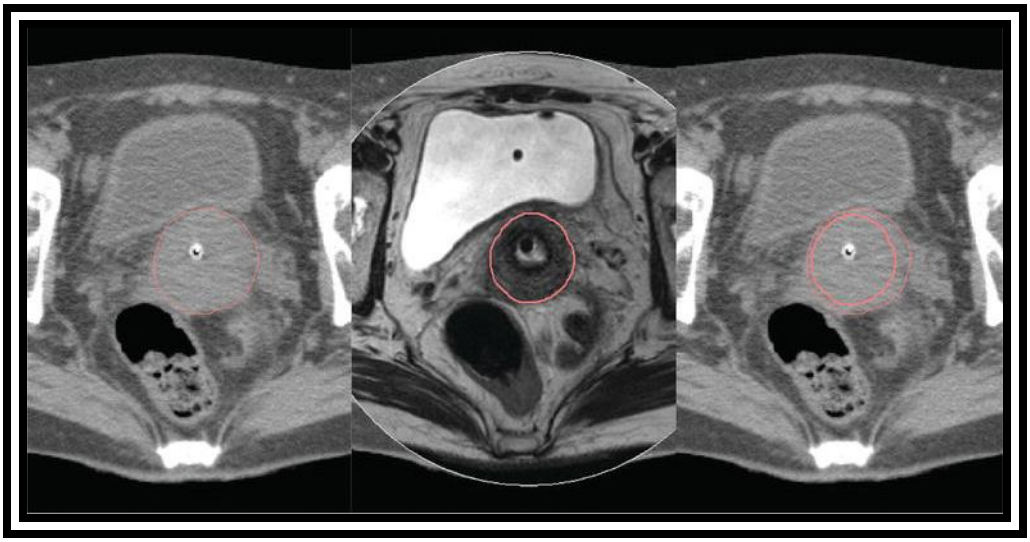
The Danish group from Aarhus used 99 patients treated in the NOCECA study (EBRT with a simultaneous integrated boost and pulsed-dose-rate BT planned on X-ray imaging) as historical controls, and compared them to their first 5-year experience of IGBT (140 patients from 2005) [25]. The IGBT period used MRI scans with applicators in situ for each implant. Overall survival (OS) was significantly improved with IGBT (63% to 79%, p = 0.005). It should be noted that concurrent chemotherapy was not given to patients in NOCECA but was given to 79% of patients treated in the IGBT era, and therefore will account for some of the improvement in OS. However, the use of concomitant chemotherapy has been associated with increased toxicity and yet moderate to severe toxicity was reduced by 50% (p = 0.02) in the IGBT group [26].

TARGETS IN IMAGE GUIDED BRACHYTHERAPY



The GEC-ESTRO guidelines [27] were devised for MRI based IGBT. However, not all institutions have the resources to provide MRI-based brachytherapy planning for each fraction. Therefore, many institutions use other imaging modalities such as CT and/or US in combination with MRI. In a survey of American Brachytherapy Society members in 2014, 95% of respondents always use CT and 34% always use MRI (an increase from 2% in 2007) [28].

CT AND MRI IN DELINEATING HRCTV



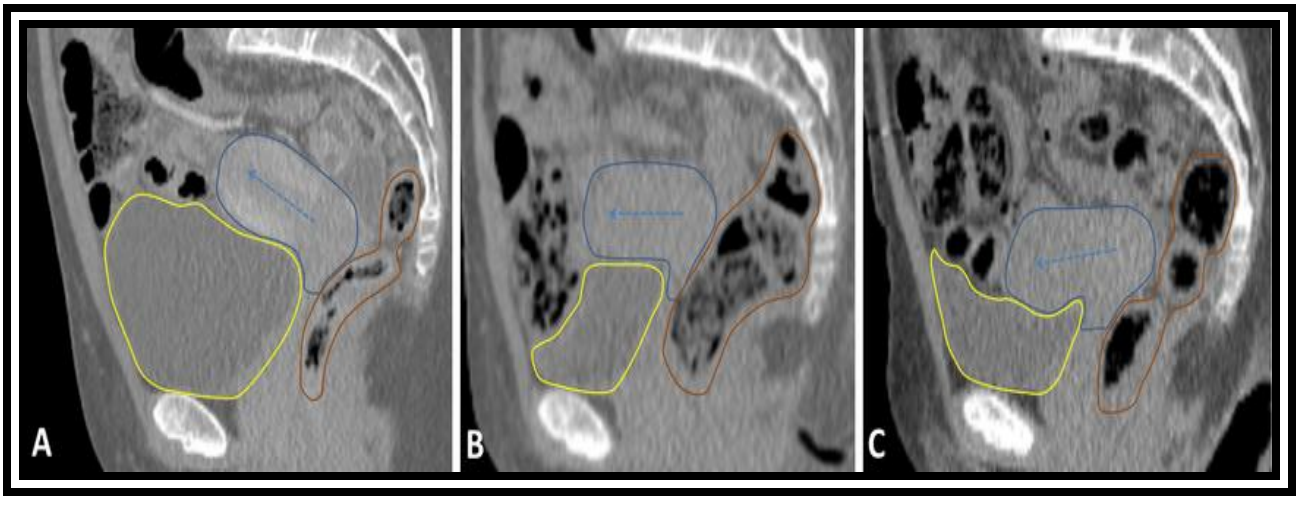
A smaller HRCTV with MRI guided brachytherapy planning

The first report of a hybrid technique using MRI with applicators in situ for the first fraction and CT for subsequent fractions was in 2011. The 2-year local control rate was 88%, DFS 85%, and OS 86% [29]. Choong et al. [30] have

reported results comparing this hybrid technique with IGBT planning based on MRI at each fraction, and showed that the 3-year local control and survival rates were similar. The dosimetry achieved and late toxicity were also similar between the two groups.

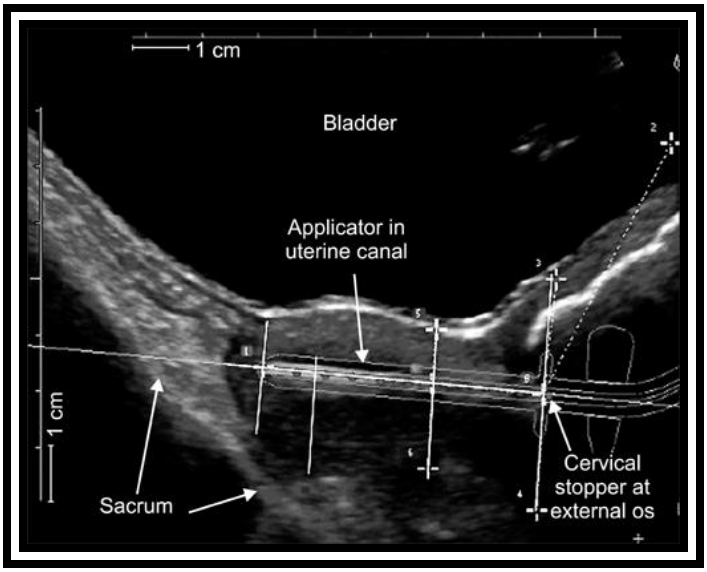
Computed tomography-based tumor contours have been shown to over-estimate tumor width [31, 32], which can lead to reductions in D90 and D100 . However, Eskander et al. [33] showed that delineation of OAR on both MRI and CT gave similar DVH parameters except for D2cc for bladder, which was higher when outlined on CT than MRI. Therefore, any overestimation of CTV and OAR contours on CT seems to have little clinical significance.

ORGAN AT RISK DELINEATION IN CT



Magnetic resonance imaging with applicators in situ has also been used to pre-plan brachytherapy [34]. Patients had the applicators inserted in the radiology department and had an MRI scan prior to fractions 1 and 4. The applicators were then removed and the patients returned on a subsequent day for re-insertion and treatment. When compared to conventional planning to point A, pre-planning on MRI increased the target dose (5.3 Gy compared to 4.5 Gy) and significantly reduced bladder and rectal maximum doses. However, the disadvantage is that patients require more insertional procedures and the reproducibility of inserted applicators needs to be validated. Alternatively, if resources are limited, a standard pre-brachytherapy MRI (without applicators in situ) can be obtained to evaluate tumor shrinkage and to increase the accuracy of HR-CTV contouring on the CT with applicator in situ [35].

ULTRASOUND GUIDANCE IN CONFORMAL BRACHYTHERAPY



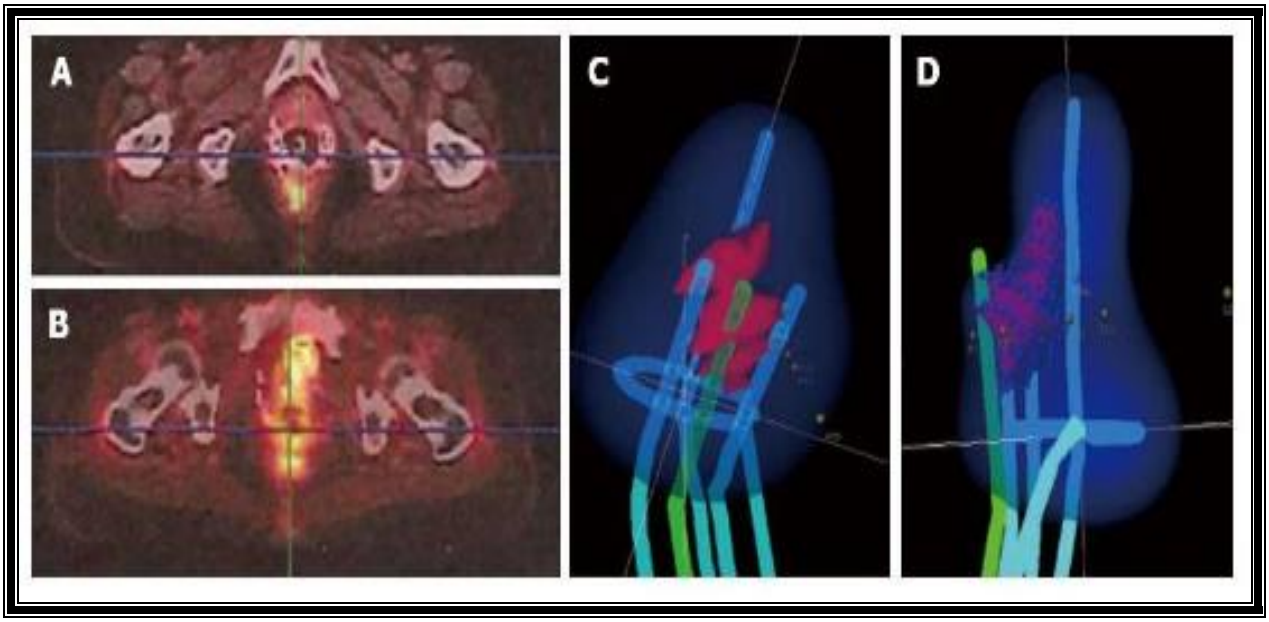
An alternative method is US planning, which is used in Melbourne [36]. Ultrasound and MRI are performed at the first fraction with applicator in situ to ensure the differences in measurements of the cervix and uterus are within acceptable limits [37]. For subsequent fractions, US was used to reproduce the position of the tandem in the uterus and the uterus in the pelvis. 5-year local control was 87.5%, which is comparable to results achieved in MRI-based IGBT studies . Transcervical US planning has also been shown to be feasible and accurate, based on comparison with a post-insertion MRI [38] . Ultrasound is potentially more cost effective and therefore may be a more feasible option in less developed countries where incidence of cervical cancer is greater.

For these reasons, whilst MRI scanning with applicators in situ for each fraction of IGBT is the gold standard, hybrid techniques with CT or US can give similar results in terms of survival outcome and toxicity rates.

Newer imaging modalities such as PETCT is also used in planning brachythetrapy.Olsen et al[39] recently reported on a comparative evaluation of PET-CT and MRI. Functional images were compared to the diffusion weighed images in MRI and the concordance of two functional imaging techniques and observed a good correlation of functional imaging between FDG-PET and DWI for cervical cancer. Areas with increased density in MRI had higher metabolic activity in PETCT and they concluded that with the availability of PET-MRI in clinics, it

could be expected that in near future the IGABT could be based not just on anatomic imaging as evident on MRI or CT, but on an anato-metabolic-imaging using PET- CT/MRI.

PETCT BASED TREATMENT PLANNING WITH APPLICATOR INSITU

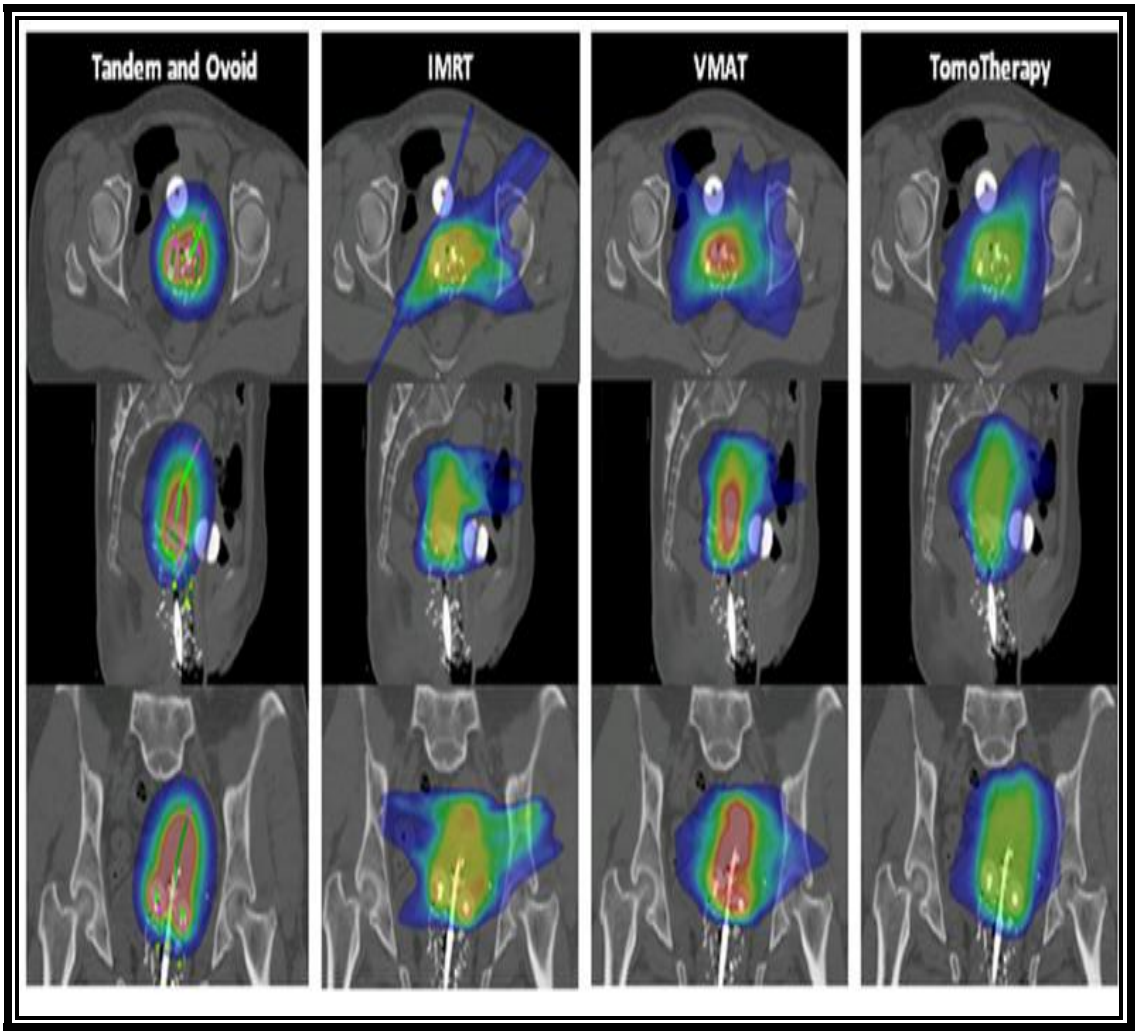


IMPACT OF BRACHYTHERAPY IN CURE OF CERVICAL CANCER

Brachytherapy has been an essential component in the successful treatment of cervical cancer for more than 100 years. When 25-MV photon beams became available in the 1970s, investigators seeking to exploit the new technology in stage IIIB patients explored the use of shrinking EBRT fields to deliver central doses of

60-70 Gy; brachytherapy was markedly reduced or even eliminated (40). This apparently logical approach resulted in significantly poorer survival rates (and higher complication rates) than treatments that emphasized brachytherapy.

CONFORMITY ACHIEVED WITH DIFFERENT TECHNIQUES



Brachytherapy offers the highest degree of conformity

Although it took years to recognize the inferiority of this approach, it was eventually abandoned . Patterns of Care studies (PCS) from the 1970s also consistently demonstrated significantly worse outcomes when brachytherapy was not used (41). Despite this evidence, PCSs from the 1990s demonstrated a disturbing failure of cervical cancer treatments to meet guidelines for optimal treatment with an unacceptably high proportion of patients treated using EBRT only (42). This trend persists in the most recent PCS from 2005 to 2007, where nonacademic centers, in particular, failed to consistently use brachytherapy (43).

Data from the US Patterns of Care Study in 1973 and 1978 showed that the combined use of intracavitary brachytherapy and external beam radiotherapy (EBRT) lead to a 4 year in-field failure rate of 17% compared to 47% without brachytherapy ($p < 0.001$), and a 4 year survival of 70% compared to 37% ($p < 0.001$) for all stages of disease [44]. Similarly, Montana et al. showed an improvement in disease free survival (DFS) at 2 years from 36% for EBRT alone to 61% with the addition of brachytherapy and a reduction in failure rates within the volume of irradiated tissue from 60% to 48% in stage III disease [45].

The improved survival benefit and complete response rate with different modalities of treatment for cervical cancer as published by Shantha et al,in a paper

tiltled the evolution in management of locally advanced cervical carcinoma,analysed the data of 3892 cervical cancer patients between the year 19990-1999 ,and showed that brachytherapy provided superior survival benefit and disease control.[46].

5,10 AND 15 YEAR SURVIVAL RATE

Table 3. Disease Free Survival % by Modality of Treatment and Stage for Locally Advanced Cervical Cancer Cases in Chennai Treated During 1990-1999

Modality of treatment	Stage	Cases		Disease free survival%		
		Number	%	5-year	10-year	15-year
External Beam RT (EBRT) only		1371	35.2	37	29	24
	IIB	414	30.2	49	39	32
	III	871	63.5	32	26	21
	IVA	86	6.3	23	20	20
Concurrent chemoradiation (CCRT) (EBRT+chemotherapy)		386	9.9	41	35	31
	IIB	168	43.5	50	44	38
	III	218	56.5	34	28	26
EBRT+Brachytherapy		1990	51.1	58	48	42
	IIB	1028	51.7	61	51	44
	III	954	47.9	54	45	40
	IVA	8	0.4	50	-	-
CCRT + Brachytherapy		78	2.0	69	69	63
	IIB	45	57.7	77	77	67
	III	33	42.3	58	58	58
EBRT+Surgery (Salvage)		67	1.7	71	63	63
	IIB	62	92.5	74	65	65
	IIIB	5	7.5	40	-	-
All modalities together						
	IIB	1717	44.1	58	49	42
	III	2081	53.5	43	35	31
	IVA	94	2.4	25	22	22
All modalities and stages together	IIB-IVA	3892	100.0	49	41	36

Picture curtosy:Shantha et al,asia pacific journal of cancer prevention

A comparison on 5year,10 year and 15 year survival revealed that the arm which received concurrent chemoradiation along with brachytherapy had the best outcome,which was more than the only radiation and brachytherapy arm and significantly higher than the concurrent chemoradiation arm without brachytherapy,thus proving that brachytherapy is not optional.[46].

COMPLETE RESPONSE RATE AND RECURRENCE RATE

Table 4. Complete Response and Recurrence Pattern by Modality of Treatment and Stage of Locally Advanced Cervical Cancer in Chennai, 1990-99

Treatment modality	Stage	Total number of cases	Complete response (CR)		Recurrence (out of CR cases)	
			Number	%	Number	%
External Beam RT (EBRT) only		1371	876	63.9	155	17.7
	IIB	414	318	76.8	43	13.5
	III	871	522	59.9	106	20.3
	IVA	86	36	41.9	6	16.7
Concurrent chemo-radiation (CCRT) (EBRT + chemotherapy)		386	252	65.3	52	20.6
	IIB	168	125	74.4	31	24.8
	III	218	127	58.3	21	16.5
EBRT + Brachytherapy		1990	1373	69.0	178	13.0
	IIB	1028	828	80.5	101	12.2
	III	954	541	56.7	77	14.2
	IVA	8	4	50.0	0	0.0
CCRT + Brachytherapy		78	64	82.1	5	7.8
	IIB	45	40	88.9	3	7.5
	III	33	24	72.7	2	8.3
RT + Surgery (Salvage)		67	52	77.6	5	9.6
	IIB	62	48	77.4	4	8.3
	IIIB	5	4	80.0	1	25.0
All modalities and stages together	IIB-IVA	3892	2617	67.2	395	15.1

A similar outcome in complete response rate and recurrence pattern was also observed, the arm which received concurrent chemoradiation along with brachytherapy had the highest complete response rate and the lowest recurrence rate when compared to the only radiation and brachytherapy arm and the concurrent chemoradiation arm without brachytherapy arm.[46].

Several studies have compared the dosimetry of Intensity modulated radiation therapy and SBRT as an alternative to brachytherapy[47]. .But ,the dose constraints to organs at risk are not achienable if D2cc is compared.Other potential disadvantages with these external beam techniques are that ,

1)Although the dose distribution is homogenous with external beam boost techniques ,the high dose delivered to tumour area next to applicator(central dose) achieved with brachyttherpy cannot be reproduced with external beam techniques

2)Radiobiologically, hypofractionationed schedule as in brachytherapy should be reproducible with external beam techniques, maintaining the tumour control probability (TCP) and the normal tissue complication probability (NTCP) .

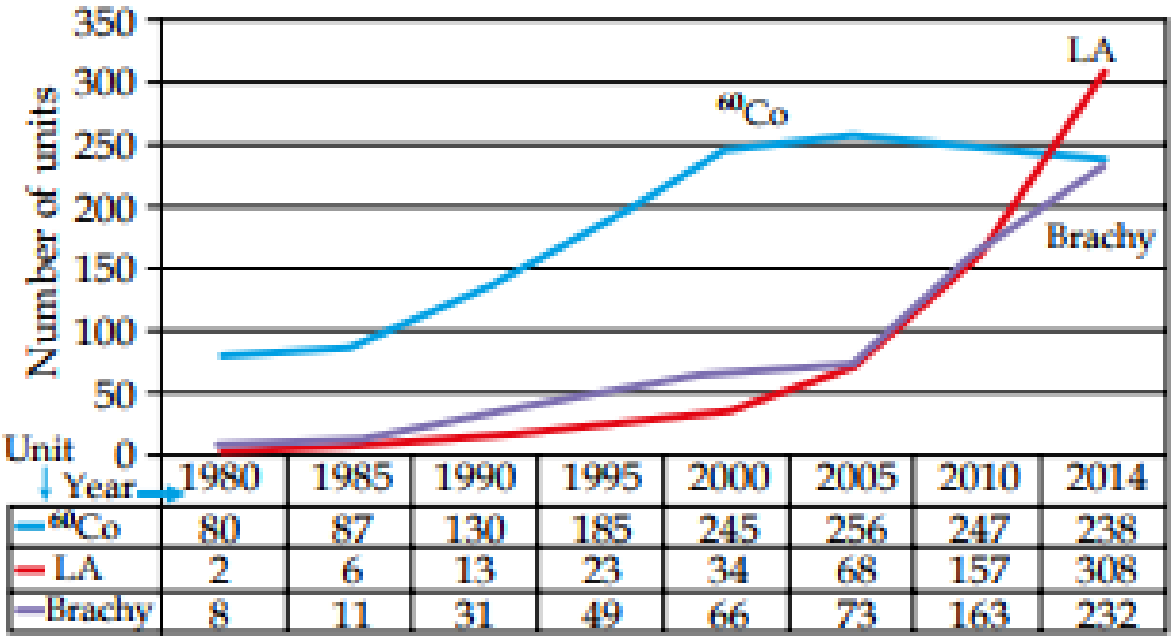
3)The margin to target volume due to internal target motion and the need for strict immobilisationa and to track the target continuously with external beam boost techniques.Hence sophisticated external beam techniques may be considered in patients who are not fit for brachytherapy and cannot be considered a replacement.

INTERNATIONAL SCENARIO OF BRACHYTHERAPY AVAILABILITY

Country	Manual LDR	Auto remote LDR	HDR			brtx-cap	brtx-cap per million population	brtx-cap per cervical cancer
			Co HDR	Ir HDR	HDR total			
Australia	3	11	na	12	12	7030	374.9	6.66
Bangladesh	3	1	2	2	4	2230	17.9	0.23
China	171	na	na	30[b]	302	159550	127.1	6.46
India	81	35	4	24	28	20850	21.5	0.24
Indonesia	2	6	3	2	5	3080	15.1	0.27
Japan	2[b]	8	187[c]	74	198	99740	789.0	11.67
Korea, Rep.	3	10	3[b]	4[b]	30	15950	343.5	2.68
Malaysia	15	2	1	6[b]	9	5410	257.6	6.10
Mongolia	na	1	1	0	1	580	241.7	16.57
Myanmar	9	0	0	0	0	450	10.1	0.12
New Zealand	15	2	na	1	1	1410	372.0	5.51
Pakistan	5	4	5	1	6	3570	27.3	3.29
Philippines	1	0	na	na	2	1050	14.0	0.24
Singapore	na	1	0	3	3	1580	408.3	8.02
Sn Lanka	0	0	1	1	2	1000	53.3	0.49
Thailand	1	13	2	8	10	6090	99.5	1.16
Viet Nam	5	8	1	0	1	1390	17.9	0.36

This evidence suggests that ,worldwide,the number of brachytherapy units available when compared to the teletherapy units is less and the difference is more so in developing countries.A similar pattern is observed with the availability of treatment planning system aswel. There is a need for the radiotherapy centres which do not have the facilities for brachytherapy ,to refer their patients to a higher centre.With the available infrastructure and patient load at centres with brachytherapy availability, execution of image guided brachytherapy ,may not be feasible for every case.Hence the need to identify the subgroup with maximal benefit with IGBT.[48].

NATIONAL SCENARIO OF BRACHYTHERAPY AAILABILITY



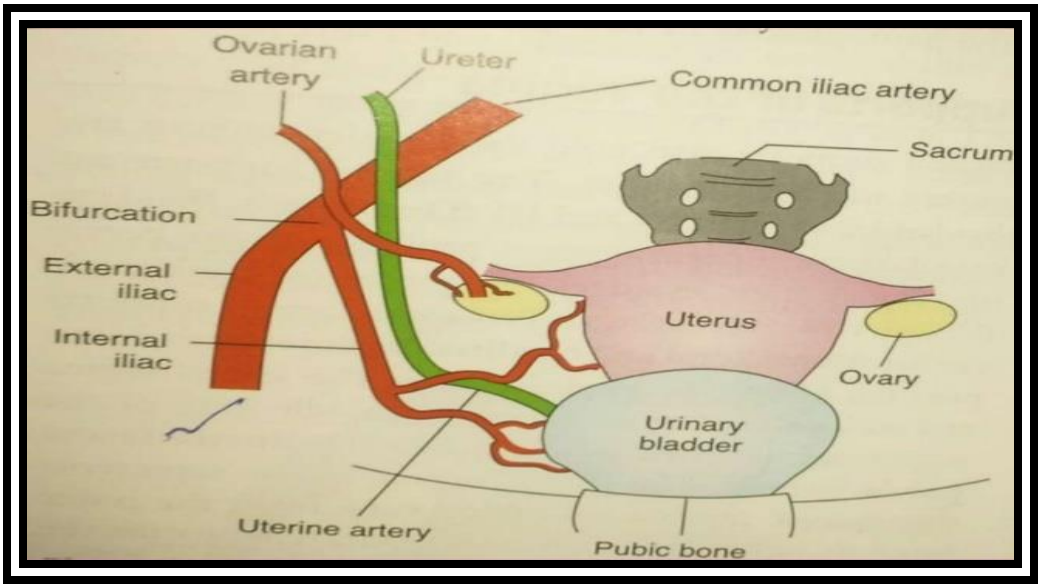
Unit ↓ Year →	1980	1985	1990	1995	2000	2005	2010	2014
^{60}Co	80	87	130	185	245	256	247	238
LA	2	6	13	23	34	68	157	308
Brachy	8	11	31	49	66	73	163	232

Fig. 1. Increase in the number of radiotherapy units in India

In India, there is a steady increase in availability of brachytherapy units. But,despite the increase in number of brachytherapy units,there is still an existing demand for more number of brachytherapy units. The latest developments in brachytherapy such as incorporation of newer imaging modalities (MR, PET), better brachytherapy applicators, powerful planning systems with a potential to improve the therapeutic ratio have been successfully implemented in clinical practice of the developed world. However, their implementation and wide practise across the bulk of centres in India will be a major challenge .[49].

POINT A DOSIMETRY

Point where ureter crosses uterine artery-Dose limiting Point



The origin of Point A dates back to the Manchester system and was defined by Tod and Meredith in a paper that detailed the nature and course of radiation necrosis following radium-based brachytherapy. They noted that, following radiation, there was necrosis at the paracervical vessels. They defined point A within this paracervical triangle (commonly thought of as where the ureter crosses the uterine artery) as a point of limiting tolerance.

The International Commission on Radiation Measurements and Units published the ICRU report 38 in the year 1985 regarding the Dose and volume specification as well as reporting of intracavitary brachytherapy in gynecology. For a uniform reporting of brachytherapy application, ,the following dose specifications were advised to be reported.[50].

1)Complete description of the technique

2)Complete description of the Time-dose pattern

3)Treatment prescription

4)Total Reference Air Kerma

5)Dose description

-Prescription points/surface

-Reference dose in central plane

-Mean central/Peripheral dose

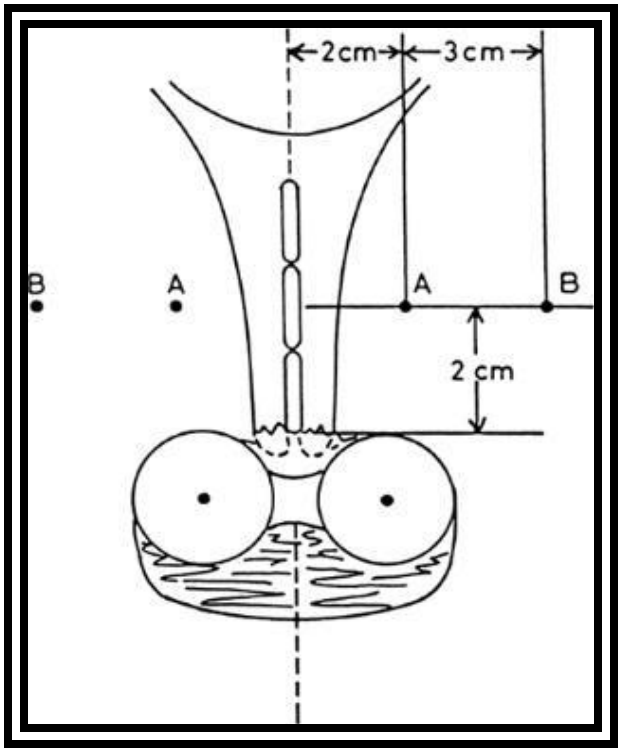
6)VolumeTreated/Point A/Reference volume

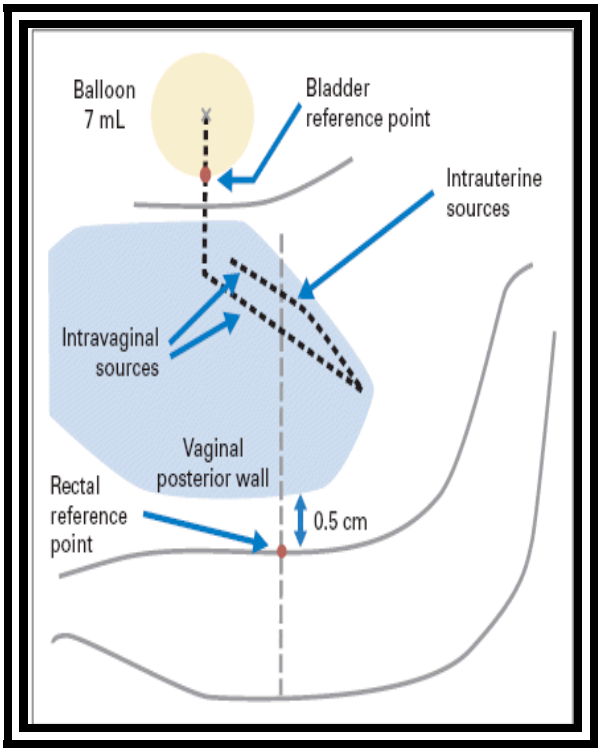
7)Dose to organs at risk-Bladder/Rectum

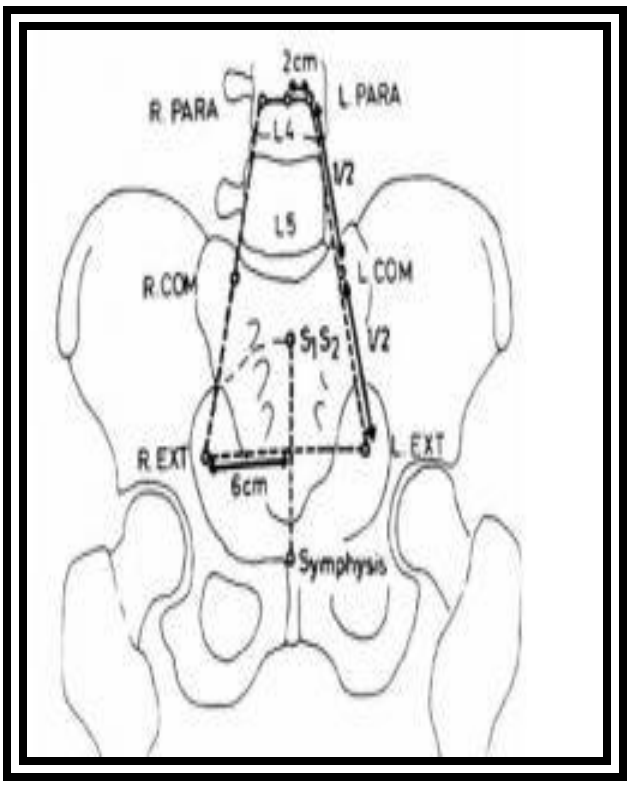
Prescription Points

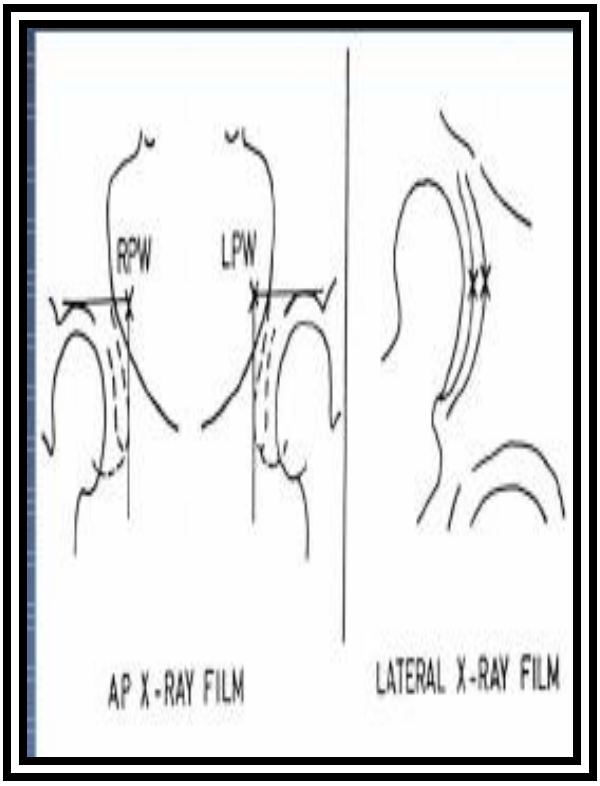
Point A	ICRU Rectal point
Point B	Lymphatic trapezoid of fletcher
ICRU Bladder point	Pelvic wall point

SURROGATE POINTS MENTIONED IN ICRU 38 REPORT









A.**PointA/B B.Bladder/Rectal point C.Trapezoid 4.Pelvic wall point**

DEFINITION OF SURROGATE POINTS

Point A (Dose limiting point)	2cm lateral to and 2cm superior from the external cervical os in a plane perpendicular to the uterine canal(Tandem)
Point B (Dose to obturator nodes)	5cm lateral to the patients midline and 2cm superior from the external cerical os
ICRU Bladder Point	On the lateral radiograph,,AP line drawn through the centre of a 7cc balloon,on the posterior surface of the blloon .On AP radiograph located in the centre of the balloon
ICRU Rectal Point	On the lateral radiograph,located on an AP line drawn from the lower end of intrauterine source or middle of intravaginal source,point is located 5mm posterior to posterior vaginal wall,on AP film midpoint of colpostats

Lymphatic Trapezoid of Fletcher:

These are surrogate points which represents the dose to the paraaortic, common and external iliac nodes.

1)A line drawn from S1-S2 junction to the top of symphysis pubis

2)A line is drawn from midline of this line to the middle of anterior aspect of L4.

3)A point 2 cm from the L4 point on either side, gives the dose to lower paraaortic nodes

4)A point 6cm from the midline,on either side of the line drawn from S1-S2 to pubic symphysis

5)The dose to the common iliac is calculated on a point at midline ,on the line drawn between these two points

Pelvic wall point:

Represents the dose at the distal part of the parametrium and at the obturator lymph nodes

1)On AP radiograph,a horizontal line drawn through the highest point on acetabulum and a vertical line tangential to the medial surface of acetabulum

2)On lateral radiograph,the highest points of the right and left acetabulum

VOLUME BASED DOSIMETRY

The GEC-ESTRO group published the guideline for image based brachytherapy using MRI .The following target volumes was defined.[51].

GTV-D	GTV AT DIAGNOSIS	Macroscopic tumour extension at diagnosis as detected by clinical examination and visualization on MRI
GTV-B	GTV AT BRACHYTHERAPY	Macroscopic tumour extension at brachytherapy as detected by clinical examination and visualization on MRI
HRCTV	HRCTV AT BRACHYTHERAPY	Whole cervix,residue by clinical examination and MRI-T2 signal intensities
IRCTV	IRCTV AT BRACHYTHERAPY	Margin to HRCTV.Never less than GTV-D

DOSE PRESCRIPTION TO TARGET VOLUME –GEC ESTRO

HRCTV	**85Gy-EQD2**
IRCTV	**60Gy-EQD2**

DOSE REPORTING-GEC ESTRO

TARGET VOLUME-FOR GTV / HRCTV / IRCTV	D100- DOSE RECEIVED BY 100% VOLUME	D90- DOSE RECEIVED BY 90% VOLUME
ORGAN AT RISK	D0.1/1/2cc Bladder	D0.1/1/2cc Rectum
ICRU Point	Dose to Point A ICRU Bladder/Rectal Point	Time/Dose/Pattern

CT BASED CONTOURING GUIDELINES

Majority of the centres which practice brachytherapy,might have resource limitation to practice MRI guided brachytherapy and hence most centres use CT guided brachytherapy for planning.

A corresponding target volume(as in MRI) in CT based planning is defined and in CT based planning due to poor delineation between the uterus and the cervix,GTV cannot be defined.

Viswanathan et al ,have compared delineating Targets with CT and MRI . [52].

Comparison of contouring guidelines in locally advanced cervical cancer

Clinical Target Volume Contouring Guidelines for MR and CT	
MR (2005)[32]	Contour the whole cervix and the presumed extracervical tumor extension at time of BT. Tumor extension is defined by clinical examination (visualisation and palpation) and by MRI findings at time of brachytherapy (BT) taking into account tumor spread at diagnosis as indicated on clinical examination and initial MRI for staging. Pathologic residual tissue(s) as defined by palpable indurations and/or residual grey zones in parametria, uterine corpus, vagina or rectum and bladder on MR are included in HR CTV. No safety margins are added.
CT (2007)[20]	Contour entire cervix as seen on CT 1. Inferiorly, start contour at superior level of applicator. 2. Superiorly, contour to level at which uterine vessels first abut cervical tissue (if intravenous (IV) contrast administered) to point at which volume expands (indicating presence of uterine tissue), or to point at which uterine cavity appears. a. Add two slices of contour (with decreasing diameters) around tandem superiorly to cover conical cervical apex. b. Measure height of cervix to ensure adequate coverage (average height approximately 3 cm). Divide parametria into inner half and outer half. Contour parametria entire height of the cervix.
CT (2014, this manuscript)	1. Inferiorly at the level of the ring, contour tissue inside the central ring. For ovoids, contour tissue to the level of the ovoids. Add vaginal tissue adjacent to the ring if involved at the time of BT. 2. Superiorly, contour superiorly to the level where the uterus indents (internal os); draw the next 1 cm as a pointed shape (cone). The approximate dimension (height) of cervix should be 3 cm. 4. Laterally, parametrial extension should be included in the CT-CTV (and not a separate structure) if it appears "grey/ white" on the CT (i.e., a similar density to the cervix). There is no need to draw the parametrial region if it does not have stranding visible on the CT or it is not noted in the clinical drawing. IV Contrast is not mandated. 5. Take into account tumor present on clinical examination and MRI findings at time of BT if available. Disease extension on clinical exam and MRI at the time of diagnosis should be contoured in a low dose region (Intermediate Risk (IR)-CTV). 6. Pathologic residual tissue(s) identified in the uterus, vagina or rectum and bladder are included in the CT-CTV.

Table 1. Contouring recommendations for a computed tomography–based high-risk clinical target volume

Direction and tumor extension	Contouring recommendations
1. Caudal boundary	
(a) Vaginal invasion (−)	Contouring commences at the cervical tissue at the level of the tandem applicator fringe. The applicators are excluded, as are the vaginal packing material and vaginal vault.
(b) Vaginal invasion (+)	In addition to '1a', the residual vaginal tumor lesions at the time of brachytherapy are included.
2. Cranial boundary	
(a) Uterine corpus invasion (−)	Defined as the upper margin of the uterine cervix. Contouring starts at the junction of the uterine artery or isthmus. The upper border of the serosal side is enclosed at a level of 1 cm in the cranial direction in a cone-shaped contour, along with the uterine cavity.
(b) Uterine corpus invasion (+)	Defined as the upper border of the residual tumor (i.e. the abnormal signal intensity) as detected on MRI just before brachytherapy of the uterine corpus.
3. Lateral boundary	
(a) Parametrial invasion (−)	Consists of the border between the uterine tissue and surrounding adipose tissue at the time of brachytherapy. The intestinal tract, adnexa, ascites, and visible linear structures that run laterally (e.g. vessels, nerves and fibrous structures) are excluded.
(b) Parametrial invasion (+)	Consists of the border between the uterine tissue or residual tumor and the surrounding adipose tissue at the time of brachytherapy.
4. Posterior boundary	
(a) Rectum or sigmoid colon wall invasion (−)	Defined as the border between the uterine tissue or residual tumor, whichever is more posterior, and adipose tissue.
(b) Rectum or sigmoid colon wall invasion (+)	Invasion of the rectum or sigmoid colon that is evident at the time of brachytherapy is included. Tumor progression is determined by reviewing MR images. Other posterior boundary sites are managed as described in '4a'.
5. Anterior boundary	
(a) Bladder wall invasion (−)	Includes the border between the uterine tissue or residual tumor, whichever is more anterior, and the adipose tissue.
(b) Bladder wall invasion (+)	Any residual bladder-invading tumor tissue that is clearly evident at the time of brachytherapy is included. Tumor progression is determined by reviewing MR images. Other anterior boundary sites are managed as described in '5a'.
6. General	Clinical examination findings at the time of brachytherapy should be taken into account.

Choice of technique and applicator

Based on the response, residual disease and vaginal space, appropriate applicator is selected.

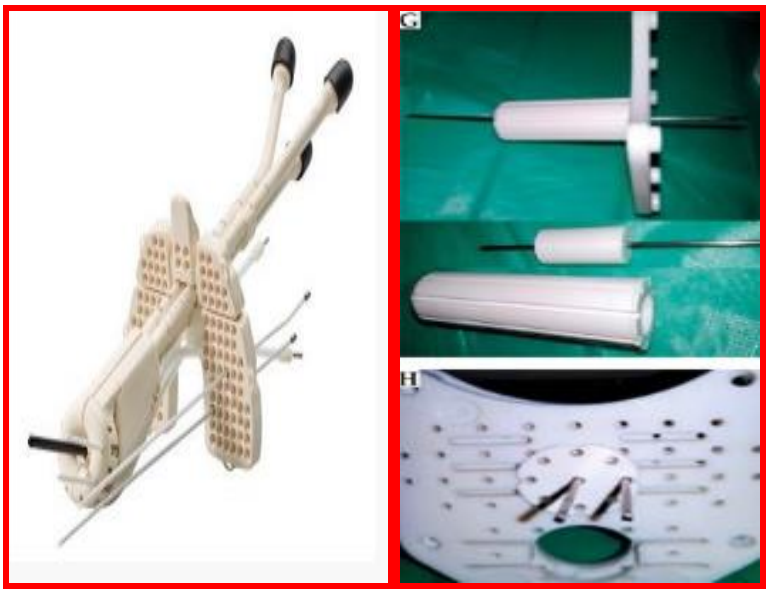
A tandem and ovoid/Fletcher – If vagina is spacious

Tandem and cylinder - For narrow vagina

Combined intracavitary and interstitial needles-VIENNA-If residue is on one side of pelvis/large volume residual disease.

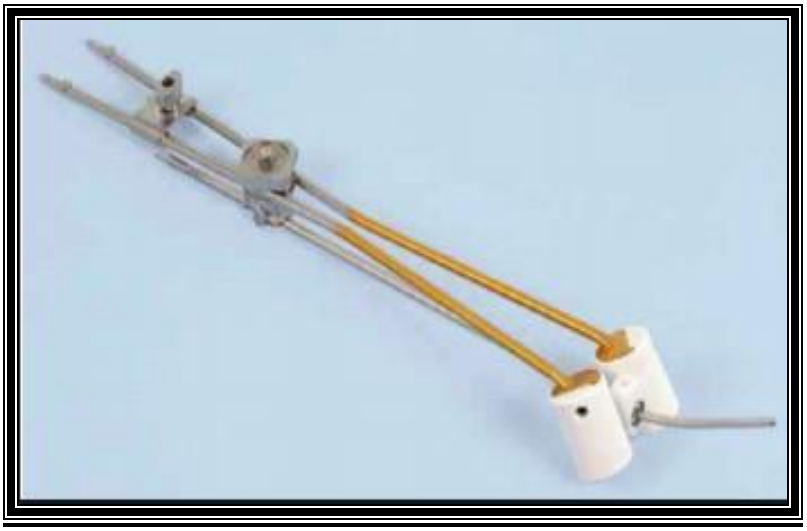
Newer applicators which permit combined intracavitary and interstitial permits its usage in patients with narrow vagina also

APPLICATORS USED IN BRACHYTHERAPY:



VENEZIA APPLICATOR

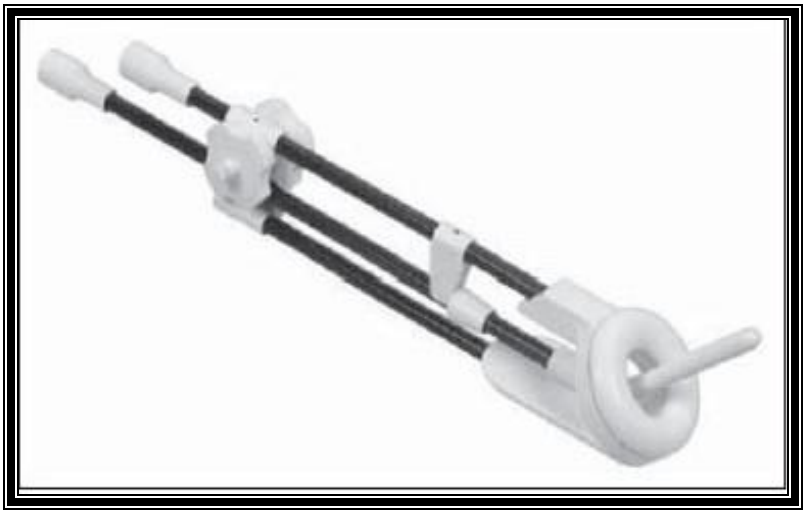
BENEDORM APPLICATOR



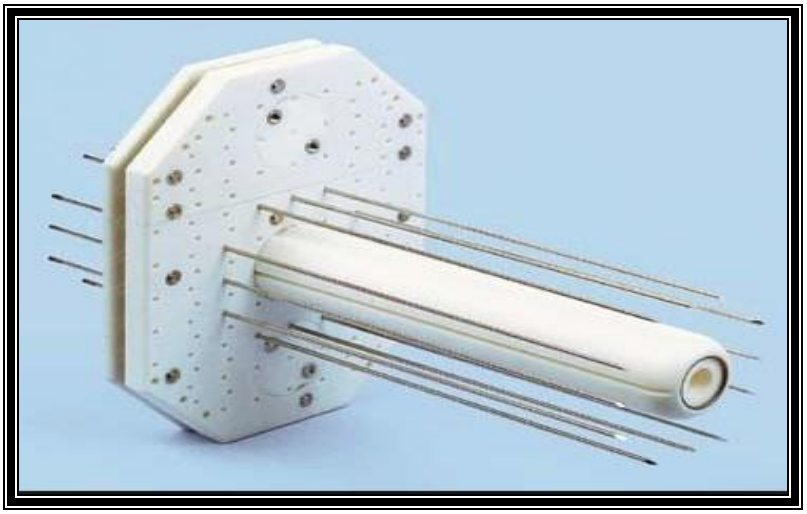
FLETCHER SUITE DELCHOS WITH RECTAL SHIELD

CT/MRI COMPATABLE FLETCHER APPLICATOR

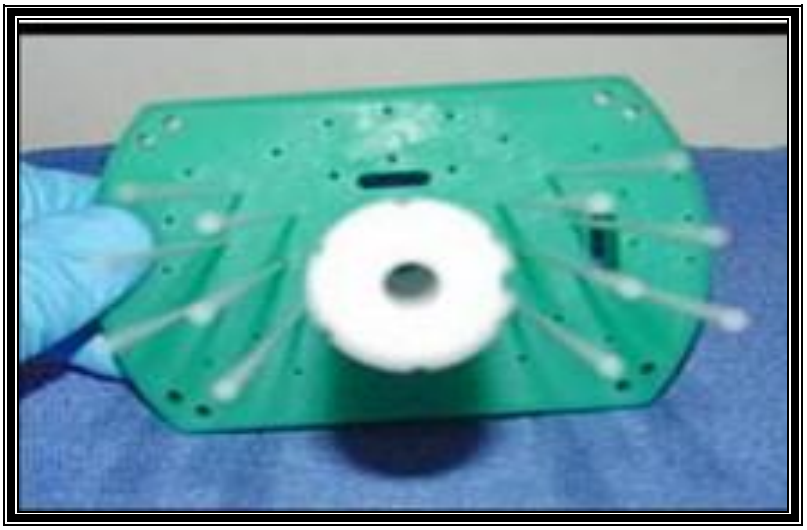
FLETCHER APPLICATOR WITH RECTAL RETRACTOR



VIENNA APPLICATOR



MUPIT APPLICATOR



SYED NEBLATE APPLICATOR

IDEAL APPLICATION

An ideal application should fulfill the following criteria

1)The geometry of the insertion must prevent underdosing around the cervix

2)Sufficient dose must be delivered to the paracervical area

3)Vaginal mucosal,bladder and rectal tolerance doses must be respected.

Optimisation

The various methods of optimization are

1) Dose Point Optimisation 2)Graphical optimization

3) Geometric optimization 4)IPSA 5) HIPO

In dose-point optimization, the desired dose at a number of dose points at a certain distance from the catheter are defined. The optimal set of dwell times is obtained using the least squares method. The sum of squares of the difference between the actual and prescribed dose at each dose point and the difference between the successive dwell times is minimized by setting the derivative of the objective function to each dwell time equal to zero .

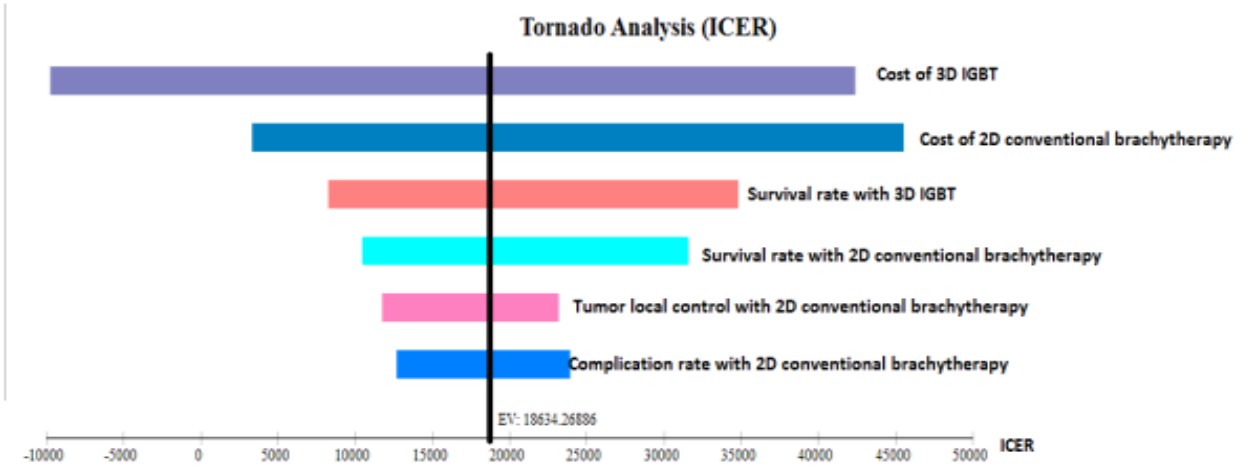
In geometric optimization, the dwell locations themselves act as dose points. The dwell time in a dwell location is inversely proportional to the sum of the inverse squares of the distances to the other dwell positions

Graphical optimization is the last method. In using graphical optimization, the isodose curves of the radiation plan the computer displays are changed manually with the mouse. Isodose curves are curves that indicate a similar radiation dose. After manual adjustment, the algorithm calculates the exact corresponding dwell times.

Inverse Planning Simulated Annealing optimization algorithm (IPSA), is an anatomy-based algorithm which optimizes the source dwell times using a simulated annealing algorithm, IPSA gives an acceptable conformal plan in a matter of seconds by providing the distribution of the dwell times within the catheters. However, the dwell times have an inhomogeneous distribution in which there are a number of dominating dwell times in particular positions within the catheter, usually at both ends, leaving the others with very small times or empty. This behavior could potentially lead to localized hot spots

HIPO is a hybrid inverse planning method that uses both a stochastic and a deterministic heuristic. The objective function is the weighted sum of objectives for different anatomical structures. Dose values for the target volume that are above or below a dose limit are penalized. For the critical organs and normal tissue, only the dose values above a dose limit are penalized. HIPO optimizes not only the dwell times of the dwell location in each catheter, but also the position of the catheters. In this respect, it differs from all other techniques.[53].

COST BENEFIT OF VOLUME BASED DOSIMETRY



ICER-Incremental cost benefit ratio

An analysis of cost effectiveness of image guided brachytherapy using MRI,CT was compared with conventional brachytherapy planning and concluded that image guided brachytherapy is cost effective as the benefits of higher local control and reduced morbidity with image guided brachytherapy offered the effectiveness for the cost spent.[54].

But, in developing countries,the cost involved in setting up image guided brachytherapy facility and treatment planning would incur a 15-25% more investment and considering the time involved in planning and patient load at brachytherapy treating centres, infrastructure, equipment, and human resources considerations, commissioning, training, and clinical implementation of brachytherapy IGBT would be a potential challenge to get implemented at all centres.[55].

LEARNING CURVE OF VOLUME BASED DOSIMETRY

In India,brachytherapy faces a number of challenges,many of the radiotherapy centres ion India lack dedicated operating theatres, anaesthetists, and equipment]. The patient to oncologist ratio in India is 1 per 16 000 cancer patients and there is a deficit of 2186 radiation oncologists, 1217 medical physicists, and 3787 radiotherapy technologists in India . Therefore, the chance of getting a personalised and individualised care such as brachytherapy remains a challenge in the less affluent centres. The latest developments in brachytherapy such as incorporation of newer imaging modalities , better brachytherapy applicators, powerful planning systems etc. with a potential to improve the therapeutic ratio have been successfully implemented in clinical practice of the developed world and the affluent centres of India. However, their implementation and wide practise across the bulk of centres in India will be a major challenge .Also, the status of training on brachytherapy in many of the teaching centres is suboptimal due to lack of advanced facilities. Hence, for most of the beginners pursuing training in radiotherapy in India and other developing countries, the knowledge on brachytherapy is theoretical, and practical experience on brachytherapy is lacking ,and hence the need and the challenge for learning and practicing the art of brachytherapy.[56].

AIM

To compare conventional point A based brachytherapy planning and conformal planning in patients with differential response to EBRT and to analyse if Point A based planning is non-inferior to IGBT.

OBJECTIVES

Primary Objective:

To compare and analyse the variations in dose to target volume and OAR in orthogonal ICRU 38 recommendation based planning versus CT based volumetric planning in patients with differential response to EBRT and to identify the subgroup of patients in whom point A based planning may be non-inferior to IGBT.

Secondary Objective:

To identify the subgroup in which IGBT offers maximal benefit in terms of Target coverage and therapeutic ratio.

METHODOLOGY

STUDY DESIGN:Prospective Dosimetric study

TYPE OF STUDY:Case series

STUDY PERIOD:March 2017-August 2017

NO OF PATIENTS:40(20 in Group A & 20 in Group B)

ELIGIBILITY CRITERIA:

Inclusion criteria:

Histologically proven Squamous cell carcinoma of the uterine cervix(Stage IB,IIA,IIB,IIIA,IIIB),treated with curative intent with initial EBRT of 45-50Gy using conventional/conformal technique,with or without concurrent chemotherapy.

Exclusion criteria:

Patients with stage IV disease were excluded

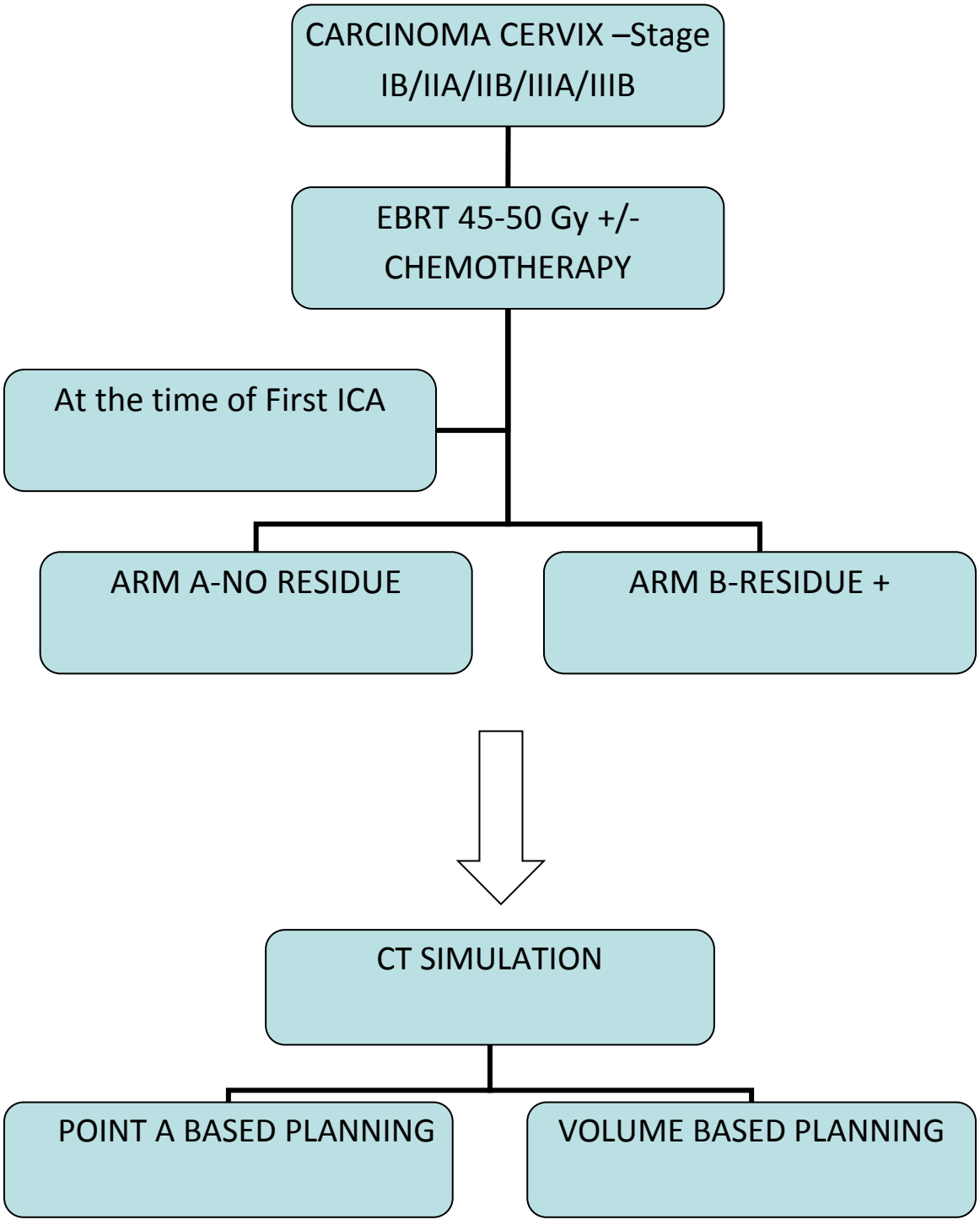
Patients with non squamous histologies were excluded

Patients with uterine anomalies were excluded

GENERAL PLAN OF TREATMENT:

All consecutive eligible patients of locally advanced carcinoma of uterine cervix ,who underwent initial radiation therapy with or without chemotherapy upto 45-50Gy,using conventional or conformal technique, at the time of first intracavitary/combined intracavitary and interstitial application , will be randomized to Arm A(with residue) or Arm B(No residue) based on their response to EBRT. A CT based brachytherapy plan will be generated based on both Point A dosimetry and Volume based dosimetry .

FLOW DIAGRAM OF PLAN:



PROCEDURE:

Initial Evaluation

After a thorough history taking patients undergo clinical examination with inspection ,per speculum examination ,palpation ,Rectal examination ,per abdomen ,supraclavicular region and Breasts examination. .A punch biopsy is done from the growth in cervix.Patients then undergo basic blood investigations such as Liver function test,Renal function test,hematological examination,Blood sugar profile,Serum electrolytes,Blood grouping typing ,virology ,chest x-ray, electrocardiogram and echocardiogram.Patients with suspected anterior fornix inolement/cbladder base involvement and all II.B cases undergo cystoscopy and on clinical suspicion of rectovaginal septum invasion/uterosacral ligament invasion undergo sigmoidiscopy and on presence of suspicious lesion undergo scopy guided biopsy.

External Beam Radiation

Patients underwent conventional or conformal treatment planning. Conventional treatment plans are simulated using x-ray ,and a four-filed box plan is executed.Dose is prescribed to the posterior depth.

For the AP-PA field,the borders are,

Superior-L4-L5 Junction'

Inferior-Obturator Foramen

Lateral-2cm from the pelic brim

For the lateral field,

Superior-Same as AP-PA field

Inferior-Same as AP-PA field

Anterior-Pubic symphysis

Posterior-Sacral notch

Conformal treatment planning:

Patients undergo ct simulation in planning position with arms crossed on shoulders and with bladder filling protocol-20 minutes post voiding.The planning ct is transferred to the treatment planning system ,where it is imported and target volume (GTV/CTV/PTV) and organs at risk(Bladder/Rectum/Rectosigmoid/Both kidney/Femur) are contoured.

A treatment prescription of 180cGy per day,5 days a week for a total dose of 45-50Gy depending on response to External beam radiation along with chemotherapy-weekly cisplatin at 40mg/m2 in patients who are fit.

Reassessment

Patients are assessed for response at 30Gy and 45Gy respectively,and based on feasibility and fitness for brachytherapy,the decision to continue external beam radiation.A thorough clinical examination coupled with imaging(USG) in necessary cases is used for response assessment.

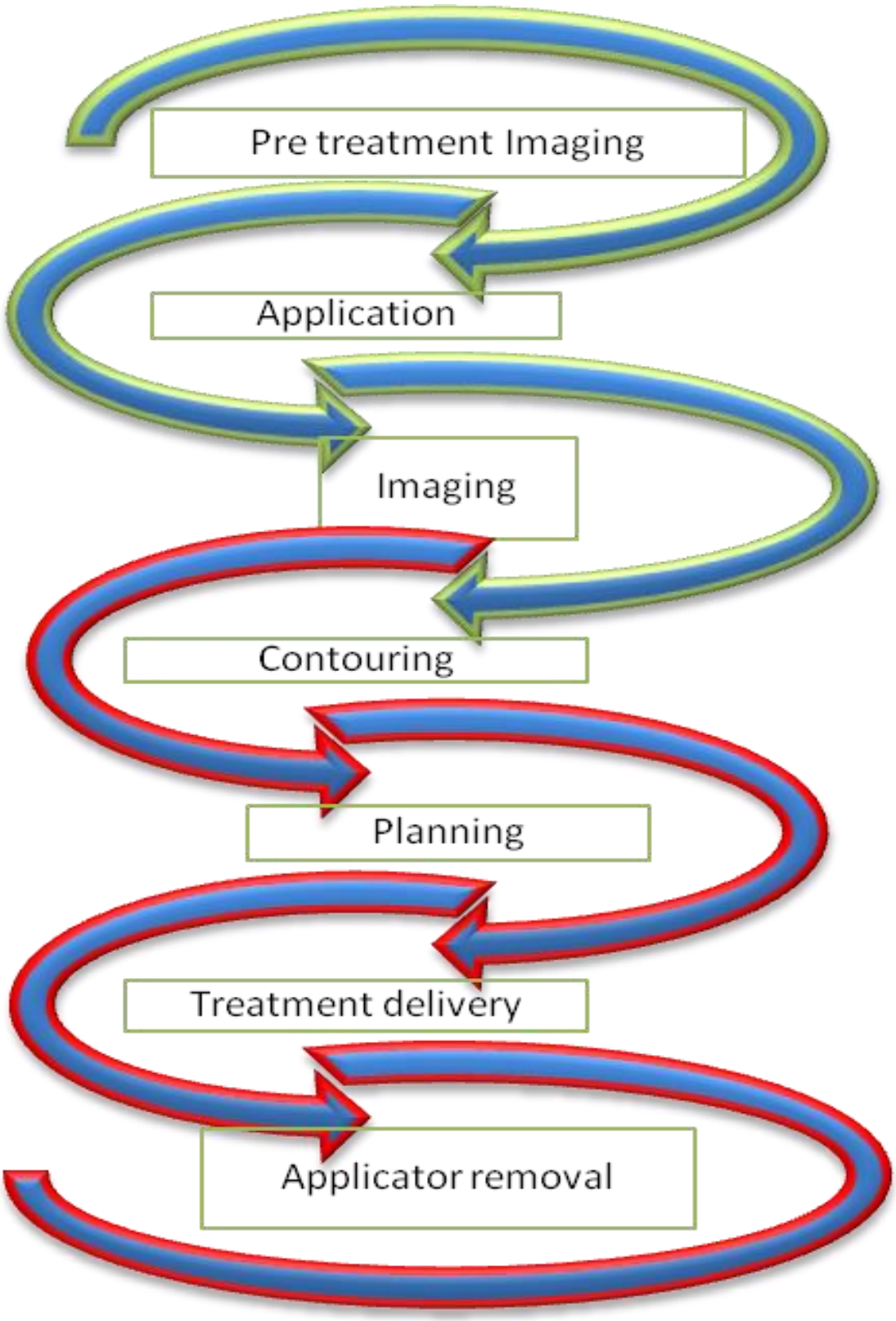
Procedure

After anesthetic fitness examination ,patients undergo the procedure in the operating theatre,under anesthesia,patient is put in lithotomy position,parts painted and draped,bladder is catheterized and balloon is inflated with 7cc contrast and applicator is inserted ,vaginal packing is done.Patients are shifted to recovery room and after recovery patients are shifted for xray simulation and ct simulation.

Treatment planning

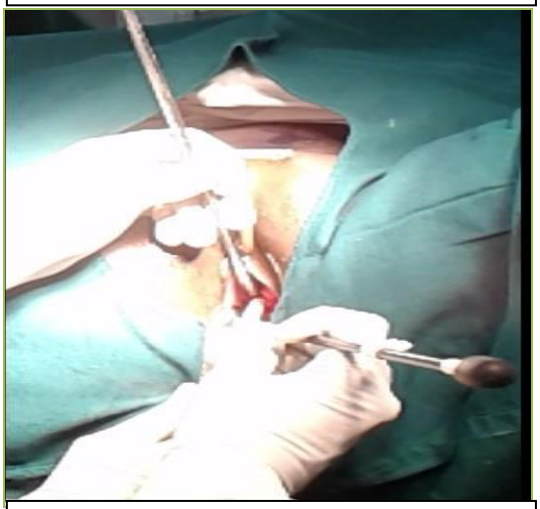
The images are transferred to the treatment planning system and the target volume/bladder ,rectum and recto sighmoid are contoured.Treatment planning is done after reconstruction of the catheter identified in axial cuts .In conventional planning dose is calculated to point A ,based on ICRU 38 recommendation. Conformal plans are optimized to HRCTV and the bladder and rectal doses based on GEC- ESTRO guidelines are calculated Plan evaluation and approval is done following which treatment is executed and the applicators are removed.

PROCEDURE

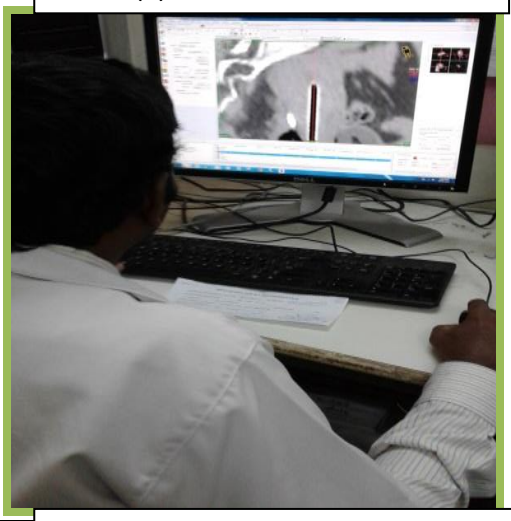

Pre treatment Imaging
Application
Imaging
Contouring
Planning
Treatment delivery
Applicator removal

PROCEDURE

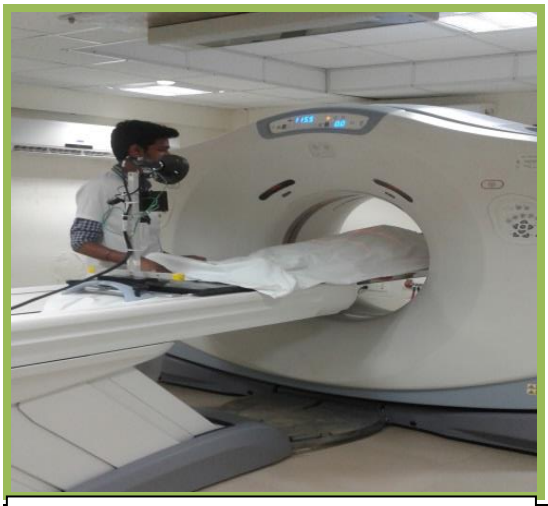
(1)APPLICATOR INSERTION



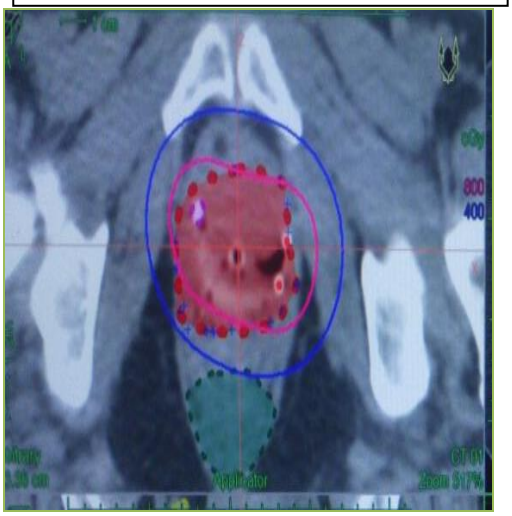
(4) PLANNING



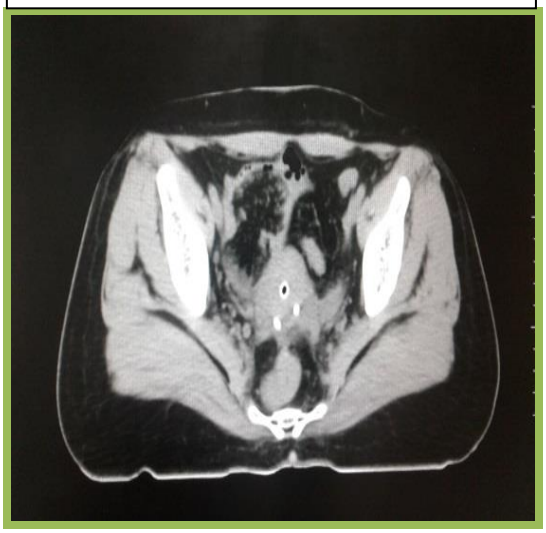
(2)IMAGING



(5 VERIFICATION



(3))CONTOURING



(6)TREATMENT DELIVERY

METHODOLOGY:

The following parametres will be generated for both point A and volumetric plan

Tumour characteristics:

1)D90-Dose received by 90% volume
2)D100-Dose received by 100% volume
3)V100-Volume receiving 100% dose
4)Volume of HRCTV (High risk clinical target volume) in cc
5)Whether the 95% isodose line generated in Point A based plan covered the target volume
6)Dose to Point A in image based plan

Organ at risk characteristics :

1) D0.1cc of bladder
2) D2cc of bladder
3) D5cc of bladder
4) D0.1cc of rectum
5) D2cc of rectum
6) D5cc of rectum
7) R0 and Bladder point dose in point A based plan

ARM A

Point A based planning

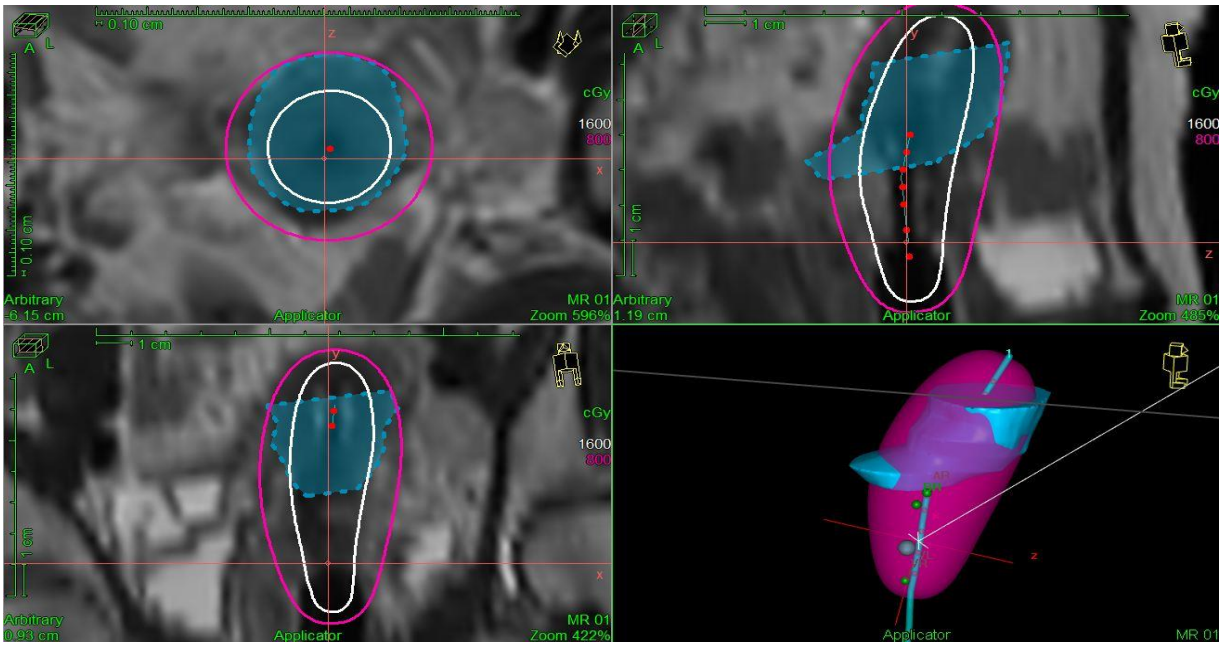
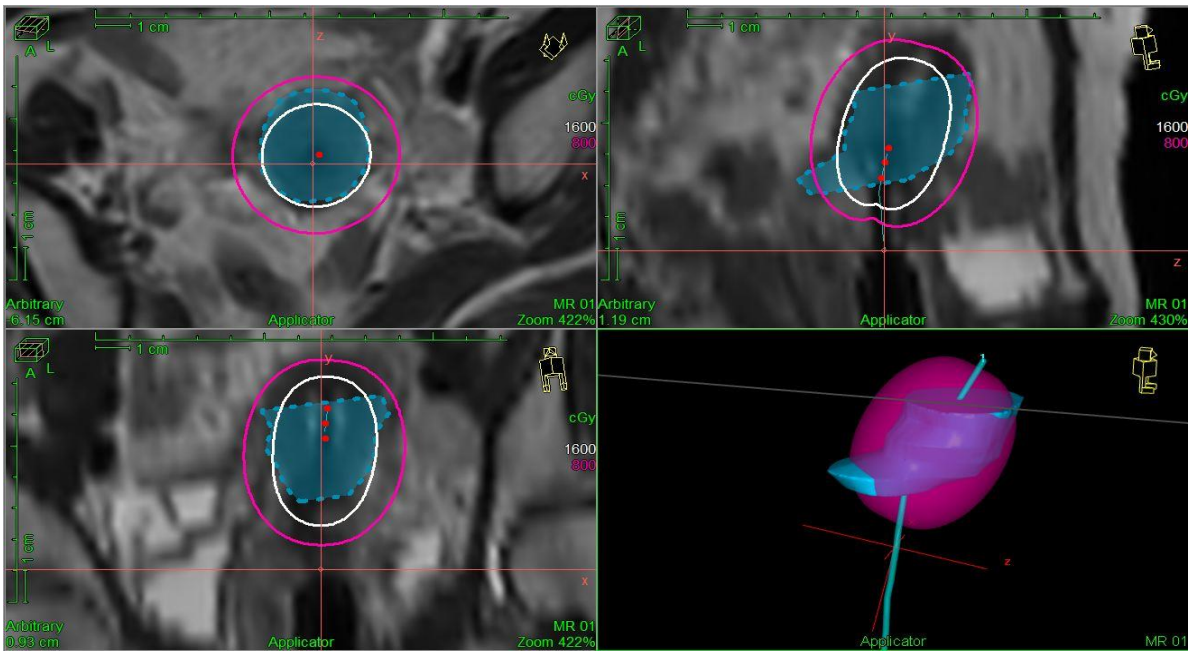
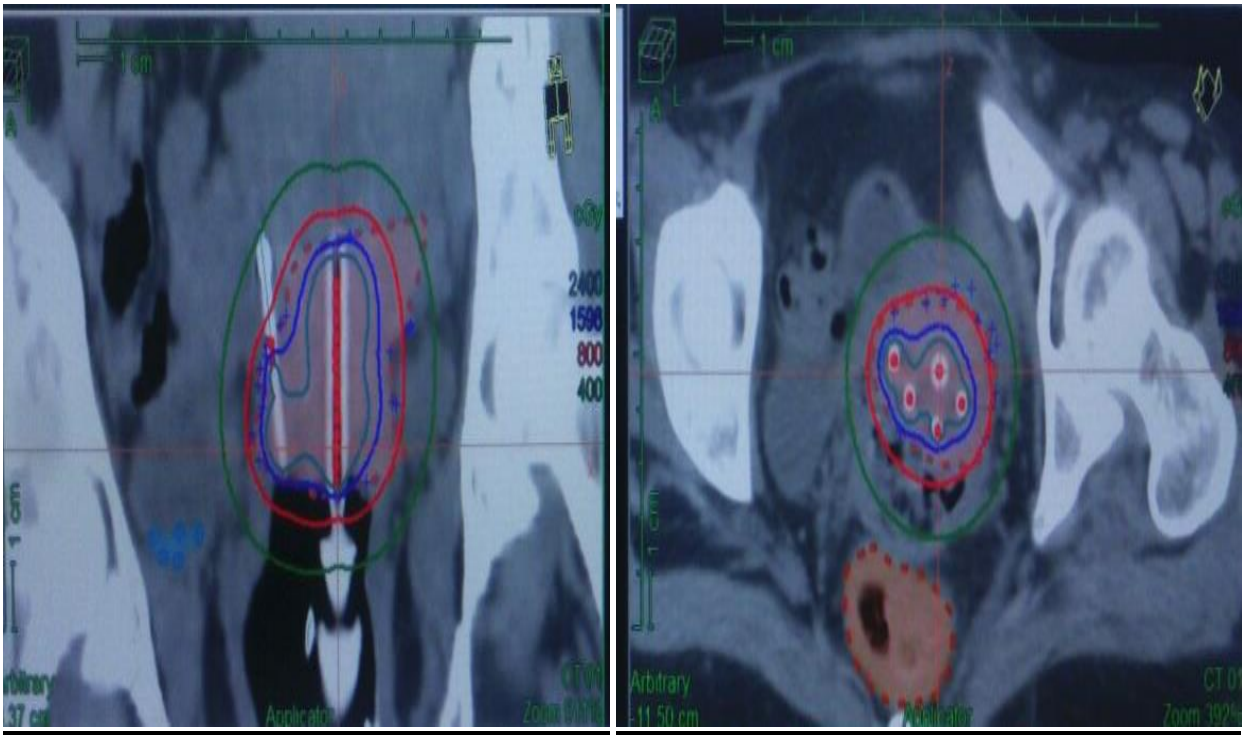


Image guided planning-Volume based

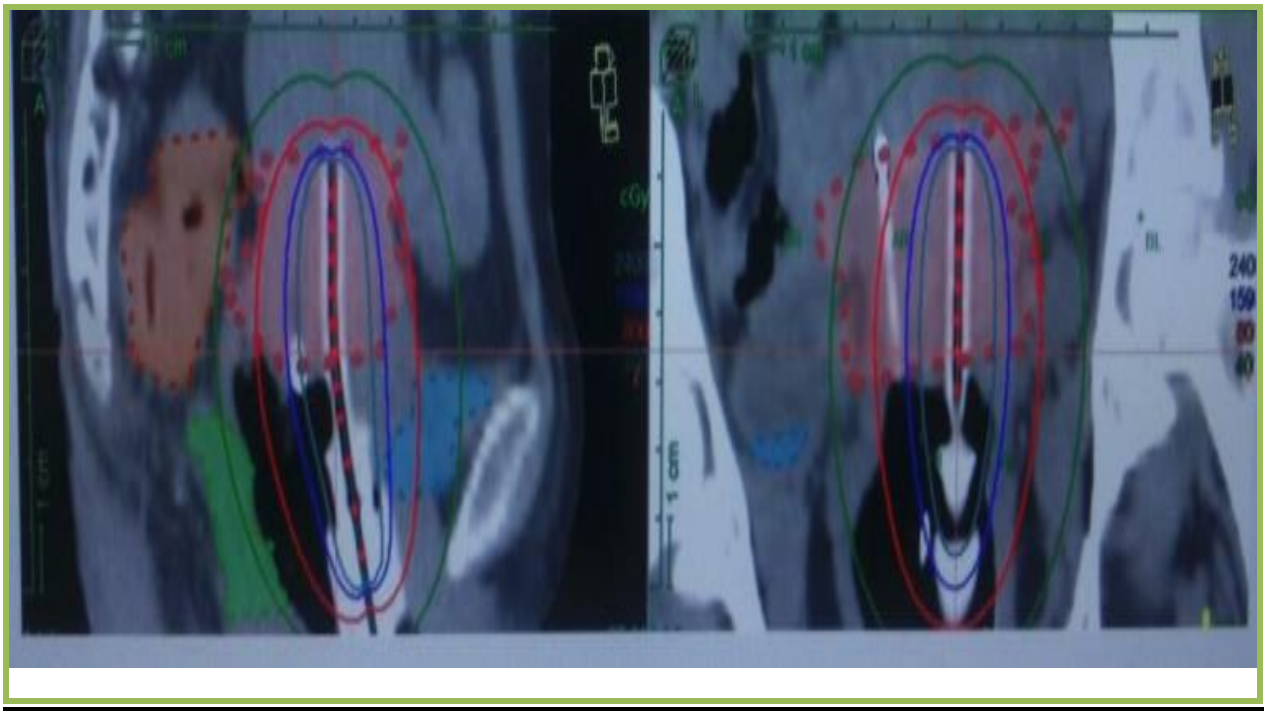


ARM B

ISODOSE CURVE WITH INTERSTITIAL NEEDLE



ISODOSE CURVE WITHOUT LOADING INTERSTITIAL NEEDLE



PATIENT CHARACTERISTICS

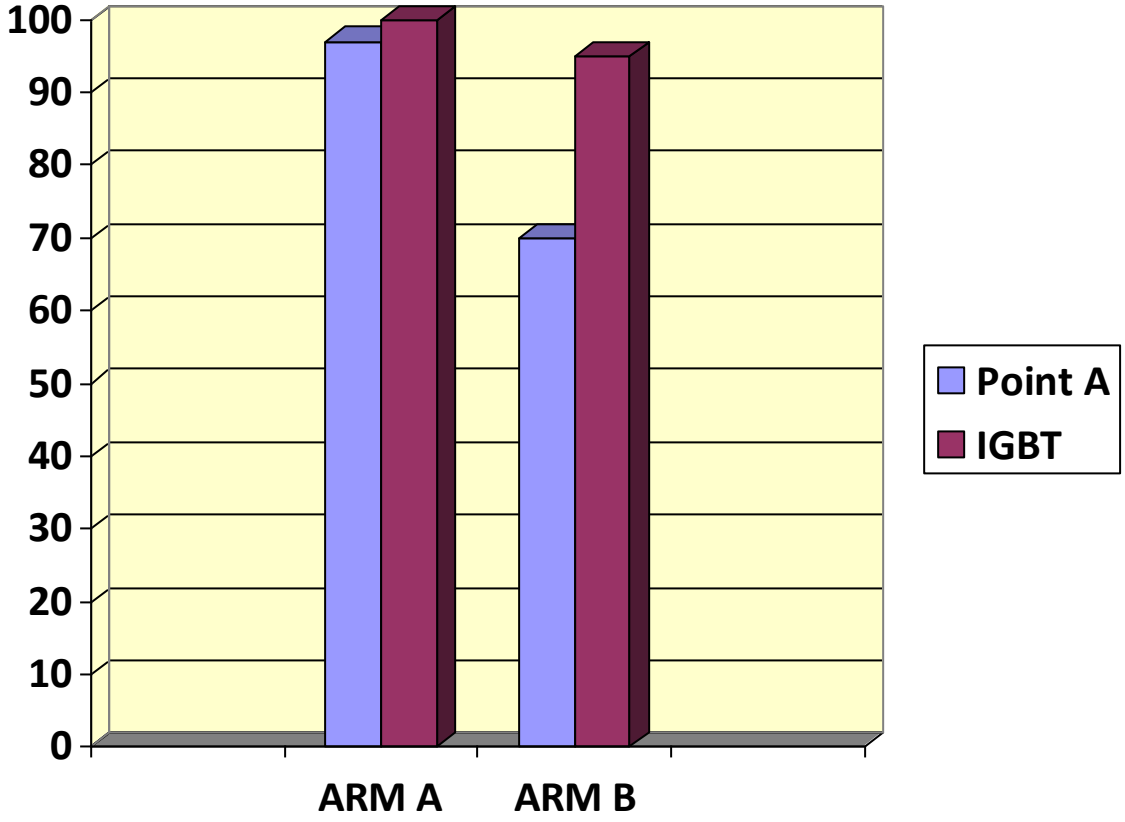
GROUP	NO RESIDUE	RESIDUE
PATIENT AGE	Mean Age-52 Years	Mean Age-54 Years
HISTOLOGY	Squamous cell carcinoma- 16/20(80%)	Squamous cell carcinoma- 17/20(85%)
GRADE	Grade III	Grade III
STAGE	III.B-10/20(50%) II.B-10/20(50%)	III.B-16/20(80%) II.B-4/20 (20%)
CHEMOTHERPY	15/20(75%)	17/20(85%)
EBRT TOTAL DOSE	45-50Gy	45-50Gy

RESULTS

V100: Percentage by which Target coverage was improved in IGBT

Arm A -No Residue- 3%

Arm B-Residual Disease-25%

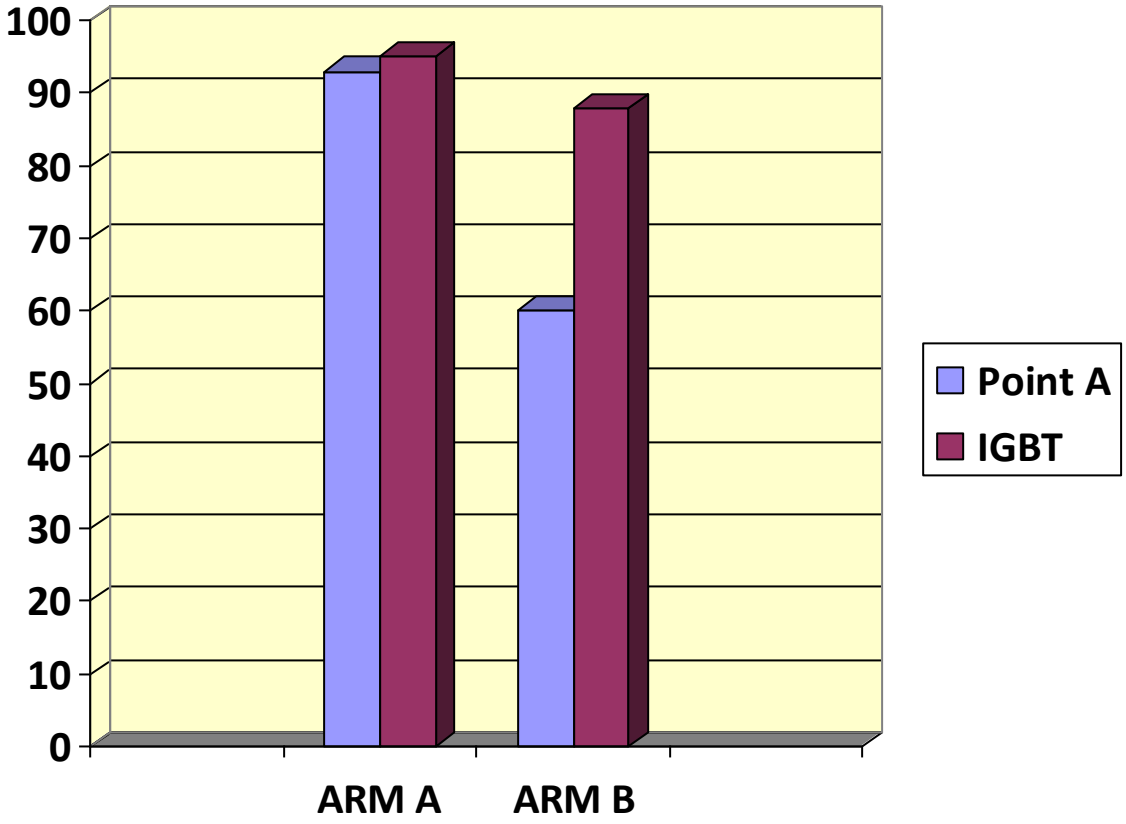


POINT A	IGBT
NO RESIDUE-97%	NO RESIDUE-100%
RESIDUE-70%	RESIDUE-95%

D100: Percentage by which Target coverage was improved in IGBT

Arm A -2%

Arm B-28%

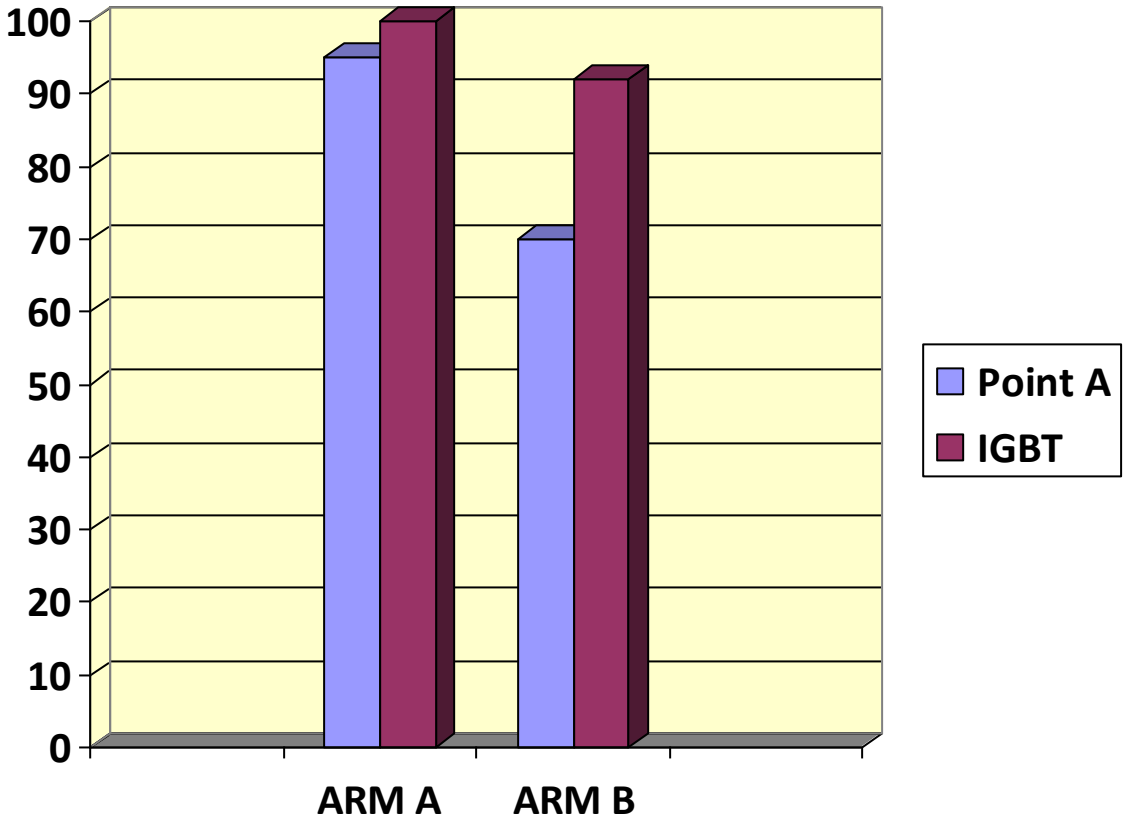


POINT A	IGBT
NO RESIDUE-93%	NO RESIDUE-95%
RESIDUE-60%	RESIDUE-88%

D90: Percentage by which Target coverage was improved in IGBT

Arm A -5%

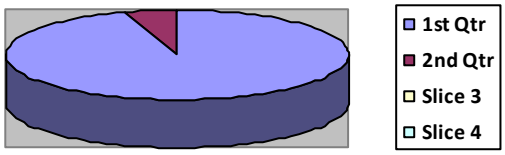
Arm B-22%



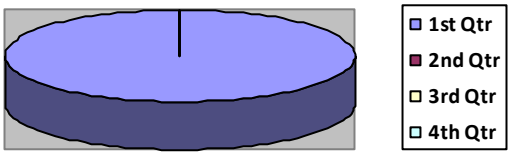
POINT A	IGBT
NO RESIDUE-98%	NO RESIDUE-100%
RESIDUE-70%	RESIDUE-93%

95% ISODOSE line covered HRCTV

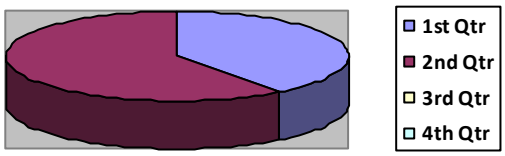
Arm A	Arm B
Point A-95%	Point A-40%
IGBT-100%	IGBT-90%



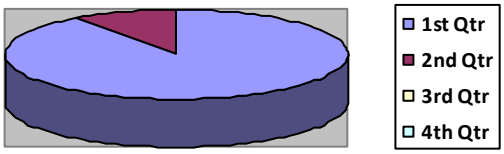
ARM A-POINT A



ARM A-IGBT



ARM B-POINT A

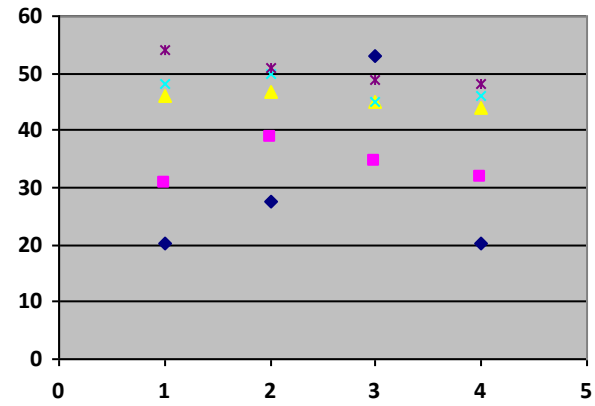


ARM B-IGBT

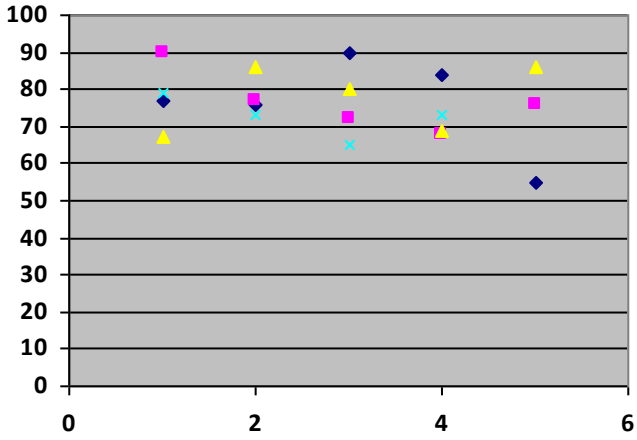
Volume of HRCTV (High risk clinical target volume) in cc

Arm A –Mean 44cc

Arm B-Mean 77cc

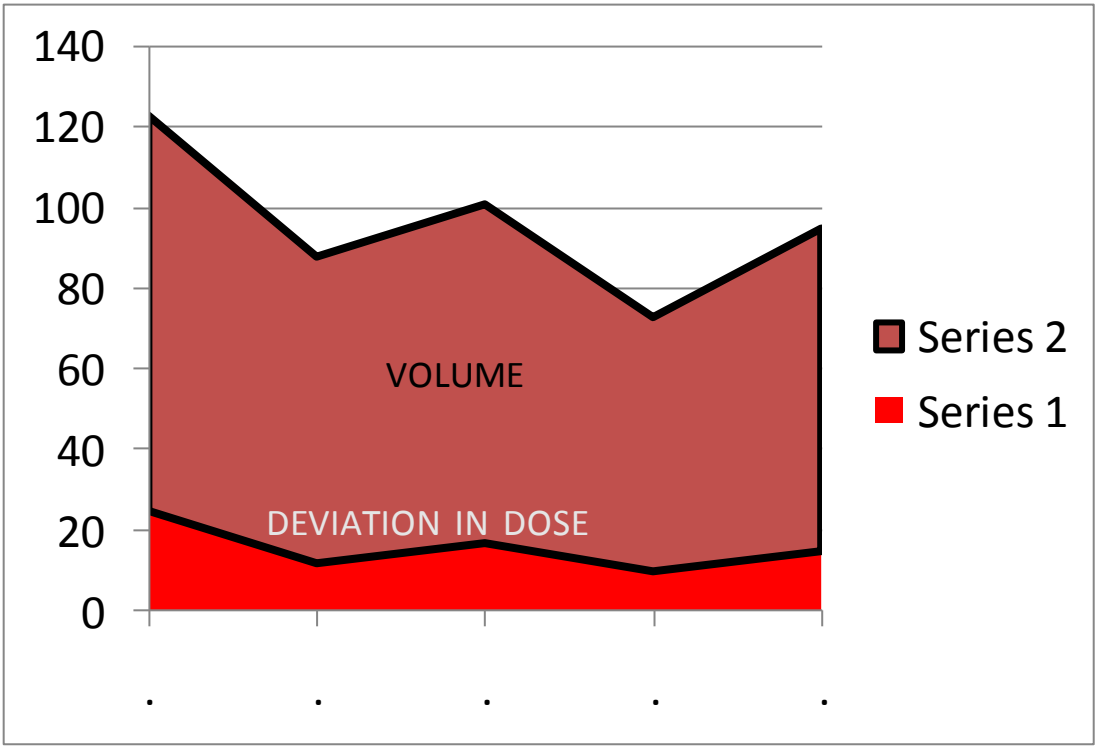


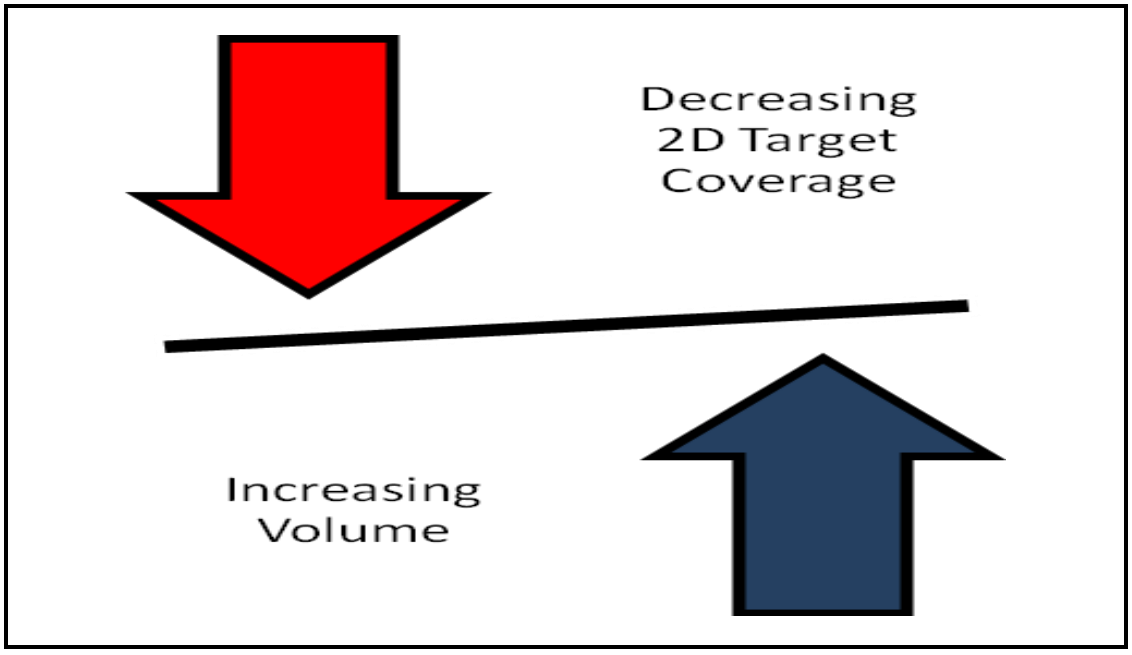
Arm A-VOLUME OF RESIDUE



ARM B-VOLUME OF RESIDUE

TARGET VOLUME AND DEVIATION IN DOSE

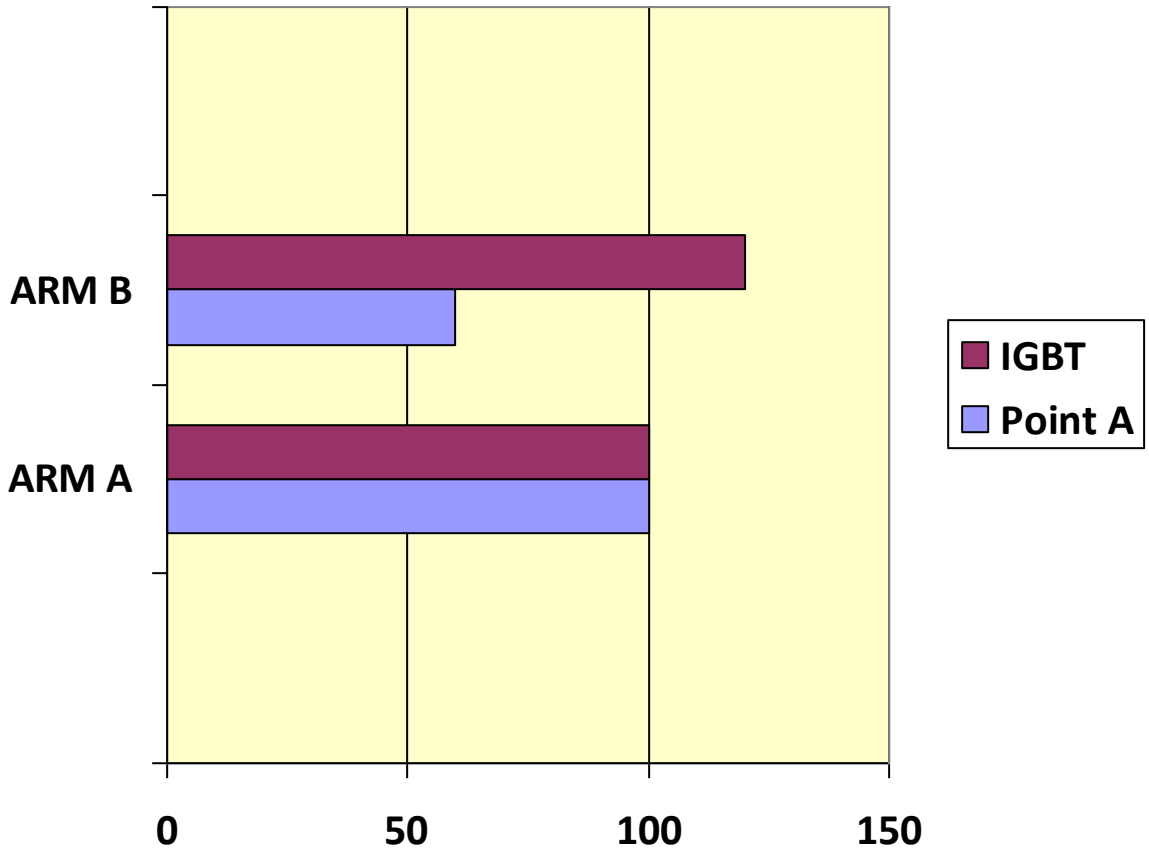




Dose to point A in IGBT

Arm A -100% of prescribed dose

Arm B-60% of prescribed dose

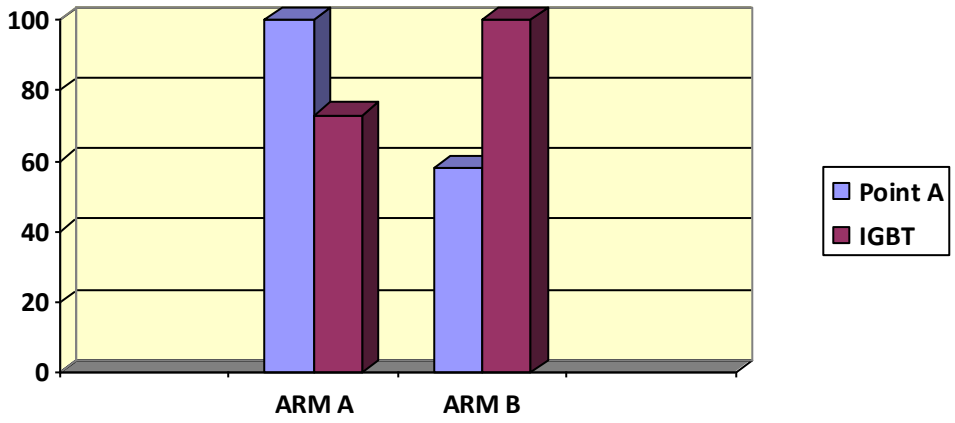


POINT A	IGBT
NO RESIDUE-100%	NO RESIDUE-100%
RESIDUE-60%	RESIDUE-120%

D0.1CC Rectum

Arm A –27% Reduction in mean dose with IGBT

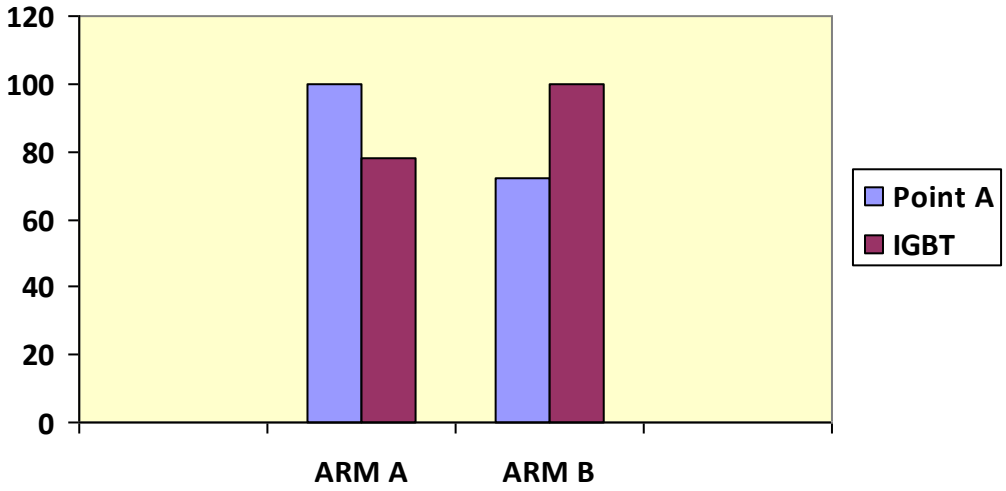
Arm B-32%increase in mean dose with IGBT (Probably due to Interstitial needles)



D1CC Rectum

Arm A -22% reduction in mean dose with IGBT

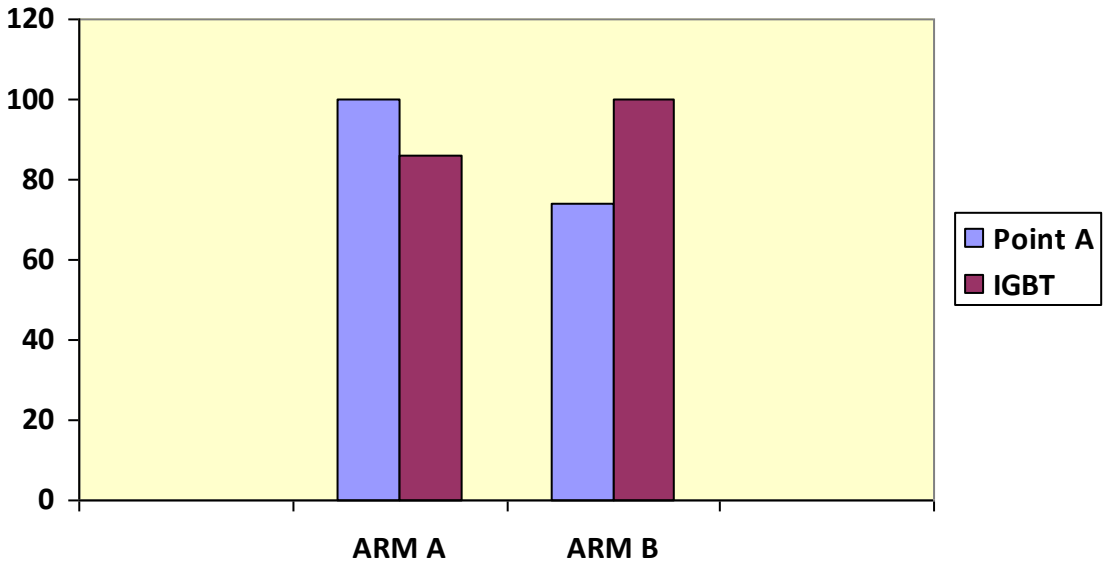
Arm B-28% increase in mean dose with IGBT (Probably due to Interstitial needles)



D2cc Rectum

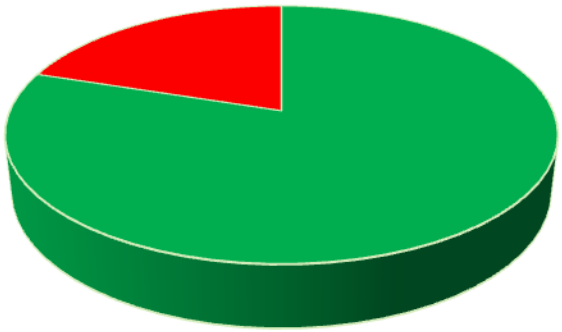
Arm A -14% reduction in mean dose with IGBT

Arm B-26% increase in mean dose with IGBT (Probably due to Interstitial needles)



Rectal point and its correlation to Volume parameters(No Residue)

16/20 Patients



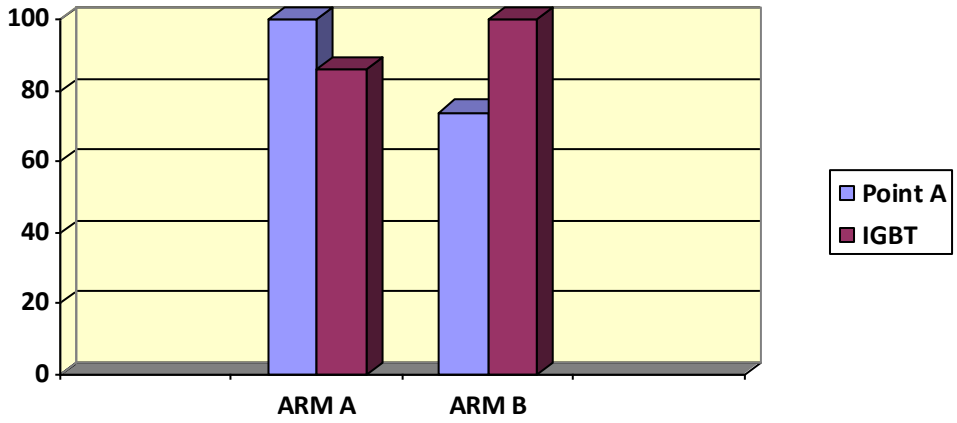
D2cc- Rectal point Dose +/- 20%.

D0.1/1cc >50% variation

D0.1CC Bladder

Arm A –14% Reduction in mean dose with IGBT

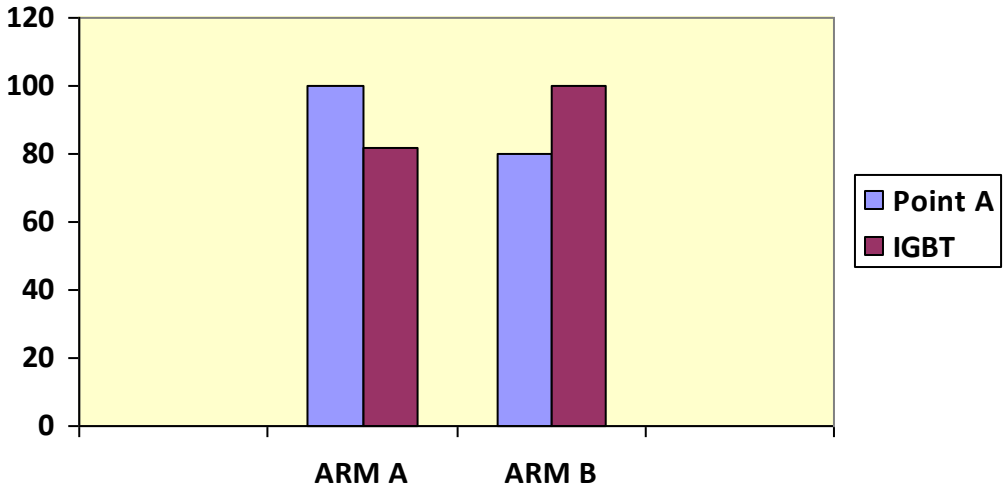
Arm B-26%increase in mean dose with IGBT (Probably due to Interstitial needles)



D1CC Bladder

Arm A -18% reduction in mean dose with IGBT

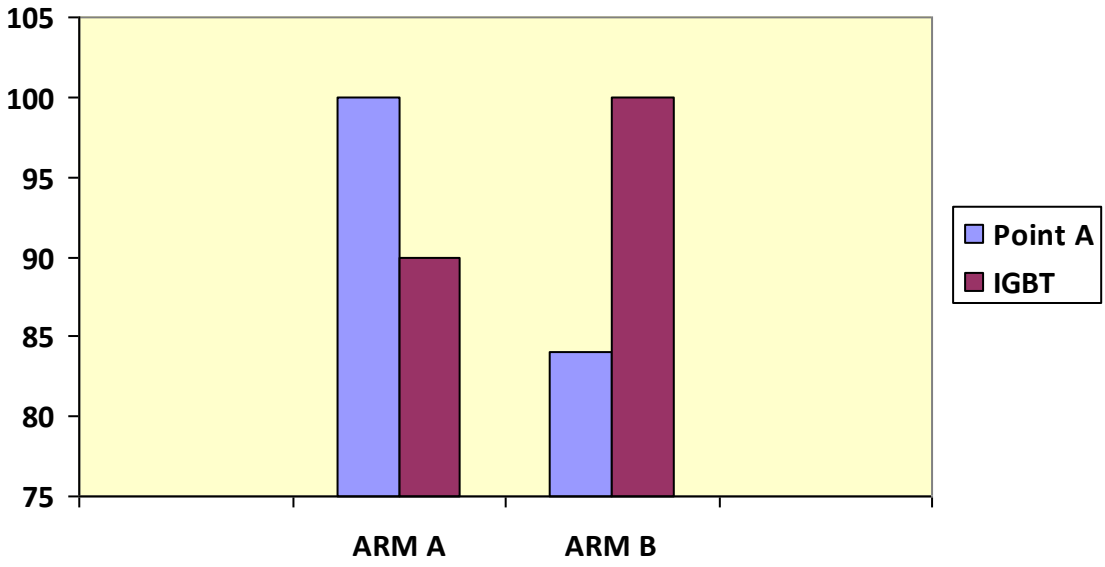
Arm B-20% increase in mean dose with IGBT (Probably due to Interstitial needles)



D2cc Bladder

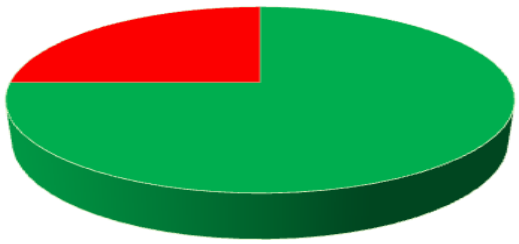
Arm A -10% reduction in mean dose with IGBT

Arm B-16% increase in mean dose with IGBT (Probably due to Interstitial needles)



Bladder point and its correlation to Volume parameters(No Residue)

15/20 Patients



D2cc- Rectal point Dose +/- 20%.

D0.1/1cc >50% variation

DISCUSSION

Cervical cancer is the 4th most common cancer in females worldwide with an annual incidence of 510,000 cases and approximately 288,000 deaths per year. In south asia, India has the highest age standardized incidence of cervical cancer at 22 [57]. In India, cervical cancer is the 2nd most common cancer in females with an annual incidence of 122,844 cases and approximately 288,000 deaths per year.

Intracavitary brachytherapy (ICBT) with external radiotherapy (ERT) is an essential component of cervical cancer management and has a high therapeutic index by delivering a high dose to the primary cervical lesion and lower doses to adjacent organs, resulting in increased local control and survival without increased in toxicity [58-60].

However the doses delivered to tumor and normal tissues from ICBT are difficult to quantify accurately in conventional brachytherapy (BRT) planning. To ensure consistency in the reporting of ICBT applications in cervical cancer, the International Commission on Radiation Units and Measurement (ICRU) recommended a number of parameters for doses and volumes to be considered. These include points A and B, representing the doses in the parametria and the

pelvic wall, and the rectal and bladder points representing the organs at risk (OARs), respectively [61]. Physicians have used these reference point doses to report treatment intensity and to estimate the maximal dose to normal tissues, which can predict late complications.

A modern approach in treatment planning for cervical carcinoma is based on computed tomography (CT)/Magnetic Resonence Imaging (MRI) sections and on a 3D dose distribution. This allows better assessment of dose distributions in different volumes, such as the gross tumor volume (GTV), clinical target volume(CTV), and OARs (rectum, bladder, and intestines).

A shift from conventional orthogonal treatment planning to image guided brachytherapy (IGBT), has been emphasized in various recent studies. Although it has been quoted that conventional Point A based treatment planning overestimates the dose to target volume and underestimates the dose to organs at risk (OAR)(62),there are studies which quotes that difference in doses to target volume and OAR between orthogonal and image based planning,depends on the volume of the target(63) .Our study aims at identifying the subgroup among differential responders to EBRT in which there is maximal therapeutic benefit with IGBT and hence the others in whom IGBT may be avoided .

Rationale:

Traditionally, intracavitary brachytherapy treatment planning and technique has been based on 2D orthogonal film-based approach. The dose was prescribed to point A, a position defined with respect to the applicators. A standardized system of dose reporting has been established by the ICRU report 38. The reporting is based on points representative of the parametria, pelvic side walls and organs at risk - the rectum and bladder. However, these points are not the best surrogates. Many studies have reported inconsistencies between these points compared with volumetric image-based 3D dose calculation and they cannot be the best estimate to predict late complication to organs at risk .

Image-based brachytherapy allows more conformal treatment, integrating the concepts of anatomy, tumour features, and tumour response with time. It enables reconstruction of cross-sectional images of the applicators, tumour and the neighbouring normal structures in chosen image plane and creates spatial 3D representations of them. This provides accurate and reproducible delineation of the

tumour, as well as critical organs at risk and allows a clinically meaningful dose escalation in the target, while respecting normal tissue tolerance.

Various studies have quoted that Point A prescription may overtreat small tumours but may result in suboptimal dose distribution for larger tumours .A shift from conventional orthogonal treatment planning to image guided brachytherapy (IGBT), has been emphasized in various recent studies. Although it has been quoted that conventional Point A based treatment planning overestimates the dose to target volume and underestimates the dose to organs at risk (OAR), we wanted to identify the subgroup of patients in whom significant variation in doses does not occur between the orthogonal and image based planning and hence to obviate the need for IGBT in every patient.

Hypothesiss:

Although , a lot of studies are available on image based brachytherapy planning,not many of these studies have quoted the size of tumour and the response to EBRT.Among the studies which have compared these data have concluded that the difference in target volume coverage between conventional and image based planning does not vary with statistical significance in small tumours.

Supporting Literature: In an article titled Dosimetric comparison between three-dimensional magnetic resonance imaging-Guided and conventional two-dimenssional point A –Based intracavitary brachytherapy planning for cervical

cancer,by Ren et al,they compared in 79 patients with cervical cancer, the 3-dimensional (3D) magnetic resonance imaging (MRI)-guided &conventional 2-dimensional(2D) point A-based intracavitary brachytherapy (BT) planning for cervical cancer with regard to target dose coverage and dosages to adjacent organs-at risk (OARs) and they found that in small tumors, there was no significant difference in most of the DVHs between 2D and 3D planning (all $p>0.05$). While in big tumors, 3D BT planning significantly increased the DVHs for most of the GTV, HR-CTV and IR-CTV, and some OARs compared with 2D planning (all $P<0.05$) .(64)

Hypothesis:

The comparability of surrogate points on orthogonal planning to the volume based planning, has been studied in various articles and found that the rectal points may underestimate the true dose to rectum and the bladder point may be a reasonable surrogate.

Supporting Literature: In an article titled Ct based 3-dimensional treatment planning of intracavitary brachytherapy for cancer of the cervix :comparison between dose volume histograms and ICRU point doses to the rectum and bladder analysed 55 intracavitary applications In the majority of applications, the

maximum dose point was not the ICRU point. On average, the rectum received 77% and bladder received 92% of the prescribed dose.OARs doses assessed by DVH criteria were higher than ICRU point doses. The estimated dose to the ICRU bladder point may be a reasonable surrogate for the D 2cc and rectal DMax for D 2cc. However, the dose to the ICRU rectal point did not appear to be a reasonable surrogate for the D 2cc.(65)

Hypothesis:

Image guided brachytherapy could yield better locoregional control in more locally advanced cases,probably due to greater volume of residual disease and possible tumour under coverage in conventional planning,whereas in early stages the volume of residual disease could be well encompassed with conventional planning only.

Supporting literature: In the retrospectiove study,retroembrace-a multicenter retrospective study on image guided brachytherapy in locally advanced cervical cancer,they analysed 600 patients from 11 institutions and concluded that in locally advanced stage IIIA,IIIB cervical cancers it yielded better local control at 3 years.(98.8%,90%,91.8% and 85.5% for stage IB,IIA,IIB & IIIA&B respectively).

The reported local control for early stages in this study is similar to other studies using conventional brachytherapy planning techniques,however with a lower bladder and rectal morbidity.(66)

OUTCOMES WITH IMAGE GUIDED BRACHYTHERAPY:

Hypothesis:

All these studies have reported a beetr local control when compared to historic series in advanced stages and most patients required a combined interstitial and intracavitary approach. Also in all these studies,the benefit with image guided brachytherapy in early stage is not remarking.

Supporting Literature: (66-68)

Potter et al,VIENNA	LCR-3 Years	IB-100%,IIB-96%,IIIB-86%
RETROEMBRACE	LCR-3 Years	IIB-93%;III.B-79%;IV-A-75%
Mahantshetty et al	LCR-3 Years	IIB-100%;III.B-85%;IV-A-100%

CONCLUSION

- From our observation ,based on the response to EBRT ,the benefit obtained from Image guided brachytherapy(Dosimetrically), differed.
- Based on the response to EBRT patients can be classified into 3 groups

GROUP 1	COMPLETE RESPONSE
GROUP 2	LOW VOLUME RESIDUE-Central
GROUP 3	LOW VOLUME RESIDUE-Lateral LARGE VOLUME RESIDUE

- In the complete responders, target coverage was achievable with conventional planning only.However the dose to organ at risk could be moderated .
- In patients with low volume central residue, complete target coverage was achievable. However with image guided brachytherapy, the shape of the isodose curves could be altered to fit the bulk of the residual disease.
- In patients with low volume disease confined to one side of pelvis and large volume residue, , the actual dose received by the target volume is less when compared to the dose calculated using Point A based conventional planning due to incomplete target coverage.

- However in this last subgroup, target coverage with intracavitary application alone was not adequate ,even if done with image guidance. Combined intracavitary and interstitial techniques wqere necessary to escalate the dose to target.
- Hence,it was the choice of technique which was the most important factor for adequate target coverage in this sub group.

. From our observation, IGBT is essentially important to treat a larger target volume , in patients who have residue after initial chemo radiation for adequate target coverage,provided the choice of technique such as combined intracavitary and interstitial brachytherapy were utilized . IGBT also improves the therapeutic ratio in patients who do not have a central residue. In patients with good response after external beam radiation to pelvis, IGBT could be used to reduce the dose to the organ at risk thus improving the therapeutic ratio ,however without much difference with respect to target coverage in comparison to orthogonal planning.

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