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Co^{60} May be the Acceptable Alternative Radionuclides of Ir^{192} used in HDR Brachytherapy for the Treatment of Inoperable Carcinoma Cervix in the Treatment Modality of Concurrent Chemoradiation

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ABSTRACT

Background: Cancer of the uterine cervix is the eighth most common cancer among women worldwide and third among all malignancies and the second most common cancers in female in Bangladesh. The treatment of cervical cancer requires multidisciplinary approaches Concurrent chemoradiation is the treatment of choice in locally advanced carcinoma cervix uteri. Radiotherapy is the primary local treatment for most patients having FIGO stage IIB to IVA diseases. The success of treatment depends on a careful balance between EBRT and Brachytherapy that optimizes the dose to tumor. $Iridium^{192}$ is highly used radionuclide for modern remote after loading HDR brachytherapy till date. Recently Co^{60} source is available with miniature size and identical physical properties for remote after loaders.

Methods: 60 patients with biopsy proven locally advanced carcinoma of the uterine cervix were enrolled in the study. Arm A was formed comprising 30 patients who were treated by Ir^{192} HDR brachytherapy and Arm B formed with equal number of 30 patients who received HDR brachytherapy treated with Co^{60} radionuclide. This prospective observational study was carried out to compare the treatment effect between two Arm.

Results: 60 patients were enrolled in this study with age range from 35 to 63 years. Most of the patients presented with stage IIB disease, consisting of 39 patients (65.3%). Among them 48 patients had squamous cell carcinoma (80.60%), adenocarcinoma trailing with 9 patients (15.3%) and rest were adenoid-squamous carcinoma 2 and small cell carcinoma.

In all three insertions, urinary bladder dose distribution was slightly smaller by HDR Co^{60} irradiation than HDR Ir^{192} exposure. These differences were statistically significant in first two insertions but not in third one

Conclusion: In this study radiation dose distribution at OARs i.e. urinary bladder and rectum were compared between Arm A and Arm B. In all three insertions in urinary bladder the mean dose distribution was slightly smaller in HDR Co^{60} irradiation than HDR $Iridium^{192}$ exposure. These differences were statistically significant in first two insertions but not in third one. In case of rectum point, the mean dose distribution was significantly lower in all three insertions of Co^{60} exposure than Ir^{192} exposure.

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Introduction

Cervical cancer is the eighth most common cancer in women, and the seventh overall, with an estimated incidence of 528,000 new cases and 266,000 deaths from the disease worldwide in 2012 [1]. Cervical cancer also contributed nearly 8% of all cancers among women and around 4% in all population. However, global cervical cancer incidence increased from 378,000 cases per year in 1980 to 454,000 cases per year in 2010, a 6% annual rate of increase [2]. approximately 1.6% c all cancer deaths in women and 13% of deaths from gynecologic cancers. However, for women aged 20 to 39 years cervical cancer remained the second leading cause of cancer deaths after breast cancer [3].

Cervical cancer is highly prevalent in developing nations. There exist wide geographic variations. Cervical cancer is more common in Latin America and less frequent in Jewish and European women and Fiji Islanders [4]. International incidences of cervical cancer tend to reflect differences in cultural attitudes toward sexual promiscuity and differences in the penetration of mass screening programs. Countries that have well-advanced screening programs (e.g., the United States and the countries of western Europe) or strict religious regulation of sexual behavior (e.g., Muslim countries of the Middle East or Asia) tend to have low rates of invasive disease [5]. The highest: incidences tend to occur in

populations that have low screening rates combined with a high background prevalence of human papillomavirus (HPV) infection and relatively liberal attitudes toward sexual behavior [6]. Although there is no national cancer registry in Bangladesh, the hospital-based cancer registry of National Institute of Cancer Research and Hospital for the period of 20082010 showed that 43.95% of all registered cases were female. The male female ratio was 1.28:1. The report also revealed that cervical cancer ranks the third among all malignancies during this period an.: the second most common cancers in female (Cancer Registry Report; NICRH, 2013). The treatment of cervical carcinoma requires multimodality approaches and depends largely on the stage of disease. Radiotherapy plays a major role in the management of locally advanced cervical cancer. Currently, the two main modalities of irradiation are external photon beam and brachytherapy. Both EBRT and ICRT are used, often in combination with chemotherapy. External irradiation is used to treat the whole pelvis and the parametrium including the common iliac and para- aortic lymph nodes, whereas cervix and parametrium is primarily irradiated with intracavitary sources. The techniques described applied, with some individualization, to most patients with cervical carcinoma. To achieve local control, and subsequently patient cure, very high doses have to be delivered to patients with locally advanced cervical cancer. Traditionally this treatment has been rather toxic and it has been reported that up to 20 - 25 % of the patients experience adverse side effects [7]. To optimize the treatment of locally advanced cervical cancer it is important to establish a firm knowledge about dose response relationship in cervical tumours as well as in OARs those are in close vicinity of the uterus. The urinary bladder and the rectum stand for most important OARs in radiation therapy of carcinoma cervix due to their anatomical position. For ICRT it is usual to prescribe treatment a dose point (the Manchester point A, in Manchester System, the dose is specific at point A) or isodose (reference isodose surface). In 1985 the ICRU published report 38 making recommendations on dose and volume specifications in intracavitary brachytherapy. Two points were defined for reporting the dose respectively the rectum and the urinary bladder. Traditionally, High Dose Rate after loaders has been based on Ir^{192} radionuclide. The high specific activity of iridium allowed very small sources to be used interstitially despite its short half-life period. Typically, Ir^{192} source exchange is required each 4-6 months to keep the treatment times within the limits required by clinical practice. A few years ago, new HDR after loaders have been introduced using Co^{60} instead of Ir^{192}; which are provided with sources having the same size as the Ir^{192} ones and have been already implemented in some institutes which shows a clear tendency to increase their number. In fact, these sources have been considered in the recent AAPM-ESTRO Report [8] with recommendations about dosimetry methodology and consensus datasets have been presented for the two commercially existing sources. The Co^{60} introducers claim important economic advantages because of the larger half-life period and the improved technology. At present there is no clear position on advantages or disadvantages of both HDR modalities, to be taken into account in future HDR facility implementation.

In this thesis acquired data from study subjects, diametrical as well as clinical data ware used to elucidate the comparison between dose distribution of two HDR brachytherapy radionuclides in the tumour and organs at risk during ICRT for cervical cancer.

Research Methodology

The study was designed as prospective observational study. This study conducted in the Department of Clinical Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka; Lab Aid Specialized and Cancer Hospital, Green Road, Dhaka; and Delta Hospital Ltd. Mirpur, Dhaka were done during the period of July 2021 to December 2022. Target population was patients with histopathologically proven cervical cancer having FIGO stage I1B - IVA disease, at these above-mentioned hospitals during the period of July 2021 to December 2022. They were convinced to participate in the study after giving written informed consent and satisfying inclusion and exclusion criteria and enrolled in the study.

Study population and sample were patients with locally advanced cervical cancer & received EBRT with concurrent chemotherapy. The objective this study was to compare the radiation dose distribution among tissue including reference point "A", urinary bladder points and rectum point.

All patients were received EBRT 50 Gy in 25 fractions at 2 Gy per fraction with concurrent chemotherapy with low dose weekly Cisplatin 40 mg/m2 weekly. Followed by 3 insertions of intracavitary HDR brachytherapy at a dose of 7 Gy per insertion weekly. This hospital based comparative study in used histologically diagnosed 98 patients of cervical carcinoma. All the patients received external beam radiotherapy at a total dose of 50 Gy in 25 fractions, at a rate of 200 Gy per fraction, each fraction per day; five fractions per week. The EBRT treatment period was 5 weeks. All the patients also received concurrent chemotherapy with inj. Cisplatin 40 mg/m2 weekly. The 98 patients who enrolled in this study were divided in two arms. 30 patients for Arm-A and 30 patients for Arm-B. Arm-A were treated with Ir^{192} HDR Brachytherapy and Arm-B treated with Co^{60} HDR Brachytherapy.

Results

In this chapter the results of the data analysis of the study are presented. The data were collected and then processed in response to the study question. This study set out to investigate comparison of dose distribution in organs at risk and reference point "A" in treatment of carcinoma cervix using Co^{60} and Ir^{192} HDR Brachytherapy. The principal goal is to investigate the clinical feasibility of the two aforesaid radionuclides in treatment of advanced stage carcinoma cervix by HDR brachytherapy. The objectives were accomplished. The findings presented in this chapter demonstrate the potential for merging theory and practice.

This hospital based comparative study have done on the basis of histopathologically diagnosed 60 patients of cervical carcinoma. All the patients received external beam radiotherapy at a total dose of 50 Gy in 25 fractions, at a rate of 200 Gy per fraction, each fraction per day; five fractions per week. The EBRT treatment period was 5 weeks. All the patients also received concurrent chemotherapy with inj. Cisplatin 40 mg/m2 weekly. The 60 patients who enrolled in this study were divided in two arms. 30 patients for Arm-A and 30 patients for Arm-B. Arm-A were treated with Ir^{192} HDR Brachytherapy and Arm-B treated with Co^{60} HDR Brachytherapy. All patient in both arm completed treatment. No drop out was noticed during treatment (Tables 1-6).

Table 1: Distribution of the Patients by Stage of the Disease

Stage	Frequency	Percentage
IIB	39	65.30
IIIA	11	17.35
IIIB	09	15.31
IVA	01	2.04
Total	60	100.0

Table 2: Distribution of the Patients by types of Irradiation and Stage of the Disease

Stage	Group	
	Ir^{192} (Percentage)	Co^{60} (Percentage)
IIB	20 (67.35)	20 (65.3)
>IIIA	10 (32.65)	10 (34.7)
Total	30 (100.0)	30 (100.0)

Table 3: Distribution of the Patients by Histopathological types of Cancer

Morphological types	Frequency	Percentage
Squamous cell carcinoma	48	80.6
Adenocarcinoma	9	15.30
Adeno-squamous cell carcinoma	2	3.1
Small cell carcinoma	1	1.02
Total	60	100.0

Table 4: Dose Distribution at Urinary Bladder Point of the Patients

Point of irradiation	Group	Mean	Std. deviation (±)	t-test	p-value
Bladder point 1st insertion	Ir^{192}	5.0952	1.91421	2.394	0.019
	Co^{60}	4.2704	1.42599		
Bladder point 2nd insertion	Ir^{192}	4.8400	1.30849	2.510	0.014
	Co^{60}	4.572	1.35571		
Bladder point 3rd insertion	Ir^{192}	4.5037	1.63573	1.090	0.279
	Co^{60}	4.8034	1.24406		

Table 5: Dose Distribution at Rectum Point of the Patients.

Point of irradiation	Group	Mean	Std. deviation (±)	t-test	p-value
Rectum point 1st insertion	Ir^{192}	4.3210	1.30049	5.985	<0.001
	Co^{60}	3.0014	.80139		
Rectum point 2nd insertion	Ir^{192}	4.5970	1.25732	7.053	<0.001
	Co^{60}	2.9763	.97664		
Rectum point 3rd insertion	Ir^{192}	4.2416	1.27164	5.007	<0.001
	Co^{60}	3.1150	0.90191		

Table 6: Distribution of the Toxicities by Group of Irradiation

Toxicities		Group		t-test	p-value
		Ir^{192}	Co^{60}		
Nausea	Yes	15	17	0.209	0.647
	No	45	43		
Anaemia	Mild	10	12	0.43	0.807
	Moderate	35	32		
	Severe	15	16		
S. creatinine	Normal	50	54	0.798	0.372
	Raised	10	6		
Rectal irritation	Yes	17	10	1.47	0.225
	No	43	50		

Discussion

Patients with locally advanced cervical cancer in stage IIB to IVA are treated with irradiation including external beam and brachytherapy combined with concurrent chemotherapy. Traditionally LDR brachytherapy was used to treat cervical cancer. But the advent remote after loader HDR brachytherapy ensures some realistic benefit over LDR. From the early ages of HDR, Iridium^{192} was very much popular as radionuclide. Recently Cobalt^{60} radionuclide has

been introduced with equivalent structural and physical properties.

The objective this study was to compare the radiation dose distribution among the site of tissue including reference point "A", urinary bladder points and rectum point. 60 patients were enrolled in the study with an age range from 35 to 63 years. Arm A was formed comprising 30 patients who were treated by Ir^{192} HDR brachytherapy and Arm B formed with equal number of 30 patients who received HDR brachytherapy treatment with Co^{60} radionuclide.

The patients of different stages were enrolled in this study. Most of the patients presented with stage IIB disease, consisting of 39 patients (65.3%). The next leading stage was IIIA with 11 (17.35%) and 9(15.31%) patients were suffering from stage IIIB disease and stage IV was 1 patient (2.04%).

The study subjects were included as histopathologically diagnosed carcinoma cervix. Different histopathological types were found. Among them 60 patients had squamous cell carcinoma (80.60%), adenocarcinoma trailing with 9 patients (15.3%) and rest were adenoid- squamous carcinoma 2 and small cell carcinoma 1.

In this study radiation dose distribution in tissues by HDR brachytherapy using Ir^{192} & Co^{60} radionuclides were compared among carcinoma cervix patient. All the patients were biopsy proven, locally advanced between stages of IIB - IVA. The brachytherapy was completed with the insertion of central uterine Tandem and two vaginal ovoids. The treatment planning being done with optimizing dose to reference point "A" to a dose of 7 Gy per insertion. Each patient received 3 insertions of intracavitary brachytherapy, to total dose 21Gy contributing to reference point "A". After computerized planning, 100% dose distribution was confirmed to point "A". Thus, all the patients received 7 Gy at point 'A' in both arm of the study subjects.

In this study radiation dose distribution at OARs in consideration i.e., urinary bladder and rectum were compared between Arm A and Arm B. Independent sample t test were done to find whether any significant difference is existing or not. In all three insertions, urinary bladder dose distribution was slightly smaller by HDR Co^{60} irradiation than HDR Ir^{192} exposure. These differences were statistically significant in first two insertions but not in third one. The analysis of data reveals that radiation dose distribution in case of rectum points, the mean dose distribution was significantly lower in all three insertions of Co^{60} exposure than Ir^{192} exposure ($p<0.001$). Richter compared a Co^{60} and Ir^{192} source of identical dimension and construction and discussed [9] tissue absorption, geometry function and integral dose of the two sources and revealed that the dose for Co^{60} sources in fat tissue is 0.4 percent higher and 0.8 percent lower for the rectum than for Ir^{192} sources. Islam [10] has also showed no significant advantages or disadvantages found in dosimetry aspect comparing with two sources.

The study was set out to explore the comparison of dose distribution of two radionuclides used in remote after loading HDR brachytherapy, Ir^{192} and Co^{60} respectively, at reference point 'A' and OARs in the treatment of locally advanced carcinoma cervix. EBRT followed by HDR-ICRT is considered as standard radiation treatment strategy for patients with locally advanced carcinoma cervix. Especially in developing country like Bangladesh; where high number of patients with cervical cancer requires the brachytherapy service, low-cost sustainable technology is utmost need.

In this study, ICRT treatment planning dose was prescribed and normalized at reference point 'A'. So, both radionuclides contributed the same dose as prescribed and achieved 100% coverage.

Therefore, both the radionuclides are identical at this point. Hence difference would be at OARs. Normal tissues like rectum and urinary bladder remain as organs at risk for HDR brachytherapy treatment of locally advanced carcinoma cervix due to their close vicinity.

Conclusion

In this study radiation dose distribution at OARs i.e., urinary bladder and rectum were compared between Arm A and Arm B. In all three insertions in urinary bladder the mean dose distribution was slightly smaller in HDR $Cobalt^{60}$ irradiation than HDR $Iridium^{192}$ exposure. These differences were statistically significant in first two insertions but not in third one. In case of rectum point, the mean dose distribution was significantly lower in all three insertions of Co^{60} exposure than Ir^{192} exposure.

Recommendation

This observational study concerned with radiation dose distribution to OARs. Taking into the account of long half-life of Co^{60} and subsequent economic considerations (low cost), distribution by the two radionuclides are comparable and Co^{60} can be the acceptable alternative radionuclide used in HDR brachytherapy.

Conflict of interest:

There was no conflict of interest in this study.

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