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Original Research Article

PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT-60 RADIONUCLIDE SOURCE-A TERTIARY CENTER EXPERIENCE

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Abstract

Background: Cervical cancer is the second most common malignancy among women worldwide, accounting for nearly 500,000 cases and 250,000 deaths annually. With the availability of the miniature Cobalt60(Co60) radionuclide source in brachytherapy, this study aimed to evaluate the acute genitourinary (GU) and gastrointestinal (GI) toxicity using a C060 source in high-dose brachytherapy for carcinoma cervix, with the feasibility of twice-weekly brachytherapy and response assessment at the end of treatment. **Material and Methods:** This single-arm prospective study was conducted at the Department of Radiotherapy, Barnard Institute of Radiotherapy, Madras Medical College, Chennai from June 2017 to September 2018. Thirty-eight uterine cervix carcinoma patients with stage IB2-IIIB (FIGO-2009) were treated with radiotherapy 50 gy-50. Gy/25#-28# in Theatron Phoenix with sensitiser chemotherapy with cisplatin 40 mg/m2 followed by intracavitary brachytherapy with BEBIG machine with C060 of 7 Gy in 3# with a minimum gap of 72 h between each fraction was performed and assessed for acute GI and GU toxicity using the Radiotherapy Oncology Group (RTOG) acute toxicity scale. **Results:** The study analysed 38 patients with carcinoma cervix with a mean age of 53 (30-65). Complications were mostly grade 1 and grade 2, while one patient (2.63%) had grade 3 GI toxicity. Twenty-seven patients (71%) had a complete response, and 11 (29%) had a partial response at the end of 8 weeks. **Conclusion:** Cervical cancer patients treated with Co60 brachytherapy twice weekly mostly had grade I and II toxicities. Using co60 HDR Brachytherapy seems to be a better and more economical option in high-volume centers.

INTRODUCTION

According to the Indian Council of Medical Research (ICMR) 2012, the Chennai metropolitan area ranks first compared to other metropolitan areas, with 236 per 100,000 people. The average annual number of cases increased since 2012. Over 80% of patients present at a locally advanced stage. Around 80,000 deaths were reported due to cervical cancer in India.[1-3] Radiotherapy is an effective treatment modality for uterine cervical carcinoma. Radiotherapy for cervical carcinoma usually comprises a combination of external beam radiation and intracavitary brachytherapy. The curative potential of radiotherapy is greatly enhanced by intracavitary brachytherapy.[4,5] The success of brachytherapy depends on delivering a high radiation dose to the uterine cervical tumour volume and considerable sparing of the surrounding normal structures.

The Radiation Therapy Oncology Group (RTOG) and Gynecologic Oncology Group (GOG) have incorporated a high dose rate (HDR) as a component in treating cervical cancer. With a 5-year survival rate after radiotherapy in the range of 30% to 50%, even for advanced cases of carcinoma cervix, brachytherapy with External Beam radiotherapy (EBRT) has become the standard of care.[6] For HDR, various dose-fraction schedules have been used worldwide For HDR. Although iridium 192 has been widely used as a radionuclide source, it was our institute's first cobalt 60 radionuclide (CO60) source for treatment. Due to their similarity in properties, the clinical outcomes of toxicity are comparable with the additional advantage of less change in the source of cobalt 60. Therefore, this study aimed to evaluate acute genitourinary and gastrointestinal toxicity using a C060 source in high-dose brachytherapy for cervical carcinoma with the feasibility of twice-

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weekly brachytherapy and response assessment at the end of treatment.

MATERIAL AND METHODS

This single-arm prospective study was conducted at the Department of Radiotherapy, Barnard Institute of Radiotherapy, Madras Medical College, Chennai from June 2017 to September 2018. Thirty-eight cervical carcinoma patients who had completed their EBRT and were slated for brachytherapy with minimal or no parametrial disease were selected for the study.

Inclusion Criteria : Biopsy-proven newly diagnosed carcinoma cervix, age - 30-65 years, stage-IB2-IIIB, histology - squamous cell carcinoma and its variants, Eastern Cooperative Oncology Group (ECOG) 0-2, previously not exposed to any chemotherapy or radiotherapy, no major life-threatening complications, HIV negative, the patient should be fit for anaesthesia, cystoscopy – for ruling out bladder invasion, urine routine, culture, and sensitivity to rule out other causes of cystitis before brachytherapy, and written and informed consent were included.

Exclusion Criteria: Patients aged < 30 and > 65 years, ECOG -3 or more, stage IVA –involvement of the bladder and rectum, inadequate hepatic and renal functions, patients not consenting to chemotherapy, previously treated for any other malignancy, metastatic or recurrent disease, HIV-positive patients, and patients unfit for anaesthesia were excluded.

A comprehensive investigation plan included obtaining a biopsy from the tumour, conducting a complete blood count, liver and renal function tests, assessing viral markers, performing a CT scan or MRI of the abdomen and pelvis before and 6-8 weeks after treatment, obtaining a chest X-ray (PA view), ECG, and blood grouping, along with a cardiology evaluation for fitness, and monitoring the weekly complete blood count (CBC) and renal function test (RFT) before each brachytherapy fraction.

The study enrolled eligible patients who underwent radiotherapy, consisting of external beam radiotherapy to deliver a total dose of 50 Gy-50.4 Gy to the pelvis (180-200 cGy per fraction, 25 -28 fractions over five days a week, Monday to Friday), utilising a cobalt teletherapy machine. This was followed by brachytherapy delivered at a dose of 21 Gy (7 Gy per fraction, three fractions) with a minimum 72-hour interval between each fraction, utilising a cobalt-60 source and the BEBIG Brachytherapy Machine.

Concurrently, the patient received weekly cisplatin chemotherapy at 40 mg/m2 with appropriate premedication. The patients were clinically evaluated for acute gastrointestinal and genitourinary symptoms throughout the treatment course, with response levels graded accordingly. At 6-8 weeks post-treatment, CT abdomen-pelvis or MRI scans were conducted to assess the treatment response. Toxicity levels were graded according to the RTOG acute toxicity criteria, and patient compliance during brachytherapy sessions was assessed.

For EBRT treatment planning, the entire pelvis, including the cervix, vagina, parametrium, iliac, and pelvic lymph nodes, was treated. The following treatment portals and borders were utilised: superior border: L4-L5 interspace (including iliac and hypogastric nodes). Inferior border: Lower border of the obturator foramen if the vagina was uninvolved; if the vagina was involved, the entire vagina up to the introitus was included. Lateral border: 2 cm lateral to the bony pelvis.

The treatment field was verified using X-ray simulation. The treatment portals were as follows: anteroposterior (AP) and poster anterior (PA) portals were used if the field separation was less than 20 cm. Field separation of more than 20 cm was treated with a 4-field box technique, with the anterior border in front of the pubic symphysis and the posterior border at the S2-S3 junction.

Chemotherapy involved cisplatin at a dose of 40 mg/m² administered weekly, with pre-medications, including Inj. Dexamethasone, Inj. Ranitidine, and Inj. Ondansetron. Adequate hydration was provided before and after chemotherapy. Chemotherapy was administered as a radiosensitiser, and 4-5 cycles were planned.

After the teletherapy phase, all the patients were assessed for intracavitary application. Those suitable for brachytherapy underwent the procedure using HDR brachytherapy. This technique was employed remotely after loading with a cobalt-60 source using a BEBIG machine. The activity used was 1.82 curie (67.484 GBq), and an intracavitary applicator modified from the Fletcher suit with 15 and 20-degree angulation was utilised. Brachytherapy was delivered in three fractions, with a minimum gap of 72 h between each fraction. The prescribed dose to Point A was 7 Gy.

Under anaesthesia, with the patient positioned in lithotomy, the perineum and upper half of the thighs were cleansed with beta-iodine and draped. A vaginal examination was performed, followed by catheterisation of the urinary bladder and injection of 7 ml of diluted contrast (3 ml contrast + 4 ml distilled water) into Foley's balloon. The uterine length was measured using a uterine sound, and the cervical stopper was adjusted accordingly and secured. Two ovoids were introduced and positioned as required. Vaginal packing was applied, and a rectal tube was inserted. A CT simulation was performed, and the resulting images were used for applicator reconstruction in the treatment planning system. Points A and B were defined, with dose prescription to Point A calculation of bladder and rectum points as per the International Commission on Radiation Units (ICRU)38 guidelines. The bladder and rectum doses were limited to < 80% of the Point A dose. Optimisation was achieved through adjustments in dwelling positions and times. After attaining the desired prescription isodose, the patient was

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connected to the BEBIG machine with a cobalt-60 source via catheters (transfer tubes) and treated accordingly.

Assessment of gastrointestinal (GI) and genitourinary (GU) toxicities occurred on a defined schedule: First assessment: After applying the initial HDR intracavitary brachytherapy (ICBT). Second assessment: Upon completion of the final HDR application. Third assessment: One month after the last HDR ICBT application. Fourth assessment: Two months after the last HDR ICBT application. Fifth assessment: Three months after the last HDR ICBT application.

RESULTS

The average age of the patients was 53 years, and most had stage IIIB disease. The predominant HPE was moderately differentiated squamous cell carcinoma. The histological type was well differentiated (2.6%), moderately differentiated (47.3%), poorly differentiated (28.9%), large cell non-keratinising (21%); time interval - < 1 week (60.5%), > 1 week (39.4%); cisplatin cycles - 2 cycles (5.2%), three cycles (15.7%), four cycles (31.5%), five cycles (47.36%); ECOG performance status: 0 (7.8%), 1 (55.2%), 2 (36.8%); clinical tumour response - complete response27 (71%), partial response 11(29%). [Table 1, Table 2]

Most of the patients in the study could tolerate the chemotherapy cycle and complete all five weekly schedules. There was a delay of more than a week to 12 days for nearly half of the patients due to grade 3 - 4 skin reactions due to EBRT and referral from other centres, but this was compensated with twice weekly brachytherapy with a minimum gap of 72 hours between each fractionation. There were no patient-related factors for the delay between the fractions except for one patient who had Grade III GI toxicity and was managed with symptomatic and supportive care. 27 [71%] patients had complete clinical and radiological responses at the end of 3 months. [Table3]

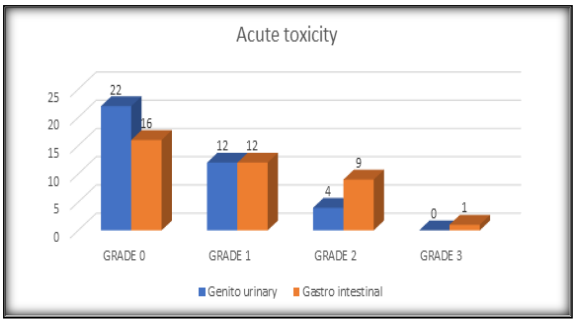

Figure1: Toxicity-assessment

Table 1: Demographic data of the study

		Frequency (%)
Age (years)	30- 40 years	1 (3%)
	41 -50 years	10 (27%)
	51-60 years	18 (49%)
	61 -65 years	08 (21%)
FIGO *staging	IB2	Nil
	IIB	15 (39.4%)
	IIIA	2 (5.2%)
	IIIB	21 (55.2%)
Squamous cell carcinoma	Well-differentiated	1 (2.6%)
	Moderately differentiated	18 (47.3%)
	Poorly differentiated	11 (28.9%)
	Large cell non-keratinizing	8 (21%)
Time interval	< 1 week	23 (60.5%)
	>1 week	15 (39.4%)
Cisplatin (cycle)	Two cycles	2 (5.2%)
	Three cycles	6 (15.7%)
	Four cycles	12 (31.5%)
	Five cycles	18 (47.36%)
ECOG+	0	3 (7.8%)
	1	21 (55.2%)
	2	14 (36.8%)
Tumor response (clinical)	Complete response	27 (71%)
	Partial response	[1]11 (29%)

* FIGO: International Federation of Gynecology and obstetrics 2009

\+ ECOG: Eastern cooperation oncology group

Table 2: Brachytherapy Characteristics

CA Cervix [1-III]	Median	Range
EBRT [Whole Pelvis]	50GY	-
HDR	7/3#	-
Point A	7gy	7-7.5GY
ICRU Bladder Point	5.6GY	4.2-6GY
ICRU Rectal Point	5.4GY	3.2-6GY
BED DOSE++ [EBRT+HDR]	124.4	120-133
EQD2§ Tumour [EBRT+HDR]	83.6GY	78.8-86GY

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1 ++ BED: Biologically Effective dose
§ EQD2 : Equivalent dose

Table 3: RTOG Acute Toxicity Grading

Toxicity	Grade				
	0	1	2	3	4
Genitourinary	22 (57.8%)	12 (31.5%)	4 (10.50%)	0	0
Gastrointestinal	16 (42.1%)	12 (31.5%)	9 (23.60%)	1 (2.60%)	0

DISCUSSION

In our study, the average age group of presentation was 53 years, whereas it was 45 years and 50 years in other studies. Most of the patients had stage IIIB disease. Predominant Histopathology (HPE) is moderately differentiated squamous cell carcinoma. Atara Ntekim et al. reported (that 3%) had grade 3 gastrointestinal toxicity, while all others had grade 2 toxicity.[7] Jain Abhay Kumar et al. reported that only two patients [3%] had acute diarrhoea, comparable to the iridium source.[8] Pesee M et al. 96.5% had complete response rates, but morbidity rates of grade 1 and grade 2 radiation proctitis were 27.0% and 10.6 %, respectively. The treatment with HDR-60 brachytherapy less than 850 cGy per fractionation for decreasing the grade 2 and grade 3 radiation morbidity was recommended in the study.[9]

Gurjar OP et al. reported that the mean dose to high-risk clinical target volumes (HRCTV) for D90 (dose to 90% volume) was 102.05% (SD: 3.07). The mean D2cc (dose to 2 cubic centimetre volume) of the bladder, rectum and sigmoid were 15.9 Gy (SD: 0.58), 11.5 Gy (SD: 0.91) and 4.1 Gy (SD: 1.52), respectively. This study concluded that the Co-60 HDR brachytherapy unit is a good choice, especially for centres with few brachytherapy procedures, as no frequent source replacement is required, like in an Ir-192 HDR unit.[10] Nandwana U et al. reported that Co-60 is a logical alternative to Ir-192 in low socio-economic settings when repeated source changes are not an option.[11] Tantivatana T et al. reported that the grade and clinical stage of cancer significantly affect survival outcomes. Patients treated with HDR Co-60 brachytherapy were comparable in survival and toxicity outcomes to those with HDR Ir-192 brachytherapy, concluding that the Co-60 source has economical advantages over Ir-192 and is suitable for low-resource settings.[12] Strohmaier S et al. showed no advantages or disadvantages for Co60 sources compared with 192Ir sources regarding clinical aspects. Nevertheless, there are potential logistical advantages of Co60 sources due to their longer half-life (5.3 years vs. 74 days), making it an interesting alternative, especially in developing countries.[13]

Lee Y et al. reported a statistically significant difference in brachytherapy EQD2 among the four pelvic lymph node (LN) groups ($p < 0.05$), with the Obturator lymph nodes receiving the most dose. This study highlights a 4.1% to 9.5% variation in brachytherapy dose contribution to the total EQD2 among pelvic LN groups. This difference in HDR contribution needs to be considered when prescribing an EBRT boost dose to each pelvic LN group for the optimal therapeutic total dose.[14] Nikam DS et al. reported the feasibility and cost-effectiveness of a high dose rate (HDR) cobalt60 (60Co) source versus Iridium-192 (192Ir) source brachytherapy in government-funded hospitals and the treatment interruption gap due to the exchange of sources. This study concluded that treatment interruption due to source exchange is longer and can be minimised using a cobalt source, as it is cost-effective and has a 5-year working life. Thus, the Co60 source for brachytherapy is a feasible option for government-funded institutions.[15]

In studies comparing ≥III gastrointestinal (GI) and genitourinary (GU) acute toxicity of chemo-radiation using Ir-192 and Co-60 as high-dose-rate (HDR) sources, various researchers have reported distinct outcomes. Chung YL et al. observed 0% GI and 2% GU toxicity [grade 3] in their Iridium-based study with fractionation of 25/5 for HDR and 45/25 for EBRT.[16] Chen et al. (2006), using Ir-192, reported 0% GI and 4.3% GU [grade 3] toxicity with a 24/4 HDR fractionation and 45/25 EBRT.[17] Notably, no significant GI or GU toxicities were observed in the study by Shakespeare TP et al. (2006) involving Ir-192 with a fractionation of 31.8/6 for HDR and 45/25 for EBRT.[18] In a Co-60 study by Atara Ntekim et al. (2008), a fractionation of 19.5/6 for HDR and 45/22 for EBRT led to 3% [grade 3] GI and no GU toxicity.[7] Similarly, the study conducted by Jain Abhay Kumar (2017) with Co-60 exhibited no GU toxicity and 3.07% GI toxicity [grade 3] using a 21/3 HDR fractionation and 50/25 EBRT.[8]

A comparison of early < grade 2 toxicity across various studies revealed diverse outcomes regarding specific toxicities. In the study by Chung et al. (2005), while no data was provided for proctitis and vomiting, diarrhoea was reported in 77% of cases, nausea in 44%, and GU complications in 22% of cases.[16] In Chen et al.'s study (2006), no toxicities were mentioned except for a low % GU toxicity of 5.7%.[17] Conversely, Shakespeare et al. (2006) noted a 4.8% incidence of proctitis and 23.8% cystitis, while other toxicities were not specified.[18] Atara Ntekim et al. (2008) documented 57% proctitis, 59% diarrhoea, 11% nausea, 10% vomiting, and 40% cystitis, with corresponding GU complications affecting 40% of cases.[7] Jain Abhay Kumar's study (2017) observed 56.92% proctitis, 58.46% diarrhoea, 10.76% nausea, 13.84% vomiting, 38.46% cystitis, and a 40% GU complication rate.[8]

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Compared to these studies, which used iridium and cobalt 60 for brachytherapy, the acute toxicities were comparable, with no significant grade III complications. Most patients had early symptoms; only one had grade III GI toxicity. Our study was comparable to that of Atara Ntkeim et al. and Jain Abhay et al., which used cobalt 60 as the brachytherapy source for treatment.[7,8]

In our study, all patients received chemotherapy, although some could not complete all five cycles. Three fractions of 7 Gy, with a gap of 72 h between each fraction, was a feasible option, similar to the study by Kumar et al.[8] This compensates for the time delay between EBRT and brachytherapy. The dose per fraction in our study was 7 Gy, according to the American Brachytherapy Society (ABS) guidelines. The secondary endpoint was the response rate of the primary tumour. The acute toxicity profile was assessed using the RTOG scale, which differs from the above two studies using the Common Terminology Criteria for Adverse Events(CTCAE). All patients completed the treatment within seven weeks, though one patient with Grade III toxicity during brachytherapy could not. 27 [71%] patients had complete clinical and radiological responses, 10 (26.3%) had a partial response, and 1 (2.63%) had progressive disease at the end of 3 months.

CONCLUSION

According to GLOBOCON 2018, it is the second most common malignancy in women in India. Carcinoma cervix turnover accounts for 10-15% of cases in our hospital, with additional patients referred for brachytherapy from most government hospitals in Tamil Nadu. A shorter overall treatment time for this malignancy will result in better patient compliance if no toxicity or locoregional failure increases.

The study found that cobalt radionuclide brachytherapy has a toxicity profile similar to iridium, making it suitable for treating patients in low-resource settings with high patient loads. This study highlighted that cobalt radionuclide brachytherapy has a toxicity profile comparable to iridium. This would translate to treating many patients in low-resource settings with high patient load and no frequent source change, as cobalt 60 has a long half-life with similar dosimetry properties and an acute toxicity profile.

Cervical cancer patients treated with Co60 brachytherapy twice weekly [minimum of 72 h between each fraction] had mostly grade I and II toxicities. Using co60 HDR Brachytherapy is a better and more economical option in high-volume centres. The follow-up period in this study was limited to 90 days after treatment. Further, follow-up is needed to assess the late toxicity effects of cobalt brachytherapy.

Conflicts of interest: None

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