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HDR BRACHYTHERAPY IN CERVICAL CANCERS WITH CO 60 SOURCE: A SINGLE INSTITUTION EXPERIENCE

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Abstract

Background: For High-dose-rate (HDR) brachytherapy in gynecological cancers, the most commonly used isotope is Ir-192. Co 60, with its longer half-life, is cost effective in high volume centres, but there have been concerns regarding its toxicity and safety. **Aim:** This study aimed to investigate the clinical profile, outcome and tolerance of HDR Brachytherapy using a Co 60 source in cervical cancer treated with primary radiation. **Material and Methods:** This retrospective study included 172 patients with cervical cancer treated with HDR Brachytherapy between March 2021 and March 2023. Patients with Stage II-IVA cervical cancer were treated with definitive chemoradiation with External Beam RT (3DCRT 4 field box technique) 50 Gy/25 # at 200 cGy/# for 5 weeks, along with 3 to 5 cycles of cisplatin 40 mg/m2 weekly followed by Co 60 HDR brachytherapy. **Results:** This retrospective study included 172 patients with cervical cancer treated with HDR Brachytherapy between March 2021 and March 2023. Patients with Stage II-IVA cervical cancer were treated with definitive chemoradiation with External Beam RT (3DCRT 4 field box technique) 50 Gy/25 # at 200 cGy/# for 5 weeks, along with 3 to 5 cycles of cisplatin 40 mg/m2 weekly followed by Co 60 HDR brachytherapy. **Conclusion:** Our study shows that HDR with a Co-60 radionuclide source and concurrent chemotherapy is well tolerated in cervical cancer patients, with comparable treatment outcomes.

INTRODUCTION

Brachytherapy plays a major role in the effective treatment of gynaecological malignancies, the most common of which are carcinoma cervix and carcinoma endometrium.[1] Brachytherapy sources are typically unstable gamma-emitting radioisotopes, classically radium (which is no longer in clinical use), and isotopes of caesium or iridium. Traditionally, treatments were low dose rate (LDR) and occurred for 40–60 h. The patient was non-ambulatory during the duration of treatment, and as such, the treatment would require inpatient hospitalisation with regional or general anaesthesia. The clinical use of high-dose-rate (HDR) brachytherapy has dramatically increased, significantly decreasing treatment time. As a result, these treatments can occur on an outpatient basis with patient preparation, implantation procedure, imaging and treatment being completed within a few hours and hence, more cost-effective. Additionally, there are opportunities to perform adaptive treatment planning and dosimetry with each fraction. From a radiation biology perspective, HDR has been proposed to be superior if adequate time is allotted between fractions for normal tissue to repair sublethal damage between fractions.[2] A final modern improvement in gynecologic brachytherapy has arisen from the development of computer-controlled remote after-loading devices for brachytherapy, which eliminates radiation exposure to healthcare workers in contrast to manual application or manual after-loading.

Ir-192 isotope is the most commonly employed one for the same due to its smaller size and higher

specific activity. Co 60 was not used because of the bigger source size. However, Co 60 is now available in a miniature size and has radiobiological and dosimetric properties similar to those of Ir192; its main advantage is a longer half-life and hence avoids the issue of frequent replacement.[3] This is a great advantage for high-volume centres. However, the higher energy of 1.25 Mev for Co 60 compared to 0.38 Mev for Ir 192 raises concerns regarding toxicity and safety.

Aim

This study aimed to investigate the outcome and tolerance of HDR Brachytherapy using a Co 60 source in cervical cancers treated with primary radiotherapy in our centre and to analyse their clinical and treatment profiles.

MATERIALS AND METHODS

This retrospective study included 172 patients with cervical cancer who were treated with primary radiotherapy, including HDR Brachytherapy in Department of Radiotherapy, Coimbatore Medical College between March 2021 and March 2023.

Inclusion Criteria

Case records of histology-proven carcinoma cervix cases with intact uterus treated with primary curative radiotherapy, including brachytherapy, in our centre were included.

Exclusion Criteria

Posthysterectomized Ca cervix cases, cancer cervix cases not taken up for brachytherapy, and metastatic carcinoma cervix cases were excluded from the study.

Data from all patients with biopsy-proven cervical cancers, who met the inclusion criteria were collected. This study was undertaken after obtaining institutional ethical board clearance.

The cases were treated according to department protocols. In general, patients with Stage II-IVA cervical cancer were treated with definitive chemoradiation with External Beam RT (3DCRT 4 field box technique) 50 Gy/25 # at 200 cGy/# for 5 weeks, along with 3–5 cycles of cisplatin 40 mg/m2 weekly, after assessing fitness for chemo.

Intracavitary brachytherapy (ICA) was administered using metal Fletcher Suit applicator-uterine tandem and ovoids in all cases. In all ICA cases, the application was performed under spinal anaesthesia. CT simulation after applicator placement was done and CT-based volumetric planning was performed using Saginova 2.0 TPS. The Brachytherapy machine used was Saginova 2.0, developed by Bebig-Eckert & Ziegler. The dose to the HR-CTV D90 and D2CC bladder and rectum were documented. Combined EQD2 and BED received from a combination of EBRT and brachytherapy for all three structures were recorded in all patients. The treatment plans were approved according to the ABS guidelines.

The follow-up protocol after treatment completion was a monthly clinical examination for 1 year and imaging (CT/MRI pelvis) at 2 months after RT completion in all patients. The treatment profile was analysed, and treatment outcomes, including tolerance (acute and chronic toxicities) and response to treatment, were assessed retrospectively for at least 6 months after treatment completion for all patients.

RESULTS

Of the 172 patients who underwent brachytherapy in the study period, 122 (carcinoma cervix) with an intact uterus underwent intracavitary brachytherapy and 50 post-hysterectomised patients underwent vaginal brachytherapy.

Carcinoma cervix patients treated with Intracavitary application: Clinical profile

The median patient age was 55 years. Histologically, 93 (76.3%) of the 110 patients had moderately differentiated carcinoma, and the remaining 29 (23.6%) had adenocarcinomas. 4% of patients had Stage I disease, 26.2% of the patients had Stage II disease,56.6% of patients had Stage III disease, and 13.2% had Stage IVA disease. [Table 1]

EBRT

In most cases (98%), the dose of EBRT delivered was 50-50.4 Gy/25-28 # at 180-200 cGy/# over 5-5.5 weeks to the pelvis. Eighteen patients received pelvic + para-aortic nodal RT, and nine patients received hypofractionated RT, treated during the time of 2nd wave of COVID. Except for 19 patients who received IMRT simultaneous integrated boost (SIB) to involve bulky pelvic nodes, all other patients were treated with 3D conformal radiation therapy.

Intracavitary brachytherapy

During the study period, none of the patients underwent interstitial or hybrid brachytherapy. All the patients underwent intracavitary application. The most common dose of fractionation used was 7 Gy/#, treated 1 # per week. A few cases were also treated with 8 Gy/# * 2 fractions,1 week apart. The entire treatment was completed within an average of 3 months (Range 60-100 days). Approximately 84% of the patients received concurrent platinum-based chemotherapy, while the remaining 16% received only radical RT. The reasons for avoiding chemotherapy as per records were advanced age, deranged renal parameters, and poor performance status.

Biologically Equivalent Dose (BED) calculations were performed using the linear quadratic formula, assuming an alpha-beta ratio of 10 for tumours and 3 for normal tissues. Combined EQD2 received by the tumour (HR CTV D90), bladder, and rectum from EBRT and brachytherapy was calculated for each patient, and the mean was arrived at. The mean EQD2 for the HR CTV D90 was 85.5 Gy (Range

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[80.5-92.55]), the mean D2cc bladder was 85.51 Gy and the mean D2cc rectum was 70.8 Gy. [Table 2]

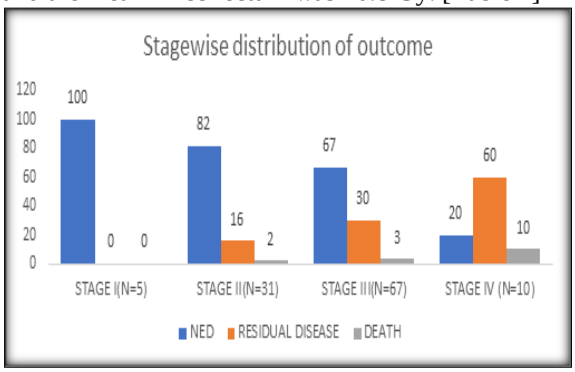

Figure 1: Stagewise distribution of outcome

Carcinoma cervix patients treated with Intracavitary application: Treatment outcome

Of the 122 patients treated with ICA during this period, 12 were lost to follow-up. The remaining 110 patients were followed for a minimum of 6 months to a maximum of 24 months. Of the 110 patients analysed, 86 (78%) achieved a complete response, as assessed at least six months after treatment completion. Sixteen patients (14.6%) had locoregional residual disease, and eight patients (7.4%) died. None of the patients developed distant metastasis during the study period.

The most common acute reaction was proctitis, with 45% of patients having grade 1 and 10% having grade 2 proctitis. Diarrhoea was the second most common acute reaction experienced by patients, with 35% having grade 1 and 12.5% having grade 2. Grade 3 diarrhoea was the worst reaction noted among all patients, and this occurred in three (2.5%) patients. Genitourinary toxicity was generally mild (grade 1) in 55% of the patients and did not disrupt treatment. [Figure 1]

Table 1: Patient demographics and tumour characteristics

		Number (%)
Median Age at Diagnosis		55 years (34-72 years)
Median follow up		17 months (6-24 months)
Histology (n) %	Squamous cell carcinoma	84%
	Adenocarcinoma	16%
Pelvic/paraaortic Lymphnode inv	Yes	38.20%
	No	61.80%
FIGO Stage	I	5 (4%)
	II	32 (26.2%)
	III	69 (56.6%)
	IV	16 (13.1%)

Table 2: Combined mean EQD2 (Gy)

Volume	Combined mean EQD2 (Gy), Range
HRCTV D90	85.5 Gy (80.5-92.55)
RECTUM D2CC	70.8 Gy
BLADDER D2CC	85.51 Gy

DISCUSSION

The iridium 192 (Ir-192) radionucleide source is widely used for HDR brachytherapy because it is easier to manufacture iridium-192 of smaller size for brachytherapy applications. The Cobalt-60 (Co-60) HDR source was available but unpopular because the earlier source sizes were larger than Ir-192.[4] It is now possible to produce miniaturised Co-60 radionuclides for HDR applications. This has been shown to have identical geometric and dosimetric properties as Ir-192.[5] The advantage of Co-60 over Ir-192 is its longer half-life (5.2 years compared to 73.8 days of Ir-192. This implies that instead of changing the Ir-192 source every 3–4 months, the Co-60 source can be changed every 6–8 years, which is much more economical and attractive for low-resource settings with a disproportionate higher load of cervical cancer cases. However, the higher energy of 1.25 MeV of Co-60 compared with 0.6 MeV of Ir-192 raises concerns about possible increases in toxicity to patients. While Iridium-192 is widely used as an HDR source and has been widely discussed in the literature, reports on studies with cobalt 60 HDR radionuclide sources are very scarce, especially with concomitant treatment with chemotherapy.

Therefore, this study was carried out to assess the acute gastrointestinal and genitourinary toxicities and the disease outcomes associated with Co-60 as an HDR source compared with published results in patients with cancer of the uterine cervix with similar characteristics treated with Ir-192 HDR brachytherapy. This study also analysed the clinical profile and dosimetric parameters as all patients were treated with CT-based HDR brachytherapy.

Local control in Carcinoma cervix

Since our study reports a short-term analysis, survival analysis may not be possible. However, the local control rate observed in our study (No Evidence of Disease NED vs. residual disease) at 6 months, (78% NED) is a good predictor of overall survival. These figures correlate with the long-term survival data reported in the Embrace I study, where the radioisotopes used were iridium 92. The local control reported in the Vienna study (1993-97) with a median follow-up time of 2.8 years, where CT-based planning was carried out, was 78%.[6] In more

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recent Vienna studies, using MRI-based planning, local control rates reported were better when compared to our study, probably because of improved target delineation and the use of interstitial and hybrid brachytherapy in deserving cases.[7] From this,we can draw a reasonable conclusion that there is no difference in the local control rates when the Co 60 isotope is used instead of the Iridium 192 source. Therefore, it makes sense to use the Cobalt 60 radioisotope in gynaecological brachytherapy in high-volume centres such as ours. Replacing CT-based planning with MRI might significantly improve the treatment outcomes further.

The total combined EQD2 dose with EBRT and ICRT should be in the range of 80–90 Gy 4 The current recommendation is to complete the entire protocol of EBRT and brachytherapy within 8 weeks. In cervical cancer, each additional day of treatment beyond 55 days has been shown to decrease overall survival by 1%.[8] In our study, due to caseload, technical limitations, lower socioeconomic status of the patients, and frequent defaulting, treatment in most cases could not be completed in this ideal period, ranging from 60 days to 100 days.

Dosimetric analysis

Dyk et al. have shown that the dosimetric parameters D100 (minimum dose covering 100% of the cervical target), D90, and Dmean of the gross tumour volume (GTV) as defined by MRI are associated with improved local tumor control.[9] The Vienna study showed a strong dose-effect relationship for local control, with local control rates >90% being associated with HR-CTV D90 of >86 Gy.[10] Similar importance of D90 was presented at ESTRO 2013, on retro-EMBRACE data (patients with MRI- or CT-guided 3D treatment before the start of the EMBRACE study). It was demonstrated that in 592 patients (with a median follow-up of 31 months), a D90 to HR-CTV of >92 Gy resulted in an overall local control rate of 95%. The results of this study are following the ABS guidelines15 (80–90 Gy for D90 HRCTV, 70–75 Gy for D2cc to the rectum and sigmoid, and approximately 90 Gy for D2cc to the bladder).[11] The doses to the rectum, bladder, and sigmoid were well within the tolerance limit, without compromising the doses to the target. Also, the planning dosimetric parameters of this study concurred with the results of already published studies on Ir-192 HDR brachytherapy unit-based planning.

Rectal toxicity

Our results showed that HDR with a Co-60 radionuclide source and concurrent chemotherapy is well tolerated in cervical cancer patients. Only three patients (2.5%) had grade 3 acute diarrhoea that necessitated treatment suspension for one week. There was no grade 3 or 4 acute genitourinary toxicity among the patients. The acute toxicity rates found in this study are among the lowest when compared with those reported in studies using Ir-192 HDR radionuclide source. In these studies, the reported rates of acute toxicity grade 3 ranged from 0%–8% for gastrointestinal and 0%–3% for genitourinary toxicities. Other studies with low-dose-rate brachytherapy reported acute toxicity grade 3, ranging from 0% to 15% for gastrointestinal toxicities and 1% to 8% for genitourinary toxicities. It was also observed that the influence of chemotherapy regimens on gastrointestinal and genitourinary toxicities was less apparent. The early (grade 2) gastrointestinal and genitourinary toxicities experienced by patients in this study are similar to outcomes from other studies, although comparison is difficult because most authors ignore these mild symptoms; hence, they are not reported, and if reported, consistent scoring criteria are not used. Ours being a retrospective study, we can rely only upon the records for data collection on toxicity. Further prospective studies on this aspect are required to accurately compare the grade 2 side effects.

Genitourinary toxicity

The acute genito-urinary toxicity in this study was relatively low, although the risk of late treatment-related toxicity is yet to be evaluated. The results of MRI-guided adapted brachytherapy in the LACC (EMBRACE-I) study showed an actuarial cumulative 5-year incidence of grade 3–5 morbidity as follows: 6.8% for genitourinary events, 8.5% for gastrointestinal events, 5.7% for vaginal events, and 3.2% for fistulae.[12]

Tantivatana et al. observed in their comparative study of patients with cervical cancer, they did not find any significant difference either in overall survival (77% vs. 81.9%) or disease-free survival (73.1% vs. 74.7%), and grade 3 and grade 4 complications were found (4.7% vs. 3.4%) at the 5-year follow-up between Ir-192 and Co60 sources, respectively.[13]

Since our study is not a comparative study, we may not be able to extract direct conclusions like in the Tantivatana study in treatment results and toxicity profile between Iridium and Cobalt 60 treated cervix cases. But based on previously published data, our local control rates and toxicity rates with Cobalt 60 source seem to be similar.

CONCLUSION

Our study shows that HDR with a Co-60 radionuclide source and concurrent chemotherapy is well tolerated in cervical cancer patients with comparable treatment outcomes. The acute gastrointestinal and genitourinary toxicity following HDR brachytherapy with a Co-60 source in chemoradiation treatment of cervical cancer is low and comparable with those reported for Iridium-192. Cobalt 60 has many economic advantages over Ir-192 and is suitable for low-resource radiotherapy.

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