

Clinical and dosimetric correlation in terms of treatment response, bladder and rectal toxicities in cervical cancer patients treated with cobalt 60 high dose rate brachytherapy (#97366)

1

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Clinical and dosimetric correlation in terms of treatment response, bladder and rectal toxicities in cervical cancer patients treated with cobalt 60 high dose rate brachytherapy

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Background: HDR image-guided brachytherapy with Co-60 isotope being a relatively recent approach. Our aim of study is to evaluate clinical and dosimetric parameters in terms of tumour response, bladder, and rectal toxicity in patients undergoing Cobalt 60 HDR Brachytherapy. **Materials and Method:** All patients were initially treated with EBRT in our center or other referral centers with a total dose of 45Gy-60Gy at 1.8-2Gy/fraction (including nodal boost) with concomitant chemotherapy with either cisplatin/ carboplatin. Patients were then scheduled for brachytherapy usually within 1week after completion of CRT and are assessed by local examination. Depending on local examination parameters at the time of brachytherapy they were posted either for ICBT/ ISBT. **Results:** The CR observed in stage I, II, III, IVA are 60%, 79.4%, 86% and 76.2% respectively. Complete response was seen in patients with mean EQD₂ of 78.67 Gy₁₀, 83.33 Gy₁₀, 84.23 Gy₁₀, 85.63 Gy₁₀ in stages I, II, III, IVA respectively. 79.2 % of cisplatin-treated patients and 87.5 % of carboplatin-treated patients had a complete response indicating that patients treated with either chemotherapy had similar response rates. **Conclusions:** According to results obtained from the study we conclude by saying that higher rates of complete response to treatment in cervical cancer is seen in patients with shorter OTT, shorter interval between end of definitive CT-RT and beginning of brachytherapy and squamous cell histology

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Abstract

Background: HDR image-guided brachytherapy with Co-60 isotope being a relatively recent approach. Our aim of study is to evaluate clinical and dosimetric parameters in terms of tumour response, bladder, and rectal toxicity in patients undergoing Cobalt 60 HDR Brachytherapy.

Materials and Method: All patients were initially treated with EBRT in our center or other referral centers with a total dose of 45Gy–60Gy at 1.8-2Gy/fraction (including nodal boost) with concomitant chemotherapy with either cisplatin/ carboplatin. Patients were then scheduled for brachytherapy usually within 1week after completion of CTRT and are assessed by local examination. Depending on local examination parameters at the time of brachytherapy they were posted either for ICBT/ ISBT.

Results: The CR observed in stage I, II, III, IVA are 60%, 79.4%, 86% and 76.2% respectively. Complete response was seen in patients with mean EQD₂ of 78.67 Gy₁₀, 83.33 Gy₁₀, 84.23 Gy₁₀, 85.63 Gy₁₀ in stages I, II, III, IVA respectively. 79.2 % of cisplatin-treated patients and 87.5 % of carboplatin-treated patients had a complete response indicating that patients treated with either chemotherapy had similar response rates.

Conclusions: According to results obtained from the study we conclude by saying that higher rates of complete response to treatment in cervical cancer is seen in patients with shorter OTT, shorter interval between end of definitive CT-RT and beginning of brachytherapy and squamous cell histology

Introduction

Cervical cancer is the second most frequent malignancy among Indian women(International Agency for Research on Cancer, 2020). Patients with cervical cancer may experience vaginal discharge or bleeding, flank or abdominal pain, haematuria, or rectal bleeding(Gupta et al., 2014). They present at an advanced stage as a result of their poor socioeconomic position and inadequate utilization of screening facilities in developing countries. Standard treatment for stage IB to stage IVA cancers consists of external beam radiation therapy(EBRT) and concurrent chemotherapy, followed by brachytherapy(Chargari et al., 2019; Gupta et al., 2014). Brachytherapy(BT) is a form of radiotherapy in which a radioactive source is kept either directly into or adjacent to the tumor(Chargari et al., 2019). From manual pre-load Low dose rate (LDR) to remote-controlled after-load High dose rate brachytherapy(HDR-BT), radioactive sources have undergone evolution(Chargari et al., 2019; Gupta et al., 2014). Brachytherapy of cervical cancers can be of two types based on anatomy and extent of residual disease, ~~which are~~ Intracavitary brachytherapy (ICBT) & Interstitial brachytherapy (ISBT). BT has its own set of potential side effects such as bleeding, uterine perforation, bladder or rectal perforation, abdominal pain, diarrhoea, discomfort in the lower abdomen and lower back(Gupta et al., 2014). HDR image-guided brachytherapy with Co-60 isotope is a relatively recent approach. The aim of our study is to ~~evaluate~~ clinical and dosimetric parameters in terms of tumour response, bladder, and rectal toxicity in patients undergoing Cobalt 60 HDR Brachytherapy.

Materials & Methods

A longitudinal descriptive study was conducted at Kasturba Medical College Hospital, Attavar, Mangalore between September 2020 to June 2022 after obtaining the institutional ethics approval (Kasturba Medical College, Mangalore , Manipal academy of higher education, Deemed to be university granted ethical approval to carry out the study within its facilities with Protocol No. IEC KMC MLR 12/2022/420)

Patients who met the eligibility criteria of histopathologically proven carcinoma cervix FIGO stage 1B to IV^A, with their written informed consent to participate were provided a questionnaire with demographic, basic medical information. According to the proforma, retrospective analysis parameters of the patients was extracted from medical records department and for prospective analysis data was collected on case to case basis. Dosimetric parameters was extracted from SAGI plan.

All patients were initially treated with EBRT in our center or other referral centers with a total dose of 45Gy–60Gy at 1.8-2Gy/fraction (including nodal boost) with concomitant chemotherapy with either cisplatin/ carboplatin. Carboplatin was administered to patients who were unfit for receiving cisplatin due to creatinine clearance being <50 ml/min (Cockcroft-Gault). Patients were then scheduled for brachytherapy usually within 1week after completion of CTRT and are assessed by local examination (per vaginal, per speculum, per rectal) for any residual disease, vaginal status, cervical Os, parametrial extent, rectal mucosal involvement. Depending on these parameters at the time of brachytherapy they were posted either for ICBT/ ISBT.

In ICBT uterine tandem with flange and two vaginal ovoids are inserted under anaesthesia (spinal/ general). In ISBT, interstitial needles are inserted using vaginal obturator in the Syed-Neblett template under epidural anaesthesia through transperineal route. First a guide needle is

inserted into anterior cervical lip and remaining needles depending on extent of disease is inserted. Utmost care was taken not to perforate bladder/ rectum.

CT scan simulation was done with applicators in-situ with 50ml of diluted contrast in bladder without intravenous contrast. ~~CT 3mm thickness axial sections were taken. The CT files were then transferred to SAGI TPS.~~ Applicators and catheters were reconstructed in the brachytherapy planning module (**Figure 1**). We prescribed the High-risk clinical target volume (HR CTV) and contours the organs at risk (OAR) such as bladder and rectum as per Gyn GEC  TRO contouring guidelines. Inverse planning technique was followed. Further optimization was done manually by dragging isodose line using graphical tool. This was a trial and error process where dwell time/dwell position are adjusted to achieve optimal dose coverage to High risk clinical target volume (HRCTV) ($EQD_2 > 80 \text{ Gy}_{10}$) with constraints to bladder D_{2cc} ($EQD_2 < 85 \text{ Gy}_3$) and rectum D_{2cc} ($EQD_2 < 75 \text{ Gy}_3$) (Viswanathan et al., 2009).

Clinical response was assessed at 3 months after brachytherapy completion. Response was evaluated with MRI in accordance with RECIST criteria 1.1. Bladder and rectal acute toxicities were assessed at end of 3 months. Acute complications were assessed according to RTOG acute toxicity criteria at end of 3 months (Cox et al., 1995).

The statistical analysis was carried out using the statistical tool SPSS version 22.0. Continuous variables were presented as Mean $\pm$ Standard Deviation, Median, Min: Max, Q1:Q3. Categorical variables were presented as frequency and percentage. Fisher's exact test was performed to see the association between two categorical variables. P value of less than 0.05 was considered significant.

Results

Study included 150 patients diagnosed with Carcinoma cervix (**Table 1**), out of which 6 patients were excluded due to loss of follow-up and since they did not receive chemotherapy. The mean age was 53.63 ± 10.21 years. The CR observed in stage I, II, III, IVA are 60%, 79.4%, 86% and 76.2% respectively. In the ulceroproliferative group, 113 patients (81.3%) had a complete response while 1 patient (33.3%) had a complete response in the endophytic group. CR was observed in 82.7% of patients in the squamous cell variant while 64.8% of patients with adenocarcinoma variant had a complete response. ~~P value found to be significant. P value was 0.0149, depicting that the histopathological variant of cervical cancer had a statistically significant effect on the outcome in our study, showing squamous cell carcinoma has the higher chance of clinical complete response when compared to adenocarcinoma.~~

79.2 % of cisplatin-treated patients and 87.5 % of carboplatin-treated patients had a complete response (**Figure 2**). ~~It was found that there is no significant association between the type of chemotherapy received by the patient and clinical response at the end of three months. The p-value is 0.837, indicating that both carboplatin and cisplatin had similar outcomes and did not cause any significant alteration in the outcome.~~

Lymph nodal status in the initial MRI was compared with the radiological response (MRI) at the end of three months. Patients without significant regional lymphadenopathy had 79.6% complete response, patients with pelvic lymphadenopathy had a 80% complete response and patients with paraaortic lymphadenopathy had a 100% complete response at the end of 3 months in the current study. ~~Patients with pelvic lymphadenopathy also showed a higher percentage of progressive disease (12.5% versus 10.2%) when compared to patients with no significant lymphadenopathy.~~

Out of 144 pts, 85 patients (58.8%) had CR in which 31 patients (53.4%) had complete response for whom treatment was completed within 56 days and more than 56 days respectively (**Figure 3**). Patients in more than 56 days arm had higher number of progressive diseases (24.1% vs 1.2%). A significant difference (P value <0.001) was noted among the groups depicting that outcome worsens as overall treatment time increases. Patients whose brachytherapy was scheduled within 14 days after the end of definitive CT-RT had higher complete response rates (92.8 % versus 69.3%) and less percentage of progressive disease (7.2% versus 13.3%). P value was <0.001 which is statistically significant implying better outcomes when brachytherapy is scheduled within 2 weeks of completion of CT-RT. Majority of patients (56.3%) did not show any bladder toxicity. 31.2% had grade 1 toxicity, 11.1% had grade 2 and 1.4% had grade 4 toxicity of the bladder. 43% of patients showed $\leq$ grade 2 toxicities of bladder toxicity. Most patients received EQD₂ between 70-80 Gy₃. It is noted that majority of patients who received EQD₂ 70-90 Gy₃ had grade 1 toxicity (36%) when compared to other subsets (7%). Majority of patients received 70-75 Gy₃ as mean EQD₂ to rectum. Majority of the toxicities noted are of acute grade 1 and 2 (53.5%). 43.8% of patients did not show any rectal toxicity. Grade 3 rectal toxicities are seen in 3 patients.

Complete response was seen in patients with mean EQD₂ of 78.67 Gy₁₀, 83.33 Gy₁₀, 84.23 Gy₁₀, 85.63 Gy₁₀ in stages I, II, III, IVA respectively (**Table 2**). In stage I disease, a complete response was observed with a mean EQD₂ of 78.67 Gy₁₀, whereas progressive disease was observed with an EQD₂ of 77.0 Gy₁₀. In stage II mean EQD₂ for complete response is 83.33 Gy₁₀ while mean EQD₂ of progressive disease was 82.29 Gy₁₀. In stage III disease complete response was noted with mean EQD₂ of 84.23 Gy₁₀ while progressive disease was seen with 82.50 Gy₁₀. In stage IVA patients with complete response had a mean EQD₂ of 85.63 Gy₁₀ whereas 83.50 Gy₁₀

was noted in progressive disease group. 5 patients showed ~~locoregional failure~~ in absence of distant metastasis at the end of 3 months. Out of 5 patients with locoregional failure, 4 patients had local failure and 1 patient had significant paraaortic lymphadenopathy. 10 patients showed evidence of distant metastasis mainly to liver.

Discussion

The aim of HDR brachytherapy is to administer high doses of radiation to tumor, to achieve greater control of disease with less toxicity to adjacent normal tissues. The advantage of brachytherapy comes from its dosimetric benefits, including the ability to deliver high and conformal doses to the site of disease with a rapid dose fall-off. The advantage of a Co-60 brachytherapy source is that it is a miniature source with longer half-life of 5.2 years when compared to the 73.8-day half-life of an Iridium 192 source.

The outcome of ICBT/ISBT depends on many factors - individual expertise, quality and timing of implantation, anatomy of treatment site, extent of vaginal packing, and type of source. This can lead to an excess of toxicity if the source is placed too close to a critical structure(Chargari et al., 2019).

A study by Krebs et al., which included patients with carcinoma cervix of FIGO stage IB1-IIIB, showed that 45% of patients had complete response and 55% patients had recurrent disease at end of 6 weeks post brachytherapy(Krebs et al., 2015). In a study by Susmitha pathy et al., which included patients with carcinoma cervix Stage IIB-IIIB who received definitive CT-RT followed by HDR brachytherapy, showed complete response of 76.0% at  end of 3 months; this is similar to the outcomes from our study which showed 80.6% complete response at end of 3 months(Pathy et

al., 2015). Similarly, we observed 60.0%, 79.4%, 86.0% and 76.2% complete responses in stages I, II, III, and IVA respectively. In a study by Hockel et al., including 100 patients demonstrated that tumor oxygenation in locally advanced cervical cancer is independent of its clinical stage, size, histological type, or grading(Höckel et al., 1996). Radiation to the primary disease in patients with hypoxic tumors revealed significant disadvantages in the outcome(Höckel et al., 1996). ~~In our study, among the patients with stage IB₂ cervical cancer, 40% (2 patients) had progressive disease at end of 3 months, which can be attributed to tumor hypoxia.~~ Tumor biology phenomenon must be taken into consideration when evaluating the effect of hypoxia on non-surgical anticancer treatments(Höckel et al., 1996). This may be a possible explanation for stage IB tumors (2 patients) showing progressive disease in our study.

While early outcomes are usually not important for survival variables and might be reflecting the tumors' sensitivity to RT, a study by Katanyoo et al., demonstrated that only 89 out of 367 patients (24%) who clinically had complete response were found to have disease recurrence with a median follow-up of 10.2 years(Huang et al., 2010; Katanyoo et al., 2012). A study by Pesse et al., showed one-year overall survival rates of 93.8% across all non-metastatic stages(Pessee et al., 2012). In a study by Afshin Rakhsha et al., 3 years DFS stages rates for patients who underwent EBRT (with or without concomitant chemotherapy followed by HDR Co 60 brachytherapy) were 85.7%, 70.4%, 41% and 16.6% for stages I, II, III, and IVA respectively(Rakhsha et al., 2015). With a median follow-up of 18 months, the 6-, 12-, 18-, and 24-month overall survivals were 98%, 86%, 75%, and 50%, respectively in a study by Javadinia et al.,(Javadinia et al., 2020). Thanatip et al., compared outcomes of HDR intracavitary brachytherapy using Ir 192 versus Co 60 source, ~~which showed no statistically significant differences~~ in 2 years OS (89.4% vs 91.6%)(Tantivatana &

Rongsriyam, 2018). In a study by Katanyoo et al., including 423 patients with stages IIB–IVA, 367 (95.3%) patients had clinical CR(Katanyoo et al., 2012). ~~In our study, we observed 60%, 79.4%, 86% and 76.2% complete responses in stages I, II, III, and IVA respectively at end of 3 months after completion of brachytherapy.~~

While some reports showed no difference in survival outcomes between Adenocarcinoma and Squamous cell carcinoma(Kilgore et al., 1988; Lee et al., 2006), other authors reported poorer treatment outcomes for Adenocarcinoma when compared to Squamous cell carcinoma - especially in stages I and II(Chen et al., 1999; Kleine et al., 1989). A retrospective study by Kleine et al., in 1989, (which included 268 squamous cell carcinoma patients and 144 adenocarcinoma patients of carcinoma cervix FIGO stages I-IV) there was decreased 5 year (53% vs 68%) and 10 year OS (42% vs 58%) rates in the adenocarcinoma group when compared to squamous cell carcinoma group(Kleine et al., 1989). Chen et al., in a retrospective study consisting of 3678 patients of carcinoma cervix FIGO stage I-IV with either squamous cell carcinoma (91.4%) or adenocarcinoma (8.2%), showed decreased 5 year OS in adenocarcinoma group (66.5% vs 74.0%) when compared to squamous cell carcinoma group(Chen et al., 1999). Histopathological variants like squamous cell carcinoma and adenocarcinoma showed variable 1 year survival rates of 75.2% and 88.9% respectively(Pesee et al., 2012). In a retrospective analysis by Katanyoo et al., 389 patients out of 423 patients had complete responses (CR), with squamous cell carcinoma and adenocarcinoma patients having 94.7% and 86.5 % CR, respectively(Katanyoo et al., 2012). In our study, we noted 82.7% and 64.8% CR in squamous cell carcinoma and adenocarcinoma respectively at end of 3 months.

Overall survival and progression-free and are significantly improved in the patients receiving Chemotherapy concurrently with radiation in a study by William A. Peters et al., (Peters et al., 2000). In a study by Keys et al., 79% of patients in cisplatin plus radiation arm and 63% of patients in radiation alone arm had no evidence of disease after 36 months follow-up, concluded that, by adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers (City, 1999). Higgins et al., concluded that carboplatin appears to be an effective alternative for cisplatin when combined with radiation therapy for cervix cancer upon evaluating in a study that included 31 patients with carcinoma cervix FIGO stage IB1-IIIB who underwent definitive radiation concurrently with carboplatin followed by brachytherapy and found evidence that 90% of patients had complete response rates (Higgins et al., 2003). In our study, similar results were noted with the usage of carboplatin and cisplatin. 79.2% of cisplatin-treated patients and 87.5% of carboplatin-treated patients had a complete response in our study.

There were treatment delays due to lack of brachytherapy facilities geographically, lack of coordination between EBRT and brachytherapy scheduling, delays from referral institutions, hematologic toxicities (neutropenia, thrombocytopenia), anaesthesia fitness, and severe vaginal mucosal reactions. A correlation was found between OTT and pelvic control in a study of a series of several patients with stage I-III lesions with the cut off taken at 7 weeks (Perez et al., 1995). Prolongation of OTT resulted in a decreased pelvic tumor control rate of 0.85% per day for all patients, 0.37% per day in Stages IB and IIA, 0.68% per day in Stage IIB, and 0.54% for Stage III patients treated with ≥ 85 Gy to point A in a study by Perez et al., (Perez et al., 1995). Kari tanderup et al., also showed that Overall treatment time is an independent factor for local

control(Tanderup et al., 2016). We observed a similar decrease in complete response rates if the treatment was not completed within 56 days (53.4% vs 98.8%) when compared to patients who completed treatment within 56 days.

A study by Afshin et al., was conducted with 154 patients of carcinoma cervix who underwent Co 60 brachytherapy, comparing patients having a gap of 1 week and ≥ 3 weeks between definitive RT and brachytherapy. This study showed improved 3 year disease free survival (72% vs 49%) in patients who were scheduled for brachytherapy within 1 week of completion of external beam radiation(Rakhsha et al., 2015). Similarly, in our study, patients whose brachytherapy was scheduled within 14 days of the end of definitive CT-RT had higher complete response rates (92.8 % versus 69.3%) and lower progressive disease when compared to those whose brachytherapy was scheduled >14 days after definitive CT-RT (7.2% versus 13.3%). ~~P value was <0.001 which is statistically significant - implying better outcomes when brachytherapy is scheduled within 2 weeks of completion of CT-RT.~~

In a study by Ntekim et al., that included 70 patients of carcinoma cervix patients who underwent definitive chemo-radiation followed by brachytherapy and were then followed up for 3 months, 56% of patients were identified to have $\leq$ Grade 2 acute toxicities of bladder(Ntekim et al., 2010). Patients frequently complained of cystitis (40%), increased frequency of urination (40%) and urinary urgency (60%)(Ntekim et al., 2010). We observed approximately 43% of $\leq$ grade 2 toxicities of bladder in our study. No grade 3 acute genitourinary toxicities were seen and 2 patients had grade 4 acute toxicities in our study.

According to a study by Jain et al., patients with acute gastrointestinal toxicities $\leq$ grade 2 were having proctitis (56%) and diarrhoea (58%)(Singh & Vaibhav, 2017). Grade 2 acute toxicities of the rectum were seen in 38 percent of patients in a study by Ntekim et al., where 70 patients of carcinoma cervix who underwent definitive chemo-radiation followed by brachytherapy were followed up for a 3 month period. In the study by Singh et al., 3% of patients had grade 3 diarrhoea among those patients who underwent Co 60 HDR intracavitary brachytherapy(Singh & Vaibhav, 2017). We observed $\leq$ grade 2 toxicities of rectum in 54% of patients in our study. 2.1% (3 patients) had grade 4 acute rectal toxicities in our study. Out of 3 patients with grade 4 acute rectal toxicities, 1 patient was on anticoagulant and antiplatelet therapy due to an underlying heart disease, which is a possible confounding factor in our study. In a study, the incidence of metastases to other organs was 56%, with most frequent sites being lung, abdominal cavity, liver, and gastrointestinal tract, and the incidence of clinically apparent lymph node involvement(Fagundes et al., 1986). In our study, out of the 5 patients with locoregional failure, 4 patients had local failure and 1 patient had significant paraaortic lymphadenopathy. In our study 10 patients showed evidence of distant metastasis mainly to liver (4 patients), lung (2 patients) and non-regional lymph nodal metastasis (supraclavicular and inguinal lymph nodes).

Several studies showed relationship between local control and dose in carcinoma cervix. In a study from Gustave Roussy Cancer Campus, crude control rates of $>90-95\%$ were seen when $CTV_{HR} D90 > 85-87Gy_{10}$ (Mazeron et al., 2015). Mean total dose to point A EQD2Gy of $91.04Gy_{10}$ over stages IB2-IIIB showed 2 year and 5 year OS of 91.6% and 81.9% respectively(Mazeron et al., 2015). Dose escalation from 75Gy to 85Gy resulted in a 3% increase in local control in limited to intermediate size ($20-30cm^3$), and 7% increase in large size ($70 cm^3$) to CTV_{HR} (Tanderup et al.,

2016). Javadinia et al., study showed trend of reduced survival in patients with higher disease stages who were receiving lower doses to the tumor; however, the results were not significant(Javadinia et al., 2020). Similarly, our study showed that an increase in stage of the disease (from stage I to IVA) was associated with a trend of increasing mean EQD₂ Gy₁₀ for obtaining complete responses. Compared to the complete responses, the mean EQD₂ Gy₁₀ for the progressive disease was lower in each stage.

Conclusion

According to results obtained from the study we conclude by saying that higher rates of complete response to treatment in cervical cancer is seen in patients with shorter OTT, shorter interval between end of definitive CT-RT and beginning of brachytherapy and squamous cell histology. In our study we also noted trend of increasing mean EQD₂ to tumor with increasing stage for achieving complete response. Higher acute bladder and rectal toxicity is seen in patients who received EQD₂ of >70-90Gy₃ and >70Gy₃ respectively. Long follow-up periods are necessary for the evaluation of response, long-term or late toxicity, and survival outcomes,  which could be a limitation of our study. We also did not have an uniform pattern of scheduling between EBRT and brachytherapy in patients referred from several other centers in the city for brachytherapy at our center.

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Table 1(on next page)

Demographic data

1

N	144
Age(years)	
Mean ± SD	53.63±10.21
Median	53.00
Range	33.00: 82.00
Histopathology	n(%)
Squamous cell carcinoma	127(88.2%)
Adenocarcinoma	17(11.8%)
FIGO Staging 2018	n(%)
I	05(3.5%)
II	68(47.2%)
III	50(34.7%)
IV A	21(14.6%)
Lymph nodal status on initial MRI	n(%)
Lymph node negative	98(68.1%)
Positive pelvic node	40(27.8%)
Positive paraaortic lymph node	06(4.2%)
Clinical Morphology	n(%)
Ulceroproliferative	139(96.5%)
Ulcerative	02(1.4%)

Endophytic	03(2.1%)
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2

3
Table 1- Demographic Details and Observational data

4

Table 2(on next page)

EQD2 and response

Staging	Response	n	Mean $\pm$ SD (Gy ₁₀)	Median	Min :Max
I	Complete response	03	78.67 $\pm$ 2.89	77.00	77.00 : 82.00
	Partial response	00	NA	NA	NA
	Progressive disease	02	77.00 $\pm$ 0.00	NA	NA
II	Complete response	54	83.33 $\pm$ 3.08	83.00	76.00 : 90.00
	Partial response	07	84.29 $\pm$ 4.31	83.00	78.0 : 90.0
	Progressive disease	07	82.29 $\pm$ 2.36	83.00	77.00 : 84.00
III	Complete response	43	84.23 $\pm$ 4.52	83.00	77.00 : 96.00
	Partial response	03	84.67 $\pm$ 5.77	88.00	78.00 : 88.00
	Progressive disease	04	82.50 $\pm$ 0.58	82.50	82.00 : 83.00
IV A	Complete response	16	85.63 $\pm$ 3.05	85.50	80.00 : 90.00
	Partial response	03	88.67 $\pm$ 2.31	90.00	86.00 : 90.00
	Progressive disease	02	83.50 $\pm$ 0.71	83.50	83.00 : 84.00

Table- 2 Association of EQD₂ with response in different stage

Figure 1

Catheter reconstruction

Figure 1 – 3 D Reconstruction ICBT (A) and ISBT (B) applicator in situ

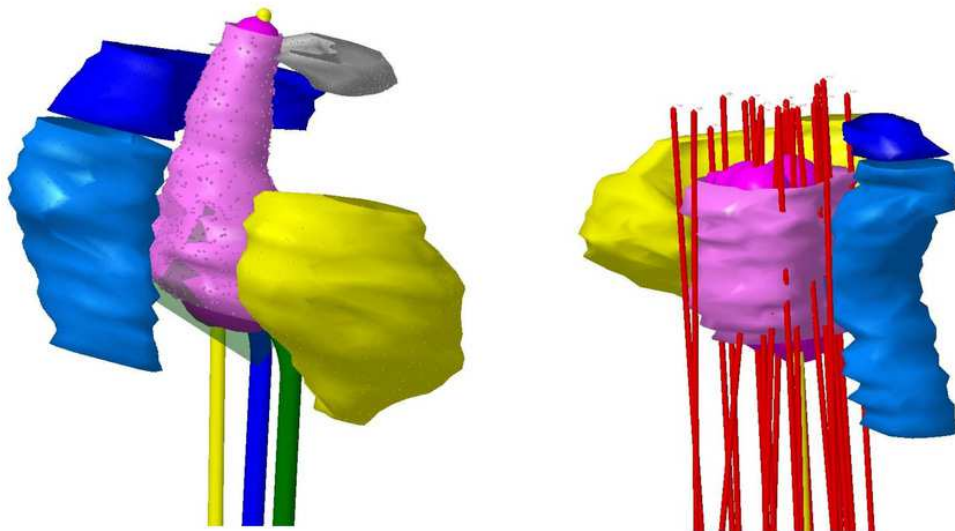


Figure 2

response assessment

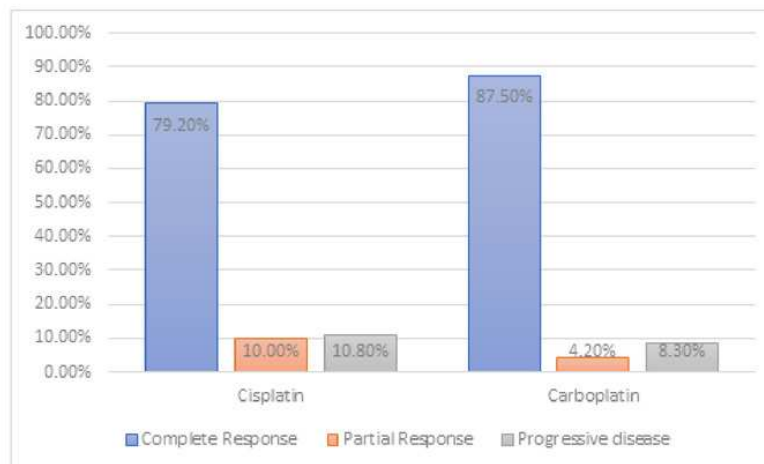


Figure 2- Association of Concurrent chemotherapy and response

Figure 3

OTT and response

Figure 3- Association of overall treatment time and response

