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A PROSPECTIVE RANDOMISED STUDY TO COMPARE IINTERINDIVIDUAL VARIATION IN EFFECT OF RADIOTHERAPY ON URINARY BLADDER AND RECTAL TOXICITY IN PRONE AND SUPINE POSITION IN LOCALLY ADVANCED CANCER OF CERVIX

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Abstract

Introduction: Cancer of the cervix has been the most important cancer among women in the past two decades. In India the peak age for cervical cancer incidence is 55–59 years. In India in every 8 minutes one woman dies of cervical cancer.Radical radiotherapy along with concurrent chemotherapy is the standard of care of advanced carcinoma cervix. Combination of teletherapy and brachytherapy is a conventional practice. Teletherapy includes whole -pelvic radiotherapy which consists of external beam irradiation to the primary tumor and regional lymphatics followed by brachytherapy to boost the gross tumour in the cervix. However, success achieved with this treatment carries a risk of inadvertent normal tissue irradiation of the small bowel, bladder and rectum.

Aims: To study the anticipated reduction in dose in small bowel, urinary bladder irradiated in prone position during pelvic radiotherapy and whether it results in decreased toxicity.

Materials and methods: Prospective randomizedly allocated control study from January 2017 to January 2018 Patients visiting at Radiotherapy department Out door of Nilratan Sirkar Medical College and Hospital,Kolkata-700014.

Result: We found that for the urinary bladder (UB), V20, V30, and V40 showed no significant variance between the two positions ($p > 0.05$). However, UB V45 demonstrated a notable difference ($p = 0.9$), while UB V50.4 indicated a statistically significant variance ($p = 0.021$), indicating higher radiation exposure in the supine position. UB Dmean and total volume did not exhibit substantial differences ($p > 0.05$) and Regarding the rectum, V20, V30, V40, and V45 showed no significant variation between positions ($p > 0.05$). However, rectum V50.4 indicated a significant difference ($p = 0.004$), implying higher radiation exposure in the prone position. Rectum Dmean and total volume did not display substantial differences ($p > 0.05$).

Conclusion: In conclusion, our study revealed varied radiation exposure in prone versus supine positions. The urinary bladder indicated higher exposure in supine (V50.4 $p = 0.021$), while the rectum exhibited increased exposure in prone (V50.4 $p = 0.004$). Overall, patient positioning significantly influences organ-specific radiation doses.

Keywords: Cervical Cancer, Locally Advanced, Chemoradiation, Adjuvant Chemotherapy and Randomized Study

INTRODUCTION

Cancer of the cervix has been the most important cancer among women in the past two decades. In India the peak age for cervical cancer incidence is 55–59 years. In India in every 8 minutes one woman dies of cervical cancer.
Radical radiotherapy along with concurrent chemotherapy is the standard of care of advanced carcinoma cervix. Combination of teletherapy and brachytherapy is a conventional practice. Teletherapy includes whole -pelvic radiotherapy which consists of external beam irradiation to the primary tumor and regional lymphatics followed by brachytherapy to boost the gross tumour in the cervix. However, success achieved with this treatment carries a risk of inadvertent normal tissue irradiation of the small bowel, bladder and rectum.In, order to cover tumour and locoregional lymph nodes adequately with 2D or 3D conformal radiotherapy technique large portions of bowel gets included in the radiation ports. Consequently, acute and chronic bowel sequels are the most important side effects of pelvic radiotherapy.The risk of

damage to the small bowel is related to the total dose delivered to the pelvis, the fraction size, and the presence of physical factors such as multiple abdominal surgical procedures or pelvic inflammatory disease.Various efforts have been made to reduce bowel toxicity by pelvic radiotherapy. Among them radiotherapy in prone position have been matter of interest for long. Several studies showed superiority of prone positioning in comparison to supine position of radiotherapy in regard to bowel protection.

Purpose of this study is to compare bowel toxicity between prone and supine positions with the help of Dose Volume Histogram, and to find out whether prone positioning results in reduced bowel toxicity.
Efforts have been made to reduce the incidence and severity of gastrointestinal toxicity, like treatment with a full bladder aiming at reducing the irradiated small bowel volume.
As the most common gynecologic malignant neoplasm reported in women worldwide, the treatment of cervical cancer remains a challenge due to the lack of health infrastructure. In 2018, there were about 36,000 new cases, with 311,365 cancer-related deaths [1] .In many developing countries, patients were diagnosed with cervical cancer at at a locally advanced stage, indicating a poor outcome .

MATERIALS AND METHODS

Source of data:- Patients visiting at Radiotherapy department Out door of Nilratan Sirkar Medical College and Hospital,Kolkata-700014.

Investigations:

- Baseline complete hemogram (Hemoglobin, Total count, Differential count, Platelet count) and biochemistry (RBS, LFT, RFT, Serum Electrolytes). .
- Baseline chest x-ray.
- ECG.
- Echo Cardiogram.
- Creatinine clearance
- Baseline ultrasound abdomen and pelvis.
- Cystoscopy.
- Virtual simulation CT scan for radiotherapy planning.

Inclusion criteria:
1. Informed consent from study group.
2. Aged 18-75 years
3. Newly diagnosed, histologically proven cervical cancer of FIGO stage I-IVA
4. Karnofsky performance status of more than or equal to 70.
5. Adequate baseline hematological, hepatic and renal functions.

Exclusion criteria:
1. Pregnant and nursing mothers .
2. Karnofsky performance status of less than 70.
3. FIGO Stage IV B.
4. Active uncontrolled tuberculosis / other comorbidities which preclude the use of radiotherapy.
5. Uncontrolled diabetes / hypertension.

Study period: January 2017 to January 2018
Study Design: Prospective randomizedly allocated control study.

RESULTS

Dose Volume Histogram data tabulated in Dosimetric Chart.

DOSIMETRY	PRONE POSITION			SUPINE POSITION			P.VALUE
	MEAN	MEDIAN	STD.DV	MEAN	MEDIAN	STD.DEV	
URINARYBLADDER V20	100	100	0	100	100	0	Not Significant
UB V30	100	100	0	100	100	0	Not Significant
UB V40	98.003	99.995	4.07	99.109	99.87	1.166	Not Significant

UB V45	94.087	98.87	9.5027	96.78	98.13	3.272	0.9NS
UB V50.4	23	22.735	17.276	37.302	39.293	21.708	0.021
UB Dmean	98.308	100.015	3.98	98.17	100.415	12.0375	Not Significant
UB TOTAL VOLUME in cc	190.25	175.4	75.79	217.01	180.53	108.56	0.17 NS
RECTUM V20	92.483	97.965	9.558	92.462	96.05	8.072	0.9 NS
RECTUM-V30	89.187	95.76	11.669	88.756	91.195	10.778	0.87 NS
RECTUM V40	85.248	91.22	13.9693	83.987	86.495	12.277	0.68 NS
RECTUM V45	77.9	80.19	15.366	77.395	77.75	12.725	0.7NS
RECTUM V50.4	27.672	23.645	13.102	13.739	6.31	17.594	0.004
RECTUMDmean	91.994	97.495	10.417	90.289	91.76	7.793	0.18 NS
RECTUM TOTAL vOLUME	87.37	83.95	18.51	82.02	81.84	11.83	0.28
BOWEL BAG V20	89.98	91.44	6.247	89.965	92.09	8.84	0.9
BB V30	72.011	71.09	6.358	81.743	83.235	9.076	<0.001
BB V40	46.524	44.415	11.13	66.589	67.01	12.18	<0.001
BB V45 cc	194.2596	193.94	13.344	216.358	219.5915	12.088	<0.001
BB V50.4	3.99	3.745	3.34	13.009	14.395	5.41	<0.001
BB Dmean	59.297	59.22	8.778	80.59	81.7285	10.93	<0.001
BB D195	44.83	44.73	3.08	49.92	50.623	2.78	<0.001
PTV 95	94.165	93.975	0.6474	94.046	93.9	0.829	NS,0.25
PTV Dmean	99.59	100	0.797	99.49	99.84	0.7125	Ns,0.13
PTV vol	890.25	908.2995	83.11	958.271	997.915	231.91	0.01

Insightful conclusions can be drawn about the radiation exposure of vital organs and target volumes from the dosimetric analysis comparing the prone and supine positions in radiotherapy. The possible differences between the prone and supine positions were investigated by calculating the mean, median, and standard deviation of certain dosimetric parameters.
For the urinary bladder (UB), V20, V30, and V40 showed no significant variance between the two positions ($p > 0.05$). However, UB V45 demonstrated a notable difference ($p = 0.9$), while UB V50.4 indicated a statistically significant variance ($p = 0.021$), indicating higher radiation exposure in the supine position. UB Dmean and total volume did not exhibit substantial differences ($p > 0.05$).

Regarding the rectum, V20, V30, V40, and V45 showed no significant variation between positions ($p > 0.05$). However, rectum V50.4 indicated a significant difference ($p = 0.004$), implying higher radiation exposure in the prone position. Rectum Dmean and total volume did not display substantial differences ($p > 0.05$).
Table of the bowel bag (BB) revealed significant differences between prone and supine positions across various parameters: V20, V30, V40, V45, V50.4, Dmean, and D195 (all $p < 0.001$), illustrating higher radiation exposure in the supine position.

Notably, for the planning target volume (PTV), parameters PTV 95, PTV Dmean, and PTV volume exhibited no significant differences between positions ($p > 0.05$), indicating comparable radiation coverage and dosimetry for both prone and supine setups.

These findings suggest varying degrees of organ and tissue exposure to radiation based on patient positioning during radiotherapy. The urinary bladder and rectum showed nuanced differences in exposure levels, while the bowel bag demonstrated considerably higher radiation exposure in the supine position across multiple parameters.
Understanding these dosimetric variations between prone and supine positions is critical for optimizing treatment planning and minimizing radiation-related side effects. The observed differences underscore the importance of patient positioning considerations in radiotherapy planning, particularly concerning critical organ sparing and target volume coverage. Further exploration of these findings may aid in refining treatment protocols to enhance therapeutic outcomes while mitigating adverse effects for patients undergoing radiotherapy.

DISCUSSION

Initially 66 patients were selected for the study, and they were given serial number in a sequence as they were selected. Following selection 2 patients were excluded from the study according to exclusion criteria, rest 64 patients were randomized in two groups (Group A or Prone group and Group B or Supine group) in consort flow chart (REF-, with Graph Pad Quick-calcs Randomization tool. No statistically significant difference was there in terms of stage, age and ECOG status of patients. Among 64 patients, 4 patients were excluded due to other reasons mentioned in consort flow chart.

Rest 60 patients allocated in two groups each of thirty, were finally analyzed.

1st group will receive external beam radiotherapy treatment or EBRT in prone position only, and another group will receive EBRT in supine position.

Each patient received dose of 50Gy in 25 fractions over 5 weeks with concurrent Cisplatin at 40mg/m2 weekly followed by Brachytherapy with 7 Gy X 3 fractions.
Treatment was completed within 8 to 9 weeks in all cases.

Before initiating treatment with EBRT, CT-simulation was done with SOMATOM EMOTION in each patient, thickness of each section kept at 5 mm,after transferring data to contouring station, contouring was done as per RTOG ATLAS-0418 and PGI review guideline for contouring.
Gross tumor volume included gross disease involving cervix vagina and uterus, CTV included ovary, parametrium, pelvic nodes, up-to L4-L5, above and around external iliac vessels below. Separate Nodal contouring was not done.PTV created with 1 cm margin around CTV, excluding bones.OAR or organ at risk was contoured for Rectum,Bowel Bag, and Urinary Bladder.

Rectum-contoured from Recto-sigmoid junction to anus, though patients were instructed and followed rectum protocol at CT-simulation, but such protocol was not stringently followed during treatment with EBRT.
Urinary Bladder-each patient was asked to drink 250 ml of clear water, 30 minutes before CT simulation and EBRT, following complete voiding.

Bowel bag was contoured as entire peritoneal cavity and not as individual bowel loops. Bowel bag contoured upto 2 slice above highest margin of PTV and upto rectosigmoid junction.No differentiation was made between small or large gut.No belly board or any other device were used during prone positioning,
I have compared the dose-volume histograms of PTV and organs at risk in a four-field box technique treatment plan in supine and prone patient position. Each patient was planned by 3DCRT in VARIAN ONCENTRA system and dose volume histogram of Planning Target Volume, Bowel, Urinary Bladder, and rectum was done.OAR delineation: OAR includes bowel, bladder, rectum and these are contoured according to the RTOG normal tissue contouring guidelines.
Many studies were done in prone position with belly board, which was not used in my study [5,6,7]

In my study I found significant less bowel volume receiving more than 20 Gy in prone position than in supine position, though no statistically significant different was seen in dose <=20 Gy. Dose received by 195 cc of bowel bag was significantly more in supine position than in prone position with a P Value of <0.001, also 45 Gy dose received by Bowel volume was more in supine position than in prone position mean V45 in prone position was 193 cc with STD.DEV of 13, and in supine position mean V45 was 216cc with STD.Dev of 12 cc,P-value <0.001.
Volume of PTVmean in prone position 890.25 cc with STD.DEV. of 83.11 and in supine position PTVmean was 958 with STD Dev. Of 231.91, P-Value being 0.01.

Field size in prone and supine also differs significantly .Mean lateral Width (x axis) size in supine position was 17.4 and in prone position it was 16.6, with a P-Value of 0.034, which is statistically significant, also Lateral width in Lateral field in prone position was 14.00 and in supine position 14.66, with a P-value of 0.008.
Such difference in Bowel dose may be attributable to upward displacement of bowel loops in prone position there by moving away from area near PTV, more PTV in Supine position due to anterior movement of uterus,tumour with adnexa,and this finding was consistent with finding by PINKAWA et AL[8],increased field size in AP-PA and Lateral Portal due to compression of Abdominal wall in prone position .Well filled urinary bladder also helps to keep away bowel loops ,but such change is evident on both positions [9].
Difference in irradiated volume of Urinary Bladder and Rectum seen only at 50.4Gy, and no statistically significant difference of irradiated volume found at 20Gy,30Gy, 40Gy and 45Gy .

Statistical analysis was done with Exel Sheet and SPSS-21 using Wilcoxon Signed Rank test. Toxicity assessment was done with Chi-Square test and graded according to CTCAE-4 criterias. Such difference in bowel dose is also reflected in development of toxicity during treatment. A significant portion of patients in supine group developed acute diarrhea, few developed Haematochezia and also some needed hospitalization in comparison to patients treated in prone position. Bladder toxicity in the form of urgency and dysuria were observed more in patients treated in supine position and was statistically significant.

Within 3 months of follow-up period no patients developed rectal toxicity in the form of new onset rectal bleeding, tenesmus.

CONCLUSION

Prone position can be used instead of supine position for Pelvic field radiation, in patients of Carcinoma Cervix for better bowel protection.

Volume of Urinary Bladder receiving above 50 Gy is smaller in prone position than in supine position, thus better Urinary Bladder protection was seen in higher dose in prone position.

Optimal bladder filling with bladder protocol also needed for bladder sparing and also for keeping away bowel loops from irradiated zone around PTV.

Volume of Rectum at 50.4 Gy was higher in prone position, than in supine position, thus rectal toxicity is more when treated in prone position, though no patients complained of rectal toxicity in first 3 months of observation.

Better Bowel sparring in my observation was result of

1) Upward movement of gut loops in prone position, together with pressure effect from optimally filled urinary bladder which is also compressed in prone position.

2) Compression of abdominal wall in prone position, causes reduced anterior-posterior inter field distance in prone position (P-0.034), thus to achieve at least 93% dose at 95% of PTV lesser field dimension was needed in prone position than in supine position.

In my study I also found average PTV volume was less in prone position than in supine position and such difference is statistically significant(P-0.01). Due to lesser volume of PTV, field size in prone position was less, which also spares more bowel volume in prone position, though I could not find any explanation for the same, further studies may be done to explain such observation.

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