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Bone Marrow Dosimetric Parameters and Hematological Toxicity In Cervical Cancer Patients Undergoing Concurrent Chemoradiation.

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Abstract:-Title: - *Bone Marrow Dosimetric Parameters And Acute Hematological Toxicity In Cervical Cancer Patients Undergoing Concurrent Chemoradiation.* ***Objective:-*** *To Study The Incidence Of Hematological Toxicity In Relation To Bone Marrow Dosimetric Parameters In Cervical Cancer Patients Undergoing Concurrent Chemoradiation.* ***Material And Methods:-*** *The Data Of 23 Cervical Cancer (Stage IIb-IIIb) Patients Who Underwent Concurrent Chemoradiation During March 2017- June 2017 Were Analyzed. Radiation Was Delivered In A Dose Of 46gy In 23 Fractions With Weekly Cisplatin (40 Mg/M^2) On Days 1,8,15 And 22 Of The Treatment. The Clinical Target Volume Consisted Of Uterus, Cervix, Vagina, Parametrial Tissue And Pelvic And Presacral Lymph Nodes. Pelvic Bone Marrow Was Defined Within The Treatment Field Which Comprised Of (I) Lumbosacral Spine (Ii) Ilium,Ischium,Pubis And (Iii) Proximal Femora. The Volume Of Bone Marrow Receiving 10,20,30 And 40 Gy And The Median Dose To Bone Marrow Were Correlated With Haematological Toxicity , Graded By Ctcae V.4.0 Criteria.* ***Results:-*** *23 Cervical Cancer Patients Treated With Concurrent Chemoradiation Were Analyzed. Among The 17 Patients, 88% Completed 4 Cycles Of Weekly Cisplatin . Patients Treated With Weekly Cisplatin And 3dcrt Pelvic Rt Had Grades 1-5 Hematological Toxicity (26%,61%,13%,0%,0% Of Patients Respectively).The Median Percentage Volume Of Bone Marrow Receiving 10,20,30 And 40 Gy Were 95%, 91%, 44% And 24% Respectively. 78% Of The Patients With Median Percentage Of Bone Marrow Volume Receiving 40gy (V_{40}) >24% Had Grade 2 Hematological Toxicity.* ***Conclusion:-*** *Concurrent Chemoradiation Is Associated With Hematological Toxicity. The Patients With Median Percentage Of Bone Marrow Volume Receiving 40gy >24 % Were Seen To Have High Grade Of Hematological Toxicity. Evaluation Of Irradiated Bone Marrow Volume Maybe Considered To Limit Hematological Toxicity Thereby Improving Chemotherapy Tolerance.*

Keywords:- *Cervical Cancer, Concurrent Chemoradiation, Haematological Toxicity, Dosimetric Parameters, Bone Marrow.*

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I. Introduction

Concurrent Chemoradiation Alongwith Brachytherapy Is The Standard Treatment For Locally Advanced Carcinoma Cervix. However, Adverse Reactions Like Acute Hematological Toxicity Result In Delayed Or Missed Treatments, Which Impact The Prognosis [(1)].

Standard Pelvic Radiation Typically Treats A Substantial Amount Of Bone Marrow Located In Lumbar Sacrum, Ilium, Ischium, Pubis And Proximal Femur. Most Studies Have Confirmed That Myelosuppression Observed In Patients Undergoing Concurrent Chemoradiation Is Related To Bone Marrow Volume Receiving 10 Or 20 Gy. Therefore, It Is Possible To Reduce The Incidence Of Acute Hematological Toxicity By Reducing The Volume To Low Dose Irradiation[(2,3)].

In This Study, We Retrospectively Analyzed The Incidence Of Hematological Toxicity In Relation To The Bone Marrow Dosimetric Parameters In Cervical Cancer Patients Undergoing Concurrent Chemoradiation.

II. Material And Methods

- PATIENTS:- We Analyzed The Clinical Records Of 17 Patients Of Stage IIB – IIIB Cervical Carcinoma Who Underwent Concurrent Chemoradiation At Our Institution Between March 2017 To June 2017. All

Patients Were Histologically Proven Cases Of Squamous Cell Carcinoma. All Patients Received Radiation Through 3D-CRT Technique And Weekly Cisplatin (40 Mg/M^2) On Days 1,8,15 And 22 Of Radiation.

- PATIENT POSITIONING AND CT SCAN:- Virtual Simulation In Supine Position Was Performed Using CT Scanning With A Section Thickness Of 5 Mm. The CT Scans Were Obtained From L2 Vertebral Body To The Lower Edge Of Ischial Tuberosity. Images Were Then Transferred To MONACO Workstation For Analysis.
- TARGET DELINEATION:-The Target Volumes And Organs At Risk Were Delineated Following Radiotherapy Oncology Group (RTOG) Guidelines. Gross Visible Tumour And Its Visible Extension Were Contoured As Gross Tumour Volume (GTV). Whole GTV, Uterine Cervix, Uterine Corpus, Parametrium And Vagina Were Contoured As Clinical Target Volume (CTV). The Relevant Draining Nodal Groups Included Common; Internal And External Iliac (With Abdominal Aortic Bifurcation As CTV Superior Margin) , Obturator And Presacral Lymph Nodes. A Margin Of Approximately 1-1.5 Cm Around The CTV In The Region Of Uterus And Cervix And 0.7mm In The Nodal CTV Regions Were Given For Planning Target Volume (PTV) To Account For Uterine Motion And Setup Errors[(4)].
  Normal Tissues Contoured Included Bowel, Bladder, Rectum And Pelvic Bone Marrow. Pelvic Bone Marrow Comprised Lumbosacral BM , Iliac BM And Ischium, Pubis And Proximal Femora BM. The External Contour Of The Pelvic Bones Was Delineated On Planning CT Scan To Define BM. The Superior Extent Began At The Level Of L3/L4 Junction And The Inferior Most Extent Of Bone Marrow Contour Extended To The Level Of Ischial Tuberosity.
- TREATMENT PLANNING:- 3D Conformal Radiotherapy Planning Was Done For All Patients. Four Coplanar Fields (Anterior-Posterior And Two Lateral Fields With Couch Angle 0^0 Were Used, And The Isocenter Was Placed At The Geometerical Centre Of The PTV. Dose Prescription Of Pelvic EBRT By 3DCRT Was Set At 46Gy/23#. All Plans Were Normalized To Cover 95% Of PTV With 100% Of The Prescribed Dose.
- PLAN EVALUATION:- Dosimetric Parameters Of The Plans Were Generated. The PTV Coverage On The Basis Of D_{95}(Dose To 95%) And D_{max} (Maximum Dose) Was Noted. Doses To Organs At Risk Were Noted. The BM Volumes Receiving 10, 20, 30 And 40Gy (V_{10} , V_{20} Etc) From Pelvic Radiation Was Quantified.
  VWas Calculated Using The Following Formulae[(5)],
  CI_{95} = Total Volume Receiving 95% Of Prescribed Dose / PTV
  $HI_{95\%}= D_5 / D_{95}$; Where D_5 And D_{95} Were Doses Received By 5% And 95% Of PTV.
- CHEMOTHERAPY:- Patients Were Administered Cisplatin (40 Mg/ M^2) Weekly Concurrently On Days 1, 8, 15 And 22 Of Radiation. Complete Blood Counts Were Performed Weekly.
- TOXICITY EVALUATION:- Patients Were Assessed Weekly Throughout The Treatment For Acute Hematological Toxicity In Accordance With CTCAE V.4.
- STATISTICAL ANALYSIS:- Data Analysis Was Performed Using SPSS 20.0 Software. Two Tailed T-Tests Were Performed To Compare Groups. A P Value < 0.05 Was Considered Statistically Significant.

III. Results

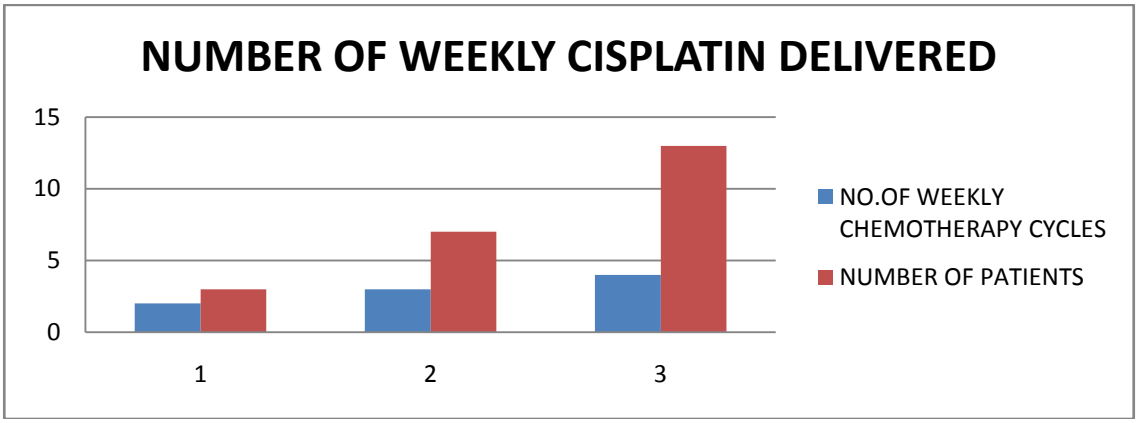
- PATIENT AND TREATMENT CHARACTRISTICS

During The Study Period Of March2017 To June2017, 23 Patients Were Analyzed For This Study. AllThe Patients Were Histologically Proven Cases Of Squamous Cell Carcinoma. The Median Age Of The Patients Studied Was 46 Years, Ranging From 24 Years To 64 Years. The FIGO Stage Ranged From IIB To IIIB ; 6 Patients Were Of IIB, 5 Patients Were Of IIIA And 12 Patients Were Of IIIB. All The Patients Were Irradiated By 3DCRT Technique With Concurrent Weekly Cisplatin Chemotherapy. Among The 23 Patients, 56% Completed 4 Cycles Of Chemotherapy.

TABLE 1:-PATIENT AND TUMOUR CHARACTERISTICS

		NUMBER	PERCENTAGE
AGE	20-39 YRS	4	17.3%
	40-59 YRS	17	73.9%
	>60 YRS	2	8.6%
STAGE	IIB	4	17.3%
	IIIA	5	21.7%
	IIIB	14	60.8%
CONCURRENT CHEM	2 CYCLES	3	8.6%
	3 CYCLES	7	13.04%
	4 CYCLES	13	56.52%

FIGURE 1:-CONCURRENT WEEKLY CHEMOTHERAPY IN CERVICAL CANCER PATIENTS



- DOSIMETRIC PARAMETERS

The Plan Achieved Adequate Coverage With 95% Of The PTV Receiving 100% Of The Prescribed Dose, And 99% Of PTV Received 95% Of The Prescribed Dose. The Volume Of Bone Marrow Irradiated Was Determined By Contouring The Entire Pelvic Bone From Superior To Inferior Extent Of PTV. The Median Percentage Volume Of Bone Marrow Receiving 10, 20, 30 And 40 Gy Were 95%, 91%, 44% And 24% Respectively.

- TOXICITY EVALUATION

In This Study, Acute Haematological Toxicity Was Noted Among The Patient, That Was Graded According To CTCAE. V.4. Of The 23 Patients Studied, 6 (26%) Patients Developed Grade 1 HT,14 (61%) Developed Grade 2 HT And 3 Patients Developed Grade 3 Haematological Toxicity (HT). There Were No Grade 4 And 5 HT Noted In The Study.

TABLE 2:-INCIDENCE OF HEMATOLOGICAL TOXICITY

GRADE OF HT	NUMBER	PERCENTAGE
1	6	26%
2	14	61%
3	3	13%

- CORRELATION OF VOLUME OF BONE MARROW IRRADIATED WITH HAEMATOLOGICAL TOXICITY.

The Median Percentage Volume Of Bone Marrow Treated To 10, 20, 30 And 40Gy Were Used As Cutoff Points For Statistical Analysis. Among 23 Patients Studied, Those With V_{40}> 24%, 75% Developed Grade 2 HT. Patients With Mean Bone Marrow Dose Of >31.47Gy Also Had Higher Grades Of HT.
No Statistically Significant Correlation Between V_{10}, V_{20}And V_{30}With HT Was Observed.
For All Patients With V_{40}>24%, A Trend Towards Correlation With Increased Grade Of HT Was Seen. 75% Of These Patients With V_{40}>24% Developed Grade 2 HT.
Among These Patients Who Had The Percentage Volume Of BM Receiving 40Gy > 24%, Only 41% Could Complete 4 Cycles Of Weekly Concurrent Cisplatin.

FIGURE 2:-CONTOURED PELVIC BONE MARROW WITHIN TREATMENT FIELD

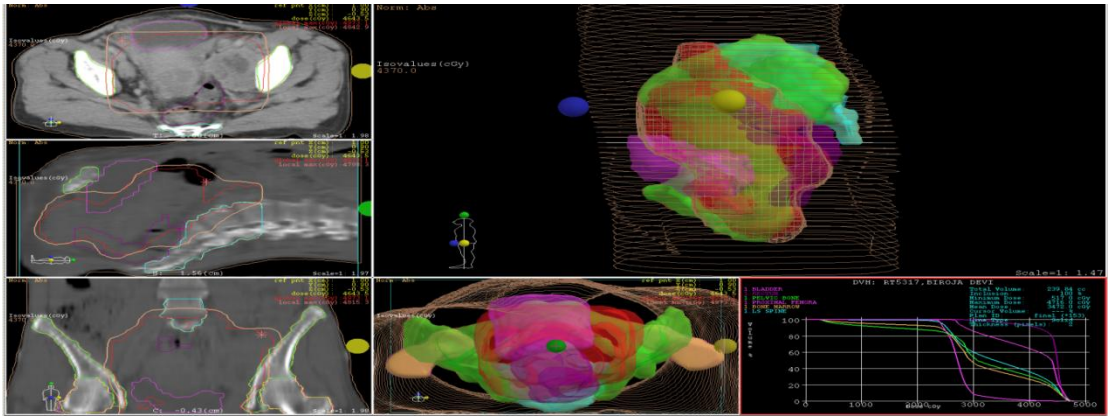
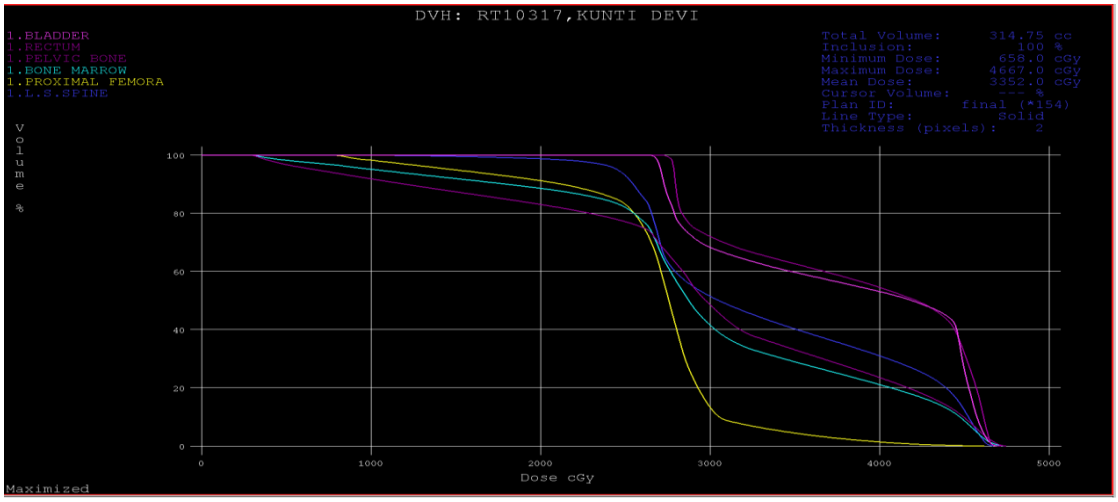


FIGURE 3:-DOSE VOLUME HISTOGRAM



IV. Discussion

Acute Haematological Toxicity Is A Common Adverse Event Encountered In Cervical Patients Undergoing Concurrent Chemoradiation. In This Study, We Noted That Patients With Higher Grade Of HT, Had Trouble In Tolerating Chemotherapy. Parker And Colleagues Reported That Distant Metastasis After Concurrent Chemoradiotherapy In Cervical Cancer Patients Was More Common In Those Patients Undergoing Less Cycles Of Chemotherapy Due To Delays Or Breaks In The Treatment Cycle Caused By Acute Haematological Toxicity[6].

Previous Published Studies Have Reported That Volume Of Bone Marrow Treated To Low Doses Predict Hematologic Toxicity In Patients Undergoing Pelvic Radiation For Cervical Cancers [7, 8, 9]. But Our Findings Of The Study Are Consistent With Other Those Reports In Which Patients With Higher Volumes Of Irradiated Bone Marrow Exhibited Higher Grades Of Hematological Toxicity.

The RTOG 0418 Phase II Clinical Trial Showed That Hematologic Toxicity Of Chemoradiotherapy For Cervical Cancer Is Related To The Mean Dose And BM Volume Receiving A Dose Greater Than 40 Gy [10].

Some Studies Have Shown That BM Volumes Receiving More Than 30 To 50 Gy Of Radiation Needed An Extended Time To Recover And Sometimes Experienced Irreversible Damage [11, 12]. Therefore, Reduction Of Irradiated BM Volume Is Required.

Mell And Co-Workers [7, 8] Divided The Pelvic Bone Into 3 Regions And Analyzed The Incidence Of Clinical HT. They Found That The Radiation Dose To The Sacral Vertebra And Low Pelvic Regions Were Closely Linked To The Occurrence Of Acute Hematologic Toxicity. In Our Study, Irradiated Lumbosacral Vertebra Volume Was Noted To Have Shown A Trend Towards Increased Grade Of HT.However, This Area Cannot Be Spared Without Affecting The Target Dose Distribution.

The Distribution Of BMContaining Red (Active) And Yellow (Inactive) Marrow Is Significantly Different Among Individuals And Conventional CT Scanning Doesn't Distinguish Between The Two. Functional Imaging Techniques Such As Positron Emission Tomography And Single Photon Computed Emission Tomography Is Required To Identify The Red Bone Marrow.[13,14]. Bone Marrow Sparing Has Particular Utility In Cervical Cancer Patients.

HT Often Limits The Full Course Of Concurrent Chemotherapy [15]In Our Study Also, We Found That Patients With Increased Grade Of HT Were Unable To Complete The Total 4 Cycles Of Weekly Concurrent Cisplatin.

The Major Limitation Of This Study Was That The Entire Bones Were Used As A Surrogate For Bone Marrow, Hence The Active Bone Marrow Couldnot Be Delineated Separately, Thereby Warranting The Use Of Functional Imaging Techniques. Secondly, Due To Small Sample Size, Statistically Significant Results Were Not Found And Hence Further Prospective Randomized Trials Should Be Done.

V. Conclusion

In Conclusion, Limiting The Volume Of Bone Marrow Irradiated Is Associated With Reduced Rates Of HT And May Improve Chemotherapy Tolerance. For Patients Receiving Chemotherapy And Pelvic Radiation, The Bone Marrow Should Be Contoured, And The Dosimetric Parameters Must Be Analyzed, With Special Emphasis On Median Dose And V_{40}With The Goal Of Reducing HT.

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