Dose-Escalated Intensity-Modulated Radiotherapy for the Management of Locally Advanced Cervical Cancer

Balaji Shewalkar 1, Asfiya Khan 1, Dnyanda Yerlekar 1, Jitendra Patel 1, Hrishikesh Khadilkar 2, Rajakumar Sakhivel 1, Reeta Kataruka 3

1. Radiation Oncology, Government Medical College and Cancer Hospital, Aurangabad, IND
2. Preventive Oncology, Government Medical College and Cancer Hospital, Aurangabad, IND
3. Pathology, Government Medical College and Cancer Hospital, Aurangabad, IND

Corresponding author: Asfiya Khan, asfiya.khn@gmail.com

Abstract

Objective

In this study, we aimed to assess the response and toxicity related to dose escalation in external beam radiation therapy (EBRT) using intensity-modulated radiation therapy (IMRT) with weekly concurrent cisplatin followed by de-escalated brachytherapy (BT) in locally advanced carcinoma cervix of International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IIB-IIIC1.

Materials and methods

Fifty-two patients diagnosed with cervical cancer FIGO 2018 stage IIB-IIIC1 were treated with curative intent from November 2019 to October 2021. The dose of 50 Gy was prescribed for the primary tumor volume and elective pelvic nodal volume followed by a primary boost to a dose of 20 Gy. Gross lymph node (LN) of size >1 cm after EBRT completion received a sequential nodal boost of 10 Gy. All patients received concurrent cisplatin to a dose of 40 mg/m\(^2\) for a total of five to six weekly cycles. All patients received two fractions of BT to a dose of 6 Gy after EBRT completion. Radiation-induced acute toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) criteria and hematologic toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Results

A median follow-up of six months was available for the 40 eligible patients. All patients tolerated treatment with an acceptable toxicity profile. Grade III dermatitis, grade III gastrointestinal (GI) toxicity, and grade III genitourinary (GU) toxicity were seen in three (7.5%), six (17.5%), and three patients (7.5%) respectively. Grade I anemia was evident in all patients. At six months after EBRT completion, 37 patients (92.5%) had a complete response and only three patients (7.5%) had residual disease.

Conclusion

Based on our findings, patients with cervical cancer treated with dose-escalated IMRT have a satisfactory outcome with reasonably low levels of treatment-related acute GI and GU toxicities. The findings of the present study endorse the notion that the application of a high dose of external radiation to the pelvis by IMRT technique with image-guided delivery could be an acceptable alternative to the standard-dose management schedule.

Introduction

Cervical cancer is a global public health concern among women, with an estimated 604,127 new cases and 3,41,831 deaths reported in 2020 [1]. Globally, it is the fourth leading cause of cancer-related deaths in women but ranks second in India despite now being recognizable in its early stages, with 77,348 annual deaths reported due to a lack of implementation of population-based cancer screening programs and human papillomavirus (HPV) vaccination [2].

A pelvic external beam radiation therapy (EBRT) dose of 50 Gy is more advantageous than that of 45 Gy in cervical cancers because it covers the whole low-risk clinical target volume (CTV) and some parts of high-risk CTV that may not be adequately covered through brachytherapy (BT) [3]. BT in cervical carcinoma safely delivers 80-85 Gy of biologically equivalent dose in 2-Gy fractions (EQD2) to the tumor periphery, whereas the central cervix receives even higher doses (>120-Gy EQD2) with rapid dose fall-off, thereby minimizing...
the dose to the adjacent organs at risk (OAR), namely the bladder, bowel, and rectum. This results in favorable local control rates of 100%, 96%, and 86% for IB, IIB, and IIIB stages of cervical cancer, respectively [4].

Three-dimensional conformal radiation therapy (3DCRT) is more beneficial than conventional therapy because it shapes the radiation beam according to the primary target, ensuring a more precise target coverage while maintaining OAR constraints [5,6]. With technological advancement, intensity-modulated radiation therapy with image-guided treatment delivery (IG-IMRT) has been commonly employed due to its low acute toxicity profile, that is, acute grade II gastrointestinal (GI) toxicity of 60% with intensity-modulated radiation therapy (IMRT) versus 91% with 3DCRT [7]. The National Comprehensive Cancer Network (NCCN) guidelines 2022 recommend the IMRT technique for EBRT delivery. A parametrial boost of 5–10 Gy can be considered in select cases with bulky residual parametrial or lateral pelvic wall disease after the completion of pelvic EBRT. Pelvic and para-aortic lymph node (LN) involvement is the most significant negative prognostic factor for locoregional recurrence and overall survival (OS). The acceptable strategies for a nodal boost in clinical practice are simultaneous integrated boost (SIB) and sequential boost (SEB). A target dose of 54–65 Gy is essential to effectively sterilize lymph nodal diseases [8,9].

Treatment-related toxicity has been observed in 84% of cervical cancer patients receiving CTRT when radiation therapy (RT) is planned with the conventional technique [10,11]. The intensity and severity of these adverse RT effects depend on patient characteristics, such as general build, comorbidities, treatment compliance, and treatment-related characteristics such as RT technique and the number of concurrent weekly cisplatin cycles administered [12].

BT applicator placement may be challenging due to multifactorial reasons such as distortion of the cervix anatomy after CTRT, insufficient primary tumor regression, lack of USG-guided intrauterine tandem placement, and a high cost of treatment in comparison with EBRT primary boost in low- and middle-income countries. Although BT treatment with the remote after-loading technique is an efficacious intervention, the chances of applicator sag still exist, leading to dosimetric discrepancies between the calculated dose and actual treatment delivery dose. This raises a concern regarding the actual dose delivered to point A and adjacent vital organs. The ABS guidelines 2012 recommended a dose to maximally exposed 2 cm³ of the organs at risk (OARsD2cc) dosimetric thresholds of 90 Gy for the urinary bladder and 75 Gy for the rectum and sigmoid colon [13]. Romano et al. concluded that the cumulative rectal D2cc threshold of even 75 Gy results in grade III or higher GI toxicity at a rate of 16.1%. Consequently, despite local control, the quality of life of cancer survivors may be poor [14].

EBRT dose escalation can be explored as an option because it aims at improving OS through the prevention of locoregional disease progression and elimination of possible foci for distant metastases. Over the past four decades, dose escalation with acceptable toxicity profiles has been achievable due to technological advancements in diagnostic imaging and radiotherapy techniques, leading to the improved delineation of the target volume. Dose escalation, in some settings such as carcinoma prostate, oesophageal cancer [15], and locally advanced pancreatic cancer [16], has been proven to be associated with OS benefit.

In this prospective study, we propose an alternative to the standard treatment practice, with EBRT dose escalation by using IG-IMRT and weekly concurrent cisplatin followed by reduced doses of BT in locally advanced cervical carcinoma [2018 revised International Federation of Gynaecology and Obstetrics staging (FIGO 2018) stage IIB-IIIC1] to overcome the challenge associated with BT applicator placement and treatment delivery. Our aim is to assess the response to EBRT dose escalation and the incidence of acute toxicity with IG-IMRT planning.

Materials And Methods
2.1. Study population
In total, 52 patients diagnosed with cervical cancer FIGO 2018 stage IIB–IIIC1 and treated from November 2019 to October 2021 at the Government Medical College and Cancer Hospital, Aurangabad, were invited to participate in the study.

2.2. Criteria for patient enrolment
Eligibility criteria for the patients were as follows: women in the age group of 18–65 years; patients who received a biopsy-proven diagnosis of cervical carcinoma stage IIB–IIIC1 (squamous cell carcinoma or adenocarcinoma); patients with Eastern Cooperative Oncology Group (ECOG) [17] performance status 0–1; patients with baseline hemoglobin level >8 g/dL; those with normal leukocyte and platelet count; those with normal renal function; and those with no cardiac comorbidities. Patients with ECOG >2, severe anemia, and glomerular filtration rate <15 mL/min/m² were excluded from the study. In total, 40 patients were included in the final analysis (Figure ).
2.3. Study design and treatment

All eligible patients received diagnostic evaluation as per the standard guidelines after they provided their written informed consent. Patients were simulated in the head-first supine position after bladder protocol of 1 liter in 45 minutes and immobilization with a 4-clamp abdominopelvic thermoplastic mold (E1). Contrast-enhanced CT (CECT) images were acquired with 3-mm slice thickness from the level of the diaphragm to the mid-thigh (Figure 2).
FIGURE 2: RT treatment protocol

Gross tumor volume (GTV) primary indicates the gross tumor volume; GTV node indicates pelvic LN of >1 cm; CTV primary includes GTV primary, uterine cervix, uterine corpus, parametrium, vagina, and ovaries; and CTV node indicates 7-mm isotropic margin to the GTV node and pelvic LNs. The planning target volume (PTV) was defined as CTV (primary + node) plus an isotropic margin of 3 mm. RT planning was performed using the IMRT technique with the Monte Carlo algorithm on the IMRT Elekta Synergy System, Monaco version 5.11.01 (Elekta, Stockholm, Sweden). The plan was evaluated and approved by a dedicated radiation oncologist.

The treatment setup was verified through onboard imaging in the form of cone-beam CT before the execution of the IMRT plan.

Phase I

Patients received 50 Gy in 25 fractions over five weeks at 2-Gy per fraction to PTV primary and draining LN with respectable normal tissue tolerance along with concurrent cisplatin administration to a dose of 40 mg/m² once a week, with weekly monitoring of blood parameters.

Phase II
SEB to primary gross residual disease to a dose of 20 Gy in 10 fractions over two weeks. Sequential nodal boost to LNs >1 cm at EBRT conclusion to a total dose of 60 Gy in 30 fractions.

The patients were reviewed after every five fractions of RT to monitor acute treatment-related toxicities as per the RTOG criteria. One week after EBRT completion, the patients received intracavitary image-based BT with a total dose of 12 Gy in two fractions for two weeks. Treatment planning and delivery were executed using the Oncentra planning system microSelectron HDR v. 2, with 18 channels, version 4.5.2.

2.4. Patient assessment

The first follow-up was conducted six weeks after the completion of chemoradiation for response assessment with the complete pelvic examination and cross-sectional imaging such as CECT (abdomen and pelvis) or MRI (abdomen and pelvis). RECIST criteria version 1.1 was used for response assessment. The Common Terminology Criteria for Adverse Events (CTCAE) version 5 was used for grading hematologic toxicities, and RTOG criteria were used for assessing radiation-related toxicities. The patients were followed up every three months and examined clinically through imaging tests, as required.

The study protocol was duly approved by the institutional ethics committee, and the patients who refused to provide consent were excluded.

2.5. Statistical analysis

All data were prospectively maintained in the SPSS Statistics software for Windows, version 24.0 (IBM Corp., Armonk, NY). Quantitative data are presented as the arithmetic mean ±standard deviation (SD), whereas categorical data are presented as the frequency and percentage. The toxicity of dose-escalated IMRT was evaluated using Kaplan-Meier estimates. The Kaplan-Meier method is used to analyze "time to event data." In the present study, the main outcome was the development of toxicities such as skin toxicity, GI toxicity, GU toxicity, and anemia after the initiation of dose-escalated IMRT at different time intervals over weeks. Kaplan-Meier graphs for toxicities such as skin, GI, and GU toxicities and anemia were plotted in the SPSS software.

Results

The six-month follow-up data were available for 40 patients. One patient defaulted on the treatment protocol and was, therefore, excluded from the study. Patient- and treatment-related characteristics are listed in Table 1 and Table 2, respectively. The overall treatment time was calculated from the date of EBRT initiation to the date of the second BT.
TABLE 1: Patient characteristics
FIGO: International Federation of Gynecology and Obstetrics

| Characteristic                          | Value       |
|----------------------------------------|-------------|
| Age at time of diagnosis, years        | 50 (45-56)  |
| FIGO stage, n (%)                      |             |
| IIB                                    | 7 (17.5%)   |
| IIIB                                   | 22 (55%)    |
| IIIC1                                  | 9 (22.5%)   |
| Size of the primary tumor, n (%)       |             |
| <4 cm                                  | 0           |
| >4 cm                                  | 40 (100%)   |
| Lymph node status, n (%)               |             |
| <1 cm                                  | 8 (19.5%)   |
| 1-2 cm                                 | 8 (19.5%)   |
| >2 cm                                  | 4 (9.7%)    |
| Tumor histology, n (%)                 |             |
| Squamous cell carcinoma                | 35 (87.5%)  |
| Adenocarcinoma                         | 3 (7.5%)    |
| Adenosquamous                          | 2 (5%)      |

The majority of the patients (35, 87.5%) were confirmed to have squamous cell carcinoma based on the histological analysis. Furthermore, 22 (55%) patients had FIGO 2018 stage IIIB. All patients had tumor diameters of >4 cm. The LN-positive status of size >1 cm at the baseline was noted in 12 patients. These 12 patients received a sequential nodal boost after the completion of 50 Gy in 25 fractions. We did not record any gap during the entire treatment period. All patients received at least four to six cycles of concurrent cisplatin to a dose of 40 mg/m².

EQD2 of the dose administered to the primary tumor was comparable to the standardized RT dose fractionation schedule (Tables 3, 4). The true biological dose delivered through EBRT to the pelvis with the dose fractionation schedule of the current study was 103.2 Gy.
**TABLE 3: BED and EQD2 in standard RT schedule**

BED: biologically effective dose; EQD2: equivalent total doses in 2-Gy fractions; RT: radiation therapy; PTV: planning target volume; SIB: simultaneous integrated boost; BT: brachytherapy

|                      | Standard RT schedule | EQD2 | BED |
|----------------------|----------------------|------|-----|
| PTV primary          | 50 Gy/25#/5 weeks    | 50 Gy| 60 Gy|
| PTV node (SIB)       | 55 Gy/25#/5 weeks    | 55.92 Gy| 67.1 Gy|
| BT                   | 7 Gy x 3#            | 29.75 Gy| 35.7 Gy|
| Total (PTV primary + BT) |                   | 79.75 Gy| 95.7 Gy|

**TABLE 4: BED and EQD2 in this study**

BED: biologically effective dose; EQD2: equivalent total doses in 2-Gy fractions; PTV: planning target volume; EBRT: external beam radiation therapy; BT: brachytherapy

|                      | Current study | EQD2 | BED |
|----------------------|---------------|------|-----|
| PTV primary + EBRT boost | 70 Gy/35#/7 weeks | 70 Gy| 84 Gy|
| PTV node + sequential boost | 60 Gy/30#/6 weeks | 60 Gy| 72 Gy|
| BT                   | 6 Gy x 2#     | 16 Gy| 19.2 Gy|
| Total (PTV primary + BT) |               | 86 Gy| 103.2 Gy|

Dosimetric characteristics are presented in Table 5 and Figure 4. The mean ±SD doses received by 15% and 50% volume of the rectum were 63.26 ±4.29 and 51.42 ±6.30 Gy, respectively. The mean ±SD doses received by 15% and 50% volume of the urinary bladder were 60.94 ±4.96 and 46.47 ±6.51 Gy, respectively. The doses received by 195 cc and 150 cc of the bowel bag were 35.26 ±6.83 and 35.26 ±6.83 Gy, respectively. Both the femoral heads received the maximum dose of 33.7 Gy.

The average doses received by 2-cc volume of the urinary bladder and 2-cc volume of the rectum with one fraction of BT were 5.5 and 7.7 Gy, respectively (Figure 5).
### TABLE 5: Dose constraints as per RTOG 0415 study

RTOG: the Radiation Therapy Oncology Group; PTV: planning target volume; CTV: clinical target volume; SD: standard deviation

| Volume          | Dose as per RTOG 0415 | Current study dose (Gy), mean ±SD |
|-----------------|-----------------------|-----------------------------------|
| PTV (max)       |                       | 74.15 ±0.83                       |
| PTV (min)       | (>98% should receive 70 Gy) | 68.73 ±0.93                      |
| CTV (min)       | (>100% should receive 70 Gy) | 64.52 ±3.02                      |
| Bladder V <15%  | 80 Gy                 | 60.94 ±4.96                       |
| Bladder V <25%  | 75 Gy                 | 56.68 ±5.43                       |
| Bladder V <35%  | 70 Gy                 | 52.73 ±5.72                       |
| Bladder V <50%  | 40 Gy                 | 46.47 ±6.51                       |
| Rectum V <15%   | 75 Gy                 | 63.26 ±4.29                       |
| Rectum V <25%   | 70 Gy                 | 59.63 ±5.20                       |
| Rectum V <35%   | 65 Gy                 | 56.15 ±5.76                       |
| Rectum V <50%   | 60 Gy                 | 51.42 ±6.30                       |
| Femur Dmax      | -                     | 34.5 ±6.3                         |
| Bowel Bag 150 cc|                       | 38.05 ±6.97                       |
| Bowel Bag 195 cc|                       | 35.26 ±6.83                       |

Figure 3 illustrates the planning system Monaco version 5.11.01 - 95% isodose distribution. Figure 4 depicts BT dose distribution.

**FIGURE 3: Planning system Monaco version 5.11.01 - 95% isodose distribution**
3.1. Treatment-related toxicity

RTOG grade III dermatitis (Table 6 and Figure 5), grade III acute GI toxicity (Figure 6), and grade III acute GU toxicity (Figure 7) were observed in three (7.5%), six (15%), and three (7.5%) patients, respectively. None of the patients had grade IV toxicity.

| Acute toxicity               | At CTRT completion |
|------------------------------|--------------------|
| Dermatitis                   |                    |
| Grade I – 18 (45%)           |                    |
| Grade II – 19 (47.5%)        |                    |
| Grade III – 3 (7.5%)         |                    |
| Gastrointestinal toxicity    |                    |
| Grade I – 9 (22%)            |                    |
| Grade II – 25 (60%)          |                    |
| Grade III – 6 (17.5%)        |                    |
| Genitourinary toxicity       |                    |
| Grade I – 21 (52.5%)         |                    |
| Grade II – 16 (40%)          |                    |
| Grade III – 3 (7.5%)         |                    |

**TABLE 6: RTOG acute toxicity at CTRT completion**

RTOG: the Radiation Therapy Oncology Group
FIGURE 5: Kaplan-Meier curve of the duration for the development of acute skin toxicity

FIGURE 6: Kaplan-Meier curve of the duration for the development of acute GI toxicity

GI: gastrointestinal
CTCAE grade I anemia was observed in all patients. White blood cell (WBC) counts, platelet counts, and serum creatinine levels were within normal limits during CTRT treatment. Anemia resolved within six weeks of RT completion (Table 7).

| Acute toxicity                        | At CTRT completion |
|---------------------------------------|-------------------|
| Hemoglobin levels, g/dL, mean ±SD     | 9.84 ±1.39        |
| Total WBC count, mean ±SD             | 5.86 ±1.57        |
| Total platelet count, mean ±SD        | 2.14 ±0.99        |
| Serum creatinine, mg/dl, mean ±SD     | 1.1 ±0.9          |

**TABLE 7: Blood investigation profile**

SD: standard deviation

Figure 8 shows the Kaplan-Meier curve of the duration for the development of anemia.
3.2. Response rate

Assessment at six weeks after treatment completion demonstrated complete response in 26 (65%) patients and partial response in 14 (35%) patients. At three and six months, seven (17.5%) and three (7.5%) patients, respectively, had residual lesions (Table 8).

| Cancer stage response assessment | At 6 weeks, n (%) | At 3 months, n (%) | At 6 months, n (%) |
|---------------------------------|-------------------|--------------------|--------------------|
| Partial response                | 15 (36.6%)        | 7 (17.5%)          | 3 (7.5%)           |
| Complete response               | 26 (63.4%)        | 33 (82.5%)         | 37 (92.5%)         |
| Stable disease                  | -                 | -                  | -                  |
| Progressive disease             | -                 | -                  | -                  |

**TABLE 8: Clinicoradiologic response assessment**

Discussion

IG-IMRT is a highly conformal technique that demonstrates an improved therapeutic ratio, and therefore, it offers the possibility of sparing adjacent normal tissues without compromising the target volume coverage [18]. The treatment of gynecologic malignancies with IG-IMRT has been on the rise in the past decade despite the dearth of data on late toxicities and disease control outcomes. Moreover, little is known regarding EBRT dose intensification with de-escalated BT. The Meta-Analysis Group of the Medical Research Council Clinical Trials Unit analyzed 13 trials comparing concurrent CTRT with chemotherapy alone in patients diagnosed with FIGO stage IB-IVA cancer receiving an RT dose ranging from 40 to 45 Gy to the whole pelvis with EBRT boost to primary up to 61.2 Gy followed by BT boost ranging from 18 to 50 Gy [19]. Remarkable improvements of 8% and 9%, respectively, were observed in terms of five-year disease-free survival (DFS) and locoregional control, with CTRT regimen at the cost of a higher rate of GI toxicity because conventional techniques were used in most of the trials. Traditionally, pelvic EBRT doses were limited to 45-50 Gy with conventional techniques primarily due to the small bowel tolerance being a limiting factor. Dosimetric studies from several retrospective cohorts have shown IMRT to be superior to the conventional technique in terms of GI and GU toxicity profiles. Mundt et al. reported a significantly lower grade of GI toxicity (grade II) with the IMRT technique compared to the conventional technique (3% vs. 20%) [20]. The use of dose-escalated EBRT with the IMRT technique followed by de-escalated BT by Nikola et al. showed a >25% incidence of grade III or higher GI and GU toxicities with conventional CTRT [21]. In our study, we observed similar acceptable rates of acute grade III GI toxicity in five (12.5%) patients and acute grade III GU toxicity in three (7.5%) patients at the sixth week of CTRT treatment.

Nikola et al. planned EBRT for primary tumors with a dose of 50.4 Gy, and for tumors >4 cm in diameter, an
additional EBRT boost of 9 Gy was administered. The total HDR-BT dose ranged from 15 to 18 Gy. At a median follow-up of 35.5 months, despite dose escalations, nine (25.1%) patients developed locoregional recurrence, with seven (77.7%) of them being in-field recurrence. In our study, all patients had tumor diameters of >4 cm, and we delivered SEB to primary tumors at a dose of 20 Gy compared with 10 Gy planned by Nikola et al., because radiobiologically, primary tumors generally have a necrotic component with a hypoxic radioresistant focus that requires higher lethal doses for tumor cell killing. The total dose received by the LN was 60 Gy in our study, which followed the NCCN 2022 recommendations of an LN boost of 56–63 Gy.

Dosimetric data from the randomized control dose-escalation trial in patients with prostate cancer performed at MD Anderson Cancer Center revealed that the risk of rectal bleeding decreased from 46% to 6% when <25% of the rectum received a 70-Gy dose [22]. This constraint has become the standard for subsequent studies such as the RTOG 9406 3D CRT study and RTOG 0415 phase III randomized study of hypo-fractionated 3D CRT/IMRT versus conventionally fractionated 3D CRT/IMRT treatment in patients with favorable-risk prostate cancer. We adopted the same dose-constraint protocol and found that <35% of the rectum received a dose of 56.15 ±5.76 Gy. Furthermore, <60 Gy was received by >50% of the rectal volume. This was in concordance with the RTOG 0415 dose constraints.

In this study, we hypothesized that an escalated dose for primary and draining pelvic LNs is essential to treat the macroscopic and subclinical primary tumor and lymph nodal disease to improve DFS and locoregional control. Furthermore, with an escalated EBRT dose, the bulk of the primary tumor is reduced, improving the chances of BT applicator placement with ideal geometry. Another reason for delivering dose-escalated EBRT to the pelvis is the fact that the cervix and uterus can tolerate >200 Gy. With this dose, the rate of necrosis is <1%. The BED of 103.3 Gy in our study is lower than the reported threshold doses of 150 Gy for vesicovaginal fistula [23].

Because the present study was conducted at a single center and involved a small sample size and noncomparative design, we recommend a randomized control study with a larger target population group to validate the CRTRT treatment protocol proposed in our study. Another limitation of our study is the disparity in the cross-sectional imaging used for staging in the target population. In the wake of the coronavirus disease pandemic and our institute being a government cancer center, positron emission tomography/CT was not performed for the baseline evaluation of LNs and disease extent during the study period. At present, our study is in the initial phases of follow-up, and hence, we do not have data regarding late toxicity, five-year OS, DFS, and LRC rates. Nevertheless, we believe that this first-of-its-kind study in the Indian population with a favorable toxicity profile holds promise for the management of cervical carcinoma in the future.

Conclusions

Our findings revealed that patients with cervical cancer treated with dose-escalated IMRT have satisfactory outcomes with reasonably low levels of treatment-related acute GI and GU toxicities. The present study indicates that the application of a high dose of external radiation to the pelvis by using the IMRT technique with image-guided delivery could be an acceptable alternative to the standard-dose management schedule.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee, Government Medical College, Aurangabad issued approval Pharma/EC-GMCA/525/2019.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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