Outcome Of Locally Advanced Cervical Cancer Patients Treated By IMRT Boost As A Non-Brachytherapy Alternative.

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ARTICLE INFO

Purpose: To study the treatment outcome with intensity modulated radiotherapy (IMRT) boost as a non-brachytherapy alternative in locally advanced stage cervical cancer patients.

Material and Methods: Nineteen histologically proven cervical cancer patients who were not fit for brachytherapy boost were enrolled in this study. All selected patients were given External Beam Radiotherapy (EBRT) 50Gy in 25-28 fractions with concurrent weekly Cisplatin (30 mg/m2) and then planned for boost dose by IMRT, 25 Gy in 10 fractions over two weeks.

Results: All 19 patients completed the treatment (3 stage II, 11 stage III, 3 stage IVA and 2 carcinoma vault). Median follow up was 27 months (range, 3-51 months). The incidence of grade I and II skin toxicities were 57.8% and 15.7% respectively. The genitourinary toxicities with respect to Grade I and II were 47.3% and 10.5% respectively. The overall complete response was found in 14 (73.68%) patients, partial response in 2 (10.52%) patients and progressive disease in three (15.78%) patients at 3 months of follow up. On last follow up 11 patients were disease free and the local control rate was 58%. Late toxicities of grade 2 bladder and rectum was seen in two patients (10.5%).

Conclusions: IMRT boost as an alternative for brachytherapy boost can be very well planned for the cervical cancer patients, in whom after completion of EBRT +/- Chemotherapy, brachytherapy is not feasible. It is possible to escalate the tumor dose by IMRT boost with manageable toxicities and good local disease control.

Keywords: Uterine cervical neoplasms, Radiotherapy, Intensity modulated radiation therapy, Brachytherapy, High dose rate

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INTRODUCTION
Worldwide, cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women as per GLOBOCAN 2018 [1]. In India, cervical cancer is the most common cancer among the rural population and in some metro cities [2,3]. In patients presenting with locally advanced disease, brachytherapy (BT) is considered the gold standard technique to deliver boost radiation dose to cervical disease. Compared to external-beam radiation therapy (EBRT) alone, BT boost improves overall survival (OAS) and reduces the local recurrence of disease [4,5]. Since then, BT boost supplementing concurrent chemotherapy and EBRT has been the treatment of choice for locally advanced cervical cancer [6]. Numerous patients are excluded from BT due to physical considerations that prevent applicator placement, such as decreased vaginal accommodation with age, uterine malformations, or excessive tumor volume [7]. Some patients simply refuse BT with concerns of invasiveness or discomfort [8]. In light of this, this dogma that BT is irreplaceable, most studies using high-tech EBRT have been carried out in patients who could not receive BT for medical or personal reasons [9].

The present study aimed to evaluate the treatment outcomes of locally advanced cervical cancer patients treated by EBRT (50 Gy) with concurrent weekly cisplatin (30 mg/m²) followed by intensity-modulated radiation therapy (IMRT) boost 2.5 Gy for 10 fractions over two weeks, who were not fit for Intracavitary radiotherapy (ICRT).

MATERIALS AND METHODS:
Patients:
A total of 334 patients of cervical cancer were registered in the department during the study period from September 2015 to August 2017 and followed up till March 2020. Out of this, 19 patients were allocated for the study. This descriptive longitudinal study was conducted in the department of Radiation Oncology in an Institute situated in the rural area of Maharashtra, India, after taking permission from Institutional Ethics Committee, Pravara Institute of Medical Sciences-Deemed University (IEC PIMS-DU) (No. PIMS/IEC-DR/2020/209). Patients who were not fit for ICRT boost and satisfied the inclusion criteria (Histopathologically proven, cervical cancer FIGO [International Federation of Gynecology and Obstetrics] stage II, III, IV A and vault, age below 70 years, normal hematological and biochemical functions, Karnofsky performance status more than 80%) were included in this study after obtaining informed consent. Patients who received chemotherapy and or radiotherapy previously, who had FIGO stage I & IVB or who had age more than 70 years were excluded from the study. Patients were staged clinically by FIGO staging and radiologically by Computed tomography (CT) scan of abdomen and pelvis.

TREATMENT PLANNING AND TREATMENT:
All the 19 patients were given EBRT by three-dimensional conformal radiotherapy (3D-CRT) on the 6-MV linear accelerator (Clinac-DBX; Varian Medical System, Palo Alto, CA, USA). Planning CT scan (CT scan machine; Siemens Healthcare, Erlangen, Germany) of abdomen and pelvis was done with Vac-Lok to maintain the patients positioning and immobilization during each treatment for all patients. Planning CT scan images were transferred to the Eclipse version 11.031 treatment planning system (TPS) contouring stations using the Digital Imaging and Communications in Medicine (DICOM) protocol. Planning was done on the Eclipse TPS. EBRT treatment was delivered 5 days a week with a fraction size of 1.8–2 Gy/day, to the total dose 50 Gy in 25–28 fractions to the pelvis by anteroposterior/posteroanterior (AP/PA) and four-field box technique and to para-aortic region for involved para-artic nodes by AP/PA fields (45 Gy) with concurrent weekly cisplatin 30 mg/m². After completion of EBRT, patients were assessed for tumor regression and ICRT boost as per department protocol. A total of 19 patients were not feasible for ICRT because of poor anatomy (09),
inadequate tumor regression (06), inability to view external os (02) and two cases with vault lesion. For these patients, IMRT boost with 25 Gy with 2.5Gy/fraction was delivered over two weeks.

Patients again underwent a Planning CT scan of 5mm thickness from mid-thorax to mid-thigh Abdomen and Pelvis with a comfortably full bladder. Patients were asked to empty bladder and bowel, and drink 200ml of water 20 minutes before the CT scan. For IMRT planning contouring, the gross tumor volume residual (GTV res.) is the residual tumor within the cervix with invasion into surrounding tissues. GTV res. was expanded 3-dimensionally uniformly by 5mm to define the clinical target volume (CTV). CTV extended to the uterus, parametria, upper vagina (3-4cm) and involved residual nodes along with external iliac, internal iliac, common iliac region. CTV was expanded 0.5 cm antero-posteriorly and 1cm in cranio-caudally and bilaterally to create Planning target volume (PTV) to account for organ motion and set up uncertainty. The organs at risk (OARs) bladder, rectum, and both femoral heads were contoured. Seven to nine fields coplanar IMRT plans were generated with a homogenous dose within 95 to 107% of the prescribed dose. OAR dose constraints were specified as per Radiation therapy oncology group (RTOG) 0126 guidelines (For urinary bladder 35% <70 Gy, 50% <75 Gy and for Rectum 35% <65 Gy, 50% <60 Gy). Patients followed the same bladder and rectal protocols every day before treatment. EPID (electronic portal imaging device) verification was done daily before the treatment with IMRT boost.

The equivalent dose for IMRT boost was calculated by biological effective dose (BED) of HDR brachytherapy as per department protocol 7 Gy of three fractions at weekly interval by Linear Quadratic model (LQ model) and equating it for 25 Gy in 10 fractions of IMRT boost dose. Thus, the total EQD2 equivalent dose of EBRT 50 Gy + 25 Gy IMRT boost / ICRT boost by HDR 21 Gy was equal to 91.35 / 95.7 Gy to PTV / point A respectively. The IMRT boost dose was kept slightly lower than the HDR brachytherapy boost dose. For planning Tumor BED10 (91.35 Gy) and normal tissue bladder and rectum BED3 (140 Gy) was kept.

Follow-up and statistical analysis:

After completion of the treatment, response evaluation was documented with clinical, hematological and radiological evaluation (ultrasonography of abdomen and pelvis routinely and CT scan/MRI as and when indicated) at 3rd and 6th month and thereafter at every 3- to 4-month follow-up until the last follow-up in March 2020. The prognostic outcome of each patient was assessed using the Response Assessment Criteria in solid tumors (RECIST) version 1.1 for the disease-free survival, locoregional control for the complete or partial response and disease failure for locoregional recurrence/distant metastases. Acute and late toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and RTOG toxicity grading. All the data collected were compiled and statistical analysis was done by simple statistical techniques using mean, standard deviation, median, range, proportion/percentage survival analysis by SPSS version 20 (IBM SPSS, Armonk, NY, USA).

RESULTS:

Various patient related parameters assessed are mentioned in Table 1. The median age of the patients was 55.5 years (range, 41 to 70 years). The most common histology of cervical tumor was squamous cell carcinoma (17 patients). As per FIGO staging for cervical cancer there were three patients from stage II, 11 were stage III, three stage IVA, and two were post-operated with vault lesion. Both the post-operated patients with big vault lesion had parametrium involvement up to the lateral pelvic wall. Overall treatment time (OTT) was ranging between 49 to 74 days and 11 patients completed in less than 56 days. Three patients were given radiation to para-aortic region along with the pelvic region.
was varying with a wide range between 201cc. to 686cc with a median volume of 349cc, as in partial response and progressive disease patient’s volume was more. Due to the close proximity of OARs this range of PTV resi. volume was giving dose effect to OARs. Details of PTV res. and OARs volume along with median dose volume to OARs at 35% and 50% of the dose is shown in Table 2 and Figure-1.

Median follow-up was 27 months (range, 3 to 51 months). On the first follow-up after 3 months, 14 patients (73%) had complete response 3 stage II, 9 stage III, 1 stage IVA, and 1 P/O vault), two patients had partial response and three patients were with progressive disease. Two of the progressive disease patients expired within 6 months of treatment completion and one patient expired within 1 year. On the last follow-up there was one local recurrence and two with local failure and distant metastases. The details of the response to the treatment till last follow-up are shown in Table 3 and Figure 2. There were 11 patients with complete response and the local control rate was 58%, till last follow-up.

There were no significant acute and chronic upper and lower gastrointestinal toxicities and the chemotherapy induced nausea vomiting (CINV) was manageable with antiemetics. The incidence of grade I and II skin toxicities were 57.8% and 15.7% respectively. The genitourinary toxicities with respect to Grade I and II were 47.3% and 10.5% respectively. There were chronic lower GI toxicities (grade- I-II) in the form of proctitis in two patients (10.5%) managed with symptomatic treatment. One patient (5.2%) with progressive disease had severe hydronephrosis and managed by percutaneous nephrostomy (PCN) but could not survive. Details of acute and chronic toxicities are shown in Table 4 and 5.

**Table 1: Patient, Disease and treatment characteristics (n=19)**

<table>
<thead>
<tr>
<th>Total patients</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cervical cancer pts. during study period</td>
<td>334</td>
</tr>
<tr>
<td>For IMRT boost of total Cervical cancer pts. during study period</td>
<td>19 (5.68 %)</td>
</tr>
<tr>
<td>Age at disease</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>00</td>
</tr>
<tr>
<td>41-50</td>
<td>06 (31.5 %)</td>
</tr>
<tr>
<td>51-60</td>
<td>06 (31.5 %)</td>
</tr>
<tr>
<td>61-70</td>
<td>07 (36.8 %)</td>
</tr>
<tr>
<td>Histopathology report</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>17 (89.5 %)</td>
</tr>
<tr>
<td>Papillary Adenocarcinoma</td>
<td>01 (5.2 %)</td>
</tr>
<tr>
<td>Adeno Sq. Carcinoma</td>
<td>01 (5.2 %)</td>
</tr>
<tr>
<td>Hemoglobin level at first visit</td>
<td></td>
</tr>
<tr>
<td>7.5-9 gms%</td>
<td>02 (10.5 %)</td>
</tr>
<tr>
<td>9.1-10 gms%</td>
<td>04 (21.05 %)</td>
</tr>
<tr>
<td>&gt;10 gms%</td>
<td>13 (68.42 %)</td>
</tr>
<tr>
<td>Stage of the Disease</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>03 (15.7 %)</td>
</tr>
</tbody>
</table>
Stage III  
Stage IVA  
Ca. Vault

Overall treatment time (OTT)

- < 56 days: 11 (57.8%)  
- > 56 days: 08 (42.10%)  
(Range 49-74 days)

IMRT - Intensity modulated Radiotherapy.

Table No. 2 - IMRT Plan Volumes and dose volume to OARs for IMRT boost dose of 25 Gy in 10 fractions, (For 19 Cases).

<table>
<thead>
<tr>
<th>Volume</th>
<th>Median Volume in cc (Range)</th>
<th>Maximum Dose (D max) in Gy Median value</th>
<th>Median % dose at 35% Volume in Gy</th>
<th>Median % dose at 50% Volume in Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV V</td>
<td>349 (201-686)</td>
<td>27.6 (26.3-28.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rectum V</td>
<td>133.6 (81.7-185.6)</td>
<td>25.7 (24.9-27.8)</td>
<td>13.95 Gy (12-15.9)</td>
<td>11.9 Gy (9.5-14.4)</td>
</tr>
<tr>
<td>Bladder V</td>
<td>201.8(32-371.7)</td>
<td>25.4 (24.7- 27.9)</td>
<td>15.15 Gy (14.6-15.7)</td>
<td>12.3 Gy (11.7-13)</td>
</tr>
</tbody>
</table>

Values are presented as median (range).
IMRT, intensity-modulated radiation therapy; PTV, planning target volume; OAR, organs-at-risk; Dmax, maximum dose.

Table 3. Treatment response till last follow-up (Total Patients for evaluation 19.)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Treatment Response</th>
<th>1st Follow Up (Three Months)</th>
<th>Last Follow Up (3 to 51 months (median 27 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II (3) III (11) IVA (3) Vault (2) Tot</td>
<td>II (3) III (11) IVA (3) Vault (2) Tot</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Complete response (CR)</td>
<td>3 (100%) 9 (81%) 1 (33%) 1 (50%) 14 (73%)</td>
<td>3 (100%) 7 (63%) 0 (0%) 1 (50%) 11 (58%)</td>
</tr>
<tr>
<td>2</td>
<td>Partial response (PR)</td>
<td>0 1 1 0 2</td>
<td>0 1a 1b 0 2a</td>
</tr>
<tr>
<td>3</td>
<td>Progressive Disease (PD)</td>
<td>0 1 1 1 3</td>
<td>0 1a 1b 1c 3a</td>
</tr>
<tr>
<td>4</td>
<td>Disease failure</td>
<td>- - - - -</td>
<td>0 2b 1b+c 0 3b+c</td>
</tr>
</tbody>
</table>

The last follow-up ranged from 3 to 51 months (median 27 months). One stage III patient from complete response group had minimum follow up of three months.

a) Expired (All patients with partial response and progressive disease expired within one year of the treatment).
b) b+c Include 1 local recurrence and 2 distant metastases and expired. (None of the patients with disease failure survived till end of this study).
Table – 4: Acute Toxicities (Total Cases 19)

<table>
<thead>
<tr>
<th>Acute Toxicities ↓</th>
<th>Grade of Severity</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td>11 (57.8%)</td>
<td>3 (15.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vagina</td>
<td></td>
<td>10 (52.6%)</td>
<td>2 (10.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>9 (47.3%)</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td>10 (52.6%)</td>
<td>3 (15.7%)</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td></td>
<td>13 (68.4%)</td>
<td>3 (15.7%)</td>
<td>2 (10.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>12 (63.1%)</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table – 5: Late Toxicities

<table>
<thead>
<tr>
<th>Late Toxicities Organ ↓</th>
<th>No of Pt</th>
<th>Grade of Severity</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proctitis</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>1 (5.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cystitis</td>
<td>3 (15.5%)</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hydronephrosis with uremia</td>
<td>1 (5.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5 (26.3%)</td>
<td>3 (15.5%)</td>
<td>2 (10.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 1. Planning images (A) and (C) for two different patients before EBRT and same patient images (B) and (D) showing clinical response after EBRT+CT and before IMRT boost plan. EBRT, external-beam radiation therapy; CT, computed tomography; IMRT, intensity-modulated radiation therapy.
DISCUSSION AND CONCLUSION:

External Beam Radiotherapy with concurrent weekly cisplatin followed by boost dose by Intracavitary / interstitial brachytherapy is the standard of treatment in stage Ib2 to IVA cervical cancer patients [10]. Furthermore, BT allows for the delivery of a high dose to tumor tissue, while maintaining a steep dose gradient to surrounding normal tissue, thus allowing better sparing of the adjacent bowel and bladder. In addition to the unique dose distribution, the superiority of BT was boosted by the introduction of high-dose-rate (HDR) BT [11,12]. Interstitial brachytherapy is often helpful in patients with cancer-cervix not suitable for ICRT (ABS guidelines), but it involves invasive procedures and its success is highly dependent on the ability of the operator [13]. In cases with inadvertent surgery for cervical carcinoma or cases with vault lesion, after EBRT, HDR vaginal vault ovoid brachytherapy is an established modality for treatment [14]. For patients with big residual vault lesion post EBRT, interstitial brachytherapy is the preference for dose delivery at the tumor site.

Patients who could not receive BT because of the insufficient tumor regression during EBRT,
irregular pelvic anatomy, or concurrent medical problems are at substantially higher risk of pelvic tumor recurrences. In such a situation high precision conformal EBRT boost by three-dimensional conformal radiotherapy (3D CRT), IMRT and stereotactic body radiation therapy (SBRT) can increase the dose to central pelvis with sufficient coverage of the target volume and dose reduction to OARs [15]. IMRT is based on the manipulation of many small subdivided beams, each with varying intensity. Because each beam can be manipulated individually, the dose distribution can be exquisitely controlled, and a highly conformal treatment field results [16]. These characteristics allow dose painting, a desirable quality of boost radiation delivery because it allows the pelvic field to receive a lower dose while delivering a high dose to the cervical PTV. Because this can reduce overall treatment time, such a method is especially favorable for rapidly proliferating tumors [17]. In fact, this strategy yielded favorable local control when delivered concomitantly with whole-pelvic irradiation SIB (Simultaneous integrated boost) [18]. IMRT is also superior to conformal radiotherapy as a boost alternative in patients unable to receive BT in respect to both target coverage and OAR sparing [19].

There are few studies of next-generation EBRT techniques use as an alternative to brachytherapy boost, some are retrospective and few done prospectively. These studies are heterogeneous in the treatment plan (delivery technique and dose fractionation) and follow-up time [9]. In most studies, the pelvic planning target volume (PTV) received photon beams to 45-50.4 Gy in 1.8 to 2 Gy per fraction and a BT alternative was either patient refusal of BT or anatomical constraints preventing proper BT delivery.

Matsuura et al used 3-DCRT alone using accelerated hyper fractionation schedule on seven patients of cervical cancer. In the fourth week, a small conformal boost volume (1.2 to 1.6 Gy per fraction) was initiated concomitant with pelvic irradiation, and continued after the fifth week twice daily, with at least 6 hours between fractions. Uniform 0.5 to 1 cm clinical target volume (CTV) to PTV expansion was used. Two-year disease control was 71.4 %, with the highest toxicity being grade 2 rectal bleeding, affecting only 2 out of 7 patients [20]. As compared to the present study, disease control was better while toxicities were comparable which might be attributed to less median overall treatment time only 42 days (as accelerated hyper fractionation was used) as compared to 56 days, but at the same time follow up was for less time. Another study was done by Park et al, by giving a high dose of 3-Dimensional conformal boost (3DCB) using a real-time tracking radiation system (RTRS) of gold fiducial markers implanted in the cervix. The total dose delivered was 50 Gy to whole pelvic and 3DCB of 25-30 Gy (5 Gy/ fraction) twice weekly to PTV. The two-year local failure free survival was 54% and observed no grade 3 or higher late toxicities [13]. Though the tumor BED delivered in this study was more (105 Gy) than our study (91.35 Gy) disease control was almost similar. Two more studies by Barraclough et al [21] and Chan et al [19], used similar conformal radiotherapy techniques and two-year local control was reported as 79% and 83% respectively. Late grade 3 urinary and rectal toxicities were 2% in Barraclough et al and 17% by Chan et al. Total dose delivered was 70-80 Gy with BED in between 66-87 and 85-90 respectively. As compared to the present study local control was better but follow up was less duration.

Some cervical cancer patients treated with radical hysterectomy are at a higher risk of recurrence due to high risk factors such as small margins, involvement of the parametrium or vagina, or lymph vascular invasion. In these patients, a BT boost is often given after EBRT [22]. Wang et al studied boost dose to vaginal cuff in high risk post radical hysterectomy cervical cancer patients. Compared the efficacy of two arms in 80 cases, 60.2 Gy in 28 fractions simultaneous integrated boost (SIB) concurrent with 50.4 Gy pelvic IMRT to a late course sequential accelerated boost of 9 Gy in 3
fractions after the conclusion of 50 Gy in 25 fractions pelvic IMRT. Both groups had comparable local control (98% vs. 100%) and late severe toxicity (both 0%) at median follow up of 34 months. BED to PTV was 72 [23]. Vandecasteele et al used simultaneous integrated boost (SIB) to perioperatively treat areas at risk by 62 Gy in 4.28 Gy per fraction concurrent with pelvic IMRT of 45 Gy in 25 fractions prior to surgical resection. At the median 2-year follow-up, a promising 96% local control and 100% regional control were observed with only 4% late grade 4 intestinal and 14% late grade 3 urinary toxicity [24]. In both the studies there was no lesion and the radiation treatment was adjuvant treatment as compared to two cases of carcinoma vault in the present study and treatment was definitive.

Prospective IMRT study done by Khosala et al included 25 post operated cervical cancer patients with incomplete surgery, who were not suitable for high dose rate vaginal vault brachytherapy because of gross disease after whole-pelvic radiotherapy (WPRT) of 46 Gy in 23 fractions. These patients were given either 30 Gy in 10 fractions to CTV concurrent with 20 Gy to the PTV, or with 35 Gy in 15 fractions to CTV concurrent with 30 Gy to the PTV. They reported local control of 76% at median 38-month follow-up, and only 8% of patients exhibited late grade 3 toxicity [14]. As compared to the present study toxicities were comparable while local control was better, which might be attributed to less OTT and higher radiation dose.

There are various retrospective and prospective studies in which SBRT has been used for boost dose delivery, with a dose range of 16 to 30 Gy to the cervix in 2 to 6 Gy per fraction with very good local control. Studies with a follow-up time of (6 to 36 months), had demonstrated encouraging results with minimal late toxicity and local control rates of 78% (Hsieh et al) [25] and 100% by Marnitz et al and Haas et al [8,26]. Helical Tomotherapy (HT) was used by Hsieh et al (TomoTherapy Inc., Madison, Wisconsin) for megavoltage CT imaging in advance of each fraction of SBRT boost dose delivery and observed no late severe toxicities by improving precision and delivery consistency. Marnitz et al and Haas et al used the CyberKnife (CK) system to track gold fiducials implanted in the cervix for precise SBRT boost dose delivery. Studies employing SBRT, Molla et al and Jorcano et al in post operated cases, used a linac-based system to deliver a 14 Gy boost in 2 fractions after 45 to 50.4 Gy of whole-pelvic irradiation [27,28]. Both studies used multiple methods to improve precision by using infrared-guided skin markers and target organ motion was limited by the insertion of an MR endorectal probe. Despite different follow-up times (Molla 13 months; Jorcano 47 months), both studies demonstrated comparable and acceptable local control (Molla 86%; Jorcano, 77%) and late toxicity rates (Molla 0%; Jorcano 7%), supporting the efficacy of image-guided SBRT techniques.

Proton beams have also been used as alternatives to BT boost delivering 86 Gy median tumor dose with 5-year local control was 100% for stage IIIB and 61% for stage IIIB/IVA lesions, and the grade 4 genitourinary and/or gastrointestinal side effects were only 4%, comparable to HDR BT outcomes [29]. Beant S Gill et al, did retrospective boost dose analyses in cervical cancer cases from January 2004 to December 2011 with a median follow up of 22.9 months (range 0-180 months). The use of brachytherapy decreased from 96.7% to 86.1% whereas IMRT boost increased from 3.3- 13.9%. Survival was compared with brachytherapy boost and IMRT/ SBRT boost and documented that IMRT/ SBRT boost was significantly associated with an increase in mortality risk [30].

In conclusion, brachytherapy (ICRT / Interstitial brachytherapy) is the best conformal boost therapy after completion of EBRT for cervical cancer treatment, as it enables delivery of very high dose at the cervical and para cervical region. Few patients in which ICRT is not feasible, or are treated at centers with limited brachytherapy options and expertise, they are considered for local boost by EBRT using 3D CRT technique. Dose escalation can
be attempted with EBRT, but internal organ motion and daily setup error require margin around the CTV and that limits normal tissue sparing. For better results by dose escalation at the tumor site and sparing normal tissue by using high tech EBRT boost like IMRT boost (in this study), SBRT, SIB, IG-IMRT, Proton therapy, etc. are to be tried. Image-guided normal tissue sparing by high-tech radiation therapy will help reducing toxicities to normal tissues to some extent and overall treatment time can also be reduced by SIB and SBRT.

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Conflicts of Interest: Nil

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