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Clinical audit of dose-escalated radical radiotherapy for advanced cervical carcinoma using a pragmatic protocol (3 fractions of 8 Gy HDR brachytherapy)

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ABSTRACT

Introduction: Recent image-guided brachytherapy data suggests, dose-escalation to a cumulative EQD2 (equivalent dose delivered at 2 Gy/#) of ≥87 Gy is associated with significantly better disease control. We present a clinical audit of a pragmatic radical radiotherapy protocol for advanced cervical cancer, using fewer fractions of brachytherapy than in the presently most popular protocol.

Material & methods: Between July 2015 and December 2018, 96 consecutive advanced cervical carcinoma patients were treated by pelvic external beam radiotherapy (EBRT) (50 Gy/25fractions/5 weeks) ± weekly intravenous chemotherapy followed by image guided high dose rate (HDR) brachytherapy, using intracavitary/interstitial/hybrid techniques (intended point A dose: 8 Gy/fractions) × 3 fractions (cumulative target EQD2 ≥ 86 Gy). Insertion was done individually for each fraction of treatment.

Results: All patients completed their intended radiation protocol. 93.8% patients achieved complete response, while 6.2% patients achieved only partial response; no patients had stable/progressive disease. Out of the patients with partial response, 4.2% (4 out of 5 cases) cases of central/nodal residual disease underwent salvage surgery. At a median follow up of 21 months, 8.3% (8) patients had local failure, 1.1% (1) had nodal failure and 3.1% (3) had distant failures. Median Failure Free Survival was 29 months (26.5–31.5 months). On follow up, 6.3% and 3.2% patients had grade 2 or worse rectal and bladder morbidities respectively.

Conclusion: The protocol under study has been safe and effective in achieving dose-escalated radical chemoradiation in advanced cervical carcinoma. The use of fewer insertions of brachytherapy is logistically easier & can also be expected to improve compliance.

1. Introduction

Radical chemoradiation followed by Brachytherapy is the standard of care for advanced stage cervical carcinoma (Thomas, 1999) Recent data from protocols using image-guided brachytherapy as per GEC-ESTRO (Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy and Oncology) guidelines suggests that dose-escalation to a cumulative EQD2 [equivalent dose delivered at 2 Gy/# using $\alpha/\beta = 10$, External Beam Radiotherapy (EBRT) and brachytherapy] of 87 Gy or beyond is associated with significantly better disease control in such cases (Haie-Meder et al., 2005; Pötter et al., 2006; Hellebust et al., 2010; Dimopoulos et al., 2012; Dimopoulos et al., 2009; Schmid et al., 2011). Commonly used HDR (High Dose Rate) brachytherapy schedules e.g. with HDR of 2 fractions of 9 Gy, 5 fractions of 5.5 Gy, or 4 fractions of 7 Gy (with 45 Gy EBRT) correspond to EQD2 of 73 Gy, 80 Gy, and 84 Gy, respectively. The recent trials of EMBRACE (image guided intensity modulated External beam radio-chemotherapy and MRI based adaptive brachytherapy in locally Advanced Cervical cancer, www.embracestudy.dk) image-guided brachytherapy have used an EBRT dose of 45 Gy/25#/5 weeks followed by HDR brachytherapy 5–7 Gy/# for 3–5 such fractions (Dimopoulos et al., 2009; Schmid et al., 2011; Tanderup et al., 2016; Sturdza et al., 2016; Potter et al., 2018). Using 4–5

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Table 1
Baseline Characteristics.

N = 96	%(n)
Age (years) [Median (Range)]	54(26–79)
Tumor size (cm)	5.2(2.5–10.2)
Stage (FIGO 2018) (n = 96)	
IB2	2.1(2)
IB3	4.2(4)
IIA1	1(1)
IIA2	2.1(2)
IIB	29.2(28)
IIIB	18.8(18)
IIIC1	17.7(17)
IIIC2	16.7(16)
IVA	2.1(2)
Vault Carcinoma	6.2(6)
EBRT Para aortic Node	14.6(14)
Pelvic Node Boost	7.3(7)
Concurrent Chemotherapy	87.5(84)
Cisplatin Q1Week	81.4(81)
Carboplatin Q1Week	2.1(3)
Maximum cycles: 5 cycles	78.1(75)
Acute Gastro-intestinal Toxicity (EBRT) ≥ Grade 2	8.3(8)
Response after EBRT (RECIST v1.1)	
Complete Response	26(25)
Partial Response	74(71)

Table 2
Brachytherapy details.

Types of Brachytherapy [n = 96]	%(n)
Intracavitary	82.3(79)
Interstitial	9.4(9)
Hybrid	8.3(8)
Dosimetry	Dose in Grey(Gy)
Point A Dose (each fraction)	8
EQD2 (α/β = 10) (EBRT + BT)	86
Rectum 2 cc Dose EQD2 (α/β = 3) (EBRT + BT)	
Mean ± Standard Deviation	70.2 ± 3.8
Median (Range)	70.3(62.9–76.4)
Bladder 2 cc Dose EQD2 (α/β = 3) (EBRT + BT)	
Mean ± Standard Deviation	74.5 ± 3.8
Median (Range)	75 (61.6–81.2)
Response during 1st Fraction of Brachytherapy	
Complete Response	67.7(65)
Partial Response	32.3(31)

Table 3
Outcome analysis.

N = 96	%(n)
Follow-up duration in months [Median (range)]	21(13–33)
Response after 6 weeks of Brachytherapy	
Complete Response	93.8(90)
Partial Response	6.2(6)
Central Residual	5.2(5)
Late Toxicity (≥Grade 2)	
Rectum	6.3(6)
Bladder	3.2(3)
Local Failure	8.3(8)
Nodal Failure	1.1(1)
Distant Failure	3.1(3)
Survival in months	
Mean Failure Free Survival	27.9(25.9–29.9)
Median Failure Free Survival	29(26.5–31.5)
Overall Survival	31.9(30.9–33)

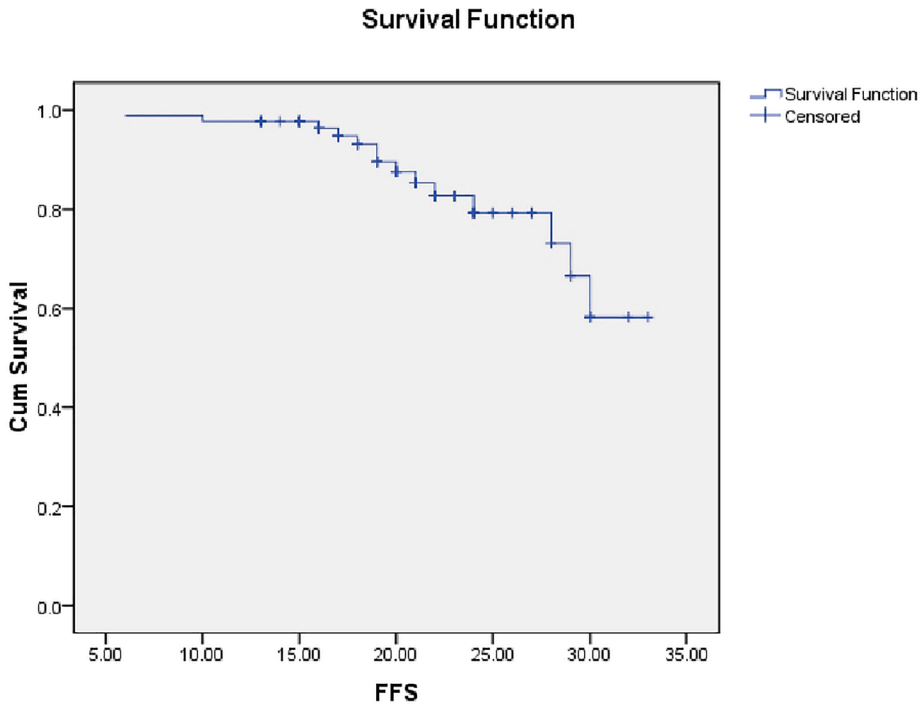
insertions of brachytherapy presents a significant load on logistics, in terms of operation room slots, anesthesia requirements and hospital stay. We present a clinical audit of a pragmatic radical radiotherapy protocol for advanced cervical cancer, using higher EBRT dose & fewer fractions of brachytherapy.

2. Material & methods

Between July 2015 and December 2018, 96 consecutive patients of advanced carcinoma of cervix were treated by radical chemoradiation with 8 Gy 3 fractions brachytherapy protocol. Clinical audit was conducted in January 2020, so that all patients had at least 1 year of follow-up post-treatment. All patients underwent planning contrast enhanced computed tomography (CT) scan using 5 mm slices; contrast was omitted in patients with deranged renal function; magnetic resonance imaging (MRI) scan was used to assist in delineation wherever possible. Patients received pelvic EBRT to a dose of 50 Gy/25#/5 weeks using conformal techniques (including intensity modulated radiotherapy); in case of bulky nodal disease, nodal boost to a dose of 55 Gy/25#/5 weeks was given; para-aortic lymph nodes were treated to a dose of 45 Gy/25#/5 weeks, only if involved. In-room image verification (2D/3D) was used as per standard protocol. Concurrent weekly intravenous chemotherapy was administered along with EBRT, depending on renal function; for creatinine clearance >60 ml/min, Cisplatin 40 mg/m2 was used while Carboplatin AUC2 was used for creatinine clearance between 40 and 60 ml/min; below this threshold, or for age >75 years, no chemotherapy was used. All patients then underwent HDR brachytherapy under spinal anesthesia, using intracavitary technique (for good responders with good anatomy), hybrid intracavitary- interstitial technique or Interstitial technique (using Syed-Neblett perineal template, for poor anatomy/extensive parametrial dose). Brachytherapy was done using CT guidance individually for each fraction of treatment. MRI guidance was used in interstitial and hybrid implant cases. The planned intended dose was 8 Gy/# to point A (optimized), for a total of 3# on a weekly basis, to achieve a cumulative target EQD2 of 86 Gy. In the final plan conventional pear shaped 100% isodose surface was graphically optimized for OAR sparing and isodose surface near the ovoids were optimized to include the target volume (whole cervix and gross residual disease visible in CT at time of brachytherapy) when needed. For interstitial and hybrid implants, high risk clinical target volume (HR-CTV) as defined by GEC-ESTRO group was delineated and dose was prescribed to the HR-CTV. Standard dose-volume constraints of urinary bladder (2 cc dose <75 Gy) & rectosigmoid (2 cc dose <70 Gy) were used. After treatment applicators were removed. As per our institutional practice we did repeat insertion and planning in each fraction, 3–7 days apart. Response assessment was done by clinical & MRI imaging assessment at 6 weeks post-treatment. Standard RTOG/EORTC acute & late toxicity criteria were used. Patients were followed up. Failure free survival and overall survival was calculated using Kaplan Meier Survival plot and the patients were censored at last follow up visit or death.

3. Results

We analyzed 96 patients who underwent radical radiotherapy with 8 Gy × 3 fractions brachytherapy protocol. Baseline characteristics and EBRT course are detailed in Table 1. All patients completed their intended protocol of radiation, though only 78.1% received the planned 5 weekly cycles of chemotherapy, 22.5% did not receive chemotherapy in view of poor renal function/extreme age. Brachytherapy treatment details and outcome analysis are elaborated in Tables 2 and 3 respectively. MRI based planning was done in 17 cases of interstitial and hybrid brachytherapy where HR-CTV was delineated. The median HR-CTV volume was 57.5 cc (range, 28.9–82.2 cc); median HR-CTV D90 dose per fraction was 7.8 Gy (range, 7.2–8.5 Gy) and the median HR-CTV D90 EQD2 was 86.2 Gy (range, 81.4–87.9 Gy). On 6 weeks post brachytherapy evaluation, 93.8% (n = 90) patients achieved complete



Failure Free Survival

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
27.920	1.039	25.883	29.956	29.000	1.266	26.519	31.481

a. Estimation is limited to the largest survival time if it is censored.

Fig. 1. Kaplan Meier Survival Plot (Failure Free Survival).

Table 4
Patterns of failure.

Type of failure	%(n)
Local Failure	8.3(8)
IIB	2
IIIB	4
IIIC1	1
IVA	1
Nodal Failure	1.1(1)
Vault Cancer	1
Distant Failure	3.1(3)
IIIB	1
IIIC1	1
IIIC2	1

response, while 6.2% (6) patients achieved only partial response; no patients had stable/progressive disease. Out of the patients with partial response, 5.2% (5) cases of central/nodal residual disease underwent salvage hysterectomy with/without nodal dissection, while 1.1% (1) was assigned to palliative chemotherapy only. At a median follow up of 15 months (5–33), 88.5% (85) patients remain alive; 4.2% (4) patients have died, 7.3% (7) patients lost to follow up. Local control was 91.7%. Median Failure Free survival (FFS) was 29 months (26.5–31.5 months) and overall survival was 31.9 months (30.9–33 months) (Vide Fig. 1 for FFS). Patterns of failure is detailed at Table 4. Most patients had grade 0–1 acute toxicities, though grade 2 & worse toxicities were seen in 8.3% (8) patients, most commonly gastrointestinal. On follow up, 6.2% (6) and 3.2% (3) patients have had grade 2 or worse proctitis and cystitis respectively. No grade 4 toxicities including fistula had occurred. Median time of appearance of late toxicities was 12 months (range, 10–21 months).

4. Discussion

Radical radiotherapy has long been the treatment of choice for cervical cancer, though in early stage disease, surgery is equivalent. While classical protocols of the past used brachytherapy alone, current practice uses a combination of concurrent chemoradiotherapy and brachytherapy.

Classically, brachytherapy doses were prescribed at point A, the hypothetical dose-limiting point, where the ureter and uterine artery cross. However, this point has no relation with the actual tumor extent; thus, smaller tumors are well-covered but larger ones with parametrial disease are not adequately encompassed by the isodose prescribed at point A. Recent advanced in technology, particularly MRI, have aided the development of image-based planning, spearheaded by the GEC-ESTRO group. The present paradigm uses two targets, as seen on T2-weighted MRI, one being the pre-EBRT disease volume, known as intermediate-risk clinical target volume (IR-CTV) and the other being the disease volume at each insertion of brachytherapy, known as HR-CTV; notably, the entire cervix must always be included in the HR-CTV. Current brachytherapy target dose prescription is to the HR-CTV rather than point A, while ensuring that the IR-CTV receives an intermediate dose (60 Gy) (Haie-Meder et al., 2005; Pötter et al., 2006; Hellebust et al., 2010; Dimopoulos et al., 2012).

While low dose rate (LDR) brachytherapy doses can be summed with the EBRT dose directly, the HDR brachytherapy doses are converted to total equi-effective dose (EQD2) conceptualized by the GEC-ESTRO group using following steps: Brachytherapy EQD2 each fraction, Total Brachytherapy EQD2, Total EBRT EQD2, Total EBRT and Brachytherapy EQD2. Considering, $\alpha/\beta = 10$ for tumors and 3 for late effects OARs (Organs at Risk), T½ ≈ 1.5 h for tumor and OARs (Kirisits, 2014). Recent retrospective data from the GEC-ESTRO group has shown that HR-CTV D90 doses (dose to 90% of HR-CTV) of 87 Gy or beyond correlates with superior disease control in advanced stage disease (Dimopoulos et al., 2009; Schmid et al., 2011).

The EMBRACE protocols have used EBRT dose of 45 Gy/25#/5 weeks followed by HDR brachytherapy 7 Gy/# for 4 such fractions, which equates to cumulative EQD2 of 84 Gy (Dimopoulos et al., 2009; Tanderup et al., 2016; Sturdza et al., 2016; Potter et al., 2018). In high volume centres & endemic countries such as India, organizing 4 insertions of brachytherapy presents a significant load on logistics, in terms of operation room slots, anesthesia requirements and hospital stay. Our protocol uses a higher EBRT dose (50 Gy/25#), a higher brachytherapy dose/fraction (8 Gy ×3fractions) and a fewer number of brachytherapy doses (3 fractions) to achieve the same EQD2(86 Gy). It also appears to be associated with good disease control rates and tolerable toxicity profile, comparable with those reported by the GEC-ESTRO group and other researchers (Dimopoulos et al., 2009; Sturdza et al., 2016). In our Centre, we are gradually moving towards MRI based (and MRI adaptive) technique from CT based one. Due to inaccuracy and interobserver variability of CT based HRCTV delineation, we restrict reporting and evaluation of HR-CTVs only in MRI based applications. For CT based planning, dose was prescribed at point A and conventional pear shaped 100% isodose surface was graphically optimized for OAR sparing. This practice of ours is also reflected in an online survey by Indian brachytherapy society done on patterns of cervical cancer brachytherapy in India, published in 2019 (Chatterjee et al., 2019). In this survey, CT imaging was used by two third respondents and despite of availability of CT, point A based dose prescription remained the most common form of prescription (66%). Optimization was done in most of the cases. 36% respondents practiced GEC-ESTRO volume-based prescription. Indian Brachytherapy Society guidelines also mentions the use of standard loading and point A based dose prescription in CT based planning (Mahantshetty et al., 2019). The main hindrance to MRI-based planning is lack of MRI in our radiation oncology department and limited access to MRI in our radiology department due to longer queues and waiting time. This problem is faced by most of the radiation oncology centres in resource limited country like India

In our practice, repeat insertions are done (Intracavitary and interstitial both) in each fraction, 3–7 days apart. Firstly, we have infrastructural limitations to keep patients under epidural analgesia. Secondly, treating two or three times under same insertion might lead to displacement of applicators and packing. In our healthcare system, the higher dose of EBRT does not incur any additional costs, while sparing the patient from undergoing one additional insertion of brachytherapy (3 vs 4 fractions), equates to savings of around INR 20,000 (around USD 280); treatment duration is also kept to below 8 weeks with this paradigm (although brachytherapy can be done more than once-weekly, in practice, most patients can realistically be scheduled for only one fraction each week).

Limitation of our study is retrospective nature and shorter follow up time. Due to logistic issues, MRI based brachytherapy was done only for interstitial and hybrid insertions.

5. Conclusion

The protocol under study has been safe & effective in achieving dose-escalated radical radiotherapy in advanced cervical carcinoma. The use of fewer insertions of brachytherapy is logistically easier & can also be expected to improve compliance

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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