Non-brachytherapy alternatives in cervical cancer radiotherapy: Why not?

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With more than 500,000 new cases diagnosed worldwide during 2014 alone,[1] cervical cancer poses a significant health problem. 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)[2,3] and reduces the local recurrence of disease (LR).[2,4] These findings affirm BT's role in the treatment of gynecologic cancers, which was first established in 1960.[5] Since then, BT boost supplementing concurrent chemotherapy and EBRT has been the treatment of choice for locally advanced cervical cancer.[6]

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The unique anatomical location of cervical tumors makes BT a superior delivery method compared to historic external-based techniques. Loading the radiation source within the cervical target volume accounts for the variations in target position (precipitated by bladder and rectal filling), a feature not shared with EBRT techniques, which would otherwise necessitate a large planning target volume (PTV) margin to account for these random variabilities in patient setup and organ motions. Furthermore, BT allows for 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. This technique not only yields equivalent tumor control and a toxicity profile as low-dose-rate (LDR) BT,[7-10] it possesses several advantages such as enhanced dosimetric accuracy via dwell-time optimization, better consistency due to shorter delivery time, greater patient convenience with potentially fewer complications secondary to shortened bed rest, and lower costs associated with outpatient delivery.[11] These considerations have led to a surge in HDR BT adoption[12] overlooking the LDR's radiobiological advantages.[13]

Regardless of the BT technique, implementing and delivering an appropriate BT plan is plagued by several challenges. Assuming that applicators are placed accurately at each treatment, significant variations in inter- and intrafraction delivery remain common.[14] Further complications arise from inappropriate placement in a technique that is sensitive to physician skills: insufficient cavity packing reduces disease-free survival (DFS), and improper ovoid placement reduces both local control (LC) and DFS.[15] Clinician skills aside, the insertion of BT applicators is associated with heightened risk due to anesthesia complications and/or increased treatment costs due to operating and recovery room time.[16] Numerous patients are excluded from BT due to physical considerations that prevent applicator placement, such as decreased

Table 1. Studies Using Nonbrachytherapy Techniques to Deliver Boost Dose in Cervical Cancer Treatment

Study	Gyn (cervical)	MFU (month)	Med Pt Age (years)	Boost Technique	Setting	WPI Dose /dose per Fx	Boost Dose /dose per Fx	Tumor BED_{10}[c]	NT(rectal/ bladder) BED_3[c]	LC(%)[a]	>G2 Tox (%)[a]
Kagei et al (2003)[33]	(25)	139	62	Proton	Def	50.4/1.8	36/2.5-4	110	166	75	4
Molla et al (2005)[32]	16(7)	12.6	53	SBRT(Linac)	Adj	45-50.4/1.8	14/7-20/4	84-88	NR	86	0
Chan et al (2006)[22]	12(8)	23	NR	3DCRT	Def	45-50/1.8-2	25.2/1.8-2	85-90	NR	83	17
Matsuura et al (2007)[20]	(7)	17	81	3DCRT	Def	45/1.8	20-24/1.2-1.6[d]	80	NR	86	0
Barraclough et al (2008)[21]	44(38)	27	56	3DCRT	Def	40-45/2-2.5	15-25/1.8-2.5	66-87	91-128	79	2
Jorcano et al (2010)[31]	26(9)	47	62	SBRT(Linac)	Adj	45-50.4/1.8	14/7	84	NR	77	7
Park et al (2010)[23]	(10)	18	64	3DCRT	Def	50/2	30/5	105	NR	60	0
Marnitz et al (2013)[18]	(11)	6	53	SBRT(CK)	Def	50.4/1.8	30/6	108	103/137	100	0
Kubicek et al (2013)[26]	11(4)	4	62	SBRT(CK)	Def	45/1.8	25/5	77	110	75	25
Hsieh et al (2013)[24]	(9)	36	68	SBRT(HT)	Def	50-50.4/2-1.8	16-27/2-4.5	91.2	197/189[b]	78	0
Vandecasteele et al (2013)[30,g,i]	(30)	24	52	IMRT	Adj	45/1.8	62/2.48[f]	77	NR	96	14
Khosla et al (2013)[29h,g]	(25)	38	47	IMRT	Adj	46/2	30-35/2.3-3	96	NR	76	8
Wang et al (2015)[28,g]	(80)	34	45	IMRT	Adj	50.4/1.8	9/3-60.2/2.15[f]	72	NR	98	0

3DCRT = 3 dimensional conformal radiotherapy, Adj = adjuvant, BED = biologic effective dose, CK = Cyberknife, Def = definitive, Fx = fraction, HT = helical tomotherapy, IMRT = intensity-modulated radiation therapy, Gyn = gynecologic tumors, LC= local control, Med = median, MFU = median follow up, NR = not reported due to absent specific parameters for calculation, NT = normal tissue, Pt = patient, Tox = late toxicity, WPI = whole-pelvic irradiation

a = At median follow up
b = Maximum point dose
c = BED approximate estimates using linear quadratic formalism: $BED = nd\,(1+d/(\alpha/\beta))$
d = The boost dose was given twice a day with 6 hours interval in a hyperfractionated fashion
e = Sequential IMRT boost to uterus and cervix in 5 patients
f = Boost dose delivered as simultaneous integrated boost
g = Prospective
h = Residual cervical disease
i = IMRT was delivered neoadjuvantly followed by surgery
j = One patient had recurrence of disease and was not scored for stage

vaginal accommodation with age, uterine malformations, or excessive tumor volume.[17,18] Some patients simply refuse BT with concerns of invasiveness or discomfort.[18] Most concerning of all may be the low availability of BT: In 2012, only 25% of gynecologic cancer clinics used high-quality image-guided BT.[19]

Fortunately, the new generation of EBRT techniques, with highly precise dose distributions, present viable options that may offer an appropriate alternative to the costly, logistically complex and invasive BT. In light of the 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. Here we propose high-precision EBRT techniques, including stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT), as clinically effective alternatives to BT. In this review, all comparisons will be made to HDR BT due to its aforementioned prevalence in current practice.

Methods

A systematic literature search was performed using PubMed, and included studies published in English between January 1, 1990 and July 7, 2015. The search terms employed were "cervical cancer" or "gynecologic cancer" with "brachytherapy alternatives," "radiosurgery," "stereotactic body radiotherapy," "SBRT," "intensity-modulated radiation therapy boost," "simultaneous integrated boost," and "IMRT boost." The abstracts of all resultant articles were screened by 2 physicians to assess relevance to this review, and 78 publications were selected. Eligibility was limited to studies that reported outcomes on at least 5 patients whose primary cervical lesion received a boost via EBRT rather than BT, and who reported follow-up at a minimum of 4 months. Fourteen studies met these criteria, and the remainder were excluded due to the following reasons: (1) featured no reported clinical outcomes; (2) contained only a review or database queries; (3) targeted pelvic and/or para-aortic volumes without replacement of BT; or (4) managed recurrent rather than primary disease.

Results

There is scarce representation of next-generation EBRT techniques as alternatives to BT in the literature (Table 1). Most studies are retrospective analyses, with only 3 prospective studies to date. These studies are heterogeneous in treatment plan (delivery technique and dose fractionation) and follow-up time, include small patient populations, and often address other gynecologic malignancies in addition to cervical cancer. 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. However, studies were inconsistent in their reporting of dosimetric information for normal tissue, precluding a dose-toxicity analysis. In most of these studies, the rationale for employing a BT alternative was either patient refusal of BT or anatomical constraints preventing proper BT delivery. In all but one study, a high-tech EBRT boost (SBRT or IMRT) of 16 to 36 Gy in 1.8 to 6 Gy per fraction was delivered after whole-pelvic irradiation.

In the exception, Matsuura et al used a hyperfractionated schedule: 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. This study did not employ image-guided radiotherapy, and uniform 0.5 to 1 cm clinical target volume (CTV) to PTV expansion was used. Two-year local control was 85.7%, with the highest toxicity being grade 2 rectal bleeding, affecting only 2 out of 7 patients.[20]

Three studies employed similar conformal radiotherapy techniques. Two-year local control was reported as 79% by Barraclough et al,[21] 83% by Chan et al,[22] and 60% by Park et al.[23] Park et al used real-time tracking of gold fiducial markers implanted in the cervix, and observed no grade 3 or higher late toxicities. Therefore, although this study delivered a higher total dose and a higher dose per fraction than the 2 aforementioned studies, Park et al observed lower toxicity rates, likely due to the use of image guidance. In contrast, late grade 3 urinary and late grade 3 rectal toxicities were 2% in Barraclough et al and 17% in Chan et al, despite delivering lower total dose with lower biologic effective dose (BED), implying the importance of image guidance for accurate EBRT delivery.

Also of note, 4 recent studies employed SBRT for boost delivery, and each delivered 16 to 30 Gy to the cervix in 2 to 6 Gy per fraction. With the caveat that follow-up time was short (6 to 36 months), 3 of the 4 studies demonstrated encouraging results, with minimal late toxicity and local control rates of 78% (Hsieh et al), 100% (Marnitz et al), and 100% (Haas et al).[18,24,25] Marnitz et al and Haas et al used the CyberKnife (CK) system (Accuray Inc., Sunnyvale, California) to track gold fiducials implanted in the cervix for precise SBRT boost delivery. This may explain the studies' high rate of local control (both 100%) compared to Hsieh et al (78%). However, the findings of Hsieh et al may also be accounted for by a longer overall treatment time (79 days) and the inclusion of patients with advanced disease. From a toxicity perspective, the use of helical tomotherapy (HT) (TomoTherapy Inc., Madison, Wisconsin) for megavoltage CT imaging in advance of each fraction by Hsieh et al likely contributed to the lack of observed late severe toxicities by improving precision and delivery consistency.

Paradoxically, Kubicek et al observed high rectal toxicity despite using multiple measures to ensure accuracy:

CTV definition by MRI and a 0.5 cm PTV to CTV expansion, in addition to CK tracking of cervical fiducials.[26] However, cautious interpretation of these results is needed due to a small patient population (only 4 patients with cervical squamous cell carcinoma), short follow-up time (median 4 months), and heterogeneity of treatment plans: Two patients received 25 Gy in 5 fractions, 1 patient received 15 Gy in 3 fractions in addition to 12 Gy HDR BT, and 1 patient received 5 Gy in 1 fraction before having a stroke and transferring to hospice care. The latter patient was the only one who developed recurrence; the 3 patients who completed treatment remained free of recurrence.

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 lymphovascular invasion. In these patients, a BT boost is often given after EBRT.[27] Five studies investigated the use of BT alternatives in this setting: 3 prospective studies using IMRT,[28-30] and 2 retrospective studies using SBRT.[31,32] Tumor control and toxicity profiles were promising: at median 13- to 38-month follow up, the local control rate was 76 to 96%, with only 0 to 14% occurrence of severe late toxicity.

In the studies employing SBRT, Molla et al and Jorcano et al used a linac-based system to deliver a 14 Gy boost in 2 fractions after 45 to 50.4 Gy of whole-pelvic irradiation.[31,32] Both studies used multiple methods to improve precision. The ExacTract infrared-guided system (Brainlab AG, Heimstetten, Germany) was used to link skin markers to the isocenter for the duration of delivery. Target organ motion was limited by insertion of an MR endorectal probe, enhancing reproducibility. 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.

In the studies using IMRT, Wang et al and Vandecasteele et al both used simultaneous integrated boost (SIB) to perioperatively treat areas at risk.[28,30] Wang et al compared the efficacy of 60.2 Gy in 28 fractions SIB concurrent with 50.4 Gy pelvic IMRT to a sequential accelerated boost of 9 Gy in 3 fractions after the conclusion of 50 Gy in 2 fractions pelvic IMRT. Both groups had comparable local control (98% vs. 100%) and late severe toxicity (both 0%).[28] Vandecasteele et al took a different approach, administering SIB of 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.[30] The final prospective IMRT study included patients with a particularly dismal prognosis exhibiting persistent gross residual disease in the vaginal vault after whole-pelvic radiotherapy of 46 Gy in 23 fractions. These patients were given either 30 Gy in 10 fractions concurrent with 20 Gy to the PTV, or with 35 Gy in 15 fractions concurrent with 30 Gy to the PTV.[29] This dose escalation proved beneficial with a local control of 76% at median 38-month follow-up, and only 8% of patients exhibited late grade 3 toxicity.

Proton beams have also been used as alternatives to BT boost delivering 86 Gy median tumor dose. The reported 5-year local control was 100% for stage IIB 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.[33]

An established association between BED and treatment outcome can, in theory, be used to select the optimal SBRT or IMRT dose/fractionation schedule, analogous to those used in BT planning.[34] Even for BT, this correlation has been difficult to define: In one study, the BED at point A could not be related to either regional control or toxicity,[35] but other studies have demonstrated that above a rectal BED_3 threshold of 125 Gy_3 (rectal point)[36,37] or 140 Gy_3 (rectal maximum dose on CT)[38], excessive toxicity results. Such a correlation for BED and local control or toxicity in these IMRT and SBRT studies could not be defined. As shown in Table 1, the studies adopted different dose fractionation schedules leading to a highly variable tumor BED_{10} and normal tissue BED_3. This variability precluded correlating treatment outcome to either the resultant BED estimations or BED constraints established in the BT literature.

Discussion

1. Dosimetric perspective

Among all EBRT techniques, SBRT is, in theory, the most likely to replicate a BT dose distribution with sharp dose gradient. In SBRT, multiple noncoplanar beams intersect within the target volume. This allows high-dose delivery directly to the tumor, while maximally sparing the surrounding tissue. In fact, several dosimetric studies have favored SBRT for optimal target coverage and OAR sparing.[39-42] In one study, SBRT boost plans were created for 11 cervical cancer patients and compared in dose distribution to BT boost plans. Rectal dose to 1 cc (d_{1cc}), bladder d_{1cc}, and median target coverage by the 100% isodose line were all superior in the SBRT plans.[39] Another study generated volumetric-modulated arc therapy (VMAT) dosimetric plans for 51 gynecologic cancer patients, and similarly demonstrated that compared to BT, SBRT yielded favorable rectal d_{1cc}, d_{2cc}, and maximum dose, with comparable doses to bladder and bowel, although BT offered superior integral dose and PTV coverage.[43] The majority of these studies compared EBRT dose distribution

with brachytherapy dose distribution prescribed to point A. Currently, image-guided tailored brachytherapy dose distribution prescribed to target volumes rivals the classic prescription to reference points and may compare favorably against the EBRT technique. Whether extreme high dosage within the tumor is needed from a radiobiologic standpoint (to overcome hypoxic foci) is a matter of debate. However, the brachytherapy profile (characterized by very high dosage within the vicinity of the applicators) cannot challenge EBRT dose homogeneity within the target volume.

On the other hand, 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.[44] 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.[45] In fact, this strategy yielded favorable local control when delivered concomitantly with whole-pelvic irradiation.[46] 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.[22]

2. Target motion and internal target volume dilemma

Variations in cervix position due to bladder and rectal filling are continuous, nonuniform, and significant: Cervical target volume motion can reach 18 mm.[47,48] Although tumor volume shrinkage during treatment is significant (reaching 79%),[49,50] target motion is so large that shrinkage cannot replace the need for large PTV margins.[51] To deliver an EBRT boost precisely, the target must be either immobilized or continuously tracked, such as with the above-mentioned gold fiducial markers or endorectal probes. A CT-compatible vaginal cylinder used in applicator-guided VMAT has been shown to decrease target volume motion such that a PTV margin of only 2 mm is necessary; the cylinder had the additional advantage of decreasing rectal dose compared to BT.[43] A study of gold fiducial markers as a readout for cervix position showed that PTV margins can drop to 6.7 to 8.3 mm when fiducials are used, and real-time tracking can further decrease these margins.[52]

3. Radiobiologic considerations

Any valid radiation treatment plan is constructed based on the balance between normal tissue complication probability (NTCP) and tumor control probability (TCP). Influencing this balance are the rate of repopulation, hypoxia and radiosensitivity, repair kinetics compared to the interfraction interval time, and the alpha/beta (α/β) ratio of normal and tumor tissues. A fractionation schedule that maximizes the therapeutic ratio must take all of these into account.[53]

Endorsed by the American Brachytherapy Society, 6 Gy for 5 fractions is the most popular HDR fractionation schedule.[54] Accordingly, radiobiologic disparities between this schedule and that adopted in most SBRT studies are expected to be negligible. When an interfraction interval sufficient to allow repair is present,[55] toxicity concern of high dose per fraction is negligible. Moreover, a hypofractionation scheme allows for reduction of the overall treatment time, a desirable feature in cervical cancer[53] with its rapid doubling time,[56] fast repopulation, and high (α/β) ratio.[57] Yet, the interfractionation gaps may lead to prolonged overall treatment time and interfraction repopulation which, consequently, leads to worse treatment outcome in cervical cancer.[58] Although, hypofractionated plans have been proven efficacious in several studies,[7,8,59] a shorter schedule avoiding interfraction gaps through dose-painting IMRT may provide a more efficacious fractionation schedule.[45]

Conclusions

Although relatively new and longer follow up is needed to ascertain favorable treatment outcomes, high-tech EBRT boost techniques, when properly executed, are highly promising for treating cervical cancer. Treatment outcomes are comparable to those reported in the BT literature: With local control, for example, values in HDR BT studies range from 62% to 84%.[8,36,60,61] Moreover, BT is associated with its own risks. The major complication rate of BT can reach 10%, including a 1.4% fatality rate,[60] largely due to the difficulty in executing appropriate BT implants in patient populations with different tumor volumes. Incorrect implementation of SBRT or IMRT can certainly lead to similar detriments. To challenge the impeccable BT dose distribution and long track record, boost techniques employing IMRT or SBRT must fulfill the following requirements:

1. Treatment volumes must be accurately defined (eg, with MRI).
2. Plans must be meticulously optimized to spare organs at risk.
3. Treatment delivery must be precise, with minimized target volume motion via applicator guidance, image guidance or target volume tracking.
4. Planning must be adaptive and modifiable based on repeat imaging.
5. Fractionation schedules must be optimized based on tumor kinetics, possibly guided by tumor kinetics biomarkers.

These measures should be considered mandatory, and boosting cervical disease with EBRT must not be delivered in their absence. Studies that use an

SBRT or IMRT boost but do not conform to these requirements may inaccurately portray these techniques as less effective.[62] Therefore, large prospective studies to definitively establish or invalidate non-BT alternatives for treating cervical cancer radiotherapy are urgently needed.

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