Brachytherapy or external beam radiotherapy as a boost in locally advanced cervical cancer: a Gynaecology Study Group in the Italian Association of Radiation and Clinical Oncology (AIRO) review

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ABSTRACT

This review analyzes the experience and trends in external beam radiotherapy for delivering a boost in locally advanced cervical cancer, identifying whether radiation therapy modalities impact clinical outcomes with the ultimate aim of evaluating alternatives to brachytherapy.
Three independent Italian radiation oncologists conducted a literature search on different external beam radiotherapy boost modalities in locally advanced cervical cancer.
The search yielded 30 studies. Eight dosimetric studies, evaluating target coverage and dose to organs at risk, and nine clinical investigations, reporting clinical outcomes, were analyzed. Dosimetric studies comparing external beam radiotherapy boost with brachytherapy produced divergent results, while clinical studies were limited by their retrospective nature, heterogeneous doses, radiation schedules, volumes and techniques, diverse follow-up times, and small cohorts of patients. Evidence emerged that high-tech external beam radiotherapy seemed no better than image-guided brachytherapy for delivering a boost in locally advanced cervical cancer. Prospective clinical studies comparing high-tech external beam radiotherapy and image-guided brachytherapy should be encouraged.

INTRODUCTION

For many years, standard treatment for locally advanced cervical cancer has included concomitant external beam radiation therapy and chemotherapy followed by a brachytherapy (also known as interventional radiotherapy)-delivered boost. External beam radiation therapy delivers a dose ranging from 45 to 50 Gy to the uterus, parametria, upper vagina, and regional pelvic lymph nodes. The brachytherapy boost, which limited exposure of healthy surrounding organs and increased to 80–95 Gy the dose to the primary tumor (biologically equivalent dose in 2 Gy fractions (EQD2) with an α/β ratio=10 for tumor effects), improved local control of locally advanced cervical cancer, strongly correlating with higher survival rates.[1 2]

In locally advanced cervical cancer treatment, brachytherapy was originally delivered using two-dimensional (2D) dosimetry under the guidance of antero-posterior and lateral X-rays to assess applicator position and estimate the cervical dose. The International Committee on Radiation Units and Measurements' Report 38 (ICRU38)[3] defined the dose prescription point, point A, as 2 cm above the cervical os and 2 cm lateral to the cervical canal where the uterine vessels and ureter are estimated to cross. The bladder dose was estimated on the Foley bulb position and the rectal dose was calculated 5 mm posterior to vaginal ovoids or packing. In the last two decades, image-guided brachytherapy using computed tomography (CT)-based three-dimensional (3D) volumetric planning, which marked the transition from dose prescription points to volumes, was introduced to optimize the target coverage and reduce the dose to adjacent healthy tissues. Magnetic resonance imaging (MRI)-based brachytherapy has more recently improved tumor imaging as it better distinguishes the target volume and soft tissue.[4]

All these technical improvements led to a 78–95% local control rate with 5-year rates of late G3–4 treatment-related toxicity ranging from 0.8% to 7%.[4–8] A further improvement in target coverage, with better local disease control in patients with large tumors and/or unfavorable topography, was achieved with concomitant intracavitary and interstitial brachytherapy (Table 1).

Despite these advantages, the use of brachytherapy has recently declined due to advances in external beam radiotherapy techniques such as intensity modulated radiotherapy,[9] volumetric arc therapy,[10] helical tomotherapy,[11] stereotactic radiotherapy,[12] and MRI-guided radiotherapy.[13 14] The Surveillance, Epidemiology, and End Results (SEER) database showed that, even though brachytherapy was independently associated with better cause-specific (64% versus 52%) and overall survival (58% versus 46%),

Table 1 Studies of image-guided brachytherapy as a boost in patients with cervical cancer

Study IGBT as boost	No of pts (cervix)	Median FU (months)	Dose rate	D90 HR-CTV (Gy EQD2)±SD	LC rate	SVV	G3 toxicity or higher (scale)
Pötter et al[4]	156	42	HDR	80.4±10.3	95% 3y	OS: 68% 3y CSS: 74% 3y	3 bladder tox, 5 rectal tox, 3 vaginal tox (LENT-SOMA)
Castelnaud-Marchand et al[5]	225	38.8	PDR	80.4±10.3	86.4% 3y	OS: 76.1% 3y DFS: 71.6% 3y	18 late GI and GU tox (CTCAE v3)
Charra-Brunaud et al[6]	117	24.3	PDR	73.1±11.3	78.5% 2y	OS: 74% 2y DFS: 60.3% 2y	1.2% of pts with GI and GU tox (CTCAE v.3)
Sturdza et al[7]	960	25.4	HDR/PDR	87±15	3/5 y actuarial LC, 91%/89%	OS 3/5 y 74%/65% CSS 3/5 y 79%/73%	5y morbidity was 5%, 7%, 5% for bladder, gastrointestinal tract, vagina (CTCAE v.3)
Horeweg et al[8]	155	57	HDR	75–88	5 y 90.4%	DMFS 70.2% 5y	5y late bladder, rectal, bowel, and vaginal toxicity were 0.8%, 3.3%, 3.6%, and 1.4% (CTCAE v.3)

CSS, cancer-specific survival; CTCAE, common toxicity and adverse event; DFS, disease-specific survival; DMFS, distant metastases-free survival; FU, follow-up; GI, gastrointestinal; GU, genitourinary; HDR, high dose rate; IGBT, image guided brachytherapy; LC, local control; OS, overall survival; PDR, pulsed dose rate; SVV, survival.

its use decreased from 83% in 1988 to 43% in 2003, rising again to 58% in 2009.[15] Commenting on this finding, Tanderup et al stated that "brachytherapy was NOT optional".[16] In another report only 55–88% of patients with locally advanced cervical cancer received utero-vaginal brachytherapy.[17] In stage IIIB and IVA cervical cancer, brachytherapy boost decreased from 96.7% to 86.1% from 2004 to 2011 in the National Cancer Database (NCDB), while intensity modulated radiotherapy and stereotactic radiotherapy increased from 3.3% to 13.9% in the same timeframe but were associated with worse overall survival than brachytherapy (HR 1.86; 95% CI 1.35 to 2.55).[18] A small retrospective study associated brachytherapy with a 49% loco-regional failure rate versus 65% after external beam radiotherapy which, however, decreased to 59% when higher external beam radiotherapy doses were delivered.[19]

Compared with external beam radiotherapy techniques, brachytherapy has an unparalleled therapeutic index. As early as 2012 the American Brachytherapy Society consensus guidelines stated that brachytherapy played an essential curative role in locally advanced cervical cancer.[20] Even in 2020 the National Comprehensive Cancer Network (NCCN) emphasized that brachytherapy was a standard of care and explicitly stated that conformal external beam radiotherapy should not be used as an alternative.[21] This review analyses the experience and trends in external beam radiotherapy for delivering the boost in locally advanced cervical cancer, identifying whether radiation therapy modalities impact clinical outcomes, with the ultimate aim of evaluating alternatives to brachytherapy.

METHODS

Three independent radiation oncologists from the Gynecology Study Group in the Italian Association of Radiation and Clinical Oncology (AIRO) each conducted a literature search on boost modalities in locally advanced cervical cancer. The MEDLINE-PubMed and Scopus databases were scrutinized for articles in English, Italian, and French that had been published between January 1990 and February 2019. The following keywords were used: cervical cancer, brachytherapy alternatives, radiosurgery, stereotactic body radiotherapy, intensity modulated radiation therapy boost and their abbreviations. Attention focused on observational and prospective studies (including single-center reports), retrospective studies, systematic reviews, meta-analyses, consensus guidelines, and position manuscripts.

The search yielded 30 studies which included seven reviews, eight dosimetric studies, nine non-randomized clinical studies, one analysis of external beam radiotherapy alone versus external beam radiotherapy plus brachytherapy, four studies on pelvic external beam radiotherapy and one on protracted radiation therapy. All authors were involved in selecting the eight dosimetric studies and the nine clinical investigations that were analyzed in this overview report.

RESULTS

In seven of the eight dosimetric studies[22–28] high dose rate brachytherapy was compared with different external beam radiotherapy boost techniques. In the other study,[29] dosimetry was performed with intensity modulated proton therapy without any comparison. None of these eight studies reported clinical outcomes. Target volumes for brachytherapy planning were defined according to the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) criteria[30 31] in three of the eight studies.[23–25] When reported, the planning target

Table 2 Volumes in dosimetric studies comparing stereotactic radiotherapy as brachytherapy boost

Study	Volumes
Georg et al[22]	HR CTV*+ 3/5 mm IR CTV*+ 3/5 mm
Clivio et al[29]	CTV=T + cervix PTV=CTV + 5 mm
Otahal et al[23]	HR CTV*=PTV
Assenholt et al[24]	HR CTV*+ 3 mm=PTV
Yin et al[25]	HR CTV* + 3 mm IR CTV* + 3 mm
Cengiz et al[26]	CTV=T + cervix PTV=CTV + 1 cm sup-inf
Neumann et al[27]	CTV=T + cervix + parametric region ±corpus uteri. No PTV
Merrow et al[28]	PTV=100% isodose volume of BT plan (BT isodose converted into structures)

*HR CTV and IR CTV according to Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO).
BT, brachytherapy; CTV, clinical target volume; HR CTV, high risk clinical target volume; IR CTV, intermediate risk clinical target volume; PTV, planning target volume.

volume in external beam radiotherapy was generally obtained by adding margins ranging from 3 mm to 1 cm around the clinical target volume (for more details, see Table 2).

One study[27] adopted GEC-ESTRO criteria only to define organs at risk. Equivalent doses in 2 Gy fractions (EQD2) with an α/β ratio of 10 Gy for tumor effects were in the range of 85–107.5 Gy cumulative with the pelvic dose. Dose volume histogram parameters varied from study to study. The results are summarized in Table 3.

In two of the eight dosimetric studies,[26 28] 3D brachytherapy planning was performed with dose prescription to point A. One study[26] compared stereotactic radiotherapy, as planned for CyberKnife (Accuray, Sunnyvale, California, USA) treatments with it, even though it may not seem valid to compare modern external beam radiotherapy techniques with the old brachytherapy to point A. Stereotactic radiotherapy provided higher target coverage with the 100% isodose line (99.1% vs 50.7%; $p<0.05$). On the other hand, dose distributions for critical organs were similar with stereotactic radiotherapy and brachytherapy, except that the 25% isodose was significantly better with brachytherapy for the rectum, and the 100% isodose exposure was higher with brachytherapy for the rectum, bladder, and sigmoid colon. With stereotactic radiotherapy the maximum dose to 2 cubic centimeter of bladder volume was significantly lower while the maximum bone marrow dose was significantly higher.[26] In the other of these two studies,[28] a tandem and ovoid brachytherapy treatment plan was exported into an external beam radiation treatment planning system and three volumetric arc therapy plans were generated to achieve the following brachytherapy dose distributions: (1) the standard pear-shape; (2) homogeneous throughout the planning target volume (brachytherapy prescription volume); (3) increased planning target volume dose without organ at risk overdose. Although volumetric arc therapy successfully reproduced brachytherapy results and achieved homogeneous dose distribution to the planning target volume, it was unable to deliver a high homogeneous planning target volume dose without an organ at risk overdose.[28]

In two of the eight dosimetric studies,[23 27] CyberKnife treatments were compared with the modern image guided brachytherapy. One study[23] reported that coverage of high-risk clinical target volume—that is, at major risk of local recurrence because of residual macroscopic disease—differed greatly. With CyberKnife, D90 was higher but the highest dose was delivered only to high-risk clinical target volume periphery (15% vs 85% clinical target volume with brachytherapy). Significant organ at risk sparing was achieved with CyberKnife (20–30% lower doses in 0.1 cubic centimeter, 1 cubic centimeter, and 2 cubic centimeter). As expected, large low-dose areas were achieved with CyberKnife. In the second study,[27] three boost technique plans were compared: stereotactic radiotherapy emulating brachytherapy with prescribed isodoses of 70% or 25% (stereotactic radiotherapy 70% and 25%, respectively) and MRI-guided brachytherapy. Even though stereotactic radiotherapy isodose 25% plans provided excellent target coverage, organ at risk exposure was unacceptably high. Target coverage and conformity were better with stereotactic radiotherapy isodose 70% than with brachytherapy while organ at risk sparing was comparable.

Two studies[24 25] evaluated boost delivery modalities for large and/or topographically unfavorable tumors. Assenholt et al[24] compared intracavitary brachytherapy, intracavitary/interstitial brachytherapy, intracavitary brachytherapy plus intensity modulated radiation therapy, and intensity modulated radiation therapy alone. Median dose coverage was 74% with intracavitary plans, 95% with intracavitary/interstitial, 96% in intracavitary brachytherapy plus intensity modulated radiation therapy, and 98% with intensity modulated radiation therapy alone. V60Gy volumes (ie, the total volume of normal tissue that is irradiated to over 60 Gy dose equivalent in 2 Gy fractions (EQD2 Gy) by the accumulated dose from external beam radiotherapy and boost) increased significantly when intensity modulated radiation therapy was used, peaking with intensity modulated radiation therapy alone. Yin et al[25] compared four boost techniques: intracavitary brachytherapy (conventional 2D and 3D optimized), intracavitary brachytherapy plus intensity modulated radiation therapy, and intensity modulated radiation therapy alone. Intracavitary brachytherapy plus intensity modulated radiation therapy was associated with significantly higher dose to 90% of the volume (D90) and dose to 100% of the volume (D100) for the clinical target volumes than 2D or 3D brachytherapy and significantly lower dose to 2 cubic centimeter (D2cc) of bladder, rectum, and sigmoid than 2D brachytherapy and intensity modulated radiation therapy alone.

Intensity modulated proton therapy dosimetry was evaluated in two of eight studies,[22 29] with one[22] comparing it with image guided brachytherapy. Although dose prescription objectives for target coverage were generally acquired with intensity modulated proton therapy, doses to the gross tumor volumes were lower. The other study[29] referred intensity modulated proton therapy results to MRI-guided brachytherapy recommendations. Intensity modulated proton therapy provided adequate target coverage, conformity, and better dose volume histogram parameters. Furthermore, both studies compared intensity modulated proton therapy with photon external beam techniques (intensity modulated radiation therapy and volumetric arc radiation therapy). They achieved worse target

Table 3 Dosimetric studies evaluating stereotactic radiotherapy as brachytherapy boost, classified according to boost technique

Study	No of pts (cervix)	Boost technique	Evaluated parameters	Boost (dose/fx)	Target coverage	Dose to OAR	P value
Cengiz et al[26]	11 (11)	SRT (CK) vs BT point A	D100 median D2cc	28/7	99.1±0.1 vs 50.7±12.7	D2cc bladder: 6.5 Gy vs 7.99 Gy D2cc rectum: 4.5 Gy vs 5.3 Gy D2cc bone marrow: 27.5 Gy vs 10.7 Gy	<0.05
Merrow et al[28]	1	SRT (VMAT) A) VMAT=ICBT (inhomogeneous) B) VMAT homogeneous C) VMAT (increased and homogeneous dose)	For PTV: 200% to 50% isodose For OAR: Dmax and D5% to rectum, bladder and femoral head	30/6 35-50/7-10	Isodose 100% A) 5.97 vs 5.99 B) 6.02 vs 5.99 C) 7.80 vs 5.99	OAR: A) Dmax higher for VMAT; D5% lower for VMAT B) Dmax rectum and femoral head higher for VMAT; Dmax bladder and D5% lower for VMAT; C) Dmax higher for VMAT; D5% bladder lower for VMAT; D5% rectum higher for VMAT	NA
Othal et al[23]	10 (10)	SRT (CK)	D100 GTV, D90 GTV, D90 HR CTV, D90 IR CTV, D100 IR CTV OAR 0.1cc, 1cc, 2cc	30/5	D100 GTV SRT=BT D90 GTV>BT D90 HR CTV>CK D90 IR CTV SRT=BT D100 IR CTV>BT	OAR <CK but low dose bath +++ for CK	<0.05
Neumann et al[27]	11 (11)	RRS with CK vs IC-BT	Dose to PTV: A) D90 B) D100 C) V90 D) V100 For OAR D2cc	30/6	A) 31±0.8 vs 32±5.6 B) 24.3±3.7 vs 18.9±5 C) 99.4±0.8 vs 94.4±7.3 D) 97.1±2.7 vs 90.9±8.9	D2cc rectal wall: 71.4±7.6 vs 76±17.4 D2cc bladder wall: 83.9±10.3 vs 101.2±26.1 D2cc sigmoid wall: 67.3±10.4 vs 70.5±12.4	NA
Assenholt et al[24]	6 (6)	IC-BT IC/IS-BT SRT (IMRT) +IC-BT SRT (IMRT)	HR-CTV/PTV: V100% D100 D90 V60 Gy; D2cc for OAR	28/7	V100%:74%-95%-96%-98% D100: 54Gy- 62Gy-69Gy- 71Gy D90: 69 Gy-90Gy-87Gy-92Gy	D2cc rectum: 75 Gy for all D2cc sigmoid: 70 Gy-71Gy-72Gy-75Gy D2cc bladder: 82 Gy-79Gy-87Gy-90Gy V60Gy: 300cc-330cc-399cc- 550cc	P<0.001 V60Gy P0.07 D2cc IMRT sigmoid P=0.09 D2cc IMRT bladder P<0.05 target IC-BT
Yin et al[25]	30 (30)	2D IC-BT 3D IC-BT SRT (IMRT) 3D IC-BT +SRT (IMRT)	D90 GTV HR CTV D90–D100 IR CTV D90–D 100 IR CTV V100 D2cc – V60Gy for OARs	24/6	D90 GTV higher for ICBT HR CTV and IR CTV 3D IC-BT + IMRT higher coverage than the three others	D2mL lower for 3D IC-BT + IMRT than 2D IC-BT and IMRT alone; only for bladder lower than 3D ICBT V60Gy higher in 3D IC-BT +IMRT than 3D IC-BT	<0.05
Georg et al[22]	9 (9)	IMRT IMPT	D90 GTV HR-CTV IR-CTV HR-PTV 5 mm HR-PTV 3 mm D1cc, D2cc for OAR	28/4	GTV doses lower for both IMRT and IMPT vs BT	Bowel volume receiving 60 Gy was twice as large for IMRT compared with BT	<0.05
Clivio et al[29]	11 (11)	IMPT	D90 and D98 CTV-PTV D0.1cc, D2cc, D5cc for OAR Prescription aim (V30Gy ≥90%)	30/5	Lower maximum dose within the target Prescription aim achieved	62.2 Gy (EBRT +IMPT) for the rectal wall; 57.8 Gy for the sigmoid wall, and 80.6 Gy for the bladder	

BT, brachytherapy; cc, cubic centimeter; CK, CyberKnife; CTV, clinical target volume; HR CTV, high risk clinical target volume; D90, dose to 90% of the volume; D98, dose to 98% of the volume; D100, dose to 100% of the volume; D1cc, dose to 1 cubic centimeter; D2cc, dose to 2 cubic centimeter; D5cc, dose to 5 cubic centimeter; Dmax, maximum dose; EBRT, external beam radiation therapy; GTV, gross tumor volume; V60 Gy, volume receiving 60 Gy; IC-BT, intracavitary brachytherapy; IMPT, intensity modulated proton therapy; IMRT, intensity modulated radiotherapy; IS-BT, interstitial brachytherapy; OAR, organ at risk; PTV, planning target volume; HR PTV, high risk planning target volume; RRS, stereotactic robotic radiosurgery; SRT, stereotactic radiotherapy; V100, volume receiving 100% of the dose; VMAT, volumetric arc therapy.

coverage than intensity modulated proton therapy, while results were discordant regarding the dose to the organs at risk.[22 29]

Table 4 summarizes the nine selected non-randomized clinical investigations into the use of different external beam radiation techniques as alternative boost treatments for cervical cancer.[32–40]

In all these clinical studies, sample sizes were small, accrual periods were long, follow-ups were short, and the boost doses, volumes, and fractionations were very heterogeneous. Most studies included patients who refused brachytherapy or were not candidates because of co-morbidities precluding anesthesia and/or anatomical features such as cervical os stenosis, risk of contact bleeding, unusual anatomic configuration due to myoma, uterus bicornuate-bicollis. Some studies included mixed patient populations with diverse gynecological malignancies and different radiotherapy aims such as radical, adjuvant, or salvage post-relapse therapy.[32–34 36] Dose equivalents in 2 Gy fractions (EQD2) were in the range of 51–89 Gy, cumulative with the pelvic dose. Although three of 10 studies[34 38 39] tried to reproduce the GEC-ESTRO criteria for contouring boost volume for external beam radiotherapy plans, volumes differed with the diverse external beam techniques and also within the same technique (Table 5).

In three of ten studies[32 35 39] the boost was delivered by 3D conformal radiotherapy, resulting in poor local control and low overall survival, particularly according to Barraclough et al.[32] In the report by Ito et al,[35] G4 cystitis was observed. Four studies[34 36–38] investigated outcomes after stereotactic radiotherapy delivered a boost by CyberKnife or Novalis (BrainLAB AG, Heimstetten, Germany). Kubicek et al[34] reported poor local control, low overall survival after a short follow-up, and one of seven patients suffered G3 rectal bleeding. In a mixed gynecological population, two of nine patients with cervical cancer in an adjuvant setting developed a central pelvic recurrence 4 and 12 months after radiotherapy.[36] Although Haas et al[37] and Marnitz et al[38] reported adequate results, follow-ups were short and sample sizes were small for proper assessment. In the latter report, four of eleven patients developed G3 hematological toxicity.

After treatment with Linac-based stereotactic radiotherapy, low toxicity rates were reported in 16 patients with endometrial and cervical cancer, with only one rectal bleeding 18 months after radiotherapy re-treatment.[33] Stereotactic radiotherapy as delivered by helical tomotherapy was evaluated in a study of nine patients with cervical cancer.[40] Outcomes were adequate in terms of local control (78%) but disappointing for overall survival (47%) and toxicity (G3 rectal bleeding in 3/9 patients, one fistula, and one G3 diarrhea).

DISCUSSION

Brachytherapy is a crucial part of therapy for locally advanced cervical cancer,[41] as suggested by the following evidence. The SEER database analysis of 7395 patients who received external beam radiotherapy with or without brachytherapy showed that brachytherapy treatment was associated with better cause-specific and overall survival rates.[15] In 2016, a brachytherapy boost was associated with a 5-year cancer-specific survival rate of 68% versus 35.4% with an external beam radiation boost.[42] A NCDB analysis of 15194 patients with locally advanced cervical cancer also concluded that brachytherapy as a boost is superior in terms of overall survival (HR 0.544, p<0.001) compared with an external beam radiation boost.[43]

Despite these outcomes, brachytherapy has gradually declined in use since the early 2000s as external beam radiation techniques advanced with developments such as stereotactic radiotherapy or proton therapy.[44 45] Apart from patients' refusal, several other factors account for its decline in locally advanced cervical cancer. It may be technically impossible because of anatomical configuration or co-morbidities that preclude anesthesia, especially in the interstitial procedure. Since it is operator-dependent, radiation centers tend to pursue alternative boost modalities. In cases of stage IVA disease, large tumors, older age, particularly in radiation oncology centers with a low volume of treatments, indications for brachytherapy were given to only one of three patients. Indeed, in the USA, the NCDB showed that brachytherapy delivered a boost to only 44.3% of patients and 26.8% did not receive any boost.[16]

European and US approaches to brachytherapy differ considerably. With a long tradition of brachytherapy deriving from the Austrian and French schools,[4 6] it is first choice in Europe for boost delivery and target definition and MRI images are recommended.[46] In decision-making, the US radiation oncologists take factors other than the clinical into account. Socio-economic reasons and reimbursement procedures may have played a role in the shift from brachytherapy to external beam radiotherapy. Furthermore, only external beam radiotherapy might have been available in radiation oncology centers that were close to patients' homes. Other factors were analyzed by Ma et al[47] in responses to an electronically mailed questionnaire to the American Brachytherapy Society: 84% of responders strongly agreed that brachytherapy was underused, 46.9% believed that residents received inadequate training in it, and 75.3% considered inadequate skill maintenance as the major obstacle to brachytherapy use. In critical scenarios, 37% of American Brachytherapy Society members would consider an alternative boost and 24.7% routinely referred brachytherapy patients to other radiation departments. Interestingly, 71.6% considered brachytherapy was time consuming. A very recent review of studies comparing stereotactic radiotherapy as an alternative to brachytherapy confirmed these insights.[48]

Our review showed that dosimetric studies comparing external beam radiotherapy with brachytherapy achieved divergent results. Early attempts to reproduce the inhomogeneity of 3D brachytherapy dose distribution to point A with image guided radiotherapy[28] resulted in higher maximum doses to organs at risk, especially the femoral heads and pelvic volumes, correlating with pelvic morbidity. Later studies showed that, compared with brachytherapy, CyberKnife planning achieved good dose distribution in the target volume, with good organ at risk sparing. However, administration of higher doses risked greater toxicity, which sometimes precluded external beam radiation. The external beam radiation boost could, however, now treat eccentric irregular tumors, extending to the lateral pelvic walls which had presented a challenge for brachytherapy. On the other hand, stereotactic radiotherapy or combined treatment (brachytherapy and external beam radiotherapy) emerged as options for boost to the parametrial region and for treating large and/or irregularly shaped tumors when intracavitary/interstitial brachytherapy, the currently recommended standard approach,[49] was ruled out. The present analysis

Table 4 Studies of external beam radiation as a boost in patients with cervical cancer, classified according to the boost technique

Author	No of pts (CC)	Accrual period	Disease stage		Median FU (range)	Boost technique	Pelvic dose (Gy)	Boost dose Gy (dose/fx)	Local/ locoregional control	Local/ locoregional recurrence	Survival (SVV)	Late ≥G3 toxicity (scale)
Matsuura et al[39]	7 (7)	2002–2005	IB IIB IIIA IVA IIIB	1 2 1 1 2	17 months (15–37)	3DCRT	45/1.8	(21–27) 1.2–1.6*	At 2 years 85.7%		At 2 years 85.7%	0
Barraclough et al[32]	44 (44)	1996–2004	IB IIB IIA IIIA IIIB IVA	7 17 4 1 11 3	2.3 years (147 days–8 years)	2D-3DCRT	40–45/2–2.5	15–25/1.8–2.5		21 (48%) at median 2.3 years	Median 3.4 years; 5y OS 49.3%	2% urinary (Franco-Italian glossary)
Ito et al[35]	37 (37)	2005–2017	IB IIA IIB IIIB IIIA IVA	3 2 3 16 1 12	17 months (2–84)	3DCRT	45–50/1.8–2	6–10/2		13 (35%)	1y OS 74%; 2y OS 43%; median 20 months; PFS 2y 30%	1 G3 GI hemorrhage; 1 G4 cystitis
Jorcano et al[36]	26 (9)	2002–2008	IB IC IIA IIB IIIB	10 7 2 5 2	47 months (4–77)	SRT	45–50.4/1.8	14/7	3-year failure-free survival 96%	2/9 patients (1 stage IIIB and 1 stage IIB) at 4 and 12 months after RT, respectively	3y OS 95%	0
Haas et al[37]	6 (6)	2009–2011	IIB IV	4 2	14 months (1–28)	SRT (CK)	50.4–61.2/1.8	19.5/6.5–20/4	100% for 5 pts with a minimum FU of 12 months		100%	0
Marnitz et al[38]	11 (11)	2011–2012	IIB IIIB	9 2	6 months	SRT (CK)	50.4/1.8 (SIB to the parametric region 59.36/2.12)	30/6 to 60–70% isodose line, 1–2 times per week	100%	0	100%	0
Kubicek et al[34]	11 (7)		Recurrent IIIB	3 4	120 days	SRT (CK)	45/50.4	25/5	73% at median FU		57% at last FU	1 G3 GI (CTCAE 4.0)
Hsieh et al[40]	9 (9)	2008–2012	IIB IIIB IVA	4 3 2	36	SRT (HT)	50–50.4/2–1.8	16–27/2–4.5	3-year actuarial locoregional control 78%		Median 13 months (4–40); 3 year actuarial OS 46.9%	1 pt fistula (CTCAE 3.0)
Mollà et al[33]	16 (7)		IB2 IIB IIIB IB–IIB	2 1 1 3	12.6 months (6–26)	SRT (VMAT/ IMRT)	45–50.4/1.8	14/7 20/4		Local recurrence 12 months after RT in 1 patient (stage I) treated postoperatively	100% at median FU	1 G3 rectal 18 months after re-irradiation for vaginal vault relapse

*Accelerated-hyperfractionated schedule.
CC, cervical cancer; CK, CyberKnife; 3D CRT, 3D conformal radiotherapy; CTCAE, common toxicity criteria of adverse events; FU, follow-up; GI, gastrointestinal; HT, helical tomotherapy; IMRT, intensity modulated radiotherapy; LC, local control; OS, overall survival; RT, radiotherapy; SIB, simultaneous integrated boost; SRT, stereotactic radiotherapy; SVV, survival; VMAT, volumetric arc therapy.

Table 5 Volumes in studies of external beam radiation as a boost in patients with cervical cancer

Study	Volumes
Matsuura et al[39]	CTV=cervix + any extracervical disease PTV=CTV + 0.5–1 cm
Barraclough et al[32]	Small pelvic box
Ito et al[35]	CTV=residual primary tumor, cervix, uterus, vagina, parametrium PTV=CTV + 10–15 mm
Jorcano et al[36]	CTV=vaginal vault (3 cm) PTV=CTV + 6–10 mm
Haas et al[37]	CTV=cervix + uterus (to 50.4 Gy), cervix alone (to 61.2 Gy) PTV=CTV + 5 mm SI, LL and 3 mm AP
Marnitz et al[38]	CTV=cervix + any extracervical disease. No PTV
Kubicek et al[34]	CTV=cervix + any extracervical disease. PTV=CTV + 5 mm
Hsieh et al[40]	CTV=residual T + initial GTV PTV=CTV + 5 mm
Mollà et al[33]	CTV=vaginal vault or uterus-parametrium or tumor residual or tumor relapse PTV=CTV + 6–10 mm

CTV, clinical target volume; GTV, gross tumor volume; PTV, planning target volume; T, tumor.

of advanced external beam techniques included two studies on image guided proton therapy. The results showed that planning target volume coverage was similar to brachytherapy,[22 29] while the maximum target dose was lower and the bowel volume receiving more than 60 Gy (EQD2) was significantly larger for image guided proton therapy. Moreover, motion management systems still remain a challenge.

One brachytherapy-related issue is inhomogeneity in dose distribution as the high doses near the source fall off steeply. Even though opinions differ on whether this is an advantage or not,[50–52] the hot spots adjacent to the source were hypothesized to increase tumor cell kill and consequently the probability of local control.[25 50] On the other hand, intensity modulated radiotherapy provides a more homogeneous dose distribution in the target since it is not associated with this intra-target dose gradient.[53] The impact of dose distribution on clinical outcomes is hard to assess as almost all external beam radiation studies[22–29 32–40] were limited by their retrospective nature, heterogeneous doses, radiation schedules, volumes and techniques. Other limitations included gynecological tumors other than cervical cancer, diverse follow-up times, and small cohorts of patients. A selection bias emerged as, since patients were generally not candidates for brachytherapy or refused it, stereotactic radiation was the only available treatment.

Three recent articles,[54–56] which were not included in the present analysis, focused on patients who received a boost with intensity modulated radiation therapy[54 55] or CyberKnife[56] because they were unfit for, or refused, brachytherapy. Lazzari et al[54] reported that 25 patients with advanced and metastatic cervical cancer received a boost of 25 Gy, delivered in five fractions. The 2-year local control and overall survival rates were 78% and 67%, respectively. Only G1–2 acute genitourinary or gastrointestinal toxicity occurred in 10 patients. Albuquerque et al[55] reported clinical outcomes in a series of 15 patients who received 28 Gy in four fractions. The 2-year local control and overall survival rates were 70.1% and 53.3%, respectively. The 2-year cumulative incidence of grade ≥3 toxicity was 26.7%. Besides co-morbidities, tumor size might account for the suboptimal outcomes in this small cohort. Finally, Morgenthaler et al[56] reported the results of the first prospective single-arm study in 31 patients with cervical cancer who received a boost of 25 Gy or 30 Gy in five fractions, delivered by robotic radiosurgery. Local control after 3 and 5 years was 92% and the 1-, 3-, and 5-year overall survival rates were 89%, 60%, and 57%, respectively, across all disease stages. General tolerance was good, with G1–G2 toxicity and only one patient with G3 diarrhea. Target volume coverage was optimal and, together with excellent organs at risk sparing, may account for these very good results. These should be confirmed in a phase III randomized trial.

CONCLUSIONS

In evaluating alternatives to brachytherapy to deliver a boost in patients with locally advanced cervical cancer, this overview showed it was difficult to draw conclusions on the real impact of external beam radiotherapy alone. High-tech external beam radiation, such as stereotactic radiotherapy, seemed no better than image guided brachytherapy; therefore, it may be suitable only for carefully selected patients who are not candidates for brachytherapy or refuse it. Prospective clinical studies comparing high-tech external beam radiation and image guided brachytherapy would be attractive. However, image guided brachytherapy still remains the clear standard of care and efforts should be made to maintain brachytherapy expertise and skills, particularly among radiation oncology trainees.

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