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Image-based brachytherapy for cervical cancer

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Abstract

Cervical cancer is the third most common cancer in women worldwide; definitive radiation therapy and concurrent chemotherapy is the accepted standard of care for patients with node positive or locally advanced tumors > 4 cm. Brachytherapy is an important part of definitive radiotherapy shown to improve overall survival. While results for two-dimensional X-ray based brachytherapy have been good in terms of local control especially for early stage disease, unexplained toxicities and treatment failures remain. Improvements in brachytherapy planning have more recently paved the way for three-dimensional image-based brachytherapy with volumetric optimization which increases tumor control, reduces toxicity, and helps predict outcomes. Advantages of image-based brachytherapy include: improved tumor coverage (especially for large volume disease), decreased dose to critical organs (especially for small cervix), confirmation of applicator placement, and accounting for sigmoid colon dose. A number of modalities for image-based brachytherapy have emerged including: magnetic resonance imaging (MRI), computed tomography (CT), CT-MRI hybrid, and ultrasound with respective benefits and outcomes data. For

practical application of image-based brachytherapy the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology Working Group and American Brachytherapy Society working group guideline serve as invaluable tools, additionally here-in we outline our institutional clinical integration of these guidelines. While the body of literature supporting image-based brachytherapy continues to evolve a number of uncertainties and challenges remain including: applicator reconstruction, increasing resource/cost demands, mobile four-dimensional targets and organs-at-risk, and accurate contouring of "grey zones" to avoid marginal miss. Ongoing studies, including the prospective EM-BRACE (an international study of MRI-guided brachytherapy in locally advanced cervical cancer) trial, along with continued improvements in imaging, contouring, quality assurance, physics, and brachytherapy delivery promise to perpetuate the advancement of image-based brachytherapy to optimize outcomes for cervical cancer patients.

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Key words: Cervical cancer; Brachytherapy; Image-based brachytherapy; 3D-planning; Magnetic resonance imaging-based brachytherapy; Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology Working Group guidelines

Core tip: Brachytherapy is an integral part of radical pelvic radiation therapy for cervical cancer. While image-based planning has gained wide acceptance in external beam radiotherapy, the integration of image-based planning for brachytherapy has lagged significantly. More recently advances in planning software/hardware have lead to increased use of image-based brachytherapy. Herein, we highlight the clinical advantages of 3D brachytherapy planning for cervical cancer. We present multiple modalities for image-based brachytherapy including outcome data and dose constraints. Finally we outline practical guidelines for contouring target volumes and critical organs; and present future

directions in image-based brachytherapy aimed towards improving cervical cancer outcomes.

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INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide with an estimated annual death rate > 275000^[1,2]. For early stage disease, prospective randomized data has established the equivalence of radical hysterectomy (\pm adjuvant radiation therapy based on risk factors) *vs* radical pelvic radiation therapy in terms of survival and disease control with increased toxicity with surgery \pm adjuvant therapy; however surgery is often the treatment of choice for early stage disease because of decreased treatment time, the potential opportunity for ovarian and/or fertility preservation, and a decreased risk of second malignancy^[3]. Definitive radiation therapy is the accepted standard of care for early stage patients not suitable for surgical resection and is integrated with concurrent cisplatin chemotherapy for patients with node positive or locally advanced tumors > 4 cm (all node positive and FIGO stage I B2, II A2, and higher). Definitive radiation therapy consists of a combination of external beam radiotherapy and brachytherapy; the addition of brachytherapy represents an integral part of definitive radiation therapy for cervical cancer shown to improve overall survival^[4,5]. Traditionally, as outlined in the International Commission on Radiation Units and Measurements (ICRU) 38 and the 2000 American Brachytherapy Society (ABS) guidelines for cervical cancer, brachytherapy dose was based on two-dimensional (2D) planning prescribed to a modification of the classical Manchester system point A for target coverage and conventional points for critical organs^[6,7]. The results for 2D X-ray based brachytherapy have been good in term of local control especially for early stage disease with acceptable toxicities, but there are unexplained toxicities and treatment failures^[8-10]. Additionally, the correlations between toxicities and critical organ point doses have not been consistent, limiting toxicity improvements through planning optimization in 2D brachytherapy^[10]. Computed tomography (CT) based three-dimensional (3D) planning and more recently more sophisticated image-based planning (Intensity Modulated Radiotherapy) has been widely accepted and implemented for external beam radiotherapy, however the acceptance and implementation of 3D image-based brachytherapy has lagged substantially. The relatively slow integration of 3D image-based brachytherapy can be attributed to a decreased availability of planning software/hardware, increased cost, and a lack of optimal training/expertise.

ADVANTAGES OF IMAGE-BASED BRACHYTHERAPY

Improvement in hardware and software for brachytherapy planning have more recently paved the way for 3D image-based brachytherapy which allows volumetric optimization improving tumor coverage and critical organ sparing which potentially increases local control, reduces toxicities, and helps predict outcomes. Early data for 3D planning has substantiated the potential improvements of 3D over 2D planning overcoming challenges in optimizing technique, reproducibility, uncertainties in target delineation, and the dosimetric planning processes. Several studies have compared the cervical tumor coverage and critical organ sparing by 3D image-based brachytherapy to doses delivered by 2D radiography-based brachytherapy^[11-18]. Investigators from University of Alabama Birmingham were some of the first to show that the 2D radiography-based approach using point A overestimates the tumor dose, especially in more advanced tumors where on average the gross tumor volume prescribed dose coverage was 98.5%, 89.5%, 79.5%, and 59.5% for stages I BI, I B2, II B, and IIIB, respectively^[11]. Others have shown that for smaller cervical tumors, the point A dose may achieve adequate tumor coverage, but over treats surrounding critical organ which can be improved with magnetic resonance imaging (MRI) image-based planning^[12]. These results were further validated by University of Pittsburgh data showing that the mean dose to 90% and its standard deviation was 83.2 ± 4.3 Gy that was significantly higher ($P < 0.0001$) than the mean dose 78.6 ± 4.4 Gy to Point A^[13]. Numerous early reports showed the orthogonal X-ray ICRU point doses underestimate doses to rectum and bladder as compared to CT based volumetric calculation by 1-5 folds (Table 1) especially for the bladder point doses^[19-22]. These results were later validated in a prospective study from MD Anderson, showing that the ICRU bladder point significantly underestimated the CT based highest dose to 2cc by a mean difference of 6.8 Gy, but did not differ significantly for the rectum with a mean difference of 0.21 Gy^[23]. Prospective studies from Korea and Vienna using all image-based brachytherapy correlated late changes in rectal mucosa on serial rectosigmoidoscopy with volumetric doses of 2cc, 1cc, and 0.1cc (D2cc, D1cc, and D0.1cc), showing significant dose cutoffs (Table 2) for both asymptomatic and symptomatic rectal changes^[24,25]. With longer-follow-up the Vienna group has established well-defined dose-response curves for D2cc doses to the rectum and bladder (Table 3), which provide an invaluable risk-assessments for rectal and bladder constraints^[26]. While with 2D planning consistent validated constraints had been elusive impeding reductions in brachytherapy toxicity, these outcome data provide practical dose constraints for 3D brachytherapy optimization to limit the risks of late toxicity.

In addition to the well-established dosimetric advantages of 3D as compared to 2D brachytherapy planning

Table 1 Discrepancies between bladder and rectal doses as assessed by two-dimensional orthogonal films and computed tomography-image based planning

	Orthogonal film based <i>vs</i>	CT based
Ling <i>et al</i> ^[19]	Bladder	1.0 - 4.1x
	Rectum	1.4 - 2.5x
Schoepel <i>et al</i> ^[20]	Bladder	2.1 - 2.3x
	Rectum	1.3 - 1.6x
Stueckelschweiger <i>et al</i> ^[21]	Bladder	1.0 - 2.2x
	Rectum	1.1 - 1.6x
Kapp <i>et al</i> ^[22]	Bladder	1.0 - 5.4x
	Rectum	1.1 - 2.7x

Table 3 Correlations for volumetric doses for risk of grade 2+ late toxicity

	5% Risk	10% Risk	20% Risk	P value
Rectum				
D2cc	67	78	90	0.0178
D1cc	71	87	104	0.0352
D0.1cc	83	132	186	0.1364
Bladder				
D2cc	70	101	134	0.0274
D1cc	71	116	164	0.0268
D0.1cc	61	178	305	0.0369

D2cc: Dose to 2 cubic centimeters; D1cc: Dose to 1 cubic centimeter; D0.1cc: Dose to 0.1 cubic centimeter.

for cervical cancer, 3D planning additionally offers clinical advantages including: confirmation of applicator placement, decreased critical organs-at risk (OAR) dose for patients with a small cervix, accounting for sigmoid colon dose, and improved coverage for large volume disease while maintaining critical organ dosimetry. At the time of brachytherapy application, tandem placement can result in unsuspected uterine perforation despite the clinical impression of adequate tandem placement (Figure 1); 3D planning increases the diagnosis of perforation and avoids overtreatment of fundus/lower uterine segment^[27]. Patients with a small cervix represent a challenge to adequate brachytherapy delivery, where suboptimal weighting and positioning can lead to over-dosage of critical organs when using the conventional 2D planning one-size-fits-all optimization process (Figure 2). Investigators from Princess Margaret Hospital compared 2D *vs* 3D (MRI based) planning for patients with small cervix showing that tumor coverage (volume receiving 100% of the prescription dose > 95% of target) was adequately in 70% of the patients with the conventional 2D plans, respectively, and in 75% of the patients with the optimized plans and the minimal dose to the contiguous D2 cc of the rectal, sigmoid, and bladder wall volume was 16 ± 6.2 Gy, 25 ± 8.7 Gy, and 31 ± 9.2 Gy, respectively^[12]. While with MRI-guided brachytherapy optimization, it was possible to maintain tumor coverage and reduce the dose to the normal tissues, especially in patients with small cervix where the target volume treated to $\geq 100\%$ of the intended dose approached 100% in all cases, and the

Table 2 Dosimetric correlates for rectal toxicity in image-based brachytherapy

	D2cc (mean)	D1cc (mean)	D0.1cc (mean)
Koom <i>et al</i> ^[24]	75 Gy <i>vs</i> 69 Gy	80 Gy <i>vs</i> 73 Gy	90 Gy <i>vs</i> 85 Gy
VRS ≥ 2	(P = 0.02)	(P = 0.02)	(P = 0.04)
Georg <i>et al</i> ^[25]	72 Gy <i>vs</i> 62 Gy	76 Gy <i>vs</i> 65 Gy	88 Gy <i>vs</i> 75 Gy
VRS ≥ 3	(P < 0.001)	(P < 0.001)	(P = 0.002)
Georg <i>et al</i> ^[26]	72 Gy <i>vs</i> 64 Gy	76 Gy <i>vs</i> 67 Gy	88 Gy <i>vs</i> 77 Gy
Symptomatic	(P < 0.01)	(P < 0.01)	(P = 0.03)

VRS: Vienna rectoscopy score; cc: Cubic centimeters; Gy: Gray; D2cc: Dose to 2 cubic centimeters.

minimal D2cc of the rectum, sigmoid, and bladder was 12%-32% less than with conventional 2D brachytherapy planning^[12]. Dose to the sigmoid colon and small bowel was not accounted for in conventional 2D planning, which can receive > 70% of the point A dose^[28]. Image-based brachytherapy offers the added advantage of sparing dose to the sigmoid colon and small bowel, which potentially reduces the risk of stricture and ulceration (Figure 3). Large volume disease creates a challenge in achieving adequate coverage as portions of the disease extend larger distances from the central applicator with increasing tumor size; image-based planning in combination with a combined interstitial/intracavitary approach (Vienna applicator) help to create an asymmetric dose distribution improving tumor control and affording dose-escalation (Figure 4); which is especially important for larger tumors > 5 cm as highlighted in the Vienna group experience where comparing outcomes for cervical cancer patients prior to the introduction of image-based brachytherapy and the Vienna applicator, 3-year actuarial overall survival was 28% for tumors > 5 cm as compared to 58% ($P = 0.003$) with image-based brachytherapy^[29,30].

MODALITIES FOR IMAGE-BASED BRACHYTHERAPY-MRI

A number of imaging modalities have emerged for image-based brachytherapy planning. The Groupe Européen de Curietherapie-European Society for Therapeutic Radiology and Oncology Working Group (GEC-ESTRO) and ABS have developed guidelines to standardize contouring definitions and dosimetry for tumor targets and OARs^[31-33]. Both the ABS and GEC-ESTRO guidelines are based on MRI-based brachytherapy planning, with MRI offering superior soft tissue contrast^[34]. The largest experience with MRI-based planning comes from the Vienna group which incorporated MRI-based planning which each fraction, the mean dose to 90% of the target volume (D90) was 86 ± 16 Gy for the high-risk clinical target volume (HR-CTV) with a mean D2cc for the bladder, rectum, and sigmoid of 95 ± 22 Gy, 62 ± 12 Gy, and 62 ± 12 Gy^[35,36]. Similar dosimetric results have been published in the Aarhus and Leuven experience for definitive chemo-radiotherapy in advanced disease^[37,38]. The long-term outcome data from the Vienna experience

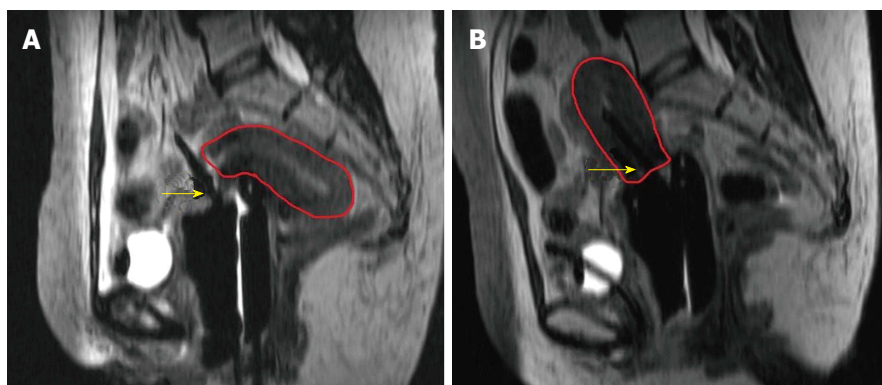


Figure 1 Uterine perforation despite perfect geometric applicator placement relative to bone anatomy. A: Shows the uterine perforation with retroverted uterus (red) diagnosed on magnetic resonance imaging (MRI) imaging for brachytherapy planning; B: Shows appropriate tandem placement (yellow arrow) ameliorated by placing the applicator under ultra-sound guidance and confirmed by MRI image-based planning.

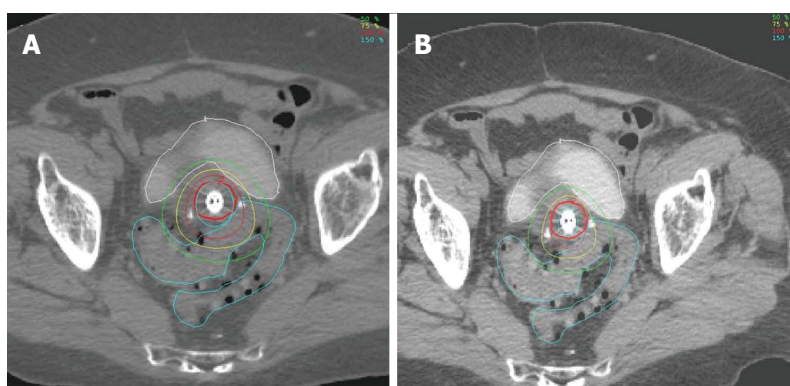


Figure 2 Conventional 2D point dose brachytherapy planning over doses critical organs for small cervix. Magnetic resonance imaging planning images showing over-dosage of critical organs with point-A image based prescription (A) for patient with small cervix which is improved with image-based brachytherapy (B).

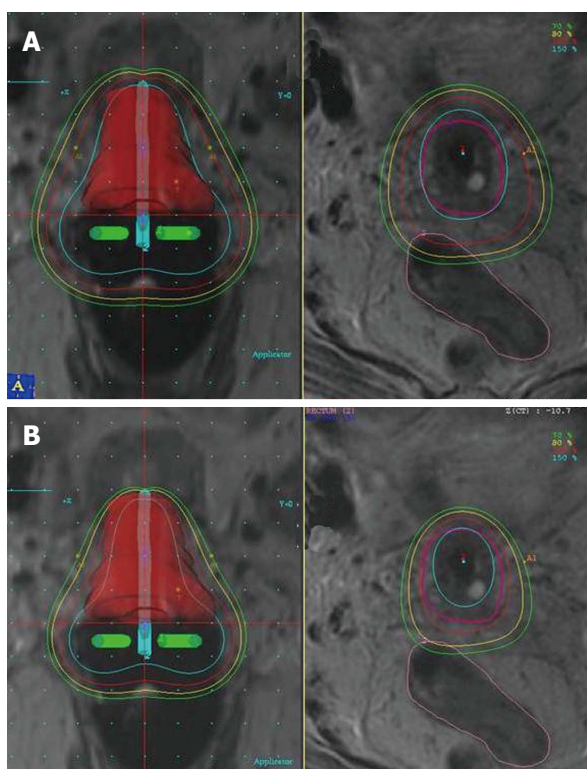


Figure 3 Sigmoid colon sparing with image-based planning. Magnetic resonance imaging planning images showing point A optimized plan with high doses to adjacent sigmoid colon (A), which is reduced with image-based 3D optimization (B).

showed an excellent 3-year 95% local control^[39].

MODALITIES FOR IMAGE-BASED BRACHYTHERAPY-CT

MRI is not universally available in radiation oncology departments; and the need for serial repeat imaging to account for changes in position of critical organs and tumor regression create logistical and financial impediments that have limited the universal applicability of MRI-based brachytherapy planning. Contrastingly, CT simulators are widely available in radiation oncology departments, thus interest grew in using CT based brachytherapy planning. To address these concerns, a prospective international cooperative group trial compared CT to MRI based planning showing that tumor height, thickness, and total volume measurements as determined by CT were not significantly different compared with the MRI volumes; similarly the MRI and CT dose-volume-histogram values of the D2cc, D1cc, and D0.1cc for the OARs were similar^[40]. However, the width measurements differed in HR-CTV for CT *vs* MRI based planning, resulting in statistically significant differences in the volume treated to the prescription dose or greater (MRI 96% *vs* CT 86%, $P = 0.01$) and dose to 90% of the treatment volume (MRI 8.7% *vs* CT 6.7%, $P < 0.01$)^[40]. Outcomes from Addenbrook, where a lack of access to MRI for brachytherapy

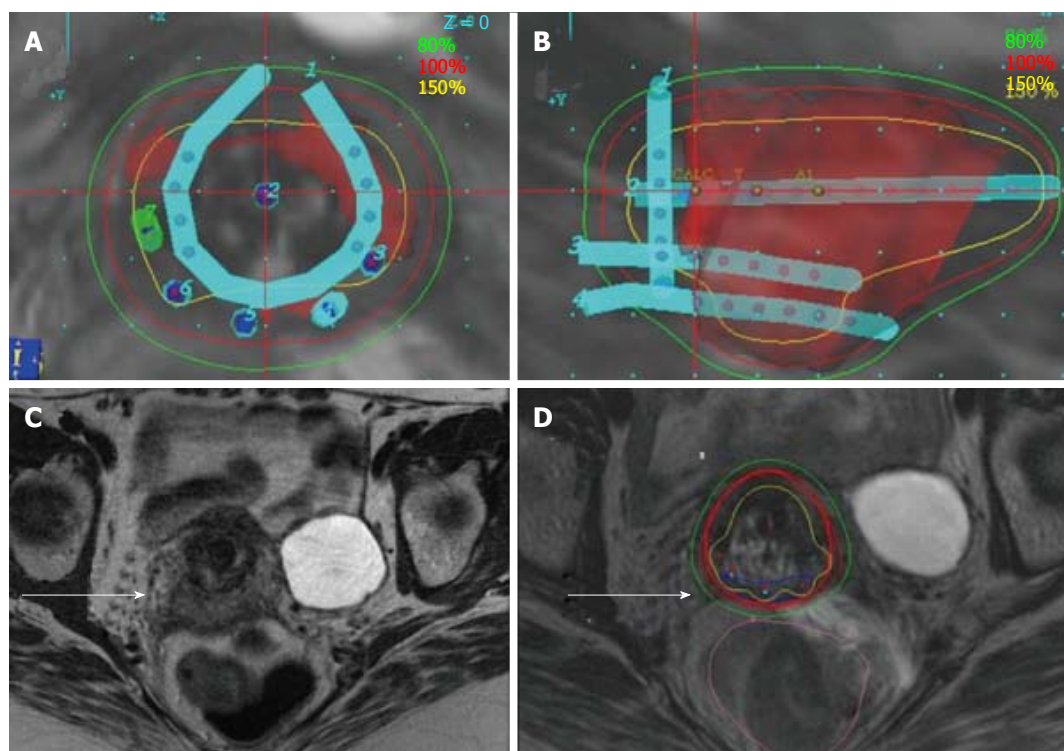


Figure 4 Use of the Vienna applicator to improve posterior disease coverage for locally-advanced cervical cancer. A and B: 3D reconstruction of Vienna applicator showing posterior needles; C and D axial magnetic resonance imaging (MRI) showing advanced disease with posterior extension, and improved coverage with combined interstitial and intracavitary MRI image-based planning.

planning forced CT image-based planning with each fraction, for 86% of the included patients the D90 was ≥ 74 Gy, with the only patient with local recurrence having a D90 of 63.8 Gy^[41]. When comparing their experience at Addenbrook with CT image-based planning to a previous institutional cohort of patients treated with chemoradiotherapy and 2D planning showed a significant 20% improvement ($P = 0.04$) in local control^[41].

MODALITIES FOR IMAGE-BASED BRACHYTHERAPY-CT AND MRI HYBRID

More recently, The University of Pittsburgh has shown a hybrid approach using MRI for first fraction and CT for subsequent fractions which allows for initial dose optimization based on the gold-standard MRI based imaging, with serial CT imaging to account for variations in applicator geometry and changes in OARs and target volumes throughout subsequent fractions^[42]. In the first report on a hybrid CT/MRI image-based approach in 42 patients we reported a mean D90 of 83.3 Gy with a mean D2cc for bladder, rectum, and sigmoid of 79.7, 57.5 and 66.8 Gy respectively. The complete response rate by PET/CT was 92.5%, with a 2-year local control rate of 88%^[43]. Dosimetric study from the Vienna group incorporating automated applicator based image registration compared the gold standard of MRI-based planning with each fraction to the hybrid MRI/CT approach, there was small systemic underestimation with the hybrid approach with

the mean difference in HR-CTV volume of $-1.7 \pm 6.6\text{cc}$ in HR-CTV, mean difference in D90 of -1.5 ± 4.3 Gy, and mean difference in D2cc for rectum, sigmoid, and bladder of 0 ± 4.9 Gy, 1.3 ± 1.2 Gy, and 1.1 ± 4.2 Gy, respectively^[44]. However all the outliers where the difference in D90 was greater than 1 Gy were large tumors requiring more complex applications (including Vienna applicator), thus the authors conclude that the hybrid approach is quite similar for small tumor and intracavitary applicators; however maybe suboptimal for larger tumors and more complex applicators^[44].

MODALITIES FOR IMAGE-BASED BRACHYTHERAPY-ULTRASOUND

Alternatively, investigators from Australia and Indian have incorporated trans-abdominal ultrasound for image-based planning, which also represents a more widely available and cost effective imaging modality that does not interfere with conventional stainless steel applicators^[45,46]. In a prospective planning study, investigators from Mumbai showed a reasonable correlation in trans-abdominal ultrasound and MRI-based planning^[45]. For outcome data, in the Australian experience planning was based on trans-abdominal ultrasound with each fraction, MRI was only available for one insertion and was used to assess response and later to validate the ultrasound volume. For ultrasound based planning, the mean D90 was 80.8 Gy with D2cc for bladder and rectum of 57.7 Gy

Table 4 Summary of clinical outcomes in published results for image-based brachytherapy for cervical cancer

	Local control	Disease free survival	Overall survival	Late toxicity (G3+)
STIC ^[47] (2-yr)	78.5%-100%	60.3%-89.7%	74%-96%	2.6%-8.9%
Vienna ^[39] (3-yr)	95%	74%	68%	7.7% crude
Pittsburgh ^[48] (2-yr)	90%	NR	82%	2%
Paris ^[49] (4-yr)	91%	86%	94%	0%
Addenbrooke ^[41] (3-yr)	96%	81%	82%	11% crude (14% actuarial)
Australia ^[50] (5-yr)	87%-88%	67%	60%	0.6%-4.6%
Korea ^[51] (3-yr)	97%	80%	NR	2%

NR: Not-reported; G3+: Grade ≥ 3 toxicity.

and 58.8 Gy, respectively^[46]. There was no significant difference in dosimetry between ultrasound and MRI planning, with a 90% local control rate^[46].

CLINICAL OUTCOMES FOR IMAGE-BASED BRACHYTHERAPY

While the integration of cisplatin chemotherapy to radical radiation therapy has improved outcomes, outcomes remain suboptimal especially for more advanced disease and novel chemotherapeutic agent development has been slow; as such improvements in radiation therapy, such as image-based brachytherapy which through improved target delineation and coverage, promises to be the next major step in improving cervical cancer outcomes. Recently international data for outcomes using image-based brachytherapy have been published (Table 4) substantiating the potential for improved outcomes suggested in prior planning studies^[39,41,47-51]. The international series outlined in Table 4 use a variety of treatment schedules, but highlight the potential advantages of image-based brachytherapy, high rates of local control 79%-100% with low rates of late complications 0%-14%. Building on these single institutional experiences, a prospective non-randomized multi-institutional series from the French Soutien aux Techniques Innovantes et Coûteuses with > 800 cervical cancer patients compared 2D PDR brachytherapy *vs* 3D (CT or MRI) PDR brachytherapy^[47]. Patients were divided into three groups based on the integration of radio-chemotherapy with surgery (pre-operative, post-operative, or no surgery). At a median 2-year follow-up, 3D planning significantly improved local (78.5%-100% *vs* 73.9%-91.9%, $P = 0.003$) and loco-regional (69.6%-96.1% *vs* 61.2%-87.9%, $P = 0.001$) relapse free survival which transcended treatment groups; there were trends towards improved disease-free (60.3%-89.7% *vs* 55.2%-86.5%, $P = 0.086$) and overall survival (74%-96% *vs* 65%-95%, $P = 0.27$) especially for the more advanced patients treated with radical radio-chemotherapy alone^[47]. Additionally 3D brachytherapy translated into statistically significant decreases in grade 3+ urinary (1.2%-5.5% *vs* 5.8%-9.2%, $P = 0.02$), gynecologic (1.4%-7.5% *vs* 5.7%-15.4%, $P = 0.01$), and global toxicity (2.6%-8.9% *vs* 12.5%-22.7%, $P = 0.002$)^[47]. The largest series using MRI based planning based on the GEC

ESTRO guidelines from Vienna group similarly showed excellent 3-year local control of 95% which represents a 65% relative improvement in local control from prior Vienna cervical cancer series using 2D planning, this local control advantage translated into 20%-30% improvement in disease-specific and overall survival primarily for more advanced tumors > 5 cm, respectively^[39]. One explanation for these improvements is dose-escalation with an increased mean dose to 90% of the volume (D90) from 90 Gy with conventional planning to 94 Gy with MRI-based planning, this is supported in a strong dose-response relationship which advocates that a D90 equivalent-dose-2 Gy (EQD₂) of at least 87 Gy is required for local control > 90% for advanced disease^[30,39,52].

RECOMMENDATION FOR PRACTICAL APPLICATION OF IMAGE-BASED BRACHYTHERAPY

For the practical application of image-based brachytherapy the guidelines published by the GEC-ESTRO and ABS working groups serve as invaluable tools for image acquisition, target/OAR delineation, and dosimetry/optimization^[31-33,53-55]. Briefly to summarize our institutional integration of these guidelines, for MRI-based planning it is recommended to use T2-weighted images, with either high signal intensity (if brachytherapy alone) or intermediate signal intensity (if brachytherapy following external-beam radiotherapy). Tumor target volumes consist of two clinical target volumes (CTV): the high-risk CTV (HR-CTV) which is optimized to receive a dose enough to sterilize macroscopic tumor representing the entire cervix plus presumed tumor extension (based on clinical assessment and/or residual grey zones on MRI) without safety margin and the intermediate-risk CTV which is optimized to received a dose enough to sterilize microscopic tumor (representing the HR-CTV plus a safety margin of 5-15 mm according to potential tumor spread-up to 5 mm anterior-posterior limited by bladder or rectum, 10 mm cranially in uterine corpus but only 5 mm if endocervical tumor, and 5-10 mm laterally into parametria). The rectum, bladder, sigmoid colon, and relevant parts of the small bowel loops adjacent to the target volumes are considered as the main OARs that are contoured with

each fraction. We typically initiate cervical brachytherapy during the 4th or 5th week of external beam radiotherapy with MRI-compatible Smit Sleeve placement. We primarily employ a ring and tandem intracavitary HDR technique (though also incorporate a Vienna applicator or template-based interstitial application where appropriate) with 5-6 Gy per fraction times 5 fractions (25-30 Gy) based on response to external beam radiotherapy using weekly fractionation during external beam radiotherapy and twice weekly after completion of external beam radiation therapy.

As outlined in the GEC-ESTRO and ABS guidelines we advocate MRI for each application; however if logistics preclude MRI-based planning with each fraction, alternative methods would be for MRI with the first fraction and serial CT-based planning for subsequent fractions^[43]. Alternatively if MRI-based planning is not available, outcome data for CT-based or US-based planning shows improved outcomes over 2D planning^[41,46,51]. An additional consideration would be to incorporate a diagnostic pre-brachytherapy MRI with CT-based or US-based brachytherapy planning to aid in soft-tissue delineation in brachytherapy planning^[56].

For optimization, we aim for a HRCTV D90 \geq 100% with a planned EQD₂ 80-85 Gy, except for patients with a poor response to external beam radiotherapy with large residual tumors where based on the Vienna dose-response data we push the dose to EQD₂ 85-90 Gy to attempt to improve local control^[52]. While based on the outcome data outlined in Table 2 and 3, we limit the rectum D2cc EQD₂ \leq 70 Gy, sigmoid D2cc EQD₂ \leq 70 Gy, and bladder D2cc EQD₂ \leq 90 Gy.

UNCERTAINTIES AND CHALLENGES IN IMAGE-BASED BRACHYTHERAPY

Despite the observed dosimetric and clinical benefits of image-based brachytherapy many uncertainties and challenges remain. Applicator reconstruction is a challenge to quality assurance in image-based brachytherapy, where a lack of a MRI compatible dummy catheter forces a reconstruction of source channels. A number of reconstruction methods have been purposed, but uncertainties in the reconstruction of source channels can generate both random and systematic errors in dose-volume-histogram (DVH) parameters^[57-59]. In an era of increasing emphasis on curtailing health-care costs, it is unclear how much the increase in demands on resources and total cost will limit applicability of image-based brachytherapy. Dosimetric uncertainties are challenged by reproducibility of mobile four-dimensional targets, OARs which can have dramatic inter-fraction differences based on distention/filling, and mobile applicators subject to intra- and inter-fraction motion^[57]. Finally the steep dose gradients of brachytherapy dose distributions place increased hopes on accurate contouring which is challenged by “grey zone” interpretation on MR imaging and evaluation of tumor response changes^[34].

FUTURE DIRECTIONS OF IMAGE-BASED BRACHYTHERAPY

To prospectively validate the adoption of image-based brachytherapy, a multi-institutional international trial, EMBRACE (an international study of MRI-guided brachytherapy in locally advanced cervical cancer) is currently accruing (<http://www.embracestudy.uk>). EMBRACE includes patients with FIGO stage IB-IVA cervical cancers, all patients receive concurrent cisplatin (40 mg/m² weekly) chemotherapy and conventionally fractionated external beam radiation therapy followed by MRI image-based brachytherapy according to the GEC-ESTRO guidelines with brachytherapy dose and DVH constraints at the discretion of the enrolling department standards. The study aims to enroll 600 patients over 3-year and promises to establish a benchmark for cervical cancer management in terms of tumor control, complications, dose specification, and a prospective assessment of quality-of-life. This trial along with continued improvements in imaging, contouring, dosimetry, quality assurance, physics, and brachytherapy delivery promise to perpetuate the advancement of image-based brachytherapy to optimize outcomes for locally-advanced cervical cancer patients.

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