Systematic review

Three-dimensional-guided perineal-based interstitial brachytherapy in cervical cancer: A systematic review of technique, local control and toxicities

Lucas C. Mendez [a], Yonatan Weiss [a], David D'Souza [b], Ananth Ravi [a], Lisa Barbera [a], Eric Leung [a,*]

[a] Odette Cancer Centre, Sunnybrook Health Sciences Centre, Department of Radiation Oncology, University of Toronto; and [b] London Regional Cancer Program, London Health Sciences Centre, Department of Oncology, Western University, Canada

ABSTRACT

Objective: To evaluate local control and toxicities of perineal-based interstitial brachytherapy (P-ISBT) in cervical cancers treated with three-dimensional (3D) image-based planning through a systematic review. The secondary objective of this review is to summarize the implant and dosimetric techniques in 3D P-ISBT.

Methods: Systematic review of the literature using the PRISMA guideline was conducted through a search of Medline, EMBASE and Cochrane databases. This search resulted in 19 relevant manuscripts. Selected studies evaluated the role of perineal ISBT in cervical tumours treated using 3D planning. Eleven of nineteen manuscripts contained sufficient information for LC and toxicity calculations. Data were extracted by at least two investigators.

Results: A total of 672 cervical cancer patients were treated with P-ISBT and planned with 3D image-based planning. Clinical outcomes could be identified for 392 patients and 60% were staged IIIB or higher. Most patients received 45–50.4 Gy EBRT to the pelvis followed by a P-ISBT boost with a range of dose between 28 and 48 Gy EQD_{2Gy}. Overall LC was 79% (310/392) with a median follow-up ranging from 14 to 55 months. Almost half of the patients (48%) had a median follow-up $\geq$35 months. Patients treated to a lower tumour EQD_{2Gy} total dose had inferior LC. Procedure-related complications were rare (7 infections and 7 episodes of bleeding) and limited. Combined late gastro-intestinal, genitourinary and vaginal grade 3 and 4 toxicity was 12.1%.

Conclusion: Promising LC rates were found in patients with cervical cancers treated with perineal ISBT with 3D image-based planning. In this systematic review, 60% had stage IIIB disease or higher and yet a LC rate of 79% was found. LC seemed to correlate with the dose delivered to the tumour, while toxicity rates were similar to other cervical cancer series using 3D image-based brachytherapy. Perineal ISBT with 3D planning seems to be an effective and safe treatment for large advanced cervical tumours and may be a reasonable alternative to the increasingly more standard and modern intracavitary/interstitial (IC/IS) approaches such as the 'Vienna' applicator.

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Brachytherapy is an essential component in the treatment of locally advanced cervical cancers and is independently associated with improved overall survival for patients with this disease [1]. In the last decade, the adoption of three-dimensional (3D) imaging for treatment planning has resulted in a paradigm shift from 2D-planning to a 3D image-guided brachytherapy (IGBT) technique [2]. Several recent observational studies have supported this trend while improvements in local control and toxicity associated with IGBT have been reported [3–5].

Current GEC-ESTRO recommendations suggest that 90% of the high-risk CTV (D90-HRCTV) should receive a minimum dose of 85 Gy (EQD_{2Gy}) [6]. Even with IGBT, this can be challenging for some tumours treated with standard brachytherapy applicators such as 'ring-and-tandem' or 'tandem-and-ovoid'. The dose profile from intracavitary techniques may not adequately cover tumour volumes greater than 30 cc, and these bulkier cancers may require interstitial catheters to improve target coverage and dose. This can lead to an improvement in local control of 2–3% increase per each Gray delivered, as seen when using effective and more modern intracavitary/interstitial (IC/IS) applicators (eg. 'Vienna' or 'Utrecht') [7].

* Corresponding author at: Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.
E-mail address: eric.leung@sunnybrook.ca (E. Leung).

Besides IC/IS applicators, another approach to interstitial brachytherapy is the perineal template technique. This has been available for over thirty years and has been shown to be superior to standard non-interstitial intracavitary applicators in delivering dose laterally to large advanced tumours [8]. Historically, perineal ISBT was planned with conventional techniques where dose is prescribed to a defined point based on two-dimensional imaging [9]. As expected, the lack of volumetric dosimetry and the uncertainty of catheter location with respect to organs-at-risk yielded high toxicity rates and as a result, the adoption of this approach has been limited due to concerns and uncertainty of potential complications.

However, with the advent of 3D image-based planning, perineal ISBT has become a more systematic technique and needle positioning with respect to organs in the pelvis can now be evaluated with CT or MRI. Furthermore, the use of ultrasound or MRI imaging for real-time guidance can also help improve the accuracy of needle placement.

The primary goal of this systematic review is to evaluate local control and toxicities following perineal ISBT for the treatment of locally-advanced cervical cancer in the era of 3D image-based planning. This review will also summarize and discuss the characteristics of implant technique and dosimetry of the P-ISBT procedures as a secondary objective.

Methods

This systematic review adheres to the Preferred Reported Items for Systematic Reviews and Meta-Analyses protocol (PRISMA) [10].

Search strategy

We first identified published manuscripts reporting the use of 3D-planned trans-perineal interstitial brachytherapy in cervical cancers from 1947 to April 2015. The search was performed in April 2015 using the National Library of Medicine (PubMed/MED-LINE), Excerpta Medica Database (EMBASE) and Cochrane database. An updated search was conducted in January 2017, identifying manuscripts from 1947 to January 2017. One recent article was found through PubMed 'Epub ahead of print' and was included in this review [11]. The full search strategy can be found in Supplementary Data.

Selection criteria

The title and abstract of the identified papers were reviewed by two reviewers (EL and YW) and irrelevant papers were excluded if agreed upon by both reviewers. Any disagreements were discussed and resolved by a third reviewer (LM) opinion.

Eligible studies met the following criteria: published manuscripts addressing adult population with cervical cancers treated with definitive perineal-based interstitial brachytherapy as a boost after external beam radiation and planned with three-dimensional imaging. For this review, three-dimensional treatment planning signifies volumetric delineation of targets and organs-at-risk (OARs) on CT or MRI with dose–volume histograms [12]. Studies that use 3D imaging exclusively for assessment of catheters position without volumetric delineation of the target and OARs were not categorized as 3D treatment planning.

Institutional series that evaluated the role of P-ISBT for other primary cancers or recurrent tumours in addition to cervix cancer were excluded from LC and toxicity calculations if the results for cervical patients could not be separated with the provided information from the manuscript. Previous series that were subsequently updated with more recent publications, with exclusive dosimetric data or using 2D techniques were also excluded from this analysis.

Data extraction

The following data were collected separately by two reviewers (EL and YW): Study design, number of patients, year of publication, age, external beam radiation therapy (EBRT) dose, use of chemotherapy, P-ISBT dose and technique, treatment volume, follow-up time, local control and toxicity. Discrepancies were resolved by the third reviewer (LM). LC was defined as the absence of disease progression in the site of P-ISBT and was calculated by dividing the number of patients with controlled localized disease by the number of patients treated with P-ISBT. Because of the heterogeneity of follow-up times among the series it was not possible to define one common time point. As such, LC and toxicity endpoints are reported with a time range. Prescribed P-ISBT dose was converted to equivalent 2 Gy dose (EQD_{2Gy}) using the linear quadratic equation and $\alpha/\beta = 10$. Treatment clinical outcomes were calculated using the number of local failures or toxicity episodes per number of patients treated. Descriptive and sensitivity analysis was used for data report. Spearman's rank correlation coefficient quantified correlation strength between LC and dose.

Results

A total of 377 citations were identified from database search. Based on the title and abstract, 27 articles were selected for full review (Fig. 1). Nineteen studies met the inclusion criteria and were fully reviewed for data extraction [11,13–30]. Eight studies were excluded after full review: three had no 3D-planning; one used P-ISBT as neoadjuvant treatment, one reported dosimetric outcomes only (no clinical data), one had no primary cervix cancers treated as definitive therapy, one did not use perineal ISBT (intravaginal) and another had a more updated series which was included in our review. Sixteen studies were retrospective and three studies were prospective in design. The combined selected studies reported on a total of 672 cervical cancer patients treated with P-ISBT, of which 392 patients had toxicity and oncological endpoints individually reported. Staging information was available for 375 patients and of these, approximately 48% had stage IIIB cervical tumours, 29% IIB, 12% IVA, 4% IIIA and 3% IB. Fourteen (4%) patients were staged as IVB.

P-ISBT technique, treatment volume and dose prescription

P-ISBT was performed using Syed-Neblett (n = 10 studies) [11, 15,17,19–22,26,28,29], custom-made (n = 4 studies) [23–25,30] or MUPIT (n = 2 studies) [14,16] templates. One study performed the procedure by free hand [18], one used a Benidorm template 27 and one study did not specify template type [13]. All studies used trans-perineal needles. Plastic catheters were used in nine studies [11,13,15,18,20,22,24,25,30], metallic in five [14,16,17,23,27]. Four studies did not mention needle characteristics [19,21,28,29] and one used either plastic or metallic needles [26]. The median number of catheters varied from 5 to 24 and insertion was guided by ultrasound in 5 studies, CT or MRI (3 studies), surgery (2 studies) and fluoroscopy (2 studies). Two studies used fluoroscopy and/or ultrasound guidance, two relied exclusively on clinical guidance for needle placement. All studies were planned on CT. Four also included MR imaging for tumour delineation (Table 1). Intra-uterine (IU) applicators were used in fourteen studies described either as a tandem or IU catheter. Three studies did not report on the use of an intrauterine source [23,25,29] and two studies did not use an IU applicator [14,15].

Targeted volumes varied between studies. Fourteen studies contoured and prescribed dose to a CTV, one to a GTV and another to PTV. Eight studies defined volumes as per GEC-ESTRO guidelines. Three studies did not state a clear target definition. All but
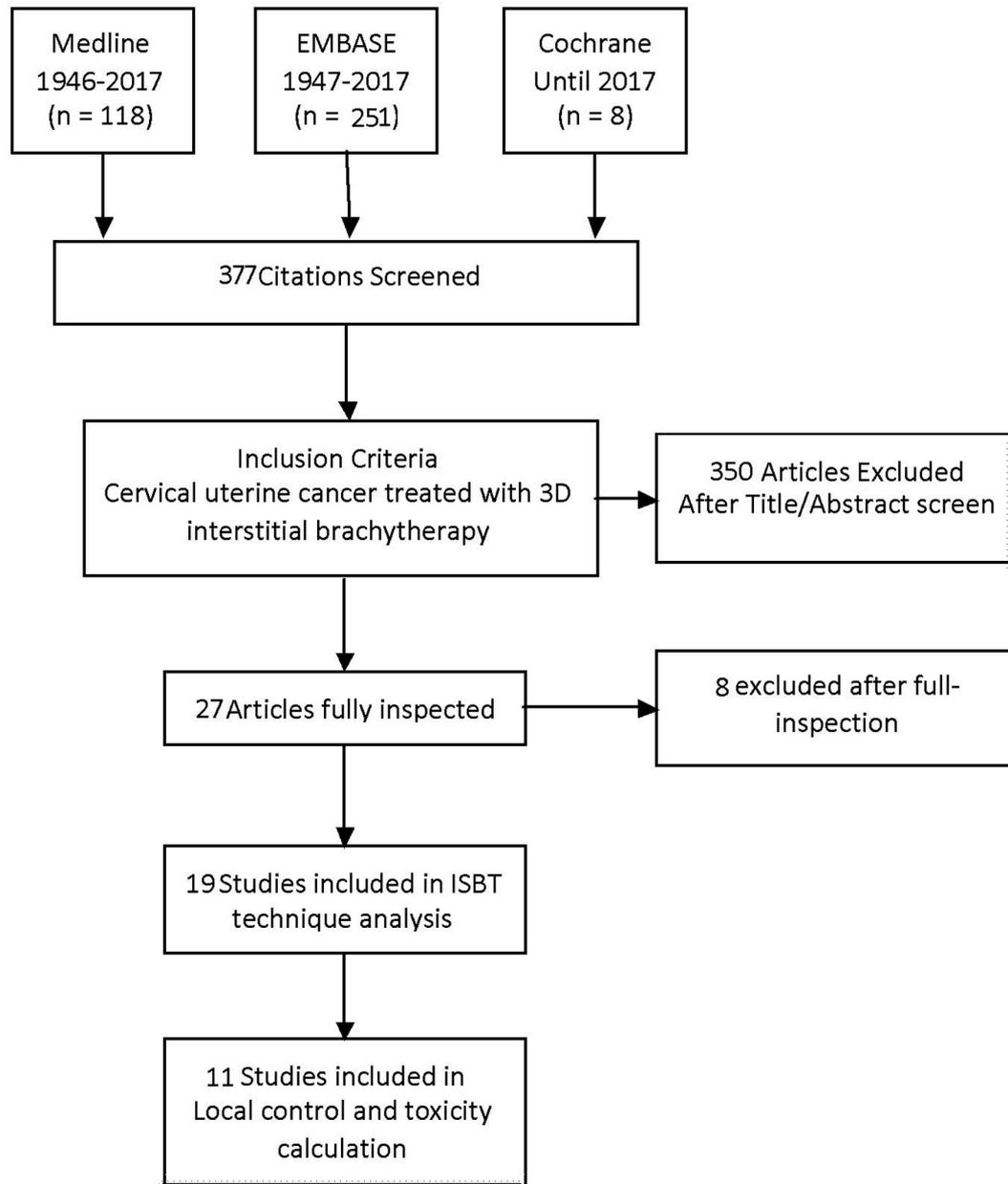
Fig. 1. Flow chart.

one study used HDR sources in treatment and two studies had patients also receiving LDR brachytherapy. Eisbruch et al. used low or intermediate dose rate brachytherapy only. Treatment was delivered in 2–8 fractions with EQD_{2Gy} ranging between 28 and 48 Gy.

Local control and toxicity outcomes

For calculation of the oncological outcomes, eight publications were excluded (Shah et al., 2010, Thibault et al., 2012, D'Souza et al., 2014, Dyk et al., 2015, Amsbaugh et al., 2016, Aridgides et al., 2016, Bailleux et al., 2016 and Fallon, 2017) due to lack of separately reported 3D planned cervical cancer endpoints. The range of median follow-up time for the remaining eight publications (392 patients in total) varied from 14 to 55 months, but almost half of this population (47.7%) had a median follow-up ≥35 months. All patients received EBRT (typically 45 to 50.4 Gy)

as a first phase of treatment and 264 of 339 patients (77.8%) that had chemotherapy information available received concomitant chemotherapy with EBRT. Overall long-term LC was reported in 310 out of 392 patients (79%) treated with P-ISBT. The range of LC was 62–93% among series. Although 29.5% of the included patients are from the Pinn-Bingham et al. study, this publication had a LC of 85%, which lies between the ranges found in the studies (Table 2). A subset analysis of local control in patients with median follow-up ≥35 months was calculated and found to be 82.8% (155 out 187 patients).

A strong correlation (Spearman's rho: 0.714) was found between delivered EQD_{2Gy} and LC (Fig. 2), with patients receiving EQD_{2Gy} ≥76 Gy having LC of 84% and <76 Gy of 67%. Four studies (Isohashi et al., Sharma et al., Yoshida et al. and Murakami et al.) were excluded from this correlation analysis since part of the EBRT dose was delivered with centre field blocks in place, complicating the calculation for the total tumour dose.

Table 1
Studies' characteristics and P-ISBT technique.

Studies (First author and published year)	Study design	Range of age	Number of patients	EBRT dose	Template type	Dose rate	Catheters material	Number of catheters (median)	Implant guidance	Target	Planning image (s)
Eisbruch et al. (1998)	Retrospective	33–71	11	40-45 Gy	NR	L-IDR	Plastic	19	Surgical	GTV	CT
Isohashi et al. (2009)	Retrospective	35–77	25	30 Gy + 20 Gy centre shield	MUPIT	HDR	Plastic	NR	Ultrasound	CTV	CT
Shah et al. (2010)	Retrospective	NR	20	32.4–55.8 Gy	Syed-Neblett	L-HDR	Plastic	21	Fluoroscopy	PTV	CT
Sharma et al. (2011)	Prospective	26–67	42	40 Gy + 10 Gy centre shield	MUPIT	HDR	Metallic	10	Ultrasound	NR	CT
Kannan et al. (2012)	Retrospective	37–80	47	45 Gy	Syed-Neblett	HDR	Metallic	24	Ultrasound	CTV	CT
Wang et al. (2012)	Prospective	27–61	20	50 Gy	Free-hand	HDR	Plastic	5	CT	HRCTV	CT
Thibault et al. (2012)	Retrospective	30–82	12	45 Gy	Syed-Neblett	HDR	NR	17	US or fluoroscopy	HRCTV	CT and MRI
Lee et al. (2013)	Retrospective	27–89	17	45 Gy	Syed-Neblett	HDR	Plastic	12	CT	HRCTV	CT
Pinn-Bingham et al. (2013)	Retrospective	20–89	116	50.4 Gy	Syed-Neblett	HDR	NR	22	No guidance	NR	CT
Viswanathan et al. (2013)	Prospective	31–88	6	50.4 Gy	Syed-Neblett	L-HDR	Plastic	NR	MRI	HRCTV	CT and MRI
D'Souza et al. (2014)	Retrospective	NR	7	45 Gy	Custom	HDR	Metallic	12	Surgical or none	CTV	CT
Yoshida et al. (2015)	Retrospective	37–83	29	30 Gy + 20 Gy centre shield	Custom	HDR	Plastic	14	Ultrasound	HRCTV	CT and MRI
Dyk et al. (2015)	Retrospective	40–94	2	50.4 Gy	Custom	HDR	Plastic	NR	No guidance	NR	CT
Amsbaugh et al. (2016)	Retrospective	NR	36	45 Gy	Syed-Neblett	L-HDR	Plastic or Metallic	10	Fluorocopy	HRCTV	CT
Villalba et al. (2016)	Retrospective	33–79	59	50 Gy	MUPIT or Benidorm	HDR	Metallic	17	Not reported	HRCTV	CT and MRI
Murakami et al. (2016)	Retrospective	42–82	20	40 Gy + 10 Gy centre shield	Syed-Neblett	HDR	NR	18	Ultrasound	CTV	CT
Aridgides et al. (2016)	Retrospective	NR	11	45 Gy	Syed-Neblett	L-HDR	NR	15	Fluorocopy or surgical	CTV	CT and MRI
Bailleux et al. (2016)	Retrospective	27–79	33	46 Gy	Custom	HDR	Plastic	NR	Not reported	HRCTV	CT and MRI
Fallon et al. (2017)	Retrospective	22–92	159	36 Gy + 14 Gy centre shield	Syed-Neblett	HDR	Plastic	24	US and fluoroscopy	"Brachytherapy" CTV	CT

US – Ultrasound.

Late toxicity was obtained from 386 out of 392 patients, since the publication from Viswanathan et al. did not provide enough information to calculate this endpoint. Only Grade 3 and 4 gastro-intestinal (GI), genitourinary (GU) and vaginal late toxicity was calculated. Forty-seven events (12.1%) were found: three-quarters of these related to GI toxicity (G3 30; G4 5), ten with GU toxicity (G3 6; G4 4) and 2 with vaginal toxicity (one necrosis and other complete obliteration) (Table 2).

Discussion

With the advent of three-dimensional image-based treatment planning, there is a renewed interest in using interstitial techniques combined with intracavitary applicators (IC) for the treatment of locally-advanced cervical cancer. Interstitial needles can increase the conformality of the delivered brachytherapy dose thereby allowing safe dose escalation and improvement in the therapeutic ratio [6]. Combined intracavitary/Interstitial (IC/IS) applicators (eg 'Vienna' or 'Utrecht') [31,32] are becoming a standard approach due to their similarity to traditional IC applicators, making the transition to interstitial brachytherapy more natural. However, it has not been directly addressed whether perineal-based interstitial brachytherapy can confer the same advantages as IC/IS while achieving reasonable toxicity rates.

Three-dimensional image-based planning in cervical cancer brachytherapy has transformed perineal ISBT into a more systematic and safe approach. Perineal ISBT has already been widely well-established and may be effective at controlling bulky advanced tumours given the multiple needle positions. Furthermore, cancers with significant vaginal involvement may benefit from the perineal template approach by placing needles into the vaginal portion of the tumour. In fact, newer models of commercially available IC/IS applicators have incorporated a perineal template into the system for reasons such as these.

Table 2
Local control and toxicity.

Studies (First author and published year)	Number of patients	Median follow up time (m)	Stage	Total EQD$_{2Gy}$	Local Control (%)	Late toxicity G3-4		
						GI	GU	Vagina
Eisbruch et al. (1998)	11	42	1 IIB; 9 IIIB; 1 IVA	68 to 73 Gy	7 (64%)	0	0	0
Isohashi et al. (2009)	25	55	1 IB2; 1 IIA; 3 IIB; 1 IIIA; 16 IIIB; 3 IVA	Not possible to calculate	17 (68%)	1	0	1
Sharma et al. (2011)	42	23	10 IIB; 27 IIIB; 5 IVA	Not possible to calculate	26 (62%)	2	2	0
Kannan et al. (2012)	47	14	6 IIB; 2 IIIA; 31 IIIB; 8 IVA	75 Gy	32 (68%)	2	0	0
Wang et al. (2012)	20	17	11 IIB; 9 IIIB	87 Gy	18 (90%)	1	0	0
Lee et al. (2013)	17	17	Not reported	77 Gy	15 (88%)	2	0	0
Pinn-Bingham et al. (2013)	116	35	6 IB1, 4 IB2, 48 IIB, 7 IIIA, 44 IIIB, 7 IVA	98 Gy	99 (85%)	11	7	1
Viswanathan et al. (2013)	6	45	1 IIB; 3 IIIB; 1 IVA; 1 IVB	85 Gy	5 (83%)	NR	NR	NR
Yoshida et al. (2015)	29	48	2 IIB; 1 IIIA; 18 IIIB; 5 IVA; 3 IVB	Not possible to calculate	27 (93%)	2	0	0
Villalba et al. (2016)	59	25	1 IIA; 27 IIB; 3 IIIA; 14 IIIB; 11 IVA; 3 IVB	78 Gy	46 (78%)[*]	13	1	0
Murakami et al. (2016)	20	32	2 IIIA; 10 IIB; 1 IVA; 7 IVB	Not possible to calculate	18 (90%)	1	0	0

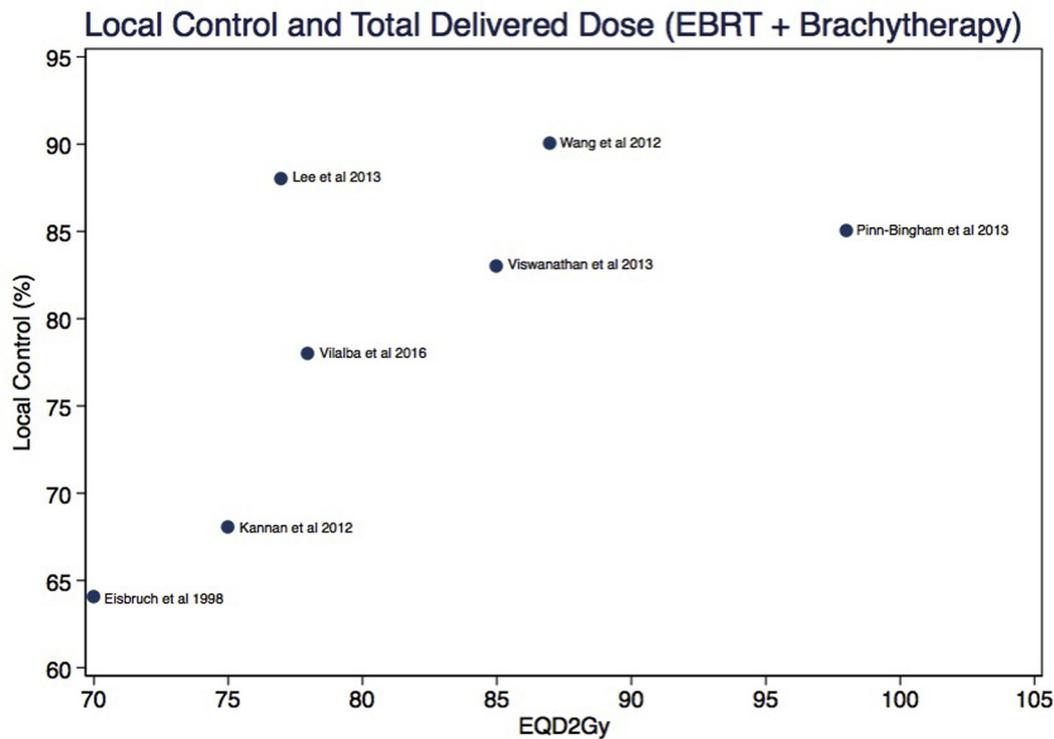[*] Local control reported in a 12 months follow up.

Fig. 2. Scatterplot. Total calculated EQD$_{2Gy}$ (EBRT + P-ISBT) plotted against local control in different published series. *Note:* Four publications with mid-line shielding were not included due to uncertainty of dose delivered to the tumour.

Historical series evaluating locally-advanced cervical cancers treated with chemoradiotherapy and 2D brachytherapy have reported a local control of approximately 64% [5]. We found through this systematic review that perineal ISBT resulted in a LC of 79% with a median follow-up range from 14 to 55 months. LC seemed to correlate with the prescribed dose (Fig. 2), similar to finding in other studies on intracavitary/interstitial radiation [7].

Also, in this review, 60% had stage IIIB disease or higher and only one-third had IB (4%) or IIB (28%) cancers. A selection bias may exist since more advanced and radio-resistant cases are often chosen for P-ISBT. In the recent retroEMBRACE study, only 19% of patients had stage IIIB tumours while 96% of all patients were treated with IC/IS applicators [4,6].

This favourable effect of P-ISBT on cervical cancer local control seems to be consistent with the recently published large series by Fallon et al. [11]. This study reported on 315 locally advanced cervical cancer patients treated with P-ISBT. Over half of the patients (51%) had 3D-CT planning and the overall local control (2D and 3D) was found to be 87% at 10 years. The 2D and 3D outcomes were not separated in the presented manuscript and therefore could not be included in our 3D local control calculation. However, this comprehensive series with long-term follow-up supports the findings that P-ISBT is a safe and effective treatment.

In the era of 2D image-based planning, concerns regarding perineal interstitial brachytherapy were related to the potential toxicities of the sharp needles and high-doses of radiation delivered

to adjacent organs. Previous 2D perineal ISBT studies have indeed shown variable toxicity rates. For instance, the seminal publication by Demanes and colleagues [33] have reported 6.5% of grade 3/4 late morbidities using the 2D technique, while other series [34,35] have found higher rates ($\cong$21%) of toxicities. Based on the results from this review, and from those of previous IC/IS brachytherapy publications, P-ISBT toxicity rates seem to be more consistent and acceptable using a 3D technique for planning. This is likely related in part to the ability of restricting loading patterns of needle dwell positions that are in close proximity (or within) organs-at-risk [14]. Overall toxicities and complications found in this systematic review are low and no grade 5 toxicity was seen. Perineal infection (7 patients) and haematuria requiring bladder irrigation (7 patients) were the most common complications. Late toxicity rates experienced by these patients are consistent with current IC/IS literature [4,6] with around 12% of the patients presenting a G3 and 4 late toxicity- 9% GI and 2.5% GU adverse reactions.

The studies analysed by this review were published over a period of 19 years (1998 to 2017) with an observed heterogeneity of 3D-image-based perineal ISBT planning protocols. Eight publications followed GEC-ESTRO recommendations [36] and prescribed treatment to an HRCTV and three others studies did not specify their target volume. While more recent publications evaluated by this review used MRI to aid in volume target contouring, the majority of the studies based their treatment on CT imaging. In these cases, tumour volumes can often be over-contoured [37]. It is likely for this reason that most of the studies included in this review prescribed total EQD$_{2Gy}$ doses lower than the current recommendation of 85 Gy as seen with MRI-based planning techniques [36]. When using CT-based planning exclusively in P-ISBT, the target volume may be poorly-defined and lower doses should be considered to minimize complication risks.

Limitations of this systematic review are related to the heterogeneity and small sample size of the studies identified. Since most of the studies are retrospective single institution reviews, toxicities were captured retrospectively and may have been underestimated. Furthermore, there was no common time-point identified among the evaluated publications for data analysis. Therefore, the LC data could not be calculated with a defined time period. As most studies reported local control as their primary endpoint, it was not possible to calculate overall and cancer-specific survivals among all the manuscripts given the lack homogeneity in the data. One study that did report on survival was Fallon et al. that showed that cause specific survival for all patients (2D and 3D planned) was 56% at 10 years.

Conclusion

There is growing interest in the use of interstitial brachytherapy for cervical cancer and the perineal template approach seems to be effective for large locally-advanced tumours. A promising local control of roughly 80% was found with the use of perineal ISBT among patients with advanced stage disease. Local control seems to correlate with higher prescribed doses in the reviewed studies. With 3D image-based planning, procedural complications from this technique are low and toxicity rates with perineal ISBT are similar to other IGBT series. Perineal ISBT may be a reasonable and safe alternative to the more standard IC/IS approach for bulky cervical tumours that would benefit from interstitial needles.

Conflict of interest statement

All authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.03.005.

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