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Systematic review

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

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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.

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].

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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/MEDLINE), 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