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Review Article

Clinical factors affecting the therapeutic dose window in cervical cancer brachytherapy: A systematic review and meta-regression

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ABSTRACT

BACKGROUND AND PURPOSE: Although dose planning aims in cervical cancer brachytherapy are well-defined, variability in clinical practices makes it difficult to draw generalizable conclusions on achievable dosimetry. This review and meta-regression aim to assess clinical practices in terms of their therapeutic dose window, that is, the balance between target and organs-at-risk (OAR) doses.

MATERIALS AND METHODS: A search of the literature was performed in Scopus, PubMed, and Web of Science databases. Peer-reviewed articles were included that described planning constraints and reported high-risk clinical target volume (CTV_{HR}) $D_{90\%}$ and OAR D_{2cm^3} for intracavitary (IC) tandem and ring (T&R) / tandem and ovoid (T&O) / mold (M) applicators, possibly supplemented with interstitial (IS) needles (+N). To determine factors associated with target volume coverage ($D_{90\%}$) and OAR sparing (D_{2cm^3}), multivariate meta-regressions were performed.

RESULTS: Out of 1590 articles, 34 met the full inclusion criteria. In most studies, the CTV_{HR} $D_{90\%}$ aimed at ≥84–86 Gy $EQD2_{\alpha/\beta=10Gy}$, and constraints for the OARs were 80–90 Gy, 65–75 Gy and 70–75 Gy $EQD2_{\alpha/\beta=3Gy}$ for the bladder, rectum and sigmoid D_{2cm^3}, respectively. Studies using IC/IS applicators were associated with a ~4 Gy increase in CTV_{HR} $D_{90\%}$ compared to IC only, with no effect on OAR dose. T&R studies achieved improvements of 3.2 Gy and 2.8–3.4 Gy at typical planning aims in comparison with T&O applicators in target and OAR doses. In 100% (15/15) of patient groups treated with T&R + N both CTV_{HR} and OAR objectives were met for the population average. For T&R, T&O, and T&O + N groups, this was the case in 89% (8/9), 43% (6/14), and 50% (4/8), respectively.

CONCLUSION: Studies using interstitial needles with T&R applicators in MR-guided brachytherapy for cervical cancer seem to be associated with a favorable therapeutic target dose/OAR sparing ratio.

Keywords: Locally advanced cervical cancer; Image-guided adaptive brachytherapy; Therapeutic dose window; Applicator use

Introduction

Cervical cancer is the fourth most common cancer in women, with 604,000 new cases and 342,000 deaths in 2020 (1). The current standard treatment with curative intent for locally advanced cervical cancer consists of external beam radiotherapy (EBRT) and concurrent chemotherapy, followed by image-guided adaptive brachytherapy (IGABT) (2,3). For IGABT, the main treatment objective is to achieve a dose distribution that balances high doses in the target volumes with maximal sparing of the organs

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at risk (OARs) (4), which is referred to as the therapeutic dose window in this work. The high-risk clinical target volume (CTV_{HR}) $D_{90\%}$ and OAR D_{2cm^3} are the most commonly used metrics for planning and reporting, and can be used to define that window. Different recommendations exist for combined EBRT and BT CTV_{HR} $D_{90\%}$ lower-bound constraints or aims, but they generally specify ≥80–90 Gy $EQD2_{\alpha/\beta=10Gy}$ (5,6). Planning aims and constraints for the D_{2cm^3} of the bladder, rectum, and sigmoid and bowel of ≤80–90, ≤65–75, and ≤70–75 Gy $EQD2_{\alpha/\beta=3Gy}$ respectively have been formulated (5,6). The introduction of MRI-based IGABT and more frequent use of combined intracavitary and interstitial (IC/IS) applications have enhanced the ability to meet these planning aims (7). This is accompanied by improvements in local tumor control and toxicity reductions over recent years (6,8). Nevertheless, even in controlled studies, compliance to planning constraints may differ per center (9,10), and mono-institutional practices vary (9,11). An overview of clinical practices in dose prescription and ability to meet planning constraints is lacking.

Applicator geometry is an important factor for the dose distribution that can be achieved (12). The most frequently used applicators for irradiating cervical cancer are tandem/ovoid (further denoted by T&O) and tandem/ring (T&R) (11,13), both of which can be supplemented with IS needles (+N) guided by IC parts or templates. Several groups have worked on patient-tailored applicators, including the vaginal mold (M) concept (14), and 3D-printed applicators (15), aiming to further conform the dose distribution to target volumes. The choice between applicator types and use of IS needles depends on numerous factors. Described advantages for T&R over T&O include the ability to better fix the geometry (16,17), to fit in patients with shallow vaginal fornices (4), and to position the source along its circumference allowing for better anterior-posterior dose control (12). T&O applicators generally maintain a larger spacing between the mucosa and source channel (18), resulting in a less steep dose gradient at the same depth from the applicator's surface compared to T&R applicators (12). Split-ring (T&SR) applicators have been introduced to aid insertion. Mold applicators are in particular useful when the target region extends inferiorly (19). The use of supplementary IS needles has been recommended in large tumors with unfavorable (asymmetric) anatomical extension, such as parametrial or vaginal extension or close proximity of OARs (12,20). An overview of IS needle implantation practices has been published previously (21). In general, however, the choice of applicator type or application technique may be motivated by institutional practice, physician's preference, and resource availability. For example, it has been reported that the majority of centers are using either T&R or T&O (12,13).

Several studies have compared the dose differences between applicator types, or IC and IC/IS techniques. In particular, differences in dose-volume histogram parameters for T&R or T&O EMBRACE centers have been evaluated (12), and also for IC or IC/IS applications (12,20). While these studies correct for differences in patient characteristics and implant quality, the centers differed in their dose prescription, planning practices, and experience levels. Some studies have prospectively compared applicator types in the same group of patients (22–24), but sample sizes have been limited. In addition, models have been made to predict the dose for a specific applicator type (25), or whether or where supplemental IS needles are required (26,27). Although these models have shown great potential, they can also be subject to confounding (institutional) factors in the training data (25). Translatability of these results to other centers should therefore be investigated (28). Lastly, reviews, meta-analyses or literature-based models have been published on the effectiveness of 3D image-guided BT versus 2D BT (29,30), or IC versus IC/IS BT (21,31). However, these have focused on evaluating treatment outcome, rather than dosimetric indices.

The objective of this systematic review and meta-regression is to assess the therapeutic dose window in terms of CTV_{HR} $D_{90\%}$ and OARs D_{2cm^3} in clinical practice, and to evaluate the impact of various clinical factors, including applicator type (T&R, T&O, or mold), application technique (IC or IC/IS), dose prescription (planning aims), and patient anatomy (FIGO and CTV_{HR} volume). As no randomized controlled trial has investigated this topic, this review concerns observational studies only. Moreover, we provide an overview of IS needle usage in clinical practice, including insertion technique (applicator-, template-, or free-hand based), number and depth of needles, use of image guidance, implantation patterns, and dose contribution (i.e., relative needle loading). This study therefore illustrates gains in the ratio of dose to the target and OAR, with different clinical practices, particularly to be balanced with complexity and potential costs.

Methodology

Search strategy

A comprehensive search of the literature was performed in Scopus, PubMed, and Web of Science. The search query was composed of synonyms/MeSH terms related to the key concepts that were searched in title/abstract: "brachytherapy," "cervical cancer," "D90 of HR-CTV," "D2cm3 of OARs," and "applicator" (see supplementary Table S.1). The search strategy was refined based on a candidate set of papers obtained in previous reviews (21,32). Backward snowballing was used to obtain other relevant articles through screening the reference lists. The search was limited to articles from 2005, the year of introduction of target volume concepts (33), and performed on April 26, 2024. The PRISMA diagram in Fig. 1 shows the article screening process.

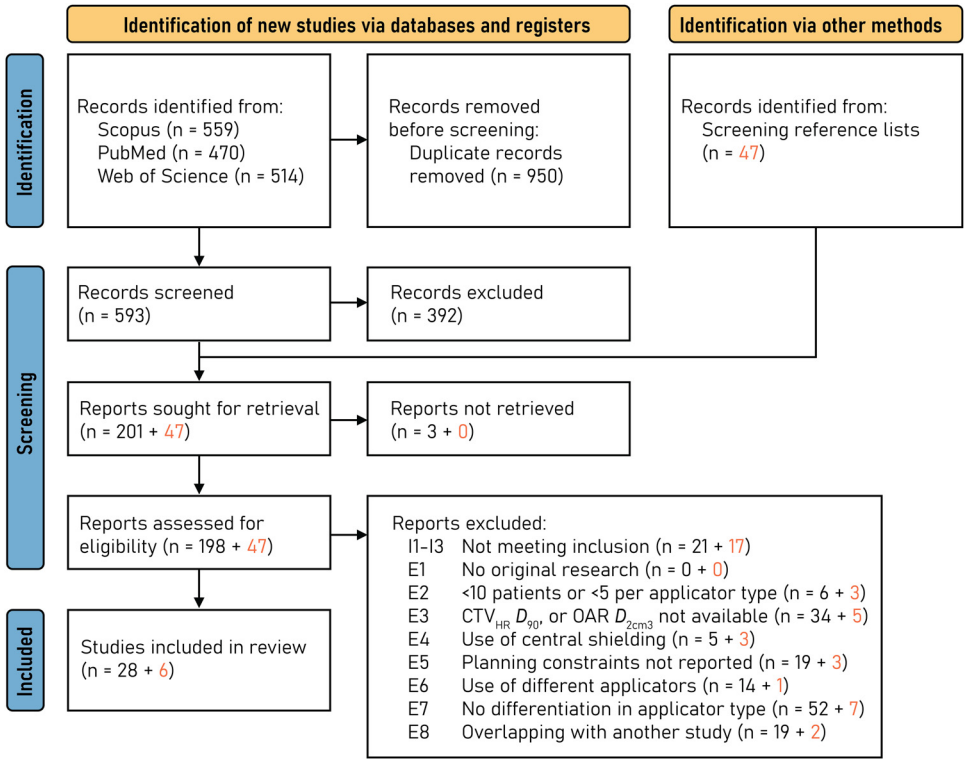

Fig. 1. PRISMA flowchart of the article selection and inclusion process in this systematic review.

Eligibility criteria

We included studies that met the following criteria: (1) original articles on HDR or PDR-BT for cervical cancer that report CTV_{HR} $D_{90\%}$ and OAR D_{2cm^3} and IC T&R/T&SR/T&O/mold applicator use (+IS needles) in clinical practice, (2) full-text articles published in peer-reviewed journal, and (3) articles in English and available online. Exclusion criteria were: (1) no original research (review articles, guidelines, etc.), (2) less than 10 patients treated overall or 5 per applicator type, (3) total treatment CTV_{HR} $D_{90\%}$, or bladder or rectum D_{2cm^3} not reported or not calculable, (4) the use of central shielding in EBRT, (5) planning constraints not reported or no prescription to CTV_{HR}, (6) use of different applicators (e.g., tandem/IS needles, or tandem/cylinder) or type unknown, (7) no differentiation in results per applicator type (e.g., studies where more than 20% of patients are treated with different applicator types without stratification), and (8) overlapping data with another study that is included. Papers were first screened based on title and abstracts, and if found to be eligible, the full text was assessed. To determine feasibility of the eligibility criteria, 50 sample papers were screened by two of the authors (RS and LP). This resulted in 92% agreement, after which interpretation of eligibility criteria was further discussed and refined. The remaining set of papers was divided by the two authors (RS and LP). Any doubts were discussed and solved by consensus.

Risk of bias

As only observational studies were included, the risk of bias was assessed using a modified version of the Joanna Briggs Institute critical appraisal tool for case series (34). The bias assessment was performed by one author (RS).

Data extraction and analysis

For all included articles, a prespecified data extraction sheet was completed. Per article, data were extracted on author(s) of the article, years of patient inclusions, number of patients, treatment center (including whether this has been part of EMBRACE I or II studies), patient characteristics (age, International Federation of Gynecology and Obstetrics (FIGO) stage, CTV_{HR} volume at BT), radiotherapy treatment characteristics (EBRT dose, fractionation schedule, applicator type used for BT, percentage of IS use, imaging technique used for treatment planning, planning constraints, and optimization method), and dosimetric indices ($D_{90\%}$ and D_{2cm^3}). Some assumptions and derivations were required to extract data. Whenever possible, data were extracted for the entire patient population rather than the subgroups. In case multiple dose optimization approaches were described, the results for graphical optimization were extracted (22). No distinction was made between reported FIGO 2009 and 2018 stages. Studies were classified based on the applicator type predominantly used. T&SR applicators were considered to be T&R applica-

tors. If IS needles were used in more than 20% of the cases, studies were classified as IC / IS studies (12,20). The percentage of IC/IS use a study was determined based on all patients who received at least one IC/IS application if this data was available, opposed to the number of IC/IS applications. Most studies described planning constraints without specifying whether these were interpreted as hard (planning limits) or soft constraints (goal values). In case this distinction was made, that is, in accordance with the EMBRACE II study, the extracted planning constraints referred to the hard constraints. In case the total CTV_{HR} $D_{90\%}$ aim was not directly described, it was calculated from the prescribed dose per fraction or the dose constraint per fraction.

Most articles reported total dose (EBRT + BT), while some reported dose per fraction (22,24,35,36). In the latter case, the total dose was calculated by summing the prescribed, uniform EBRT dose with the reported BT dosimetric indices, considering an equal dose per fraction, in accordance with the EQD2 formalism (assuming $\alpha/\beta = 10$ Gy for the CTV_{HR}, and $\alpha/\beta = 3$ Gy for OARs without half-time repair). All studies that used PDR reported the total dose in EQD2 with the linear quadratic model and used a repair halftime $T_{1/2} = 1.5$ h. Doses were usually reported as mean or median, which were considered equivalent for simplicity (37). Variations were reported as standard deviations (SD), interquartile ranges (IQR) or ranges. For the meta-regression, SDs were estimated from IQRs based on assuming normality such that $SD = \frac{q_3 - q_1}{1.35}$ (38), and from ranges based on rules by Hozo et al. (37). In order to compare studies with different planning constraints or trade-offs, $D_{90\%}$ and D_{2cm^3} indices were computed based on previously described normalized least coverage and least sparing indices (LCI and LSI) (39):

$$I^o_{D_{90\%}} = \frac{D^{CTV_{HR},\, o}_{90\%} - D^{CTV_{HR},\, constraint}_{90\%}}{D^{CTV_{HR},\, constraint}_{90\%}} \quad (1)$$

$$I^o_{D_{2cm^3}} = \min\left(\frac{D^{organ,\, constraint}_{2cm^3} - D^{organ,\, o}_{2cm^3}}{D^{organ,\, constraint}_{2cm^3}}\right)_{organ \in \{bladder,\, rectum,\, sigmoid\}} \quad (2)$$

In case $I^o_{D_{90\%}} \geq 0$, the target planning constraint for the oth study is met. When the $I^o_{D_{2cm^3}} \leq 0$, at least one of the dose constraints for the OARs is exceeded. By plotting these indices against each other, studies ending up in the top-right quadrant ("golden corner") had desirable dose plans.

To determine factors associated with target coverage and OAR sparing, multivariate random-effects meta-regression was performed with covariates based on univariate analyses to reduce the risk of potential overfitting. The complementary index, for example $I_{D_{2cm^3}}$ for the $I_{D_{90\%}}$ model, was always included to control for different planning practices. Missing values for FIGO and volume were imputed using the means calculated within each corresponding IC/IS group. The amount of heterogeneity that the covariates account for, R^2, was calculated. Model validity was furthermore checked by examining residual plots. Possible publication bias or outliers in the meta-regression were examined through funnel plots and by using Egger's tests. Two data points were identified as outliers and removed from the regression model for the $I_{D_{90\%}}$ index: the T&R results from Gursel et al. (23), and the T&O results from Jamadagni et al. (35). The T&O results from Chakrabarti et al. were considered an outlier for the $I_{D_{2cm^3}}$ model, and therefore removed (22). As there was only one study included describing a mold applicator (40), this was not considered in the meta-analyses. Calculations and analyses were performed using Matlab (R2021b, Mathworks, Natick, MA, USA), and the meta-analysis package Metafor in RStudio (2024.12.0, PBC, Boston, MA, USA).

Results

Eligibility and risk of bias

In total, 1543 records were identified in the database search and an additional 47 by screening the reference lists of included studies. Of these records, 34 original articles fulfilled all eligibility criteria (Fig. 1), with study details, patient characteristics, radiotherapy treatment characteristics, and dosimetric indices shown in Table S.2 in the Supplementary Material. The risk of bias assessment is given in Table S.3. Several studies could be subject to selection bias due to unclear or incomplete inclusion. Some studies did not report important patient characteristics such as CTV_{HR} volume at BT (6/34), or tumor staging (2/34). Lastly, statistical analyses often did not account for multiple testing, possibly leading to type I errors. Visual assessment of funnel plots did not reveal clear indications of publication bias, and therefore all articles were kept for analysis.

Institutional practices

Studies were conducted in 29 centers. The majority of centers in this analysis used HDR (24/29), opposed to PDR (5/29). Most common HDR fractionation schemes were 4×7 Gy (used in 13/29 centers), 3×7Gy (6/29), 5×6 Gy (4/29), and 3×8–9 Gy (4/29). In PDR, reported schemes were single application with 30–70 hourly pulses, and two applications of 15–30 hourly pulses. Physical EBRT doses to the pelvis ranged between 45 and 50.4 Gy for the majority of studies (e.g., 25 fractions of 1.8–2.0 Gy or 28 fractions of 1.8 Gy). Combined with EBRT, the total planning constraint was typically reaching at least a CTV_{HR} $D_{90\%}$ of 85 (23/34 studies), 80 (6/34), 84 (4/34), or 86 (3/34) Gy $EQD2_{\alpha/\beta=10Gy}$. Lower CTV_{HR} $D_{90\%}$ doses were prescribed in studies with earlier enrolment periods (41–43), in studies where lower doses were argued to be sufficient for patients with lower stage, less advanced, or well-responding disease (42), or due to limitations of CT-based planning (23,35).

Constraints for bladder, rectum, and sigmoid D_{2cm^3} were most frequently 90 Gy, 75 Gy, and 75 Gy $EQD2_{\alpha/\beta=3Gy}$, respectively, which are in line with ABS and EMBRACE II limits. Several studies with escalated CTV_{HR} $D_{90\%}$ (≥85 Gy) were still able to constrain bladder D_{2cm^3} doses to below 80–85 Gy $EQD2_{\alpha/\beta=3Gy}$. This was achieved in particular using IC/IS applicators, allowing the EMBRACE II soft planning aims to be met in the majority of patients (44–47). Similarly, rectal D_{2cm^3} and sigmoidal D_{2cm^3} dose constraints could in these studies be lowered to ≤65–70, and ≤70 Gy $EQD2_{\alpha/\beta=3Gy}$, respectively.

Based on the 34 studies, 47 groups were stratified by the type of applicator and brachytherapy technique used. Of the groups, 14 were classified as T&O (617 patients), nine as T&R (298 patients), eight as T&O + N (308 patients), 15 as T&R + N (1010 patients), and one as vaginal mold (225 patients). The reviewed studies predominantly used MR imaging (16/34 studies), CT imaging (11/34), or a combination of MR/CT (8/34) for BT planning. All EMBRACE centers used MR imaging for at least one fraction. CT contouring of the CTV_{HR} was often guided by CTV_{HR} contours derived from an MRI preceding BT (23,24,35,36,48–50), for example through rigid registration. TRUS can also be used to aid CTV_{HR} segmentation (51). Hybrid imaging was mentioned to be used when access to MRI for BT planning was limited, using MR only for the first fraction (52–55), MR preceding first and second fraction (56), or alternating MR and CT imaging per application (57,58). Some studies investigated single application treatments (53,56), which could be particularly attractive in resource-constrained settings or to limit the total treatment time. Four of the studies described the use of inverse treatment planning (24,45,48,50), with all other studies only using forward/manual dwell time optimization.

Analysis of therapeutic dose window

Results from univariate and multivariate regression analyses are shown in Table 1, and pooled and predicted estimates by the multivariate model are shown in Fig. S.1. Target coverage indices ($I_{D_{90\%}}$) were significantly higher according to the multivariate analysis in groups treated with T&R applicators (compared to T&O), and in groups in which interstitial needles were used (compared to IC only). For a planning dose of 85 Gy $EQD2_{\alpha/\beta=10Gy}$, reported values correspond to a mean increase of 3.2 Gy (95% CI 1.5–5.0 Gy), and 3.8 Gy (95% CI 1.8–5.9 Gy), respectively. No interaction effect between applicator type and IS needle use was observed. Although univariate regression indicated higher target coverage in centers using at least one fraction of MR in BT planning over centers using CT, this was not found to be significant in the multivariate analysis. Higher proportion of FIGO III-IV stage and larger CTV_{HR} volumes in patient cohorts were associated with decreasing target coverage (Fig 2a–c). At a planning constraint of 85 Gy, this amounted to –0.06 Gy per % increase in FIGO III-IV stage (median: 40%; IQR: 24–64%), and –0.09 Gy per cm^3 increase in CTV_{HR} volume (36 cm^3; 31–44 cm^3). Despite normalization of the target dose with the planning constraint, between-study heterogeneity was high, and the resulting multivariate model was able to explain 59% of the variance.

T&R groups were associated with higher OAR sparing indices ($I_{D_{2cm^3}}$) than T&O groups, which for planning constraints of 75 and 90 Gy $EQD2_{\alpha/\beta=3Gy}$ corresponded to mean decreases of 2.8 Gy (95% CI 0.5–4.2 Gy), and 3.4 Gy (95% CI 0.7–5.0 Gy) respectively (Fig. 3). However, for increasing CTV_{HR} volume this OAR sparing effect reduced with approximately 0.2 Gy/cm^3 in T&R groups specifically, to a level equivalent with that in T&O groups in higher volumes. Groups in which MRI was routinely used also had higher OAR sparing, equivalent to 3.6 and 4.4 Gy at doses of 75 and 90 Gy. Univariate analysis associated EMBRACE centers with more OAR sparing in comparison with non-EMBRACE centers, but this was not significant in multivariate analysis.

Figure 4 depicts the OAR sparing indices ($I_{D_{2cm^3}}$) and target coverage indices ($I_{D_{90\%}}$) of the included studies sorted per applicator type. In 100% (15/15) of patient groups treated with the T&R + N applicator the mean indices fell in the "golden corner." This means that both CTV_{HR} and OAR dose objectives were met for the population average. For T&R, T&O, T&O + N, and M groups, this was the case in 89% (8/9), 43% (6/14), and 50% (4/8), 0% (0/1) respectively. In particular, CTV_{HR}, bladder, rectum, and sigmoid constraints were not met for the population average in 19% (9/47; 6 T&O, 2 T&O + N, 1 M), 6% (3/47; 2 T&O, 1 T&R), 4% (2/47; 2 T&O), and 4% (2/47; 2 T&O + N) of the patient groups.

Several included studies directly compared different applicator geometries and techniques. Biltekin et al. (24) compared T&R and T&O applicators in ten patients, and found that rectal D_{2cm^3} was significantly lower for the former, with no differences in other dosimetric indices. For similar CTV_{HR} $D_{90\%}$, significantly lower D_{2cm^3} values for all OARs were obtained in the study by Chakrabarti et al. (22) in graphically optimized plans for a T&R applicator opposed to a T&O applicator. Lastly, in the study by Gursel et al. (23), CTV_{HR} $D_{90\%}$, and bladder and rectum D_{2cm^3} significantly improved in patients when treated with T&R versus T&O applicators. Studies in which IC and IC/IS applicators were directly compared showed dosimetric benefits of the latter, especially for larger CTV_{HR} volumes. In CTV_{HR} volume ≥30 cm^3 groups this amounted to roughly 4–10 Gy EQD2 improvement in total CTV_{HR} $D_{90\%}$ (35,45,48,59,60), with in general no difference in OAR dose. In studies in which historical cohorts were compared, benefits in the same range on target dose were demonstrated due to adoption of IC/IS technique (42,61).

Table 1
Effects of covariates on target coverage ($I_{D_{90\%}}$) and OAR sparing ($I_{D_{2cm^3}}$) indices in univariate and multivariate meta regression analysis

	Target coverage index $I_{D_{90\%}}$					OAR sparing index $I_{D_{2cm^3}}$				
	Univariate		Multivariate *Statistics:* R^2 = 59.4% τ^2 = 0.0007 I^2 = 83.3%		*Effect:* CTV_{HR} $D_{90\%}$ = 85 Gy EQD2	Univariate		Multivariate *Statistics:* R^2 = 35.0% τ^2 = 0.0020 I^2 = 95.5%		*Effect:* OAR D_{2cm^3} = 75/90 Gy EQD2
Covariate (*Reference*)	Est. (SE)	*p*	Est. (SE)	*p*	Est. (Gy, CI)	Est. (SE)	*p*	Est. (SE)	*p*	Est. (Gy, CI)
Intercept	–	–	**0.026** (0.012)	**0.037**	2.2 (0.1–4.3)	–	–	**0.032** (0.012)	**0.011**	-2.4/2.8 -(4.2–0.5) / -(5.0–0.7)
App. *T&R*[1]	**0.050** (0.008)	**0.000**	**0.038** (0.011)	**0.000**	3.2 (1.5–5.0)	**0.040** (0.016)	**0.015**	**0.038** (0.019)	**0.047**	-2.8/3.4 -(5.7–0.0) / -(6.8–0.1)
IC/IS +*N*[2]	**0.040** (0.015)	**0.008**	**0.045** (0.012)	**0.000**	3.8 (1.8–5.9)	-0.004 (0.020)	0.855	–	–	–
Vol. (cm^3)	**-0.001** (0.001)	**0.032**	**-0.001** (0.000)	**0.018**	-0.09 per cm^3 -(0.16–0.01)	-0.001 (0.001)	0.136	-0.004 (0.001)	0.647	–
FIGOIII_IV (%)	**-0.057** (0.029)	**0.048**	**-0.074** (0.026)	**0.004**	-0.06 per % -(0.11–0.02)	-0.057 (0.038)	0.126	–	–	–
$I_{D_{2cm^3}}$ (−) / $I_{D_{90\%}}$ (−)	0.114 (0.079)	0.149	-0.047 (0.064)	0.464	–	0.233 (0.169)	0.169	–	–	–
Imaging *MRI*[3]	**0.031** (0.013)	**0.017**	0.012 (0.012)	0.306	–	**0.053** (0.016)	**0.001**	**0.048** (0.021)	**0.023**	-3.6/4.4 -(6.8–0.5) / -(8.1–0.6)
EMBRACE *Yes*[4]	0.021 (0.013)	0.111	–	–	–	**0.037** (0.017)	**0.029**	0.008 (0.019)	0.680	–
Period (yr)	-0.001 (0.001)	0.443	–	–	–	-0.003 (0.002)	0.072	–	–	–
App:Vol. (cm^3) *T&R*[1]	-0.001 (0.001)	0.564	–	–	–	**-0.003** (0.001)	**0.022**	**-0.003** (0.001)	**0.015**	0.2/0.2 per cm^3 (0.0–0.4) / (0.0–0.5)
IC/IS:Vol. (cm^3) *IC/IS*[2]	0.000 (0.001)	0.959	–	–	–	-0.000 (0.002)	0.797	–	–	–
IC/IS:FIGOIII_IV (%) *IC/IS*[2]	0.031 (0.066)	0.635	–	–	–	-0.145 (0.098)	0.129	–	–	–
IC/IS:App. *IC/IS*[2] + *T&R*[1]	-0.017 (0.025)	0.500	–	–	–	-0.011 (0.038)	0.782	–	–	–

Multivariate analyses were performed using all significant variables from univariate analyses and the complementary index as to balance out planning practices. Effects were quantified based on conventional planning constraints; CTV_{HR} $D_{90\%}$ = 85 Gy $EQD2_{\alpha/\beta=10Gy}$, and OAR D_{2cm^3} = 75 or 90 Gy $EQD2_{\alpha/\beta=3Gy}$.

Bold values indicate statistically significant variables.

Est = estimate; SE = standard error; CI = confidence interval; App = applicator; Vol = CTV_{HR} volume; FIGOIII_IV = proportion of ≥FIGO III patients; EMBRACE = EMBRACE centre.

[1]reference T&O.
[2]reference IC.
[3]reference CT.
[4]reference no EMBRACE.

Clinical implementation of IC/IS

Table 2 shows an overview of all included IC/IS implementations. Although the majority of studies used commercially available IC/IS applicators, several articles described the use of in-house modified (62), or produced applicators (35,42,44,63,64). On average, studies used between 2 and 12 needles, with depths varying between 20 and 50 mm. The number of needles was typically related to the CTV_{HR} volume (45,65). For one in-house produced applicator, needles were used to replace conventional IC channel dwell positions (44). Depth could be determined by the maximum cranial extent of the CTV_{HR} (66), possibly taking into account needle tip to first dwell position distance (dead-space). The use of supplemental free-hand or template-guided needles was not commonly reported amongst the included studies. In the study by Jääskeläinen et al. (45) freehand needles were used next to applicator-guided needles in 20% of the patients. For resource-constrained settings, the insertion of needles transperineally or through

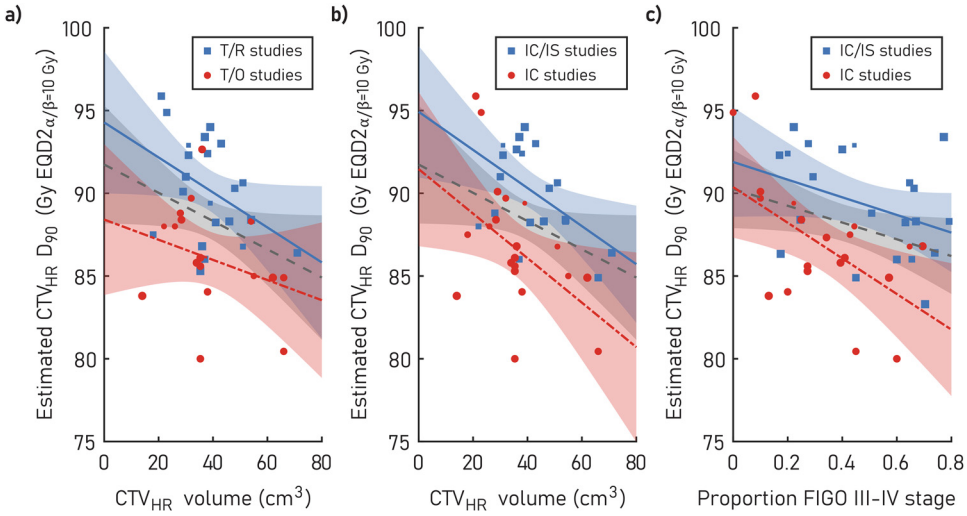

Fig. 2. Weighted regression models showing the relationship between studies estimated CTV_{HR} $D_{90\%}$ and either CTV_{HR} volume or FIGO stage. The estimates are obtained by multiplying and adding the studies' target coverage indices $I^{o}_{D_{90\%}}$ with a dose constraint of 85 Gy $EQD2_{\alpha/\beta=10Gy}$. Relationships are shown for estimated CTV_{HR} $D_{90\%}$ and: (a) mean CTV_{HR} volume for T&R(+N) and T&O(+N) studies, (b) mean CTV_{HR} volume for IC/IS and IC studies, and (c) proportion of patients having FIGO stages III-IV for IC/IS and IC studies. Individual data points denote studies, with marker sizes scaled by the weights used in regression. Solid and dotted lines indicate the linear regression models. Grey lines and areas represent models for the combined dataset. Shaded areas denote the 95% confidence interval.

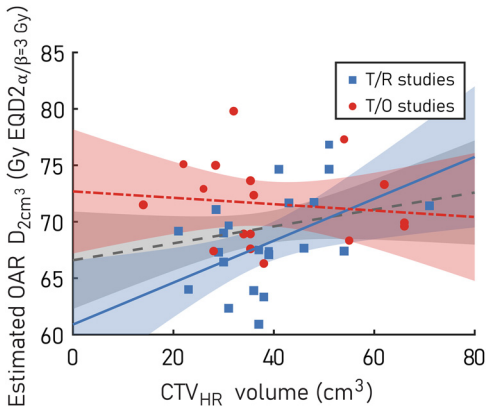

Fig. 3. Weighted regression model showing the relationship between studies' estimated OAR (bladder, rectum, or sigmoid) D_{2cm^3} and CTV_{HR} volume for T&R(+N) and T&O(+N) studies. The OAR estimate is obtained by multiplying and adding the studies' OAR sparing indices $I^{o}_{D_{2cm^3}}$ with a dose constraint of 75 Gy $EQD2_{\alpha/\beta=3Gy}$. Individual data points denote studies, with marker sizes scaled by the weights used in regression. Solid and dotted lines indicate the linear regression models. Grey lines and areas represent models for the combined dataset. Shaded areas denote the 95% confidence interval.

vaginal fornices, alongside conventional IC applicators, has been described (35,59). Several advanced hybrid applicators can guide oblique needles to reach parametrial extensions. In studies specifically describing these advanced applicator cases, 4 oblique needles were used on average (66,67). These needles were in general well-tolerated, but bleeding after removal may be more frequent (66).

Most studies use some form of image guidance to confirm correct applicator and needle placement (44), or facilitate needle selection and positioning (42,47,60,65,66,68). IS needles were most often inserted in laterodorsal sections of the applicator (44,46,47,60,68), which corresponds with common target region extensions to the distal parametria, sacro-uterine ligament, and pelvic wall. Whereas Jamadagni et al. (35) required coverage extension mainly unilaterally, in other cohorts with advanced disease the extensions were primarily bilateral (44,66), and needles were distributed equally on both sides. With regards to needle dose contribution, studies in this review often limited the individual dwell times in needles to a specific ratio (e.g., 10–25%) of a standard loading pattern (51,53,67–70). Average cumulative dwell time contributions of individual needles were 7–11% (60,65), and average total IS dwell time contributions ranging from 7% to 44% of the total dwell time (44,46,59,65). High needle contributions were required in large GTV_{RES} or CTV_{HR} volumes (46,67).

Discussion

The aim of this study was to provide an overview of clinical practices in cervical cancer brachytherapy and to evaluate their impact on achieving target and OAR planning aims, termed the therapeutic dose window. A total of 34 studies (amongst 29 centers) were included in this review. With the introduction of MRI-guided brachytherapy and more advanced hybrid applicators, planning aims that could be achievable have changed considerably. Multivariate analysis showed that the ability to meet the institute's CTV_{HR} $D_{90\%}$ planning objective was influenced by the used applicator type (T&R over T&O), brachytherapy technique (IC/IS over IC only), proportion of FIGO III–IV patients, and CTV_{HR} volume. Centers routinely using

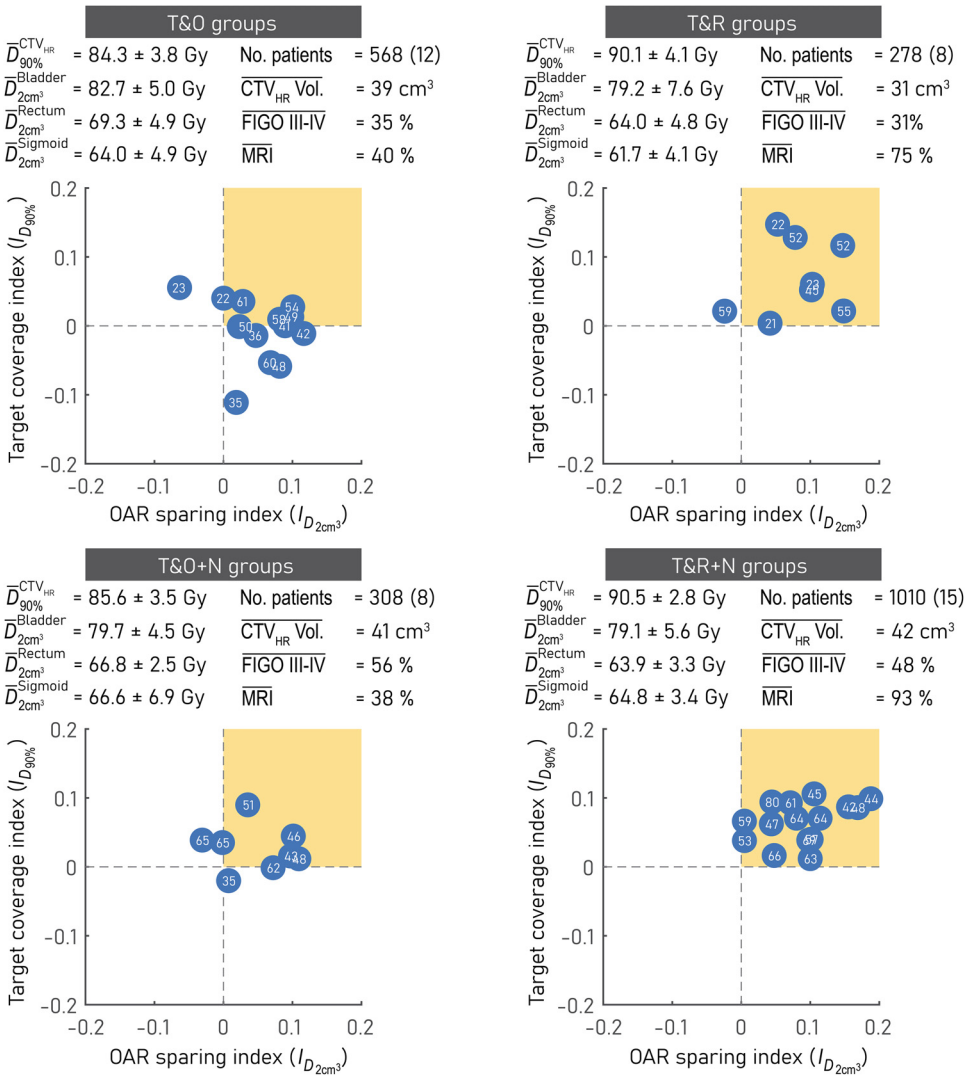

Fig. 4. Summary plot of OAR sparing indices $I_{D_{2cm^3}}$ and target coverage indices $I_{D_{90\%}}$ sorted per applicator type used per study group. Individual study groups in which CTV_{HR} $D_{90\%}$ constraints were met without exceeding OARs D_{2cm^3} constraints are positioned in the "golden corner" (39). Numbers in the markers correspond to the reference numbers in this article and Table S.1. Averages are given per group-with outliers removed- for the reported CTV_{HR} $D_{90\%}$ ($\bar{D}^{CTV_{HR}}_{90\%}$), OAR D_{2cm^3} ($\bar{D}^{Bladder}_{2cm^3}$, $\bar{D}^{Rectum}_{2cm^3}$, or $\bar{D}^{Sigmoid}_{2cm^3}$), number of patients (groups), CTV_{HR} volume ($\overline{CTV_{HR}\ Vol.}$), proportion of FIGO III-IVB patients ($\overline{FIGO\ III-IV}$), and proportion of patients with at least MRI used for one fraction ($\overline{MRI}$).

MRI for planning and using T&R applicators reported better OAR sparing, although the benefit of the latter seemed to decrease for larger CTV_{HR} volumes. The findings of this study further demonstrate some potential dosimetric advantages associated with changing brachytherapy practices.

Dose prescription of the CTV_{HR} $D_{90\%}$ differed per centre, but in general aimed to achieve an EBRT + BT dose of ≥84–86 Gy $EQD2_{\alpha/\beta=10Gy}$. This is in line with ABS guidelines (≥80–90 Gy), and follows known fractionation schemes to achieve high local control (11,71,72). Although studies comparing the effectiveness of different fractionation schemes have been rare, several retrospective studies demonstrated that with a 3×8 Gy scheme similar dosimetric and treatment outcomes could be achieved in comparison to schemes with more fractions (73,74). It must be noted that due to differences in radiosensitivities of healthy tissues and that of the tumor in cervical cancer, higher fraction doses pose a higher risk for normal tissue morbidity (75). Whereas the EMBRACE II study imposes a hard lower constraint on the CTV_{HR} $D_{90\%}$ of 85 Gy $EQD2_{\alpha/\beta=10Gy}$ (6), the ABS suggests a lower constraint of 80 Gy for lower stage and well-responding tumors (5). From data of the retro EMBRACE and the EMBRACE I studies it can be observed that in patients with limited target volume size and stage, and squamous carcinoma a CTV_{HR} $D_{90\%}$ of 80 Gy can still lead to an average local control of ~90% (8,76). Some of the included studies that reported lower CTV_{HR} doses indeed were able to achieve excellent local control in patient cohorts with rel-

Table 2
Overview included studies with details on IC/IS practices

Ref.	Type	Needle types	Number of needles	Depth (mm)	Guidance	IS loading	Pattern
Bajwa et al. (51)	C T&O+N	P(&O)	6 (2-10)	40	TRUS	DC 10–20%	-
Cobussen et al. (44)	IH T&R+N	P (49%) P&O (51%)	8 {8-9} 12 {9-13}	33 {21-42}[1]	TRUS	T 44%[1] DC <20%[1]	LD 73%[1]
Jääskeläinen et al. (45)	C T&R+N	P(&O) (93%) FH (20%)	5 [0–16]	-	-	-	-
Jamadagni et al. (35)	IH T&O+N	FH[2]	3 [2-6]	40	No	-	UL 93% BL 7%
Lindegaard et al. (64)	IH T&R+N	P[3]	5 ± 3[3]	30 ± 10[3]	US[3]	DC 20%[3]	LD 69–73%[3]
Lombe et al. (59)	C T&R+N	P(&FH)	2 [1-6]	-	US	T 7 [1-39]%	-
Mahantshetty et al. (53)	C T&R+N	P(&O)	4 [3-11]	-	-	DC 10–20%	-
Mahantshetty et al. (66)	C T&R+N	P&O O	7 [3-15] 4 [1-7]	50 ± 15	TRUS	-	-
Möller et al. (57)	C T&R+N	P	6 [2-9]	-	-	-	-
Nomden et al. (60)	C T&O+N	P	3 [1-6]	25 [15-35]	US	I 7 [2-14]% T 19 [4-35]%	LD 50%
Pötter et al. (62)	IH T&R+N	P	4 [1-8][4]	37 ± 7[4]	-	DC 16%[4]	-
Rogowski et al. (58)	C T&R+N	P(&O)	4 [1-8]	-	US	-	-
Sarwar et al. (48)	C T&O+N	P	4	-	CT	-	-
Smolic et al. (46)	C T&O+N	P	6 [1-10]	20 [10-40]	-	T 22 [2-58]%	L 89% V 69% D 54%
Tambas et al. (65)	C T&O+N	P	4 [0-8]	10-45	CT	I 11 ± 8% T 37 ± 19%	-
Zhao et al. (47)	C T&R+N	P	4	41	US	-	L 39% LD 40%

C = commercial; IH = in-house developed; P = parallel; O = oblique; FH = free-hand; US = ultrasound; TRUS = transrectal ultrasound; T = IS contribution relative to total dose; DC = IS dwell contribution relative to IC standard plan; I = contribution of individual needle relative to total dose; L = lateral; V = ventral; D = dorsal; UL = unilateral; BL = bilateral.

Notation for continuous variables: mean or median; ±standard deviation; {interquartile range}; [range].

[1]Serban et al. (67).

[2]needles were inserted through pieces of suction catheter.

[3]Fokdal et al. (68).

[4]Dimopoulos et al. (89), and Kirisits et al. (70).

atively large proportions of FIGO IB1-IIB cases (40,43). Planning aims for the OARs generally comprised 80–90 Gy EQD2$_{\alpha/\beta=3Gy}$ for the bladder D_{2cm^3}, 65–75 Gy for the rectum D_{2cm^3}, and 70–75 Gy for the sigmoid D_{2cm^3}. Several studies indicated lowering of these aims over time or maintaining these with increased target dose (41,42,61,64), especially driven by the introduction and use of MRI-guided IC/IS BT.

The ability to meet planning constraints for the CTV$_{HR}$ $D_{90\%}$ and OAR D_{2cm^3} depends on numerous factors. EMBRACE II planning constraints are evidence-driven, and hard constraints can realistically be fulfilled in 80–90% of patients (6,64), and soft constraints in approximately 50% of all patients (76). Although the majority of the included studies on average met their planning aims, there were large differences in the remaining margin between the constraints and obtained values, as well as in the variability among patients. One important factor to achieve compliance with planning aims is the use of interstitial needles. From retroEMBRACE data IC/IS was noted to in general increase target dose by 9 Gy, and from EMBRACE I data by ~5–9 Gy in large CTV$_{HR}$ volumes (12,20). In our multivariate regression, the use of the IC/IS technique was shown to be an independent factor of target dose. The difference in target dose between IC and IC/IS centers was ~4 Gy at a CTV$_{HR}$ volume of 30 cm^3. While patients with larger CTV$_{HR}$ volumes would have greater benefit from IC/IS applications, our analysis uses only mean volumes per cohort and does not account for volume distribution. Moreover, our analysis lacks cohorts with predominantly large volumes (see Figure 2b). Although OAR doses were also lower in IC/IS centers in EMBRACE I (12), this was not observed in our analyses. Another important predictor for meeting target and OAR constraints was the use of T&R applicators, with improvements of 3.2 Gy and 2.8–3.4 Gy respectively at typical planning aims in comparison with T&O applicators. A 2.8–3.3 Gy increase in CTV$_{HR}$ $D_{90\%}$ was observed for T&R versus T&O centres from EMBRACE I data (12). However, their observed differences in OAR doses were larger between T&R and T&O centers, that is, 4.8–7.7 and 3.2 Gy lower for T&R centers for the bladder and rectum D_{2cm^3} at a median CTV$_{HR}$ volume of 30 cm^3, respectively. Although Fig. 3 shows similar differences at 30 cm^3, a volume effect appeared to be

present, which was also significant in the meta-regression. Similarly, based on the EMBRACE I data it was noted that the differences between T&R and T&O doses become smaller at a larger CTV_{HR} volume (12). In general, the predictions of the multivariate models in this study show great uncertainty at larger CTV_{HR} volumes, largely due to the limited number of included cohorts.

Next to target volume, the proportion of FIGO III–IV of patients was shown to be an important predictor for the target dose. This effect has been observed in several studies (40,77,78). An effect on OAR dose (12), was not observed in this study. The use of MR imaging for at least one fraction opposed to a CT-only workflow was associated with higher target doses in univariate analysis, and with lower OAR doses in the multivariate model. Overestimation of the CTV_{HR} width on CT has been documented compared to MRI-based planning, which may result in a small underestimation of the actual $D_{90\%}$ (35). In addition, organ involvement may be underestimated on CT. However, the routine use of MR imaging may also be an indicator for other factors affecting ability to meet planning aims. For example, resource-constrained hospitals may face other difficulties such as more complex anatomies, and more limited access to trained and experienced personnel, and advanced applicators or software (69). The CT-only studies included in this review were conducted in settings possibly facing these constraints (at the time), as associated centers were located in India (3), Turkey (3), China (3), Thailand, and Pakistan. EMBRACE centers on average showed better OAR sparing in univariate models, however, this was not an independent factor in multivariate regression. Both training and experience in these centers may contribute to increased adherence to planning aims (9).

In this study, an overview was provided of interstitial needle insertion and planning practices in the included IC/IS studies. It has been estimated that needles are needed in approximately 30–60% of patients to achieve planning aims for T&R applicators (26,68,79). However, the dosimetric benefits of IC/IS approaches may extend to a wider range of patients, including those with smaller target volumes with asymmetric target volumes or a close proximity to OARs, particularly when using T&O applicators (12,26). The use of hybrid IC/IS applicators seems to have increased over time, along with increases in the number of needles used and associated loading (7,45,60,65,80). Interestingly, needle loading practices differed among included studies, often exceeding the 10–20% contribution relative to the IC components as typically recommended (5,6). To achieve lateral coverage in larger target volumes, IS needle contribution may be increased taking into account high dose volumes and specifically aiming to optimize positions in the GTV_{RES} or CTV_{HR} (67). This practice should be done with care to prevent ureteral stricture (81), or damage to other critical structures (67,70). In addition to commercially available IC/IS applicators, several custom 3D-printed IC/IS applicators with oblique needle trajectories have demonstrated the ability to achieve excellent dosimetric results (44,82,83).

This literature review and meta-regression have several limitations. First, this review concerned observational studies only, resulting in large interstudy heterogeneity in our analyses. Although we adjusted for several confounding factors in our meta-regression, this was limited by the number of included studies, the risk of potential overfitting, and limited data of potential confounders. Potentially important factors in achieving high-quality plans and ensuring adherence to planning aims are training and experience of the center (9), and several studies indicated learning curves/periods (45,61). Moreover, although FIGO staging distribution was accounted for as a confounding factor, no distinction was made between studies reporting the use of FIGO 2009 or 2018 staging systems (seven of the 34 studies explicitly mentioned using the latter). Specifically, in comparison to studies using the FIGO 2009 system, those using the FIGO 2018 system may have led to a higher classification of the local tumor stage (84). The proportion of FIGO III–IV patients was indeed considerably higher in these studies (63% on average), but TNM data was generally not available. Consequently, target coverage metrics could appear higher, and the dependence of local staging/extent may be greater than shown here. Another factor that was not accounted for was applicator positioning, along with related aspects such as the use of rectal retractors, vaginal packing or bladder filling practices. From EMBRACE I data it was shown that the bladder D_{2cm^3}/ICRU-point ratio, used as an estimator of the applicator position along the vaginal axis, was related to OAR dose (12). The presence of a rectal retractor or packing practices have for example been linked to rectal or sigmoid dose (23,24,85), and bladder filling has been associated with bladder dose (85). Other center effects, such as in dose reporting, contouring protocols, planning methods, and the number and type of inserted needles have not been taken into account in this study as well. Of note, studies using central shielding were excluded from this review as this affects dose calculations. A recent multicenter study in Asian centers, where the majority of patients received treatment with central shielding, reported reasonable local control and a low incidence of OAR toxicities (86), with relatively low prescribed total doses to the target region. The selected dosimetric indices for the therapeutic dose window may only partially reflect treatment effectiveness, for example as they do not capture effects of dose nonuniformity, nor take into account radiobiological factors, such as hypoxia or repopulation (87). Several reviews have compared clinical outcomes for different BT techniques (21,31). However, these end points are affected by many other confounding factors that complicate isolating the effect of BT practices. Moreover, in this review, we only considered the CTV_{HR} $D_{90\%}$, and not the CTV_{HR} D_{98}, CTV_{IR} D_{98}, or GTV_{RES} D_{98}, despite these having been associated with local control (6,8). Other relevant dosimetric indices were also not considered,

including bowel D_{2cm^3} and vaginal dose (e.g., to the rectovaginal point). Applicator type, and in particular T&O, has been associated with higher dose in the rectovaginal point and morbidity, although this effect could have also been caused by differences in packing/retraction or planning (88). In the majority of included studies, these metrics were not reported or planning aims for these indices were not given. Other planning parameters, such as the TRAK ratio and dwell time contributions, were only reported in a handful of studies. Documentation of plan quality metrics in accordance with ICRU 89, and potentially confounding factors are encouraged to aid future analyses (4).

Conclusions

This study presented an overview of clinical practices and their impact on dosimetric indices in cervical cancer brachytherapy literature. All of the included studies considered dose constraints that are in accordance with common recommendations. Nevertheless, large differences were observed in how clinical practices balanced target coverage with OAR sparing. Meta-regression showed that the ability to meet target and OAR planning constraints was primarily influenced by the applicator type (T&R favored over T&O), use of interstitial needles (IC/IS especially favored over IC for CTV_{HR} volumes >30 cm^3 and FIGO >IIB), and patient characteristics such as FIGO stage and CTV_{HR} volume. Compliance with current evidence-based guidelines and quality indicators for all patients therefore requires increased use of MR-guided optimization and advanced IC/IS BT. Hybrid MR/CT imaging or single application treatment have been investigated as alternatives for the former in resource-constrained settings. For the latter, the range of IC/IS applicator geometries reviewed in this work, from commercial to in-house developed custom applicators, illustrates the adaptability of clinical practice to accommodate for diverse patient anatomies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.brachy.2025.11.005.

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