Original Article

Point-A vs. volume-based brachytherapy for the treatment of cervix cancer: A meta-analysis

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meta-analysis reported superior overall survival [HR 0.78 (95%CI 0.62–0.98)] and pelvic disease-free survival [HR of 0.75 (95%CI 0.62–0.90)], with lower toxicities for IGBT, compared to point-A BT [15].

Although IGBT transition has been recommended across guidelines, available supporting evidence are largely prospective studies with no comparator arms. There is only one ongoing phase III trial of point-A vs. volume-based BT [16]. Transition requires modification of workflows, access to scanners, specialized equipment (MR compatible applicators) and highly skilled staff [17,18]. Introduction of such treatment modalities requiring specialized equipment and incurring significant costs require detailed evaluations of effectiveness and affordability, especially since high incidence occurs in LMICs, where access to technology and MRI scanners is limited (e.g., 27–37 MRI units per million population in high-income countries compared to 0.24–2.6 units in LMICs) [19,20]. This led to significant efforts by healthcare organisations to support research on radiotherapy resource allocation [17,18,21–23].

The present meta-analysis was undertaken to pool available contemporary evidence and evaluate if management of locally advanced cervical cancers with IGBT improves outcomes.

Methods

Literature search for this study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [26] statement, along with hand searches of reference sections of included studies.

Search strategy

PubMed/Medline, ScienceDirect, Web of Science, and Cochrane Reviews were searched in February 2019 and updated in April 2021 by the lead author (VH). A second search was done independently in February 2020 by another reviewer (BK). Search terms are provided in Supplementary Table A1. The search was restricted to studies published in English. Titles and abstracts were reviewed, and studies fulfilling selection criteria were included. Full texts were reviewed by three independent reviewers (VH, SC, BK), and discrepancies were discussed and resolved. All selected studies were included in the meta-analysis.

Article eligibility characteristics

Cohort, cross-sectional and clinical trial study designs (Phase II-III) published after 2000 (chemoradiation era) were included. Studies must have reported 3- or 5-year outcomes, with minimum 2-year follow-up. Required sample size was 50. However, articles with multiple patient group were included even if individual groups had n < 50. The following study designs were excluded: qualitative studies, reviews, abstracts, commentaries, and case reports. Studies not reporting EBRT, BT techniques or dose to point-A/ high-risk clinical target volumes were excluded.

Study population eligibility characteristics

Study samples of cervix carcinoma patients with squamous, adenocarcinoma or adeno-squamous histology were included. Other histologies (clear cell carcinoma, neuroendocrine cervix tumours, cervical sarcomas) were excluded. Studies of patients with human immunodeficiency virus infections were excluded.

Treatment eligibility characteristics

Treatment criteria for inclusion was optimal platinum-based chemo-radiotherapy and either high-dose rate (HDR) or pulsed-dose rate (PDR) BT. Treatments without chemotherapy, involving adjuvant chemotherapy or surgery were ineligible. Acceptable dose prescription modalities were point-A based (X-ray based or CT-based) or volume-based (3D CT-based or 3D MRI-based) BT.

Outcome measures

The primary outcome was DFS at three years (3yDFS). The secondary outcomes were LC at three years (3yLC), OS at three years (3yOS) and late grade 3 or grade 4 gastrointestinal and genitourinary toxicity. Outcomes should have been reported according to prescription type (point-A or volume-based), and as percentage or proportion of total sample. Results must have been reported by stage or as an aggregate of all stages combined.
**Data analysis**

**Risk of bias assessment**

Methodological Index for Non-Randomized Studies (MINORS) [27] was used for quality assessment of included studies. Studies were assessed for robustness of aims, patient inclusion criteria, data collection methods, endpoint evaluation, time and loss to follow-up and appropriateness of sample size. Thefollowing additional criteria were evaluated if studies were comparative: adequacy of the control group, comparison period, baseline characteristics and statistical analyses.

**Data extraction**

The following was extracted from included studies: publication details (author, publication year, country, study design, study population, sample size – overall, by stage), treatment details (EBRT dose, BT dose, BT technique [IC or IC-IS], BT dose prescription technique [point-A or volume-based], imaging modality used [X-Ray, CT or MRI], chemotherapy agents and schedule, tumour histology, technique [point-A or volume-based], imaging modality used [X-Ray, CT or MRI], chemotherapy agents and schedule, tumour histology, nodal staging [pelvic or para-aortic]) and outcomes (3 year LC, DFS, OS, toxicity). For each study, RT cumulative dose (EBRT and BT) was calculated using data accumulation formulae to determine equivalent dose in 2 Gy (EQD2) [28]. While final meta-analysis included all studies, additional sub-analysis was performed with studies administering EQD2 doses of at least 80 Gy (to point A or HRCTV). LC was defined across all studies as the proportion of patients who did not have local or primary relapse at three years from date of inclusion. Heterogeneity for DFS definition was noted across studies (Supplementary Table A2). For this meta-analysis, DFS definition used by most studies (proportion of patients from date of inclusion to date of disease relapse, censoring, last follow up or final analysis in case patient did not relapse) was chosen. DFS outcome was corrected by excluding “death due to other causes” and verified by contacting primary authors [5,10]. OS was defined as the proportion of patients alive three years after treatment. Late toxicity was defined as toxicity that persisted or appeared 90 days after treatment completion. It was reported as the proportion of patients with late-stage grade 3 and/or grade 4 gastrointestinal or genitourinary toxicity.

**Statistical methods**

Three-year DFS, LC, OS, and toxicity were noted for each study. If only 5-year outcomes were reported, 3-year outcomes were extrapolated from survival curves. All outcomes were treated as percentages (binary data). Data was input as proportions (numerator) and sample size (denominator). Total events were calculated from these proportions. Studies were classified according to BT prescription technique (point-A and volume-based) and subgroup meta-analysis was performed. A random-effects model was used to obtain combined effect sizes and to account for heterogeneity. Confidence intervals were calculated using exact binomial and score tests. Weighting was done using the inverse variance method. Forest plots were constructed according to BT prescription subgroups. Differences in subgroup outcomes were verified through regression analysis. Between-study variation was determined by the $I^2$ value. Funnel plots were constructed to depict publication bias. Sensitivity analysis was done for all outcomes to observe effects of each study on subgroup effect size (Supplementary Figure A1). $P$-values < 0.05 were considered statistically significant. All analyses were performed using STATA version 14 [29].

**Results**

The literature search identified 5322 studies. From these, 343 full-text studies were selected for review, and 319 were excluded (Supplementary Table A3). Thus, 24 studies [3,5,6,8-10,30-47] were included. Samples from three studies [30,31,45] were analysed as separate groups according to prescription types (point-A cohort and volume-based cohort), leading to 27 studies with 5488 patients (Fig. 1). Demographic characteristics of included studies are listed in Table 1. Eleven studies (1538 patients) were point-A based [30-32,34,39,41,42,45,46] and 16 studies (3950 patients) were volume-based [3,5,6,8-10,31,33,35-38,44,47].

**Table 1**

Demographic characteristics of included studies.

| Study      | Country | Accrual Period | Study Type     | No. of Groups | Type of BT | n   | F/U# |
|------------|---------|----------------|----------------|---------------|------------|-----|------|
| Chatani 2014 (Group A) | Japan  | 1998–2009 | Retrospective  | 2             | Point A    | 98  | 36–84 |
| Chatani 2014 (Group B) | Japan  | 1998–2009 | Retrospective  | 2             | Point A    | 120 | 36–84 |
| Derks 2018 (Group 2D) | Netherlands | 1997–2009 | Retrospective  | 2             | Point A    | 35  | 44 (6–166) |
| Derks 2018 (Group 3D) | Netherlands | 2009–2016 | Retrospective  | 1             | Volume-based | 91  | 35 (5–97) |
| Dracham 2018 | India  | 2013–2015 | Retrospective  | 1             | Point A    | 210 | 37 (15–54) |
| Gill 2015 | USA | 2007–2013 | Retrospective  | 1             | Volume-based | 128 | 24.4 (2.1–77.2) |
| Hallock 2011 | Canada | 2004–2008 | Retrospective  | 1             | Point A    | 57  | 22.6 (2.5–54.1) |
| Horeweg 2019 | Netherlands | 2008–2016 | Retrospective  | 1             | Volume-based | 155 | 56.7 (27.8–79.3) |
| Horne 2018 | USA | 2007–2018 | Retrospective  | 1             | Volume-based | 239 | 28.6 (12.7–53.8) |
| Kang 2010 | Korea | 2001–2005 | Retrospective  | 1             | Volume-based | 97  | 41 (8–60) |
| Kawashima 2019 | Japan  | 2012–2015 | Retrospective  | 1             | Volume-based | 84  | 36 (2–62) |
| Kim 2018 | Germany | 2008–2013 | Retrospective  | 1             | Volume-based | 128 | 44 (6–78) |
| Koh 2017 | Singapore | 2008–2014 | Retrospective  | 1             | Volume-based | 95  | 29 (6–76) |
| Lindegaard 2013 | Denmark | 2005–2011 | Retrospective  | 1             | Volume-based | 140 | 36 (6–78) |
| Mittal 2018 | India | 2014–2015 | Retrospective  | 1             | Point A    | 339 | 28 (4–45) |
| Murakami 2014 | Japan  | 2008–2010 | Retrospective  | 1             | Volume-based | 51  | 39.2 (24.3–52.0) |
| Parker 2009 | UK | 1999–2004 | Retrospective  | 1             | Volume-based | 156 | 42 |
| Potter 2011 | Austria | 2001–2008 | Retrospective  | 1             | Volume-based | 1318 | 51 (20–64) |
| Potter 2021 | - | 2008–2015 | Prospective    | 1             | Volume-based | 154 | 38 (6–60) |
| Rahshah 2015 | Iran | 2008–2015 | Retrospective  | 1             | Point A    | 170 | 37 (2–136) |
| Ribeiro 2016 | Belgium | 2002–2012 | Retrospective  | 1             | Volume-based | 73 | 47 (2–169) |
| Sturdza 2016 | - | 1998–2013 | Retrospective  | 1             | Volume-based | 172 | 35 |
| Tharavichitkul 2012 (Group A) | Thailand | 2004–2006 | Prospective    | 2             | Point A    | 350 | 35 |
| Tharavichitkul 2012 (Group B) | Thailand | 2004–2006 | Prospective    | 2             | Point A    | 188 | 35 |
| Tiwari 2018 | India | 2014–2017 | Retrospective  | 1             | Volume-based | 151 | 26 (9–41) |
| Wang 2017 | China | 2006–2014 | Retrospective  | 1             | Point A    | 73  | 32.4 (4.8–118.8) |
| Zolciak-Siwinska 2016 | Poland | 2010–2011 | Retrospective  | 1             | Volume-based | 216 | 52 (37–63) |

*multicentric accrual.
## Table 2
Patient and treatment characteristics of included studies.

| Study                        | Stage          | EBRT (Gy) | Imaging | BT Technique | EQD2 (Gy) | OTT (days) Median (range) | Squamous, Adeno (%) | Node * (%) | 3yLC (%) | 3yDFS (%) | 3yOS (%) | Toxicity Scoring System | GI Toxicity (%) | GU Toxicity (%) |
|------------------------------|----------------|-----------|---------|--------------|-----------|---------------------------|---------------------|------------|----------|-----------|----------|--------------------------|-----------------|-----------------|
| Chatani Group A 2014         | IB-IV          | 42        | X-ray   | IC           | 80.0      | NR                        | 89, 11              | NR         | 86       | 70.5      | NR       | NCI-CTCAE 1.1            | 1.1             | 1.1             |
| Chatani Group B 2014         | IB-IV          | 52        | X-ray   | IC           | 77.0      | NR                        | 89, 11              | NR         | 93       | 75.5      | NR       | NCI-CTCAE 1.7            | 1.7             | 1.7             |
| Derks 2D 2018                | IB-IVA         | 45        | CT/MR   | IC           | 74.0      | 47                        | 89, 11              | 29         | 84       | 57        | NR       | CTCAE 4.0                | 11.4            | 5.7             |
| Dracham 2018                 | II-III         | 46        | CT      | IC           | 74.5      | NR                        | 93, 7               | 22         | 90.5     | 80.9      | 84.2     | CTCAE 3.0                | 4.2             | 0.9             |
| Hallock 2011                 | II-IIIB        | 45        | CT      | IC           | 82.9      | NR                        | 74, 18              | 16         | 83       | 62        | 86       | NR                        | NR              | NR              |
| Mittal 2018                  | IB-IIVA        | 45        | X-ray, CT | IC*          | 84.0      | 63 (61–72)                | 93.5                | 23         | 89.5     | 71.9      | 76.2     | NR                        | 4.7             | NR              |
| Parker 2009                  | IB-IIVA        | 45        | X-ray   | IC           | 76.3      | 61 (45–94)                | 79, 17              | 39         | 70       | NR        | 70       | NCI-CTCAE 3.0            | NR              | 4               |
| Hallock 2011                 | II-IIIB        | 45        | CT      | IC           | 82.9      | NR                        | 74, 18              | 16         | 83       | 62        | 86       | NR                        | NR              | NR              |
| Mittal 2018                  | IB-IIVA        | 45        | X-ray, CT | IC*          | 84.0      | 63 (61–72)                | 93.5                | 23         | 89.5     | 71.9      | 76.2     | NR                        | 4.7             | NR              |
| Parker 2009                  | IB-IIVA        | 45        | X-ray   | IC           | 76.3      | 61 (45–94)                | 79, 17              | 39         | 70       | NR        | 70       | NCI-CTCAE 3.0            | NR              | 4               |
| Tharavichitkul Group A 2012  | IB-IIVA        | 50        | X-ray   | IC           | 81.0      | 49                        | 83, 14              | NR         | 90.5     | 71.9      | 76.2     | NR                        | 4.7             | NR              |
| Tharavichitkul Group B 2012  | IB-IIVA        | 50        | X-ray   | IC           | 82.0      | 49                        | 72, 17              | NR         | 90.5     | 71.9      | 76.2     | NR                        | 4.7             | NR              |
| Wang 2017                    | IB-IIVA        | 50.4      | CT      | IC           | 89.0      | 50 (26–87)                | 93, 5               | 15         | 79.5     | 66.5      | 64.9     | CTCAE 3.0                | 4.1             | 2.7             |

### Volume-based studies

| Horne 2018                    | IB1-IVA        | NR        | MR      | IC-IS       | 83.7      | 51 (40–55)                | 81, 19              | 49         | 88       | 71        | NR       | NCI-CTCAE 8.8            | 3.3             |                 |
| Derks 3D 2018                 | IB1-IVA        | NR        | MR      | IC-IS       | 83.0      | 50 (43–78)                | 83, 16              | 43         | 90.4     | 80        | 74.8     | CTCAE 3.0                | 3.6             | 0.8             |
| Gill 2015                    | IB1-IVA        | 45        | CT/MR   | IC-IS       | 81.8      | 57 (46–91)                | 90,7                | 64         | 93.5     | 79.8      | 85.5     | NR                        | NR              | NR              |
| Horeweg 2019                 | IB1-IVA        | 45        | MR      | IC-IS       | 83.8      | 42 (41–45.5)              | 81, 14              | 56         | 93.5     | 79.8      | 85.5     | NR                        | NR              | NR              |
| Kage 2010                    | IB1-IVA        | 45        | CT/MR   | IC           | 81.8      | 57 (46–91)                | 90,7                | 64         | 93.5     | 79.8      | 85.5     | NR                        | NR              | NR              |
| Kawashima 2019               | IB1-IVA        | 50        | CT      | IC           | 73.4      | NR                        | 85, 15              | 33         | 89       | 81        | 94       | CTCAE 4.0                | 5.5             | NR              |
| Kim 2018                     | IB1-IVA        | 45        | MR      | IC           | 90.4      | 56 (43–94)                | 82, 9               | 62         | 94.8     | 76.8      | 69.7     | CTCAE 3.0                | 11              | 2               |
| Koh 2017                     | IB1-IVA        | 51        | CT      | IC           | 80.0      | NR                        | 82, 11              | NR         | 94.8     | 76.8      | 69.7     | CTCAE 3.0                | 11              | 2               |
| Lindegaard 2013              | IB1-IVA        | 46        | MR/CT   | IC-IS       | 91.0      | 47 (36–70)                | 83, 12              | 50         | 91       | 79        | NR       | CTCAE 3.0                | 11              | 2               |
| Murakami 2014                | IB1-IVA        | 50        | CT MR   | IC           | 64.0      | 42 (36–67)                | 94, 6               | 22         | 91.7     | 85.3      | 82.4     | NR                        | NR              | NR              |
| Potter 2011                  | IA-IVA         | 45        | MR      | IC           | 93.0      | 48                        | 86, 9               | 62         | 95       | 75        | 68       | LENT SOMA 8               | 5               |                 |
| Potter 2021                  | IB-IVA         | 45        | CT/MR   | IC-IS       | 89.0      | 46 (42–50)                | 82, 14              | 52         | 92       | 72        | 81       | LENT SOMA 7.6             | 6.5             |                 |
| Ribeiro 2016                 | IB1-IVA        | 45        | MR, CT  | IC-IS       | 85.0      | 53.6 (41–65)              | 82, 11              | 54         | 96       | 73        | NR       | CTCAE 4.0                | 2               | 11              |
| Sturdza 2016                 | IB1-IVA        | 46        | MR, CT  | IC-IS       | 83.0      | NR                        | 85, 9               | 40         | 91       | 74        | NR       | CTCAE 3.0                | 6.5             | 4.5             |
| Tiwari 2018                  | IB1-IIIB       | 45        | MR/CT   | IC-IS       | 79.0      | 48 (33–76)                | 94, 5               | 50         | 88.7     | 82.2      | NR       | CTCAE 3.0                | 1.9             | 1.9             |
| Zolciak-Siwinska 2016        | IB1-IWA        | 45        | CT      | IC           | 88.0      | NR                        | 92, 5               | 23         | NR       | 75        | NR       | LENT SOMA 4.2             | 3.3             |                 |

*% IC-IS.

*in months, median (minimum – maximum).
Point-A studies were published from 2009 to 2018, and volume-based studies were published between 2010 and 2021. Median accrual period for point-A patients was 2004 – 2009, and for volume-based patients, it was 2008 – 2011. Twenty-five studies were retrospective cohorts, and 2 reported prospective cohorts (Potter 2021 [3] and Tharavichitkul [45]). The proportion of prospectively enrolled patients was 23% for point-A studies and 33% for volume-based studies. Three studies [30,31,45] had comparative arms; 2 studies compared fractionation schedules [30,45] and 1 [31] compared patients with and without MRI guidance during BT. Treatment characteristics are summarized in Table 2. Mean EBRT dose was 47 Gy (range 42 Gy – 52 Gy). Twenty-five studies used cisplatin-based chemotherapy, one used carboplatin, and one did not report chemotherapy details. Following was the distribution of imaging modalities used for BT planning: X-ray (7 studies), CT (6 studies), MR (5 studies), CT and X-ray (1 study), CT and MR (8 studies). Mean cumulative EQD2 dose was 80 Gy (74 Gy – 89 Gy) to point-A for point-A studies and 83.3 Gy (64 Gy – 93 Gy) to CTVHR D90 for volume-based studies. Risk of bias in the included studies was low to moderate (supplementary Table A4). The results of individual study outcomes are provided in Table 2.

Disease-Free survival

Nineteen studies (4011 patients) reported a 3yDFS of 75% (95% CI 72%-78%). Seven were point-A studies (1193 patients) and 12 (2818 patients) were volume-based. Point-A 3yDFS was 68% (95% CI 61%–74%) and volume-based 3yDFS was 79% (95% CI 76%-82%) (Fig. 2), p = 0.001. Point A heterogeneity was $I^2 = 82\%$, $p < 0.05$ and volume-based heterogeneity was lower ($I^2 = 58\%$, $p = 0.01$). Between-group heterogeneity was considerable ($I^2 = 77\%$, $p < 0.01$).

A sub-analysis comparing 3yDFS for 15 studies (3515 patients) administering minimal EQD2 of 80 Gy (to point A or HRCTV was done. Overall 3yDFS was 73% (95% CI 69% – 76%). Six point A (983 patients) and 9 volume-based studies (2532 patients) reported 3yDFS of 64% (95% CI 59% – 70%), and 77% (95% CI 74% – 80%) respectively. This 13% difference was significant ($p < 0.001$). Within-group heterogeneity was similar among both groups ($I^2 = 64\%$, $p = 0.02$) and ($I^2 = 60\%$, $p = 0.01$). Between-group heterogeneity was higher ($I^2 = 78\%$, $p < 0.05$). (Supplementary Figure A2).

Local control

Twenty-four studies (4974 patients) reported 91% (95% CI 89%-92%) 3yLC. Eight point-A studies (1024 patients) 16 volume-based studies (3950 patients) reported 3yLC of 86% (95% CI 81%-90%) and 92% (91%-94%) respectively (Fig. 3), $p = 0.01$. Heterogeneity was higher for point-A studies ($I^2 = 75\%$, $p < 0.05$) compared to volume-based ($I^2 = 47\%$, $p = 0.02$). Between group heterogeneity was substantial ($I^2 = 67\%$, $p < 0.05$).

The sub-analysis of 16 studies (4015 patients) prescribing EQD2 ≥ 80 Gy reported 92% (95% CI 90% – 93%) 3yLC. Four
Point-A studies (567 patients) and 12 volume-based studies (3448 patients) reported 3yLC of 86% (95% CI 81% – 90%) and 93% (95% CI 92% – 94%) respectively, for which the 7% difference was significant ($p = 0.005$). Within-group heterogeneity was 45% for both subgroups ($p = 0.14$, $p = 0.04$). Between-group heterogeneity was 61% ($p < 0.05$). (Supplementary Figure A3).

**Overall survival**

Twenty-one studies (4536 patients) reported 3yOS of 76% (95% CI 73% – 80%). Nine point-A (1178 patients) and 12 volume-based (3358 patients) had 3yOS of 72% (95% CI 66–79%) and 79% (95% CI 75–83%) respectively (Fig. 4), $p = 0.125$. Heterogeneity was high both within subgroups ($I^2 = 83$, $p < 0.05$, $I^2 = 87$, $p < 0.05$) and overall ($I^2 = 86$, $p < 0.05$).

EQD2 ≥ 80 Gy sub-analysis included 15 studies (3932 patients) reporting 3yOS of 75% (95% CI 73% – 78%). Five point-A (721 patients) and 10 volume-based studies (3211 patients) reported 3yOS of 71% (95% CI 63% – 80%) and 77% (95% CI 73% – 81%) respectively, where the difference was not significant ($p = 0.255$). High heterogeneity was present both within groups ($I^2 = 84$, $p < 0.05$, $I^2 = 83$, $p < 0.05$) and overall ($I^2 = 85$, $p < 0.05$). (Supplementary Figure A4).

**Gastrointestinal toxicity**

Twenty-three studies (5050 patients) reported late-stage grade 3/4 gastrointestinal toxicity of 3% (95% CI 3% – 4%). Nine point-A (1389 patients) and 14 volume-based results (3661 patients) showed gastrointestinal toxicity of 3% (95% CI 2% – 4%) and 4% (95% CI 2% – 5%) respectively (Supplementary Figure A5), $p = 0.765$. Point-A heterogeneity was lower ($I^2 = 23$, $p = 0.24$) than volume-based heterogeneity ($I^2 = 78$, $p < 0.05$). Overall heterogeneity was $I^2 = 69$, $p < 0.05$.

**Genitourinary toxicity**

Seventeen studies (4074 patients) reported late-stage grade 3/4 genitourinary toxicity of 3% (95% CI 2% – 4%). Seven point-A (850 patients) and 10 volume-based studies (3224 patients) reported genitourinary toxicity of 2% (95% CI 1% – 3%) and 3% (95% CI 2% – 5%) respectively (Supplementary Figure A6), $p = 0.455$. Point-A heterogeneity was moderate ($I^2 = 45$, $p = 0.09$) compared to volume-based studies ($I^2 = 82$, $p < 0.05$). Overall heterogeneity was considerable ($I^2 = 77$, $p < 0.05$).

Funnel plots (Supplementary Figure A7), secondary analysis of point-A versus MRI-based studies (Supplementary Figures A8, A9, and A10).
A10) and stage-wise results (Supplementary Table A5) are provided as supplementary material.

Discussion

Though IGBT confers excellent results [3,15,48], there is only one ongoing randomized trial comparing point-A and volume-based BT outcomes [16]. It is unlikely that level 1 evidence supporting IGBT will be accessible soon. Thus, synthesis of available evidence in the form of a meta-analysis may provide the best attestation supporting IGBT implementation in real world.

Kim et al. [48] conducted a meta-analysis of six cervix cancer studies assessing whether 3D-BT reduces toxicity and improves survival, compared to 2D-BT. Lower toxicity (HR 0.54, 95% CI 0.37–0.77), improved loco-regional recurrence-free survival (HR 0.61, 95% CI 0.40–0.93) and progression-free survival (HR 0.75, 95% CI 0.59–0.96) were reported for 3D-BT. Improvement in OS was not demonstrable. Suzumura et al. [15] conducted a meta-analysis with twenty studies demonstrating superior OS (HR 0.78, 95% CI 0.62–0.98), LC (HR 0.77, 95% CI 0.59–0.99), pelvic disease-free survival (HR 0.75, 95% CI 0.62–0.90), and lower grade 3–4 overall (9% lower, 95% CI 6% – 11%) and gastrointestinal toxicities (5% lower, 95% CI 2% – 8%) for 3D-BT. Metastasis-free survival and genitourinary toxicity demonstrated no differences.

The present meta-analysis examines cervix cancer patients treated with point-A versus volume-based BT and demonstrates improvements in 3yLC (6%) and 3yDFS (12%), favouring IGBT. Superior LC in IGBT was previously demonstrated [35,43] as IGBT and IC/IS allow for escalation of target doses [4,35,49]. While a consistent improvement in outcomes is reported in overall cohort or when limited to patients receiving optimal radiation doses, a lower LC benefit compared to DFS can be attributed to separate cohorts reporting each outcome. Alternatively, reduced pelvic nodal failure due to differences in adoption of diagnostic imaging between point-A and volume groups could be responsible. Improved pelvic control rates could have contributed to improved extra-pelvic disease control. Our meta-analysis differs from previous studies through its strict inclusion criteria, applied to reproduce the reality of clinical practice and allow for precise reflection of the differences in outcomes between subgroups.

Our analysis shows small and non-significant differences in toxicities between subgroups. While there was no statistical difference, the slight excess in toxicity from IGBT studies [9] may be attributed to rigorous toxicity reporting, and not necessarily from increased symptoms. Furthermore, larger irradiated volumes (e.g., in poor responders) could have contributed to toxicity. The proportion of patients with prospective morbidity assessment is higher in the volume-based group, which can lead to higher reported incidence, as compared to retrospective assessment.
Therefore, it should be interpreted favourably that the incidence of morbidity in the volume-based group is not significantly higher than the point-A group. A decrease in morbidity after IGBT introduction was reported in several mono-institutional cohorts [4,6,8,35,43] and may be likely when targets are not large. This is expected since average doses to OARs and irradiated volumes [4,33,49] significantly decrease for most patients who responded well to chemoradiation.

While this meta-analysis generates structured evidence, there are limitations. Firstly, included studies demonstrated some heterogeneity. Although this can be explained by differences in populations, methods, BT techniques and follow-up, effect size was affected. Second, we observed disparity in DFS definitions. We considered “any relapse” as DFS definition, but recent (especially IGBT) studies included “death due to other causes” within this definition. This bias was corrected by including the definition used by most studies. Authors of disparate studies were contacted, and corrected DFS values were obtained. Thirdly, stage-wise analysis was not feasible due to inadequate samples and non-reporting of stage-wise outcomes by individual studies. Furthermore, there will continue to be a population of good responders where point-A based approach may provide equivalent outcomes [51].

Based on our results, results of other meta-analyses, and multiple guidelines (ASTRO [13], ESGO-ESTRO [12], National Cancer Grid of India [14]), transition to IGBT from X-ray-based BT is advisable and renders superior outcomes. Volume-based BT improves LC and DFS, with no increase in late toxicity, and should be considered as preferred treatment for locally advanced cervical cancer. Nonetheless, this transition incurs additional costs, resources, training, and personnel [18]. Robust economic evaluation is needed to aid financial comprehension of this transition [52,53]. While studies have demonstrated IGBT cost-efficiency, these are mono-institutional, historical data comparisons, or cost recovery models [35,36]. Linkage with implementation programmes is crucial for wide-spread adoption of IGBT.

Conclusion

These results can be used to inform healthcare systems of the incremental benefits of IGBT for treatment of cervical cancer; and for international development agencies in designing appropriate technical assistance to countries in need.

Disclaimer

Views expressed in this article are authors’ own and not an official position of any institution or funder.

Conflicts of interest statement

None.

Source of support

Professor Chopra acknowledges grant support from IAEA through Coordinated Research Project no. E33042 for this research.

Data sharing statement

This is not an IPD based meta-analysis; however, information on data handling over and above included in methodology can be obtained by contacting corresponding authors.
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