Original paper

Variations and effects of bladder and rectal volume following uniform preparation procedure in cervical cancer: Five fractions of 6 Gy

Bin-Qiang Ye, Master, Cheng-Zong Zhao, Bechelor, Prof. Peng-Fei Sun, PhD

Department of Radiotherapy, Second Hospital Affiliated to Lanzhou University, Lanzhou, 730030, China

Abstract

Purpose: To analyze the effects of different bladder and rectal volumes on the dose of organ at risks (OARs) and primary tumors following uniform preparation procedure.

Material and methods: In this retrospective study, a total of 60 patients with cervical cancer treated with external beam radiation therapy (EBRT) combined with chemotherapy and brachytherapy (BT) during 2019-2022 were included (300 insertions). Then, tandem-ovoid applicators were placed and computed tomography (CT) scanning was performed after each insertion. Delineation of OARs and clinical target volumes (CTVs) were done according to GEC-ESTRO group recommendations. Finally, doses of high-risk clinical target volume (HR-CTV) and OARs were obtained from dose volume histogram (DVH) automatically generated by BT treatment planning system.

Results: Following a uniform preparation procedure, the median bladder volume of 68.36 cc (range, 29.9-235.68 cc) was in optimal agreement with the recommended bladder volume of ≤ 70 ml, which avoided more manipulation and possible risk of adverse events during general anesthesia. As the bladder filling volume increased, there was no corresponding increase in rectal, HR-CTV, and small bowel volumes, while the sigmoid colon volume decreased. The median rectal volume was 54.95 cc (range, 24.92-168.1 cc), and as the rectal volume increased, HR-CTV, sigmoid colon, and rectum volumes increased, and conversely, small bowel volume decreased. HR-CTV changes with volume affected the rectum, bladder, and HR-CTV, but not the sigmoid colon and small intestine.

Conclusions: Following a uniform preparation procedure, the bladder and rectum can also be controlled to an optimal volume (B ≤ 70 cc, R ≈ 40 cc), which is related to the dose of the bladder, rectum, and sigmoid colon.

J Contemp Brachytherapy 2023; 15, 2: 123–129
DOI: https://doi.org/10.5114/jcb.2023.126863

Key words: bladder volume, rectal volume, brachytherapy, cervical cancer, OARs.

Purpose

According to the 2020 Global Survey, cervical cancer is the fourth most common cancer and the fourth leading cause of cancer-related deaths in women [1]. External beam radiotherapy (EBRT) combined with chemotherapy and brachytherapy (BT) is the standard of care for locally advanced cervical cancer (LACC) [2, 3]. Brachytherapy is an essential component of treatment for locally advanced cervical cancer. BT involvement throughout the treatment of cervical cancer, not only improves local tumor control and overall survival [4, 5], but minimizes treatment-related adverse effects [6, 7]. Benefits from advances in sophisticated planning and delivery techniques over the last two decades as well as the introduction of computer and imaging technologies have stimulated the development of radiotherapy (RT) [8, 9]. The use of three-dimensional (3D) high-dose-rate (HDR) BT has increased the local control rate of cervical cancer to 88%, and organ-threatening radiation damage to nearly 5% [10].

During RT of cervical cancer, the exposed dose of the bladder, rectum, and small intestine has always been the focus of radiotherapists. Filling degree of the bladder and rectum affects the dose of the tumor and the organs, exceeding a limited dose, which leads to radiation cystitis and proctitis. In some developed countries, about 50% of patients with locally advanced cervical cancer do not receive guided treatment, and about 20-25% do not receive BT [11-13], where the general condition of patient (Karnofsky Performance Scale – KPS), complications, time required for BT, and inadequate health insurance payment are considered common reasons for non-compliance with guided treatment [14]. Bladder volume is one of the most critical variables. Several studies have shown that the bladder filling receives a higher dose during BT, with re-

Address for correspondence: Peng-Fei Sun, PhD, Department of Radiotherapy, Second Hospital Affiliated to Lanzhou University, Lanzhou, 730030, China, phone: +86-13919485464, fax: +86-0931-8458109, ✉ e-mail: ery_sunpf@lzu.edu.cn

Received: 29.10.2022
Accepted: 12.03.2023
Published: 28.04.2023

duced dose to the small intestine and increased dose to the rectum, while the rectum and sigmoid colon receive a lower dose when the bladder is empty [15]. However, other research indicated no significant difference in the bladder and rectal doses if the bladder is full or not [16]. Therefore, there is no clinical consensus on the effect of bladder volume on the dose of organ at risks (OARs) and bladder irradiation [17-19]. Therefore, it is crucial to understand the uncertainty of target area and OARs to minimize the risk of complications [20-22].

The purpose of this paper was to analyze the effects of different bladder and rectal volumes on OARs and primary tumors between different fractions following a uniform preparation procedure, and to provide objective basis for the treatment of cervical cancer and guidance for clinical application.

Material and methods

Patients' selection

This retrospective study included 74 patients with cervical cancer who received radical RT at the Lanzhou University Second Hospital from June, 2019 to July, 2022, with information obtained from medical records.

Inclusion criteria: 1) Patients aged ≥ 18 years with pathologically confirmed squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix; 2) Patients with FIGO (2018) staging [23] IB1-IVB; 3) KPS score ≥ 70, and being able to cooperate in order to complete the treatment; 4) A signed informed consent before the treatment.

Exclusion criteria: 1) Patients with other tumors in combination; 2) Active inflammatory bowel disease; 3) Active infection; 4) Other serious diseases, such as heart or kidney diseases that required treatment.

Applicator insertion

Intra-cavitary brachytherapy (ICBT) was performed 2-3 weeks after initiation of EBRT to ensure that the target covered the lesion in 100%. One hour before treatment, all patients received rectal enemas, and were requested to go to the toilet and empty their bladders before insertions [24]. Uterine applicator was placed at the bottom of the uterus in lithotomy position, and vaginal applicator was fixed at the level of the vaginal fornix 3 cm apart. Then, the uterine source applicator was adjusted at the middle of the vaginal source applicator, the vagina was packed with gauze, source devices were relatively fixed, and finally were placed on the treatment bed. In all patients' preparation, scanning, and transfer steps, a flat transfer vehicle was used, and the patients were fixed in a supine position, as during the treatment.

Imaging and contouring

All patients underwent CT simulation with 3 mm axial image slices in treatment position using Brilliance CT Big Bore Oncology spiral CT scanner (Philips; The Netherlands) from the L5 vertebra to the vaginal orifice, both sides containing the pelvic wall. Patients' CT images were imported to 3D brachytherapy treatment planning system (version TCS4; Beijing Kelinzhong Medical Systems, China).

High-risk clinical target volume (HR-CTV) and OARs (the bladder, rectum, and sigmoid colon) were delineated on CT image with available information, including gynecological examination and magnetic resonance imaging before BT. This was done by a radiation oncologist according to the GEC-ESTRO GYN Working Group recommendations [25].

Treatment planning

All 74 cases received VMAT (volumetric modulated arc therapy) technique, and EBRT was delivered on a 6 MV linear accelerator (Elekta Corporation, Stockholm, Sweden). The prescription dose was ranging between 46.0 and 50.4 Gy in 23-28 fractions to the whole pelvis with a simultaneous integrated boost of 60.2 Gy to the pelvis or retro-peritoneal metastatic lymph nodes. Concurrent paclitaxel at 135-175 mg/m^2 and cisplatin at 40 mg/m^2 were administered every 3 weeks during EBRT.

Three-dimensional (3D) conformal BT was performed with an HDR ^{192}Ir BT device (Kelinzhong Institute of Medical Technology, Beijing, China). Prescription dose was 6 Gy in 1-2 fractions weekly, 5 fractions in total. The dose prescription was based on a linear quadratic model and EQD_2 concept, considering an α/β of 10 Gy for tumors and 3 Gy for late-responding normal tissue. The treatment plan, including EBRT and BT was evaluated for OARs in all patients using the following criteria: rectum, $D_{2cc} \leq$ 65-75 Gy (EQD_2); sigmoid colon, $D_{2cc} \leq$ 70-75 Gy (EQD_2); bladder, $D_{2cc} \leq$ 80-90 Gy (EQD_2). Doses of D_{2cc}, D_1, D_m (median), Dave (average), and D_{99} for HR-CTV, bladder, rectal, and sigmoid colon were obtained from dose volume histogram (DVH) automatically generated by BT treatment planning system.

Statistical analysis

Statistical analysis was performed using SPSS statistical package version 25 (IBM Corporation, Illinois, USA). Clinico-pathological and treatment-associated characteristics were assessed using descriptive statistics. A paired *t*-test (mean ±SD) was used to compare the means between the two groups. Pearson's test was applied to analyze the correlation between the two groups. Association between the bladder or rectum volume and the dose to OARs and HR-CTV were evaluated using a linear regression model. *P*-value < 0.05 was considered statistically significant.

Results

Patients' characteristics

A total of 74 patients with 356 ICBT insertions were included in this study, and 63 patients (85.1%) completed the five scheduled BT sessions; 3 patients with incomplete data were excluded, resulting in total of 60 cases included. The median age was 55.25 years (range, 28-80 years).

Fifty-eight patients (96.7%) were squamous cell carcinoma, and 2 (3.3%) presented with adenocarcinoma. FIGO staging (2018) I-IV were IB1: 3 (5%), IB2: 0 (0%), IIA: 18 (13.3%), IIA2: 15 (25%), IIB: 11 (18.3%), IIIA: 6 (10%), IIIB: 7 (11.6%), IIIC1: 6 (10%), and IIIC2: 0 (0%). Late adverse events in the lower gastrointestinal and genitourinary tracts were observed in 30 and 8 patients, respectively, and most of them were classified as grade 1 or 2. Two patients had stage IVA disease with rectal invasion, and two patients had stage IVA bladder invasion. Patients' characteristics are shown in Table 1.

Variations in bladder volume and dose

The median volumes of the bladder, rectum, sigmoid colon, small intestine, and HR-CTV for all 300 brachytherapy insertions on simulated CT during BT were 68.36 cc (range, 29.9-235.68 cc), 54.95 cc (range, 24.92-168.1 cc), 75.79 cc (range, 6.6-147.58 cc), 144.24 cc (range, 18.60-340.42 cc), and 80.19 cc (range, 36.44-138.16 cc), respectively.

Increasing the number of BT implants, paired *t*-test (Table 2) showed a significant decrease in bladder volume at the 3rd insertion compared with the first insertion (mean ±SD: 72.83 ±53.31 cc vs. 60.76 ±30.38 cc, $p < 0.05$).

Linear regression models included the rectum, sigmoid colon, small bowel, and HR-CTV. Bladder volume during BT was associated with rectum volume (R: 0.50, 95% CI: 0.20-0.80%, $p < 0.05$), sigmoid colon (R: 0.28, 95% CI: –0.36-–0.01%, $p < 0.05$), and HR-CTV (R: 0.27, 95% CI: 0.02-0.65%, $p < 0.05$), irrelevant to small bowel volume (Table 3). As bladder volume increased, there was no corresponding increase in D_1, D_{2cc}, D_{99}, Dm, Dave of the rectum, HR-CTV, and small bowel; inversely, sigmoid D_{2cc} (R: 0.26, 95% CI: –1.294-0.02%, $p < 0.05$) decreased with increasing bladder volume. Bladder volume was significantly correlated with bladder D_{99} (R: 0.43, $p < 0.001$), D_{mean} (R: 0.52, $p < 0.001$), D_{ave} (R: 0.52, $p < 0.001$), and not with bladder D_1 (R: 0.20, $p > 0.05$) and D_{2cc} (R: 0.06, $p > 0.05$).

Variations in rectum volume and dose

The paired *t*-test (Table 4) showed that with the increasing number of BT insertions, the rectal volume increased significantly at the 3rd insertion compared with that at the 1st and 2nd insertions, respectively (ME ±SD: 50.59 ±22.59 cc vs. 60.97 ±40.83 cc, $p < 0.05$; ME ±SD: 50.54 ±25.92 cc vs. 60.97 ±40.83 cc, $p < 0.05$).

Linear regression analysis (Table 5) showed that rectal volume during BT was associated with bladder (R: 0.40, 95% CI: 0.20-0.80%, $p < 0.01$), HR-CTV (R: 0.31, 95% CI: 0.02-0.57%, $p < 0.05$), and small bowel volume

Table 1. Patient and clinico-pathological characteristics

Characteristic	Number (%), *n* = 60
Median age (years)	55.25 (28.0-80.0%)
ECOG score	
0-1	57 (95.0)
2	3 (5.0)
Histology	
Squamous cell carcinoma	58 (96.7)
Adenocarcinoma	2 (3.3)
Adenosquamous carcinoma	0 (0.0)
FIGO staging	
IB1, IB2	3 (5.0), 0 (0.0)
IIA1, IIA2, IIB	8 (13.3), 15 (25.0), 11 (18.3)
IIIA, IIIB, IIIC1, IIIC2	6 (10.0), 7 (11.6), 6 (10.0), 0 (0.0)
IVA, IVB	4 (6.6), 0 (0.0)
Brachytherapy insertion	
4	11 (15.0)
5	63 (85.0)
Tumor size	
< 4 cm	11 (18.3)
≥ 4 cm	49 (81.7)
Applicator type	
Ring	0 (0.0)
Ovoid	60 (100.0)
Tandem length	
< 4 cm	11 (18.3)
> 4 cm	49 (81.7)

ECOG – Eastern Cooperative Oncology Group; FIGO – International Federation of Gynecology and Obstetrics

Table 2. Change in bladder volume between brachytherapy insertions

Pair		*n*	Bladder volume (cc) (mean ±SD)	Change in bladder volume (cc) (mean ±SD)	*t*	*P*-value
1	1st insertion	60	72.83 ±53.31	10.87 ±51.49	1.64	0.11
	2nd insertion	60	61.96 ±36.57			
2	1st insertion	60	72.83 ±53.31	12.07 ±43.68	2.14	0.04
	3rd insertion	60	60.76 ±30.38			
3	1st insertion	60	72.83 ±53.31	1.19 ±60.75	0.15	0.88
	4th insertion	60	71.64 ±50.68			
4	1st insertion	60	72.83 ±53.31	7.62 ±47.66	1.24	0.22
	5th insertion	60	65.21 ±27.76			

(R: 0.43, 95% CI: 0.66-2.27%, $p < 0.05$), and was unrelated to sigmoid colon volume (R: 0.06, 95% CI: –0.59-0.36%, $p > 0.05$). As rectal volume increased, HR-CTV D_{ave} (R: 0.00, 95% CI: –2.68-2.75%, $p < 0.05$), sigmoid D_{2cc} (R: 0.00; 95% CI: –0.82-0.84%, $p < 0.05$), and rectal D_{2cc} (R: 0.34; 95% CI: 0.17-1.10%, $p < 0.01$) volumes subsequently increased, whereas small bowel volume D (med) (R: 0.25, 95% CI: –0.77-0.00%, $p < 0.05$) decreased with increasing rectal volume.

Variations in HR-CTV volume and dose

The paired *t*-test (Table 6) showed a gradual decrease in HR-CTV volume with an increasing number of BT insertions, with a significant difference between the 1st and 5th comparisons (ME ±SD: 84.93 ±28.81 cc vs. 76.03 ± 26.53 cc, $p < 0.01$).

Linear regression analysis showed that HR-CTV volume affected rectal D_{2cc} (R: 0.43, 95% CI: 0.37-1.25%, $p < 0.01$), rectal D_{99} (R: 0.60, 95% CI: 0.40-0.85%, $p < 0.01$), bladder D_{99} (R: 0.41, 95% CI: 0.14-0.54%, $p < 0.01$), HR-CTV D_{2cc} (R: 0.50, 95% CI: 9.74-26.1%, $p < 0.01$), and HR-CTV D1 (R: 0.52, 95% CI: 8.47-21.40%, $p < 0.01$), but did not influence the volume of sigmoid colon and small intestine (Table 7).

Discussion

Dilalla *et al*. [26] reported that > 60% of cancer patients would survive ≥ 5 years after diagnosis, and nearly 40% of them have received at least one course of RT. Pelvic tumors are even more frequently involved in RT, and accordingly, pelvic RT has the greatest impact on a patient's quality of life [27]. Fuccio *et al*. [28] noted that ≥ 50% of patients experienced common adverse effects, including diarrhea, abdominal pain, rectal bleeding, and urinary urgency after pelvic radiotherapy, and two important organs involved were the bladder and rectum. In the present study, we analyzed the effects of bladder, rectum, and HR-CTV volumes on OARs and HR-CTV during BT in cervical cancer, aiming to provide suggestions for the bladder and rectal volume control during brachytherapy.

There are many studies on the degree of bladder emptying or filling, affecting dose to target area or dose to OARs, ranging from 0 ml to 200 ml [16-19, 29]. Mahantshetty *et al*. [16] reported no significant difference in

Table 3. Linear regression model of factors associated with bladder volume during brachytherapy

Factor	*R*	95% CI		*P*-value
		Lower limit	Upper limit	
Rectum volume	0.40	0.20	0.80	0.00
Sigmoid volume	0.28	–0.36	–0.01	0.03
HR-CTV volume	0.27	0.02	0.65	0.04
Intestine volume	0.20	–0.02	0.17	0.12

HR-CTV – high-risk clinical target volume

Table 4. Change in rectum volume between brachytherapy insertions

Pair		*n*	Rectum volume (cc) (mean ±SD)	Change in rectum volume (cc) (mean ±SD)	*t*	*P*-value
1	1st insertion	60	50.59 ±22.59	0.05 ±28.00	0.15	0.98
	2nd insertion	60	50.54 ±25.92			
2	1st insertion	60	50.59 ±22.59	–10.37 ±37.99	–2.11	0.04
	3rd insertion	60	60.97 ±40.83			
3	1st insertion	60	50.59 ±22.59	–4.34 ±20.20	–1.67	0.10
	4th insertion	60	54.93 ±25.01			
4	1st insertion	60	50.59 ±22.59	–6.45 ±26.33	–1.90	0.06
	5th insertion	60	57.04 ±34.84			
5	2nd insertion	60	50.54 ±25.92	–10.43 ±32.70	–2.47	0.01
	3rd insertion	60	60.97 ±40.83			

Table 5. Linear regression model of factors associated with rectum volume during brachytherapy

Factor	*R*	95% CI		*P*-value
		Lower limit	Upper limit	
Bladder volume	0.40	0.20	0.80	0.00
Sigmoid volume	0.06	–0.59	0.36	0.62
HR-CTV volume	0.31	0.02	0.57	0.02
Intestine volume	0.43	0.66	2.27	0.00

HR-CTV – high-risk clinical target volume

Table 6. Change in HR-CTV volume between brachytherapy insertions

Pair		*n*	HR-CTV volume (cc) (mean ±SD)	Change in HR-CTV volume (cc) (mean ±SD)	*t*	*P*-value
1	1st insertion	60	84.93 ±28.81	7.06 ±2.62	2.69	0.00
	4th insertion	60	77.87 ±24.97			
2	1st insertion	60	84.93 ±28.81	8.90 ±2.44	3.63	0.00
	5th insertion	60	76.03 ±26.53			
3	2nd insertion	60	81.79 ±29.80	5.76 ±2.29	2.51	0.01
	5th insertion	60	76.03 ±26.53			
4	3rd insertion	60	79.84 ±24.40	3.80 ±1.81	2.10	0.04
	5th insertion	60	76.03 ±26.53			

HR-CTV – high-risk clinical target volume

Table 7. Linear regression model of factors associated with HR-CTV volume during brachytherapy

Factor	*R*	95% CI		*P*-value
		Lower limit	Upper limit	
Rectum D_{2cc}	0.43	0.37	1.25	0.00
Rectum D_{99}	0.60	0.41	0.85	0.00
Bladder D_{99}	0.41	0.14	0.53	0.00
HR-CTV D_{2cc}	0.50	9.74	26.19	0.00
HR-CTV D_1	0.52	8.47	21.40	0.00

HR-CTV – high-risk clinical target volume

bladder dose whether the bladder was filled or empty. Siavashpour *et al*. [18] demonstrated that a bladder volume of ≤ 70 ml was optimal. However, there is no clinical consensus on the effect of bladder volume on the dose of OARs and bladder irradiation [17-19]. Most previous studies have used Foley catheters to control bladder volume [30, 31], but bladder volume remained highly variable, which may be related to poor catheter drainage, impaired bladder function, and general anesthesia. All patients in this study followed a uniform preparation procedure (emptying the bladder and rectum before BT), and Foley catheter was not used to control bladder volume. Davidson *et al*. [32] noted that following a uniform bladder filling or emptying procedure could also minimize changes due to organ deformation.

Our results showed the median bladder volume of 68.36 cc (range, 29.9-235.68 cc), only 4 cases with bladder volumes > 100 ml, and a significant reduction in bladder volume at the third insertion ($p < 0.05$). More than 90% of the patients had bladder volumes controlled at around 70 cc, which avoided more manipulation and possible risks of accidents during general anesthesia. Linear regression analysis further showed that bladder volume during BT correlated with sigmoid colon and HR-CTV, unrelated to small bowel volume. As bladder filling volume increased, there was no corresponding increase in rectal, HR-CTV, and small bowel receptive volumes, and sigmoid D_{2cc} decreased. Nesseler *et al*. [19, 29] indicated that bladder expansion reduced the dose received by the small bowel, without altering the dose received by other OARs. In addition, we found that bladder volume was significantly correlated with bladder D_{99}, D_m, and D_{ave}, but not with bladder D_1 and D_{2cc}, which is not consistent with previously reported data, probably owing to the late tumor (T) stage (81.7% of tumors ≥ 4 cm) and tandem lengths (TL), all > 4 cm in our study cases. In a study [15], when TL was > 4 cm and T ≤ 4 cm, bladder dose was significantly affected by bladder volume and TL, while when T > 4 cm, there was no correlation between the change in bladder dose and volume.

Furthermore, we analyzed the effect of rectal volume change on OARs and HR-CTV. Rectal volume was correlated with the bladder, HR-CTV, and small bowel volume, but not with sigmoid volume. The median rectal volume was 54.95 cc (range, 24.92-168.1 cc), and as rectal volume increased, HR-CTV D_{ave}, sigmoid D_{2cc}, and rectal D_{2cc} also increased, while small bowel D_{mean} decreased. Siavashpour *et al*. [18] stated that when the rectal volume was < 40 cc, the difference between rectal $D_{0.1cc}$ and D_{2cc} was about 3%, which is similar to our results. The rectal dose was greatest with the bladder volume being 120-140 cc. When the bladder volume was > 140 cc, the rectal dose started to decrease. Rectal $D_{0.1cc}$ and D_{2cc} were similar when bladder volume was < 70 cc or bladder volume was > 170 cc. Additionally, we did not observe the influence of rectal volume on bladder volume. It may be that the fixed applicator plays a key role as the rigid support of HR-CTV and rectum, which can resist the downward pressure from expanding bladder. A study [32] reported that using the same applicator for each insertion could minimize changes caused by the placement of applicator.

In addition, we analyzed the changes in HR-CTV volume per fraction and the consequent dosimetric changes. The HR-CTV volume gradually decreased with the increasing number of brachytherapy insertions, which

may be related to clinician experience and image alignment, with a significant difference between the 1st and 5th comparisons; the median HR-CTV volume was 80.19 cc (range, 36.44-138.16 cc). Linear regression analysis showed that HR-CTV variation with volume affected rectal D_{2cc}, rectal D_{99}, bladder D_{99}, and HR-CTV D_{2cc} and HR-CTV D_1, and did not affect the volume variation of the sigmoid colon and small intestine.

Unlike other research, this study followed a uniform preparation process and did not use a Foley catheter for bladder volume control, showing similar study results. However, the present study had several limitations. First, it was a single-institution retrospective study. Second, it applied a conventional point A-based ICBT (AICBT) planning technique, and brachytherapy plan could only be performed within dose limits of OARs, with a disadvantage of dose optimization not applied to the target volume of conformal ICBT [33]. Third, the number of cases was small, and the target area, OARs, were delineated based on CT images, with some errors in image alignment, whereas international recommendations advocated the use of MRI as the preferred imaging modality [34]. However, it is difficult to design a case study that includes more stratification factors, and a specific protocol is recommended to be developed prior to the study in order to obtain more accurate results.

Conclusions

Following a uniform preparation process and controlling the bladder filling status before brachytherapy is an important factor to ensure accurate radiotherapy of the primary tumor and OARs. Limiting bladder volume can reduce the dose to the bladder and sigmoid colon. Restricting rectal volume decreases the dose to the small intestine. HR-CTV volume does not affect the volume change in the sigmoid colon and small intestine.

Disclosure

The authors report no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209-249.
2. Datta NR, Stutz E, Liu M et al. Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis. *Gynecol Oncol* 2017; 145: 374-385.
3. Shrivastava S, Mahantshetty U, Engineer R et al. Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: a randomized clinical trial. *JAMA Oncol* 2018; 4: 506-513.
4. Viswanathan AN, Cormack R, Rawal B et al. Increasing brachytherapy dose predicts survival for interstitial and tandem-based radiation for stage IIIB cervical cancer. *Int J Gynecol Cancer* 2009; 19: 1402-1406.
5. Chargari C, Deutsch E, Blanchard P et al. Brachytherapy: An overview for clinicians. *CA Cancer J Clin* 2019; 69: 386-401.
6. Suzumura EA, Gama LM, Jahn B et al. Effects of 3D image-guided brachytherapy compared to 2D conventional brachytherapy on clinical outcomes in patients with cervical cancer: A systematic review and meta-analyses. *Brachytherapy* 2021; 20: 710-737.
7. Kim YJ, Kang HC, Kim YS. Impact of intracavitary brachytherapy technique (2D versus 3D) on outcomes of cervical cancer: a systematic review and meta-analysis. *Strahlenther Onkol* 2020; 196: 973-982.
8. Dutta S, Nguyen NP, Vock J et al. Image-guided radiotherapy and brachytherapy for cervical cancer. *Front Oncol* 2015; 5: 64.
9. Harkenrider MM, Alite F, Silva SR et al. Image-based brachytherapy for the treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 2015; 92: 921-934.
10. Patel RB, Gururajachar JM, Revathy T. Implications of bladder volume on target coverage and dose to critical structures during high dose rate intracavitary brachytherapy for cervical cancer: A dosimetric study. *J Cancer Res Ther* 2019; 15: 1207-1211.
11. Chiew KL, Chong S, Duggan KJ et al. Assessing guideline adherence and patient outcomes in cervical cancer. *Asia Pac J Clin Oncol* 2017; 13: e373-e380.
12. Espenel S, Garcia MA, Trone JC et al. From IB2 to IIIB locally advanced cervical cancers: report of a ten-year experience. *Radiat Oncol* 2018; 13: 16.
13. Watanabe T, Mikami M, Katabuchi H et al. Quality indicators for cervical cancer care in Japan. *J Gynecol Oncol* 2018; 29: e83.
14. Mayadev JS, Ke G, Mahantshetty U et al. Global challenges of radiotherapy for the treatment of locally advanced cervical cancer. *Int J Gynecol Cancer* 2022; 32: 436-445.
15. Siavashpour Z, Aghamiri MR, Jaberi R et al. A comparison of organs at risk doses in GYN intracavitary brachytherapy for different tandem lengths and bladder volumes. *J Appl Clin Med Phys* 2016; 17: 5-13.
16. Mahantshetty U, Shetty S, Majumder D et al. Optimal bladder filling during high-dose-rate intracavitary brachytherapy for cervical cancer: a dosimetric study. *J Contemp Brachytherapy* 2017; 9: 112-117.
17. Harmon G, Chinsky B, Surucu M et al. Bladder distension improves the dosimetry of organs at risk during intracavitary cervical high-dose-rate brachytherapy. *Brachytherapy* 2016; 15: 30-34.
18. Siavashpour Z, Aghamiri MR, Jaberi R et al. Optimum organ volume ranges for organs at risk dose in cervical cancer intracavitary brachytherapy. *J Contemp Brachytherapy* 2016; 8: 135-142.
19. Nesseler JP, Charra-Brunaud C, Salleron J et al. Effect of bladder distension on doses to organs at risk in pulsed-dose-rate 3D image-guided adaptive brachytherapy for locally advanced cervical cancer. *Brachytherapy* 2017; 16: 976-980.
20. Manea E, Escande A, Bockel S et al. Risk of late urinary complications following image guided adaptive brachytherapy for locally advanced cervical cancer: refining bladder dose-volume parameters. *Int J Radiat Oncol Biol Phys* 2018; 101: 411-420.
21. Mazeron R, Maroun P, Castelnau-Marchand P et al. Pulsed-dose rate image-guided adaptive brachytherapy in cervical cancer: Dose-volume effect relationships for the rectum and bladder. *Radiother Oncol* 2015; 116: 226-232.
22. Zakariaee R, Hamarneh G, Brown CJ et al. Bladder accumulated dose in image-guided high-dose-rate brachytherapy for locally advanced cervical cancer and its relation to urinary toxicity. *Phys Med Biol* 2016; 61: 8408-8424.
23. Matsuo K, Machida H, Mandelbaum RS et al. Validation of the 2018 FIGO cervical cancer staging system. *Gynecol Oncol* 2019; 152: 87-93.
24. Georg P, Pötter R, Georg D et al. Dose effect relationship for late side effects of the rectum and urinary bladder in

magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2012; 82: 653-657.
25. Pötter R, Tanderup K, Kirisits C et al.; EMBRACE Collaborative Group. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; 9: 48-60.
26. Dilalla V, Chaput G, Williams T et al. Radiotherapy side effects: integrating a survivorship clinical lens to better serve patients. *Curr Oncol* 2020; 27: 107-112.
27. Adams E, Boulton MG, Horne A et al. The effects of pelvic radiotherapy on cancer survivors: symptom profile, psychological morbidity and quality of life. *Clin Oncol (R Coll Radiol)* 2014; 26: 10-17.
28. Fuccio L, Frazzoni L, Guido A. Prevention of pelvic radiation disease. *World J Gastrointest Pharmacol Ther* 2015; 6: 1-9.
29. Patra NB, Manir KS, Basu S et al. Effect of bladder distension on dosimetry of organs at risk in computer tomography based planning of high-dose-rate intracavitary brachytherapy for cervical cancer. *J Contemp Brachytherapy* 2013; 5: 3-9.
30. Yamashita H, Nakagawa K, Okuma K et al. Correlation between bladder volume and irradiated dose of small bowel in CT-based planning of intracavitary brachytherapy for cervical cancer. *Jpn J Clin Oncol* 2012; 42: 302-308.
31. Guler OC, Onal C, Acibuci I. Effects of bladder distension on dose distribution of vaginal vault brachytherapy in patients with endometrial cancer. *J Contemp Brachytherapy* 2015; 6: 371-376.
32. Davidson MT, Yuen J, D'Souza DP et al. Image-guided cervix high-dose-rate brachytherapy treatment planning: does custom computed tomography planning for each insertion provide better conformal avoidance of organs at risk? *Brachytherapy* 2008; 7: 37-42.
33. Ju SG, Huh SJ, Shin JS et al. Different effects of bladder distention on point A-based and 3D-conformal intracavitary brachytherapy planning for cervical cancer. *J Radiat Res* 2013; 54: 349-356.
34. Viswanathan AN, Thomadsen B; American Brachytherapy Society Cervical Cancer Recommendations Committee; American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy* 2012; 11: 33-46.