Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(6): 134
https://doi.org/10.31083/j.ceog5006134

Systematic Review

Recurrent Gynecological Tumors in Previously Irradiated Patients. Does Re-Irradiation with Stereotactic Body Radiotherapy Have a Role? A Systematic Review

Antonio Pontoriero[1,†], Paola Critelli[1,†], Alberto Bosurgi[1,*], Chiara Carrubba[1], Corrado Spatola[2], Giacomo Ferrantelli[1], Federico Chillari[1], Valentina Zagardo[1], Anna Brogna[3], Gianluca Ferini[4], Silvana Parisi[1], Stefano Pergolizzi[1]

[1]Radiation Oncology Unit, Department of Biomedical, Dental Science and Morphological and Functional Images, University of Messina, 98100 Messina, Italy
[2]Radiodiagnostic & Oncological Radiotherapy Unit, Department of General Surgery & Medical-Surgical Specialties, University of Catania, 'Policlinico G. Rodolico - San Marco', 95124 Catania, Italy
[3]Medical Physics Unit, A.O.U. "G. Martino" of Messina, 98100 Messina, Italy
[4]Department of Radiation Oncology, REM Radioterapia srl, 95029 Viagrande, Italy
*Correspondence: alberto.bosurgi@libero.it (Alberto Bosurgi)
[†]These authors contributed equally.
Academic Editor: Christos Iavazzo
Submitted: 20 December 2022 Revised: 21 February 2023 Accepted: 13 March 2023 Published: 29 June 2023

Abstract

Background: Re-irradiation of patients with previously irradiated gynecological tumors represents one of the hot topics of modern oncology. It is generally performed using Brachytherapy (alone or after external beam radiation therapy (EBRT) re-treatment) or Stereotactic Body Radiotherapy (SBRT). Literature provides few data concerning SBRT re-irradiation (re-RT). Here we provided a statistical and comparative analysis of the studies to make a general assessment of the efficacy and reliability of SBRT, considering the potential benefits achievable in terms of local control, overall survival and toxicity. **Methods**: A computerized literature search was performed in 3 electronic databases (MEDLINE, EMBASE, and Cochrane) from 1996 to 2020. Only studies analysing outcomes of re-irradiated (re-I) patients were taken into consideration. Quality assessment score and risk of bias were assessed for each article. Random-effects models were used due to great subjectivity given the lack of related control groups in the non-comparative studies and a tendency towards high heterogeneity (examined by the Cochran Q chi-square test and the I^2 statistic). To determine the pooled 2-year Overall Survival (OS) and 2-year Local Control (LC) and $\geq$Grade 3 (G3) treatment-related toxicities, an established meta-analysis technique over single and multi-arm studies was performed. **Results**: Of 21 articles focusing on the role of SBRT in recurrent gynaecological cancers, were identified. Only 7 articles, published between 2009 and 2020, with outcomes limited to re-I patients and specific radiotherapy techniques were included. The selected studies counted a total of 196 patients, 157 of whom were previously irradiated. With a median follow up time of 14.5 months, using SBRT re-I technique, the pooled 2-year OS of 52.7% (95% confidence interval (CI): 0.372 to 0.651) and 2-year LC of 75.7% (95% CI: 0.614 to 0.852) were observed. SBRT re-irradiation technique does not affect toxicities with pooled $\geq$G3 late toxicities being 8.7% (95% CI: –0.0944 to 0.267). **Conclusions**: According to our review, SBRT re-irradiation technique seems to be feasible and safe, when brachytherapy re-RT technique is not available. Further studies are warranted to standardize the best radiation therapy in recurrent gynaecological cancer.

Keywords: stereotactic radiation therapy; re-irradiation; reirradiation; gynaecological cancer; recurrent cervical cancer; recurrent endometrial cancer

1. Introduction

Gynecological tumors represent 7.7% of all malignancies [1] with 2.3% and 3.3% of them respectively represented by endometrial cancer and cervical cancer.

The management of primary tumors requires a multidisciplinary approach with surgery, radiation therapy, and chemotherapy being the different kinds of treatment we can employ to achieve local control and reduce the risk of death.

Recurrence rates for endometrial and cervical cancer after surgery and adjuvant radiotherapy (RT) for endometrial cancer and after radio-chemotherapy treatment for cervical cancer is respectively about 5% and 10% with differences according to the International Federation of Gynecology and Obstetrics (FIGO) stage to they belong [2,3].

The main treatments for local recurrences are surgery (i.e., surgical exenteration) and radiotherapy.

Literature provides few data concerning gynecological tumors re-irradiation. It must be planned and performed considering already delivered doses to both targets and organs at risk (OARs) and normal tissues' tolerance in previous RT course. It may be performed using Brachytherapy (BT) (alone or after external beam re-irradiation) or Stereo-

tactic Body Radiotherapy (SBRT).

To date, the treatment of pelvic recurrences, due to their proximity to radiosensitive anatomical structures (urinary tracts and the bowel), is controversial and associated with disappointing outcomes [4–24].

According to recent systematic reviews, brachytherapy may be used in the management of women with recurrent gynaecologic tumors with negligible toxicities [2]. When brachytherapy is not available, SBRT represents a feasible alternative [25–27].

Stereotactic radiation therapy, in combination with Intensity Modulated Radiation Therapy/Volumetric Modulated Arc Therapy (IMRT/VMAT), permit to perform a dose escalated treatment delivering high dose within bulky tumors to intra- and extracranial lesion, minimizing side effect and obtaining better clinical outcome [28–31].

SBRT may be described as a form of external beam radiation therapy (EBRT) that accurately delivers high and conformed doses to an extracranial target through hypofractionated radiation schemes (usually $\leq$10 fractions), with results which are equivalent to those obtainable using classic dose fractions. This technique employs an image-guided patients' setup with the possibility to introduce active or passive intrafraction motion control systems adapting the treatment to the natural movement of the anatomical structures [32–35]. SBRT may be used for inoperable small pelvic wall lesions and isolated pelvic or para-aortic lymph node recurrences [26,36,37], allowing us to deliver high doses to small treatment volumes, limiting those to the OARs, which is very important since these patients already underwent a primary RT course.

Several reviews reported promising results in terms of local control and survival regarding use of SBRT in recurrent gynaecological cancer [38,39].

Here we provided a statistical and comparative analysis of the studies to make a general assessment of the efficacy and reliability of SBRT, considering the potential benefits achievable in terms of local control, overall survival and toxicity.

2. Materials and Methods

2.1 Study Selection

A systematic review was conducted employing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The computerized literature search was performed in 3 electronic databases (MEDLINE, EMBASE, and Cochrane) from 1996 to 2020.

The search strategy included terms related to "stereotactic radiation therapy", "re-irradiation", "reirradiation" and "gynaecological cancer", "recurrent cervical cancer", "recurrent endometrial cancer".

Criteria for inclusion and exclusion:

Inclusion and exclusion criteria were predetermined. Full-text screening without duplicate citations was carried out. Articles, including <5 re-irradiated patients, abstracts,

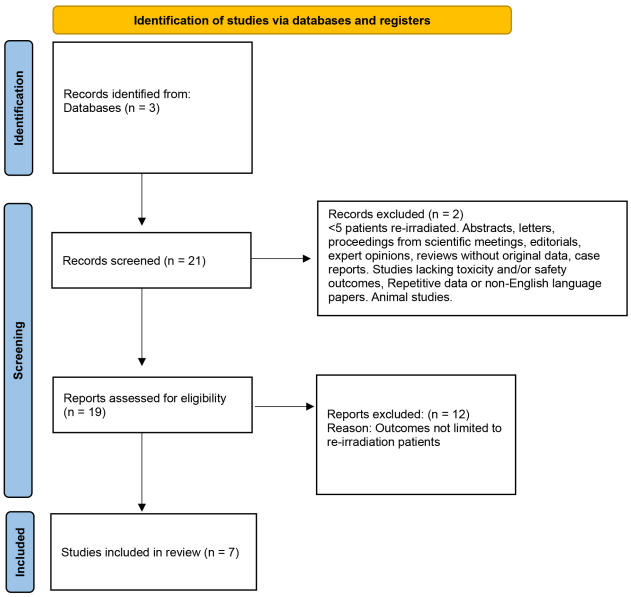


Fig. 1. PRISMA flow diagram detailing how articles were selected for inclusion in the systematic review.

letters, reports from scientific meetings, editorials, expert opinions, reviews without original data, case reports, studies lacking toxicity and/or safety outcomes, repetitive data or non-English written papers and animal studies, were excluded.

Two studies with outcomes limited to re-irradiation patients were screened.

Included studies were retrospective, analysing more than 5 patients. Only studies analysing outcomes of re-irradiated (re-I) patients, where re-I field overlaps with that from primary RT course, were taken into consideration. Discrepancies among reviewers were solved by discussion (Fig. 1).

Review of the trials:

Studies were first reviewed using a list of predefined, pertinent issues concerning the characteristics of patients and treatments. Quality assessment score of included studies was assessed according to checklist for quality appraisal of case series studies produced by Institute of Health Economics (IHE) and modified to improve applicability (Table 1, Ref. [17–21,23,27]). Risk of bias was assessed for each article using quality assessment tool for domain of hypothesis stated, multicentric studies, prospective study, patients' selection, consecutive patients, described characteristics of patients, clearly stated eligibility criteria, described intervention, reported losses to follow-up and adverse events. Risk-of-bias assessment resulted in a low risk of bias in all included papers (Fig. 2a,b, Ref. [17–21,23,27]).

Overall Survival (OS) and Local Control (LC) were analysed and to improve the comparability of the different re-irradiation studies and to assess the relationship between re-irradiation and 2-year OS and 2-year LC, we calculated

Table 1. Quality assessment score of included studies.

Reference	Was hypothesis stated?			Was the study prospective?			Is multicentric?			Consecutive patients			Described characteristics of patients			Clearly stated eligibility criteria			Described intervention			Reported losses to follow-up and adverse events			Conclusions of the study supported by the results			Patients' selection			Final score
	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	Yes	Partial	No	
Deodato *et al.* [23]	2	-	-	2	-	-	-	1	-	-	-	0	2	-	-	2	-	-	2	-	-	2	-	-	-	1	-	-	1	-	15
Yazici *et al.* [21]	2	-	-	2	-	-	-	-	0	-	1	-	2	-	-	2	-	-	2	-	-	-	1	-	2	-	-	-	1	-	15
Seo *et al.* [19]	2	-	-	2	-	-	-	-	0	2	-	-	2	-	-	2	-	-	2	-	-	-	1	-	-	1	-	2	-	-	16
Park *et al.* [20]	2	-	-	2	-	-	2	-	-	2	-	-	-	1	-	2	-	-	2	-	-	-	1	-	2	-	-	2	-	-	18
Hasan *et al.* [17]	2	-	-	-	-	0	-	-	0	-	1	-	2	-	-	2	-	-	2	-	-	2	-	-	2	-	-	-	1	-	14
Pontoriero *et al.* [18]	2	-	-	1	-	-	-	-	0	2	-	-	2	-	-	2	-	-	2	-	-	2	-	-	2	-	-	2	-	-	15
Hsin-Yi Cheng *et al.* [27]	2	-	-	2	-	-	-	1	-	-	-	0	2	-	-	2	-	-	-	1	-	-	1	-	-	1	-	-	1	-	14

Table 2. Patient characteristics and details of radiation delivery.

Author and year	Study type	Pts with P-RT (total)	Pts with P-RT (ReIrradiation)	Primary site	Treatment at primary diagnosis	P-RT technique, dose (range), franctionation	Recurrent site	Re-RT technique, dose (range), fractionation	Toxicities ≥G3 % (pz)
Deodato *et al.* [23]	R	11	6	Cervix/Endometrium/ Vagina/Vulva	Surgery: CT: CTRT: CT + CTRT: Surgery + CT: Surgery + CT + RT: RT + BT	37.5 Gy, 50 Gy, 65 Gy, 50.4 Gy, 63 Gy, 45 Gy (Median dose 51.82 Gy)	Local and distant recurrence (not specified)	SBRT 30 Gy/6 fx or 25 Gy/5 fx or 20 Gy/4 fx	0
Yazici *et al.* [21]	R	16	11	Cervix, Endometrium, Ovary	S: S + EBRT/S + CTRT/CTRT + BRT/S + CT	EBRT 50.4 Gy (range 45–60 Gy) with BT doses until to a 85–90 Gy)	pelvic wall, para-iliac nodes, low para-aortic	SBRT 15–40 in 3–5 fx	G3 toxicities: 19% (3) proctitis; G4 toxicities: fistula 19% (3)
Seo *et al.* [19]	R	23	23	Uterus, Cervix	Surgery: Surgery + EBRT: Surgery + EBRT + BT: EBRT + BT	EBRT 40–70 Gy	Local progression	SBRT 36–45/3 fx	G4 toxicities: retto vaginal fistula 13% (3)
Park *et al.* [20]	R	85	68	Cervix	Surgery + RT/CTRT	IMRT, 50,4 Gy (28 fx)	Paraortic, Common iliac, external and internal iliac nodes	SBRT 39 Gy in 3 fx (median)	G3 toxicities: 3% (1) urethral stricture, 3% (1) ileus, 3%(1) enterocolitis; G4 toxicities: 6% (2) rectovaginal fistula
Hasan *et al.* [17]	R	30	13	Cervix, Endometrium, Ovary	OP ± RT or RT ± CT	NR	Cervix, vaginal vault, pelvic nodes, PAN, distant metastases	SBRT median dose 27.5 Gy (15–40)/3–5 fx	7.7% (1) rectovaginal/vesicovaginal fistulas
Pontoriero *et al.* [18]	R	5	5	Endometrium	EBRT + BT	EBRT 45 Gy in 25 fx + BT 15 Gy in 3 fx	pelvic recurrence	SBRT 18 Gy in 3–4 fx	0
Cheng et al. [27]	R	25	14	Endomethrium/ Cervix/Vulva	OP/NCT + OP/OP + ACT/RT	NR	Central (3), Central extending to pelvic side wall (6), Pelvic wall (1), vulva (1)	45 Gy in 25 fx + SBRT 25 Gy in 5 fx	Diarrhea (7%), Hemorrhage (7%), Fistula (14%), Sigmoid Perforation (7%)

R, retrospective; P-RT, previous radiotherapy; re-RT, re-irradiation; pts patients; fx, fractions; adj, adjuvant; OP, operation; RT, radiotherapy; CT, chemotherapy; CTRT, chemoradiotherapy; NCT, Neoadjuvant chemotherapy, ACT, Adjuvant chemotherapy, BRT, external beam radiotherapy; BT, brachytherapy; SBRT, stereotactic body radiotherapy; NR, Not reported; IMRT, Intensity Modulated Radiation Therapy; EBRT, external beam radiation therapy; S: Surgery; G3, Grade 3; G4, Grade 4; EBRT, external beam radiation therapy; PAN, Para-aortic nodes.

*Related to re-irradiated patients.

the estimated sub-population of Grade 3 (G3) and Grade 4 (G4) treatment-related toxicities.

2.2 Statistical Methods

To determine the pooled OS and local control at 2-year and G3–G4 toxicity rate, an established meta-analysis technique over single and multi-arm studies was performed. We calculated the estimated population proportion of toxicity, 2 years overall survival, 1-year locoregional control with 95% confidence interval (CI) for each separate study [40]. Pooled effect size aided the general evaluation of re-irradiation risk and effect. Heterogeneity across studies was examined by the Cochran Q chi-square test and the I^2 statistic. Studies with an I^2 statistic of 0–50%, 50–75%, and >75% were considered to respectively have low, moderate, and high heterogeneity [41]. We used random-effects models because there was great subjectivity given the lack of related control groups in the non-comparative studies, and a tendency towards high heterogeneity.

3. Results

21 articles, focusing on the role of SBRT in recurrent gynaecological cancers, were identified. Only those with outcomes limited to re-I patients and specific radiotherapy techniques were included, and 7 articles fulfilled the inclusion criteria.

The selected studies, published between 2009 and 2020, counted for a total of 195 patients, 140 of whom were previously irradiated.

Patient characteristics:

The study populations were heterogeneous. Six studies included patients with primary cervical [17,19–21,23,27] and endometrial cancer [17–19,21,23,27]. Two studies reported a combination of patients with primary vulvar cancer [23,27], vaginal cancer [23] and ovarian cancer [17,21].

Primary treatment:

Patients were mainly treated with a combination of surgery, neoadjuvant/adjuvant chemotherapy, and external beam radiation therapy (range 37.5 Gy-70 Gy in 25–28 fx) with or without brachytherapy (range 15–21 Gy in 3 fractions). Data about primary radiotherapy treatment schedule were not available in two studies alone [17,27].

Recurrent Site and treatment schedule:

The recurrence site had different locations and the main site were pelvic recurrence in two studies [18,28], pelvic lymph node (para-iliac nodes, low para-aortic and Common iliac) [17,20,21]. Hasan *et al*. [17] and Hsin-Yi Cheng *et al*. [27] reported a case of cervical and vulvar recurrence, respectively.

Two cases of local progression [19,23] and only one of distant recurrence (but not specified) [23] were observed.

The recurrence treatment was generally a radiotherapeutic approach with SBRT. Only one studies reported an association of EBRT [27]. Reirradiation dose and schedule were heterogeneous (range 15 Gy–66 Gy in 3–6 fractions).

Cumulative Biologically effective doses (Cum BED) were calculated according to the linear-quadratic model assuming an alpha/beta value of 10 Gy. In only three studies, dose to OAR were reported [18,19,27].

Patient characteristics and details of radiation delivery are resumed in Table 2 (Ref. [17–21,23,27]).

OS, LC, and Toxicity

Outcomes were evaluable for 140 patients.

4 studies were analysed for 2-year OS [17,19–21] and 3 for 2-year LC [17,19,20] respectively. The median 2-year OS was of 46.5% in 115 patients evaluated; 2-year LC was analysed in 104 patients with a median of 65%.

Data on G3 toxicity were available in 129 patients [17–20,23,28]. The most frequent G3 toxicities were urethral stricture (3%), enterocolitis (3%), fistula (14%), sigmoid perforation (7%), recto-vaginal fistula (3%), enterovaginal/vescicovaginal fistula (7.7%), genitourinary (not specified). Only two cases of G4 toxicity (recto-vaginal fistula) was registered (19%) [19,20].

The toxicities related to doses to the OARs are tabulated in Table 3 (Ref. [18,19,27]).

With a median follow up time of 14.5 months, using SBRT re-I technique, the pooled 2-year OS of 52.7% (95% CI: 0.372 to 0.651) and 2-year LC of 75.7% (95% CI: 0.614 to 0.852) were observed (Fig. 3a,b, Ref. [17–21,23,27]).

SBRT re-irradiation technique does not affect toxicities with pooled ≥G3 late toxicities being 8.7% (95% CI: –0.0944 to 0.267) (Fig. 4, Ref. [17–20,23,27]).

4. Discussion

Re-irradiation for gynaecological tumors has traditionally been associated with high morbidity. With the development of image-guided techniques as brachytherapy and stereotactic radiotherapy, it's now possible to deliver higher and conformal dose, reducing exposure of normal tissues.

SBRT may be considered as an alternative to brachytherapy for local symptom control [42].

Re-irradiation with brachytherapy results in relatively reasonable local control and toxicities. Local control ranged from 44% to 88% over 1 and 5 years; OS from 39.5 e 82% at 2 and 5 years; late G3 and 4 toxicity varied very broadly from 0% to 42.9% [2].

Cyberknife system, with prescription to specific isodose lines, precise targeting and delivery of radiation, allow to deliver inhomogeneous dose and dose escalation respecting the normal tissue tolerance of OAR, improving local control and toxicity profiles [25]. On the other hand, Hsieh *et al*. [26] suggested the possibility of replacing brachytherapy with SBRT administered through helical tomotherapy.

Brachytherapy is supposed to be used for recurrences involving the primary tumor site and near ones (such as cervix, parametria and vagina) thanks to high dose gradients with major dose distribution to the site of interest and

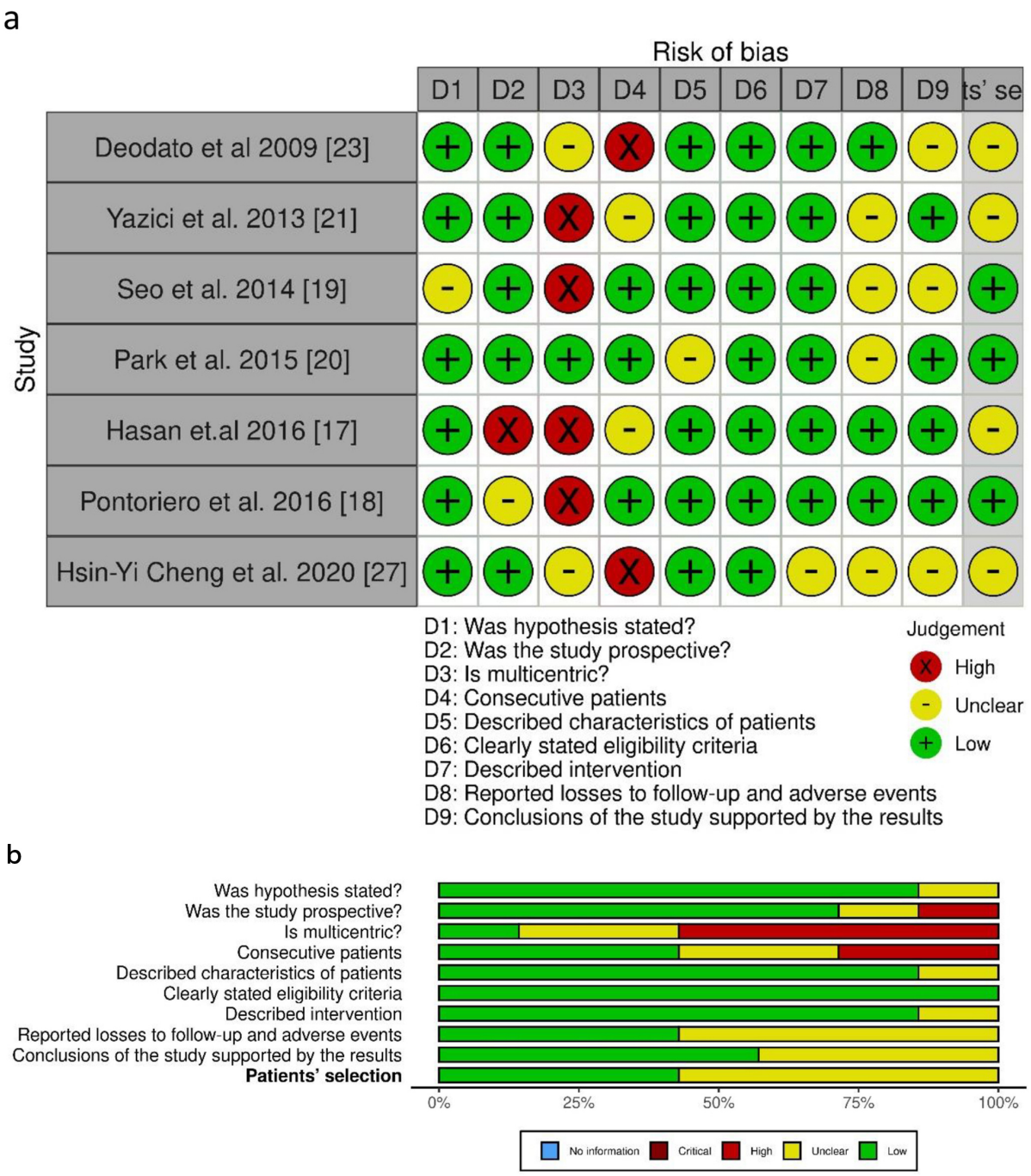


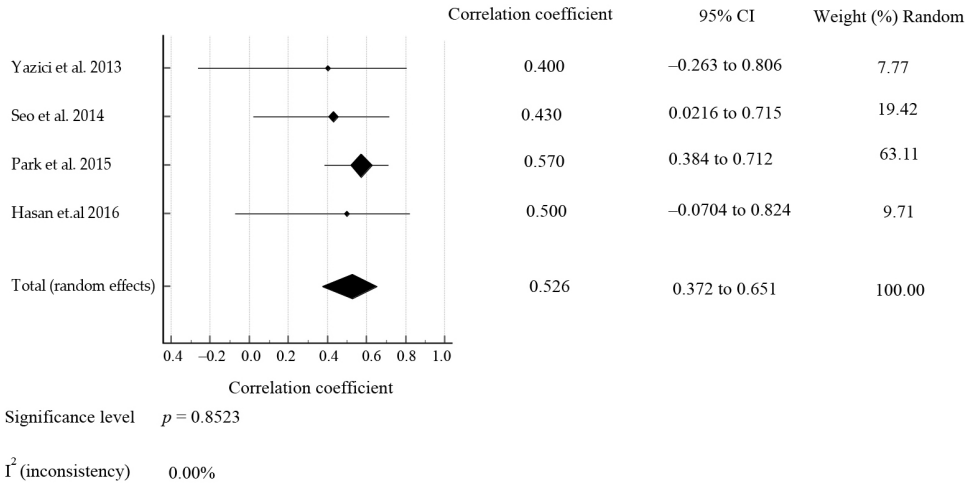
Fig. 2. Risk of bias assessment. (a) Author's judgments about each risk of bias items. Risk of bias was assessed for each article using quality assessment tool for domain of hypothesis stated, multicentric studies, prospective study, patients' selection, consecutive patients, described characteristics of patients, clearly stated eligibility criteria, described intervention, reported losses to follow-up and adverse events. (b) Risk of bias summary. Risk-of-bias assessment resulted in a low risk of bias in all included papers.

Table 3. Toxicities related to doses to the OARs.

References	Rectum	Bladder	Bowel loop	Late toxicities Grade >3 (%)
Seo *et al.* [19]	D5cc <30 Gy V40 <50 cc GTV <50 cc	Dmax 3–35 Gy (median 13 Gy)	Dmax 7–30 Gy (median 20 Gy)	retto vaginal fistula (13%)
Pontoriero *et al.* [18]	Dmax 13 Gy	Dmax 5 Gy	Dmax 5 Gy	0
Cheng, *et al.* [27]	D2cc-EQD2 68.82 (median, Gy)	D2cc-EQD2 73.1 (median, Gy)	D2cc-EQD2 66.86 (median, Gy)	Diarrhea (7%), Hemorrhage (7%), Fistula (14%), Sigmoid Perforation (7%)

EQD2, Equivalent dose in 2; D2cc, dose received by 2 cc of OAR; D5cc, dose received by 5 cc of OAR; GTV, gross tumor volume; V40, volume of rectum receiving 40 Gy.

a



b

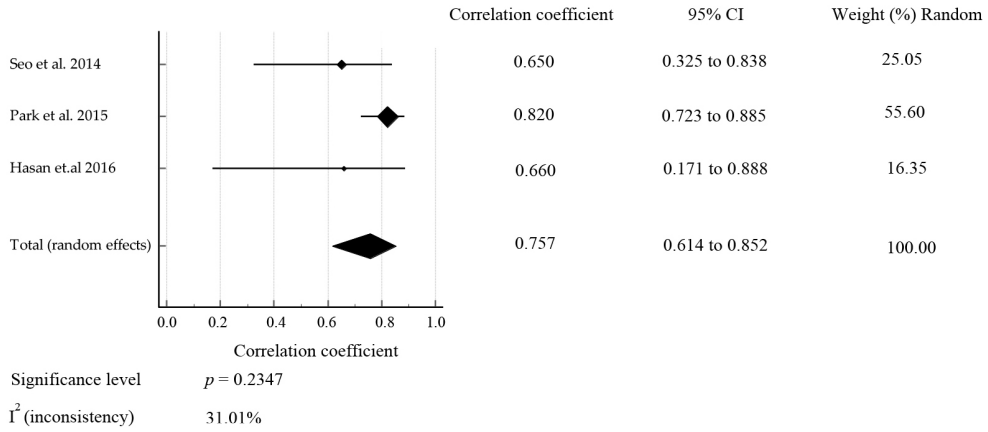


Fig. 3. Pooled 2-year OS. (a) Pooled objective 2 years overall survival in re-irradiated patients for included studies: pooled 2-year OS of 52.7% (95% confidence interval (CI): 0.372 to 0.651) was observed; (b) Pooled objective 2 years local control in re-irradiated patients for included studies: pooled 2-year LC was of 75.7% (95% CI: 0.614 to 0.852). OS, Overall Survival; CI, Confidence interval.

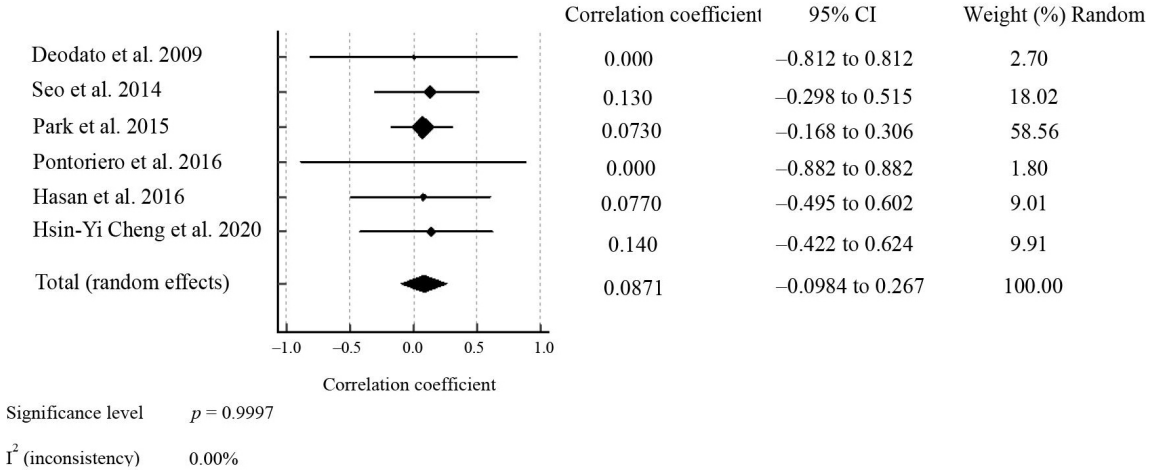


Fig. 4. Pooled ≥G3 late toxicities. Pooled ≥G3 late toxicities of 8.7% (95% CI: –0.0944 to 0.267) was observed in SBRT re-irradiation technique.

minor spread to the surrounding structures.

SBRT may be used for both local and distant recurrences, being the preferrable alternative especially in case of pelvic ones with high tumor burden and nodal ones, considering the possibility of target's intra-/interfraction motion. Fiducial tracking system contributes for accurate patient positioning and targeting ensuring tracking of target translation and rotational movements [43]. Some authors suggest use of SBRT with endovaginal device as "fiducials" when patients have clinical conditions that do not allow to deliver BT. Thus, SBRT represent an alternative to BT delivering high doses of external radiation resembling BT dose distribution [18].

The evidence available about SBRT re-irradiation of pelvic tumors are based on small single institutions and some studies were not considered for statistical analysis due to the high heterogeneity.

Considering adjacent normal organs, the dose that can be administered may vary depending on the site of recurrence. In selected studies recurrence site and relative re-irradiation doses were different and heterogeneous. Distant progression (not specified) were retreated with doses ranged between 20–30 Gy in 4–5 fx in [23] and 36–45 Gy/3 fx [19]. In different lymph nodes metastases were delivered doses of 15–40 Gy/3–5 fx or 39 Gy/3 fx [20,21]. Cervix, vaginal vault, pelvic wall and vulva were retreated with a range of 15 Gy–40 Gy [17,28]. Only Pontoriero *et al.* [18] define recurrence site in pelvic recurrence re-irradiated delivering 18 Gy in 3–4 fractions. More detailed data on cumulative radiation doses delivered on OAR, which can be translated in retreatment setting, derives from studies on radiation boost after external beam irradiation with curative purpose [28,30].

According to these studies, many factors may affect the probability of local control after re-I, such as SBRT re-irradiation dose, volume recurrence [19,42] and histology [22,44].

It has been shown that increasing the dose delivered to the tumor may improve local control. In Park *et al.* [20] achieving a BED >89.7 Gy (≥39 Gy in three fractions, p = 0.072) and 69.3 Gy (≥33 Gy in three fractions, p = 0.059) may be predicted to marginally-superior local control [Park *et al.*] [20]. Abusaris *et al.* [24] in a retrospective study, reported a 1–2-LC of 100% and 1-year OS of 71% when more than 60 Gy were delivered.

Volume recurrence (cc) is related to better prognosis, both in term of local control and overall survival [19,42]. A longer 2-year OS and 2 year local progression free survival (LPFS) in patients with small volume (89%, p = 0.0001 and 85%, p = 0.0199, respectively) were observed [19]. In Reshko *et al.* [44] a local control resulted slightly inferior in larger tumors (hazard ratio (HR) 1.01, 95% CI: 1.00–1.01, p = 0.02). When average tumor was 18 cc, a complete response rate was observed, than higher volume that are associated with progression of disease [42]. Dewas *et al.* [22] reported 1-year LC rates of 51.4% in 15/16 patients who receiving SBRT re-irradiation for pelvic recurrence of different histology of the primary lesion.

Adenocarcinoma are associated with higher chances of recurrence and worse OS if compared with other histology (HR 1.66, 95% CI: 1.03–2.68, p = 0.038) [42]. Conversely, Dewas [22] showed a better LC of adenocarcinoma than squamous carcinoma (p = 0.09).

Deodato *et al.* [23] reported acceptable outcomes of SBRT in 11 patients with locally recurrent gynaecological cancer (uterine cervix [n = 4], ovary [n = 4] and endometrial [n = 3]) with 2-OS of 63.6% and 1-year LC of 93%.

Two Korean groups reported results in patients treated with SBRT for recurrent or metastatic uterine cervical cancer with OS at 2 years of 43% and 57.5% respectively [19,20].

In Park, 68 out of 85 patients were treated with SBRT for recurrent or metastatic uterine cervical cancer. With a median follow up of 20.4 months a 5y OS 32.9% were reported and only 5 patients showed toxicities >grade 3 [20].

In our analysis, pooled 2-year OS and 2-year LC were of 52.7% and 75.7%.

The main concern of salvage SBRT is the potential severe late toxicity.

Retrospective studies demonstrate that despite high cumulative dose were delivered with SBRT after a previous external beam radiation with or without brachytherapy, the toxicity was rather low.

In our analysis, few studies reported late toxicities related to re-irradiated patients.

In Pontoriero *et al.* [18] 60% showed Grade 1 (G1) toxicities (two patients genitourinary (GU) and only one gastrointestinal (GI)); 20% showed Grade 2 (G2) Cystitis and diarrhea; Hsin-Yi Cheng *et al.* [27] reported 14% GU late toxicities (Grade 1) and 3 patients genitourinary gastrointestinal and legs edema (Grade 2).

In Yazici *et al.* [21], sixteen patients with recurrent gynaecological cancer treated with mixed approach, showed a grade >3 toxicities rate of 19% with 1–2 year OS of 60.3% and 40.2% respectively.

In Pontoriero *et al.* [18], patients were retreated with median cumulative Equivalent dose in 2 (EQD2) Gy fractions of 85 Gy; after a median follow-up of 12 months (range, 8–34 months), no severe (>Grade 3) acute/late genitourinary or low gastrointestinal toxicity was observed.

More recently, Reshko *et al.* [44] and Hsin-Yi Cheng *et al.* [27] showed that SBRT re-irradiation in feasible with acceptable toxicities in patients unable to have brachytherapy. Our pooled analysis showed ≥G3 late toxicities of 8.7%.

5. Conclusions

According to our review, SBRT re-irradiation technique seems to be feasible and safe, when brachytherapy re-RT technique is not available.

The data underlined high heterogeneity and further studies, randomized clinical trials, prospective studies and analysis of large real-world high-quality datasets are warranted to standardize the best radiation therapy in recurrent gynaecological cancer.

Author Contributions

AP and Sper designed and coordinated the study and the analysis. ABos, CC, GFerr, FC, VZ performed the literature search and selected included studies. PC revised the literature search and performed data extraction. GFeri, SPar and CS checked data extraction. AP, PC and ABro performed statistical data analysis and provided graphics. AP and PC drafted the manuscript. AP and SPer critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Antonio Pontoriero is serving as one of the Guest editors of this journal. We declare that Antonio Pontoriero had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Christos Iavazzo.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5006134.

References

[1] World Cancer Research Fund International. 2020. Available at: https://www.wcrf.org/cancer-trends/worldwide-cancer-data/ (Accessed: 30 October 2022).

[2] Sturdza A, Viswanathan AN, Erickson B, Yashar C, Bruggeman A, Feddock J, *et al*. American Brachytherapy Society working group report on the patterns of care and a literature review of reirradiation for gynecologic cancers. Brachytherapy. 2020; 19: 127–138.

[3] Zanagnolo V, Ming L, Gadducci A, Maggino T, Sartori E, Zola P, *et al*. Surveillance procedures for patients with cervical carcinoma: a review of the literature. International Journal of Gynecological Cancer. 2009; 19: 194–201.

[4] Martínez-Monge R, Valtueña Peydró G, Cambeiro M, Aramendía JM, Gimeno M, Santisteban M, *et al*. Perioperative high-dose-rate brachytherapy in locally advanced and recurrent gynecological cancer: Final results of a Phase II trial. Brachytherapy. 2018; 17: 734–741.

[5] Badakh DK, Grover AH. Reirradiation with high-dose-rate remote afterloading brachytherapy implant in patients with locally recurrent or residual cervical carcinoma. Journal of Cancer Research and Therapeutics. 2009; 5: 24–30.

[6] Ling DC, Vargo JA, Glaser SM, Kim H, Beriwal S. Outcomes after definitive reirradiation with 3D brachytherapy with or without external beam radiation therapy for vaginal recurrence of endometrial cancer. Gynecologic Oncology. 2019; 152: 581e586.

[7] Umezawa R, Murakami N, Nakamura S, Wakita A, Okamoto H, Tsuchida K, *et al*. Image-guided interstitial high-dose-rate brachytherapy for locally recurrent uterine cervical cancer: A single-institution study. Brachytherapy. 2018; 17: 368–376.

[8] Kamran SC, Manuel MM, Catalano P, Cho L, Damato AL, Lee LJ, *et al*. MR- versus CT-based high-dose-rate interstitial brachytherapy for vaginal recurrence of endometrial cancer. Brachytherapy. 2017; 16: 1159–1168.

[9] Kamran SC, Harshman LC, Bhagwat MS, Muralidhar V, Nguyen PL, Martin NE, *et al*. Characterization of efficacy and toxicity after high-dose pelvic reirradiation with palliative intent for genitourinary second malignant neoplasms or local recurrences after full-dose radiation therapy in the pelvis: A high-volume cancer center experience. Advances in Radiation Oncology. 2017; 2: 140–147.

[10] Feddock J, Cheek D, Steber C, Edwards J, Slone S, Luo W, *et al*. Reirradiation Using Permanent Interstitial Brachytherapy: A Potentially Durable Technique for Salvaging Recurrent Pelvic Malignancies. International Journal of Radiation Oncology, Biology, Physics. 2017; 99: 1225–1233.

[11] Huang K, D'Souza D, Patil N, Velker V, Leung E, Stitt L, *et al*. High-dose-rate interstitial brachytherapy for the treatment of high-volume locally recurrent endometrial carcinoma. Brachytherapy. 2016; 15: 543–548.

[12] Murakami N, Kato T, Miyamoto Y, Nakamura S, Wakita A, Okamoto H, *et al*. Salvage High-dose-rate Interstitial Brachytherapy for Pelvic Recurrent Cervical Carcinoma After Hysterectomy. Anticancer Research. 2016; 36: 2413–2421.

[13] Amsbaugh MJ, Bhatt N, Hunter T, Gaskins J, Parker L, Metzinger D, *et al*. Computed tomography planned interstitial brachytherapy for recurrent gynecologic cancer. Brachytherapy. 2015; 14: 600–605.

[14] Zolciak-Siwinska A, Bijok M, Jonska-Gmyrek J, Kawczynska M, Kepka L, Bujko K, *et al*. HDR brachytherapy for the reirradiation of cervical and vaginal cancer: analysis of efficacy and dosage delivered to organs at risk. Gynecologic Oncology. 2014; 132: 93–97.

[15] Mahantshetty U, Kalyani N, Engineer R, Chopra S, Jamema S, Ghadi Y, *et al*. Reirradiation using high-dose-rate brachytherapy in recurrent carcinoma of uterine cervix. Brachytherapy. 2014; 13: 548–553.

[16] Mabuchi S, Takahashi R, Isohashi F, Yokoi T, Okazawa M, Sasano T, *et al*. Reirradiation using high-dose-rate interstitial brachytherapy for locally recurrent cervical cancer: a single institutional experience. International Journal of Gynecological Cance. 2014; 24: 141–148.

[17] Hasan S, Ricco A, Jenkins K, Lanciano R, Hanlon A, Lamond J, *et al*. Survival and Control Prognosticators of Recurrent Gy-

necological Malignancies of the Pelvis and Para-aortic Region Treated with Stereotactic Body Radiation Therapy. Frontiers in Oncology. 2016; 6: 249.
[18] Pontoriero A, Iatì G, Aiello D, Pergolizzi S. Stereotactic Radiotherapy in the Retreatment of Recurrent Cervical Cancers, Assessment of Toxicity, and Treatment Response: Initial Results and Literature Review. Technology in Cancer Research & Treatment. 2016; 15: 759–765.
[19] Seo Y, Kim MS, Yoo HJ, Jang WI, Rhu SY, Choi SC, *et al*. Salvage stereotactic body radiotherapy for locally recurrent uterine cervix cancer at the pelvic sidewall: Feasibility and complication. Asia-Pacific Journal of Clinical Oncology. 2016; 12: e280–e288.
[20] Park HJ, Chang AR, Seo Y, Cho CK, Jang WI, Kim MS, *et al*. Stereotactic Body Radiotherapy for Recurrent or Oligometastatic Uterine Cervix Cancer: A Cooperative Study of the Korean Radiation Oncology Group (KROG 14-11). Anticancer Research. 2015; 35: 5103–5110.
[21] Yazici G, Cengiz M, Özyğgit G, Yavas G, Ayhan A, Gurkaynak M, *et al*. Salvage Stereotactic Body Radiosurgery in the Management of Recurrent Gynecological Cancer. International Journal of Hematology and Oncology. 2013; 32: 007–012.
[22] Dewas S, Bibault JE, Mirabel X, Nickers P, Castelain B, Lacornerie T, *et al*. Robotic image-guided reirradiation of lateral pelvic recurrences: preliminary results. Radiation Oncology. 2011; 6: 77.
[23] Deodato F, Macchia G, Grimaldi L, Ferrandina G, Lorusso D, Salutari V, *et al*. Stereotactic radiotherapy in recurrent gynecological cancer: a case series. Oncology Reports. 2009; 22: 415–419.
[24] Abusaris H, Hoogeman M, Nuyttens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. Technology in Cancer Research & Treatment. 2012; 11: 591–597.
[25] Haas JA, Witten MR, Clancey O, Episcopia K, Accordino D, Chalas E. CyberKnife Boost for Patients with Cervical Cancer Unable to Undergo Brachytherapy. Frontiers in Oncology. 2012; 2: 25.
[26] Hsieh CH, Tien HJ, Hsiao SM, Wei MC, Wu WY, Sun HD, *et al*. Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result. OncoTargets and Therapy. 2013; 6: 59–66.
[27] Cheng HY, Liang JA, Hung YC, Yeh LS, Chang WC, Lin WC, *et al*. Stereotactic body radiotherapy for pelvic boost in gynecological cancer patients with local recurrence or unsuitable for intracavitary brachytherapy. Taiwanese Journal of Obstetrics and Gynecology. 2021; 60: 111–118.
[28] Pontoriero A, Critelli P, Conti A, Cardali S, Angileri FF, Germanò A, *et al*. The “Combo” radiotherapy treatment for high-risk grade 2 meningiomas: dose escalation and initial safety and efficacy analysis. Journal of Neuro-Oncology. 2023; 161: 203–214.
[29] Ferini G, Parisi S, Lillo S, Viola A, Minutoli F, Critelli P, *et al*. Impressive Results after “Metabolism-Guided” Lattice Irradiation in Patients Submitted to Palliative Radiation Therapy: Preliminary Results of LATTICE_01 Multicenter Study. Cancers. 2022; 14: 3909.
[30] Parisi S, Ferini G, Cacciola A, Lillo S, Tamburella C, Santacaterina A, *et al*. A non-surgical COMBO-therapy approach for locally advanced unresectable pancreatic adenocarcinoma: preliminary results of a prospective study. La Radiologia Medica. 2022; 127: 214–219.
[31] Ferini G, Valenti V, Viola A, Umana GE, Illari SI, Parisi S, *et al*. First-ever Clinical Experience with Magnetic Resonance-based Lattice Radiotherapy for Treating Bulky Gynecological Tumors. Anticancer Research. 2022; 42: 4641–4646.
[32] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, *et al*. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Medical Physics. 2010; 37: 4078–4101.
[33] Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, *et al*. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. International Journal of Radiation Oncology, Biology, Physics. 2010; 76: 326–332.
[34] Kirkbride P, Cooper T. Stereotactic body radiotherapy. Guidelines for commissioners, providers and clinicians: a national report. Clinical Oncology. 2011; 23: 163–164.
[35] Sahgal A, Roberge D, Schellenberg D, Purdie TG, Swaminath A, Pantarotto J, *et al*. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. Clinical Oncology. 2012; 24: 629–639.
[36] Guckenberger M, Bachmann J, Wulf J, Mueller G, Krieger T, Baier K, *et al*. Stereotactic body radiotherapy for local boost irradiation in unfavourable locally recurrent gynaecological cancer. Radiotherapy and Oncology. 2010; 94: 53–59.
[37] Higginson DS, Morris DE, Jones EL, Clarke-Pearson D, Varia MA. Stereotactic body radiotherapy (SBRT): Technological innovation and application in gynecologic oncology. Gynecologic Oncology. 2011; 120: 404–412.
[38] Shenker R, Stephens SJ, Davidson B, Chino J. Role of stereotactic body radiotherapy in gynecologic radiation oncology. International Journal of Gynecological Cancer. 2022; 32: 372–379.
[39] Kubicek GJ, Xue J, Xu Q, Asbell SO, Hughes L, Kramer N, *et al*. Stereotactic body radiotherapy as an alternative to brachytherapy in gynecologic cancer. BioMed Research International. 2013; 2013: 898953.
[40] . Julious and Campbell, 1998 Sample size calculations for paired or matched ordinal data. Stat. Med. 17, 1635–1642.
[41] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British Medical Journal. 2003; 327: 557–560.
[42] Mantel F, Flentje M, Guckenberger M. Stereotactic body radiation therapy in the re-irradiation situation–a review. Radiation Oncology. 2013; 8: 7.
[43] Scher N, Bollet M, Bouilhol G, Tannouri R, Khemiri I, Vouillaume A, *et al*. Safety and efficacy of fiducial marker implantation for robotic stereotactic body radiation therapy with fiducial tracking. Radiation Oncology. 2019; 14: 167.
[44] Reshko LB, Baliga S, Crandley EF, Harry Lomas IV, Richardson MK, Spencer K, *et al*. Stereotactic body radiation therapy (SBRT) in recurrent, persistent or oligometastatic gynecological cancers. Gynecologic Oncology. 2020; 159: 611–617.