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Review Article

Uterine transposition versus uterine ventrofixation before radiotherapy as a fertility sparing option in young women with pelvic malignancies: Systematic review of the literature and dose simulation

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ABSTRACT

Background: (Chemo)radiation may be a required treatment in young women with pelvic malignancies. Irradiation may result in ovarian and uterine failure, compromising the fertility of those patients. While ovarian transposition is an established method to move the ovaries away from the irradiation field, similar surgical procedures regarding the uterus remain investigational. The aim of this study was to carry out a systematic review of the literature on uterine displacement techniques (ventrofixation/transposition) and to simulate the radiation dose received by the uterus in different heights place after the procedures.

Methods: The systematic review was performed according PRISMA guidelines. PubMed, Scopus, Web of Science and EMBASE were queried to identify included study until March 2023. Retrospectively, a dosimetric study was also performed and Volumetric Modulated Arc Therapy (VMAT) radiotherapy treatment plans were calculated, to assess the dose received by the uterus according to hypothetical different displacement positions taking the case of irradiation for rectal or anal cancer as model.

Results: A total of 187 studies were included, after the screening 9 studies were selected for synthesis. Data from the dose simulation revealed that the transposition approach was the most protective with a maximum dose of about 3 and 8 Gy for anal and rectal cancer respectively. None of the simulated ventrofixation positions received a Dmean surpassing 14 Gy.

Conclusion: According to the literature review and the simulation results of the present study we may conclude are feasible and safe as fertility sparing approach in young rectal/anal cancer patients.

1. Introduction

According to the estimation, the new cases of pelvic malignancies (i.e. anus, rectum, vagina, cervix) in young women aging <44 are going to increase by 13.5 % from the 2020 to the 2040 worldwide, and especially in low income countries [1]. In parallel, the average age for first pregnancy is going to raise due to cultural and social changes, making the issue of fertility sparing surgery a relevant clinical need [2]. This discrepancy could be challenging when patients are diagnosed with pelvic malignancy requiring (chemo)radiotherapy treatment.

While the radiation dose resulting in loss of reproductive function of the ovary is known and decreases with age [3], there is less data on the dose causing permanent loss of uterine function. The uterine tissues may be injured after pelvic irradiation, leading to a reduction in the organ's volume, distensibility, blood flow, and endometrial layer scarring, which makes getting pregnant impossible. Some authors stated that the

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maximum uterine radiation dose compatible with pregnancy is 14 Gy [4], others comparing it with other organs advise not to exceed 20–25 Gy [5].

Nowadays advanced radiotherapy techniques such as intensity modulated and image-guided treatments make it possible to deliver ultra-conformal treatments and monitor the target and organs at risk and allow to better spare the uterus during pelvic irradiation for pelvic malignancies (i.e. anus, rectum, vagina, bladder, sarcomas), however due to the nature of the treatment (external beam) a part of the dose is always delivered on the uterus. In this context, similarly to ovarian transposition, a surgical procedure usually performed in young patients in order to preserve ovarian function before pelvic irradiation [6–8], some authors have described the displacement of the uterus from the pelvis as an option to prevent uterine radiation damage and preserve fertility in these women [9–17].

Two main approaches have been reported for the displacement: uterine transposition (UT) and uterine ventrofixation/suspension (UV). UT is a sophisticated complex surgical technique based on the awareness of uterus viability even when uterine arteries are transected as in trachelectomies [18]. In this procedure the uterus is detached from the vagina and shifted in the upper abdomen together with tubes and ovaries with the suture of the cervix to the paracolic gutter in the hypochondrium (if menses are suppressed by hormonal therapy) or to the umbilical scar with the creation of a stoma for menstrual bleeding [11,12,14–17]. UV has to be preceded by ovarian transposition and it includes two different options, as suspension that can be obtained using the round ligaments or directly ventrofixating the uterine fundus to the abdominal wall [9,10,13].

Several uterine displacement procedures have been reported earlier, but there is no agreement on the optimum balance between the largest dose reduction and the best technical reproducibility. The aim of this study was to carry out a systematic review of the literature on uterine displacement techniques and to simulate the radiation dose received by the uterus in different heights place after transposition and ventrofixation taking the case of irradiation for rectal or anal cancer as model.

2. Materials and methods

2.1. Search strategy

The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Before data extraction, the review was registered with the International Prospective Register of Systematic Reviews PROSPERO (Registration No CRD42023391278).

The articles cited in this systematic review were obtained querying the PubMed database, Scopus, Web of Science and EMBASE filtered by the English language. No additional filters were applied to the search strategy. The research was started in January 2023 and completed in March 2023.

The keywords used were “uterine transposition” or “uterine fixation” or “uterine ventrofixation” AND “rectal cancer”; “anal cancer”; “cervical cancer”; “vaginal cancer”; “sarcoma” AND “radiotherapy”. The term “AND” was used to find the intersection.

2.2. Data extraction

After removing duplicate publications at the title/abstract level, MP and NB independently reviewed titles, abstracts and keywords for first selection purpose. In case of differences in the selection, the final decision was taken through a discussion with a third author (DQ).

In all articles potentially suitable for the purposes of this analysis, the full text was examined independently by MP and NB. In the event of discrepancies, we proceeded as described above.

Studies were selected according to the criteria based on the following items: 1) description of uterine transposition surgical technique 2) patients with pelvic malignancies with life conceive possibility (<44 y. o.) 3) the type of outcome assessment of interest. In Table 1 are reported the selected studies.

2.3. Simulation according to uterine different displacements

The dose distribution through the uterus has been investigated in two scenarios of radiation therapy (RT) for locally advanced rectal cancer (LARC) and squamous cell anal cancer (SCAC).

Retrospectively, a dosimetric study was performed to assess the dose received by the uterus according to hypothetical different displacement positions (i.e. Uterine ventrofixation/suspension or Uterine transposition, as per literature review) [19].

The uterine structure (US) and the vagina were contoured using computed tomography (CT) and magnetic resonance (MR) simulation scans carried out in the supine position with an empty and a full bladder, respectively. The simulation of the uterine ventrofixation/suspension (UV) surgical approach was performed as follows: the US uterine fundus was virtually ventrofixed at the level of the umbilicus with a concomitant stretching of the vagina and progressively moved downwards by 2 cm to different positions. On the other hand, the simulation of the uterine transposition (UT) procedure was performed placing the US in the abdominal region (US P-UT), and the cervix at the level of the umbilicus. Position 1 (US–P1) is basal and numbering increases cranially; the ventrofixed uterus is the most cranial position (US–P-VT). Position numbers is different according to the height of patient. Vagina position are not simulated. (Figs. 1–2).

Subsequently, Volumetric Modulated Arc Therapy (VMAT) radiotherapy plans were calculated, with the primary objective of adequately covering RT volumes and secondly of avoiding the US in the simulated different positions.

The maximum and mean doses, the V14 and V20 Gy (i.e. the volume of uterus receiving 14 and 20 Gy, respectively) and the doses below 14 Gy for each simulated fixation point were registered and evaluated in the dosimetric study.

3. Results

3.1. Systematic review

A search strategy was developed and applied to PubMed, Scopus, Web of Science and EMBASE to identify previous studies reporting uterine transposition surgical technique. Fig. 3 shows the flowchart of the studies selection. Initial research led to the identification of 186 studies. One additional congress abstract was found. After screening at the level of titles and abstracts, 79 full texts were selected. At the end of the selection of the latter, 9 studies, published between 2010 and 2023, were included in qualitative synthesis for the systematic review [9–17]. Table 1a summarizes the characteristics of the included studies. For narrative purposes we divided the results according to the surgical procedure performed: uterine ventrofixation/suspension and Uterine transposition. No study was included for a quantitative analysis. Details about patients and surgical techniques are available in Tables 1b and 1c Concerning the study design, the majority were case reports or video articles, one was a retrospective study. A total of 15 patients, mean age 28-years-old, with their respective surgical procedures were described. Five patients had rectal cancer, six had cervical cancer, and one had anal cancer, or yolk sac tumor, vaginal cancer or liposarcoma. Except for one robotic-assisted surgery, all of the described procedures were performed by laparoscopy. Six studies described the transposition technique [11,12,14–17] while three the ventrofixation/suspension option [9,10,13]. Notably, only two of the reviewed articles reported obstetrical outcomes [13,16].

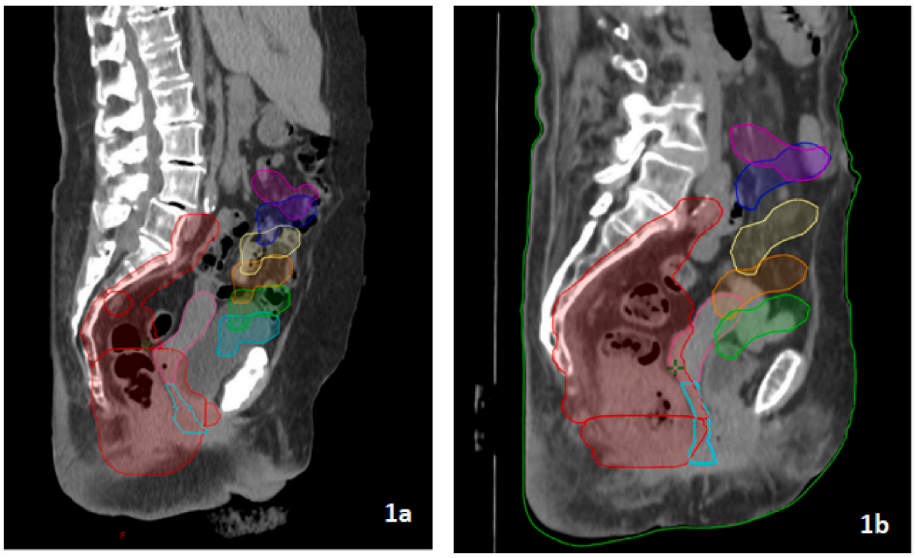

Fig. 1. The US ventrofixation, the US P-UTransposition and PTV representation in rectal cancer (1a) and anal cancer (1b). *Legend:* Fig. 1a: *Vagina: light blue line; US P1 (basal): pink line; US P2: green line; US P3 orange line; US P4: yellow line; US P5: blue line; US P-UT: purple line; PTVs: red volumes.* Fig. 1b: *Vagina: light blue line; US P1 (basal): pink line; US P2: light blu line; US P3: green line; US P4 orange line; US P5: yellow line; US P6: blue line; US P-UT: purple line; PTVs: red volumes.*

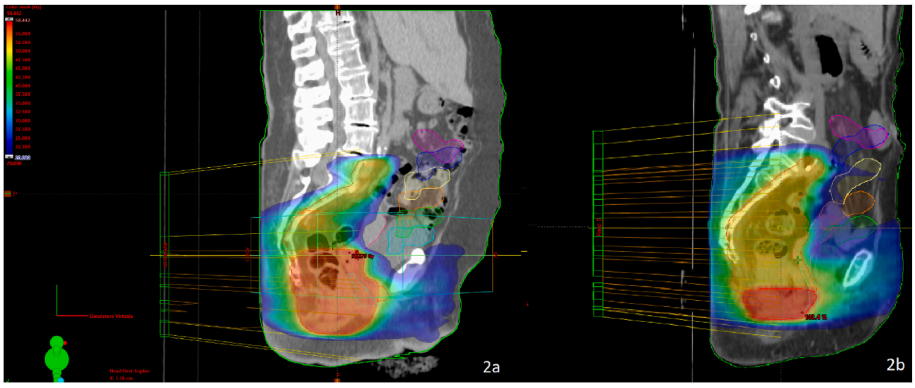

Fig. 2. Dose distribution on PTV and US P1–P2-Pn, US P-UT in rectal cancer (2a) and anal cancer (2b) at 5 Gy isodose. *Legend:* Fig. 2a: *Vagina: light blue line; US P1 (basal): pink line; US P2: green line; US P3 orange line; US P4: yellow line; US P5: blue line; US P-UT: purple line; PTVs: red volumes.* Fig. 2b: *Vagina: light blue line; US P1 (basal): pink line; US P2: light blu line; US P3: green line; US P4 orange line; US P5: yellow line; US P6: blue line; US P-UT: purple line; PTVs: red volumes.*

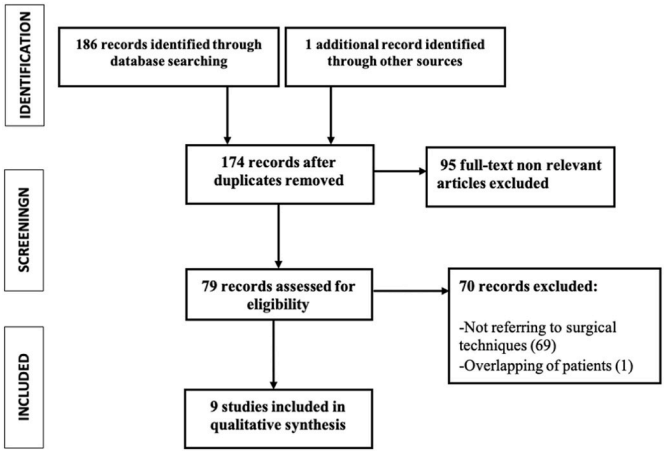

Fig. 3. PRISMA flow diagram of study selection.

3.2. Simulation according to uterine different displacements

The two RT plans were calculated on the basis of radiotherapy prescription doses and optimized according to International Committee for Radiological Units (ICRU) 83 [20]; these were the original plans for radiation treatment in clinic. The first case was a 38-year-old female patient carrying out a cT3N1M0 adenocarcinoma of the lower-middle rectum, staged by pelvis MR and chest and abdomen CT scan. According to stage, neoadjuvant chemoradiation plus chronomodulated oral capecitabine was prescribed. Radiotherapy doses were 55 Gy (Gy)/2.2 Gy per fraction on the rectal disease (Gross Tumor Volume-GTV) plus the corresponding mesorectum and 45 Gy/1.8Gy per fraction to the pelvic lymph nodes and the entire mesorectum [19]. The second case was a 41-year-old female patient, recently diagnosed with HPV-related squamous cell carcinoma of the anal canal with involvement of the right inguinal lymph nodes, staged as cT3N1cM0. Exclusive chemoradiation with 5-fluorouracil and mitomycin drugs was prescribed. Radiotherapy doses were 55 Gy/2.2 Gy per fraction on the macroscopic disease and the corresponding anal canal, 50 Gy/2.0 Gy per fraction on the metastatic inguinal lymph nodes and 45 Gy to the pelvic and inguinal drainage plus the entire mesorectum. The US volumes were 31.2 cc and 56.3 cc for rectal and anal case, respectively.

Table 1a
Selected studies.

ARTICLES	TYPE OF STUDY	SAMPLE SIZE	CANCER	SURGICAL TECHNIQUE
Querleu et al. Journal of clinical oncology 2010 [9]	Abstract	3	Rectal cancer	Uterine Ventrofixation
Köhler et al. Oncology 2016 [13]	Case report	1	Anal cancer	Uterine Ventrofixation
Ribeiro et al. Fertility and sterility 2017 [15]	Case report	1	Rectal adenocarcinoma	Uterine Transposition
Azaïs et al. Fertility and sterility 2018 [10]	Video article	1	Rectal cancer with liver metastasis	Uterine Ventrofixation
Baiocchi et al. Gynecologic Oncology 2018 [11]	Video article	1	Cervical cancer	Uterine Transposition
Baiocchi et al. International Journal Gynecologic Cancer 2020 [12]	Retrospective study	5	Cervical and vaginal cancer	Uterine Transposition
Vieira et al. International Journal Gynecologic Cancer 2021 [16]	Video article	1	Yolk sac tumor	Uterine Transposition
Odetto et al. International Journal Gynecologic Cancer 2021 [14]	Case report	1	Cervical cancer	Uterine Transposition
Ribeiro et al. Fertility and sterility 2023 [17]	Case report	1	Liposarcoma	Uterine Transposition

Table 1b
Clinical characteristics of the patients.

AUTHOR	CASE	CANCER	AGE	TRAC.	Radiotherapy/ dose (Gy)	CHT	Transposition/ Ventrofixation	TT UT-RT (days)	TT RT-UR (days)	FUP (months)	R	RM	P
Querleu et al 2010 [9]	1	Rectal cancer	NA	No	EBRT	No	Ventrofixation	NA	NA	NA	NA	Yes	No
Querleu et al 2010 [9]	2	Rectal cancer	NA	No	EBRT	No	Ventrofixation	NA	NA	NA	NA	No	No
Querleu et al 2010 [9]	3	Rectal cancer	NA	No	EBRT	No	Ventrofixation	NA	NA	NA	NA	Yes	No
Köhler et al 2016 [13]	4	Anal cancer	36	No	EBRT/45 Gy	No	Ventrofixation	NA	NA	NA	NA	Yes	Yes
Ribeiro et al 2017 [15]	5	Rectal cancer	26	No	EBRT	Yes	Transposition	21	25	18	No	Yes	No
Baiocchi et al 2018 [11]	6	Cervix	33	Yes	EBRT/45 Gy	No	Transposition	NA	7	6	No	Yes	No
Azaïs et al 2018 [10]	7	Rectal cancer	26	No	EBRT	Yes	Ventrofixation	NA	NA	NA	NA	Yes	No
Baiocchi et al 2020 [12]	8	Cervix	32	Yes	EBRT/45 Gy	No	Transposition	18	5	30	No	Yes	No
Baiocchi et al 2020 [12]	9	Cervix	29	Yes	EBRT/45 Gy	Yes	Transposition	28	Hysterectomy	27	No	NA	No
Baiocchi et al 2020 [12]	10	Cervix	28	Yes	EBRT/45 Gy	Yes	Transposition	10	39	25	No	Yes	No
Baiocchi et al 2020 [12]	11	Vagina	35	No	EBRT/45 Gy + 20 Gy BRT	Yes	Transposition	14	31	2	No	Yes	No
Baiocchi et al 2020 [12]	12	Cervix	38	Yes	EBRT/45 Gy	No	Transposition	10	30	1	No	Yes	No
Vieira et al 2021 [16]	13	Yolk sac tumor	3	No	EBRT	No	Transposition	NA	90	15	No	NA	NA
Odetto et al 2021 [14]	14	Cervix	27	Yes	EBRT	Yes	Transposition	15	25	12	No	Yes	No
Ribeiro et al 2023 [17]	15	Liposarcoma	28	No	EBRT/60Gy	No	Transposition	NA	60	36	No	NA	Yes

TRAC: Trachelectomy; EBRT: external beam radiotherapy; BRT: brachytherapy; CHT: chemotherapy; TT UT-RT: time from uterine transposition and radiotherapy; TT RT-UR: time from radiotherapy and uterine reimplantation; FUP: follow up; R: recurrence; RM: regular mensens; P: pregnancy.

In the anatomical position (US P1) for the rectal cancer example, the maximum and median doses were 46.5 and 25.2 Gy respectively, while 65 % and 50 % of US volume received at least 14 Gy or 20 Gy, respectively. Even worse, in the anal cancer case, at US P1, the maximum and median doses were 58.4 and 34.5 Gy, while 92 % and 71 % of US volume received at least 14 Gy or 20 Gy, respectively.

The uterine transposition approach was the most protective from radiation doses in both simulated cases (rectal and anal cancer) with a maximum dose of approximately 3.05 and 7.9 Gy, respectively. (Table 2).

As per ventrofixation, in both cases, none of the simulated US ventrofixation positions received a Dmean surpassing 14 Gy, and the US volumes receiving 14 or 20 Gy for all simulated ventrofixation positions were remarkably small. Starting from the rectum's US P4 position and the anus's US P3, the Dmax was always less than 14 Gy, but still the volume receiving a dose higher than 14 Gy was negligible in the rectum's US P2-US P3 positions (0.08 cc and 0.03 cc, respectively) and the anus's US P2 position (4 cc) (Table 2). The area of maximum US dose was the posterior wall of the uterus, in all simulated positions from US P1 to US P6.

Table 1c
Surgical details.

AUTHOR	CASE	CANCER	AGE	Transposition/ Ventrofixation approach	Menses suppressed	OT	EBL	IOC	POC	Hospital stay	HT	Reimplantation approach	OT2	EBL2	IOC2	POC2
Querleu et al 2010 [9]	1	Rectal cancer	NA	Laparoscopic	NA	NA	NA	No	No	NA	No	Laparoscopic	NA	NA	No	No
Querleu et al 2010 [9]	2	Rectal cancer	NA	Laparoscopic	NA	NA	NA	No	No	NA	No	Laparoscopic	NA	NA	No	No
Querleu et al 2010 [9]	3	Rectal cancer	NA	Laparoscopic	NA	NA	NA	No	No	NA	No	Laparoscopic	NA	NA	No	No
Köhler et al 2016 [13]	4	Anal Cancer	36	Laparoscopic	NA	NA	NA	No	No	NA	No	Laparoscopic	NA	NA	No	No
Ribeiro et al 2017 [15]	5	Rectal cancer	26	Laparoscopic	No	NA	NA	No	Vaginal cuff dehiscence	4	No	Laparoscopic	NA	NA	No	No
Baiocchi et al 2018 [11]	6	Cervix	33	Laparoscopic	Goserline	NA	NA	No	No	2	No	Laparoscopic	NA	NA	No	No
Azaïs et al 2018 [10]	7	Rectal cancer	26	Laparoscopic	NA	NA	NA	No	No	NA	No	Laparoscopic	NA	NA	No	No
Baiocchi et al 2020 [12]	8	Cervix	32	Laparoscopic	Goserline	205	100	No	No	3	No	laparoscopic	170	20	No	Cervical stenosis 12 months after reimplantation resolved with resection of the fibrotic area of the cervix and dilatation
Baiocchi et al 2020 [12]	9	Cervix	29	Laparoscopic	No	90	30	No	No	1	Yes	NA	NA	NA	No	No
Baiocchi et al 2020 [12]	10	Cervix	28	Robotic	Dienogest	150	25	No	No	3	No	Robotic	210	20	No	No
Baiocchi et al 2020 [12]	11	Vagina	35	Laparoscopic	Dienogest	80	20	No	No	3	No	Laparoscopic	90	20	No	No
Baiocchi et al 2020 [12]	12	Cervix	38	Laparoscopic	Dienogest	85	30	No	No	3	No	Laparoscopic	80	30	No	Partial dehiscence of uterine anastomosis 8 months after surgery. The uterus was re-sutured under general anesthesia
Vieira et al 2021 [16]	13	Yolk sac tumor	3	Laparoscopic	NA	NA	NA	No	No	NA	No	Laparoscopic	NA	NA	No	No
Odetto et al 2021 [14]	14	Cervix	27	Laparoscopic	Goserline	150	180	No	No	2	No	Laparoscopic	310	300	Injury to the right ureter with ureteral reimplantation with a psoas hitch	No
Ribeiro et al 2023 [17]	15	Liposarcoma	28	Laparoscopic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

OT operating time: EBL estimated blood loss; IOC intra-operative complications; POC post-operative complications; HT Hysterectomy.

Table 2
Uterus Structure doses.

a) Rectal cancer				
Structure	Dmax (Gy)	Dmean (Gy)	V14Gy (cc)	V20Gy (cc)
US P1	46.5	25.2	20.4	15.7
US P2	16.1	10	0.08	NA
US P3	14.8	8.5	0.03	NA
US P4	11.5	7.2	NA	NA
US P5	13.2	3.7	NA	NA
US P-UT	3.05	1.9	NA	NA
b) Anal cancer				
Structure	Dmax (Gy)	Dmean (Gy)	V14Gy (cc)	V20Gy (cc)
US P1	58.4	34.5	52	40
US P2	31.3	10	4	0.2
US P3	12.8	7.3	NA	NA
US P4	11	7	NA	NA
US P5	11.2	7.1	NA	NA
US P6	12.4	7	NA	NA
US P-UT	7.9	3.6	NA	NA

Gy: Gray; US: Uterus structure; UT: Uterine transposition; NA: not achieved.

4. Discussion

Herein, we present a comprehensive analysis of the literature on uterine displacement techniques and simulate the radiation dose that the uterus would have received by shifting it using two different surgical displacement techniques.

4.1. Summary of main results

Uterine ventrofixation and uterine transposition techniques as options to spare uterine function in patients undergoing radiotherapy for rectal or anal cancer have been described by various authors for over a decade but are not frequently used in clinical practice. From the result of the dose simulations the uterine transposition was the most protective from radiation doses in both simulated cases (rectal and anal cancer) with a maximum dose of approximately 3.05 and 7.9 Gy, respectively. As per ventrofixation, in both cases, none of the simulated US ventrofixation positions received a Dmean surpassing 14 Gy, and the US volumes receiving 14 or 20 Gy for all simulated ventrofixation positions were remarkably small. Few patients were analyzed in the reported studies, and even fewer obstetric data were recorded. Uterine ventrofixation technique appears to be an easier procedure with no complication reported, potentially reducing side effects and need of a second surgery, due to the fact that the suspension can be detached at the time of colo-rectal surgery. This technique, however, has to be always performed together with ovarian transposition [6]. On the contrary, uterine transposition appears to be a more complex procedure, requiring a longer operative time, more blood loss, and the possibility of complications similar to those that can arise during a standard hysterectomy (vascular and ureteral injuries, intestinal or bladder lesions, etc.) [21] as well as those related to the devascularization of the organ (uterine necrosis or cervical stenosis). Indeed, according to the Clavien Dindo [22] classification in our review we reported three grade IIIb complications and one major intra-operative complication in the UT group and no severe complications in the UV group. But, the low number of UV and UT cases reported in literature prevent us to draw strong conclusions about which technique should be preferred.

Because radiotherapy treatment is frequently required in patients with pelvic malignancies, and radiation damage to the genital tract is a concern for young women with a diagnosis of pelvic cancer and a desire for fertility, the findings of this simulation study could serve as a guide for the type of surgical approach to be taken in the event of pelvic irradiation.

Although an accurate dose-effect association for uterine functional malfunction is still unknown, evidence collected from total body irradiation suggests that the dose of 14 Gy is still compatible with gestation but with lower fecundity and more complications [4,23]. However, some authors point out that the uterus shares similarities with other glandular organs, such as the parotid gland, and advise limiting the absorbed dose to no more than 20–25 Gy [5,24]. Additionally, published cases of successful pregnancies in rectal cancer radiotherapy with precisely defined dose are lacking.

In this study, we calculated the uterus doses at each simulated fixation point, starting from the hypothesis that the distance between the organ and the irradiation field is the most significant factor in the displacement procedures, and we found that the mean dose in all uterine positions was always less than 14 Gy in rectal and anal cancer cases.

4.2. Results in the context of published literature

As per uterine ventrofixation is concerned, in 2010 Querleu et al. described for the first time the procedure of UV with ovarian transposition on 3 rectal cancer patients before chemoradiation. The shift of the uterus from the pelvis was obtained either through the ventrofixation of the uterine fundus to the abdominal wall or through the round ligament's suspension (Fig. 4a). Fixation and repositioning procedures were performed using a laparoscopic approach, one patient died for the disease and the other two were lost in the follow up. No obstetrical data were available. When the natural vaginal elasticity is not enough to perform the ventrofixation of the uterus up to the umbilicus (for example in case of inflammatory disease or endometriosis), dissection of posterior uterine compartment could help in the organ mobilization [9]. Köhler et al., in 2016 described the case of 36-year-old women with anal cancer who underwent uterine ventrofixation and ovarian transposition before chemoradiation. This is the only one study on UV available in the literature reporting a positive obstetric outcome after a total dose of 45 Gy pelvic radiation [13]. The laparoscopic uterine ventrofixation procedure before radiotherapy was also described by Azaïs et al., who showed in a video article the detailed surgical procedure in a 26-year-old patient with rectal cancer and liver metastasis [10]. No complication was reported in any of the cited papers for both the ventrofixation and ovarian transposition procedures.

As far as Uterine Transposition, Ribeiro et al. [15], in 2017, first presented UT in a 26-year-old patient diagnosed with rectal adenocarcinoma with no distant metastasis. The case report describes all the steps of the surgical procedure (Fig. 4b). Chemoradiation was started 10 days later and during the treatment migration of the left adnexa to the lower abdomen occurred, causing abdominal pain. Five weeks after treatment laparoscopic rectosigmoidectomy with total mesorectal excision was performed together with the uterine reimplantation. The uterus was detached from the abdominal wall and the cervix re-sutured to the vagina. Round and broad ligaments were then reconstructed by suture. After 18 months follow up no recurrence was observed, and the cervix appeared normal. The same procedure in its modified version was proposed as a fertility sparing solution in patients underwent trachelectomy in early-stage cervical cancer by Baiocchi et al., in 2018 [11]. In this video article the uterine isthmus was not sutured to the umbilical scar, but to the upper abdominal wall with a non-absorbable trans parietal suture. Menses was in this case suppressed due to the administration of 10.8 mg of gosereline aceate to prevent intra-abdominal menstrual bleeding. One week after external beam radiotherapy (45 Gy) uterus and ovaries were repositioned in the pelvis. No recurrence or complications were reported at 6 months follow up. Two years later the same authors published the first multicentric retrospective case series in UT for gynecological malignancies [12]. Four cervical and one vaginal cancer patients, mean age 32 years, underwent trachelectomy with sentinel lymph node mapping [25], UT and subsequently radiotherapy. The uterus was repositioned after radiotherapy in all but one patient who underwent simple hysterectomy after refusing the reimplantation and declining further fertility sparing options. Two late complications were reported after the surgery: a vaginal cuff dehiscence 8 months after the

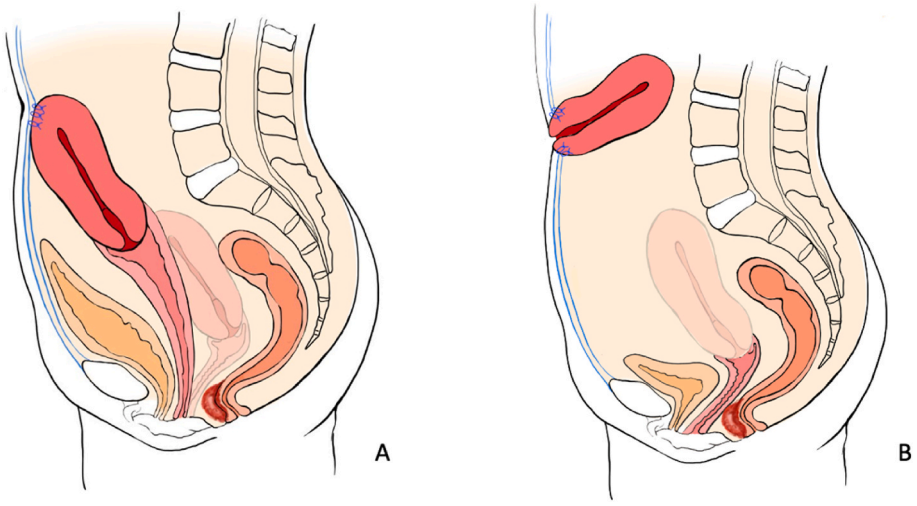

Fig. 4. Uterine ventrofixation (A) uterine transposition (B).

reimplantation procedure and a cervical stenosis after 12 months resolved with cervical dilatation. Regular menses occurred in the four patients with uterus reimplantation. No evidence of recurrence appeared after median follow up of 25 months. One patient attempted in vitro fertilization with no success. Furthermore, the UT technique was also described in a 3-year-old patient underwent radiation therapy for a yolk sac tumor [16]. Uterine and ovarian transposition according to Ribeiro et al. [15] was laparoscopically performed and the uterus was reimplanted 90 days after the radiotherapy with no complications at 15 months follow-up. A major complication was reported by Odetto and coll. in a case report published in 2021. A 27- year-old woman with cervical cancer underwent trachelectomy and UT. Ten days after the radiotherapy treatment, the uterus was repositioned. During the dissection of the vaginal angle a ureteral injury was visualized in its juxta-vesical portion. The previous radiation therapy and the site of the injury made a ureteral reimplantation with a psoas-hitch needed [14]. Finally, the first positive obstetric outcome following UT is reported in a 28-year-old patient diagnosed with a left iliac and thoracic synchronous myxoid low-grade. The tumor was resected, and uterus transposed. She underwent to pelvic (60 Gy) and thoracic (60 Gy) radiation in October 2018. After the radiotherapy treatment was completed, her uterus was reimplanted in the pelvis in February 2019. The patient conceived in June 2021 and she delivered a healthy boy (2686 g) by cesarean section at 36 weeks of gestation [17].

4.3. Strengths and weakness

To the best of our knowledge this is the first simulation study that describe dose variations according to uterus different positions after UT or UV. It is unquestionable that a simulation of only two examples cannot generalize the dose received by uterus transposed in different locations. In fact, it may change depending on several parameters, including patient's anatomy, surrounding organs (e.g. bladder filling, rectum filling), and tumor sites. In the case of rectal cancer, different sites of the tumor (e.g. medium or lower rectum) should be taken into account as could result in potential dosimetry changes. Moreover, it should be noted that the treatment plans were those that were originally employed for the actual treatment and were not adjusted to account for uterine constraints. Uterine displacement techniques are usually performed together with ovarian transposition. A major limitation of this study is we did not perform the simulation of dose received by the ovaries in both techniques. In addition, the uterine transposition technique always involves colpotomy but then, the cervix can be sutured at the umbilicus or in the abdominal cavity, and the uterus ventrofixed, or free in the abdomen. In our dosimetry simulation, we considered the option in which the organ was moved as far away from the irradiation field as possible. Possible anatomical modifications, moreover, of pelvic organs resulting from vaginal and uterine stretch were not considered in the dosimetric simulation. From the results of this systematic review, it appears that both UV and UT could be options to spare uterine function in patients undergoing RT for rectal or anal cancer, and the low number of UV cases reported, prevent us to draw strong conclusions about which technique should be preferred. However, performing a simulation before choosing the displacement surgical option could be a useful choice tool in case of pelvic irradiation with fertility sparing intent.

4.4. Implications for practice and future research

Besides uterine displacement, modern radiation oncology may play a role in the attempt to lower the dose to the uterus. To date, radiation treatment plans optimized for uterus constraints, the image-guided radiotherapy machines (e.g. linear accelerator magnetic resonance based), and the gating techniques (i.e. the possibility to avoid uterine irradiation when it moves in high-dose area) represent a latest generation technology extremely useful in an organ preservation approach [26]. Different portions of the uterus may be exposed to different amounts of radiation and side effects even when raised from the pelvis. In both techniques, at the end of radiotherapy treatment and after organ reimplantation, there should be the possibility of spontaneous conception. Saving the endometrium for a spontaneous pregnancy, however, is only useful if the cervix, closer to the radiation field, is also preserved from possible stenosis. Future research involving this advanced radiotherapy technique are needed to prove their potential. Also, the uterine transplant can be an opportunity to preserve the uterine reproductive function, but it is still experimental and comes with all the immunological challenges associated with transplant surgery [27].

5. Conclusions

According to the simulation results of the present study performed in the context of modern high-quality radiotherapy, we may conclude that uterine ventrofixation and uterine transposition are feasible procedures both with a simulated radiation dose compatible with pregnancy. Uterine displacement techniques should be further evaluated as a fertility sparing approach in young rectal/anal cancer patients. However, the reported obstetrical results are not yet sufficient to draw solid conclusions. A prospective clinical trial on the assessment of uterine displacement effectiveness in fertility outcomes is needed to test the hypothesis generated with the present study. These results could also be extended to other malignancies, adapting the simulation to the clinical

case. Oncologists and surgeons should be made aware of these chances to be done in highly specialized institutes, with sufficient radiation facilities and close collaboration among specialists in that field.

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Availability of data

All data generated or analyzed in this review are included in this article and/or its figures. Further enquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Dr. Matteo Pavone, Dr. Nicolo' Bizzarri and Prof. Denis Querleu contributed to the study design, literature research and wrote the first draft. Dr. Rosa Autorino, Dr. Giuditta Chilorio, Dr. Giacomo Corrado, Dr. Gabriella Macchia and Prof. Gabriella Ferrandina contributed to the writing of the first draft. Prof. Denis Querleu, Prof. Giovanni Scambia, Prof. Maria Antonietta Gambacorta and Prof. Vincenzo Valentini are responsible for the critical revision of the manuscript and for important intellectual content. All Authors have read and commented on the previous version of the paper. All Authors approved the final version of the paper before submission.

Declaration of competing interest

Authors declare no conflicts of interests.

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Appendix A. Supplementary data

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