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Ovarian function after ovarian transposition and additional pelvic radiotherapy: A systematic review

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ABSTRACT

Objective: To investigate the ovarian survival (OS) after ovarian transposition (OT) and pelvic radiation.
Design: Systematic review.
Electronic databases were searched to identify studies on OT prior to external beam radiation therapy (EBRT, to the pelvic). Primary outcome was the ovarian function after radiotherapy and ovarian transposition. Secondary outcomes were complication-rate. Only studies in English, German or French were included.
Setting: Not applicable.
Patients: Fertile women undergoing ovarian transposition prior to pelvic radiation therapy.
Interventions: We included all studies, containing >5 patients, treated with OT prior to radiation therapy.
Main outcome measure: Ovarian function.
Results: Our search yielded a total of 1130 studies of which 38 were eligible with a total of 765 patients. All studies were cohort studies or case-series. Heterogeneity among studies could not be rejected hence meta-analysis could not be performed.
OS after OT and EBRT ranged from 20% to 100%. The median follow-up ranged from 7 to 102 months. OS was higher after OT and brachytherapy (OS 63.6–100%) when compared to OT and EBRT (20–100%) and OT concomitant chemoradiotherapy (0–69.2%).
Only 22 studies (with 112 patients) reported on complications: among these studies the complication-rate was 0%–28.6%.
Conclusion: From our systematic review of literature we conclude that the preservation of ovarian function after OT prior to EBRT is successful in 20–100% of patients. Most favorable outcome with regard to preservation of ovarian function is seen in patients after OT and BT, followed by OT and EBRT and OT and RT combined with chemotherapy.

Introduction

In premenopausal women, pelvic radiation therapy (PRT) is often indicated in genitourinary- and rectal cancer as well as Hodgkin lymphoma [1–3]. One of the side effects of PRT is Premature Ovarian Insufficiency (POI) resulting in infertility, decreased bone mineral density and impaired lipid profile over time [4,5].

Complete ovarian failure occurs with a dose of 20Gy in women under 40 years of age while the mean lethal dose for the human oocyte is estimated to be 2Gy [6]. The magnitude of the risk is related to the position of the ovary, the exact radiation field and total dose of radiation. Moreover, it has been shown that, in total body irradiation, fractionated irradiation is less toxic to the ovaries than one single dose of irradiation [7].

One of the options to prevent POI due to PRT is ovarian transposition (OT). OT is a simple technique, in which the ovaries are placed outside the radiation field thereby reducing the exposure to radiation and total dose of irradiation. First the Fallopian tube and the vascular pedicel between the uterus and the ovary are ligated. After that the ovarian artery and vein can be dissected and the ovary can be positioned outside the radiation field and attached to

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the abdominal wall. This procedure was first performed and described in 1952 by Batten to preserve ovarian function in a patient with a pelvic neuroblastoma receiving pelvic radiation therapy [8]. OT can either be performed by laparotomy, especially in combination with therapeutic surgery, or by laparoscopy. Positioning the ovaries above the pelvic brim and as lateral as possible will result in a position outside radiation field in case of PRT, but special care with regard to the definite position should be taken when lymph node regions along the compon illac or para-aortic region are included in the radiation field. Additionally, medial transposition (to a position just above the abdominal wall) with or without shielding by a lead block, has also been described in patients with pelvic node involvement of Hodgkin's lymphoma receiving a so-called inverted Y radiation treatment [9,10].

Complications after OT have been described due to a compromised vascularization, leading to ischemia and/or higher incidence of ovarian cysts within the transposed ovary [11,12]. Finally, by leaving ovaries in situ, the risk of not treating ovarian metastases must be considered depending the indication for PRT, in selected cases [13,14].

Despite the fact that numerous studies and narrative reviews on OT have been published, there is still debate whether OT prior to PRT is effective with regard to preservation of ovarian function. Moreover there is concern about the safety and complication rate. Therefore, we conducted a systematic review to evaluate the effectiveness and safety of ovarian transposition prior to pelvic radiation.

Materials and methods

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines (PRISMA guidelines).

A systematic literature search was performed by a librarian (JS) with predefined search terms in MEDLINE, EMBASE and ISI Web of Knowledge to identify studies describing the ovarian survival after ovarian transposition and pelvic radiation therapy. Combinations of the following keywords and MESH search terms were used: Oophoropexy, ovariope, ovarian, ovarium, ovaria, ovary and transposition. Year of publication was not limited and the final search was performed in January 9th' 2018. All identified articles were screened for cross-references and citation sections.

Inclusion and exclusion criteria

Title and abstract of all identified articles were screened according to subject, language (included English, German, French) and study design. Articles were included for full reading when the ovarian function was determined in a minimum of 5 patients who underwent radiotherapy and ovarian transposition.

Articles were excluded if they did not meet the inclusion criteria and in case of: descriptive study design, if patients were treated with chemotherapy (CT) only, if the article concerned previous published data or incomplete follow up data. Conference abstracts were not included.

Outcomes of interest

Primary outcome was the ovarian function after radiotherapy and ovarian transposition. Different outcome measures were allowed: described by the author as functional ovaries or not; presence of climacterial complaints, use of hormonal replacement therapy, hormonal measurements, radiological ovarian activity and or pregnancy.

Secondary outcomes were complications of the OT.

Data extraction and quality assessment

Data were extracted independently by two authors (EB and EH). In case of discrepancies, a discussion or consultation of a third person (CdeK) resulted in consensus. Reference Manager Software (RefMan© v.12) and Microsoft Excel 2010 were used for data management.

The following variables were extracted from each study: author; year of publication; study purpose; primary disease; uni- or bilateral transpositions; location of the transposed ovaries (e.g. paracolic gutter, medial behind uterus etc.); age at intervention or at radiotherapy (years, mean/median, range); radiotherapy (irradiated area, dose (Gy), external and/or brachytherapy); additional CT, ovarian function after O; length of follow up (months, mean, range, general and/or follow up of ovarian function); complications and (re)interventions. All included studies were critically appraised using the MINORS criteria [14].

Statistical analysis

Collected data was analyzed Microsoft Office Excel 2010 and Prism GraphPad 5 (GraphPad Software Inc., La Jolla, CA, USA). Continuous variables were described as mean or median with range. Categorical variables were described as counts and percentages.

Results

The systematic literature search yielded 1130 publications, of which the first article was published in 1952. After screening and assessment of eligibility (Fig. 1), 38 publications, with a total of 765 patients who underwent OT prior to PRT were included and data was extracted accordingly. The mean MINORS criteria score was 10.34 (range 5–13) out of a maximum possible score of 16 (Table 1). The characteristics of the included studies are shown in Table 2. Comparative studies have not been published hence only cohort studies and case studies could be included.

The main indication OT and for pelvic radiation therapy was cervical carcinoma (50% of included studies, 375 patients), followed by 8 studies with lymphoma patients (n = 233) and 10 studies included combined data of patients with more than one type of cancer (Table 2).

Technique, site and number of transposed ovaries

The primary technique for transposing the ovaries consisted of ligation of the proprial ligament and Fallopian tube and dissection and sparing the ovarian vascularity in the infundibulopelvic ligament upwards along the ovarian artery and vein to allow transposition of the ovary outside the scheduled radiation therapy fields.

In the case of lymphoma the ovary was transposed medially and attached anterior or posterior to the uterus, while sparing the infundibulopelvic ligament, when the pelvic organs were the main target of radiation therapy the ovary was transposed to a more cranio-lateral position. Two studies reported fixation of the transposed ovaries into the subcutis of the abdominal wall [15,16], 1 study reported a retroperitoneal fixation of the ovaries at the posterior wall [17]. Furthermore, 13 studies performed a bilateral ovarian transposition, 1 study a unilateral transposition, and 15 studies reported on patients with both uni- and bilateral transposition (Table 2).

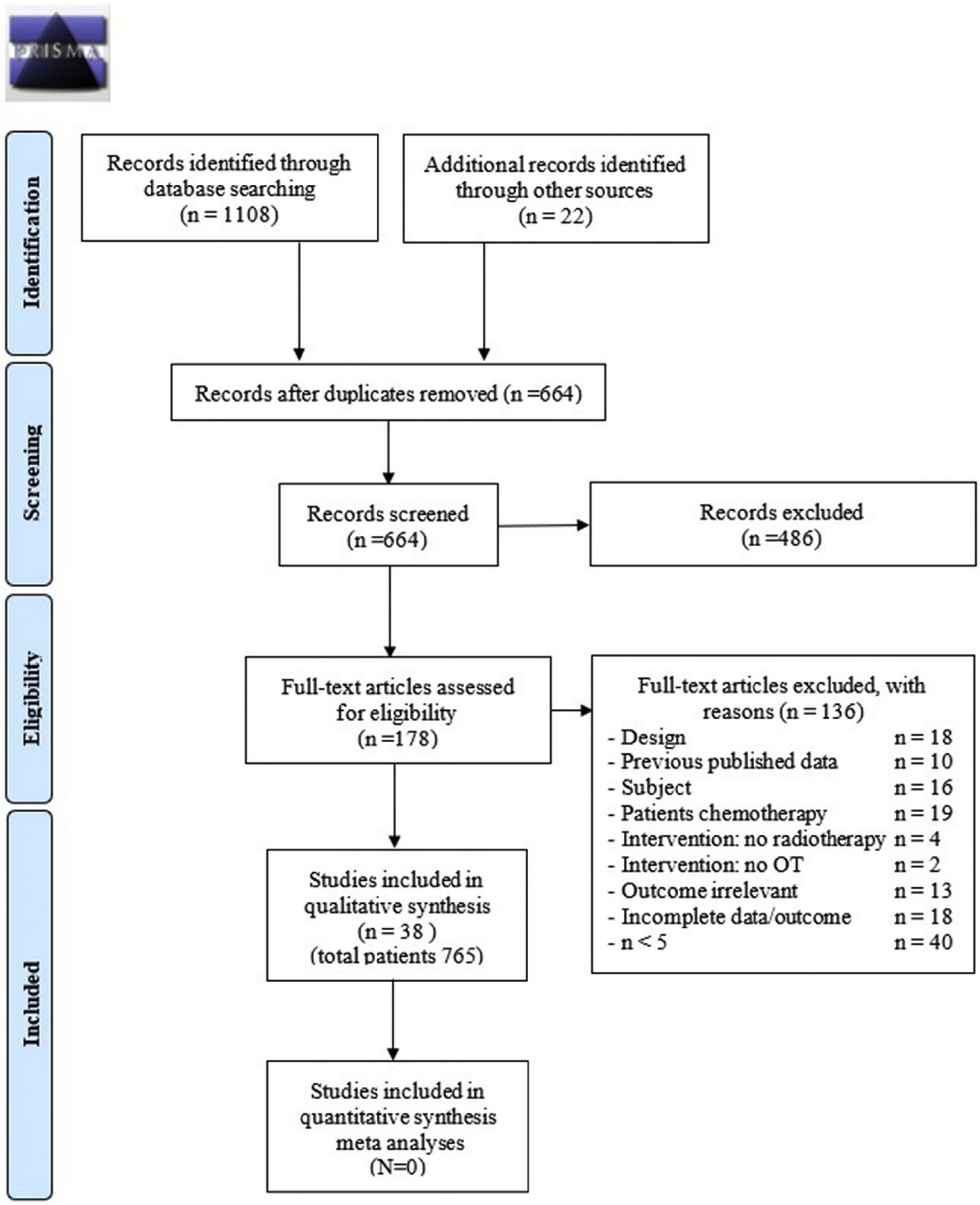

Figure. 1. PRISMA flow diagram.

Cancer therapy

Treatment regimens of patients in the included studies differed significantly Table 3. Not only with regard to technique (External Beam Radiation Therapy (EBRT) only, brachytherapy (BT) only, or a combination of EBRT and BT) but also with regard to field arrangement (8 fields, 4 fields or 2 fields technique), total dose (Gy) and whether either Cobalt or photons were used. In 5 studies, a percentage of patients received additional (neo)adjuvant CT or chemoradiation in which radiation therapy and chemotherapy are administered concomitant.

Ovarian preservation

Due to clinical heterogeneity a meta-analysis of data extracted from the included studies could not be performed. In total, all studies represent 1809 patients (for example, some studies included patients receiving OT but without radiation therapy), which 1154 patients received at least OT and radiation therapy, of which 765 patients could be included into the review. In 12 studies, it possible to split the results in order to identify women who received respectively external RT only, BT only, a combination of EBRT and BT, chemoradiation, additional CT or no therapy. Patients who did not receive RT were excluded. In 7 studies, we were unable to split these ovarian survival rates of which 2 studies also included patients receiving CT [12,17–22].

Ovarian function was preserved after OT in 15.4–100% of patients after any kind of RT without CT (Fig. 2 and Table 4) [9–46]. The measurement or definitions of the ovarian function ranged from only climacteric complaints or lab values, until the combination of menses, lab values, climacteric complaints, imaging and/or pregnancy (Table 4).

Successful preservation of ovarian function after OT and EBRT (with or without BT) ranged from 20% to 100% (26 studies n = 401), and after BT only from 63.6% to 100% (8 studies, n = 148) (Fig. 2). Only 1 study reported ovarian preservation rates over time: ovarian

Table 1
Critical appraisal using the MINORS criteria for selected papers.

Author, year	Clear Aim	Inclusion of consecutive patients	Prospective data	Endpoints appropriate	Unbiased assessment of endpoints	Follow-up period	Loss to follow up <5%	Prospective calculation of study size	Total (max. 16 points)
Al-badawi (2010)	2	2	2	2	2	1	2	0	13
Anderson (1993)	2	2	2	2	0	2	2	0	12
Baker (1972)	0	2	1	2	1	1	1	0	8
Beurden (1990)	2	2	2	2	2	1	2	0	13
Bidzinski (1993)	2	2	1	2	2	1	2	0	12
Bieler (1976)	2	1	1	2	2	0	2	0	10
Bilek (1984)	0	1	0	2	1	0	1	0	5
Le Bouedec (2000)	2	1	0	2	1	2	2	0	10
Chambers (1991)	2	1	2	2	1	1	2	0	11
Chung (2007)	2	1	2	2	1	1	1	0	10
Clough (1996)	2	1	2	2	2	1	1	0	11
v. Eijkeren (1999)	2	2	2	2	1	1	2	0	12
Feeney (1995)	2	2	1	2	1	1	2	0	11
Gabriel (1986)	0	1	2	2	1	0	2	0	8
Gallocher (2002)	1	2	1	2	1	0	2	0	9
Gareer (2011)	2	1	2	2	2	0	1	0	10
Grabenbauer (1990)	1	1	1	2	1	2	1	0	9
Gugliemi (1980)	2	1	0	2	1	0	1	0	7
Hadar (1994)	2	2	1	2	2	1	2	0	12
Han (2011)	2	2	1	2	2	1	1	0	11
Hodel (1982)	2	2	0	2	2	0	2	0	10
Husseinzadeh (1994)	2	1	1	2	1	1	1	0	9
Husseinzadeh (1984)	2	1	1	2	1	0	1	0	8
Michel (1983)	2	1	0	2	1	0	1	0	7
Morice (2000)	2	1	2	2	2	0	1	0	10
Morice (1998)	2	1	1	2	2	1	1	0	10
Nagao (2006)	2	2	1	2	2	1	2	0	12
Nahhas (1971)	0	2	0	2	1	0	2	0	7
Olejek (124)	2	2	2	2	2	0	1	0	11
Ortin (1990)	2	2	1	2	1	2	2	0	12
Owens (1989)	1	2	2	2	1	1	1	0	10
Pahisa (2008)	2	1	2	2	2	1	2	0	12
Perri (2014)	2	2	1	2	2	1	1	0	11
Ploch (1988)	2	2	1	2	2	1	2	0	12
Ray (1970)	2	2	2	2	1	1	2	0	12
Stockle (1996)	2	2	1	2	2	1	2	0	12
Thomas (1976)	2	2	1	2	2	1	1	0	11
Yamamoto (2001)	2	2	1	2	2	2	2	0	13

The items are scored 0 (not reported); 1 (reported but inadequate) or 2 (reported and adequate).

function was preserved in 65.3% and 38.5% after respectively 1 and 5 years after OT and PRT [15]. Preservation of ovarian function was successful in 0%–69.2% of patients who received radiation therapy and CT (5 studies, n = 81) (Fig. 2) [9,19,30,32,36,39]. Median or mean of follow-up was described in only 26 studies and ranged between 7 and 102 months [9,10,13–16,18–20,23–28,31,32,34,35,37,39–42,44,46].

Complications

Twenty-two studies (872 patients, Table 2), including patients with OT and with or without additional irradiation therapy) described a total of 112 (12.8%) complications after OT (Table 5) [11–14,16,18–23,25,27,28,30,33,37–40,45]. Complications consisted of ovarian cyst development (93/112; 83.0%), abdominal pain (6/112; 5.4%), hematoma (2/112; 1.8%), tubal ligation (1/112; 0.9%), ischemia (1/112; 0.9%), and unspecified complications (2/112; 1.8%) (Table 5). Furthermore, small bowel obstructions due to adhesion after the operation were reported. Reoperation was necessary in 40 of 112 complications (34.7%), although the reason for the intervention was unknown in 26 patients. Ovarian metastasis were described in 5 cervical cancer patients (in a total of 538 cervical cancer patients, 0.9%) (Table 5).

Ovarian shielding

Apart from OT, 8 studies (21.1%) reported the use of an external lead shield to preserve ovarian function in all patients. Ovarian shielding was used in 6 studies with patients suffering from pelvic lymphomas [9,10,33,36,41,42] and in 2 studies with other pelvic

Table 2
Study design and patients characteristics.

Author Year	Study design Pro-/ Retrospective	Study purpose	Number of patients Included[a]/ total study OT[b]	Age years (range, number)	Cancer	Bi-/Unilateral OT Location fixation
Al-Badawi '10	Retrospective	Ovarian survival	23/23	Mean: 21 (12–28; EBRT; EBRT & BT) Mean 38 (32–42; RT& Chemo)	Cervix (n = 15) Rectum (n = 4) Ewing's sarcoma (n = 3) Hodgkin lymphoma (n = 1)	8/0 (EBRT; EBRT& BT) 15/0 (RT& CT) Site: Lateral, fixed to abdominal wall
Anderson '93	Retrospective	Ovarian survival & risk metastasis	12/82	Mean 31 (all patients, incl. No RT)	Cervix	Not reported
v. Beurden '90	Retrospective	Ovarian survival & complications	6/44	Mean 36.8 (33–40)	Cervix	2/4 Site: Lateral, fixed to the abdominal wall
Bidzinski '93	Prospective	Imaging & Ovarian survival	39/48	- (23–27)	Cervix	31/17
Bieler '76	Prospective	Ovarian survival	5/10	Mean 29.9 (26–34; n = 10)	Cervix	10/0 Site: Retroperitoneal, fixed to the posterior wall
Bilek '84	Unknown	Ovarian survival	25/44	Mean 32.5 (20–44; n = 30)	Cervix	24/20 (all patients incl. No RT): Site: Lateral
Bouedec '00	Unknown	Localization ovaries after OT and Ovarian survival	11/13	Mean 32 (32–40)	Cervix	Uni- or bilateral not reported Site: Lateral
Chambers '91	Retrospective	Ovarian survival &complications	14/38	–	Cervix	6/8 Site: Lateral, fixed to the abdominal wall
Chung '07	Retrospective	Ovaries at imaging	11/84	Median 39.8 (33–49; n = 11)	Cervix	5/6 Site: Lateral
Clough '96	Prospective	Ovarian survival	14/20	Mean 25 (EBRT) Mean 34 (22–44; BT) Mean 35 (35-35; BT and RT) Mean 31 (25–35; RT and chemo)	Cervix (n = 17, 5 lost) M. Hodgkin (n = 1, 1 lost) Cauda equina ependymoma (n = 1)	All: 20/0 Site: Lateral
V Eijkeren '99	Retrospective	Ovarian survival & complications	18/54	Mean 37.2 (29–49)	Cervix	40/14 Site: Lateral, fixed to the abdominal wall
Feeney '95	Retrospective	Ovarian survival & risks	28/32	Mean 33.7 (24–41)	Cervix	Uni or bilateral not reported Site: Lateral
Gallocher '02	Prospective	Follow up of cervical cancer	14/14	Mean 35 (25–45; n = 14)	Cervix	Uni or Bi: not reported, Site: Lateral, paracolic
Hadar '94	Prospective	Localization ovaries after OT & Ovarian survival	8/15	(23–36)	Cervix (n = 6) M. Hodgkin (n = 2)	8/0 Site: Cervix: paracolic gutter, fixed to lateral abdominal wall M. Hodgkin: Medial
Han '11	Retrospective	Ovarian survival	19/31	Mean 34.5 (22–40)	Cervix (n = 29) Rectum (n = 1) Endometrium (n = 1)	19/0 Site: Lateral
Hodel '82	Unknown	Ovarian survival	9/9	31 (25–38; EBRT) 21 (13–28; BT and EBRT)	Diverse	9/0 Site: Lateral
Husseinzadeh '84	Prospective	Ovarian survival	16/18	28.0 (21–38)	Cervix (n = 15, 2 lost) Vagina (n = 1)	17/1 Site: Lateral
Husseinzadeh '94	Prospective	Ovarian survival	11/22	Mean 32.4 (20–39)	Cervix	11/0 Site: Lateral, fixed to the posterior wall
Morice '98	Prospective	Fertility (pregnancy)	37/79	Mean: Clear cell: 19.6 (SD 5.6) Others 24 (SD 5.1)	Clear cell carcinoma (n = 27) Ovarian dysgerminoma (n = 9) Pelvic soft tissue sarcoma (=1)	Not reported Site: Lateral
Morice '00	Prospective	Ovarian survival & complications	84/107	Mean 34 (26–42; BT) Mean 32 (21–39; EBRT & BT/RT & chemo)	Cervix	All: 104/3 Site: Lateral
Nagao '06	Prospective	Ovarian survival	5/27	Mean 37 (n = 27)	Vagina	0/5 Site: Ovaries fixed in subcutis, abdominal wall
Olejek '01	Prospective	Ovarian survival	25/101	Mean 34.5 (20–40; n = 101)	Cervix	43/1 Site: Lateral, fixed to the posterior wall
Owens '89	Retrospective	Ovarian survival	8/14	–	Cervix	1 or 2 unilateral, others bilateral Site: Lateral (paracolic gutters)
Pahisa '08	Prospective	Ovarian survival	11/28	Mean 36 (BT, n = 7) Mean 37 (BT&EBRT n = 5)	Cervix	11/0 Site: Lateral
Perri '14	Retrospective	Comparing fixation methods, Describe outcome ovarian location and function	26/30	Median 35.4 (10–43)	Cervix (n = 28) Pelvic sarcoma (n = 2)	16/14 Site: lateral abdominal wall (paracolic gutters) 2 ovaries trough retroperitoneal tunnel
Ploch '88	Prospective	Ovarian survival	17/22	Mean: 28.4 (22–33; BT) 32.3 (28–37; BT& EBRT)	Cervix	3/2 (VBRT) 3/9 (ERT and VBRT) Site: Lateral, fixed to the abdominal wall
Stockle '96	Prospective	Ovarian survival	10/11	43 (EBRT) Mean 40 (39–40; BT) Mean 41 (39–44; BT& EBRT) Mean 39 (36–42; RT& Chemo)	Cervix	4/6 Site: Lateral
Yamamoto '01	Prospective	Follow up metastasis & ovarian survival	26/56	Median 35 (24–44; n = 26)	Cervix	Uni or bi: number nor reported Site< '90: Ovaries fixed in subcutis, abdominal wall Site>'90: Lateral

Table 2 (*continued*)

Author Year	Study design Pro-/ Retrospective	Study purpose	Number of patients Included[a]/ total study OT[b]	Age years (range, number)	Cancer	Bi-/Unilateral OT Location fixation
Lymphoma patients						
Author		**Purpose**		**Age years (range)**	**Indication**	**Uni/bi/Site**
Baker '72	Retrospective	Ovarian survival	8/8	Mean 25.4 (16–33)	M. Hodgkin	Not reported Site: Medial
Gabriel '86	Retrospective	Ovarian survival	17/27	–	M. Hodgkin	Not reported
Gareer '11	Prospective	Ovarian survival	11/15	23 (15–32; all patients)	Rectal cancer (n = 10) M. Hodgkin (n = 5)	11/0 Site: Lateral, fixed to the abdominal wall
Grabenbauer '90	Prospective	Ovarian survival	13/15	Mean 25 (22–29; EBRT) Mean 22 (13–34; RT & Chemo)	M. Hodgkin	13/0 Lateral (n = 9) Medial (n = 4)
Gugliemi '80	Unknown	Ovarian survival	66/66	(14–50) (all patients)	M. Hodgkin	66/0 Site: Medial
Michel '83	Unknown	Ovarian survival	54/87	–	M. Hodgkin (n = 50) Vagina (n = 1) Rhabdomyosarcoma (n = 3)	18/36 Site Lateral, fixed to the iliac spine
Nahhas '71	Unknown	Ovarian survival and dosimetric study	6/6	–	M. Hodgkin	5/1 Site: Lateral
Ortin '90	Retrospective	Ovarian survival & reproduction	20/20	(2–15) (all patients, n = 240)	M. Hodgkin	Not reported Medial
Ray '70	Retrospective	Ovarian survival	22/25	Mean 18.5 (13–25)	M. Hodgkin (n = 21) Nodular hystiocitic lymphoma (n = 1)	22/0 Site: Medial
Thomas '76	Retrospective	Ovarian survival & reproduction	16/33	Mean 27 (18–36)	M. Hodgkin & Non Hodgkin	16/0 Site: Medial

EBRT = External beam radiation therapy, BT = brachytherapy, CT = chemotherapy; - = unknown or not reported.
[a] Number of patients included (without lost to follow up and receiving radiation therapy).
[b] Number of patients at study-entry (and excluded due not receiving radiation therapy).

malignancies [18,38]. In patients with OT and ovarian shielding during RT, ovarian function preservation ranged from 16.7% to 88.9%, with a total of 106 patients of which 72 patients continued normal hormonal function (67.9%) (Fig. 2, Table 6).

Discussion

This systematic review shows that ovarian transposition (OT) in order to prevent POI due to pelvic radiation therapy (PRT) is successful in 20–100% of patients. Although OT has been performed for a long time and was reported for the first time in 1952, the effectiveness of this procedure has not systematically been studied [8]. A meta-analysis of the data extracted from the studies that were included in our review could not be performed due to heterogeneity. However, OT prior to brachytherapy seems to be most successful (63.6–100% preservation of ovarian function) when compared to other methods of pelvic radiation.

As mentioned, significant clinical heterogeneity is present in the included studies. This heterogeneity regards duration of follow-up (reported in only 23 of 38 studies (60.5%), range 7–102 months), definition of POI/ovarian survival (either not defined at all, based on laboratory tests, climacteric symptoms and/or pregnancy rate) and treatment regimens (either BT or EBRT or in combination, and with or without chemotherapy) (details of the different studies are presented in Table 2).

The addition of BT to EBRT or BT alone, allows the delivery of a sufficient dose in a short overall treatment time to the primary tumor while sparing normal adjacent structures as bladder and rectum, thus increasing the therapeutic ratio [47]. Concerning the ovaries and BT, Covens et al. estimated the mean radiation dose to each ovary without transposition for a course of intracavitary radiation as 1.26Gy [48]. Additionally, 8 studies included in the review, reported ovarian survival after BT only of respectively 100% [24,26,49], 90% [12], 85.7% [45], 83.3% [25]; 77.8% [46], and 63.3% [14]. This allows to conclude that OT is most successful with regard to ovarian survival after BT only.

Position of the transposed ovary may have important impact in ovarian function after OT and RT. The proper location to transpose the ovary depends on the scheduled treatment and the patient's anatomy. In cervical or vaginal cancer patients receiving external pelvic radiation, the ovaries can be transposed lateral, above the pelvic brim without tension on the vascular pedicle [15–18,22,39,50]. In patients receiving pelvic lymph node irradiation or an inverted Y field for Hodgkin's disease, the ovaries should be transposed medially and be attached to the uterus itself which allows the use of a lead shield to reduce the effect of scatter radiation [10,35,36,41,42]. This technique showed to be effective in 31.3%–88.9% of patients [9,10,36,41,42]. Additionally, Grabenbauer et all reported only a small difference in ovarian dose after median versus lateral transposition: 4.9Gy (range 3.9–5Gy) versus 3.25Gy (2.6–5Gy). By attaching radio-opaque markers to the ovaries, the position of the ovaries can be identified which allows the radiotherapist to adjust the radiation field when necessary. However despite all these measures, there is still a risk for the ovaries to receive a small amount of radiation which may indeed damage the transposed ovaries. Taking all these considerations into account, it seems important to transpose the ovary a far as possible outside the radiation field in order to prevent damage.

Another possible explanation of POI after OT and PRT is the migration of the ovaries back into the pelvic irradiation fields as a result of their release from the fixation point. Williams et al. reported ovarian migration, diagnosed at laparoscopy 5 and 6 months after ovarian transposition despite the use of permanent sutures. Therefore, it is recommended to time the procedure shortly before beginning radiation treatment [51] thereby taking into account the possible delay of radiation therapy due to physical recovery, pain, pelvic effusion etc. Which can influence the correct set up position for the radiotherapy CT scan. Moreover decreased blood supply to the transposed ovaries due to the formation of scar tissue [38], or kinking of the infundibulopelvic ligament may result in POI after OT. Therefore, we stress the need for sufficient dissection of the vascular pedicle and prevent kinking after surgery. Eitan et al., have argued that tunneling the ovaries retroperitoneal may prevent torsion of the vessels, may reduce the dose of radiation to the

Table 3
Cancer treatments.

Author Year	Radiation Therapy			
	EBRT	BT	EBRT & BT	RT with chemo
Al-Badawi '10	Not specified (n = 7)	–	Not specified (n = 1)	Chemo&1x EBRT (n = 1) EBRT&BT (n = 14)
Anderson '93	–	–	12 × 2/4Fields, 10Mv; Gy 45 VRT 5–6 g/hr.	–
v. Beurden '90	Whole pelvic, 2Fields 5-10Mv; Gy40-45 3 x + shield 3/6 ovaries with in RTfield	-	-	–
Bidzinski '93		Gy 40–45 (n = 24)	Whole pelvic; 3x 2Fields 12x 4Fields, Co-60 or Mv Gy 44 & BT (n = 15)	–
Bieler '76	Gy 60 (n = 3)	–	BT& EBRT (n = 3) 1x 8 Fields, 4x 2Fields 2x 2 Moving beam fields Total Gy 60	–
Bilek '84	Gy 52, Pelvic	–	–	–
Bouedec '00	–	Estimated dose on the ovaries Gy:2.6 (1.2–5.9; n = 20)	–	–
Chambers '91	9x Pelvic, 2Fields, 6-25Mv Gy 40-48	–	4x EBRT &VRT 22–50 Gy	1x EBRT & Chemo
Chung '07	Radiation and/or chemoradiation therapy not specified			
Clough '96	Gy 35-50 2Fields 6-25Mv (n = 1)	Gy 65 (n = 7)	BT&EBRT (Gy 30 &;35; n = 3)	BT& Chemo (n = 2) EBRT& Chemo (3 cycle MOPP, n = 1)
	RT Fields: Medial lumbar region/Pelvic/Inverted Y region/iliac region Estimated dose on ovaries: Gy 1.75 (0.4–3.7)			
V Eijkeren '99	Pelvic Scatterdose: Gy 1–3.45	–	–	–
Feeney '95	Pelvic; 2Fields; Gy:45-50	–	–	–
Gallocher '02	–	Gy: 70, 0.68 Gy received by the ovaries	–	–
Hadar '94	Cervix: pelvic (n = 6, 1 patients ovaries still within RT field) M.Hodgkin: Inverted Y-field (n = 2, 1 patients ovaries still within field)	–	–	–
Han '11	Gy45-50 Whole pelvic (n = 18) + para-aortal/parametrial (n = 2)	–	EBRT & BT (unspecified, n = 1)	–
Hodel '82	Whole pelvic Gy 40-52	–	EBRT& BT Gy30/45	–
Husseinzadeh '84	4Fields; Whole pelvic 16 × 10Mv; 2x 4Mv	–	–	– Ovarian shields+
Husseinzadeh '94	–	–	Whole Pelvic; 4Fields; Gy 36 –50 + BT Gy 10; 4- 16Mv 1x2Fields; 25 MV 1x cobalt	- Ovarian shields+
Morice '98	Inverted Y; Gy 25–35 (n = 9) Gy 10 (n = 1) Mean ovarian RT-dose: Clear cell: Gy 2.2 Other: Gy 1.9	Gy 60 (n = 20)	45Gy& BT boost Gy 15 (n = 7)	–
Morice '00	–	Gy 60 (n = 59) Mean dose at ovaries: Gy 1.2	Whole pelvic Gy 45& BT Gy 15 Mean dose at ovaries: Gy 5.2 (n = 18)	7x Chemo &EBRT Gy 45 & BT Gy 60
Nagao '06	Yes, not specified	–	–	–
Olejek '01	–	Gy: 30–38, Iridium-192 (n = 11)	2Fields; Gy 30–96 &BT (n = 9), and (n = 5) + Lymph node RT Gy 45	-
Owens '89	Pelvic	–	–	–
Pahisa '08	–	Gy: 20–30 (n = 6)	Whole pelvic, 4fields, Cobalt Gy: 40–50 & BT (n = 5)	–
Perri '14	Gy 50, pelvic (n = 7)	–	EBRT+ 45Gy BT (n = 17)	–
	*N = 13; ERT + chemo therapy, not specified (n = 13) **N = 2; RT unspecified			
Ploch '88	–	Gy 50-80	9x 4Fields; 3x 2Fields 10x Cobalt; 2 × 9/18Mv Gy 43 –44 + BT 2 x ovarian shields	–
Stockle '96	Pelvic; Gy43; 18/25Mv; (n = 1)	Gy 60 (n = 2)	Whole pelvic, 18/25Mv + BT. Total Gy 60 1x + lumbo-aortal RT (n = 5)	CT & EBRT& BT, Total Gy 60 (n = 2) 2 + lateral pelvic RT 6/16Gy 1+lumbo-aortal RT
	Estimated dose: left ovary: Gy 0.85–3.43, 1x Gy 64 + Gy 5.42 right (&chemo→ POI) Right ovary: 0.3–2.16; 1 × 45Gy (+chemo→ POI)			
Yamamoto '01	Whole pelvic, 10Mv 2Fields or 4Fields; Gy 50	–	–	–
Lymphoma patients				
Author	**ERT ******	**Shielding**	**ERT& Chemotherapy**	
Baker '72	Whole pelvic& pelvic nodes Gy 36.6 (34–40)	Yes Scatterdose maximum 13%	–	–
Gabriel '86	Mantle (+Para-aortal); or Total node	–	–	–
Gareer '11	Whole pelvic	–	–	–
Grabenbauer '90	inverted Y; 6-10Mv; Gy 38–50 (n = 6)	–	EBRT + CT (unspecified) (n = 7)	–
Gugliemi '80	Pelvic/Mantle/Para-aortal (n = 18) Total nodal (n = 5)	Yes	CT (MOPP)+ –24x Total nodal (n = 24) Pelvic& Mantle& Para-aortal (n = 19)	–
Michel '83		–		–

Table 3 (*continued*)

Author Year	Radiation Therapy			
	EBRT	BT	EBRT & BT	RT with chemo
	Bilateral OT: Gy 40 Lumbo-aortal (n = 12) Inverted Y (n = 15) Unilateral OT, Gy 30-40 Lumbo-aortal (n = 16) Inverted Y (n = 2) OT and diverse RT treatments (n = 6)		CT + bilateral OT & inverted Y (n = 5) (unknown which RT)	
Nahhas '71	2x Para-aortal, L4 and lower; 4x modified.Y field Gy: minimum of 36	Yes (n = 5/6)	–	–
Ortin '90	Mantle & inverted Y Gy 40–44 (n = 9)	Yes	CT&EBRT; (n = 6) CT& EBRT Gy 20–35 (n = 5)	–
Ray '70	Whole pelvic, 6.0Mv 43 Gy (31.5–45)	Yes	–	–
Thomas '76	Gy 35 Inverted Y (n = 12) Lumbo-aortal (n = 4)	Shielding at Inverted Y radiation field	–	–

EBRT = External beam radiation therapy, BT= Brachytherapy, CT = chemotherapy; - = unknown or not reported.

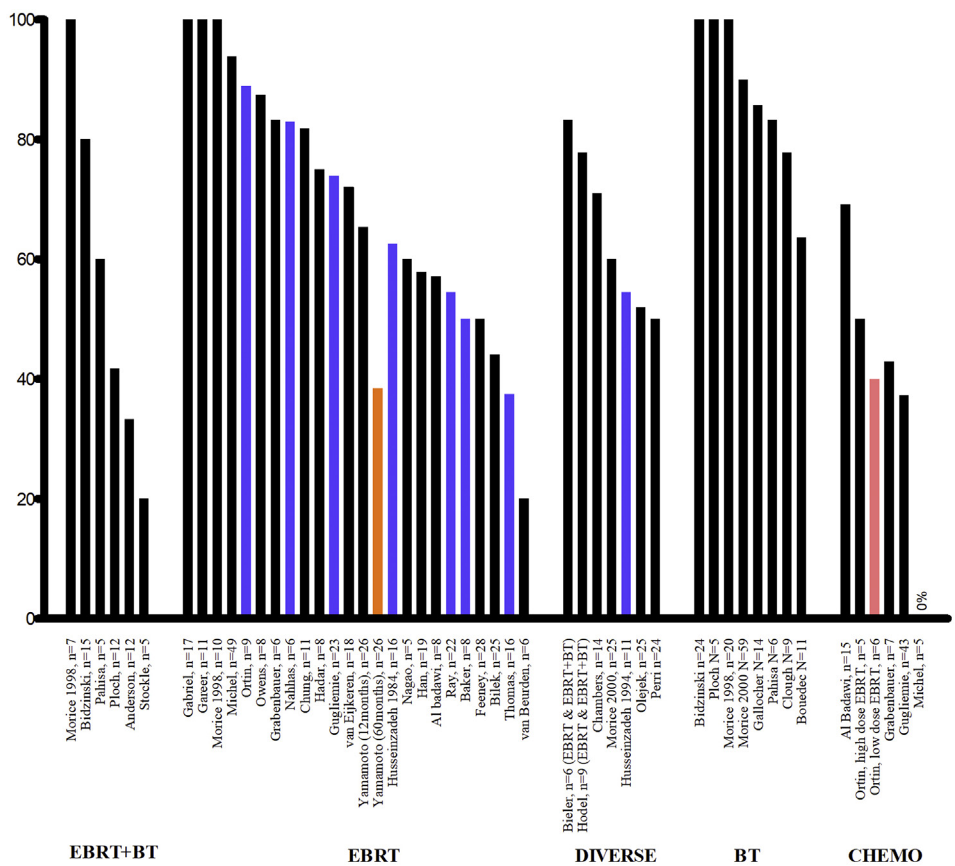

Figure. 2. Ovarian survival after OT gonadotoxic treatment in 765 patients. Black: patients treated without external lead shield, Blue: patients treated with the addition of an external lead shield. Orange (n = 1): Yamamoto, ovarian follow up after 5 years. Pink: Ortin, patients treated with low dose chemotherapy. Eleven patients in 2 studies are excluded, due to numbers <5 within treatment group.

ovarian vessels and prevent both kinking of the ovarian vessels and migration of the transposed ovary to the original location iside the radiation field [52]. However, it is unclear whether tunneling indeed results in improved ovarian survival.

OT may reduce ovarian damage caused by radiation but does not protect against the detrimental effects of chemotherapy (CT). Effectiveness of OT prior to combined chemotherapy and radiation therapy is considered to be reduced. In 6 studies, a part of the patients ($n \geq 5$) received additional (neo) adjuvant CT or chemoradiation therapy [9,19,30,32,36,39]. Ovarian survival ranged from 0 until 69.2%, although different types and doses of chemotherapy were used. Hence robust conclusions cannot be drawn with regard to the effectiveness of OT in patients who receive both pelvic radiation and chemotherapy but effectivity of OT seems to be reduced.

Despite of ovarian damage due to radiation, the uterus must not forgotten when still in situ. Critchley et al. showed that the uterine musculature and blood flow are irreversibly affected by high dose irradiation in childhood [53]. Additionally, Signorello et al. showed that the children of cancer survivors in whom the uterus had been radiated, were more likely to be born preterm and had lower birth weight. These risks started from 50 cGy to 250 cGy radiation at the uterus for respectively preterm birth and low birth weight [54]. Thus ovarian transposition is an option in women who need BT and/or EBRT, however only when ovarian function is desirable to prevent side effects of POI like flushes, decreased bone mineral density

Table 4
Outcome of de ovarian transposition and follow up.

Author Year	Evidence ovarian function			Follow Up Months (range)	Ovarian Survival% After OT and RT
	1 result	2 results	3 results		
Al-Badawi ‘10	–	1 lab value (FSH) & menses (n = 20) FSH 6 months after therapy	–	EBRT 29.5months (10–60) With chemo 34.5months (12–66)	All: 65% RT: 57.1% +CT: 69.2%
Anderson ‘93	1 lab result/climacteric l symptoms or both	–	–	POI: 68 months No POI: 77 months	33%
v. Beurden ‘90	2x climacteric symptoms (1 patient died)	2 × 3 lab values + climacteric symptoms 1 × 2 lab values + climacteric symptoms 1 × 3 lab values & no climacteric symptoms	–	19 (10–37)	1 died 20%
Bidzinski ‘93	38 × 4 lab values	1x climacteric symptoms & 4 lab values	–	POI at 0 and after 6 months	BT: 100% EBRT&BT: 80%
Bieler 76	–	3 lab values & Clomiphene stimulation (n = 6)	–	–	83.3% (4 lost)
Bilek ‘84	–	Symptoms and lab values (not specified/patient)	–	–	44%
Bouedec ‘00	climacteric symptoms /2 lab values /Estragenization of vaginal epithelium	–	–	All patients: 102 (60–156)	Transposition: 68% (fixation: 50%)
Chambers ‘91	10x no climacteric symptoms	4x climacteric symptoms & 2 lab values (FHS& LH)	–	No POI Median 36 months; : median 35 months	71%
Chung ‘07	9x no climacteric symptoms	2 × 2 lab values (FSH and E2) & climacteric symptoms	–	28.3 (7.5–101.4)	81.8%
Clough ‘96	–	4 lab values + postmenopausal symptoms Lab at 1,6,12 months	–	23.5months (12–33)	All: 87.5% Only BT: 77.8%
V Eijkeren ‘99	13x no climacteric symptoms	5 × 2 lab values& climacteric symptoms	–	36–84months (n = 54)	72%
Feeney ‘95	14x no climacteric symptoms	8x climacteric symptoms & use of HRT	6x climacteric symptoms, lab value & HRT	POI& HRT mean 6.2 months Mean of all OT: 24 (3–80)	50%
Gallocher ‘02	12x no climacteric symptoms	2x climacteric symptoms & use of HRT	–	–	85.7%
Hadar ‘94	–	5 × 1 lab value + imaging (CT)	1 lab value& postmenopausal symptoms& imaging (CT scan) (n = 1)	- (2–60months)	All: 75% Cervix: 83.3% (n = 1 within field) M. Hodgkin: 50%
Han ‘11	2 lab values (FSH& E2, n = 19)	–	–	17.2 months (1–68)	57.9% (excl. 11 lost)
Hodel ‘82	Lab value (FSH) (n = 4) No climacteric symptoms (n = 3)	2x climacteric symptoms and 1 lab value (FSH)	–	–	77.8%
Hussein-zadeh ‘84	‘Normal or elevated gonadotrophin levels’ (FSH/LH)	–	–	–	62.5%
Hussein-zadeh ‘94	3x normal lab values (FSH) 3x ‘no evidence’ of ovarian failure 2x high FSH 4x lost to follow up	3x Lab values (FSH) & HRT	–	Mean: 7 months (0–24)	54.5%
Morice ‘98	–	–	2 lab values &imaging &menses (n = 25) pregnancy (n = 12)	Minimum. 24 months	100% 32% pregnancies
Morice ‘00	–	–	Imaging + menses +2 lab values every 12 months	–	BT 90% EBRT&BT/EBRT& Chemo 60%
Nagao ‘06	5 × 1 lab result (FSH) Every 6–12 months	–	–	ovarian failure at 59 & 71 months (n = 2)	60%
Olejek ‘01	13 × 5 lab values Twice in 1 week	6x climacteric symptoms & use of HRT (patients after OT and RT)	6 × 5 lab values & climacteric symptoms & use of HRT	–	52%
Owens ‘89	No climacteric symptoms (n = 7)	1x climacteric symptoms &HRT		Median 18 months, (6–36 months)	87.5%
Pahisa ‘08		All patients: 2 lab values/6 months Sometimes climacteric symptoms	–	All patients: mean 44.3 months (16–84)	BT: 83.3% EBRT&BT 60%
Perri ‘14		Lab value (FSH) & climacteric symptoms (imaging to localize the ovaries)	–	Median 27.25 months (2.2–67.7)	All 50%
Ploch ‘88	4 lab values	–	–	BRT 8.8 (2–15) EBRT&BT 16.4 (9–26)	BT: 100% EBRT&BT: 41.7%
Stockle ‘96		3 × 3 lab values & climacteric symptoms 4 × 3 lab values & no climacteric symptoms 1 × 2 lab values & no climacteric symptoms	1 × 3 lab values; 1 × 2 lab values& climacteric symptoms & use of HRT	11 months (3–19)	All 33.33% (1 lost) EBRT&BT: 20%
Yamamoto ‘01		Lab values (E2 or Progesterone) & basal body temperature	–	12 months 60 months	65.3% 38.5%

Table 4 (*continued*)

Author Year	Evidence ovarian function			Follow Up Months (range)	Ovarian Survival% After OT and RT
	1 result	2 results	3 results		
Lymphoma patients					
Author	**1 result**	**2 results**	**3 results Or pregnancy**	**FU months (range)**	**Ovarian survival%**
Baker '72	menses	–	Pregnancy (n = 1)	22.5months (0–72) Pregnant at 72 months	50%
Gabriel '86	menses (n = 9);		Pregnancy (n = 8)	–	100%
Gareer '11	'functioning ovaries'	–	–	–	100%
Grabenbauer '90	menses (n = 1)	2 lab values + climacteric symptoms (or not) (n = 12)		EBRT 60 (24–108) EBRT &Chemo 66.9 (24–108)	Lateral: 77.8% Medial: 25% EBRT: 83.3% &CT: 42.9%
Gugliemi '80	menses	–	Pregnancy (n = 8)	–	RT: 73.9% Para-aortal: 94.5% Total nodal: 0% RT&CT: 37.2% Para-aortal: 84.2% Total nodal: 0%
Michel '83	Menses (n = 50) Puberty (n = 1)	–	Pregnancy (n = 3, bilateral OT, after Lumbo RT)	–	RT: 93.9 RT&CT: 0%
Nahhas '71	menses	–	–	–	83%
Ortin '90	'functioning ovaries' (n = 16)	–	Pregnancy (n = 4)	General, median 108	EBRT: 88.9% EBRT& CT: 50% EBRT low dose & CT: 40%
Ray '70	menses	–	Pregnancy (n = 1)	10.05 months (2–48)	54.5%
Thomas '76	–	2 lab values + menses (n = 15)	Pregnancy (n = 1)	POI at 0 months (n = 10) No POI 96 (n = 1) & 6 months (n = 1) ikRT Para-aortal: Not reported (n = 4)	37.5%

EBRT = External beam radiation therapy, BT = brachytherapy, CT = chemotherapy; - = unknown or not reported; E2 = Estradiol.

Table 5
Complications after ovarian transposition.

Author, No. of OT	No. Complications	Sort complication	Interventions
Han (2011), 31	3 (9.7%)	Ovarian cysts	–
Al- Badawi (2010), 23	0 (0%)	–	–
Nagao (2006), 27	3 (11.1%)	3 cysts	None
van Eijkeren (1999), 54	3 (5.56%)	3 cysts	–
Le Bouedec (2000), 13	4 (30.8%)	3 cysts, 1 metastasis	4 operations
Morice (1998), 97	9 (9.3%)	9 cysts	1 puncture, 1 medical intervention, 7x -
Stockle (1996), 11	1 (9.1%)	1 cysts	–
Husseinzadeh (1994), 22	2 (9.1%)	2 cysts	1 oophorectomy, 1x -
Anderson (1993), 82	16 (19.5%)	15 cysts, 1 metastasis	10 oophorectomies, 6 medication
Gallocher (2002), 14	4 (28.6%)	3 ovarian cysts, 1 abdominal pain	None
Nahhas (1971), 6	1 (16.7%)	1 infectious hematoma	1 Laparotomy
Hodel (1982), 9	1 (11.1%)	1 cyst	–
Husseinzadeh (1984), 18	0 (0%)	–	–
Gabriel (1986), 27	6 (22.2%)	3 cysts; 1 tubal ligation, 1 ischemia, 1 ectomy because of endometriosis	1 oophorectomy, 5x -
Chambers (1991), 38	7 (18.4%)	7 cysts	5 operations, 2 no operations
Olejek (2001), 101	11 (10.9%)	11 cysts	1 oophorectomy, 2 cyst extirpations, 8x -
Morice (2000), 107	27 (25.2%)	22 cysts, 1 metastasis, 3 abdominal pain, 1 bowel obstruction due to adhesions	19x OC, 4 operations, 1 bowel operation, 3 pain: none (1 bowel obstruction due to adhesion band)
Pahisa (2008), 28	2 (7.1%)	2 cysts	2 oophorectomies
Feeney (1995), 32	6 (18.8%)	4 cysts, 2 metastasis	2 operations
Michel 1983), 87	4 (4.6%)	2 small bowel obstructions,1 infectious hematoma, 1 cyst	–
Hadar (1994), 15	2 (13.3%)	2 cysts	Oophorectomy, 1 operation undefined
Perri (2014), 30	0 (0%)		
Total n = 872	**112 (12.8%)**		**Total operations: 40 (35.7%)**

No. = number, - = not known or reported, OC = Oral Contraceptives.

Table 6
Ovarian survival after OT and radiation therapy and ovarian shielding.

Author Year	N	Primary tumor	Survival %	Age Mean (range)	FU time months Mean (range)
Baker (1972)	8	M. Hodkgin	50	25 (16–33)	22.5 (0–72)
Gugliemi (1980)	23	M. Hodgkin	73.9	- (14–50)	NR
Ortin (1990)	9	M. Hodgkin	88.9	- (2–15)	108 (median)
Nahhas (1971)	5	M. Hodgkin	83.3	–	NR
Ray (1970)	22	M. Hodgkin	54.5	19 (13–25)	10.05 (2–48)
Thomas (1976)	12	M.H.& N·H	16.7	27 (18–36)	10x POI at 0 months 2x No POI at 6 & 96 months
Husseinzadeh (1984)	16	Cervix	62.5	28 (21–38)	NR
Husseinzadeh (1994)	11	Cervix	54.5	32 (20–39)	7 (0–24)
Total	**106**		**67.9%**		

FU = follow up. M.H. = M. Hodgkin, N·H. = Non Hodgkin; POI= Premature Ovarian Insufficiency, NR = not reported.

and impaired lipid profile with increased risk of ischemic heart disease [4,5]. A few studies reported spontaneous pregnancies after ovarian transposition and radiation therapy, of which almost all patients were treated for Hodgkin lymphoma, irradiated with an inverted Y field, transposed ovaries to the uterus and the use of an lead shield [9,10,36,41,55]. Only one study reported successful pregnancies in women with pelvic/vaginal cancer [49]. Morice et al. reported 12 pregnancies, after surgery, OT and RT (and in some cases chemotherapy), in which the received radiation dose to the ovaries was estimated to be 1.9Gy. The radiation dose those received by the uterus was not mentioned. Kurt and Cantor both reported a pregnancy after rectal carcinoma and aneurysmal bone cyst, treated with radiation therapy and ovarian transposition of which the pregnancy resulted in a second trimester miscarriage [56,57]. In case of child wish in patients with an abnormal uterus after radiation, surrogacy can be an option. Although only four case reports have been published, surrogate pregnancy after ovarian transposition and pelvic radiation can be an option and is probably the only option [58–62].

Apart from the effectiveness of OT, the risk of both complications and transposing an ovarian metastasis have to be taken into account when considering OT. Twenty-two studies (920 patients) described complications after OT either with or without RT, with a total of 112 complications (12.2%). In 5 patients a metastasis within the transposed ovary was reported [12–14,27]. Complications included development of benign ovarian cysts, chronic pelvic/abdominal pain, vascular injury and ischemic injury of the transposed ovary [11,12,16,18,20–23,25,28,30,37,40,45]. A surgical procedure was necessary in 40 of the 112 complications (35.7%), although the precise surgical in 26 patients was unknown. Intraoperative and immediate complications are rare but can include fallopian tube infarction and hematoma [11,12,33]. Furthermore, OT seems to induce a higher incidence of symptomatic cysts of 10.1% compared to the normal cyst incidence of 2.5% women which should be mentioned during counseling [63]. Thus, especially when an additional surgical procedure has to be performed, the risk of complications must be considered.

When appraising our results we have to bear in mind that significant improvements in radiation treatment planning systems now allow for meaningful assessment of the planned dose to the ovaries through dose–volume histograms. Furthermore, daily image guided treatment delivery allows for a more accurate assessment of the effect of intrafraction movement of the ovaries and the subsequent dose received. Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) allows for more conformal dose to target tissues, however the volume of surrounding tissue receiving a low dose is usually increased, and care should be taken when using these techniques to properly identify the transposed ovary to assure maximal sparing [64–67]. In contrast, proton therapy is both conformal and allows for an important reduction of low dose exposure outside the target area. In none of the included studies more modern image guided RT using IMRT, VMAT or proton therapy techniques was used. However Du et all, calculated that in young patients with cervical cancer who underwent radical hysterectomy and OT without receiving adjuvant radiotherapy, a limited ovarian radiation dose ≤20% in a set IMRT pelvic radiation dose of 4500–5000 cGy, prevents the disruption of ovarian function (P = 0.003) [68]. Hence the effectiveness of OT may increase using these new techniques.

In summary, we concluded a most favorable outcome in patients after OT and brachytherapy with an ranges from 63.6 to 100%, followed by followed by OT and PRT, and lastly OT and EBRT combined with chemotherapy. Taking all considerations, pitfalls, moderate effectiveness and improved treatment planning into account, ovarian transposition in order to preserve ovarian function should be offered to young patients that will undergo pelvic radiation as part of cancer treatment. However, patients should be selected carefully regarding primary goal of ovarian preservation, tumor type, treatment regimen, radiation field and transposition site to maximize benefits versus side effects and complication ratio. Finally, it is of utmost importance to initiate an international prospective study with standardized reporting of radiation dose and technique to the transposed ovarian, ovarian function measurement and long term follow-up to evaluate the effectiveness of OT more precisely.

Conflicts of interest

The authors declare no competing interests, all have read and approved the manuscript and agreed to its submission. The manuscript is original work and not under consideration for publication elsewhere. The guidelines of the STROBE statement have been followed in the preparation of the manuscript.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.017.

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