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Case series

Laparoscopic ovarian transposition prior to pelvic radiation for gynecologic cancer

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ABSTRACT

This study evaluates a novel technique of laparoscopic ovarian transposition performed by Gynecologic Oncologists prior to pelvic radiation for gynecologic cancer. A retrospective review was completed of all patients that underwent laparoscopic ovarian transposition from February 2007 to June 2017 at one tertiary care cancer. The technique involves salpingectomy, followed by retroperitoneal dissection to move the ovaries lateral to the hepatic and splenic flexures of the colon. Normal ovarian function was defined by the absence of vasomotor symptoms, FSH and menstrual history (if menstruating). The radiation dose to the ovary was calculated through dose volume histograms from three-dimensional image planning. Ten patients had laparoscopic ovarian transposition, of which, eight patients received post-operative external beam radiation to the pelvis (45–59.4 Gy). Four had additional brachytherapy (35.5–40 Gy). Median age and follow up were 29 years (18–37), and 20 months (6–103). Nine patients had cervical and one had vaginal cancer. Four patients were treated with primary radiation, three had radical trachelectomy with adjuvant radiation, and three had radical hysterectomy with one of three receiving adjuvant radiation. No patients developed vasomotor symptoms (0/8 (95% CI 0–19%)). FSH was normal in 2/2 patients. Menses continued post-radiation in 5/7 women who retained their uterus. The median radiation dose to the right and left ovary was 0.51 (0.23–1.1) Gy and 0.53 (0.23–1.1) Gy, respectively. Laparoscopic ovarian transposition with mobilization to the hepatic and splenic flexures of the colon achieves preservation of ovarian function in women prior to pelvic radiation.

1. Introduction

Ovarian transposition is a surgical technique moving ovaries out of the pelvis prior to pelvic radiation for gynecologic or non-gynecologic cancers. In young patients, ovarian preservation is important, as early menopause is associated with increased osteoporosis, cardiovascular disease, hot flushing, urogenital atrophy and sexual dysfunction (Mytton et al., 2017). Additionally, fertility preservation is possible as ovarian transposition theoretically enables women to genetically produce offspring by transabdominal ultrasound-guided oocyte retrieval and use of a gestational carrier (Willows et al., 2016).

As half of cervical cancer patients are premenopausal when diagnosed, ovarian transposition prior to radiation therapy to preserve ovarian function is beneficial. Adjuvant radiotherapy is required when there are risk factors for recurrence; including lymph node metastasis, deep stromal invasion with lymphovascular space invasion, positive margins, or parametrial involvement (Waggoner, 2003). Additionally, stages IB2 and greater are usually treated with primary chemoradiation.

A systematic review and meta-analysis of open and laparoscopic ovarian transposition demonstrated high rates of ovarian preservation at 90% (95% CI 92–99) in the surgery alone group (Gubbala et al., 2014). However, studies assessing ovarian function after surgical transposition and pelvic radiation report a much lower rate of ovarian preservation. Most studies are small ranging from 3 to 31 patients. The ovarian preservation rate after ovarian transposition and external beam pelvic radiation and/or brachytherapy is 65% (95% CI 56–74) (Gubbala et al., 2014).

Low rates of ovarian preservation after surgical transposition and radiation result from placement within the radiation field, or proximity to the radiation field (subjecting ovaries to internal scatter, or vascular compromise) (Huang et al., 2007). The patient's age at the time of surgery is important as the number of primordial oocytes decline with increasing age until menopause. As the number of oocytes decline, smaller doses of radiation are more harmful to the ovaries (Wallace et al., 2003).

This study describes our results with a laparoscopic surgical

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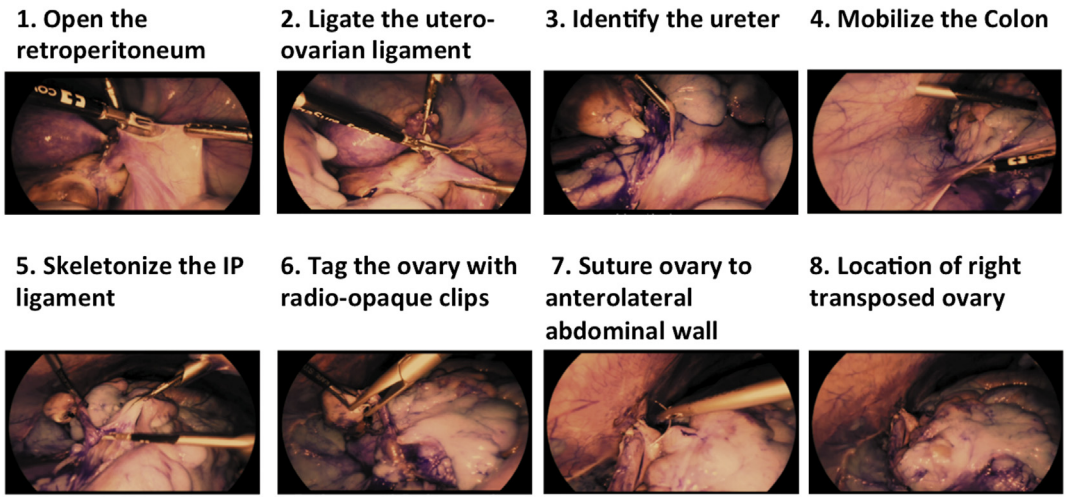

Fig. 1. Laparoscopic ovarian transposition sequential surgical steps.

technique for ovarian transposition involving retroperitoneal dissection making it possible to move ovaries higher and out of the pelvic radiation field.

2. Methods

2.1. Study population

A retrospective chart review was completed for patients aged 18–40 that underwent a laparoscopic ovarian transposition at the Odette Cancer Centre from January 1st, 2007 until June 30th, 2017. Postmenopausal or patients over the age of 40 at the time of diagnosis were excluded. The study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre.

2.2. Laparoscopic ovarian transposition surgical procedure

The peritoneum was insufflated with CO_2 gas. Four ports were placed for the procedure, a 10 mm umbilical and 10 mm suprapubic port with 5 mm right and 5 mm left mid quadrant ports. Beginning on one side, the fallopian tubes were removed. The utero-ovarian ligament was cauterized and divided. The retroperitoneum was opened and the ureter was identified. The infundibulopelvic ligament was mobilized along its entirety with a vessel sealer/divider. Incising the peritoneum overlying the paracolic gutters facilitated mobilization of the ascending and descending colon to the level of the hepatic and splenic flexures, respectively. The ovary was brought up to the costal margin with the infundibulopelvic ligament traversing the retroperitoneal space underlying the colon. Care was taken to avoid torsion of pedicle. Hemoclips were placed on the distal side of each ovary for radiologic marking. The ovary was sutured to the intraperitoneal surface of the anterior abdominal wall with a barbed suture.

2.3. Radiation dose to the ovary

All patients underwent CT simulation as part of radiation planning such that the transposed ovaries could be identified on the scan and contoured. The radiation dose (mean) received by the ovary was determined through volumetric dosimetry of the contoured ovaries. In cases where the location of the ovaries were above the superior limit of the CT scan, the max dose at the superior CT scan slice was used as a surrogate for ovary dose. In patients that received brachytherapy, dose distributions were conformal and confined centrally in the lower pelvis, and the contribution to the ovaries were negligible.

2.4. Evaluation of ovarian function

Normal ovarian function prior to the surgical procedure was defined as regular menstrual periods and the absence of vasomotor symptoms. Ovarian function was assessed by either; FSH < 25 IU/L, continued menses without exogenous hormones, or the absence of vasomotor symptoms (surrogate marker) if FSH was not measured and the patient was not menstruating.

3. Results

Ten patients with gynecologic cancers had laparoscopic ovarian transposition at the Odette Cancer Centre from February 2007 to June 2017. Sequential images describing the surgical procedure are shown in Fig. 1.

Patient characteristics are summarized in Table 1. The median age of patients undergoing ovarian transposition was 29 years (18–37 years). Nine patients had cervical cancer (six squamous cell, three adenocarcinomas, two of which were clear cell and one mucinous), and one had vaginal cancer (clear cell carcinoma). Bilateral ovarian transposition was performed in eight patients. Unilateral transposition was performed in two patients due to endometriosis presenting as an ovarian mass and adhesions. Three patients had a radical trachelectomy followed by adjuvant chemoradiation. Three patients had a radical hysterectomy, with one patient requiring adjuvant chemoradiation treatment. The other two patients treated with a radical hysterectomy did not require adjuvant radiation. Four patients received primary treatment with three of the four patients receiving primary chemoradiation, one patient declined cisplatin and was treated with primary radiation. Three patients received external beam radiation and 4 patients received external beam radiation with brachytherapy. The median follow up after surgery was 22 months (8–103 months). All patients were alive and free of disease at last follow up.

Table 2 summarizes each patient's treatment and ovarian function. All patients were pre-menopausal at the time of surgery. Four patients treated with primary chemoradiation received 45–50.4 Gy by external beam radiation therapy (EBRT) and 39.6–40 Gy by brachytherapy. Four patients treated with adjuvant EBRT received 45–59.4 Gy. The median follow up after radiation was 20 months (6–103 months). No patients developed vasomotor symptoms (0/8) (95% CI 0–19%). Two patients had their FSH measured after treatment, and both were normal. Five women continued to have regular menses post-radiation.

The location of the transposed ovaries are identified by placement of surgical clips at the time of surgery as shown by abdominal xray in Fig. 2. The distance of the transposed ovary from the radiation field and

Table 1
Patient characteristics.

Study #	Age	Diagnosis	Treatment			Status at last follow up	
			Surgery	Chemotherapy	Radiation	Months post-op	Status
1	27	Stage IBI mucinous adenocarcinoma of the cervix	Radical trachelectomy, sentinel nodes	Cisplatin	EBRT	21	Alive
2	22	Stage I clear cell carcinoma of the vagina	None	Cisplatin	EBRT and brachytherapy	23	Alive
3	36	Stage IBI squamous cell carcinoma of the cervix	Laparoscopic radical hysterectomy, right salpingo-oophorectomy, sentinel nodes	None	None	43	Alive
4	27	Stage IB2 squamous cell carcinoma of the cervix	None	Cisplatin	EBRT and brachytherapy	103	Alive
5	18	Stage IBI clear cell adenocarcinoma of the cervix	Radical vaginal trachelectomy	Cisplatin and Adriamycin	EBRT	16	Alive
6	33	Stage IBI squamous cell carcinoma of the cervix	Radical vaginal trachelectomy, sentinel lymph nodes	Cisplatin	EBRT and brachytherapy	12	Alive
7	30	Stage IBI squamous cell carcinoma of cervix	Laparoscopic radical hysterectomy, sentinel nodes	Cisplatin	EBRT	54	Alive
8	37	Stage IIB squamous cell carcinoma of the cervix.	None	Cisplatin	EBRT and brachytherapy	8	Alive
9	32	Stage IIA squamous cell carcinoma of the cervix.	None	None (pt declined)	EBRT and brachytherapy	24	Alive
10	32	Stage IBI clear cell adenocarcinoma of the cervix	Laparoscopic radical hysterectomy, bilateral salpingectomy, sentinel nodes	None	None	22	Alive

the radiation dose to the ovary was calculated through dose volume histograms from three-dimensional image planning as shown in Fig. 2B. Eight patients received pelvic radiation after ovarian transposition. The dose of pelvic external beam radiation was 45–59.4 Gy. The median (range) distance of the right and left ovary to the radiation field was 6.7 (4.2–14) cm and 6.2 (4.2–14) cm, repectively. The median (range) dose of radiation to the right and left ovary was 0.51 (0.23–1.1) Gy and 0.53 (0.23–1.1) Gy, respectively.

Surgical morbidity and estimated blood loss were minimal. All but one patient receiving surgery were discharged the same day. The exception required a two day admission for pain control. Ultrasound doppler flow was confirmed to both ovaries during this admission. This same patient presented with a ruptured ovarian cyst causing pain in the right ovary at 6 months post-operatively. One patient had bilateral transposition, but one ovary slipped back into the pelvis as seen on imaging after completion of radiation. She did not experience any vasomotor symptoms.

4. Discussion

Ten patients had laparoscopic ovarian transposition, of which, eight patients received post-operative pelvic radiation (EBRT 45–59.4Gy ± brachytherapy 35.5–40 Gy). Ovarian preservation was demonstrated in all patients. Previous studies assessing ovarian function following transposition and external beam pelvic radiation with brachytherapy indicate an ovarian preservation rate of 65% (95% CI 56–74) (Gubbala et al., 2014). This is likely due to the age of the patients included in the studies and the location of the transposed ovaries relative to the radiation field.

The median (range) distance of the right and left ovary from the radiation field in our study was 6.7 (4.2–14) cm and 6.2 (4.2–14) cm, respectively. Other studies have shown that a distance of > 1.5 cm from the iliac crest with the vascular supply to the ovary outside the radiation field is associated with ovarian preservation after pelvic radiation. A univariate and multivariate analysis demonstrated the most important factor for ovarian preservation was distance from the radiation field (Gubbala et al., 2014).

In our study, the median age of patients undergoing ovarian transposition was 29 years, ranging from 18 to 37 years. Several other studies have shown higher rates of ovarian preservation in women < age 40 (Huang et al., 2007). Ovarian tissue is sensitive to radiation and as the age of the patient increases, smaller doses of radiation to the ovaries cause ovarian failure. Half of immature oocytes will be destroyed with ≤ 2 Gy (Wallace et al., 2003). With a radiation dose of 4 Gy, a third of young women and almost all women over 40 will experience cessation of ovarian function (Ghadjar et al., 2015). In our study, the median (range) radiation dose to the right and left ovary was 0.51 (0.23–1.1) and 0.53 (0.23–1.1) Gy, repectively, which is considerably lower than the suggested cut off to preserve half of oocytes. Similarly, Clough et al., demonstrated ovarian preservation in all cases after pelvic radiation and calculated a mean (range) dose to the ovaries of 1.75 (0.4–3.7) Gy as did Covens et al., with a mean dose of 1.26 Gy. Similarly, Morice et al. (2000) and Pahisa et al. (2008) calculated a mean (range) dose of 5.2 (2.1–13.4) Gy and 2.5 (1.3–5.2) Gy, respectively with an ovarian preservation rate of 60%.

Similar to radiation exposure, gonadotoxicity from chemotherapy also increases with age due to declining primordial follicle reserve (Meirow, 2000). One study found an odds ratio of 1.77 (p = .32) for cisplatin causing ovarian failure, but this was not statistically significant (Meirow, 2000) and the data regarding oophorotoxicity from cisplatin is controversial.

Two cases of ovarian metastasis on transposed ovaries have been reported in the literature from stage IB cervical SCC with aggressive pathology showing positive LVSI and involvement of the uterine corpus (Morice et al., 2001). A large meta-analysis in 2014, reported no cases of metastasis to the ovaries after transposition in 892 cases (Gubbala

Table 2
Patient treatment and ovarian function.

Study #	Pre-op menstrual Hx/ Vasomotor symptoms	Ovarian transposition	Total radiation dose (Gy)	Vasomotor symptoms (post radiation)		FSH (post radiation)		Ovarian function (yes/no)
				Time post radiation (mon)	Vasomotor symptoms	Time post radiation (mon)	FSH	
Primary chemoradiation								
2	Regular menses	Bilateral	EBRT = 45 Gy Brachytherapy = 39.7 Gy	21	Regular menses			Yes
4	Regular menses	Right	EBRT = 50.4 Gy Brachytherapy = 40 Gy	101	Regular menses	6	3	Yes
8	IUD, no symptoms	Bilateral	EBRT = 45 Brachytherapy = 39.7 Gy	6	No symptoms			Yes
9	No vasomotor symptoms	Bilateral	EBRT = 45 Brachytherapy = 35.5 Gy	21	No hot flushes, premarin for vaginal dryness			Yes
Radical trachelectomy with adjuvant radiation								
1	Regular menses	Bilateral	EBRT = 54 Gy	15/19	Regular menses/ amenorrhea	7	7	Yes
5	No symptoms	Bilateral	EBRT = 55 Gy	15	Regular menses			Yes
6	Regular menses	Bilateral	EBRT = 59.4 Gy	10	Regular menses			Yes
Radical hysterectomy ± adjuvant radiation								
3	No symptoms	Left	No radiation	No radiation	No symptoms			Yes
7	Regular menses	Bilateral	EBRT = 45 Gy	51	No symptoms			Yes
10	Regular menses	Bilateral	No radiation	No radiation	No symptoms			Yes

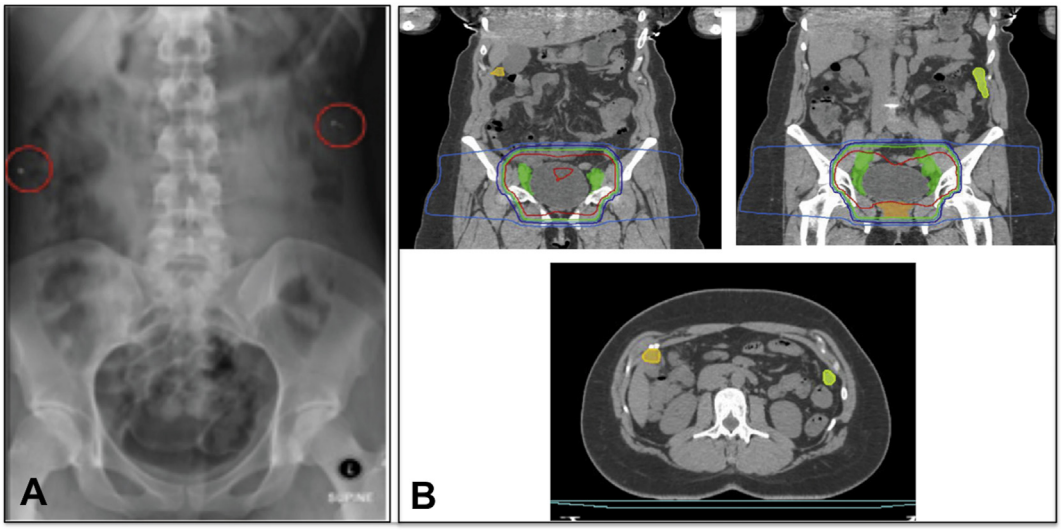

Fig. 2. A: Location of the transposed ovaries marked by radio-opague surgical clips. **B:** Dose volume histogram for contouring location of the ovaries and calculating the radiation dose to each ovary.

et al., 2014). Other risks of ovarian transposition include torsion, ovarian cysts, bleeding, pain and endometriosis (Moawad et al., 2017). Five to 16% of patients developed ovarian cysts after transposition in a large meta-analysis that was treated either conservatively or surgically (Gubbala et al., 2014).

The main limitation of our study is that it was retrospective; therefore FSH levels were not available for all patients. Anti-mullerian hormone (AMH) would also be a useful marker for pre-operative selection of patients based on ovarian reserve, rather than solely using age as a criterion. The pretreatment AMH has been shown to significantly correlate with the rate of AMH recovery after treatment (Iwase et al., 2015). It would also be a useful marker for assessing ovarian preservation in all patients after completion of radiation treatment as AMH has greater intra- and intercycle consistency compared to FSH as a marker for ovarian function (Iwase et al., 2015) It would be anticipated that almost all young women rendered menopausal from radiation would experience vasomotor symptoms within a short period of time. The length of follow up in our study was another limitation, however symptoms of menopause are reportly evident 4–8 wks after radiation treatment as serum E2 levels fall and FSH levels increase (Meirow & Nugent, 2001). No patients experienced disease recurrence, however, the short length of follow up limits the ability to evaluate disease recurrence in our patient population. Finally, selection bias should be considered in this study as it was not possible to identify patients who were offered the procedure, but declined.

Although ovarian transposition has been described since 1958, the number of eligible patients being offered this procedure remains low. Among 108 eligible patients at one institution, only 31 (28.7%) received ovarian transposition prior to pelvic radiation (Han et al., 2011). Similarly, in the meta-analysis from 1980 to 2014, only 321 patients were reported in literature to undergo this procedure prior to external beam radiation therapy and brachytherapy (Gubbala et al., 2014).

In conclusion, laparoscopic ovarian transposition by individuals knowledgeable in the concepts of radiation field, dose (including scatter), and ovarian tolerance, can achieve ovarian preservation with the proposed technique. Ovarian transposition should be offered to young female patients requiring pelvic radiation for cancer treatment.

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

References

Ghadjar, P., Budach, V., Kohler, C., Jantke, A., Marnitz, S., 2015. Modern radiation therapy and potential fertility preservation strategies in patients with cervical cancer undergoing chemoradiation. Radiat. Oncol. 10 (50), 1–6.

Gubbala, K., Laios, A., Gallos, I., Pathiraja, P., Haldar, K., Ind, T., 2014. Outcomes of ovarian transposition in gynaecological cancers; a systematic review and meta-analysis. J. Ovarian Res. 7 (69), 1–10.

Han, S.S., Kim, Y.H., Lee, S.H., Kim, G.J., Kim, H.J., Kim, J.W., et al., 2011. Underuse of ovarian transposition in reproductive-aged cancer patients treated by primary or adjuvant pelvic irradiation. J. Obstet. Gynaecol. Res. 37 (7), 825–829.

Huang, K.G., Lee, C.L., Tsai, C.S., Han, C.M., Hwang, L.L., 2007. A new approach for laparoscopic ovarian transposition before pelvic irradiation. Gynecol. Oncol. 105 (1), 234–237.

Iwase, A., Nakamura, T., Nakahara, T., Goto, M., Kikkawa, F., 2015. Anti-Mullerian hormone and assessment of ovarian reserve after ovarian toxic treatment: a systematic narrative review. Reprod. Sci. 22 (5), 519–526.

Meirow, D., 2000. Reproduction post-chemotherapy in young cancer patients. Mol. Cell. Endocrinol. 169 (1–2), 123–131.

Meirow, D., Nugent, D., 2001. The effects of radiotherapy and chemotherapy on female reproduction. Hum. Reprod. 7 (6), 535–543.

Moawad, N.S., Santamaria, E., Rhoton-Vlasak, A., Lightsey, J.L., 2017. Laparoscopic ovarian transposition before pelvic Cancer treatment: ovarian function and fertility preservation. J. Minim. Invasive Gynecol. 24 (1), 28–35.

Morice, P., Juncker, L., Rey, A., El-Hassan, J., Haie-Meder, C., Castaigne, D., 2000. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. pp. 743–748.

Morice, P., Haie-Meder, C., Pautier, P., Lhomme, C., Castaigne, D., 2001. Ovarian metastasis on transposed ovary in patients treated for squamous cell carcinoma of the uterine cervix: report of two cases and surgical implications. Gynecol. Oncol. 83 (3), 605–607.

Mytton, J., Evison, F., Chilton, P., Lilford, R., 2017. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. BMJ 356 (j372), 1–9.

Pahisa, J., Martinez-Roman, S., Martinez-Zamora, M.A., Torne, A., Caparros, X., Sanjuan, A., et al., 2008. Laparoscopic ovarian transposition in patients with early cervical cancer. Int. J. Gynecol. Cancer 18 (3), 584–589.

Waggoner, S., 2003. Cervical Cancer. Lancet 361 (9376), 2217–2225.

Wallace, W.H., Thomson, A.B., Kelsey, T.W., 2003. The radiosensitivity of the human oocyte. Hum. Reprod. 18 (1), 117–121.

Willows, K., Lennox, G., Covens, A., 2016. Fertility-sparing management in cervical cancer: balancing oncologic outcomes with reproductive success. Gynecol. Oncol. Res. 3 (9), 1–14.