Ovarian Function Preservation in Patients With Cervical Cancer Undergoing Hysterectomy and Ovarian Transposition Before Pelvic Radiotherapy

Wonguen Jung
  Ewha Women's University Mokdong Hospital
Yun Hwan Kim
  Ewha Women's University Mokdong Hospital
Kyung Su Kim (✉ happyend67@gmail.com)
  Dongnam Institute of Radiological and Medical Sciences

Research

Abstract

Background: To examine the factors associated with ovarian failure (OF) and assess the effectiveness of ovarian transposition (OT) before pelvic irradiation for preserving ovarian function in patients with cervical cancer (CC) undergoing hysterectomy.

Methods: During 2003-2017, patients who underwent hysterectomy with preservation of one or both ovaries were retrospectively enrolled. Patients were divided into 4 groups, depending on whether radiotherapy (RT) and OT were performed: group 1, RT(+) and OT(+); group 2, RT(+) and OT(-); group 3, RT(-) and OT(+); group 4, RT(-) and OT(-). OF was defined as serum follicle-stimulating hormone levels of ≥30 mIU/mL.

Results: Sixty-six patients (59 [89.4%] invasive CC and 7 [10.6%] cervical intraepithelial neoplasia) were included. The 2-year ovarian failure-free survival (OFFS) rate was 61.4% (95% confidence interval (CI) 37.8−86.0), 0%, 91.7% (95% CI 76.0−100), and 75.8% (95% CI 58.2−93.4) for groups 1, 2, 3, and 4, respectively. In groups 1 and 2 receiving RT, OT and combination of external beam radiotherapy and vaginal brachytherapy (VB) were associated with OF on multivariate analysis (MVA) (p-value=0.002 and 0.046, respectively). In groups 3 and 4 without RT, older age (40 years) and OT did not affect OF; however, the number of remaining ovaries was independently associated with OF in MVA (p=0.035).

Conclusions: OT could effectively preserve ovarian function in adjuvant RT-treated patients. Lower location of transposed ovary with VB boost was significantly associated with early OF.

Background

The incidence rates of cervical cancer has been decreasing in Korea and it is the third most common cancer in women of reproductive age (15−34 years) [1]. Patients with early stage cervical cancer who undergo radical hysterectomy and pelvic lymphadenectomy are treated with adjuvant radiation therapy (RT) or concurrent chemoradiotherapy (CCRT) according to pathological risk factors.

However, when ovaries are within the field of pelvic irradiation, ovarian failure can occur after adjuvant pelvic RT [2−4]. Because oocytes are sensitive to radiation damage, ionizing radiation can cause irreversible damage such as oocyte loss, decline in follicle number, and ovarian atrophy, leading subsequently to irregular menstruation, ovarian failure and infertility [5−7].

Ovarian failure for premenopausal women is also associated with cardiovascular disease and osteoporosis in addition to poor quality of life as a result of hot flashes, vaginal dryness, and sexual dysfunction [8]. Thus, it is important to improve the quality of life and maintain fertility by preserving ovarian function in premenopausal women with uterine cervical cancer receiving RT.

Ovarian transposition (OT) before pelvic irradiation is used to minimize ovarian follicle exposure to radiation and to preserve ovarian function by transposing the ovaries outside the irradiation field [9−11].

The purpose of this study was to examine the factors associated with ovarian failure and to evaluate the effectiveness of OT before pelvic irradiation for preserving ovarian function in patients with cervical cancer who underwent hysterectomy.

Methods

Patients

Patients who underwent hysterectomy in our institution from April 2003 to March 2017 were retrospectively reviewed. The present study was approved by the institutional review board of our institution (approval number: 2019-11-005 at Ewha Womans University Seoul Hospital). The study inclusion criteria was as follows: (1) patients with histologically confirmed uterine cervical cancer who were >18 years old and <50 years old; (2) patients with preservation of one or both ovaries after hysterectomy; and (3) patients with serum follicle-stimulating hormone (FSH) level measured in peripheral blood during follow-up. OT during radical hysterectomy was performed in younger patients or those who wanted to preserve ovarian function and were candidates for adjuvant RT or CCRT.

Patients were divided into 4 groups, depending on whether the patients received OT during hysterectomy and adjuvant RT. Patients in group 1 received both OT and RT. Patients in group 2 received adjuvant RT but not OT. Patients in group 3 received OT but not RT. Patients in group 4 did not undergo both OT and RT.

Postoperative treatment

Adjuvant whole-pelvis external beam radiation therapy (EBRT) was initiated within 4-6 weeks after hysterectomy. A total dose of 41.4-54.0 Gy in 23-30 fractions over 5-6 weeks was delivered. Vaginal brachytherapy (VB) was administered with an Ir-192 brachytherapy unit (Microselectron; Nucletron, The Netherlands), after 41.4-45.0 Gy of EBRT. Additional VB dose of 15-24 Gy in 4-6 fractions was prescribed at 0.5 cm depth from the surface of the cylinder.

Evaluation of location of the transposed ovary

The transposed ovary was identified by placement of the radio-opaque surgical clips at the time of hysterectomy as shown by the erect plain abdominal x-ray. For patients without abdominal x-rays, scout views of abdomen pelvis computed tomography were used. The distance of the transposed ovary was calculated as the perpendicular length between the surgical clip of the transposed ovary and the horizontal line to the iliac crest (Figure 1). When bilateral ovarian transposition was performed, the location of the transposed ovary was measured by the distance from the higher transposed ovaries.

Evaluation of ovarian failure

Ovarian function was assessed by measurement of serum FSH levels after surgery. In patients aged under 45 years during the follow-up period, the lowest serum FSH level data was collected. In patients

aged over 45 years during the follow-up period, the latest serum FSH level data without ovarian failure was collected and considered censored. Ovarian failure was defined as serum FSH levels of 30 mIU/mL or higher. Ovarian failure-free survival (OFFS) was defined as the time from the end date of RT in groups 1 and 2 or the surgery date in groups 3 and 4 to the date of ovarian failure.

Statistical analyses

The normality of data distribution was tested using the Kolmogorov Smirnov test. The chi-squared test or Fisher's exact test were performed to compare the difference among groups. Survival curves were generated using the Kaplan−Meier method, and a log-rank test was used to compare survival between groups. In terms of the multivariate analysis (MVA) conducted to identify prognostic factors of OFFS, a Cox proportional hazards regression model was used to analyze independent risk factors for ovarian failure. All p-values were 2-sided, and $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using SPSS software version 18.0 (SPSS Inc, Chicago, USA).

Results

A total of 66 consecutive cervical cancer patients who underwent hysterectomy with preservation of one or both ovaries were enrolled in this study. The patients and tumor characteristics are summarized in Table 1. The median age at hysterectomy was 39.5 (26.7 − 48.4) years. According to the 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria, most patients were FIGO stage I (IA1, n=7; IA2, n=6; IB1, n=32, IB2, n=7), and 7 patients were FIGO stage II (IIA, n=3; IIB, n=4). Moreover, seven patients had cervical intraepithelial neoplasia.

In 52 of 66 (78.8%) patients, radical hysterectomy was performed (group 1, n=16, 100%; group 2, n=6, 85.7%; group 3, n=13, 100%; group 4, n=17, 56.7%). OT was performed on a single ovary in 20 patients and on both ovaries in 9 patients. The median distance between the iliac crest and transposed ovaries was -0.7 cm (range -5.4-7.4). Twenty-three patients received adjuvant EBRT with a median dose of 50.4 Gy (range 41.4-54) in groups 1 and 2. Five of these patients received an additional high-dose-rate VB with a median dose 24 Gy (range 15-24). Adjuvant chemotherapy was performed in 25.7% (17/66) of the patients. Of these, 15 patients in group 1 and 2 received concurrent chemoradiation. The most common regimen was cisplatin-based chemotherapy (cisplatin alone, n=8; paclitaxel and carboplatin, n=5; cisplatin and 5-flurouracil, n=3; cisplatin and etoposide, n=1).

The median follow-up of patients from surgery or end of RT until the serum FSH level date of ovarian function was 15.4 months (range, 0.2-126.3). About 63.6% (42/66) of the patients had normal ovarian function. The rates of preservation of ovarian function by group are as follows: 56.3% (9/16) in group 1, 0% (0/7) in group 2, 84.6% (11/13) in group 3, and 73.3% (22/30) in group 4 (p=0.001). OFFS at 2 years was 61.4% (95% confidence interval (CI) 37.1-85.7) for group 1, 0% for group 2, 91.7% (95% CI 76.0-100) for group 3, and 75.8% (95% CI 58.2-93.4) for group 4 (p<0.001, Figure 2).

In group 1, age (p=0.014), VB (p=0.003), and the location of transposed ovaries (p=0.007) were associated with OFFS in univariate analysis but not in MVA. All four patients treated with EBRT plus VB had transposed ovary below the iliac crest (median -1.9 cm, range -5.1- [-0.5]), and all of them experienced early ovarian failure (median OFFS 2.3 months, 95% CI 0-6.8). The number of transposed ovaries was not significantly associated with ovarian failure in this group.

For patients in groups 1 and 2 who received RT, associations between prognostic factors and OFFS are shown in Table 2. OT was only significantly associated with OFFS in univariate analysis (p=0.001). MVA demonstrated that ovaries without transposition and VB boost were significant prognostic factors affecting OFFS. The hazard ratios were 3.452 (95% confidence interval [CI], 1.023-11.654; p=0.002), and 6.362 (95% CI, 1.9320.963, p=0.046) for ovaries without transposition and VB boost, respectively. Additional VB showed significant difference in OFFS versus patients who received EBRT alone: 2 years OFFS 0% versus 83.3% (p=0.03, 95% CI 62.1-100, Figure 3).

In patients in groups 3 and 4 who did not receive RT, the number of residual ovaries were the only significant prognostic factor affecting ovarian failure in univariate analysis and MVA (p=0.035, Table 3, Figure 4). Older age (40 years) and OT did not affect ovarian failure.

Discussion

The current study showed that OT could effectively preserve ovarian function in patients treated with adjuvant RT, and EBRT and VB were significant prognostic factors affecting OFFS. Moreover, the preservation of both ovaries resulted in a significant increase in OFFS in the group without RT.

OT is a surgery to transpose the ovaries out of the field of radiation to protect them from radiation damage [12]. Hoekman et al. [11] noted that the 5-year ovarian survival rate was 60.3% in patients who underwent OT before RT, whereas all patients who received RT without OT had ovarian failure, which is similar to our study. The degree of ovarian damage and ovarian failure is affected by the radiation dose of ovaries [13, 14]. Several studies reported that the OT before pelvic RT reduces the ovarian dose received to approximately 5–10% of that in the untransposed ovaries [6, 15, 16]. Winarto et al. demonstrated that the lateral transposed ovaries receives about 0.45–4.5 Gy, corresponding to 1–10% of the total RT dose of 45 Gy [16]. Our study showed that the rate of OFFS at 2 years was 61.4% for patients with OT before pelvic RT, whereas all patients who received adjuvant RT without OT had ovarian failure. Therefore, OT before pelvic RT could be helpful for preserving ovarian function for candidates for adjuvant RT or CCRT.

Our results showed that in groups 1 and 2, 78% (18/23) of the patients received EBRT alone, and 22% (5/23) had an additional VB in addition to EBRT. The rates of ovarian preservation at 2 years after RT were 54.5% in EBRT alone and 0% in patients with EBRT plus VB. Morice et al. [17] reported that the ovarian survival was 100% (11/11) after OT, 90% (53/59) after OT and VB, and 60% (15/25) after OT, VB and EBRT. Clough et al. [18] reported that the mean dose of transposed ovary was 2 Gy, whereas the untransposed ovary was 32.2 Gy on pelvic dosimetry of patients who received 65 Gy with VB alone.

Although the number of patients with VB in our study was small, additional VB was a significant prognostic factor in ovarian survival.

Several studies reported that location of transposed ovary was associated with ovarian survival, and the distance between the edge of the RT field and the transposed ovaries affects the successful preservation of ovarian function. Winarto et al. suggested the above iliac crest as the suboptimal placement of the ovary [16]. Yoon et al [10] also noted that location of transposed ovaries may be associated with ovarian failure after RT. They suggested that young women with early-stage cervical cancer who might be a candidate for postoperative RT should be transposed to the ovaries as highly as possible during radical hysterectomy to avoid ovarian failure. Hwang et al [19] suggested that location of transposed ovary more than 1.5 cm above the iliac crest was recommended to preserve ovarian function after pelvic RT in uterine cervical cancer. In addition, even if the ovaries are sufficiently outside the RT field, ovarian damage can also occur as a result of scattered radiation doses. Van et al. [20] reported that patients experienced ovarian failure if the scatter radiation dose to the transposed ovaries was more than 300 cGy. The current study showed that in group 1, all four patients treated with EBRT plus VB had transposed ovary below the iliac crest (median – 1.9 cm, range – 5.1-[-0.5]), and all experienced early ovarian failure. The location of the transposed ovary was associated with OFFS in univariate analysis. Thus, the ovaries should be transposed as high and laterally as possible from the pelvic brim, especially in candidates who received definitive CCRT with EBRT and brachytherapy.

The degree of ovarian damage is dependent on the patient's age as well as the irradiated ovarian dose and type of gonadotoxic agent used [6, 14, 21, 22]. OT has been generally suggested for patients aged under 40 years because the patient's age is also known to be a crucial factor to determine the success of OT for candidate patients [4, 14, 17, 18]. Morice et al. [17] reported the limited value of OT in patients over 40 years because they have an intrinsically decreased fertilization possibility as well as a much higher risk for ovarian failure despite OT. They noted that the rate of menopause after hysterectomy is clearly too high to recommend OT to patients tagged 40 years and older treated for cervical cancer. It has been reported that for patients who undergo hysterectomy with OT procedure, ovarian failure occurred in 14.3% (1/7) of patients under 40 years of age, compared with 85.7% (6/70) in patients over 40 years of age [23]. In contrast to previous studies, our study demonstrated that older age (≥ 40 years) did not affect the ovarian failure in the groups with RT (groups 1 and 2) or without RT (groups 3 and 4). Moreover, OT procedure itself did not affect ovarian failure in patients without RT. The median age at menopause among Korean women is approximately 50 years [24]. The age of menopause ranged from 33 to 61 years, with 88.2% between 45–55 years, 9.4% under 44 years, and 2.4% over 56 years. Considering that ovarian failure can affect the quality of life as well as lead to hot flashes, vaginal dryness, and cardiovascular disease, OT could be sufficiently considered even in Korean women aged over 40 years.

The sequelae of OT such as ovarian cysts, ovarian torsion, ovarian metastasis and bowel obstruction is considered when performing OT [25]. Morice et al. [17] reported that for patients undergoing radical hysterectomy and OT, the development of benign ovarian cyst was reported in 23% (22/95) patients, three of whom required surgical intervention. The rates of ovarian cysts were 18% (2/11) in the radical

hysterectomy alone group, 34% (20/59) in the group that underwent radical hysterectomy and VB, and 0% (0/29) in patients who underwent radical hysterectomy, EBRT and VB (p = 0.01) in their study. Chambers et al. [26] reported that the incidence of symptomatic ovarian cysts was 7.4% in patients who underwent radical hysterectomy alone and 7% in patients who also received RT as compared to 24% in those who underwent OT, and most ovarian cysts required surgical intervention. Gomez-Hidalgo et al. reported two cases of ovarian torsion after OT [27]. The current study showed that OT did not affect the ovarian failure in the group without RT. Although OT did not affect ovarian failure, consideration should be given to the surgical morbidity mentioned in previous studies.

The number of remaining ovaries can affect ovarian failure. In a previous study, Buekers et al. [3] noted that ovarian failure was significantly different between patients of unilateral oophorectomy and contralateral OT and those with ovaries preserved and transposed (4 months vs 43 months, p = 0.003). All patients with unilateral oophorectomy had ovarian failure by 1 year after treatment, but 41% patients with both ovaries retained maintained ovarian function after one year in their study. Our result showed that in the group without RT, the number of remaining ovaries was an independent factor for ovarian failure, which is similar to previous study. However, unilateral oophorectomy also showed favorable outcome with 75.8% of 2-year OFFS in patients without RT in the current study.

The current study had several limitations. First, this study was retrospective; therefore, serum FSH levels were not collected regularly during the follow-up period. Second, the number of patients included in this study was small. The number of patients in group 1, 2, and 3 was less than 30, making it difficult to divide into subgroups for analysis. Third, this study did not address the dosimetry effects of the transposed ovary on ovarian failure. Since ovarian dose is associated with ovarian function preservation, analysis on the dosimetric impact of pelvic irradiation received by the transposed ovary is required in the future.

Conclusions

If the location of the transposed ovary is low, it should be considered that additional radiation dose may be added to the transposed ovary when performing VB. In addition, OT procedure itself did not affect the ovarian failure, while unilateral oophorectomy showed inferior ovarian survival than those who had both ovaries. These findings may help to inform preservation strategies of ovarian function in young patients with cervical cancer.

List Of Abbreviations

CCRT: Concurrent chemoradiotherapy

EBRT: External beam radiation therapy

FSH: Follicle-stimulating hormone

FIGO: International Federation of Gynecology and Obstetrics

MVA: Multivariate analysis

OFFS: Ovarian failure-free survival

OT: Ovarian transposition

RT: Radiation therapy

VB: Vaginal brachytherapy

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the institutional review board of Ewha Womans University Seoul Hospital (approval number: 2019-11-005). The participants' informed consent requirement was waived due to the retrospective nature of this study.

Consent for publication

The authors agreed to publish this paper in Radiation Oncology.

Availability of data and materials

All data were stored in the hospital database and extracted for research.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Kyung Su Kim and Wonguen Jung conceived and designed the research. Wonguen Jung analysed the data and wrote the manuscript with support from Kyung Su Kim and Yun Hwan Kim. Kyung Su Kim supervised the findings of this study. All authors discussed the results and commented on the manuscript.

Acknowledgements

None of the authors had a personal or financial conflict of interest.

References

1. Jung K-W, Won Y-J, Kong H-J, Lee ES. Cancer research and treatment: official journal of Korean Cancer Association. Cancer Res Treat. 2019; 51:417-30.

2. Anderson B, LaPolla J, Turner D, Chapman G, Buller R. Ovarian transposition in cervical cancer. Gynecol Oncol. 1993; 49:206-14.

3. Buekers TE, Anderson B, Sorosky JI, Buller RE. Ovarian function after surgical treatment for cervical cancer. Gynecol Oncol. 2001; 80:85-8.

4. Feeney DD, Moore DH, Look KY, Stehman FB, Sutton GP. The fate of the ovaries after radical hysterectomy and ovarian transposition. Gynecol Oncol. 1995; 56:3-7.

5. Sonmezer M, Oktay K. Assisted reproduction and fertility preservation techniques in cancer patients. Curr Opin Endocrinol Diabetes Obes. 2008; 15:514-22.

6. Haie-Meder C, Mlika-Cabanne N, Michel G, Briot E, Gerbaulet A, Lhomme C, et al. Radiotherapy after ovarian transposition: ovarian function and fertility preservation. Int J Radiat Oncol Biol Phys. 1993; 25:419-24.

7. Winarto H, Febia E, Purwoto G, Nuranna L. The need for laparoscopic ovarian transposition in young patients with cervical cancer undergoing radiotherapy. Int J Reprod Med. 2013; 2013:1-6.

8. Absolom K, Eiser C, Turner L, Ledger W, Ross R, Davies H, et al. Ovarian failure following cancer treatment: current management and quality of life. Hum Reprod. 2008; 23:2506-12.

9. Falcone T, Attaran M, Bedaiwy MA, Goldberg JM. Ovarian function preservation in the cancer patient. Fertil Steril. 2004; 81:243-57.

10. Yoon A, Lee Y-Y, Park W, Huh SJ, Choi CH, Kim T-J, et al. Correlation between location of transposed ovary and function in cervical cancer patients who underwent radical hysterectomy. Int J Gynecol Cancer. 2015; 25:688-93.

11. Hoekman EJ, Knoester D, Peters AA, Jansen FW, de Kroon CD, Hilders CG. Ovarian survival after pelvic radiation: transposition until the age of 35 years. Arch Gynecol Obstet. 2018; 298:1001-7.

12. Swift BE, Leung E, Vicus D, Covens A. Laparoscopic ovarian transposition prior to pelvic radiation for gynecologic cancer. Gynecol Oncol Rep. 2018; 24:78-82.

13. Damewood MD, Grochow LB. Prospects for fertility after chemotherapy or radiation for neoplastic disease. Fertil Steril. 1986; 45:443-59.

14. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005; 62:738-44.

15. Howell SJ, Shalet SM. Fertility preservation and management of gonadal failure associated with lymphoma therapy. Curr Oncol Rep. 2002; 4:443-52.

16. Winarto H, Febia E, Purwoto G, Nuranna L. The need for laparoscopic ovarian transposition in young patients with cervical cancer undergoing radiotherapy. Int J Reprod Med. 2013; 2013.

17. Morice P, Juncker L, Rey A, El-Hassan J, Haie-Meder C, Castaigne D. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. Fertil Steril. 2000; 74:743-8.

18. Clough KB, Goffinet F, Labib A, Renolleau C, Campana F, Rochefordiere Adl, et al. Laparoscopic unilateral ovarian transposition prior to irradiation: prospective study of 20 cases. Cancer. 1996; 77:2638-45.

19. Hwang JH, Yoo HJ, Park SH, Lim MC, Seo S-S, Kang S, et al. Association between the location of transposed ovary and ovarian function in patients with uterine cervical cancer treated with (postoperative or primary) pelvic radiotherapy. Fertil Steril. 2012; 97:1387-93. e2.

20. Van Eijkeren MA, Van Der Wijk I, El Sharouni SY, Heintz AP. Benefits and side effects of lateral ovarian transposition (LOT) performed during radical hysterectomy and pelvic lymphadenectomy for early stage cervical cancer. Int J Gynecol Cancer. 1999; 9:396-400.

21. Faddy MJ, Gosden RG. A model conforming the decline in follicle numbers to the age of menopause in women. Hum Reprod. 1996; 11:1484-6.

22. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod. 1992; 7:1342-6.

23. Huang KG, Lee CL, Tsai CS, Han CM, Hwang LL. A new approach for laparoscopic ovarian transposition before pelvic irradiation. Gynecol Oncol. 2007; 105:234-7.

24. Park YJ, Kim HS, Kang HC. The age at menopause and related factors in Korean women. J Korean Acad Nurs. 2002; 32:1024-31.

25. Hoekman EJ, Broeders EA, Louwe LA, Nout RA, Jansen FW, de Kroon CD. Ovarian function after ovarian transposition and additional pelvic radiotherapy: a systematic review. Eur J Surg Oncol. 2019; 45:1328-40.

26. Chambers SK, Chambers JT, Holm C, Peschel RE, Schwartz PE. Sequelae of lateral ovarian transposition in unirradiated cervical cancer patients. Gynecol Oncol. 1990; 39:155-9.

27. Gomez-Hidalgo NR, Darin MC, Dalton H, Jhingran A, Fleming N, Brown J, et al. Ovarian torsion after laparoscopic ovarian transposition in patients with gynecologic cancer: a report of two cases. J Minim Invasive Gynecol. 2015; 22:687-90.

Tables

Table 1
Patient and tumor characteristics

Variables	Group 1		Group 2		Group 3		Group 4		p-value
	n = 16		n = 7		n = 13		n = 30		
Age (yr)*	32.6 (26.7–43.0)		37.2 (31.2–43.5)		39.9 (32.7–43.5)		41.8 (32.7–48.4)		
<40	12	(75.0)	5	(71.4)	7	(53.8)	12	(40.0)	0.110
≥40	4	(25.0)	2	(28.6)	6	(46.2)	18	(60.0)	
FIGO staging									< 0.001
IA	0	(0.0)	0	(0.0)	2	(16.7)	11	(36.7)	
IB	10	(62.5)	6	(85.7)	11	(84.6)	12	(40.0)	
IIA	2	(12.5)	1	(14.3)	0	(0.0)	0	(0.0)	
IIB	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	
CIN	0	(0.0)	0	(0.0)	0	(0.0)	7	(23.3)	
Histological types									0.005
Squamous cell carcinoma	13	(81.3)	3	(42.9)	5	(41.7)	17	(56.7)	
Adenocarcinoma	1	(6.3)	2	(28.6)	7	(53.8)	5	(16.7)	
Adenosquamous	2	(12.5)	1	(14.3)	1	(8.3)	1	(3.3)	
Others	0	(0.0)	1	(14.3)	0	(0.0)	0	(0.0)	
CIN	0	(0.0)	0	(0.0)	0	(0.0)	7	(23.3)	
Sex hormone levels									
LH (mIU/mL)*	4.3 (1.0–29.0)		39.1 (8.0–85.0)		11.1 (4.0–43.0)		6.0 (1.0–52.0)		
FSH (mIU/mL)*	18.2 (1.9–150.3)		76.0 (30.6–114.8)		8.6 (1.3–58.1)		6.5 (1.3–92.7)		
Estradiol (pg/mL)*	61.5 (5.0–784.0)		10.0 (7.0–41.0)		70.0 (5.0–395.0)		69.2 (5.0–1112.0)		

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; CIN, cervical intraepithelial neoplasia; LH, luteinizing hormone; FSH, follicle-stimulating hormone; EBRT, external beam radiation therapy; VB, vaginal brachytherapy.

*Median (range)

Variables	Group 1		Group 2		Group 3		Group 4		p-value
	n = 16		n = 7		n = 13		n = 30		
Number of residual ovary and ovarian transposition									< 0.001
One residual ovary with unilateral ovarian transposition	4	(25.0)	0	(0.0)	8	(61.5)	0	(0.0)	
Both residual ovary with unilateral ovarian transposition	5	(31.3)	0	(0.0)	3	(23.1)	0	(0.0)	
Both residual ovary with bilateral ovarian transposition	7	(43.8)	0	(0.0)	2	(15.4)	0	(0.0)	
One residual ovary without ovarian transposition	0	(0.0)	4	(57.1)	0	(0.0)	8	(26.7)	
Both residual ovary without ovarian transposition	0	(0.0)	3	(42.9)	0	(0.0)	22	(73.3)	
Location of transposed ovary (cm)*	0.01 (-5.1–7.4)				-1.1 (-5.4–6.1)				
Ovarian failure									0.001
Yes	7	(43.8)	7	(100.0)	2	(15.4)	8	(26.7)	
No	9	(56.3)	0	(0.0)	11	(84.6)	22	(73.3)	
Radiotherapy									1.000
EBRT alone	12	(75.0)	6	(85.7)					
EBRT with additional VB	4	(15.0)	1	(14.3)					
Adjuvant chemotherapy									< 0.001

Variables	Group 1		Group 2		Group 3		Group 4		p-value
	n = 16		n = 7		n = 13		n = 30		
Yes	11	(68.8)	4	(57.1)	1	(7.7)	1	(3.3)	
No	5	(31.3)	3	(42.9)	12	(92.3)	29	(96.7)	
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; CIN, cervical intraepithelial neoplasia; LH, luteinizing hormone; FSH, follicle-stimulating hormone; EBRT, external beam radiation therapy; VB, vaginal brachytherapy.									
*Median (range)									

Table 2

Univariate and multivariate analysis for ovarian failure free survival outcomes in the group 1 and 2

Variable	n	Univariate		Multivariate		
		2-year rate	P	HR (95% CI)		P
Age			0.056	2.035	(0.635−6.518)	0.232
<40 years	17	52.9%				
≥40 years	6	0%				
Residual ovary			0.871			
Both ovary	15	45.0%				
Single ovary	8	37.5%				
Ovarian transposition			0.001	3.452	(1.023−11.654)	0.002
Yes	16	61.4%				
No	7	0%				
Radiotherapy			0.065	6.362	(1.931−20.963)	0.046
EBRT alone	18	54.5%				
EBRT with additional VB	5	0%				
Adjuvant chemotherapy			0.691			
No	8	33.3%				
Yes	15	46.7%				
Abbreviations: OFFS, ovarian failure free survival; HR, hazard ratio; CI, confidence interval; EBRT, external beam radiation therapy; VB, vaginal brachytherapy						

Table 3
Univariate and multivariate analysis for ovarian failure free survival outcomes in the group 3 and 4

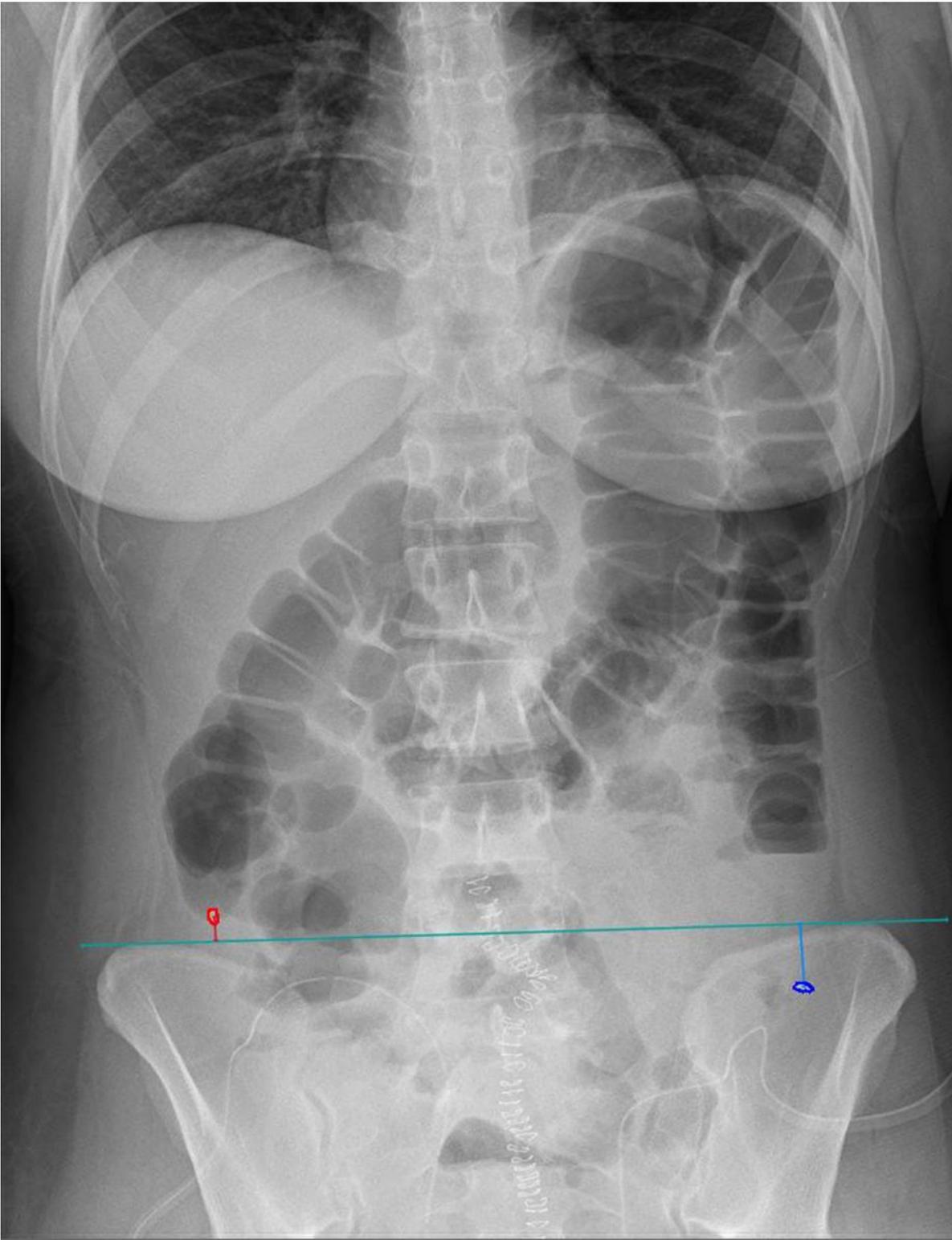| Variable	n	Univariate		Multivariate		
		2-year rate	P	HR (95% CI)		P
Age			0.182	3.723	(0.743−18.658)	0.110
<40 years	19	94.4%				
≥40 years	24	67.7%				
Residual ovary			0.047	4.633	(1.112−19.310)	0.035
Both ovary	27	84.6%				
Single ovary	16	73.3%				
Ovarian transposition			0.685			
Yes	13	91.7%				
No	30	75.8%				
Adjuvant chemotherapy			0.361			
No	41	81.9%				
Yes	2	50.0%				
Abbreviations: HR, hazard ratio; CI, confidence interval						

Figures

Figure 1

Erect abdominal x-ray of a patient who received bilateral ovarian transposition. (right ovary: red, left ovary: blue)
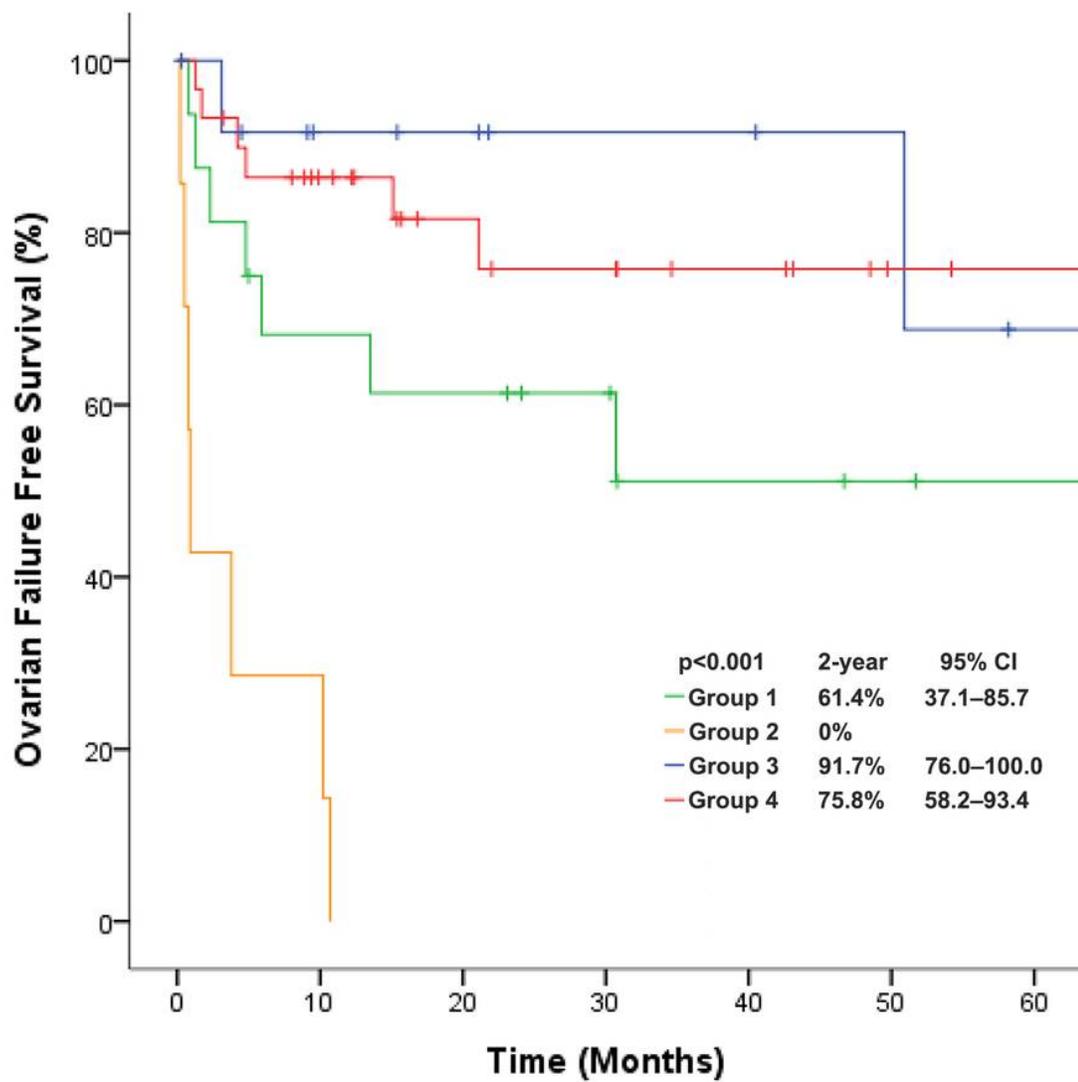
Figure 2

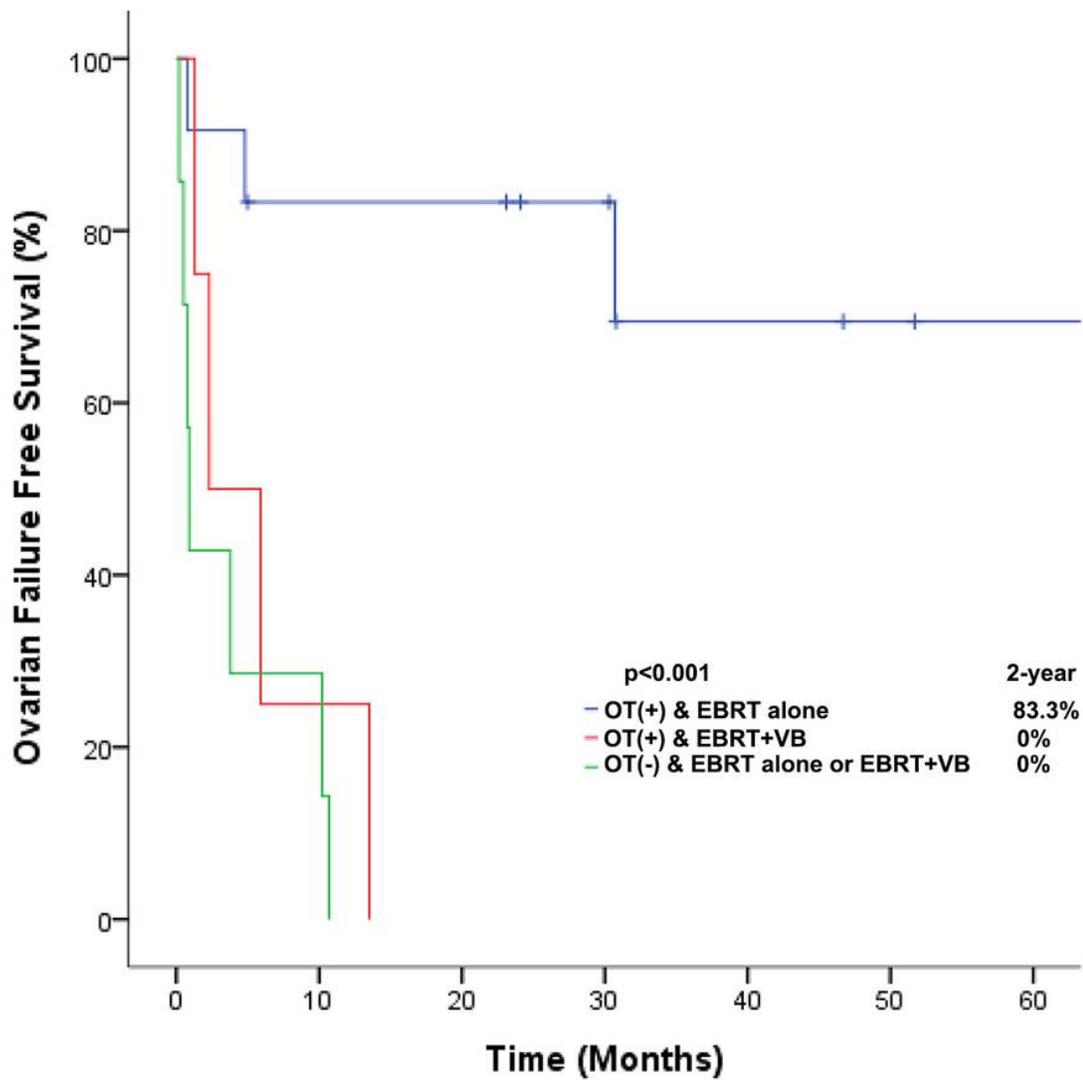Ovarian failure free survival according to the groups.

Figure 3

Ovarian failure free survival after radiation therapy by external beam radiation therapy or vaginal brachytherapy. OT, Ovarian transposition; EBRT, External beam radiation therapy; VB, Vaginal brachytherapy
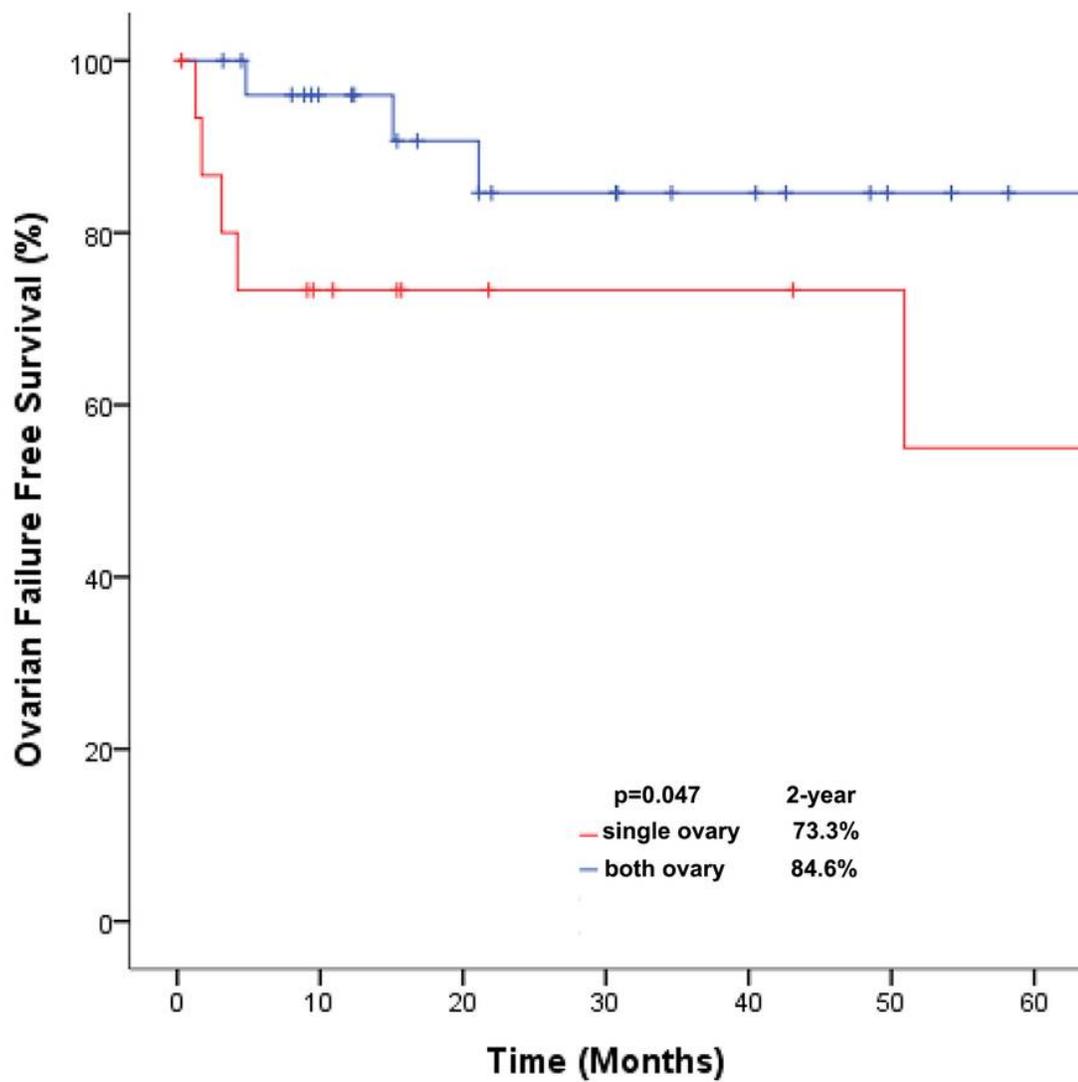
Figure 4

Ovarian failure free survival by number of residual ovaries.