

Underuse of ovarian transposition in reproductive-aged cancer patients treated by primary or adjuvant pelvic irradiation

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Abstract

Aim: To investigate the application status of ovarian transposition (OT) in reproductive-aged cancer patients undergoing radiation therapy.

Material & Methods: Between November 1999 and December 2008, 2524 patients had received pelvic irradiation at Seoul National University Hospital. We filtered the patients with the indications of (i) within 12 to 40 years of age, and (ii) receiving primary or adjuvant pelvic irradiation. There were 241 patients within 12 to 40 years of age. After excluding 133 patients with metastatic disease or under palliative radiation treatment, 108 patients were discovered appropriate for OT. We analyzed the application status of OT, surgical types of OT, cancer types and radiation types in those 108 patients.

Results: Cervical cancer was the major indication ($n = 68$, 62.9%). Another 37.1% of indicated disease were composed of rectal cancer ($n = 19$), vulvo-vaginal cancer ($n = 4$), non-Hodgkin's lymphoma ($n = 3$), and other pelvic tumors ($n = 14$). Among the 108 patients, only 31 (28.7%) patients had received OT before pelvic irradiation. Most of the operations were applied on cervical cancer patients ($n = 29$) and only two procedures on rectal and endometrial cancer, respectively. OT had been mostly performed during laparotomy. Laparoscopic procedure was applied in only one case with advanced cervical cancer.

Conclusions: Although OT could be a preventive measure of premature ovarian failure from radiation therapy, this procedure has been considerably underused at our institution. This procedure should be applied more widely to preserve the fertility and improve the quality of life in reproductive-aged cancer patients.

Key words: ovarian transposition, pelvic irradiation, premature ovarian failure.

Introduction

Nearly 8% of the cancer cases occur in women younger than 40 years.¹ Pelvic irradiation is often indicated even in young women with various types of malignancies including genitourinary cancer, Hodgkin's disease, rectal cancer and other pelvic malignancies. One of the

serious complications of pelvic irradiation in such young women is the permanent loss of ovarian function, causing loss of fertility, climacteric symptoms, and menopause-related long-term complications such as accelerated osteopenia and osteoporosis, and cardiovascular disease. Moreover, hormone replacement therapy in women with premature ovarian failure may

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raise certain serious adverse side-effects.² Therefore, preservation of ovarian function is crucial for young women with invasive cancers who need pelvic irradiation.

Ovarian transposition (OT) was first described as a way to preserve ovarian function in 1958.³ OT either by laparotomy or laparoscopy has been advocated to avoid radiation to the ovaries. The ovaries could be transposed medially behind the uterus, laterally outside the radiation field or to distant sites.⁴⁻⁶ Laparoscopic OT is associated with smaller abdominal incision, shorter hospital stay and lesser adhesion than OT by laparotomy. Previous studies have shown that ovarian preservation was achieved about 79–89% of patients during follow-up.⁷⁻⁹

OT is simple and yet effective. However, this procedure seems to be underused.⁸ The incidence of newly diagnosed malignant disease is 3835 women aged 16 to 35 years in the Netherlands, only 2% of these patients were referred for fertility preservation.¹⁰ The aim of this study is to examine the real application status of OT in reproductive young cancer patients who had undergone pelvic irradiation at a single institution.

Methods

Patient population

From November 1999 to December 2008, 2524 patients had received pelvic irradiation at Seoul National University Hospital. We reviewed the medical records and filtered the cases with the indications of (i) women with cancer aged between 12 to 40 years, and (ii) receiving primary or adjuvant pelvic irradiation. Among 2524 patients, 242 patients met the criteria of age of this study. Among 242 patients, we excluded the 134 women with palliative radiotherapy (Fig. 1). Finally

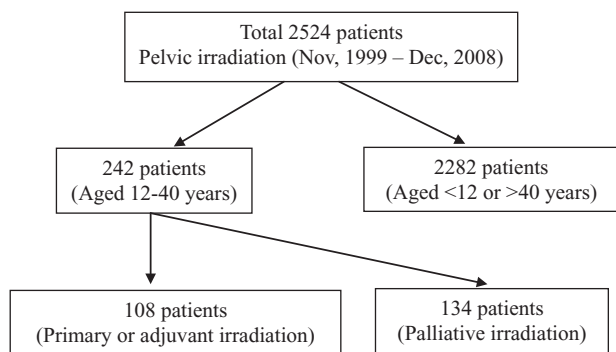


Figure 1 Selection of appropriate patients.

108 patients with primary or adjuvant pelvic irradiation were included in this study. We analyzed the cancer types, radiation types, application status of OT, surgical types of OT (laparoscopic or laparotomy). This study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

Surgical technique of OT

The operation was performed under general anesthesia. The utero-ovarian ligaments were divided. The ovaries were then mobilized on the infundibulopelvic ligaments. The peritoneum under and lateral to the infundibulopelvic ligaments were incised enough to reach the level of iliac crest, under direct vision of the ureter. The ovaries were fixed in the paracolic gutters at the level of pelvic brim with a sufficient angle to maintain good blood supply. The upper and lower poles of the ovaries were marked with hemoclips. Laparoscopic OT was performed with the same method using laparoscopy.¹¹

Results

The mean ages of OT and non-OT groups were 34.5 years (range, 22–40) and 34.6 years (range, 12–40), respectively. There was no significant difference in age between OT and non-OT groups ($P = 0.956$). Table 1 shows the characteristics of 108 patients who were thought to be appropriate for OT before pelvic irradiation. The major indication of primary or adjuvant pelvic irradiation was cervical cancer ($n = 68$, 62.9%). Among the 108 patients, only 31 patients (28.7%) had received OT before pelvic irradiation. Most of the ovarian transpositions were applied for cervical cancer patients ($n = 29$, 93.5%) and the other two cases were rectal and endometrial cancer, respectively. Table 2 shows the characteristics of patients with cervical cancer. Conventional whole pelvic radiation therapy was performed in all cases. One case with stage Ib2 had undergone intracavitary radiation in addition to whole pelvic radiation therapy. Two cases had received additional radiation therapy in para-aortic area and parametrial area, respectively. Among the 74 patients with gynecological cancer including cervical cancer, vulvo-vaginal cancer, and endometrial cancer, 30 patients (40.1%) had undergone OT. OT had been mainly performed during laparotomy except one case with advanced cervical cancer that had undergone laparoscopic OT prior to primary pelvic chemoradiation therapy.

Hormone levels such as estrogen and follicular stimulating hormone were tested in only 19 among 31

Table 1 Characteristics of OT group and Non-OT group

Cancer type	Number (%)	OT group (%)	Non-OT group (%)
Cervical cancer	68 (62.9)	29 (93.5)	39 (51.0)
Rectal cancer	19 (17.6)	1 (3.2)	18 (23.4)
Pelvic sarcoma	8 (7.4)	0	8 (10.4)
Vulvo-vaginal cancer	4 (3.7)	0	4 (5.2)
Non-Hodgkin's lymphoma	3 (2.8)	0	3 (3.9)
Pelvic neurogenic tumor	3 (2.8)	0	3 (3.9)
Endometrial cancer	2 (1.8)	1 (3.2)	1 (1.3)
Pre-sacral germ cell tumor	1 (0.9)	0	1 (1.3)

OT, ovarian transposition.

Table 2 Characteristics of patients with cervical cancer

Case	Age	Stage	LN metastasis	RT area	RT dose, cGy	Hormone test after OT, months	Ovarian function
1	30	Ib1	Yes	WP	5040		
2	35	Ib1	Yes	WP	5040	17	No
3	33	Ib1	Yes	WP	5040	19	No
4	34	Ib1	No	WP	5040	43	Yes
5	29	Ib2	Yes	WP	5040	29	Yes
6	34	IIa	Yes	WP	5040		
7	35	Ib1	Yes	WP	5040	34	Yes
8	33	Ib1	No	WP	5040		
9	28	Ib1	No	WP	5040		
10	32	Ib2	Yes	WP	5040		
11	32	Ib1	Yes	WP	5040	7	Yes
12	32	Ib1	Yes	WP + PA	5040 + 450	1	Yes
13	36	Ib1	Yes	WP	5040		
14	37	Ib1	No	WP	5040	5	No
15	37	Ib1	No	WP	5040	68	No
16	37	Ib1	Yes	WP	5040	3	No
17	36	Ib1	Yes	WP	5040		
18	36	Ib1	No	WP	5040	12	Yes
19	36	Ib2	Yes	WP	5040	5	No
20	38	IIa	No	WP	5040		
21	39	Ib2	Yes	WP	5040	31	Yes
22	38	IIa	No	WP	5040		
23	38	Ib1	Yes	WP	5040	1	Yes
24	37	Ib1	No	WP	5040	21	Yes
25	39	Ib1	No	WP	5040		
26	37	Ib2	No	WP	5040	8	No
27	37	Ib1	Yes	WP	5040	13	No
28	38	IIb	No	WP + PM	5040 + 1000		
29	29	Ib2	No	WP + ICR	4500 + 540		

ICR, intracavitary radiation; LN, lymph node; OT, ovarian transposition; PA, para-aortic area; PM, parametrial area; RT, radiation therapy; WP, whole pelvis.

patients after OT. After mean follow-up of 17.2 months, ovarian function was maintained in 11 patients (58%).

Discussion

This study shows that OT is performed in about 29% of young patients with cancer before pelvic irradiation.

This means that OT is underused in a clinical setting and many women undergo pelvic irradiation without having the chance of preserving their ovarian function.

Several factors have been identified as significant determinants of ovarian failure, including radiation dose, age at the time of radiation exposure, and extent of radiation treatment field.¹² The tolerance dose for

ovaries is much lower than other organs, with women often experiencing ovarian failure after 300 cGy. The rate of ovarian failure after pelvic radiation therapy varies from 12 to 66%.¹³ The risk of early menopause was increased 27-fold in women who underwent treatment with both pelvic irradiation and alkylating agents.¹⁴ Even for patients receiving craniospinal radiation for central nervous system malignancies, the inferior aspect of the spine field may diverge into the true pelvis and cause ovarian damage.¹⁴ If this study had included the patients receiving craniospinal radiation for central nervous system malignancies, the degree of underuse of OT would have been higher.

OT is a surgical procedure that moves the ovaries out of the radiation field. It has been demonstrated a 90–95% reduction of the ovarian irradiation dose compared with the untransposed ovaries.¹⁵ The preservation of ovarian function mainly depends on two factors: the dose of radiation and the patient age. Because the rate of ovarian preservation is low after 40 years, OT should be performed only in patients less than 40 years.^{9,16} Among the 29 patients with cervical cancer, the mean ages of patients with and without ovarian function after OT were 36.1 years (range, 33–37) and 33.8 years (range, 29–38), respectively (Table 2). There was borderline difference in age between patients with and without ovarian function after OT ($P = 0.059$). The patient age may affect the maintenance of ovarian function even after OT. This procedure has been performed via laparotomy at the time of surgery for Hodgkin's disease and cervical cancer. Recently, laparoscopic OT is preferable in patients who receive laparoscopic cancer surgery or primary radiotherapy without laparotomy. The less formation of bowel adhesions by laparoscopic surgery dramatically decreases the risk of actinic complications.¹ Morice *et al.* reported that laparoscopic OT was successfully performed in 94% of patients and ovarian preservation was achieved in 79% of subjects after a median follow-up of 31 months.⁹ For cervical cancer, the ovaries should be transposed high above the pelvic brim, as conventional pelvic field extends to the L4/L5 vertebral space. In our study, comparing the radiation field with the sites of transposed ovaries, the transposed ovaries were included in the radiation field in three cases. For patients receiving pelvic lymph node irradiation or an inverted Y field for Hodgkin's disease, the ovaries can be transposed medially.¹⁷ OT by laparotomy showed a preservation of ovarian function in 83% of patients with cervical cancer after pelvic radiation.¹⁸ A study of laparoscopic OT in women younger than 40 years shows a preservation of

ovarian function in 88.6%.⁸ In this study, the rate of ovarian preservation was 58%, relatively low. The incomplete performance of hormone tests could be the reason for the low ovarian preservation. Many other studies evaluating efficacy of OT prove that OT is a simple and effective procedure for ovarian preservation.^{7,9,19}

However, some authors have reported a greater likelihood of early menopause when the ovaries are transposed.^{13,20} The ovarian failure rate was reported to increase as the duration of follow-up prolongs, with 7–12% failure at 36 months and 33% at 47 months.¹³ However, in those studies, only a limited number (21–29%) of the patients received radiation therapy and the sample sizes of patients treated by surgery with OT and pelvic irradiation were small.^{13,20} The other problems in performing OT are the risk of ovarian metastasis and the occurrence of ovarian cysts. In cervical cancer, the risk factors for ovarian metastasis are adenocarcinoma type, deep cervical invasion and extrauterine spread.²¹ In a previous study of our institution, the authors also showed that the significant risk factors for ovarian metastasis were uterine corpus involvement and non-squamous cell type.²² Ovarian conservation should be careful and frozen biopsy of bilateral ovaries might be necessary in the patients with these risk factors. There was no case of ovarian metastasis or recurrence in 29 patients who underwent OT. Incidence of symptomatic ovarian cyst formation after OT is reported to be about 24%.^{7,23} However, 3–14% of ovarian cysts required surgery and most ovarian cysts were successfully treated by hormonal therapy.^{20,23} In this study, three cases (9.6%) developed ovarian cysts after OT, but they all had no symptom and ovarian cysts were decreased (one case) or disappeared (two cases) spontaneously.

There are also the other methods of fertility preservation including embryo cryopreservation, oocyte preservation, ovarian tissue cryopreservation, and autotransplantation of the ovary. However, the procedures have the limitations. Ovarian stimulation and oocyte retrieval necessary for oocyte preservation necessitate a delay in treatment of four to six weeks.²⁴ Embryo cryopreservation may be difficult for some women without a partner and children. The principal obstacle of ovarian cryopreservation is poor viability and ischemic damage.²⁵ Autotransplantation of the ovary is more surgically invasive and the short-term viability of the transplant is a major concern.

In spite of a small sized retrospective study at a single institution, this study shows that even

gynecologic oncologists perform the OT only in about 40% of young patients with cancer. Gynecologic oncologists should propose this option to their all patients and inform a general surgeon or pediatric oncologist or medical oncologist of the clinical efficacy and importance of OT.

In conclusion, OT, especially laparoscopic OT, is a simple and efficient procedure to preserve the ovarian function in young women less than 40 years who should undergo pelvic radiation. However, this study shows that OT is underused in clinical situation. We should increase the awareness of physicians and patients about OT for the preservation of fertility and prevention of premature menopause.

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