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Scientific Article

Factors Associated With Premature Ovarian Insufficiency in Young Women With Locally Advanced Rectal Cancer Treated With Pelvic Radiation Therapy

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Abstract

Purpose: Pelvic radiation therapy (RT) is standard of care for patients with locally advanced rectal cancer (LARC). Premature ovarian insufficiency (POI) in premenopausal women is a possible side effect. The purpose of our study was to evaluate factors associated with POI in women younger than 50 years, treated with pelvic RT for LARC, including those who underwent ovarian transposition (OT).

Methods and Materials: We retrospectively reviewed the records of women younger than 50 years treated with pelvic RT for LARC at our institution between 2001 and 2019. Clinical and hormonal data were used to determine ovarian function. The ovaries and uterus were contoured and dose volume histograms were generated. Association of clinical and dosimetric factors with POI within 12 months of RT was evaluated using Wilcoxon-rank sum test and Fisher's exact test.

Results: We identified 76 premenopausal women at time of RT with median age of 43 years (range, 20-49). Twenty-six women (34%) underwent OT. Neoadjuvant, concurrent, and adjuvant chemotherapy was administered in 56 (74%), 69 (91%), and 26 (34%) women,

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respectively. Median RT dose was 50 Gy/25 fractions. Among 75 women with 12 months of follow-up, 25% had preservation of ovarian function, all in the OT group. Ovarian function was preserved in 19 (76%) women who underwent OT. The median of ovarian mean dose was 1.7 Gy in the OT group versus 44.8 Gy in the non-OT group ($P < .001$). OT and age at RT were significantly associated with POI ($P < .001$). No patient with ovarian mean dose less than 1.36 Gy developed POI.

Conclusions: OT was significantly associated with reduced risk of POI by enabling lower radiation doses to the ovaries. OT should be considered in young patients undergoing pelvic RT. Although there appears to be a significant association between ovarian mean dose and POI, larger studies are needed to find a dosimetric threshold. Our results suggest keeping the dose to the ovaries as low as reasonably achievable in patients who undergo OT and pelvic RT.

Introduction

Colorectal cancer is the third most common cancer among women.[1] Standard of care treatment for locally advanced rectal cancer (LARC) includes pelvic RT.[2] One of the well-documented possible adverse effects of pelvic radiation therapy (RT) in younger women is premature ovarian failure. With long-term survivors, this not only affects young women's childbearing ability, but is also associated with increased risks of early osteoporosis and cardiovascular diseases.[3]

The risk for treatment induced ovarian failure is becoming a more pertinent issue given the predicted rising incidence of rectal cancer in the younger age group. Using the Surveillance, Epidemiology, and End Results database, Bailey et al, predicted the incidence of rectal cancer to increase in 2030, by 124.2% for patients 20 to 34 years and by 46.0% for patients 35 to 49 years old.[4]

There is accumulating evidence that discussions about fertility and fertility preservation are of great importance to young patients receiving treatment for cancer.[5,6] The American Society of Clinical Oncology recommends discussing the option of ovarian transposition whenever pelvic radiation therapy is offered for premenopausal women.[5]

In a study by Sioulas et al, ovarian transposition before pelvic radiation therapy in 22 patients treated for lower gastrointestinal malignancies preserved ovarian function in around two-thirds.[7] More evidence is needed on the dosimetric constraints that should be achieved after OT in premenopausal women undergoing pelvic radiation therapy for rectal cancer. The purpose of our study was to evaluate the association of clinical and dosimetric factors with treatment-induced premature ovarian insufficiency (POI) in premenopausal women, treated with pelvic RT for LARC, including those who underwent ovarian transposition (OT).

Materials and Methods

Study design and participants

This is a retrospective single institution study. Using our institutional database, all female patients, younger than 50 years old, with a diagnosis of rectal cancer that received pelvic RT, from January 1, 2001 to August 1, 2019 were identified. Premenopausal women who received curative intent radiation therapy to the pelvis for rectal cancer were included. Among those patients, was a subgroup that underwent ovarian transposition before pelvic RT. Ovarian transposition aims to reposition the ovaries outside the irradiation fields. The ovaries are laparoscopically transposed to the paracolic recesses lateral to the ascending and descending colon (Fig. 1).[7] Of the 267 patients who were identified, we excluded patients who already had menopause at the time of RT, patients with a history of bilateral salpingo-oophorectomy, and patients who underwent bilateral salpingo-oophorectomies at the time of rectal cancer surgery. We also excluded patients who underwent palliative pelvic radiation or who received pelvic radiation therapy at an outside institution. Of the remaining 135 patients, we then excluded those who did not have documentation of their menopausal status, by history or laboratory tests, in addition to patients who had more than 35 days between their last menstrual period and RT start date and thus were already menopausal at the start of radiation. Seventy-six patients remained for analysis (Fig. 2).

This study was approved by the institutional review board, which waived the need for obtaining informed patient consent for this retrospective case series and dosimetric study.

Ovarian function and POI

To assess ovarian function preservation, reports of absent menses and menopausal symptoms were collected from the patients' records. In addition to that, endocrine laboratory results of follicular stimulating hormone (FSH), luteinizing hormone, and estradiol levels, before and after RT, were collected to objectively assess menopausal status and ovarian function. Data on pregnancy was also collected, when available.

POI was defined, in this study, as elevated FSH level higher than 20 mIU/mL and a low estradiol level, lower than 30 pg/mL whenever laboratory tests were available. When hormonal levels were not available, absent menses

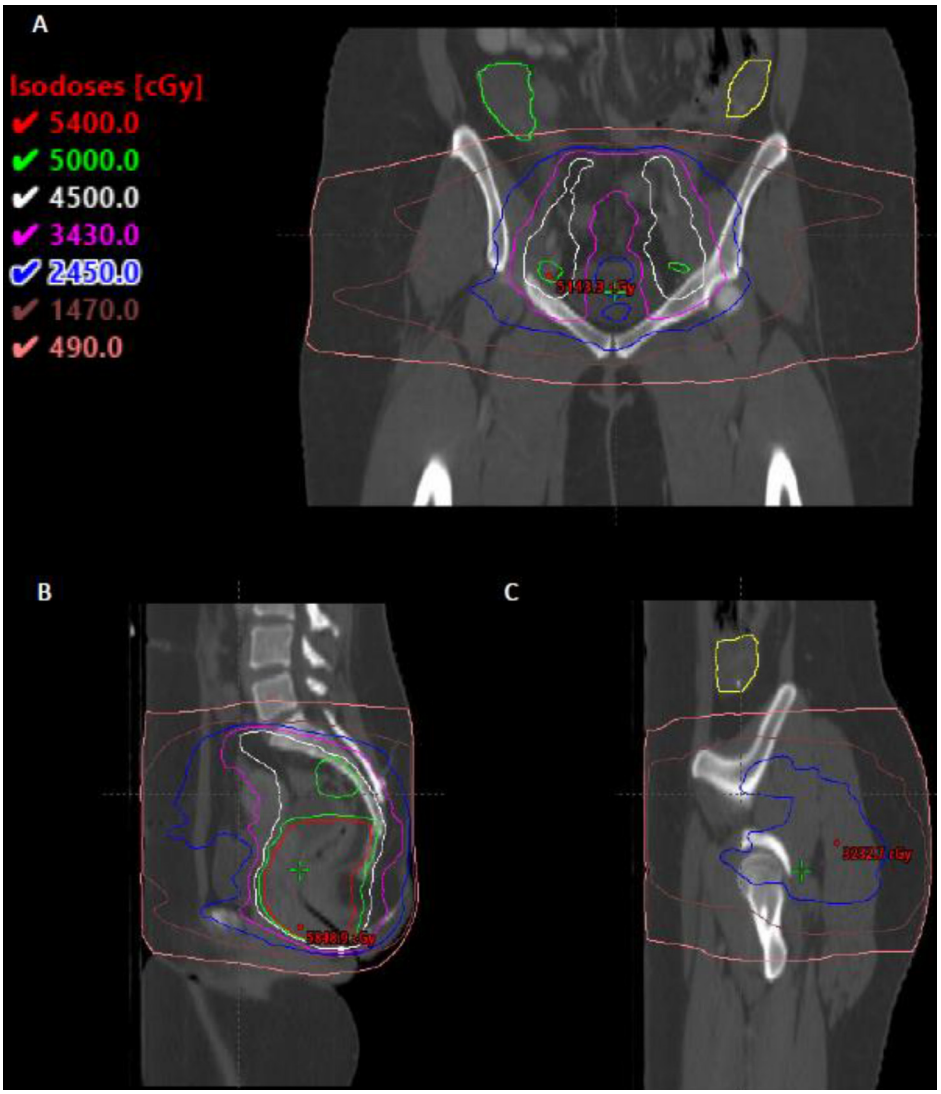

Figure 1 A, The coronal isodose distribution at midline of a 180 cGy × 25 fractions rectum plan with the 200 cGy × 2 fractions cone down. The left (yellow) and right (green) transposed ovaries in the abdomen are shown. B, Sagittal distribution at midline and C, sagittal distribution bisecting the left ovary.

with the presence of menopausal symptoms were used to define premature ovarian insufficiency.[7]

When endocrine tests were available, the date of elevation of FSH and decrease in estradiol as per above criteria was considered as the date of menopause, and the last menstrual period was considered as date of menopause when endocrine tests were not available. For all patients, follow-up gynecologic notes and endocrine laboratory results were reviewed up to at least 12 months after the date of menopause to ensure durability of menopause.

Dosimetric data

Computed tomography (CT) simulation scans of pelvic RT treatment plans for all the included patients were retrieved from the department's treatment planning system and a single dosimetrist contoured the ovaries and uterus for each patient.[8,9] Dose volume histogram data were extracted to determine the ovarian minimum, maximum, and mean doses, as well as uterine body and fundus mean and maximum doses.

Outcomes

We evaluated the practice of fertility clinic referrals at our institution for patients receiving pelvic radiation therapy for rectal cancer. We examined the percentage of patients referred to fertility clinics before starting pelvic RT and evaluated the type of fertility preservation procedures that they underwent. The primary outcome was premature ovarian insufficiency within 12 months after pelvic RT for the whole cohort including patients who

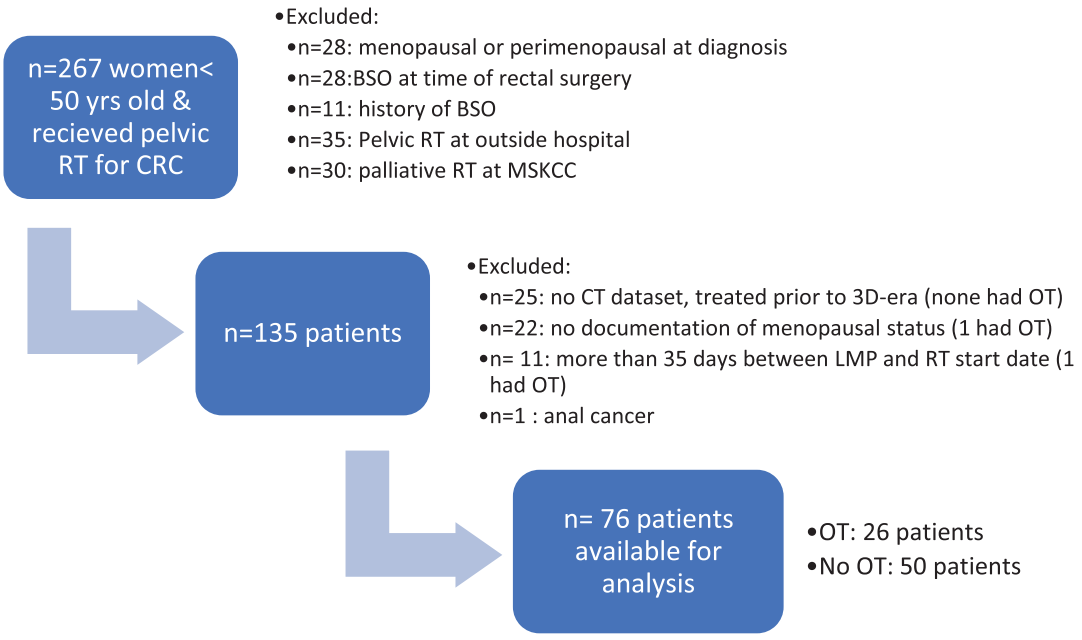

Figure 2 Flow chart showing the identification of rectal cancer female patients, premenopausal, treated with pelvic radiation therapy for inclusion in the analysis. *Abbreviations:* BSO = bilateral salpingo-oophorectomy; LMP = last menstrual period.

underwent OT. We evaluated the association of clinical characteristics and dosimetry parameters with probability of POI within 12 months after RT. We also attempted to investigate a dosimetric threshold for POI in the subgroup of patients who underwent OT. The means and medians of the ovarian and uterine dose volume histogram parameters were compared among the group who underwent OT and those who did not.

Statistical analysis

Patient characteristics, treatment characteristics, and dosimetric variables were summarized with medians, interquartile range, range, means, and standard deviation for continuous variables, and frequency and percentages for categorical variables. The minimum, mean, and maximum doses to the ovaries and uterus were compared using the Wilcoxon-rank sum test among the patients who underwent OT and those who did not.

The primary outcome was POI by 12 months after RT. We included patients with more than 12 months of follow-up in the analysis and 1 patient with only 6.9 months of follow-up was excluded. The association of clinical and dosimetric variables with having POI by 12 months was evaluated using the Wilcoxon-rank sum test and Fisher's exact test. Overall survival, calculated from the end of RT until death or last follow-up, was estimated using Kaplan-Meier method. All statistical analyses were performed using R, version 3.6.1 (R Foundation), and a $P < .05$ was considered statistically significant.

Results

A total of 76 women, premenopausal at time of pelvic RT, were included in the study. Median age at RT was 43 years (range, 20-49). Patient and tumor characteristics are summarized in Table 1. Neoadjuvant, concurrent and adjuvant chemotherapy was administered in 56 (74%), 69 (91%), and 26 (34%) of women, respectively. Median RT dose was 50 Gy in a median of 25 fractions. Intensity modulated RT (IMRT) was used in 46 patients (61%), and 30 (39%) had three dimensional- conformal radiation therapy (3D-CRT) (Table 1). With a median follow-up among survivors of 53.8 months (range, 5.8- 185.3), the 5-year overall survival (OS) for the whole cohort was 85% (95% confidence interval, 76%-95%).

Approximately half of the women (53%) were referred to a fertility specialist before the start of pelvic radiation therapy. The referral to fertility clinics became more common after the year 2009. Twenty-six patients (34%) underwent ovarian transposition. All women had bilateral OT except one patient where pelvic adhesions necessitated only unilateral OT. Three patients also underwent oocyte/embryo cryopreservation in addition to OT.

Among 75 patients with at least 12 months of follow-up, 19 women (25%) had preservation of ovarian function within 12 months after RT, all were in the OT group, and 1 woman carried a high-risk pregnancy 15 years after end of treatment, with premature birth at 25 weeks. Ovarian function was preserved in 19 (76%) out of the 25 women who underwent OT (Table 2).

The median and the mean of the ovaries mean dose was 1.7 Gy and 2.7 Gy in the OT group versus 44.8 Gy

Table 1 Patient, tumor, and treatment characteristics for patients with rectal cancer who received pelvic RT

N = 76	Median (range) or Frequency (%)
Age (years)	43 (20-49)
Histology	
Pure adenocarcinoma	74 (97.4)
Adenocarcinoma with neuroendocrine features	1 (1.3)
Mixoid chondrosarcoma	1 (1.3)
Clinical T stage	
Tx	1 (1.3)
T1	2 (2.6)
T2	8 (11)
T3	52 (68)
T4a	4 (5.3)
T4b	9 (12)
Clinical N stage	
Nx	3 (3.9)
N0	17 (22)
N1	46 (61)
N2	10 (13)
Clinical M stage	
M0	68 (89)
Limited M1 (liver most common site)	8 (11)
RT total dose (Gy)	50 (25-56)
RT Fractions	25 (5-28)
RT Modality	
3D-CRT	30 (39)
IMRT	46 (61)
Neoadjuvant chemotherapy	56 (74)
Adjuvant chemotherapy	26 (34)
Chemotherapy drugs	
FOLFOX/XELOX	69 (92%)
5FU/LV or Xeloda	5 (6.7%)
Cisplatin-Etoposide	1 (1.3%)
Unknown	1

Table 2 Fertility preservation (FP) procedures and outcomes

N = 75	Frequency (%)
FP Referral	40 (53)
FP Procedure	26 (34)
Type of FP Procedure	
BOT alone	22 (85)
BOT and cryopreservation	3 (12)
Unilateral ovarian transposition	1 (3.8)
POI after RT	56 (75)
Pregnancy after RT	1 (1.3)
POI after RT in patients who underwent OT (n = 25)	6 (24)

Abbreviations: BOT = bilaterial ovarian transportation; OT = ovarian transportation; POI = premature ovarian insufficiency; RT = radiation therapy.

and 41.9 Gy for the patients who did not undergo OT respectively (P <.001). Uterine doses were similar (medians >40 Gy) in both groups. Table 3 summarizes the means and medians for the ovarian and uterine doses, stratified by OT.

Ovarian dosimetry parameters were highly correlated with ovarian transposition status. The effect of dosimetry on the likelihood of POI could not be separated from ovarian transposition. The dot plot (Fig. 3) is a descriptive summary of ovarian mean doses and POI status by 12 months, stratified by ovarian transposition. It shows that all patients who did not receive ovarian transposition had ovarian mean doses ≥15 Gy and experienced POI by 12 months. As for the patients who underwent OT, those who had POI appear to have higher dosimetric parameters in the plot, with the 15 Gy ovarian mean dose corresponding to the patient who underwent unilateral OT due to pelvic adhesions; her right ovarian mean dose was around 20 Gy and left ovarian mean dose was around 8 Gy.

With a total of 75 patients who were followed up for more than 12 months from RT start, OT patients had significantly lower probability of POI by 12 months (24% vs 100%, P <.001) Patients who had POI were significantly older (median 44 vs 34, P <.001). RT modality (IMRT vs 3D-RT) was not significantly associated with the risk of POI (69% vs 83%, P = .2). Receipt of neoadjuvant chemotherapy (76% vs 70%, P = .6), concomitant chemotherapy (78% vs 43%, P = .064), and adjuvant chemotherapy (62% vs 82%, P = .092) were also not significantly associated with POI.

Among patients who received OT, those who experienced POI within 12 months had significantly higher ovarian doses for the following dosimetry parameters: ovaries maximum dose (18 vs 3 Gy, P = .021), ovaries minimum dose (0.86 vs 0.40 Gy, P = .001), and ovaries mean dose (3.8 vs 1 Gy, P = .009) compared with patients who did not experience POI within 12 months. No patient with ovarian mean dose less than 1.36 Gy experienced POI by 12 months. Also, 2 of the patients who had POI in the OT group were 38 years old and the other 4 patients were between 43 to 45 years old. With only 6 menopause events in the OT group, we could not investigate an optimal cut-off for the ovarian dose.

Discussion

The results of our study show that ovarian transposition is significantly associated with preserving ovarian function by decreasing the mean radiation doses to the ovaries in premenopausal women undergoing pelvic irradiation for rectal cancer. With the improvement of oncologic outcomes of cancer therapy, survivors are experiencing

Table 3 Ovarian and uterine dosimetric parameters stratified by OT

	Ovarian Transposition				*P* value
	No (N = 50) [Unknown: 15]		Yes (N = 26)		
Dose (Gy)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	
R ovary Max	47.7 (26.3-54.4)	47.2 (5)	3 (0.5-33)	6.1 (7.7)	<0.001
R ovary Min	43.5 (2.6-49.3)	37.8 (12)	0.5 (0.1-13.5)	1.5 (2.8)	<0.001
R ovary mean	45.7 (21.3-52.5)	43 (8)	1.3 (0.3-19.9)	2.9 (4.2)	<0.001
L ovary Max	47.9 (12.4-65.9)	45.7 (9)	5.8 (0.6-23.6)	6.6 (6.2)	<0.001
L ovary Min	34.1 (10.0-63.1)	34.8 (12)	0.8 (0.2-5.5)	1.3 (1.5)	<0.001
L ovary mean	44.3 (11.1-64.3)	41.4 (10)	1.5 (0.4-11.9)	2.7 (2.9)	<0.001
Ovaries Max	48.6 (26.3-65.9)	48.5 (6)	6.1 (0.6-33)	8.2 (7.9)	<0.001
Ovaries Min	30.7 (2.6-47.3)	31.9 (12)	0.5 (0.1-4)	0.9 (1)	<0.001
Ovaries mean	44.8 (15-52.5)	41.9 (9)	1.7 (0.4-15.4)	2.7 (3.3)	<0.001
Uterine Fundus Max	47.3 (6.2-54.5)		47.5 (18.6-54)		0.8
Uterine Fundus Mean	42.9 (3.4-50.7)		44.0 (9.3-49.6)		0.7
Lower Uterine Segment Max	52.3 (26.8-65.6)		52.6 (25.7-58.4)		0.4
Lower Uterine Segment Mean	45.8 (24.6-53.1)		46.2 (17.1-52.5)		0.7

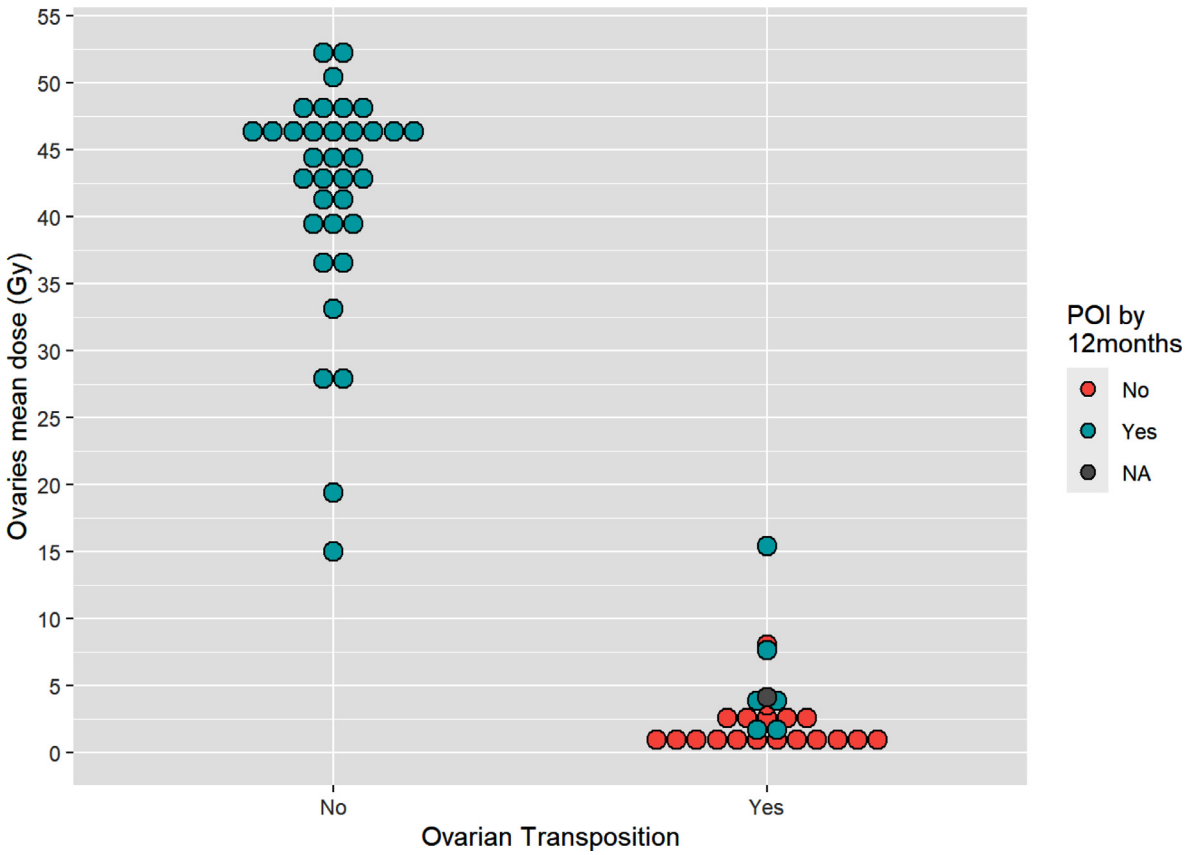

Figure 3 Dot plot summarizing ovarian mean doses and premature ovarian insufficiency status stratified by ovarian transposition.

significant long-term side effects related to their treatments. Referrals to fertility clinics at our institution became more consistent after the year 2009. This is in line with increased awareness among both health care providers and patients as to the importance of ovarian function preservation, to increase chances of preserving reproductive ability as well as to avoid the deleterious effects of early menopause.[5,6]

Regarding the effect of chemotherapy, our study did not detect a significant association with POI, however sample size was small and there was heterogeneity in the timing and the type of chemotherapy used. In addition, those patients were a selected group because a small percentage of patients who were excluded in the beginning of the study had menopause after diagnosis but before the start of radiation therapy, which might have happened after neoadjuvant chemotherapy. From a study on 123 patients with colorectal cancer, 40 years old or younger,[10] only 3 patients (4.2%) experienced long-term amenorrhea among those who received chemotherapy alone for colon cancer (Leucovorin calcium, Fluorouracil, and Oxaliplatin, Capecitabine and Oxaliplatin, or Capecitabine) and around 94% of patients with rectal cancer who had chemoradiotherapy had persistent amenorrhea suggesting the importance of pelvic RT as the main factor in causing persistent amenorrhea and POI.[10] Also Hyman et al reported that 5-FU in general has low potential to cause ovarian damage and platinum agents are considered probably but not definitely associated with ovarian damage.[11]

On the other hand, ionizing radiation used in pelvic radiation therapy is widely known to cause POI by depleting ovarian reserve, especially in older premenopausal women where the primordial follicle pool is already limited. This mainly depends on the age at time of receipt of radiation therapy and the dose received by the ovaries.[12,13] Ovarian transposition as an endocrine preservation procedure removes the ovaries from the pelvis and thus increases the distance between the ovaries and the high radiation therapy doses. It has been reported to preserve ovarian function in a significant percent of women undergoing pelvic RT for cervical or rectal cancer.[7,14] In a study on 22 patients with lower gastrointestinal malignancies (rectal and anal cancer), ovarian function was preserved in 12 (67%) of 18 patients, including 9 (90%) of 10 patients 40 years old or younger and 3 (38%) of 8 patients older than 40 (P = .07).[7] The results of the present study show a similar benefit, with OT and age at RT as the clinical factors highly correlated with avoidance of POI.

In our study, all patients who did not undergo OT experienced menopause after completion of RT, and they all had ovarian mean doses higher than or equal to 15 Gy. In the OT group, the average of the ovarian mean doses was 1.7 Gy and was significantly correlated with the risk of POI. Of note, the ovarian mean doses for the 6 patients who experienced POI in the OT group appear to be more elevated than their counterparts who had no POI. However, with the relatively small number of events in this group, it is not feasible to derive a dosimetric threshold that discriminates patients who experience POI from those who do not.

Wallace et al in their study on the risk of POI suggested a dose dependent relationship such that the dose required to destroy 50% of the immature oocytes was predicted to be less than 2 Gy.[15] They also developed a mathematical model that predicts the age of ovarian failure after treatment with a known dose of radiation therapy.[16] Wo et al extrapolated data from that model and predicted that for patients who are around 30 years of age, a dose of about 6 Gy to the ovaries is enough to place them at an intermediate risk of acute ovarian failure.[16,17] The effective sterilizing dose, defined as the dose of fractionated radiation therapy (Gy) at which premature ovarian failure occurs immediately after treatment in 97.5% of patients, was predicted to be around 14.3 Gy at age 30 and around 6 Gy at 40 or more years.[16] In another study by Ogilvy-Stuart et al, a 4 Gy limit was reported to cause sterility in 30% of women younger than 30 years and 100% of women older than 40 years who undergo pelvic RT.[12] In more recent studies on cervical cancer patients who underwent ovarian transposition and pelvic RT, V7.5 Gy <26%[14] ovarian maximum dose <9.985 Gy, mean dose <5.32 Gy, and V5.5 <29.65% were predictive of ovarian function preservation.[18]

Even though we could not identify an optimal dosimetric threshold to protect against POI in this study due to the low number of events, it is the first study on patients with rectal cancer who includes a subgroup who underwent OT before pelvic RT and quantifies the doses received by the ovaries. It is evident that higher doses to the ovaries are more likely to be associated with POI in patients who undergo OT and no patient in our cohort with a dose below 1.36 Gy developed POI within 12 months of RT.

However, even with ovarian transposition, in our study, maximum doses to the ovaries approached 4 to 6 Gy limits. It is reported that even with OT and placement of a lead block over the ovaries, the ovaries can still receive 8% to 15% of the prescribed dose due to scatter and transmission through the shield.[19] In a study by Perez-Andujar et al, they found that the use of proton based radiation therapy has a lower risk of premature ovarian failure than photon-based radiation, with 3D-CRT or IMRT, regardless of uncertainties in ovarian location.[20] Thus, we are currently designing a dosimetric study on the subgroup of patients who underwent OT to investigate dosimetrically whether the use of proton therapy could potentially decrease the dose delivered to the ovaries even further thus decreasing the potential adverse effects of ovarian failure, including menopause, infertility, osteoporosis, and cardiovascular diseases.

Finally, it is important to note that with our follow-up, only one patient was able to carry a high-risk pregnancy

with premature delivery. Efforts are underway to develop combined uterine and ovarian transposition procedures to further preserve the chance of fertility and viable pregnancies after pelvic RT.[21]

Although we made sure to include only premenopausal women, one limitation is that it cannot be affirmed with certainty that ovarian insufficiency is not due to natural menopause in some of the patients who are close to this life event in our cohort. Some of the other limitations of our study include its retrospective nature with its inherent missing data and selection bias, lack of homogeneity with respect to type and timing of chemotherapy, and a limited sample size to identify ovarian dosimetric threshold among patients who underwent OT. Our institution is more frequently offering ovarian transposition procedures to eligible young patients with LARC undergoing pelvic radiation therapy. We will update our study in the future with a larger sample size. This will probably allow us to find ovarian dosimetric thresholds and thus better define radiation dose constraints in such a population.

Conclusions

In conclusion, OT significantly enabled a reduced dose of radiation to the ovaries and reduced the risk of POI in our cohort. OT should be considered in young patients undergoing pelvic RT. Our results that no patient with ovarian mean dose less than 1.36 Gy experienced POI by 12 months and that among patients who received OT, those who experienced POI within 12 months had significantly higher ovarian doses compared with patients who did not experience POI within 12 months, suggest keeping the dose to the ovaries as low as reasonably achievable, during radiation therapy planning in patients who undergo OT. However, a larger cohort of patients undergoing OT is needed to confirm the effect of dose on menopause and find an optimal dose threshold. In addition to this, our planned dosimetric study of protons versus photons might provide valuable information on RT techniques to further lower ovarian doses in premenopausal patients who undergo OT and pelvic RT.

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