advances
in radiation oncology

Scientific Article

Ovarian Transposition Before Pelvic Radiation Therapy: Spatial Distribution and Dose Volume Analysis

Christopher Gay, MD,[a] Yaniv R. Raphael, MD,[b] Jennifer Steers, PhD,[a] Diana J. Lu, MD,[a] John H. Lewis, PhD,[a] John DeMarco, PhD,[a] Benedick Fraass, PhD,[a] Bobbie J. Rimel, MD,[c] Roja Zakariaee, PhD,[a] Mitchell Kamrava, MD,[a] and Katelyn M. Atkins, MD, PhD[a,*]

aDepartment of Radiation Oncology; bDepartment of Radiology; cDepartment of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California

Abstract

Purpose: There is a paucity of data analyzing the anatomic locations and dose volume metrics achieved for surgically transposed ovaries in patients desiring fertility or hormonal preservation receiving pelvic radiation therapy (RT), which were examined herein.

Methods and Materials: This is a retrospective study including women who underwent ovarian transposition before pelvic RT between 2010 to 2020. The craniocaudal (CC) distance of the ovary centroid to the (1) plane of the sacral promontory, (2) iliac crest, and (3) the nearest distance between the ovary edge and RT planning target volume (PTV) were measured (cm). The area under the receiver operating characteristic curve and cut-point analysis estimating ovary location outside the PTV was performed.

Results: Thirty-one ovaries were analyzed from 18 patients. Thirteen (72.2%) were treated with intensity modulated RT, and 5 (27.8%) were treated with 3-dimensional conformal radiation therapy. Most ovaries were located above the sacral promontory (64.5%, n = 20), below the iliac crest (96.8%, n = 30), and outside the PTV (64.5%, n = 20). The median distance from the ovaries to the sacral promontory, iliac crest, and PTV was 0.8 cm (interquartile range [IQR], −0.83 to 1.59 cm), −3.22 cm (IQR, −5.12 to −1.84 cm), and 0.9 cm (IQR, −1.0 to 1.9 cm), respectively. The area under the receiver operating characteristic curve and cut-point analysis demonstrated that distance from the iliac crest predicted an ovary to be outside the PTV with an optimal cut-point of −3.0 cm (C-index = 0.82). The median mean and maximum (Dmax) ovary doses were 15.5 Gy (IQR, 9.6-20.2 Gy) and 32.2 Gy (IQR 24.8-46.5 Gy), respectively.

Conclusions: Despite most transposed ovaries being located outside the PTV, nearly all remained below the iliac crest and received RT doses associated with a high risk of ovarian failure. These findings deepen our understanding of the spatial relationship between transposed ovaries and dose to inform surgical and pre-RT planning and suggest that more aggressive ovary-sparing strategies are warranted.

Introduction

Pelvic irradiation is an integral component of therapy for a variety of pelvic malignancies, including rectal cancer, anal cancer, gynecologic malignancies (vaginal, cervical, uterine), lymphoma, sarcomas, and others. A

known complication from pelvic irradiation is unavoidable radiation exposure to organs adjacent to the treatment field. For premenopausal women desiring fertility or ovarian hormonal preservation, the ovarian radiation dose is of critical concern, as studies have consistently demonstrated that higher ovarian doses are associated with increased risk of acute ovarian failure, infertility, and premature menopause.[1-5] The latter of which can result in premature onset of comorbidities associated with estrogen withdrawal, including decreased bone mineral density, genitourinary atrophy, and an impaired lipid profile with increased risk of ischemic heart disease.[6-12]

Ovaries are exquisitely radiosensitive, with doses less than 2 Gy associated with up to 50% oocyte destruction,[3] doses of 6 Gy resulting in a moderate risk of ovarian failure,[13] and doses more than 14 Gy resulting in ovarian failure in nearly all patients, with effective doses decreasing with age.[4] This radiosensitivity can be challenging, as treatment plans for pelvic RT are typically prescribed to doses of 45 Gy or greater and large clinical treatment volume margins are often required for optimal local control. One strategy to facilitate ovary dose reduction is surgical transposition of the ovaries before radiation therapy. In this procedure, the ovary vascular pedicle remains intact, and the ovaries are relocated with the goal of being located above the pelvic brim and as lateral as possible.[1,14-18] Although this procedure is being used with increasing frequency, reported success rates have high variability and ovarian function preservation rates after transposition and RT range from 32% to 88%.[14,15,18-25]

Although there has been a growing interest in characterizing the relationship between ovary location and RT dose in the modern treatment era, there is a paucity of data analyzing the anatomic locations and dose volume metrics achieved for transposed ovaries. In this study, we sought to examine the spatial distribution of surgically transposed ovaries in premenopausal patients who were treated with pelvic radiation therapy, the relationship to the planning target volume (PTV), and the resultant ovary dose volume metrics achieved.

Methods

Patient population and treatment

This retrospective cohort study included 18 consecutive patients at Cedars-Sinai Medical Center (CSMC) who underwent surgical ovarian transposition before pelvic radiation therapy between January 2010 and September 2020. Patients were identified for inclusion using the machine learning-based platform DEEP6 AI (Pasadena, CA) to search the electronic medical record using the terms/concepts "ovarian" and "transposition" in patients who had received a radiation therapy planning CT scan.

The above search criteria identified 32 patients, which were manually screened to yield a final cohort of 18 patients meeting the above inclusion criteria. This study was approved by the CSMC Institutional Review Board.

Patients with pelvic malignancies were treated with a combination of surgery and radiation therapy plus or minus chemotherapy for curative intent. Unilateral or bilateral ovarian transposition was performed before radiation therapy. External beam radiation therapy (EBRT) was planned using 3-dimensional conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy techniques and delivered in 1.8 to 2.0 Gy fractions to total doses of 45 Gy to 50.4 Gy in 21 to 28 fractions. Although no strict ovary dose constraint was used, for the majority of patients, it was attempted to limit the amount of the 10 Gy isodose line falling within the ovary contour in at least one ovary.

Ovarian spatial distribution analysis

Surgically transposed ovaries were manually delineated in Varian Eclipse (Varian Medical Systems, Palo Alto, CA) on radiation therapy planning computed tomography (CT) scans with accuracy verified by an expert radiologist (Y.R.). The craniocaudal (CC) distance (cm) from the plane of the sacral promontory (or the iliac crest) to the centroid of each ovary contour was measured in Varian Eclipse, where positive and negative values represent distances cranial and caudal to the reference landmark, respectively. Although the iliac crest has historically been reported as a bony landmark in surgical series, the sacral promontory was additionally used as a bony landmark reference due to its anatomic consistency and ease of precise identification on sagittal CT imaging compared with the iliac crest, which depending on pelvis position/tilt during CT simulation can confer more variability in determining the most cranial axial slice. Here, the most cranial aspect of the iliac crest in any sagittal slice was used for the point of measurement. The distance (cm) between the nearest edge of the ovary and the nearest edge of the radiation therapy PTV in any dimension (axial, coronal, sagittal) was measured with negative values representing overlap of ovary and PTV. Each individual radiation therapy planning CT scan underwent rigid registration in Varian Velocity (Varian Medical Systems, Palo Alto, CA) to a single reference scan to visually depict the spatial location of all surgically transposed ovaries.

Radiation therapy dose volume analysis

Radiation therapy dose-volume histograms were recalculated in Varian Eclipse, excluding contribution from intracavitary or interstitial brachytherapy procedures.

Mean (Gy), maximum (Gy), and volume (percent) receiving 5 Gy doses to the transposed ovaries were calculated. One patient had ovarian transposition and definitive RT for locally advanced rectal cancer performed outside the United States (DICOM data unavailable) and subsequently underwent RT planning at CSMC for recurrent disease. This planning CT was used to delineate her unilateral transposed ovary and to recreate a typical 3D-CRT rectal RT plan to estimate likely radiation dose exposure. The intent to spare the ovaries from RT dose exposure was determined based on whether they were contoured and/or included within the treatment planning optimizer.

Clinical outcomes

In-depth manual medical record review was performed to ascertain baseline medical and posttreatment fertility and ovarian functional status. Available ovarian endocrine function data were assessed for all patients at any time point post completion of radiation therapy, including estrogen, follicle stimulating hormone (FSH), luteinizing hormone, or anti-Mullerian hormone levels, as well as any documented in vitro fertilization procedure (including oocyte retrieval), or pregnancy (including embryo transfer for surrogate pregnancy). Normal ovarian function was defined as FSH <40 mIU/mL and estrogen >50 pg/mL and without symptoms of menopause.

Statistical analysis

Area under the receiver operating characteristic curve was calculated and cut-point analysis performed using the Liu method.[26] The distribution of continuous radiation therapy variables was compared using the Wilcoxon rank-sum test. Correlation between ovarian CC distance to the sacral promontory and mean ovary radiation therapy dose was assessed using Pearson's correlation coefficient and the coefficient of determination (R^2) was calculated to assess the proportion of variance in CC distance predictable from mean ovary dose ($R^2 \geq 0.70$ was considered sufficient for prediction). Stata, version 16.1 (StataCorp LLC) statistical software was used for all analysis.

Results

Clinical characteristics

A total of 31 transposed ovaries were analyzed from 18 patients. Most patients (72.2%, n = 13) underwent bilateral ovarian transposition, whereas 16.7% (n = 3)

Table 1   Patient and treatment characteristics

Characteristic	Total cohort (N = 18)
Age, median (IQR, y)	40 (36.0-43.0)
Race	
Black	0 (0)
Hispanic White	6 (33.3)
Nonhispanic White	9 (50)
Other	3 (16.7)
BMI (median, kg/m^2)	21.1 (IQR 20.7-23.5)
History of pregnancy	7 (38.9)
PCOS	1 (5.6)
Hypertension	0 (0)
Congestive heart disease	0 (0)
Diabetes	0 (0)
Hyperlipidemia	0 (0)
Primary cancer	
Cervical	14 (77.8)
Rectal	3 (16.7)
Endometrial stromal sarcoma	1 (5.6)
Tumor classification	
T1	11 (61.1)
T2	5 (27.8)
T3	2 (11.1)
Node positive	12 (66.7)
Histology	
Well-differentiated	1 (5.6)
Moderately differentiated	3 (16.7)
Poorly differentiated	12 (66.7)
Chemotherapy	
Cisplatin single agent	10 (55.6)
Cisplatin/gemcitabine	2 (11.1)
5-FU based	2 (11.1)
Carboplatin/paclitaxel	1 (5.6)
Disease recurrence	9 (50.0)
Side of transposed ovaries	
Right	3 (16.7)
Left	2 (11.1)
Bilateral	13 (72.2)
Ovarian transposition technique	
Laparoscopic	10 (55.6)
Open	7 (38.9)
RT modality	
IMRT	13 (72.2)
3D-CRT	5 (27.8)
EBRT dose (median)	45 Gy (IQR 45.0-50.0 Gy)
RT field	
Pelvic	15 (83.3)
Pelvic + para-aortic	3 (16.7)

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; 5-FU = 5-fluorouracil; BMI = body mass index; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; PCOS = polycystic ovarian syndrome; RT = radiation therapy.
Values are listed *n* (%) unless otherwise specified.

underwent unilateral right and 11.1% (n = 2) underwent unilateral left transposition (Table 1). Ten patients (55.6%) had a laparoscopic transposition and 7 (38.9%)

had an open procedure. The median age was 40.0 years (interquartile range [IQR], 36.0-43.0 years). Most patients (77.8%, n = 14) were treated for cervical cancer, 16.7% (n = 3) for rectal cancer, and 1 patient (5.6%) for endometrial stromal sarcoma. Half (50.0%, n = 9) of patients received cisplatin chemotherapy, and 2 each (11.1%) received cisplatin/gemcitabine, carboplatin/paclitaxel, or 5-fluorouricil-based regimens. Most patients (72.2%, n = 13) were treated with intensity modulated RT and 27.8% (n = 5) were treated with 3D-CRT. The median prescribed EBRT dose was 45.0 Gy (IQR, 45.0-50.0 Gy). Three of the 14 patients with cervical cancer (16.7% overall) were treated with RT fields that included the paraaortic region. One patient (5.6%) had a history of polycystic ovarian syndrome, and no patients had a history of diabetes, hypertension, coronary heart disease, or hyperlipidemia. The median pretreatment body mass index was 21.1 (IQR, 20.7-23.5).

Analysis of ovarian spatial distribution

The median CC distance from the centroid of the 31 transposed ovaries to the plane of the sacral promontory was 0.8 cm (IQR −0.83 to 1.59 cm; range −4.8 to 4.9 cm). For the 16 right-sided and 15 left-sided ovaries, the median CC distance to the sacral promontory was 0.2 cm (IQR −1.7 to 1.2 cm; range, −4.8 to 4.5 cm) versus 1.2 cm (IQR −0.4 to 2.2 cm; range, −2.0 to 4.9 cm; $P = .14$). The majority (64.5%, n = 20) of transposed ovaries were located above the sacral promontory and 35.5% (n = 11) were located below the sacral promontory (Fig. 1a). The median CC distance from the centroid of the 31 ovaries to the iliac crest was −3.22 cm (IQR −5.12 to −1.84 cm; range, −9.89 to 0.38). Only one ovary (3.2%) was located above the iliac crest (Fig. 1b). The spatial location of the 31 transposed ovaries were visually depicted by rigid registration to a single reference CT (Fig. 2), demonstrating significant variability in location.

The median distance between the nearest edge of the ovary and the nearest edge of the PTV in any dimension was 0.9 cm (IQR −1.0 to 1.9 cm; range, −2.2 to 6.6 cm). For the 16 right-sided versus 15 left-sided ovaries, the median distance to the PTV was 0.0 cm (IQR −1.2 to 1.8 cm; range, −2.2 to 4.6 cm) versus 0.9 cm (IQR 0.4-3.0 cm; range, −2.0 to 6.6 cm; $P = .23$), respectively. The majority (64.5%, n = 20) of transposed ovaries were located outside the PTV and 35.5% (n = 11) were located within the PTV (Fig. 1c). Area under the receiver operating characteristic curve analysis demonstrated that CC distance from the sacral promontory had a concordance C-index of 0.70 (95% confidence interval [CI], 0.52%-0.89%) for predicting a transposed ovary to be outside the PTV with an optimal cut-point of 1.2 cm (C-index = 0.73) with 55% sensitivity and 91% specificity. Similarly, for distance from the iliac crest predicting the ovary to be outside the PTV,
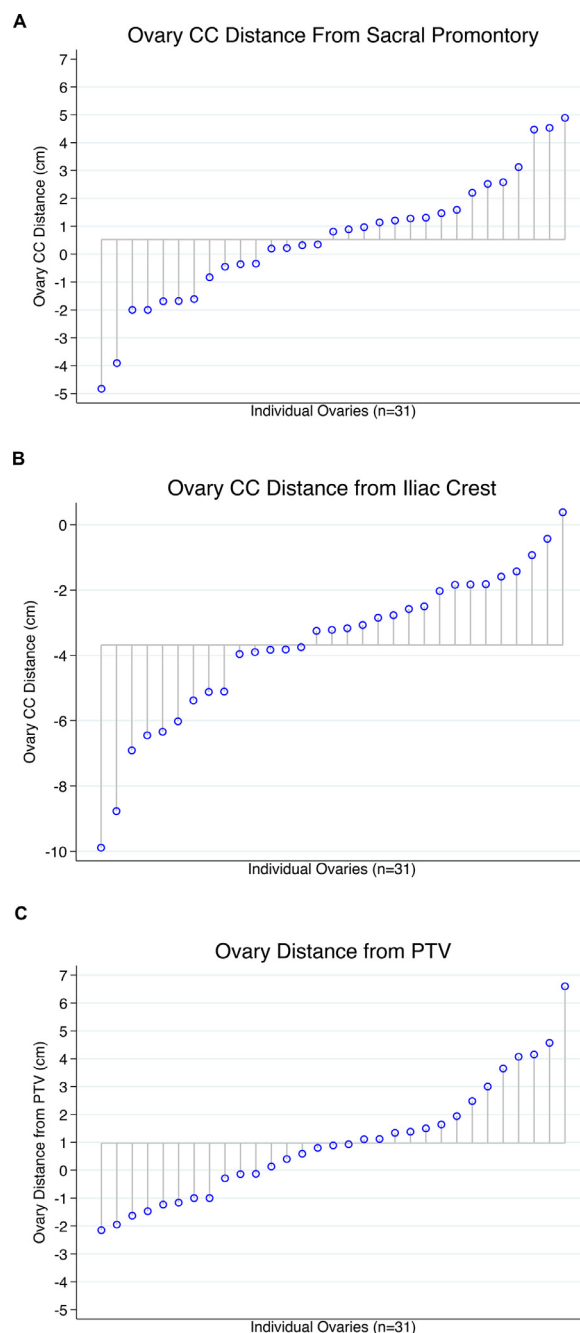

Figure 1 Waterfall plots of craniocaudal distance of the ovary centroids to (a) sacral promontory or (b) iliac crest, and the distance between the nearest edge of the ovary to the planning target volume in any plan (c). Negative and positive values correspond to ovary location below or above the sacral promontory (a), iliac crest (b), or within or outside the planning target volume (c), respectively. *Abbreviations:* CC = craniocaudal; PTV = planning target volume.

the C-index was 0.78 (95% CI, 0.61%-0.94%) with an optimal cut-point of −3.0 cm (C-index 0.82) with 65% sensitivity and 100% specificity.

Figure 2 Rigid fusion of individual transposed ovary contours (n = 31) with coronal, axial, and sagittal views showing progressively more posterior slices (top to bottom).

Ovary radiation therapy dose volume analysis

Among the 18 patients, there was intent to limit the ovarian RT dose in 10 of 18 RT plans (55.6%). The median mean bilateral ovary dose was 14.6 Gy (IQR 11.0-18.9). Three patients (16.7%) had a mean bilateral ovary dose less than 6 Gy. Among all 31 transposed ovaries, the median mean ovary dose was 15.5 Gy (IQR 9.6-20.2 Gy). Five ovaries (16.1%) had a mean dose less than 6 Gy. The median ovary Dmax was 32.2 Gy (IQR 24.8-46.5 Gy) and median ovary V5 Gy was 100% (IQR 85.8%-100.0%).

When comparing the radiation dose of transposed ovaries located outside (n = 20) versus any degree of overlap (or within) the PTV (n = 11), there was a significant increase in median Dmax (25.4 Gy [IQR, 11.5-32.8 Gy] vs 46.8 Gy [IQR, 37.1-47.7 Gy]; P = .0001), but no significant difference in median mean (14.2 Gy [IQR 6.1-18.9 Gy] vs 17.4 Gy [IQR, 13.6-29.3 Gy]; P = .10) or median V5 Gy dose (100% [IQR, 68.4%-100%] vs 100% [IQR, 92.4%-100%]; P = .23). Notably, among the 11 ovaries with any degree of overlap with the PTV, 3 had maximum doses less than 45 Gy (32.2 Gy, 37.0 Gy, and 37.1 Gy). The first was located just outside traditional bony field borders of a 4-field box but overlapped with the PTV contour (ie, fields were not fit to the PTV but set by bony landmarks), and the latter 2 are from a single patient treated with extended field RT (to cover the para-aortic lymph nodes) with ovary-PTV overlap volumes <0.1 cm^3, with the PTV under-covered at this interface. The location of individual transposed ovaries relative to each EBRT PTV and associated mean and max ovary dose is depicted in Figure 3.

When analyzing the relationship between the spatial location of transposed ovaries and radiation dose, there was a significant inverse correlation between CC distance of transposed ovaries to the sacral promontory and ovary mean dose (−0.72, P < .0001), Dmax (−0.74, P < .0001), and to a lesser extent V5 Gy (−0.54, P = .0018). Similar results were observed for the CC distance of transposed ovaries to the iliac crest and ovary mean dose (−0.59, P = .0004), Dmax (−0.63, P = .0002), although not V5 Gy (−0.33, P = .07). The proportion of variance in CC distance from the sacral promontory explained by ovary mean, Dmax, and V5 Gy dose was 51.6%, 54.5%, and 28.9%, respectively (Fig. 4). Although the proportion of variance in CC distance from the iliac crest explained by ovary mean, Dmax, and V5 Gy dose was only 35.2%, 39.2%, and 11.2%, respectively.

Clinical outcomes

The median clinical follow-up was 2.2 years (IQR, 0.9-4.6 years). Nine patients (50.0%) had clinical symptoms of premature ovarian insufficiency. Six patients (33.3%) had posttreatment ovarian hormonal function data available and all 6 had serologic evidence of premature ovarian insufficiency with FSH levels >40 mIU/mL. There was no difference in median mean ovarian dose between patients with or without symptoms of premature ovarian insufficiency, with doses of 15.4 Gy versus 15.5 Gy, respectively (P = .86). Similarly, we observed no significant correlation
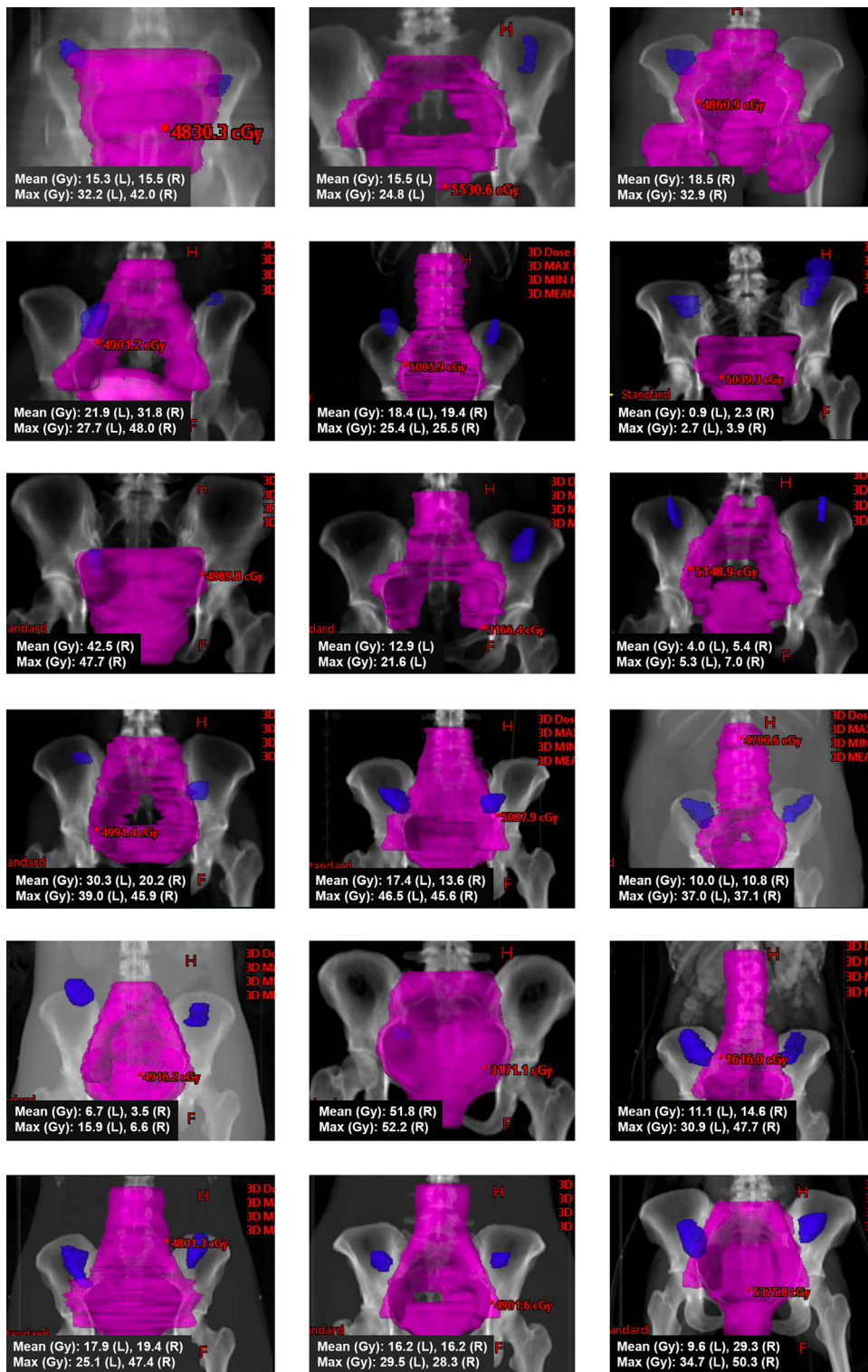
Figure 3 Individual radiation therapy planning target volumes (n = 18, magenta) and transposed ovary locations (blue). Mean and maximum radiation values displayed (in Gy) for individual ovaries.

between premature ovarian insufficiency and ovary mean, ovary Dmax, or CC distance to the sacral premontory or iliae crest (all $P > .35$). No patients became pregnant or underwent oocyte retrieval for surrogacy pregnancy after radiation therapy. Limited available data for ovarian hormonal status precluded more detailed analysis of predictors of ovarian failure, including clinical and radiation dosimetric factors.
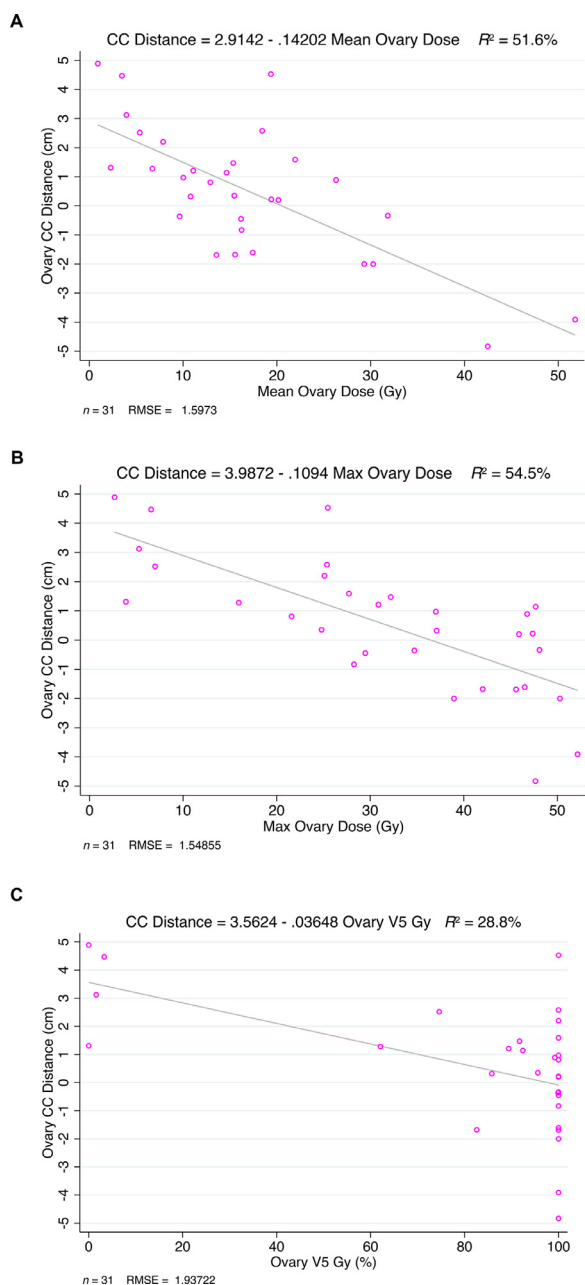
Figure 4 Relationship between (a) mean, (b) maximum, and (c) volume receiving 5 Gy ovarian radiation dose exposure and craniocaudal distance from the sacral promontory. *Abbreviations*: CC = craniocaudal; RMSE = root mean squared; V5 Gy = volume receiving 5 Gy.

Discussion

We observed that although the majority of transposed ovaries were surgically relocated outside the PTV (20/31), nearly all transposed ovaries (30/31) were below the cranial aspect of the iliac crest and received ovary doses associated with a high rate of ovarian failure (>5 Gy). There was a significant inverse correlation between ovary

CC distance from the sacral promontory or iliac crest and the median and maximum ovary RT doses. Together, these observations suggest that for patients desiring fertility or hormonal preservation, more aggressive ovary-sparing strategies may be warranted.

Several points warrant further consideration. Although larger patient cohorts have been analyzed for clinical outcomes,[14,15,19,22,27] there is a paucity of data analyzing the spatial locations of individual transposed ovaries. Indeed, we observed considerable variation in the spatial location of the ovaries after surgical transposition, despite surgical relocation as far laterally and superiorly as anatomically feasible. Notably, there are several anatomic landmarks used as reference points when measuring ovary location, the most common of which being the iliac crest.[1,28] Indeed, Hwang et al and Lv et al reported optimal distances of 1.5 cm and 1.1 cm, respectively, from the iliac crest to avoid premature ovarian insufficiency and remain outside the PTV, respectively.[25,29] More specifically, Lv et al reported an ideal distance between the ovary and PTV of >3.3 cm to achieve <4 Gy or >2.4 cm to achieve <5 Gy.[29] Similarly, we observed an optimal distance of 1.2 cm from the sacral promontory and −3.0 cm from the iliac crest to predict the ovary being outside the PTV. However, our study did observe a high proportion of ovaries receiving greater than 5 Gy, which is consistent with the median distance between ovary edge and PTV being less than 1 cm. Moreover, despite the common use of the iliac crest for an anatomic landmark in measuring ovary location, several factors can influence the precision of this measurement on CT, such as individual pelvic tilt or where along the slope of the iliac crest the measurement is obtained. We found the sacral promontory to be a useful radiographic marker for ease and consistency in measurements across scans.

Second, the cause for poor ovarian function preservation rates after transposition and pelvic RT remains unclear but is likely multifactorial. Possible mechanisms include intraoperative trauma, use of chemotherapy agents (particularly alkylating agents), variability in ovary tolerance to radiation exposure (eg, depending on baseline age and follicle status), insufficient distance from ovary to RT PTV or suboptimal ovary-sparing during RT planning, or individual patient characteristics such as medical comorbidities.[1,15,22,30-32] There is evidence that ovarian transposition alone does not increase the risk of premature ovarian insufficiency,[30] supporting the likely multifactorial nature. In addition, RT planning techniques have evolved such that improved OAR sparing may be achievable in the modern treatment era. For example, aggressive ovary sparing intensity modulated radiation therapy techniques have been explored by Kovtun et al for RT patients with lower extremity soft tissue

sarcomas. Here, the authors showed that for proximal medial thigh lesions, significant reduction in mean ovarian dose could be achieved, although this came at a cost of slightly lower plan conformality and higher bone V50.[33] Moreover, even in cases where one ovary is not spared from radiation, there is evidence of decreased incidence of premature ovarian insufficiency if the contralateral ovary is spared.[34,35] There are also emerging data suggesting potential use of proton radiation therapy in preserving ovarian function if ovaries are positioned outside the spread-out Bragg peak.[36] It should be noted that ovaries can be difficult to delineate on noncontrast planning CTs and may require careful review with other diagnostic imaging studies or discussion with an experienced radiologist to appropriately determine.

Several limitations of this study should be discussed. Our retrospective cohort size included only 18 patients and a cumulative 31 ovaries. There was limited clinical follow up (hormone and fertility status) on these patients. Indeed, posttreatment hormonal data were only available in 6 patients, and all of these patients demonstrated symptoms of premature ovarian insufficiency, suggesting labs were likely being obtained to confirm a diagnosis of premature ovarian insufficiency as opposed to monitoring for it. Furthermore, it is worth noting that although hormonal function may be preserved in a subset of patients, pelvic radiation therapy to the uterus typically precludes successful and safe intrauterine pregnancy. Thus, any preservation of fertility in these patients would be via post-RT oocyte stimulation and retrieval, with subsequent embryo transfer and surrogate pregnancy, for which there has been documented cases of success,[37,38] however higher-level data on frequency and success rates are lacking.

Conclusions

Despite most transposed ovaries being located outside the PTV, nearly all remained below the iliac crest and received RT doses associated with a high risk of ovarian failure. Thus, it is important to emphasize that ovary location adjacent or just outside the PTV may not be sufficient to meaningfully spare the ovaries during RT planning and that multidisciplinary discussion with the surgeon and radiation oncologist upfront may improve optimization, feasibility, and anticipated clinical benefit of ovarian transposition. These findings deepen our understanding of the spatial relationship between transposed ovaries and RT dose to inform surgical and pre-RT planning. Given the considerable quality of life and health benefits associated with preserved fertility or hormonal function in these patients, more aggressive ovary-sparing strategies, including optimization of surgical placement and consideration of experimental technologies, such as proton RT, are warranted.

References

1. Chambers SK, Chambers JT, Kier R, Peschel RE. Sequelae of lateral ovarian transposition in irradiated cervical cancer patients. *Int J Radiat Oncol Biol Phys*. 1991;20:1305–1308.
2. Green DM, Sklar CA, Boice Jr JD, Mulvihill JJ, Whitton JA, Stovall M, Yasui Y. Ovarian failure and reproductive outcomes after childhood cancer treatment: Results from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27:2374–2381.
3. Wallace WHB, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. *Hum. Reprod*. 2003;18:117–121.
4. Wallace WHB, 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;62:738–744.
5. Byrne J, Fears TR, Gail MH, et al. Early menopause in long-term survivors of cancer during adolescence. *Am J Obstet Gynecol*. 1992;166:788–793.
6. van der Stege JG, Groen H, van Zadelhoff SJN, et al. Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. *Menopause*. 2008;15:23–31.
7. Atsma F, Bartelink M-LEL, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: A meta-analysis. *Menopause*. 2006;13:265–279.
8. Kalantaridou SN, Naka KK, Papanikolaou E, et al. Impaired endothelial function in young women with premature ovarian failure: Normalization with hormone therapy. *J Clin Endocrinol Metab*. 2004;89:3907–3913.
9. de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol*. 2002;155:339–345.
10. Vega EM, Egea MA, Mautalen CA. Influence of the menopausal age on the severity of osteoporosis in women with vertebral fractures. *Maturitas*. 1994;19:117–124.
11. Pouillès JM, Trémollières F, Bonneu M, Ribot C. Influence of early age at menopause on vertebral bone mass. *J Bone Miner Res*. 1994;9:311–315.
12. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: Long-term health consequences. *Maturitas*. 2010;65:161–166.
13. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys*. 2009;73:1304–1312.
14. Feeney DD, Moore DH, Look KY, Stehan FB, Sutton BP. The fate of the ovaries after radical hysterectomy and ovarian transposition. *Gynecol Oncol*. 1995;56:3–7.
15. 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;74:743–748.
16. van Beurden M, Schuster-Uitterhoeve AL, Lammes FB. Feasibility of transposition of the ovaries in the surgical and radiotherapeutical treatment of cervical cancer. *Eur J Surg Oncol*. 1990;16:141–146.
17. Farber LA, Ames JW, Rush S, Gal D. Laparoscopic ovarian transposition to preserve ovarian function before pelvic radiation and chemotherapy in a young patient with rectal cancer. *MedGenMed*. 2005;7:66.
18. Husseinzadeh N, Nahhas WA, Velkley DE, Whitney CW, Mortel R. The preservation of ovarian function in young women undergoing pelvic radiation therapy. *Gynecol Oncol*. 1984;18:373–379.
19. Yin L, Lu S, Zhu J, Zhang W, Ke G. Ovarian transposition before radiotherapy in cervical cancer patients: functional outcome and the adequate dose constraint. *Radiat Oncol*. 2019;14:100.

20. Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, Jaffe N, Li FP. Ovarian failure in long-term survivors of childhood malignancy. *Am J Obstet Gynecol*. 1981;139:62–66.

21. Morice P, Castaigne D, Haie-Meder C, et al. Laparoscopic ovarian transposition for pelvic malignancies: indications and functional outcomes. *Fertil Steril*. 1998;70:956–960.

22. Pahisa J, Martínez-Román S, Martínez-Zamora MA, et al. Laparoscopic ovarian transposition in patients with early cervical cancer. *Int J Gynecol Cancer*. 2008;18:584–589.

23. Al-Badawi IA, Al-Aker M, AlSubhi J, et al. Laparoscopic ovarian transposition before pelvic irradiation: A Saudi tertiary center experience. *Int J Gynecol Cancer*. 2010;20:1082–1086.

24. Barahmeh S, Al Masri M, Badran O, Masarweh M, El-Ghanem M, Jaradat I, Lataifeh I. Ovarian transposition before pelvic irradiation: Indications and functional outcome. *J Obstet Gynaecol Res*. 2013;39:1533–1537.

25. Hwang JH, Yoo HJ, Park SH, 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;97:1387-1393.e1-2.

26. Liu X. Classification accuracy and cut point selection. *Stat Med*. 2021;31:2676–2686.

27. Turkgeldi L, Cutner A, Turkgeldi E, et al. Laparoscopic ovarian transposition and ovariopexy for fertility preservation in patients treated with pelvic radiotherapy with or without chemotherapy. *Facts Views Vis Obgyn*. 2019;11:235–242.

28. Hadar H, Loven D, Herskovitz P, Bairey O, Yagoda A, Levavi H. An evaluation of lateral and medial transposition of the ovaries out of radiation fields. *Cancer*. 1994;74:774–779.

29. Lv X-J, Cheng X-L, Tu Y-Q, Yan D-D, Tang Q. Association between the location of transposed ovary and ovarian dose in patients with cervical cancer treated with postoperative pelvic radiotherapy. *Radiat Oncol*. 2019;14:230.

30. Chambers SK, Chambers JT, Holm C, Peschel RE, Schwartz PE. Sequelae of lateral ovarian transposition in unirradiated cervical cancer patients. *Gynecol Oncol*. 1990;39:155–159.

31. Huang K-G, Lee C-L, Tsai C-S, Han C-M, Hwang L-L. A new approach for laparoscopic ovarian transposition before pelvic irradiation. *Gynecol Oncol*. 2007;105:234–237.

32. Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol*. 1999;33:2–8.

33. Kovtun KA, Yeo W-P, Phillips CH, Viswanathan A, Baldini EH. Ovary-sparing radiation planning techniques can achieve ovarian dose reduction for soft tissue sarcoma of the buttock and thigh. *Sarcoma*. 2017;2017:2796925.

34. Schuck A, Hamelmann V, Brämswig JH, et al. Ovarian function following pelvic irradiation in prepubertal and pubertal girls and young adult women. *Strahlenther Onkol*. 2005;181:534–539.

35. Clough KB, Goffinet F, Labib A, et al. Laparoscopic unilateral ovarian transposition prior to irradiation: Prospective study of 20 cases. *Cancer*. 1996;77:2638–2645.

36. Gross JP, Kim S-Y, Gondi V, et al. Proton radiotherapy to preserve fertility and endocrine function: A translational investigation. *Int J Radiat Oncol Biol Phys*. 2021;109:84–94.

37. Zinger M, Liu JH, Husseinzadeh N, Thomas MA. Successful surrogate pregnancy after ovarian transposition, pelvic irradiation and hysterectomy. *J Reprod Med*. 2004;49:573–574.

38. Giacalone P, Laffargue F, Bénos P, Dechaud H, Hédon B. Successful in vitro fertilization-surrogate pregnancy in a patient with ovarian transposition who had undergone chemotherapy and pelvic irradiation. *Fertilit Sterilit*. 2001;76:388–389.