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Assessment of transposed ovarian movement: how much of a safety margin should be added during pelvic radiotherapy?

Itaru SODA[1,*], Hiromichi ISHIYAMA[1], Shigemitsu ONO[2], Kouji TAKENAKA[1], Masahide ARAI[2], Tsutomu ARAI[2], Haruko IWASE[2], Akane SEKIGUCHI[1], Shogo KAWAKAMI[1], Shouko KOMORI[1], Takashi ONDA[2] and Kazushige HAYAKAWA[1]

[1]Department of Radiology and Radiation Oncology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minamiku, Sagamihara, Kanagawa 252-0374, Japan
[2]Department of Gynecology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minamiku, Sagamihara, Kanagawa 252-0374, Japan
*Corresponding author. Department of Radiology and Radiation Oncology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan. Tel: +81-42-778-8111; Fax: +81-42-778-8906; Email: itaruso@kitasato-u.ac.jp

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The purpose of this study was to analyze transposed ovarian movement. Data from 27 patients who underwent ovarian transposition after surgical treatment for uterine cancer were retrospectively analyzed. Computed tomography (CT) images including transposed ovaries were superimposed on other CT images acquired at different times, and were matched on bony structures. Differences in ovarian position between the CT images were measured. The planning organ at risk volume (PRV) margins were calculated from the formula of the 90% reference intervals (RIs) and the 95% RI, which were defined as mean ± 1.65 standard deviation (SD) and mean ± 1.96 SD, respectively. The 90% RI in the cranial, caudal, anterior, posterior, left and right directions were 1.5, 1.5, 1.4, 1.0, 1.7 and 0.9 cm, respectively. The 95% RI in the corresponding directions were 1.5, 2.0, 1.7, 1.2, 1.9 and 1.2 cm, respectively. These data suggest that bilateral ovaries need a PRV margin of ~2 cm in all directions. The present study suggests that a transposed ovary needs the same PRV margin as a normal ovary (~2 cm). Even after transposition, ovaries should be kept away from the radiation field to take into consideration the degree of ovarian movement.

Keywords: cervical cancer; intensity modulation radiotherapy; ovarian preservation; postoperative radiotherapy; radiation therapy; transposed ovary

INTRODUCTION

From 1990 to 2006, the number of age-specific incidence of cervical cancer increased from 7698 to 8968 in Japan. The number of incidence of cervical cancer in younger patients (<40 years) increased from 1167 to 2392 during the same period [1, 2]. The rationale behind ovarian transposition before radiotherapy is to maintain ovarian function for premenopausal patients. Decreased ovarian function may not only cause sterilization, but may also lead to osteoporosis, cardiovascular disease, depression, insomnia, hot flashes and genitourinary atrophy [3–6]. Because of these adverse events, some premenopausal patients with cervical cancer are recommended to have ovarian transposition [5–7].

The standard recommended ovarian position during radiotherapy is 4 cm outside the radiation field, or more than 1.5 cm above the iliac crest [8, 9]. However, this recommendation is based on data from the era of 2D opposite-field radiotherapy. In current clinical practice, 2D radiotherapy is being replaced by 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT). IMRT requires precise contouring and appropriate margins for respective organs in order to compensate for set-up variations and internal organ motion. Determination of an appropriate internal margin requires precise organ motion data. Although motion of the cervix, uterus, bladder, rectum and ovary have been reported [10–12], the data regarding the transposed ovary is not sufficient. The purpose of this study was to analyze transposed ovarian movement.

MATERIALS AND METHODS

This retrospective study was approved by our institutional research ethics board. Data from 27 patients who underwent ovarian transposition were retrospectively analyzed. These patients underwent CT examination (HiSpeed Advantage SG, LightSpeed QX/i, or LightSpeed Ultra 16; GE Healthcare, Little Chalfont, UK) with 1.25- to 5-mm slices after transposition (at least three times); results smaller than 5 mm were rounded up to 5 mm in the cranial and caudal directions.

Left ovaries (22 patients) and right ovaries (5 patients) were transposed to the lower paracolic gutters. Patient characteristics are shown in Table 1.

CT images including transposed ovaries were superimposed on other CT images acquired at different times, and were matched on bony structures. The first CT after ovarian transposition was defined as the reference image data. The center of the ovary was used as a representative position for each ovary. The differences in ovarian position relative to bony structures between CT images were analyzed using the treatment planning system (Pinnacle; Philips, Fitchburg, WI, USA; Fig. 1). A total of 123 images were analyzed.

The international commission on radiation units and measurements (ICRU) recommends that planning organ at risk volume (PRV) margins should be added because uncertainties and variations in the positioning of the organ at risk (OAR) during treatment must be considered to avoid serious complications [13].

The PRV margins were calculated from the formula of the 90% reference interval (RI) and the 95% RI, which were defined as the mean ± 1.65 standard deviations (SD) and mean ± 1.96 SD. Univariate and multivariate analyses were performed to assess the relationship between risk factors (age, body mass index (BMI), body weight, height, side of ovary, and interval time) and movement in six directions: cranial, caudal, anterior, posterior, left and right. CT interval was defined as the time from the first-performed CT. The standard plan for IMRT is shown in Fig. 2.

Table 1. Patient characteristics

Age (years)	36	(28–43)
Height (cm)	159	(147–165)
Body weight (kg)	52	(41.9–91.5)
Body mass index (kg/m^2)	21.1	(17.3–36.5)
Right ovary	$n = 5$	
Left ovary	$n = 22$	

Values are median (range) or number.

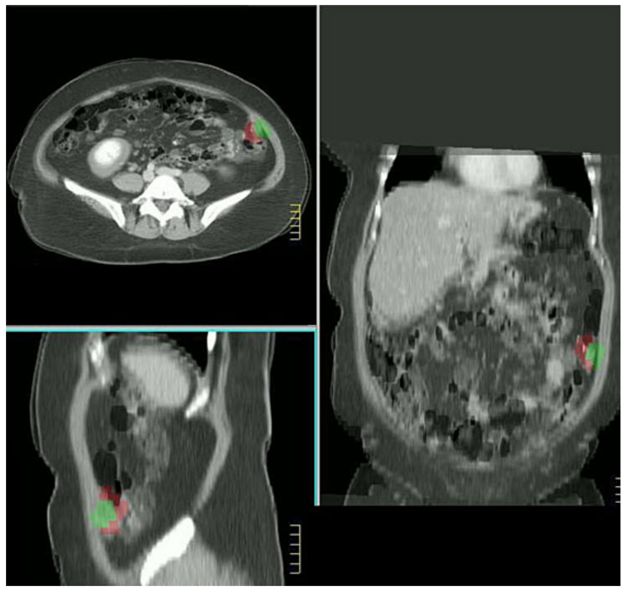

Fig. 1. Superimposed pelvic CT images. Two images taken at different times were matched on bony structures. The differences in ovarian position (red and green lines) between CT images were measured.

RESULTS

The 90% RI in the cranial, caudal, anterior, posterior, left and right directions were 1.5, 1.5, 1.4, 1.0, 1.7 and 0.9 cm, respectively. The 95% RI in the cranial, caudal, anterior, posterior, left and right directions were 1.5, 2.0, 1.7, 1.2, 1.9 and 1.2 cm, respectively.

The median interval time from the first-performed CT was 712 days (range, 36–1960 days). The interval was determined to be a significant risk factor for the caudal direction, the patient's age was determined to be a significant risk factor for the anterior and left directions, and the height was considered a significant risk factor for the caudal direction (Table 2). The interval time was only significantly associated with movement in the caudal direction in multivariate analysis.

DISCUSSION

To our knowledge, this is the first report on the movement of transposed ovaries. Peters *et al.* [12] reported the movement of normal ovaries using CT and magnetic resonance imaging (MRI) (Table 3). Their results were comparable with the results of the current study, except for smaller movement of the left ovary compared with the right ovary in their report. They hypothesized that the smaller movement of the left ovary was caused by the overlying sigmoid colon. The present study found no significant difference in movement between the left and right transposed ovaries. The present results suggest that bilateral ovaries need a PRV margin of ~2 cm in all directions.

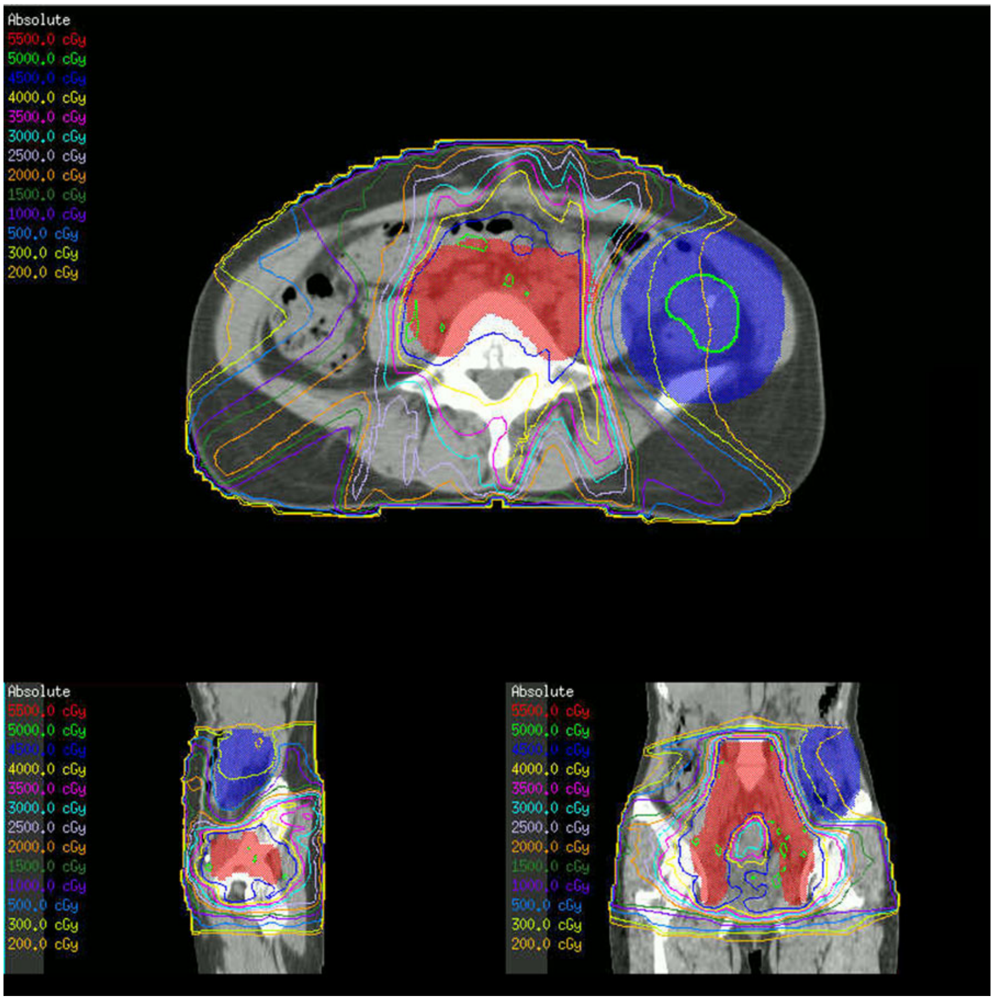

Fig. 2. Typical case of intensity-modulated radiotherapy for a cervical cancer patient. The planning target volume (PTV) was extended from the pelvic lymph node region (with a 0.8-cm margin) and the vaginal cuff region (with a 3.0-cm margin in the caudal direction) and the vaginal paracolpium (red line). The prescribed dose was 45 Gy in 25 fractions for 95% of the PTV. The minimum PTV dose was 4450 cGy, the maximum PTV dose was 4550 cGy, and the uniform PTV dose was 4500 cGy. The maximum dose to the ovarian planning organ at risk volume (PRV) was 500 cGy (blue line).

Table 2. Univariate analyses between patient characteristics and movement

	Cranial	**Caudal**	**Anterior**	**Posterior**	**Left**	**Right**
Interval time between CTs (1st and 2nd or later)	NS	$P = 0.0033$	NS	NS	NS	NS
Age	NS	NS	$P = 0.037$	NS	$P = 0.014$	NS
Height	NS	$P = 0.0075$	NS	NS	NS	NS
Body weight	NS	NS	NS	NS	NS	NS
BMI	NS	NS	NS	NS	NS	NS
Side of ovary	NS	NS	NS	NS	NS	NS

BMI = body mass index, CT = computed tomography, NS = not significant.

Table 3. Movement of transposed ovaries between CT images

			Cranial	**Caudal**	**Anterior**	**Posterior**	**Left**	**Right**
Peters *et al*. (normal ovary)	95% RI (cm)							
		Left	1.2	1.6	2.6	3.4	0.7	0.6
		Right	1.8	2.3	1.1	1.4	1.9	2.5
Present study (transposed ovary)	95% RI (cm)	Total	1.5	2.0	1.7	1.2	1.9	1.2
		Left	1.5	2.0	1.8	1.3	2.0	1.1
		Right	1.5	2.0	1.1	0.7	1.5	1.7
	90% RI (cm)	Total	1.5	1.5	1.4	1.0	1.7	0.9
		Left	1.5	1.5	1.6	1.0	1.7	0.8
		Right	1.5	2.0	1.0	0.6	1.2	1.0

RI = reference interval.

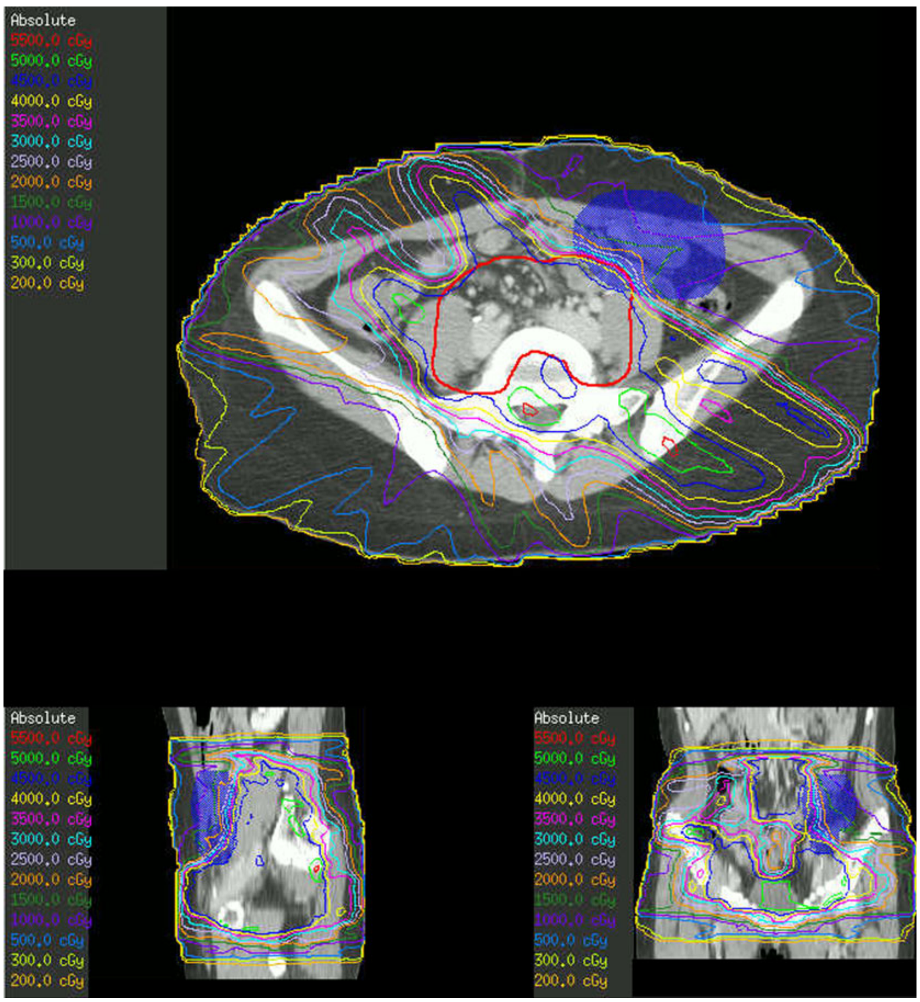

Fig. 3. There exists a small overlapping region between the planned target volume (red line) and the planning organ at risk volume (blue line). Therefore, part of the planning organ at risk volume (PRV) receives high-dose radiation.

However, this 2 cm margin would be excessively large in many cases. As shown in Fig. 3, delineation of the planning target volume (PTV) and the PRV often resulted in overlapping regions. The overlapping regions inevitably caused a high-dose area within the PRV. In the case of overlapping volumes, it is often difficult to satisfy both dose constraints and coverage of the PTV. When the patient is younger, the dose constraint of the ovarian PRV should be able to be increased. When preservation of ovarian function is required, the dose constraint of the ovarian PRV should take priority over coverage of the PTV.

Even without an overlapping region, IMRT inevitably caused higher scattered radiation than that received in conventional radiotherapy, which leads to low-dose exposure to the out-of-field area, (including the transposed ovaries). In addition, image-guidance using fluoroscopy or cone-beam CT also causes low-dose exposure to regions out of the field. Kan *et al*. [14] reported that absorbed doses of out-of-field pelvic organs were from 1–1.9 cGy per fraction of conventional fractionated radiotherapy. Therefore, it is difficult to completely exclude ovaries from the area of radiation, even if they are transposed away from the direct radiation field.

The sterilizing dose of radiation for the ovary greatly depends on the patient's age and the number of primordial oocytes. Wallace *et al.* [15] reported that the effective sterilizing dose after radiotherapy decreases with increasing age. They estimated that the sterilizing dose at birth is 20.3 Gy; at 10 years is 18.4 Gy, at 20 years is 16.5 Gy, and at 30 years is 14.3 Gy. For women in their 30 s, 5–10 Gy is required to induce amenorrhea. For women older than 40 years, 3.75 Gy can induce amenorrhea [16]. Therefore, a very limited radiation dose should be permitted for most cancer patients to avoid the above-mentioned side effects.

On the other hand, it is not certain that ovarian transposition is a safe procedure. Ovarian transposition is a procedure in which the ovaries (with their attached blood supply) are surgically detached from the uterus and transposed to an area outside the planned radiation field, away from the uterus. However, the procedure carries a 25% risk of causing ovarian cysts and a 50% risk of ovarian failure due to ischemia [17]. In addition, there are some reports of ovarian recurrences of cervical cancer following ovarian transposition, though the actual rate of ovarian recurrence is rare (1.9%) [18, 19]. Taken together, clinical decision-making needs to balance curing cancer and preventing ovarian failure.

Movement in the anterior and left directions is larger for older patients, and movement in the caudal direction is larger for taller patients.

There was no correlation between the CT interval and movement in five directions (cranial, anterior, posterior, left and right). In the current study, univariate analysis demonstrated that interfractional organ motion could be evaluated with long CT intervals. Long CT intervals were associated with increased movement in the caudal direction. CT intervals were not considered in the present study when determining the caudal margin for postoperative irradiation, because the interval was at most 5 weeks. The exact cause of the relationship between risk factors and ovarian movement was unknown.

In conclusion, the present study proposes that the PRV margin for transposed ovaries is ~2 cm in all directions. This information is essential for radiotherapy planning for patients with uterine cancer with transposed ovaries. Even after transposition, ovaries should be kept away from the radiation field and it is necessary to take into consideration the degree of ovarian movement.

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