RESEARCH ARTICLE

Ovarian Transposition for Stage Ib Squamous Cell Cervical Cancer - Lack of Effects on Survival Rates?

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Abstract

Background: To investigate the impact of ovarian transposition (OT) on survival rates of the patients with stage Ib squamous cell cervical cancer. Materials and Methods: Ninety-two subjects who underwent a radical hysterectomy including oophorectomy were evaluated. For nineteen (20.7%) , OT was performed. Patients were divided into two groups, OT versus oophorectomy alone. The primary end-point of this study was to investigate the impact of OT on tumor recurrence rate and time, 5-year disease-free survival (DFS) and overall survival (OS) . These comparisons were performed for subgroups including patients who received radiotherapy versus who did not. Statistical analyses were conducted using the Chi-square test, T-test and Mann-Whitney test. OS was examined using the Kaplan-Meier method. P≤0.05 was considered to be statistically significant. Results: The median follow-up period was 89 months for OT and 81 months for the oophorectomy group (p>0.05). Both groups experienced similar recurrence rates (31.6% vs. 26.4%, p=0.181). The median duration from surgery to recurrence, and surgery to death were also similar between the groups (p>0.05). The 5-year DFS and OS rates were both 68.4% for the OT group, and 73.6% and 77.8% for the oophorectomy group (p=0.457 and p=0.307, respectively). While the 5-year DFS rate was not statistically significant between the OT and oophorectomy groups who did not receive radiotherapy (p=0.148), the 5-year OS rate was significantly higher in the oophorectomy group (95.4% vs 66.7%, respectively) without radiotherapy (p=0.05). The 5-year DFS and OS rates were statistically similar between the groups who received adjuvant radiotherapy (p>0.05). Conclusions: Ovarian transposition has not significantly negative effect on the survival rates when adjuvant radiotherapy will be applied, while 5-year OS may be less in OT group if radiotherapy is not mandatory.

Keywords: Cervical cancer - ovarian transposition - survival rate

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Introduction

An ovarian-sparing radical hysterectomy has become a standard procedure for the treatment of early stage cervical cancer in young women in order to preserve ovarian hormonal function (Morice et al., 2000). For this procedure, the ovaries, normal to inspection and palpation, are transposed and fixed outside of the pelvis to the paracolic space higher than 1.5 cm above the iliac crest in order to be outside of an applied radiation field (Hwang et al., 2012). This is intended to protect ovaries from postoperative pelvic radiation, and the safety of this procedure has been reported (Windbichler et al., 1999; Pahisa et al., 2008). However, complications associated with ovarian transposition (OT) procedures have included chronic ovarian pain, and reports of metastasis to the transposed ovaries (Rasool and Rose, 2010).

The risks of ovarian involvement, especially for early squamous lesions of the cervix, are extremely rare. Moreover, a gonadectomy is typically not required in the absence of visible metastases. While Tabata et al. previously reported that metastatic spread to the ovary is associated with more advanced tumors and has been associated with a frequency as high as 17.4% in autopsy cases of epidermoid carcinoma (Tabata et al., 1987), generally, ovarian metastasis is identified in less than 1% of all cases involving squamous cell carcinoma (Morice et al., 2001; Yamamoto et al., 2001).

Typically, OT is performed for patients who are below 40 years, have a small invasive cervical carcinoma (<3 cm, or stage Ib or II) that can be treated with a combination of radiotherapy and surgery, and have an absence of other risk factors for ovarian metastases (Yamamoto et al., 2001). The risk factors for ovarian metastases and criteria for transposition of the ovaries include uterine corpus invasion, a non-squamous histological type,

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and lymphovascular space invasion (LVSI) (Morice et al., 2001; Yamamoto et al., 2001). Nonetheless, there is ongoing debate about the effectiveness of ovarian transposition with respect to protecting gonadal functions and metastasis to the transposed ovaries (Dursun et al., 2009) and there are very few studies that have evaluated the prognosis of OT in cervical cancer (Windbichler et al., 1999) Therefore, the impact of OT on survival rates for patients with stage Ib squamous cell cervical cancer (SCCC) was investigated in this study.

Materials and Methods

In this observational study, medical data for 92 patients diagnosed with stage Ib cervical cancer between 1993 and 2007 in a single, tertiary center, who underwent a type III radical hysterectomy and systematic bilateral pelvic and para-aortic lymphadenectomy, were reviewed. These patients also had a pathological diagnosis of squamous cell cancer confirmed, and did not receive neoadjuvant chemotherapy. This study was approved by the Local Ethics Committee of the Hospital.

Patients were clinically staged according to the FIGO staging system. Patients who were treated before 1995 were re-staged as Ib1 and Ib2.

High-risk patients received radiotherapy following radical surgery (n=65; 70.7%). Prior to 2001, major criteria for radiotherapy included positive lymph nodes, parametrial invasion, surgical margin involvement, and tumor size ≥4 cm. Additional considerations included lymphovascular space involvement (LVSI), stromal invasion >½, a tumor size from 2-4 cm, and >2 microscopic metastatic lymph nodes. After 2001, adjuvant radiotherapy was applied when at least one positive lymph node, parametrial invasion, or surgical margin involvement was detected.

In 20.7% cases (19/92), the ovaries were fixed to the abdominal lateral walls over the pelvic girdle and outside the radiotherapy area. The regions were marked with endoclips. In 18 of these cases, both ovaries were transposed, and in one case, only one ovary was repositioned and the other ovary was removed.

Patients were divided into two groups according to the procedure performed, OT or oophorectomy. The primary end-point of this study was to investigate the impact of OT on survival rates for patients with stage Ib SCCC. For these patient groups, tumor recurrence, 5-year disease-free survival (DFS) rates, and overall survival (OS) rates were analyzed. In additional, these comparisons were done for the subgroups included the patients who received radiotherapy versus who did not.

SPSS version 17.0 software (SPSS, Chicago, IL, USA) was used for statistical analyses. Categorical variables between groups were compared using the Chi-square test, and differences between groups were analyzed using t-tests for normally distributed variables. For non-normally distributed data, the Mann-Whitney test was used. OS was examined using the Kaplan-Meier method. P≤0.05 was considered to be statistically significant.

Results

The median age of this cohort was 49.0 years (range, 30-78), and the median tumor size was 30 mm (range, 5-45). For 92.4% (n=85) cases, a stage Ib2 diagnosis was established. In addition, 30.4% (28/92) patients were associated with pelvic lymph node metastases, while 4.3% (4/92) patients experienced para-aortic metastases. For two of the patients with para-aortic lymph node metastases, lymph node metastasis was not detected in the pelvic region. Ovarian metastasis was not detected in any of the patients treated with oophorectomy. Surgical pathologic factors for the cohort are listed in Table 1.

A total of 73 patients underwent oophorectomy, and 19 patients underwent OT. There was also one patient from the oophorectomy group who died due to a pulmonary embolism within the first month following the procedure. This patient was not considered during the survival analysis.

The median follow-up period was 89 (range, 8-183) months for OT group and 81 (range, 9-179) months for oophorectomy group. During the follow-up period,

Table 1. Surgical, Pathologic and Follow-up Features of the Cohort

Age*		49 (30-78)
Tumor size (mm) *		30 (5-45)
Ovarian status**:	Ovarian transposition	19 (20.7)
	Bilateral oophorectomy	73 (79.3)
Stage**:	IB1	85 (92.4)
	IB2	7 (7.6)
Grade**:	1	9 (9.8)
	2	80 (87.0)
	3	3 (3.3)
Parametrial invasion**		
	Negative	81 (88)
	Positive	11 (12)
Surgical border invasion**		
	Negative	87 (94.6)
	Positive	5 (5.4)
Lymphovascular space invasion**		
	Negative	38 (41.3)
	Positive	54 (58.7)
Stromal invasion**		
	< ½	34 (37)
	> ½	58 (63)
Number of removed LN*		52 (18-102)
Pelvic LN metastasis**		
	Negative	64 (69.6)
	Positive	28 (30.4)
Para-aortic LN metastasis**		
	Negative	88 (95.7)
	Positive	4 (4.3)
Adjuvant radiotherapy**		
	Not received	27 (29.7)
	Received	64 (70.3)
Follow-up (months) *		82 (8-183)
Recurrence**:	No	66 (72.5)
	Yes	25 (27.5)
Time to recurrence (months) *		11 (3-66)
Last status**:	Living	69 (75)
	Deceased	23 (25)
Time to death (months) *		17 (8-83)

*Median (range), **n (%), LN: Lymph node

Table 2. Surgical Factors and Follow-up Comparisons of the Two Treatment Groups

		Ovarian transposition (n =19)	Bilateral oophorectomy (n =73)	p
Age*		39 (30-47)	50 (37-78)	< 0.001
Tumor size (mm)*		30 (5-45)	30 (5-45)	0.665
Number of removed LN*		52 (18-93)	53 (20-102)	0.900
Stage**	IB1	17 (89.5)	68 (93.2)	0.590
	IB2	2 (10.5)	5 (6.8)	
Grade**	1	1 (5.3)	8 (11.0)	0.485
	2	18 (94.7)	62 (84.9)	
	3	-	3 (4.1)	
Pelvic LN metastasis**				
	Negative	14 (73.7)	50 (68.5)	0.661
	Positive	5 (26.3)	23 (31.5)	
Para-aortic LN metastasis**				
	Negative	18 (94.4)	70 (95.9)	0.826
	Positive	1 (5.3)	3 (4.1)	
Parametrial invasion**	Negative	17 (89.5)	64 (87.7)	0.829
	Positive	2 (10.5)	9 (12.3)	
Surgical border invasion**				
	Negative	18 (100)	68 (93.2)	0.241
	Positive	-	5 (6.8)	
Lymphovascular space invasion**				
	Negative	8 (42.1)	30 (41.1)	0.937
	Positive	11 (57.9)	43 (58.9)	
Stromal invasion**	< 1/2	9 (47.4)	25 (34.2)	0.291
	> 1/2	10 (52.6)	48 (65.8)	
Adjuvant radiotherapy**				
	Not received	6 (31.6)	21 (29.2)	0.811
	Received	13 (68.4)	51 (70.3)	
Follow-up (months) *		89 (8-183)	81 (9-179)	0.976
Recurrence**	No	13 (68.4)	53 (73.6)	0.980
	Yes	6 (31.6)	19 (26.4)	
Time to recurrence (months) *		4 (3-15)	14 (6-66)	0.078
Last status**	Living	13 (68.4)	56 (77.8)	0.477
	Deceased	6 (31.6)	16 (22.2)	
Time to death (months) *		18 (8-35)	17 (9-83)	0.322

*Median (range), **n (%), LN: Lymph node

27.5% (25/91) patients developed tumor recurrence, and 23.9% (n=22) patients died. For two of the cases involving recurrence, the patients responded positively to chemotherapy, currently remain disease-free, and had both undergone an oophorectomy.

For the patients who experienced tumor recurrence, the median time from treatment to recurrence was 11 months (range, 3-66), and the median time between treatment and death was 17 months (range, 8-83).

Patients undergoing Ovarian Transposition vs. Oophorectomy

The surgical pathologic factors and rate of adjuvant radiotherapy for the patients who underwent OT or oophorectomy were similar, except for age. The median age of the patients who underwent OT was significantly lower than of the oophorectomy group (39 vs. 50 years, p< 0.001) (Table 2).

Tumor recurrence and death were determined earlier in the OT group compared with the oophorectomy group. The median duration from surgery to recurrence, and surgery to death, was 4 months (range, 3-15) and 18 months (range, 8-35) versus 14 months (range, 6-66) and 17 months (range, 9-83), respectively in each case. However, these differences were not statistically significant (p=0.078 and p=0.322, respectively).

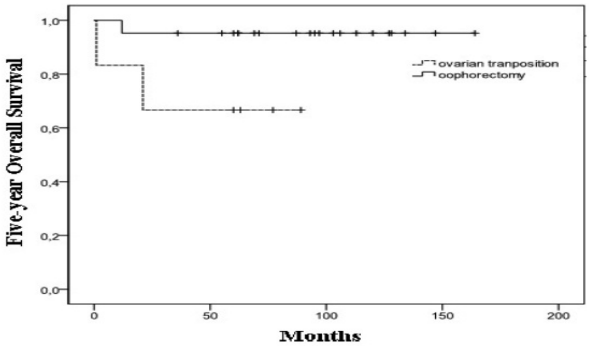

Figure 1. Five-year OS Rates of the Patients who Underwent Ovarian Transposition or Oophorectomy

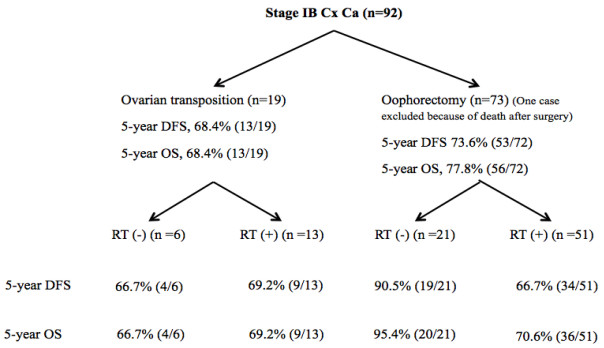

Figure 2. 5-year Disease-Free Survival (DFS) and Overall Survival (OS) Rates of the Subjects According to Main Groups and Subgroups (RT; Radiotherapy)

For 31.6% (6/19) patients who underwent OT, tumor recurrence was detected. In 5 cases central recurrence (in the vaginal cuff) developed, and in the other case, pulmonary metastasis was observed. For the oophorectomy group, 26.4% (19/72) cases involved tumor recurrence. Of these cases, 10/19 were observed in the pelvic region, while 9/19 were distant from the primary site. Both groups experienced similar rates of distant recurrence (p=0.181).

The survival rates were also similar for the two treatment groups (Figure 1). The 5-year DFS and OS rates were same (68.4%) for the OT group, and 73.6% and 77.8% for the oophorectomy group (p=0.457 and p=0.307, respectively) (Figure 2).

Patients received vs. did not receive radiotherapy

A total of 27 patients did not receive radiotherapy. Of these patients, 6 underwent OT and 21 patients underwent bilateral oophorectomy. Furthermore, the 5-year DFS rate was 66.7% (4/6) for the OT group and 90.5% (19/21) for the oophorectomy group who did not receive radiotherapy. However, this difference was not statistically significant (p=0.148). In contrast, the 5-year OS rate was higher for the oophorectomy group (66.7% vs. 95.4%, respectively), and this difference between the OS rates was at the borderline of being statistically significant in the cases who did not receive radiotherapy (p= 0.05) (Figure 2).

Sixty-four cases (13 in OT group and 51 in oophorectomy group) received radiotherapy. 5-year DFS and OS rates were same (69.2%, 9/13) in OT group, while these rates were 66.7% (34/51) and 70.6% (36/51) in oophorectomy group who received radiotherapy after surgery. The 5-year DFS and OS rates were statistically

similar between the groups who received adjuvant radiotherapy (p>0.05) (Figure 2).

Discussion

In this study, the 5-year DFS and OS rates were approximately 5% and 9% lower for patients whose ovaries were preserved during a radical surgery for SCCC compared to patients who underwent oophorectomy, however these differences were not statistically significant.

Initially, none of the patients who underwent oophorectomy had tumors present in their ovaries. Moreover, for recurrences who did develop, similar sites were detected in the two treatment groups. The two groups were also associated with similar surgical pathologic factors and rates of adjuvant radiotherapy. Not surprisingly, only patient age varied between the two groups, with patients undergoing OT being younger. As such, age needs to be considered as one of the factors that affect patient survival following OT. Patient age has also been shown to be an independent prognostic factor in cases of cervical cancer, with a decrease in recurrence rate and an increase in survival rate associated with advanced age (Turan et al., 2010). However, other studies have indicated that a younger age is an advantage for survival (Chen et al., 1999; Bulk et al., 2003) and that age has not any prognostic value on survival rate (Ho et al., 2004; Behtash et al., 2009).

Although the laparotomic approach has been used as a parallel to development in endoscopic surgery, nowadays it is generally performed laparoscopically or through robotic procedure (Pahisa et al., 2008; Al-Badawi et al., 2010). In our study, the procedure was carried out in all cases during laparotomy.

In cases of early stage cervical cancer with squamous cell types, less than 1% involve tumor spread to the ovaries (Morice et al., 2001; Yamamoto et al., 2001; Shimada et al., 2006). For example, Morice et al. (2001) evaluated 107 cases of SCCC involving OT, and only two cases developed metastases in the ovaries (Morice et al., 2001). Moreover, the period for this recurrence was three years in each case. In cases of cervical adenocarcinoma, the reported rates of ovarian metastases vary widely from 1.7-28.6% (Tabata et al., 1987; Nakanishi et al., 2001; Yamamoto et al., 2001; Shimada et al., 2006). Moreover, a non-squamous histological type has been identified as an independent risk factor for ovarian metastases in cervical cancer (Yamamoto et al., 2001). In the present study, it is possible that the negative effect of OT on patient survival was due to microscopic metastases present in the ovary at the time of original surgery. However, recurrence was detected in the vaginal cuff in five of the cases that involved OT, and this is inconsistent with the spread of cervical cancer to the ovary. It is also important to note that the present study only included SCCC. Because of ovarian metastasis is more in cervical adenocarcinoma than in cervical cancer with squamous cell type as well as very small number of patients with cervical adenocarcinoma in which OT perform, the patients with cervical adenocarcinoma were not taken into consideration for analysis in the present study. This may be considered a limitation of our study.

Estrogen has been hypothesized to induce gene transcription via intracellular receptors that have the capacity to bind specific regions of DNA. This effect on transcription could initiate the neoplastic process, or aggravate an already established transition (Moodley et al., 2003). This is a situation that could also contribute to the negative impact of OT on patient survival in cases of cervical cancer. Estrogen has also been shown effect to the motility and invasiveness of cancer cells (Sanchez et al., 2010). However, in the current study, information regarding the estrogen levels of the patients that underwent OT, and about 70% of the patients that received adjuvant radiotherapy, were not available. Therefore, it can only be hypothesized that estrogen was a contributing factor to the survival rates associated with the OT group in this study.

To date, there are very few studies that have evaluated the prognosis of OT in cervical cancer. However, a retrospective study by Windbichler et al. (1999) is of note. In their study, 150 patients who underwent oophorectomy were compared with 150 patients who did not undergo oophorectomy, and the ovaries were retained in the pelvis. Furthermore, only 28 of the 300 patients received radiotherapy. As expected, the age of the patients who retained their ovaries was markedly lower than the patients who underwent oophorectomy (36 vs. 47 years, respectively) such as supported from the current study. For the cases with the ovaries preserved, the 5- and 10-year DFS rates were 95% and 94%, respectively, while the rates for the oophorectomy group were 97% and 93%, respectively. Similarly, the 5- and 10-year OS rates were 98% and 96% vs. 97% and 97%, respectively in each case. Windbichler et al. (1999) also noted that 1.3% of patients who underwent conservation of ovaries eventually needed an oophorectomy due to benign pathologies obtained. However, no specifics were provided regarding the sites of recurrence.

In the current study we compared the survival rates for the subgroups considering whether they received radiotherapy or not. Despite the relatively small number of cases, who did not receive radiotherapy, and although the difference was borderline significant between the oophorectomy and OT cases in this subgroup, the 5-year OS rate for this subgroup was approximately 30% higher (66.7% vs. 95.4%) for the oophorectomy group than the OT group. Especially, this state should be considered and discussed with the patients before OT performed. However, this difference was not present between the OT and oophorectomy groups that both received adjuvant radiotherapy. This fact may be explained with the ovarian failure and decrease in estrogen levels can be occurred after radiotherapy. The incidence of ovarian failure in patients that underwent radiotherapy following transposition has been reported to vary from 28-50% (Monk and Tewari, 2007).

Despite ovarian preservation being a widely performed and safe procedure for young women undergoing surgical treatment for cervical cancer, the impact of this procedure on patient survival has not been clearly established. In the present study, while the survival rates were similar in patients who underwent OT compared with oophorectomy,

with all of the cases involving early stage cervical cancer of a squamous cell type, the 5-year OS rate was less about 30% in the subgroup, who did not receive radiotherapy in which the ovaries were preserved.

Therefore, the theoretical benefits of OT and the risk of ovarian metastasis overcomes should be carefully considered and discussed with patients. Both the possible risks and the results of well-designed, prospective studies of ovarian function should be presented. Correspondingly, it will also be important for future studies to monitor individual patients with preserved ovaries following surgical treatment for cervical carcinoma.

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