Oncological Outcomes and Safety of Ovarian Preservation for Early Stage Adenocarcinoma of Cervix: A Systematic Review and Meta-Analysis

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Objectives: To evaluate the oncological outcomes and safety of ovarian preservation, and to review the prognostic factors for ovarian metastases in early stage cervical adenocarcinoma.

Methods: PubMed, Embase, and Cochrane databases were searched for publications up to January 2019. Two investigators independently screened the studies for eligibility and extracted specific data. The primary outcomes were overall survival (OS) and progression-free survival (PFS). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using STATA statistical software version 19.0.

Results: A total of 68 unique manuscripts were identified through the search strategy, and 10 studies were included in the meta-analysis of the safety of ovarian preservation. Fixed-effects model was used because of moderate heterogeneity. Pooled results of the included studies showed that ovarian preservation is not associated with a statistically significant OS (OR 1.00, 95% CI 0.64–1.56, $I^2 = 25.7\%$) or PFS (OR 0.98, 95% CI 0.57–1.66, $I^2 = 0\%$) in early stage cervical adenocarcinoma. In addition, 19 studies were included in the review of prognostic factors for cervical adenocarcinoma and risk factors for ovarian metastases. The incidence of ovarian metastases was 0% in stage IA, 2.8% in stage IB, 3.4% in stage IIA, and 11.8% in stage IIB cervical adenocarcinoma. International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, deep stromal invasion (DSI), lymph node metastasis (LNM), and vaginal invasion were significantly related to poor prognosis. Risk factors associated with ovarian metastases included age, FIGO stage, tumor size, DSI, parametrial invasion, corpus uteri invasion, LNM, vaginal invasion, and blood vessel invasion.

Conclusions: Ovarian preservation in young patients with early stage cervical adenocarcinoma is safe and has no significant effect on OS or PFS. Preserving ovaries in patients with FIGO stage IIB seems not reasonable because of the high rate of ovarian metastasis.

Keywords: cervical cancer, adenocarcinoma, ovarian preservation, outcome, risk factors
INTRODUCTION

Cervical cancer incidence has been declining for the past several decades worldwide because of the successful implementation of screening programs (1, 2). However, the proportion of young patients with early stage cervical cancer, especially adenocarcinoma, is increasing greatly (3). According to the report of the American Cancer Society (4), cervical cancer continues to be the second leading cause of cancer death in women aged 20–39 years (nine deaths per week were recorded in this age group). Adenocarcinoma accounts for ~28% of all cervical cancer cases (5). Adenocarcinoma in cervical cancer even reached to 40% in women aged ≤25 years in a recently published study (6). Conservation of ovarian endocrine function or fertility sparing is greatly desirable in this group of young patients.

Unlike squamous cell carcinoma (SCC), cervical adenocarcinoma is believed to be more aggressive and may have an inclination of blood vessel invasion, deep stromal invasion (DSI), and lymph node metastases (LNM) (7). Nevertheless, a recent study showed that early stage cervical adenocarcinoma has a good prognosis, and the 5-year survival rate is >80% (8). In the study of Kasamatsu et al. (9), no significant difference in survival or relapse between SCC and adenocarcinoma was found.

Ovarian preservation in early stage SCC has been well-established since McCall et al. (10) firstly presented it in 1958. However, no consensus about the safety of ovarian preservation in cervical adenocarcinoma exists. Studies showed that the incidence of ovarian metastases in early stage adenocarcinoma is higher than that in SCC, but mostly lower than 5% (11–15), and a few studies reported slightly high, which were 10.2% (16) and 12.9% (17). Radical bilateral salpingo-oophorectomy sacrifices endocrine function while possibly eliminating the concealed lesions in the ovaries. Young patients experience menopausal symptoms including immediate hot flashes, vaginal atrophy, osteoporosis, and emotional problems, earlier than expected (18). Performing the least aggressive procedure without sacrificing oncologic safety is vital for young women diagnosed with early stage cervical adenocarcinoma.

In this study, we systematically reviewed all available relevant studies and conducted a meta-analysis to evaluate the oncological outcomes and safety of ovarian preservation. In addition, we summarized the prognostic factors for cervical adenocarcinoma and risk factors for ovarian metastases.

MATERIALS AND METHODS

Search Strategy

PubMed, Embase, and Cochrane databases were searched for publications up to January 2019. We used the following search terms in the title or abstract: “cervical neoplasm,” “adenocarcinoma,” “ovarian preservation,” and “ovarian conservation.” Both free words and Emtree terms were applied in the search. The language was limited to “English” and the object to “human” (Supplementary Data Sheet 1).

Inclusion and Exclusion Criteria

Studies were included in this meta-analysis if: (1) the diagnosis of cervical adenocarcinoma based on International Federation of Gynecology and Obstetrics (FIGO) stage I or II adenocarcinoma of cervix; (2) they were prospective, retrospective cohort, or cross-sectional original studies; (3) they included at least 10 patients; (4) at least one outcome, such as overall survival (OS) or progression-free survival (PFS) was assessed; (5) the odds ratios (ORs) and their 95% confidence intervals (95% CIs), or the number of events used to calculate them was reported.

The inclusion criteria for the review of prognostic factors for cervical adenocarcinoma and risk factors for ovarian metastases were as follows: (1) original studies that reported the ovarian metastasis rate of FIGO stage I or II cervical adenocarcinoma; (2) studies that evaluated the prognostic factors for cervical adenocarcinoma or risk factors for ovarian metastases using a statistical analysis.

Studies were excluded if they meet following criteria: (1) review articles or case reports with fewer than 10 cases; (2) lack of sufficient data to estimate OR and 95% CI; (3) reporting duplicate or overlapping data; (4) without full text.

Data Extraction

The following information was extracted from each eligible study: first author’s name, published year, study design, country, patients’ mean age, FIGO stage, number of patients, number of patients who underwent hysterectomy and oophorectomy/ovarian preservation, incidence of ovarian metastases, and data on OS and/or PFS. Two investigators (CHY and ZLJ) extracted the data independently, and any discrepancies and disagreements were discussed and resolved by the adjudicating senior author (YJJ).

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale for case-control studies was used to evaluate the included studies. Selection, comparability, and exposure were measured. A maximum of nine stars was assigned to each study: 4 for selection, 2 for comparability, and 3 for exposure. A final score > 6 was considered as a high quality (19, 20). Two authors (KYJ and HLQ) independently assessed the quality of the included studies and disagreements were resolved by discussion (Supplementary Table 1).

Statistical Analysis

Survival data, including OS, PFS, and time-to-event were calculated as dichotomous data. STATA statistical software version 19.0 (Stata Corp. LLC, College Station, TX, USA) was used to pool the study-specific ORs and 95% CIs and generate forest plots. Cochran’s Q test and I^2 statistics were used to evaluate heterogeneity (21). Heterogeneity was considered significant when the P-value < 0.05 in Cochran’s-Q test and when I^2 > 50% in I^2 statistics. If so, random-effects model was used. Otherwise, a fixed-effects model was used. Publication bias was evaluated by funnel plots. Sensitivity analysis was performed by omitting one study at a time to assess its effect on the final result.
RESULTS

Search Results and Study Characteristics
In total, 68 unique manuscripts were identified through the search strategy, and 10 studies were included in the meta-analysis of the safety of ovarian preservation. The reasons for excluding records are depicted in Figure 1. A total of 19 studies were included in the review of prognostic factors for cervical adenocarcinoma and risk factors for ovarian metastases based on the inclusion and exclusion criteria. The included studies were all retrospective in nature, and detailed characteristics of the 10 studies are presented in Table 1 (7, 9, 12, 13, 22–28).

Oncological Outcomes
In the meta-analysis, no heterogeneity in OS and PFS among the studies was found, thus, a fixed-effects model was used. Based on the pooled results from the included studies, ovarian preservation is not associated with a statistically significant OS (OR 1.00, 95% CI 0.64–1.56, $I^2 = 25.7%$; Figure 2) or PFS (OR 0.98, 95% CI 0.57–1.66, $I^2 = 0%$; Figure 3) in early stage cervical adenocarcinoma. Subgroup analysis (Figures 4, 5) and funnel plot results (Figures 6, 7) showed that our study has a low risk of publication bias. No significant changes in the final result, after each study was omitted sequentially, were observed (Figure 8).

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**TABLE 1 | Characteristics of studies included in the meta-analysis.**

| Author          | Year | Study period | Country | Mean age (Y) | FIGO stage | No. patients | Ovarian preservation (n) | Oophorectomy (n) | Rate of ovarian metastases | Survival outcome reported |
|-----------------|------|--------------|---------|--------------|------------|--------------|--------------------------|-----------------|---------------------------|-------------------------|
| Hopkins et al.  | 1987 | 1970–1984    | US      | NA           | I          | 24           | 8                        | 16              | 0/16                      | OS                      |
| Angel et al.    | 1992 | 1966–1990    | US      | 47           | I          | 59           | 41                       | 18              | 0/41                      | OS, PFS                 |
| Sutton et al.   | 1992 | 1981–1984    | GOG     | NA           | I          | 121          | 41                       | 80              | 2/80 (2.5%)               | PFS                    |
| Kasamatsu et al.| 2009 | 1984–2003    | Japan   | 48           | I–II       | 123          | 22                       | 100             | 6/100 (6%)                | OS, PFS                 |
| Chen et al.     | 2016 | 1999–2013    | China   | 43.6         | I–II       | 194          | 33                       | 153             | 5/153 (3.3%)              | OS, PFS                 |
| Ruengkhachorn et al. | 2016 | 2006–2013        | Thailand | 44.9         | I          | 35           | 16                       | 19              | 0/19                      | PFS                    |
| Matsuo et al.   | 2017 | 1983–2012    | SEER    | 45.3         | I          | 4,019        | 960                      | 3,059           | NA                        | OS                     |
| Hu et al.       | 2017 | 1994–2015    | China   | 46.2         | I–II       | 105          | 19                       | 86              | 3/86 (3.5%)               | OS                     |
| Xie et al.      | 2018 | 2003–2015    | China   | 44.3         | I–II       | 128          | 15                       | 113             | 1/113 (0.9%)              | OS                     |
| Guo et al.      | 2018 | 1995–2017    | China   | 45.6         | I–II       | 267          | 44                       | 223             | 13/223 (5.8%)             | PFS                    |
| Total           | –    | –            | –       | 45.6         | –          | 5,075        | 1,199                    | 3,867           | 30/831 (3.61%)            | –                      |

FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; NA, not available; OS, overall survival; PFS, progression free survival.
Prognostic Factors for Cervical Adenocarcinoma and Risk Factors for Ovarian Metastases

Table 2 shows the results of the literature review. The incidence of ovarian metastases was 0% in stage IA, 2.8% in stage IB, 3.4% in stage IIA, and 11.8% in stage IIB cervical adenocarcinoma. Five studies (7, 9, 12, 22, 26) showed that FIGO stage, tumor size, DSI, LNM, and vaginal invasion are significantly related to poor prognosis. Nine studies (7, 14, 16, 17, 29–34) reported that age, FIGO stage, tumor size, DSI, parametrial invasion (PMI), corpus uteri invasion (CUI), LNM, vaginal invasion, and blood vessel invasion are significantly associated with ovarian metastases.

DISCUSSION

In this review and meta-analysis on the prognostic significance of ovarian preservation in early stage cervical adenocarcinoma, we found that ovarian preservation is not associated with a statistically significant OS or PFS in early stage cervical adenocarcinoma. Ovarian preservation has no adverse effect on the prognosis in early stage cervical adenocarcinoma (7, 24, 28). Moreover, the overall incidence of ovarian metastases is 0% in stage IA, 2.8% in stage IB, 3.4% in stage IIA, and 11.8% in stage IIB cervical adenocarcinoma, which are extremely low except that in stage IIB disease. Although some studies (11, 14, 17) proved that ovarian metastases are more
common in cervical adenocarcinoma than in SCC, patients with early stage adenocarcinoma or SCC who underwent radical hysterectomy have a similar prognosis and spread pattern according to the study of Kasamatsu et al. (18). A consensus that ovarian preservation is safe in stage IA cervical adenocarcinoma was reached because the rate of ovarian metastases was 0% in numerous studies (7, 23, 29, 32, 33). In addition, ovarian preservation also appears safe in patients with cervical adenocarcinoma that is earlier than stage IIA because ovarian metastases are rare (2.8% in stage IB, and 3.4% in stage IIA in our review). Furthermore, previous studies reported no significant difference in OS after ovarian preservation among patients...
with SCC and adenocarcinoma whose disease stage is earlier than stage IIA (13, 15). Notably, ovarian preservation must be performed carefully in stages IB and IIA because studies showed that tumor size >4 cm is related to a poorer prognosis (7, 9). For stage IIB cervical adenocarcinoma, ovarian preservation is inappropriate because of a high risk of ovarian metastases (11.8% in this review). These cases probably accompanied with other factors that are related to poor prognosis, included LNM, CUI, PMI, and DSI (7, 9).

The FIGO clinical staging system of cervical cancer has been constantly updated. Imaging and pathology have been recently used to supplement clinical findings with respect to tumor size and extent (35). The most obvious change in the different versions of the staging system is related to tumor size (≤ 2 cm, 2–4 cm, and > 4 cm), which could be because numerous studies showed that tumor size is an independent prognostic factor for OS in cervical cancer (7, 9, 36). In the retrospective study and meta-analysis of Hu et al. (30), they suggested that tumor size > 4 cm are associated with ovary metastasis. Notably, according to the latest 2018 FIGO staging system, the risk in cervical cancer mortality in stage IB2 disease increased by nearly 2-fold compared to that in IB1 disease, which suggests that identifying the tumor size (i.e., ≥ 2 or < 2 cm) is necessary when deciding whether to preserve ovaries or not (35).

For many years, ovaries were sacrificed in radical surgery for cervical cancer. However, there has been increasing awareness of the value of retaining the ovaries maintain a sense of well-being among young women. Premenopausal castration could cause immediate menopause, early hot flashes, and vaginal atrophy, as well as a number of long-term consequences, including an increased risk of cardiovascular disease, osteoporosis, hip fracture, Alzheimer’s disease, and emotional problems (37). Hence, patients would need long-term menopause hormonal therapy (MHT) to alleviate the symptoms, let alone the poor compliance and high expense of MHT (38). Maintenance of ovarian function is beneficial to the physiologic and psychosexual health of young patients without significantly increasing their risk of relapse.

Another concern of ovarian preservation is its safety. In our review, the incidence of ovarian metastases is extremely low in patients who underwent oophorectomy, except that in stage IIB cervical adenocarcinoma. A study of Greer et al. (39) including 45 patients with stage IB cervical adenocarcinoma who had ovarian

![Funnel plots of OS show a low risk of publication bias.](image1)

![Funnel plots of PFS show a low risk of publication bias.](image2)

![Sensitivity analysis of OS (A) and PFS (B) show that no significant changes in the final result after each study was omitted sequentially.](image3)
TABLE 2 | Overview of prognostic factors for cervical adenocarcinoma and risk factors for ovarian metastases reported in the studies.

| Author          | Year | No. of patients | Stage | Rate of ovarian metastases | Variables included in multivariate analysis |
|-----------------|------|-----------------|-------|-----------------------------|---------------------------------------------|
|                 |      |                 |       |                             | Age FIGO stage Tumor size Deep stromal invasion Parametrial invasion Corpus uteri metastasis Lymph node invasion Vaginal invasion Blood vessel invasion |
| Xie et al. (26) | 2018 | 128             | IA-IB | 1/113 (0.9%)                | *                                            |
| Kasamatsu et al. (9) | 2009 | 123             | I     | 1/87 (1.15%)                | *                                            |
|                 |      |                 | IIA   | 0                           | *                                            |
|                 |      |                 | IIIB  | 3/22 (13.6%)                | *                                            |
| Angel et al. (12) | 1992 | 59              | I     | 0/41                        | *                                            |
| Hopkins et al. (22) | 1987 | 24              | I     | 0/16                        | *                                            |
| Chen et al. (7) | 2016 | 194             | IA    | 0/9                         | *                                            |
|                 |      |                 | IIB   | 1/100 (2%)                  | *                                            |
|                 |      |                 | IIA   | 2/26 (7.7%)                 | *                                            |
|                 |      |                 | IIIB  | 1/18 (5.6%)                 | #                                            |
| Nakanishi et al. (29) | 2000 | 240             | IA    | 0/15                        | #                                            |
|                 |      |                 | IIB   | 7/178 (3.9%)                | #                                            |
|                 |      |                 | IIA   | 0/11                        | #                                            |
| Hu et al. (30)  | 2013 | 183             | I     | 1/130 (0.8%)                | #                                            |
|                 |      |                 | IIA   | 3/39 (7.7%)                 | #                                            |
|                 |      |                 | IIIB  | 1/14 (7.1%)                 | #                                            |
| Natsume et al. (17) | 1999 | 62              | I     | 1/31 (3.2%)                 | #                                            |
|                 |      |                 | IIA   | 1/3 (33.3%)                 | #                                            |
|                 |      |                 | IIIB  | 6/28 (21.4%)                | #                                            |
| Shimada et al. (31) | 2006 | 546             | I     | 14/376 (3.7%)               | #                                            |
|                 |      |                 | IIA   | 2/38 (5.3%)                 | #                                            |
|                 |      |                 | IIIB  | 13/132 (9.8%)               | #                                            |
| Zhou et al. (32) | 2017 | 312             | IA    | 0/9                         | #                                            |
|                 |      |                 | IIB   | 5/217 (2.3%)                | #                                            |
|                 |      |                 | IIA   | 8/74 (10.8%)                | #                                            |
|                 |      |                 | IIIB  | 1/12 (8.3%)                 | #                                            |

(Continued)
| Author                    | Year | No. of patients | Stage | Rate of ovarian metastases | Variables included in multivariate analysis |
|--------------------------|------|----------------|-------|----------------------------|-----------------------------------------------|
|                          |      |                |       | Age | FIGO stage | Tumor size | Deep stromal invasion | Parametrial invasion | Corpus uteri invasion | Lymph node metastasis | Vaginal invasion | Blood vessel invasion |
| Yamamoto et al. (16)     | 2001 | 89             | IB    | 1/50 (2%) | #                              |                                               |
|                          |      |                | IIA   | 0/2 |                              |                                               |
|                          |      |                | IIB   | 6/37 (16.2%) |                              |                                               |
| Landoni et al. (14)      | 2007 | 380            | IA-IIA | 9/380 (2.4%) | #                              | #                              | #                              |
| Lu et al. (33)           | 2016 | 101            | IA    | 0/1 |                              |                                               |
|                          |      |                | IB    | 4/88 (4.6%) |                              |                                               |
|                          |      |                | IIA   | 1/12 (8.3%) |                              |                                               |
| Toki et al. (11)         | 1991 | 36             | IB-IIB | 2/36 (5.6%) |                              |                                               |
| Tabata et al. (34)       | 1987 | 48             | IB    | 2/26 (7.7%) |                              |                                               |
|                          |      |                | IIA   | 0/2 |                              |                                               |
|                          |      |                | IIB   | 2/13 (15.4%) |                              |                                               |
| Kjorstad et al. (15)     | 1984 | 150            | IB    | 2/150 (1.3%) |                              |                                               |
| Guo et al. (27)          | 2018 | 267            | I-II  | 13/223 (5.8%) |                              |                                               |
|                          |      |                | IB    | 2/80 (2.5%) |                              |                                               |
| Sutton et al. (13)       | 1992 | 121            | IB    | 0/19 |                              |                                               |
| Ruengkhachorn et al. (23)| 2016 | 35             | IA    |                              |                                               |
| Total                    |      | 3,098          | OM:   | IA 0/53 | IB 42/1513 (2.8%) | IIA 17/208 (3.4%) | IIB 30/254 (11.8%) |

No., number; FIGO, International Federation of Gynecology and Obstetrics.

*Prognostic factors for cervical adenocarcinoma.

*Risk factors for ovarian metastases.
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CONCLUSIONS

Ovarian preservation in young patients with early stage cervical adenocarcinoma is safe and has no significant effect on OS or PFS. Preserving ovaries in patients with FIGO stage IIB seems not reasonable because of the high rate of ovarian metastasis.

AUTHOR CONTRIBUTIONS

HC, YX, JY, LZ, YK, and LH: study conception and design and manuscript review. HC, LZ, and JY: literature review and data extraction. YK and LH: quality control. HC and YK: statistical analysis. HC and LZ: manuscript preparation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00777/full#supplementary-material

Supplementary Data Sheet 1 | Search strategy detail.

Supplementary Table 1 | Quality assessment of included studies.
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