REVIEW

Short- and long term outcomes after abdominal radical trachelectomy versus radical hysterectomy for early stage cervical cancer: a systematic review of the literature and meta-analysis

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Abstract

Purpose Cervical cancer (CC) ranks 2nd for mortality among women of reproductive age in the United States. Abdominal radical trachelectomy (ART) is a fertility sparing approach that has been proposed in women with early stage CC who wish to preserve their fertility. The aim of the present meta-analysis was to evaluate the short- and long-term outcomes of RH vs ART for early stage CC.

Methods A total of 5 electronic databases were searched for articles published up to December 2018. Prospective and retrospective trials reporting outcomes for women who underwent ART or RH for the management of early stages CC, were considered eligible for inclusion. Statistical meta-analysis was performed using the RevMan 5.3 software.

Results A total of 5 studies which included 840 women who underwent ART or radical trachelectomy (RH) were included in the present meta-analysis. Among them, 324 underwent ART whereas the remaining 516 had RH. Despite the fact that ART was associated with significantly prolonged operative time compared to RH (840 patients MD 36.82 min, 95% CI 20.15–53.49, $p < 0.001$), neither 5-year OS nor 5-year DFS were different among the two groups (714 patients OR 1.39, 95% CI 0.53–3.62, $p = 0.51$ and 682 patients OR 1.08, 95% CI 0.52–2.25, $p = 0.84$, respectively).

Conclusions ART is a more complex and time consuming technique, but equally safe compared to RH in terms of oncological outcomes for selected women with early stage CC and allows for more CC survivors of childbearing age to preserve their fertility.

Keywords Cervical cancer · Fertility sparing · Abdominal radical trachelectomy · Radical hysterectomy

Introduction

Cervical cancer (CC) remains a considerable cause of cancer-related deaths among women [1]. It is considered the 4th most frequent malignancy in women worldwide and accounts of about 570,000 estimated new cases and 311,000 deaths in 2018 [1]. Interestingly, in the United States in women aged between 20 and 39 years, CC ranks 2nd for mortality [2].

Radical hysterectomy (RH) with bilateral pelvic lymphadenectomy is considered the treatment of choice for patients with CC with favorable oncological outcomes. Despite the improved reported survival rates, RH is associated with considerable morbidity and significant worsen in patient's quality of life and sexual activity, but most importantly, in patients of reproductive age it prohibits childbearing [3]. Due to population-based screening programs with Papanicolaou cytology test or HPV DNA test, a considerable proportion of CC cases are diagnosed in an early stage. Due to the fact that a significant proportion of women among them are of reproductive age, they wish to preserve their fertility.

A plethora of techniques such as Dargent's procedure, conization or radical trachelectomy (RT) have been proposed in cases of early stages CC with oncological safety and simultaneous fertility preservation being the ultimate treatment goals [4]. Among them, abdominal

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radical trachelectomy (ART) via laparotomy or laparoscopic approach, has been considered as a feasible procedure in selected patients who were not diagnosed with histological types of poor prognosis or nodal metastasis and wish to preserve their fertility [4, 5]. Furthermore, the currently available literature suggests that the abdominal approach for RT would be preferable even in cases of tumors larger than 2 cm as it offers the potential of extending the parametrial resection especially when compared to vaginal approach [6]. However, there are some oncological issues with this approach that still remain elusive.

The aim of the present meta-analysis is to accumulate the current knowledge and to evaluate the short- and long-term outcomes of RH vs ART for early stage CC as well as the pregnancy outcomes after ART.

Materials and methods

Search strategy and eligibility of studies

The present meta-analysis was designed in accordance with the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) based on the authors' predetermined eligibility criteria [7]. Three authors independently searched the literature (AP, VP, AD). No language restrictions were applied. Prospective and retrospective trials reporting outcomes for women who underwent ART or RH for the management of CC of early stages (stages IA2–IB), publications with > 20 patients were considered eligible for inclusion. Studies reporting outcomes of procedures performed with transvaginal approach, were excluded. Case reports, reviews and animal studies were additionally excluded from tabulation. Each author independently reviewed the literature; the discrepancies during the data collection were then resolved by consensus of all authors.

Literature search and data collection

A systematic search of the Medline (1966–2018), Scopus (2004–2018), Google Scholar (2004–2018), Cochrane CENTRAL Register of Controlled Trials and Clinicaltrials.gov databases for articles published up to December 2018 was performed. Reference lists of articles which were retrieved in full text, were additionally systematically searched for relevant articles in the field. The performed search included the words "radical trachelectomy", "abdominal trachelectomy", "radical hysterectomy", "abdominal hysterectomy", "early stage cervical cancer", "fertility sparing" (Fig. 1).

Data on patient characteristics included age, tumor size, histological type of the tumor, lymph node count, lymphovascular space invasion (LVSI), margin status, adjuvant

treatment and conversion rates. Intra- and postoperative outcomes were evaluated as follows: operative time (OT), estimated blood loss (EBL), blood transfusion rates, length of hospital stay (LOS) and complications (intra- and postoperative). Survival outcomes including recurrence rates, 5-year overall survival (OS) and 5-year disease free survival (DFS) as well as mortality were also appraised. Finally, fertility outcomes of patients who underwent ART were examined.

Quality assessment

The quality of all the included studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) [8]. The MINORS scale was used due to the fact that all of the studies included in our meta-analysis were non-randomized. Two authors independently performed the procedure.

Statistical analysis

Statistical meta-analysis was performed using the RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals (CI) were set at 95%. Mean difference (MD) and odds ratios (OR) were used in the analysis. The results were calculated using the DerSimonian-Laird random effect model (REM) revealing significant heterogeneity in the methodological characteristics of the included studies [9]. The cut-off for statistical significance was set at $p < 0.05$. Mean values and standard deviations were calculated according to the equations proposed by Hozo et al. [10] when not provided by the studies. Publication bias was not tested due to heterogeneity of the included studies, which is a confounder that may influence the methodological integrity of these tests.

Results

Excluded studies

A total of 5 were excluded from the present meta-analysis. Among them, two reported outcomes of patients with CC who underwent vaginal trachelectomy and were excluded [11, 12]. The study by Tseng et al. [13] was excluded due to the fact that less radical approaches including trachelectomy were compared with more radical ones including hysterectomy, but not separated outcomes for the aforementioned approaches were presented. The remaining two were not included since no separated outcomes concerning vaginal radical trachelectomy (VRT) and ART were addressed [14, 15].

Fig. 1 Search flow diagram
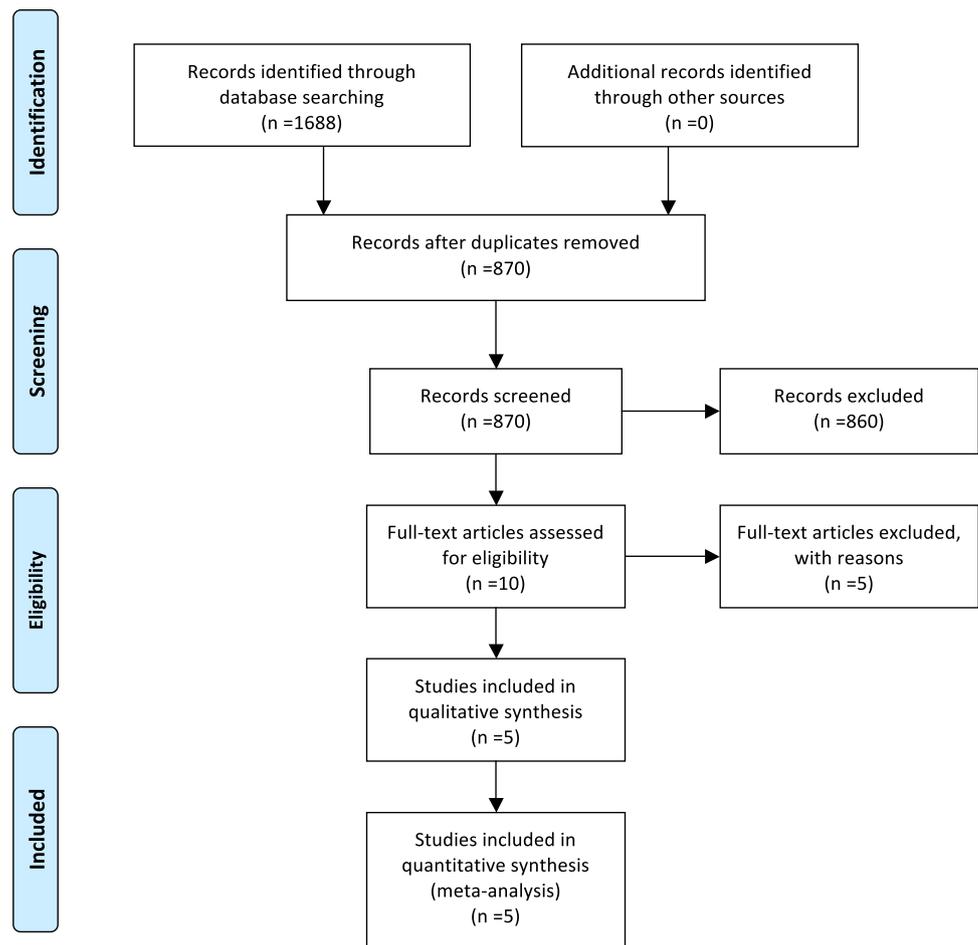
Included studies

A total of 5 studies which included 840 patients with CC of stages IA2–IB who underwent ART or RH were finally included [16–20]. Among them, 324 women underwent ART (ART group) whereas the remaining 516 comprised the RH group. The inclusion criteria were as follows: histologically confirmed CC of stages ≤ IB, no lymph node metastasis or other metastasis and tumor spread outside the cervix, women of reproductive age who desired to preserve their fertility and no known history of fertility impairment. The study by Yoshihara et al., included three groups of patients: ART-during pregnancy ($n = 6$), ART ($n = 10$) and RH ($n = 22$) [18]. We included only the groups with non-pregnant patients from this study ($n = 32$) [18]. Guo et al., enrolled patients with IA2–IB1 while Van Gent et al., reported outcomes of patients who underwent surgery for CC of stages IA2–IB. The remaining three studies included patients with IB1 CC. Additionally, Van Gent et al. [17] presented outcomes for nerve-sparing technique of ART or RH. Four studies were retrospective [16, 18–20] and the study by Van Gent et al. [17] was prospective. The analyzed indices were tabulated in a structured table (Table 1) which depicted patients' characteristics for ART vs RH, main intra-, postoperative and survival outcomes for ART vs RH and fertility outcomes for patients in ART group.

Quality assessment

The quality assessment using the MINORS scale showed that the included studies were methodologically adequate with low heterogeneity regarding their quality, providing a mean score of 14.6 (SD: 3.44) and a median score of 15 (range 12–20) (Table 1).

Operative outcomes

The main outcomes related to ART versus RH for CC are presented in Table 1. Intraoperative outcomes revealed a significantly prolonged OT among women in the ART group when compared to RH (840 patients MD 36.82 min, 95% CI 20.15–53.49, $p < 0.001$, data from 5 studies [16–20]) (Fig. 2). Moreover, despite the fact that ART group presented significantly increased EBL when compared with RH one, transfusion rates were not found different among the two groups (840 patients MD 60.42 ml, 95% CI 34.25–86.60,

Table 1 Main patients' characteristics (ART vs RH), intra- and postoperative outcomes and survival rates (ART vs RH) and fertility outcomes for patients who underwent ART

Year; author	2018; Guo	2018; Yoshihara	2016; Li	2014; Van Gent	2014; Zhang
Patient no	143 vs 186	10 vs 22	107 vs 141	28 vs 77	36 vs 90
Age (years)	31 (18–42) vs 38 (28–44)[a]	32.8 ± 5.8 vs 40.9 ± 9.0[b]	32 (20–42) vs 39 (26–45)[a]	31.2 (21–37) vs 44.2 (32–73)[c]	32 (20–41) vs 50 (20–71)[a]
Tumor size (cm)	2.2 (0.2–4.0) vs 2.3 (0.4–4.0)[a]	1.35 ± 0.77 vs 1.69 ± 0.1[b]	2 (0.4–4) vs 2 (0.5–4)[a]	N/A	2.59 ± 0.46 vs 2.63 ± 0.53[b]
Histology (SQ/AC/AS)	111/28/4 vs 139/41/6	2/4/N/A vs 11/10/N/A	91/14/2 vs 115/22/4	14/11/2 vs 55/19/2	25/8/1 vs 64/17/8
LVSI	26 vs 35	2 vs 7	19 vs 27	10 vs 39	N/A
Adjuvant treatment (N) (CT/RT)	53 vs 67	2 vs 6	31 (CT) vs 48 (RT)	0 vs 0	13 vs 47
Follow-up (months)	75.5 (6–18) vs 83 (6–168)[a]	N/A	30 (5–102) vs 49 (5–101)[a]	47.3 (6–122) vs 51.8 (11–129.6)[c]	12 (8–19) vs 12.5 (8–20)[a]
OT (min)	155 (105–280) vs 115 (95–250)[a]	369.3 ± 50.6 vs 308.4 ± 46.1[b]	145 (90–270) vs 105 (85–260)[a]	255 (165–410) vs 210 (120–360)[a]	144 (95–193) vs 108 (78–198)[a]
EBL (ml)	350 (100–1000) vs 300 (80–800)[a]	920.0 ± 521.4 vs 652.4 ± 528.4[b]	200 (50–1200) vs 200 (100–900)[a]	885 (250–3620) vs 750 (75–3420)[a]	200 (50–350) vs 150 (50–300)[a]
Transfusion (N)	5 vs 9	N/A	4 vs 8	N/A	1 vs 0
LOS (days)	8 (7–14) vs 8 (7–16)[a]	N/A	7 (3–17) vs 7 (5–38)[a]	N/A	7 (13–22) vs 8 (13–29)[a]
IO complications (N)	5 vs 2	N/A	2 vs 1	N/A	N/A
PO complications (N)	51 vs 62	N/A	39 vs 27	0 vs 2	N/A
Recurrence (N)	4 vs 8	N/A	2 vs 3	2 vs 11	0 vs 0
5-OS (%)	140 (97.8) vs 182 (97.7)	10 (100) vs 22 (100)	107 (100) vs 137 (96.9)	25 (90) vs 67 (87)	N/A
5-DFS (%)	139 (97.1) vs 177 (95.4)	N/A	105 (97.8) vs 137 (97)	22 (80) vs 66 (85)	N/A
Mortality (overall/cancer related)	3 vs 4	N/A	0 vs 3	1 vs 2	0 vs 0
No of pregnancies (no of patients/tried to conceive)	30 (19/60) ARTs:3	N/A	38 ARTs:2	17 (9/17) ARTs:2	N/A
Abortions/ preterm birth/term birth	20/06/2004	N/A	01/01/2005	0/0/17	N/A

ART abdominal radical trachelectomy, *RH* radical hysterectomy, *SQ* squamous, *AC* adenocarcinoma, *AS* adenosquamous, *LN* lymph node, *LVSI* lymph vascular space invasion, *CT* chemotherapy, *RT* radiation therapy, *OT* operative time, *EBL* estimated blood loss, *LOS* length of stay, *IO* intraoperative, *PO* postoperative, *OS* overall survival, *DFS* disease free survival, *ARTs* assisted reproductive technologies

[a]Median (range)

[b]Mean ± SD

[c]Mean (range)

Study or Subgroup	ART Mean	ART SD	ART Total	RH Mean	RH SD	RH Total	Weight	Mean Difference IV, Random, 95% CI
2014; Van Gent	271.25	225	28	255	44	77	3.6%	16.25 [−67.67, 100.17]
2014; Zhang	144	24.5	36	123	20	90	32.8%	21.00 [11.99, 30.01]
2016; Li	162.5	30	107	138.75	29.17	141	33.8%	23.75 [16.30, 31.20]
2018; Guo	450	150	143	370	120	186	16.7%	80.00 [49.97, 110.03]
2018; Yoshihara	369.3	50.6	10	308.4	46.1	22	13.1%	60.90 [24.09, 97.71]
Total (95% CI)			324			516	100.0%	36.82 [20.15, 53.49]

Heterogeneity: Tau² = 199.23; Chi² = 17.42, df = 4 (P = 0.002); I² = 77%
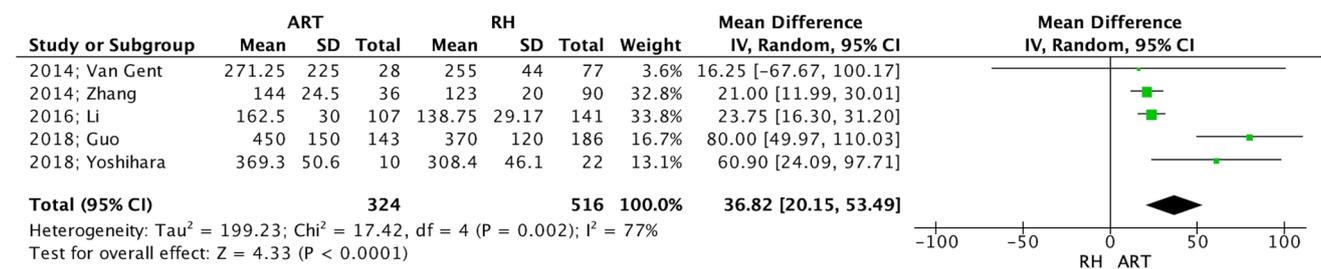Test for overall effect: Z = 4.33 (P < 0.0001)

Fig. 2 Forest plot depicting operative time

$p < 0.0001$, data from 5 studies [16–20] and 703 patients OR 0.79, 95% CI 0.35–1.79, $p = 0.58$, data from 3 studies [16, 19, 20], respectively). Concerning complication rates, no difference was detected among the two groups in the incidence of either intra- or postoperative complications (577 patients OR 3.10, 95% CI 0.79–12.15, $p = 0.10$, data from 2 studies [16, 20] and 682 patients OR 1.52, 95% CI 0.77–3.02, $p = 0.23$, data from 3 studies [16, 17, 20], respectively). Finally, there was no difference in terms of LOS between the two approaches (703 patients MD − 2.81 min, 95% CI − 5.81 to 0.20, $p = 0.07$, data from 3 studies [16, 19, 20]).

Survival outcomes

Table 1 depicts the main survival outcomes of the included patients. None of the included studies reported positive surgical margins in histology. Neither 5-year OS nor 5-year DFS were different among the two groups (714 patients OR 1.39, 95% CI 0.53–3.62, $p = 0.51$, data from 4 studies [16–18, 20], Fig. 3 and 682 patients OR 1.08, 95% CI 0.52–2.25, $p = 0.84$, data from 3 studies [16, 17, 20], respectively). The same was also observed in case of recurrence rates and occurrence of cancer related deaths (682 patients OR 0.82, 95% CI 0.27–1.46, $p = 0.28$ and 682 patients OR 0.81, 95% CI 0.25–2.65, $p = 0.73$, respectively, data from 3 studies [16, 17, 20]).

Pregnancy outcomes

Three studies reported fertility outcomes for patients after ART (Table 1) [16, 17, 20]. A total of 85 pregnancies were achieved in 66/184 (35.9%) women among patients who tried to conceive. Among them, assisted reproductive technologies (ARTs) were utilized in 7 pregnancies. A total of 21 pregnancies resulted in miscarriage. Finally, there were 33 live births (38.8%) among which 5 were preterm and the remaining 28 were term. Concerning the impact of adjuvant or neoadjuvant therapy in fertility preservation, Guo et al., reported 4 out of 53 cases with ovarian failure after postoperative chemotherapy while according to Van Gent et al.,

three patients received neoadjuvant chemotherapy and 2 of them had 3 term deliveries [17, 20].

Discussion

The present study aimed to evaluate the safety and efficacy of ART in patients with early stage CC compared to conventional RH. The meta-analysis revealed a significantly prolonged OT and increased EBL in patients who underwent ART. On the other hand, no difference was detected with regards to intraoperative and postoperative complications as well as survival rates, incidence of recurrence and cancer related deaths among ART and RH.

Fertility sparing RT in patients with CC was firstly described by Dargent et al. [21] in 1994 who reported a successful VRT including excision of the cervix with the parametria accompanied by laparoscopic pelvic lymphadenectomy. The efficacy of radical trachelectomy (RT) (abdominal or vaginal) was evaluated in a meta-analysis by Xu et al. [22]. They found no significant difference among patients who underwent RT versus RH with regards to recurrence rates ($p = 0.47$), 5-year recurrence-free survival ($p = 0.69$), 5-year OS ($p = 0.78$), postoperative mortality rate ($p = 0.80$), intraoperative complications rate ($p = 0.72$) and postoperative complications rate ($p = 0.41$) [23]. Those outcomes are in accordance with the outcomes of the present meta-analysis. However, the meta-analysis by Xu et al. [23] reported outcomes of only 3 studies which included patients who underwent VRT or ART while the short term outcomes were not analyzed due to lack of standard deviation values in the respective parameters. On the other hand, Dursun et al. [24] reviewed the short and long-term outcomes of patients with CC who underwent VRT and RH and reported comparable recurrence rates and mortality among the two groups as well as 70% pregnancy rates among women from the VRT group with the intention to conceive.

The decision on the appropriate RT approach (vaginal or abdominal) is still under estimation. The abdominal approach could be considered more familiar to gynecologic
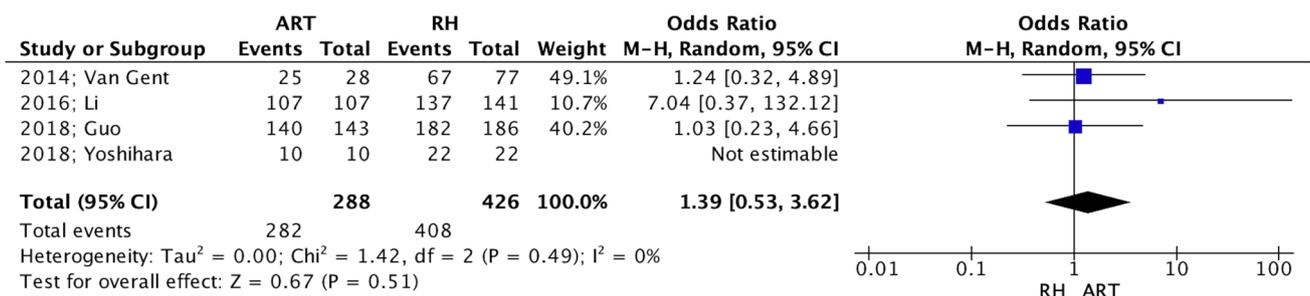

Study or Subgroup	ART Events	Total	RH Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Odds Ratio M–H, Random, 95% CI
2014; Van Gent	25	28	67	77	49.1%	1.24 [0.32, 4.89]	
2016; Li	107	107	137	141	10.7%	7.04 [0.37, 132.12]	
2018; Guo	140	143	182	186	40.2%	1.03 [0.23, 4.66]	
2018; Yoshihara	10	10	22	22		Not estimable	
Total (95% CI)		288		426	100.0%	1.39 [0.53, 3.62]	
Total events	282		408				

Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.51)

Fig. 3 Forest plot depicting 5-year OS

oncologists and potentially allows a more efficient parametrial excision compared to vaginal surgery [25]. In that setting, a case–control study by Cao et al. [22] presented outcomes of 150 patients who underwent ART versus VRT. Despite the fact that VRT resulted in significantly higher pregnancy rates (35.5% versus 8.8%, $p < 0.003$) and elevated completed deliveries rates (23.3% versus 8.8%), recurrence and disease related mortality were significantly elevated in the VRT group compared to ART (9.8% versus 0% and 2.8% versus 0%, respectively) [22]. Further trials are warranted to optimize the optimal approach which can combine the oncological safety with improved fertility outcomes in patients with early stage CC.

Concerning pregnancy outcomes, in the present study we evaluated 85 pregnancies which resulted in 33 live births (38.8%) among patients who underwent ART and tried to conceive. The calculated miscarriage and preterm birth rates were 24.7% and 15%, respectively. The currently available data with regards to the aforementioned rates is conflicting. The review by Rob et al. [26] reported pregnancy loss rates of 22% and preterm birth rates of 35%, among the total number of conceptions and deliveries, respectively. The global pregnancy rate after ART as reported in the review by Pareja et al. [27] was 16.2%. In the present study, the pregnancy rate was 35.9% which seems considerably different to those reported by Pareja et al. [27]. However, we evaluated pregnancy outcomes only among patients who tried to conceive. A narrative review by Willows et al. [25] reported outcomes of 1238 patients who underwent fertility sparing procedures for the management of early stage CC with acceptable pregnancy rates and oncological safety. More specifically, the reported recurrence and mortality rates were about 5% and 2%, respectively for all patients whereas it rises to approximately 11% and 4%, respectively for tumors ≥ 2 cm [25]. A total of 469 pregnancies were reported among 1238 women and 67% of them resulted in live birth. In this group, recurrence, and mortality rates were 4.5% and 1.7%, respectively [25].

In patients with stage IB1 CC < 2 cm fertility sparing RT has been considered feasible and oncological safe. However, for larger tumors (diameter between 2 and 4 cm) data is limited. Lintner et al. [28] reported favorable survival outcomes in patients with stage IB1 CC larger than 2 cm and 5-year OS comparable to rates reported in the literature for patients who underwent RH. Nonetheless, since those patients will need postoperative adjuvant treatment, this will potentially influence their fertility. In 80 selected patients in the study by Willows et al. [25] with tumors 2–4 cm (IIA–IB1) who received neoadjuvant chemotherapy prior to fertility sparing surgery 36 pregnancies resulted in 72.2% live births. In the present study neoadjuvant chemotherapy was administered in 3 patients due to > 4 cm tumor extension and 66.6% had a successful pregnancy.

The present study has a number of limitations. The limited number of the existing studies along with the small number of the included patients could not allow us to draw any safe conclusion. Some significant parameters have not been properly reported by the included studies; data concerning neoadjuvant chemotherapy was reported by one of the recruited studies and lymph node status was also not appropriate reported [17]. Furthermore, this study is susceptible to selection and reporting bias. Another critical factor is the lack of subgroup analysis according to stage in studies which enroll patients of various stages which constitutes a significant bias in the prediction of the disease. Thus, precludes reaching to firm results concerning the efficacy of each approach according to each separate CC stage. Finally, the significant heterogeneity of the included studies along with the fact that some parameters were omitted by some studies was another limitation and precluded reaching to firm results.

Conclusion

The present study demonstrates that ART is feasible and presents encouraging outcomes as a fertility preserving approach in selected patients with early stage CC. It also highlights that despite being a more complex and time consuming technique is of equal oncologic safety with RH for women with early stage CC and allows more CC survivors of childbearing age to preserve their fertility. As the treatment algorithm for CC is evolving with the investigation of new therapeutic modalities, in the following years, the impact of minimal invasive fertility sparing surgical techniques on the long-term outcomes and the quality of life of these patients needs to be validated. Elucidating the efficacy of minimally invasive approach is of critical importance given the recent controversial reports of worsen survival and recurrence rates after minimally invasive approach compared to open for early stage CC.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest and nothing to disclose.

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