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REVIEW

The security of radical trachelectomy in the treatment of IA–IIA cervical carcinoma requires further evaluation: updated meta-analysis and trial sequential analysis

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Abstract

Purpose The aim of this study was to assess the security of radical trachelectomy (RT) in the treatment of IA–IIA cervical carcinoma and conducted a new survey based upon the results of previous researches.

Methods The PMC, PubMed, Web of Science, Cochrane and EMBASE databases were retrieved to collect prospective clinical controlled trials (CCTs) published from 1984 to 2018. The oncologic outcomes were evaluated by meta-analysis, trial sequence analysis (TSA) and statistical analysis.

Results Five prospective CCTs were collected in this study. The recurrence rate and mortality of RT was similar to that of radical hysterectomy (RH), which was consistent with the oncologic outcomes of meta-analysis and TSA. Patients with tumors 2–4 cm in diameter were more likely to receive RH, which may be a potential factor in the higher rate of adjuvant chemotherapy in the this group, and RH was significantly associated with the risk of intraoperative blood transfusion. It is notable that considerable negative margin was achieved by radical abdominal trachelectomy (RAT), and the clinical effect of RAT was slightly better than that of radical vaginal trachelectomy (RVT). However, the TSA results showed that the cumulative cases were not up to the required sample size to obtain the true negative or positive results.

Conclusions It is safe and effective for early-stage patients with cervical cancer whose lesions are less than 2 cm to receive RVT. For those patients with lesions 2–4 cm who desire fertility preservation and without any evidence of infertility, RAT can be a feasible alternative to RH under fully informed consent. However, more CCTs with larger sample size are still required for further validation.

Keywords Cervical cancer · Radical trachelectomy · Radical abdominal trachelectomy · Update meta-analysis · Trial sequential analysis

Introduction

With the improvement of screening for cervical cancer, increasing numbers of cases are diagnosed at the early stages. Radical hysterectomy (RH) with lymphadenectomy is the standard treatment for early-stage patients with cervical cancer, which results in a loss of fertility. We previously demonstrated that fertility-sparing surgery seemed feasible for particular patients with early-stage (stages IA–IB1) diseases [1]. Radical trachelectomy (RT), which includes excision of the cervix, vaginal margins, and parametria, [2–4], has been regarded as an alternative procedure to RH to spare fertility [5]. This procedure seems to be safe for the management of patients with stages IA2 and IB1 disease, lesions less than 2 cm and negative lymph node metastasis (LNM) [6–10]. In contrast, this procedure is not recommended for

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patients with larger tumors due to the relatively higher recurrence risk and the need for postoperative adjuvant therapy, which may compromise fertility [11–13]. However, several researchers have argued that even patients with lesions 2–4 cm can be safely managed with RT [7, 14].

A systematic review [15] claimed that RT was an alternative to RH for early-stage patients with cervical carcinoma who wanted to conserve their fertility. However, in this analysis, the differences in clinical and pathologic characteristics between RH and RT subgroups and between the radical abdominal trachelectomy (RAT) and radical vaginal trachelectomy (RVT) subgroups were not explored. Moreover, the potential selection bias in the greater likelihood of patients with adverse prognostic factors being treated with radical surgeries rendered their conclusions unsound to some extent.

This study pooled prospective randomized controlled studies published in the literature to access the security of RT in the treatment of early-stage cervical cancer, with a particular focus on patients with tumor lesions 2–4 cm. An updated meta-analysis with trial sequential analysis (TSA) was performed based on current prospective clinical controlled trials (CCTs) to further verify the reliability of the conclusions.

Methods

Data search

The PMC, PubMed, Web of Science, Cochrane and EMBASE databases were retrieved to collect prospective CCTs published from 1984 to 2018. The search terms included cervical cancer (cervical neoplasm or neoplasm, uterine cervical or uterine cervical neoplasm or neoplasms, cervical or neoplasm, cervical or cervix neoplasm or neoplasm, cervix or cancer of the uterine cervix or cancer of the cervix or cervical cancer or uterine cervical cancer or cancer, uterine cervical or cervical cancer, uterine or cancer of cervix or cervix cancer or cancer, cervix) and treatment (fertility sparing or fertility preservation or preservation, fertility) or (trachelectomy or vaginal cervicectomy or cervicectomy, vaginal or vaginal trachelectomy or trachelectomy, vaginal) or (conization or conisation or cone resection) and prospective study (study, prospective or prospective study). Cross-references were retrieved from the cited literature to obtain any necessary data, and efforts were made to contact the authors of articles without complete data to obtain the relevant information, although the response rate was low.

Study selection

The inclusion criteria were as follows: (1) prospective CCTs; (2) treatment with fertility-sparing procedures or radical hysterectomy; (3) full text and complete data availability. The exclusion criteria were as follows: (1) review articles, case reports and meta-analyzes; (2) non-English language; and (3) incomplete data.

Data extraction

Article selection and data extraction were completed through a literature review by two investigators independently. The results were discussed and confirmed by the two observers in cases of ambiguity. The basic information collected included the title, authors, country, journal, publication year, inclusion year, research type, bias, number of patients, age, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, operation duration, intraoperative complications, histological type, parametrial infiltration (PI), lymphovascular space invasion (LVSI), LNM, residual lesion, postoperative complications, hospital stay, and adjunctive therapy. Information regarding subsequent pregnancies, recurrence, and survival at last contact was also collected and evaluated.

All the data in this study were derived from published literatures. Therefore, medical ethics and informed consent were not necessary.

Meta and statistical analyzes

All statistical analyzes were performed by Review Manager 5.3, IBM SPSS Statistics 21, Stata/SE 12.0 and TSA 0.9.5.5 Beta. All statistical tests were two-tailed, and $p < 0.05$ was considered to be statistically significant. Pooled risk ratios (RRs) and 95% confidence intervals (CI) were calculated by fixed or random effects models according to the heterogeneity of selected prospective CCTs. The I^2 value across studies was applied to evaluate heterogeneity. The fixed effects model was used for the absence of heterogeneity ($I^2 < 50\%$). The random effects model was used when $I^2 > 50\%$.

The Chi-square or Fisher's exact test was applied to compare the clinical and pathological features and oncologic outcomes between patients who underwent RT or RH and between those who underwent RAT or RVT. The depth of invasion was compared with a corrected T test. The risks of the FIGO stage, PI, LNM, postoperative adjunctive therapy, blood transfusion, postoperative complications, postoperative noninfectious complications, recurrence, 5-year overall survival (OS) and DOD were compared with a continuity correction test.

Results

A total of 277 papers were retrieved from the databases using search terms, 192 of which were excluded due to irrelevant information determined through reviews of the

titles and abstracts. Additionally, six duplicate papers were excluded. In addition, 44 retrospective studies, 19 review articles and nine non-controlled studies were also excluded based on inclusion and exclusion criteria, but another article was included through cross-referencing. Three of the remaining eight CCTs were excluded because these studies focused on the postoperative quality of life and without complete data regarding the patients' clinicopathological features and oncologic outcomes. Finally, five prospective CCTs [7, 16–19] and 818 patients were included in this study (Suppl. 1).

The clinical and pathological features and oncologic outcomes of the patients are shown in Tables 1 and 2, respectively. The mean age was 38.4 years (range 20–73 years). Most patients had stages IB1 and IA disease (96.1%) according to the 2014 FIGO staging system [20, 21], whereas stages IB2 and IIA disease accounted for 3.9% of the cases. The tumor size (defined as the largest diameter of a tumor) was distributed as follows: 447 (68.1%) patients with tumors less than 2 cm, 198 (30.2%) patients with tumors 2–4 cm and 11 patients (1.7%) with tumors larger than 4 cm. RT and RH were performed in 312 (38.1%) and 506 (61.9%) patients, respectively, and all of the patients received lymphadenectomy (100%). The most frequent histological types was squamous-cell carcinoma (SCC, 61.7%), followed by adenocarcinoma/adenosquamous (AD/AS, 36.6%) and other rare types (1.7%). Spread of the tumor directly or through the lymphovascular pathway to the parametrium or parametrial nodes was defined as PI. The risks of PI and LNM were as low as 1.8% and 5.0%, respectively. A section margin showing in situ carcinoma or invasive cancer was interpreted as a positive margin and was identified in 4 (0.4%) patients. Adjunctive therapy, including radiotherapy or chemotherapy, was performed in patients with at least two intermediate risk factors or one high-risk factor [10, 22]. A total of 83 (14.7%) patients received adjunctive therapy.

The average follow-up was 61.2 months. During this time, 17 (65.4%) of the 26 patients with a desire for pregnancy had a total of 23 pregnancies either spontaneously (21 pregnancies) or with the assistance of in vitro fertilization (two pregnancies). The outcomes of these pregnancies included full-term delivery through cesarean Section (17 pregnancies), premature labor at 35 weeks (one pregnancy), spontaneous abortion (one pregnancy), and termination of pregnancy at the second trimester (two pregnancies). The remaining two patients were still pregnant at last contact. Therefore, the live birth rate of the women with a desire for pregnancy who underwent RT in this analysis was 94.7% (18/19).

During the study period, 36 (4.4%) patients developed relapse and 21 (2.6%) died from the disease. Recurrence-free survival (RFS) was defined as the period from surgery to recurrence; OS was defined as the period from surgery to death; patients living free of tumor or survivors at the

Table 1 The clinicopathological characteristics of patients included in the 5 articles

Studies	Included years	No.	Age (years)	FIGO Stage				Tumor size, cm			Histological subtype			Invasion depth, mm	NACT	Positive section margins	LVSI	PI	LN	Lymph node count	LNM	Postoperative adjunctive therapy
				IA	IB1	IB2	IIA1	<2	2–4	>4	SCC	AD + AS	The others									
Zhang et al	2012–2013	126	44.9	0	126	0	0	50	76	0	89	34	3	UK	0	0	39	6	126	22	15	60
Gent et al	2000–2011	105	40.79	9	85	11	0	UK	UK	11	69	34	2	7	3	0	29	UK	105	23	0	0
Beiner et al	1994–2007	180	32.5	UK	UK	UK	UK	180	0	0	78	100	2	3.1	0	0	122	1	180	UK	0	2
Diaz et al	1991–2007	150	35.7	0	150	0	0	104	46	0	77	73	0	UK	0	0	39	1	150	27	15	UK
Marchiole et al	1986–2003	257	40.1	54	189	0	14	113	76	0	192	58	7	UK	0	4	78	UK	257	18	11	21
Total (%)	1986–2013	818 (100)	38.4	63 (9.9)	550 (86.2)	11 (1.7)	14 (2.2)	447 (68.1)	198 (30.2)	11 (1.7)	505 (61.7)	299 (36.6)	14 (1.7)	4.5	3 (0.4)	4 (0.4)	307 (37.5)	8 (1.8)	818 (100)	22	41 (5.0)	83 (12.4)

No. number of patients, *SCC* Squamous cell carcinoma, *AD* adenocarcinoma, *AS* adenosquamous, *NACT* neoadjuvant chemotherapy, *LVSI* lymphovascular space invasion, *PI* parametrial infiltration, *LN* lymphadenoectomy, *LNM* lymph node metastasis, *UK* unknown

Table 2 The oncologic outcomes of patients included in the 5 articles

Studies	No.	Operation on uterus		Operating time, min	Blood loss, ml	Blood transfusion	Hospital stay	Intraoperative complications	Postoperation complications	Post-operative infectious complications	Post-operative noninfectious complications	Pregnancies	Recurrences	5-year RFS*	DOD	5-year OS*	Follow up, months
	Total	RT	RH														
Zhang et al	126	36	90	118	164	1	8	UK	UK	UK	UK	UK	0	UK	0	UK	12.6
Gent et al	105	28	77	222	786	UK	UK	UK	4	0	2	9	13	25	4	29	50.6
Beiner et al	180	90	90	171	450	23	4	14	40	13	7	UK	6	176	4	179	54.5
Diaz et al	150	40	110	256	352	8	UK	UK	UK	UK	UK	8	1	133	1	137	44
Marchiole et al	257	118	139	184	UK	39	UK	11	104	3	49	UK	16	241	12	240	104.7
Total (%)	818 (100)	312 (38.1)	506 (61.9)	189	422	71 (1.0)	5	25 (5.7)	74 (13.7)	16 (3.0)	58 (10.7)	17 (65.4)	36 (4.4)	575 (93.8)	21 (2.6)	585 (95.0)	61.2

No. number of patients, *RT* radical trachelectomy, *RH* radical hysterectomy, *DOD* die of the disease, *RFS* recurrence-free survival, *OS* overall survival, *UK* unknown

*Calculated data

time of their last contact were censored. The 5-year RFS and OS rates were 93.8% and 95.0%, respectively.

The clinicopathological features and oncologic outcomes of the patients treated with RT or RH were compared. The random-effects model was used to compare blood transfusions, intraoperative complications, postoperative complications and postoperative infectious complications due to greater heterogeneity across the pooled studies, whereas a fixed-effects model was applied to compare postoperative noninfectious complications ($I^2 = 34\%$, Fig. 1a, b). There was no significant difference in blood transfusion (RR 0.49; 95% CI 0.12–2.01), intraoperative complication (RR 1.59; 95% CI 0.12–20.90), postoperative complication (RR 0.57; 95% CI 0.17–1.90), postoperative infectious complication (RR 0.65; 95% CI 0.09–4.57) and postoperative noninfectious complication (RR 0.85; 95% CI 0.53–1.37).

More patients with earlier stages of disease (stages IA–IB1) and a tumor less than 2 cm received RT ($p < 0.001$, Table 3). The positive section margin rate for RT was not significantly higher than the rate for RH ($p = 0.315$). Additionally, the intraoperative and postoperative complication rates for RT were similar to the rates for RH ($p = 0.201$ and 0.416, respectively). However, the risk of blood transfusion in RH group was significantly higher than that in RT group ($p = 0.018$).

The fixed effects model was used to compare recurrence, DOD and 5-year OS due to low heterogeneity across the pooled studies, whereas a random-effects model was used to compare 5-year RFS due to significant heterogeneity ($I^2 = 58\%$, Fig. 1c–e). No significant differences were identified in the comparisons of recurrence (RR 1.15; 95% CI 0.59–2.24), DOD (RR 1.30; 95% CI 0.57–2.96), 5-year RFS (RR 1.00; 95% CI 0.94–1.07), and 5-year OS (RR 1.00; 95% CI 0.97–1.04). The relapse and mortality were similar in patients receiving RT and RH. (Recurrence: 4.8% vs 4.2%, $p = 0.651$; Death: 3.2% vs 2.2%, $p = 0.362$, Table 3).

All meta-analysis data were consistent with the outcomes of the TSA (Fig. 2a–i). The *Z*-curves of the blood transfusion, intraoperative complication, postoperative complication, postoperative infectious complication, postoperative noninfectious complication, recurrence, DOD, 5-year RFS, and 5-year OS did not cross the red horizontal line ($Z = \pm 1.96$, $p = 0.05$); thus, the cumulative cases were not up to the required sample size to obtain the true negative or positive results. The required sample size for 5-year RFS, 5-year OS and DOD comparisons were 7952, 8741 and 14,724 respectively. Moreover, meta-regression analysis showed that heterogeneity mainly came from difference in regions and years (adjusted $R^2 = 72.9\%$). Therefore, the possibility of false negative results cannot be excluded, and further CCTs with large sample size are warranted to verify these conclusions.

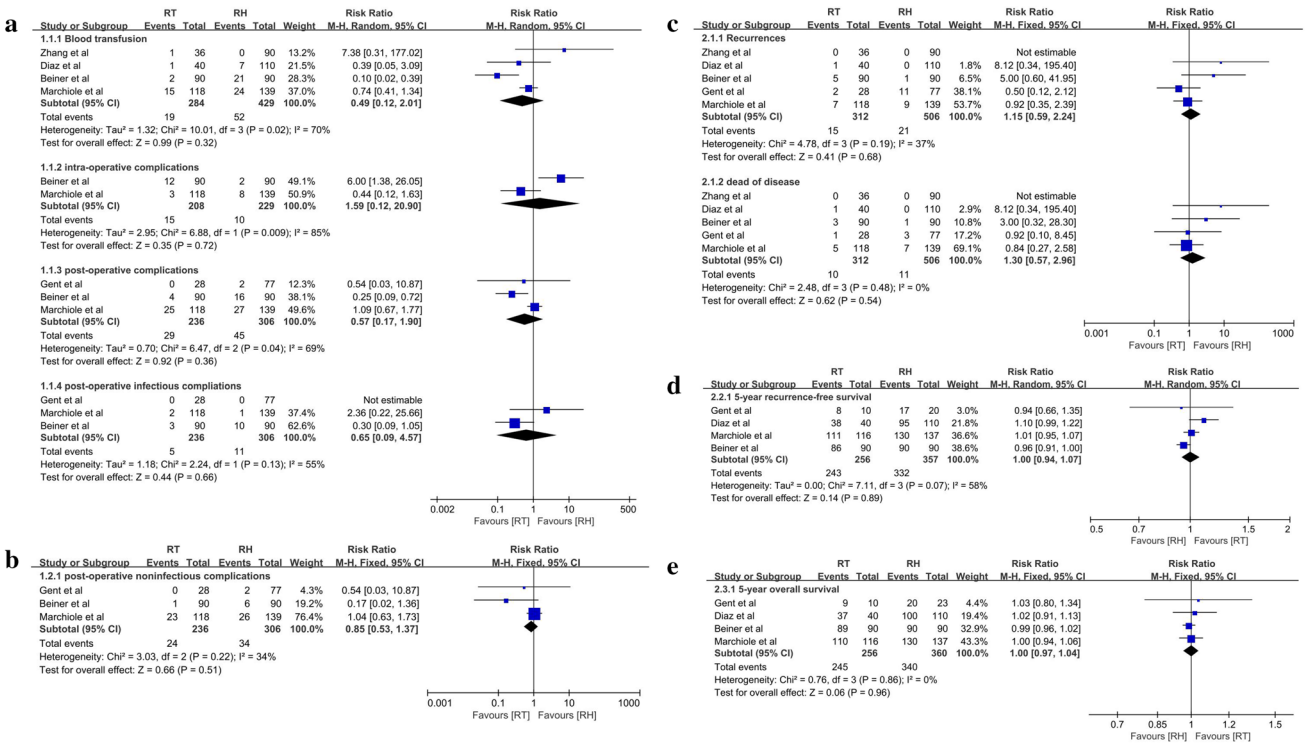

Fig. 1 Meta-analysis of the complications and oncologic outcomes between RT and RH: **a** blood transfusion (RR 0.49; 95% CI 0.12–2.01), intraoperative complications (RR 1.59; 95% CI 0.12–20.90), postoperative complications (RR 0.57; 95% CI 0.17–1.90) and postoperative infectious complications (RR 0.65; 95% CI 0.09–4.57); **b** postoperative noninfectious complications (RR 0.85; 95% CI 0.53–1.37); **c** recurrence (RR 1.15; 95% CI 0.59–2.24) and DOD (RR 1.30; 95% CI 0.57–2.96); **d** 5-year RFS (RR 1.00; 95% CI 0.94–1.07); e. 5-year OS (RR 1.00; 95% CI 0.97–1.04)

In the RT subgroup, RAT and RVT were performed in 64 (20.5%) and 248 (79.5%) patients, respectively. The clinicopathological features and oncologic outcomes of the patients in these two subgroups were compared (Table 4). Compared to RVT, more patients with lesions 2–4 cm or PI received RAT ($p < 0.001$ and $p = 0.010$, respectively). However, RAT resulted in clear margins (100%). Significantly more patients in the RAT subgroup received postoperative adjuvant therapy ($p = 0.001$). The recurrence and death rates were 3.1% and 1.6%, respectively, in the RAT subgroup, which were similar to the 5.3% and 3.7% rates obtained in the RVT subgroup, respectively ($p = 0.696$ and 0.654, respectively). The TSA and meta-analysis were not performed due to the limited data available in the RAT and RVT subgroups.

Discussion

RT is used as a fertility-sparing procedure to manage young early-stage patients with cervical carcinoma [5]. The meta-analysis in one systematic review involved three CCTs and 587 patients; the authors found that the clinical outcomes of RT group were similar to those of RH group and that this procedure resulted in normal pregnancy rates [15]. However, the heterogeneity of the clinical and pathological characteristics between the patients in the RT and RH subgroups was not evaluated in that study. The limitations, including the potential existing selection bias caused by patients with adverse prognostic factors having a greater likelihood of being treated with radical surgeries, rendered their conclusions unsound to some extent. After publication of this systematic review, the results of two new CCTs were reported [18, 19]. Therefore, an updated meta-analysis was performed.

This analysis validated that the overall oncologic outcomes of the RT group were comparable to those of the RH group. The rates of recurrence and DOD were 4.8% vs 4.2% and 3.2% vs 2.2%, respectively, whereas the 5-year RFS and 5-year OS rates were 94.9% vs 93% and 95.7% vs 93%, respectively. The pregnancy outcomes were acceptable, with 65.4% of the patients becoming pregnant successfully, and the live birth rate was as high as 94.7%, which was similar to reports in previous studies [23, 24]. More patients with lesions less than 2 cm received RT. These data validate the conclusions of previous retrospective studies, in which fertility-sparing treatment was safe for patients with FIGO stages IA2–IB1 disease and a tumor size less than 2 cm [6–9, 25, 26].

Table 3 Comparison of clinicopathologic features and oncologic outcomes between patients treated with radical trachelectomy (RT) and radical hysterectomy (RH)

Parameter	Operation on uterus		*p* value	OR (95% CI)
	RT	RH		
FIGO stage*				
IA + IB1	213 (95.9%)	400 (96.2%)	0.897[a]	0.947 (0.411–2.178)
IB2 + IIA	9 (4.1%)	16 (3.8%)		
Tumor size* (cm)				
< 2	209 (82.9%)	238 (58.9%)	–	–
2–4	40 (15.9%)	158 (39.1%)	< 0.001[a#]	3.469 (2.340–5.141)
≥ 4	3 (1.2%)	8 (2%)	0.200[a]	2.342 (0.613–8.942)
Histological subtype				
SCC	188 (60.3%)	317 (62.6%)	–	–
AD + AS	117 (37.5%)	182 (36%)	0.591[a]	0.923 (0.687–1.238)
The other	7 (2.2%)	7 (1.4%)	0.330[a]	0.593 (0.205–1.717)
Depth of invasion*, mm	4.1 ± 1.9	4.8 ± 1.9	0.005[t#]	− 1.083 to− 0.191
PI*				
+	3 (1.8%)	5 (1.7%)	1.000[b]	1.049 (0.248–4.447)
–	163 (98.2%)	285 (98.3%)		
LVSI				
+	126 (40.4%)	181 (35.8%)	0.193[a]	1.213 (0.907–1.621)
–	186 (59.6%)	325 (64.2%)		
LNM				
+	16 (5.1%)	25 (4.9%)	0.905[a]	1.040 (0.546–1.980)
–	296 (94.9%)	481 (95.1%)		
Section margins				
+	3 (1.0%)	1 (0.2%)	0.315[b]	4.903 (0.508–47.343)
–	309 (99.0%)	505 (99.8%)		
Postoperative adjunctive therapy*				
+	26 (9.6%)	57 (14.4%)	0.063[a]	0.629 (0.384–1.028)
–	246 (90.4%)	339 (85.6%)		
Blood transfusion*				
+	19 (6.7%)	52 (12.1%)	0.018[a#]	0.520 (0.300–0.900)
–	265 (93.3%)	377 (87.9%)		
Intra-operative complications*				
+	15 (7.2%)	10 (4.4%)	0.201[a]	1.702 (0.747–3.877)
–	193 (92.8%)	219 (95.6%)		
Postoperation complications*				
+	29 (12.3%)	45 (14.7%)	0.416[a]	0.813 (0.492–1.341)
–	207 (87.7%)	261 (85.3%)		
Post-operative infectious complications*				
+	5 (2.1%)	11 (3.6%)	0.314[a]	0.580 (0.199–1.694)
–	231 (97.9%)	295 (96.4%)		
Post-operative noninfectious complications*				
+	24 (10.2%)	34 (11.1%)	0.725[a]	0.906 (0.521–1.574)
–	212 (89.8%)	272 (88.9%)		
Recurrences				
+	15 (4.8%)	21 (4.2%)	0.651[a]	1.169 (0.594–2.304)
–	295 (95.2%)	483 (95.8%)		
5-year recurrence-free survivals*				
+	243 (94.9%)	332 (93.0%)	0.330[a]	1.408 (0.706–2.807)
–	13 (5.1%)	25 (7.0%)		

Table 3 (continued)

Parameter	Operation on uterus		*p* value	OR (95% CI)
	RT	RH		
Dead of disease				
+	10 (3.2%)	11 (2.2%)	0.362[a]	1.494 (0.627–3.560)
–	300 (96.8%)	493 (97.8%)		
5-year overall survivals*				
+	245 (95.7%)	332 (93%)	0.160[a]	1.677 (0.810–3.474)
–	11 (4.3%)	25 (7%)		

tt test

*Only including patients whose information was available in the pooled studies

[#]Statistically significant

[a]Chi-square test

[b]Continuity correction

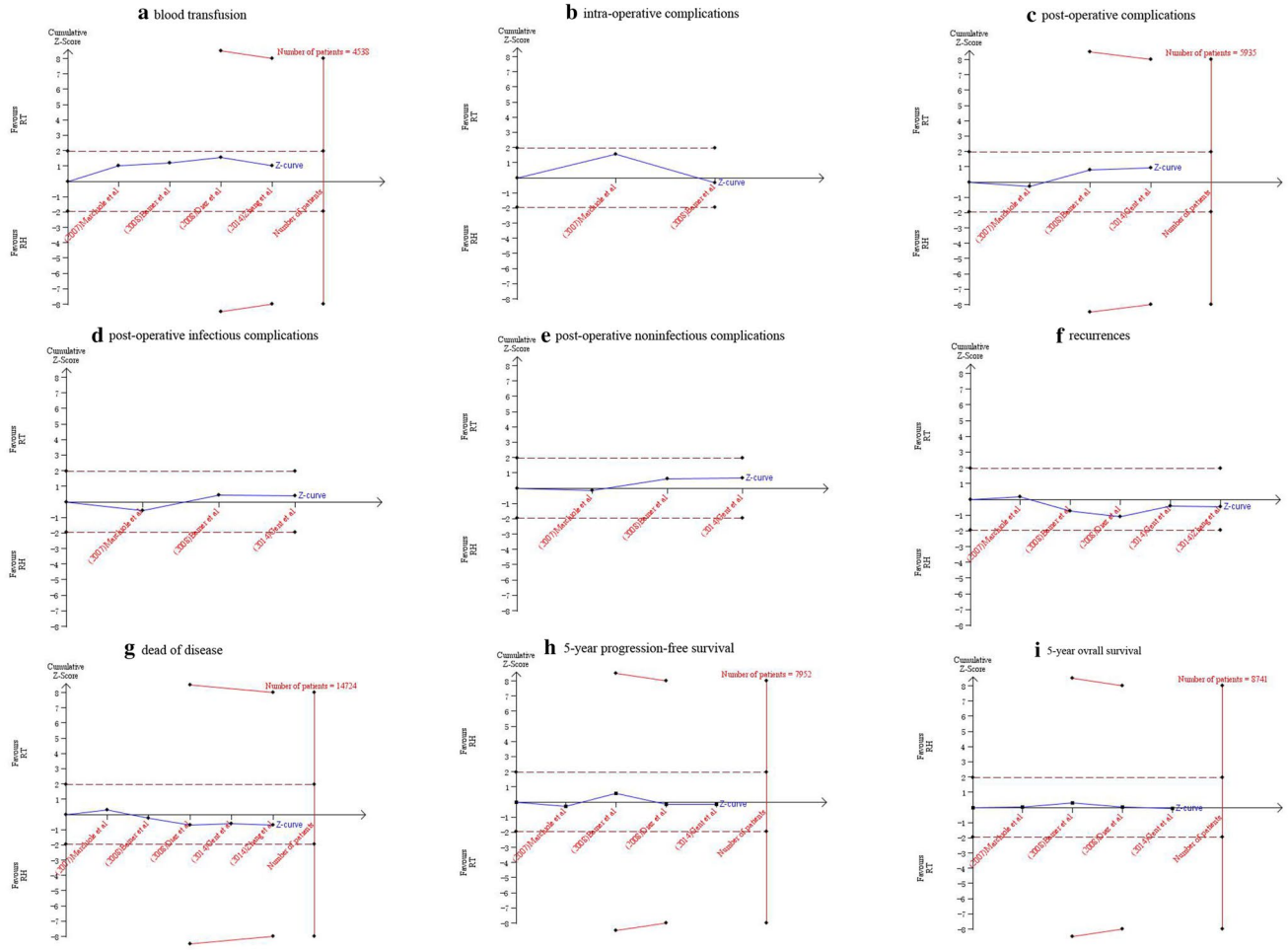

Fig. 2 Trial sequential analysis of complications and oncologic outcomes between RT and RH: the two red horizontal lines indicate that the *Z* value of the statistic is equal to ± 1.96 or $p = 0.05$. **a** Blood transfusion; **b** Intraoperative complications; **c** Postoperative complications; **d** Postoperative infectious complications; **e** Postoperative noninfectious complications; **f** Recurrence; **g** DOD; **h** 5-year RFS; **i** 5-year OS. None of the *Z*-curves intersected the red horizontal lines ($Z = \pm 1.96$, $p = 0.05$). The cumulative number of patients did not fulfill the required information size (number of patients). Therefore, the possibility of false negative results cannot be excluded, indicating that more CCTs are required to verify the results

Table 4 Comparison of clinicopathological features and oncologic outcomes between patients treated by radical abdominal trachelectomy (RAT) and radical vaginal trachelectomy (RVT)

Parameter	Surgery		*p* value	OR (95% CI)
	RAT	RVT		
Histology				
SCC	39 (60.9%)	149 (60.1%)	–	–
AC + AS	22 (34.4%)	75 (30.2%)	0.706[a]	0.892 (0.494–1.612)
Others	3 (4.7%)	24 (9.7%)	0.239[a]	2.094 (0.599–7.315)
FIGO stage*				
IA + IB1	61 (95.3%)	152 (96.2%)	1.000[b]	0.803 (0.195–3.312)
IB2 + IIA	3 (4.7%)	6 (3.8%)		
Tumor size* (cm)				
< 2	20 (55.6%)	189 (88.7%)	< 0.001[a#]	0.159 (0.073–0.347)
2 ~ 4	16 (44.4%)	24 (11.3%)		
LVSI				
+	13 (20.3%)	113 (45.6%)	< 0.001[a#]	0.305 (0.158–0.588)
–	51 (79.7%)	135 (54.4%)		
LNM				
+	5 (7.8%)	11 (4.4%)	0.439[b]	1.826 (0.611–5.457)
–	59 (92.2%)	237 (95.6%)		
Section margins				
+	0	3 (1.2%)	1.000[c]	1.012 (0.998–1.026)
–	64 (100%)	245 (98.8%)		
PI*				
+	3 (8.3%)	0	0.010[c#]	0.917 (0.831–1.012)
–	33 (91.7%)	130 (100%)		
Postoperative adjunctive therapy*				
+	13 (20.3%)	13 (6.3%)	0.001[a#]	3.824 (1.670–8.753)
–	51 (79.7%)	195 (93.8%)		
Blood transfusion*				
+	1 (2.8%)	18 (7.3%)	0.517[b]	0.365 (0.047–2.821)
–	35 (97.2%)	230 (92.7%)		
Postoperation complications*				
+	0	29 (13.9%)	0.071[b]	1.162 (1.100–1.227)
–	28 (100%)	179 (86.1%)		
Post-operative infectious complications*				
+	0	5 (2.4%)	1.000[c]	1.025 (1.003–1.047)
–	28 (100%)	203 (97.6%)		
Post-operative noninfectious complications*				
+	0	24 (11.5%)	0.118[b]	1.130 (1.076–1.187)
–	28 (100%)	184 (88.5%)		
Recurrences				
+	2 (3.1%)	13 (5.3%)	0.696[b]	0.578 (0.127–2.630)
–	62 (96.9%)	233 (94.7%)		
Dead of disease				
+	1 (1.6%)	9 (3.7%)	0.654[b]	0.418 (0.052–3.361)
–	63 (98.4%)	237 (96.3%)		
5-year recurrence-free survivals*				
+	8 (80.0%)	235 (95.5%)	0.085[c]	0.187 (0.035–0.988)
–	2 (20.0%)	11 (4.5%)		
5-year overall survivals*				
+		236 (95.9%)	0.361[b]	0.381 (0.044–3.309)
–	1 (10.0%)	10 (4.1%)		

*Only including patients whose information was available in the pooled studies

[#]Statistically significant

[a]Chi-square test

[b]Continuity correction

Table 4 (continued) [c]Fisher exact tests

Repeated statistical testing in a meta-analysis increase the risk of false positive or negative results [27, 28]. These risks can be controlled by TSA [29–32]. This analysis pooled 818 patients. However, the TSA showed that all of the *Z*-curves did not cross the red horizontal lines, indicating the possibility of false negative results; thus, the cumulative cases were not up to the required sample size. Therefore, further CCTs are warranted to validate the security of RT in the treatment of patients with lesions less than 2 cm.

Based on our data, approximately 30.2% of the patients had lesions 2–4 cm. However, few studies have specifically evaluated the safety and feasibility of fertility-preserving techniques for the management of this patient group because a larger tumor size is significantly related to LNM, positive LVSI and recurrence [1, 12, 13, 17]. RVT achieved less extensive parametrectomy in the treatment of patients with lesions larger than 2 cm [33–35]. In contrast, RAT allows larger and wider resection of the parametria than RVT [7, 36, 37] Several retrospective studies [14, 34, 38] have demonstrated that the oncological safety of RAT is equal to that of RH for the treatment of patients with lesions 2–4 cm. RAT has been considered suitable for carefully selected individuals with lesions up to 4 cm [34, 39–43]. In a systematic review, Pareja et al. [44] pooled 443 early-stage patients with cervical carcinoma treated with RAT. The authors revealed that the recurrence and death rates were relatively low in this patient group and that the pregnancy rates of patients who attempted to become pregnant were encouraging. In this analysis, the recurrence rate was 3.1% and the mortality rate was 1.6% in the RAT group. Additionally, we demonstrated that patients with lesions 2–4 cm, positive PI and LVSI were significantly more likely to be treated with RAT than RVT. These factors were definitely adverse prognostic factors for early-stage patients with cervical carcinoma [10, 22]. All these data indicated that RAT was a safe treatment option for patients with early-stage cervical cancer and an interest in preserving fertility. However, the pregnancy rates after RAT were poorer than those after RVT due to radical parametrectomy and the need for adjuvant therapy as a result of high-risk factors [44, 45]. Overall, RVT was suitable as a fertility-sparing procedure for patients with lesions less than 2 cm. RAT can be a feasible alternative to RH for patients with lesions 2–4 cm and without evidence of infertility. However, the potential recurrence risk should be fully discussed. Furthermore, the safety and feasibility of these procedures require further evaluation.

Based on our data, adjuvant chemoradiation was more likely to be performed in the RAT subgroup because this patient group had significantly more adverse survival factors. Adjuvant chemoradiation has potential prognostic benefits [22, 46, 47] but damages reproductive functions to some extent [48]. Ovarian cryopreservation and ovarian transposition during surgery has been shown to be effective for the preservation of ovarian function [49–53]. Precise radiation also has advantages in reducing the radiation dose and preserving ovarian function [54, 55]. All these methods are beneficial for reductions in the toxicity of chemoradiation.

LNM was a significant prognostic factor for early stage cervical carcinoma [1]. Lymphadenectomy was performed in all patients in this analysis. However, the rate of LNM was only 5%. Therefore, this patient group may be over-treated to some extent. Sentinel lymph node (SLN) biopsy combined with an imaging examination, such as MRI, could improve the accuracy of detection and mapping of the lymph node status and facilitate the evaluation of LNM [56, 57].

The major limitation of this study was the potential publication bias. Nevertheless, this study found that none of the meta-analyzes and TSA analyzes showed significant differences between RT and RH. More CCTs are needed to verify these conclusions. Additionally, a statistical analysis was performed for specific clinical parameters between different groups (between RT and RH and between RAT and RVT).

Conclusions

RT, especially RVT, seemed to be safe and effective for the management of early-stage patients with cervical cancer whose lesions are less than 2 cm and section margins are negative as a fertility-sparing procedure. RAT can be a feasible alternative to RH for those patients who with lesions 2–4 cm, desire fertility preservation and without any evidence of infertility under fully informed consent. However, more CCTs with larger sample size are still required for further validation.

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Compliance with ethical standards

Conflict of interest A similar abstract we wrote was published in the journal of Obstetrics & Gynecology. Author Ying Feng declares that she has no other conflict of interest. Author Zihan Zhang declares that she has no other conflict of interest. Author Tong Lou declares that she has no other conflict of interest. Author Shuzhen Wang declares that she has no other conflict of interest. Author Huimin Bai declares that she has no other conflict of interest. Author Zhenyu Zhang declares that he has no other conflict of interest.

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