RESEARCH ARTICLE

Total Laparoscopic Hysterectomy Versus Total Abdominal Hysterectomy for Endometrial Cancer: A Meta-analysis

Hui-Ling Wang[1], Yan-Fang Ren[1]*, Jun Yang[1], Rui-Ying Qin[1], Kai-Hua Zhai[2]

Abstract

The standard surgery for early-stage endometrial cancer is total abdominal hysterectomy (TAH), while total laparoscopic hysterectomy (TLH) is less invasive and assumed to be associated with lower morbidity. This meta-analysis was performed to investigate the effects of TLH versus TAH in women with early-stage endometrial cancer. We searched the PubMed, EMBASE, CBM and Cochrane Review databases for randomized trials assessing the effects of TLH versus TAH in women with early-stage endometrial cancer. The relative risks (RR) with 95% confidence intervals (CIs) from each study were pooled using meta-analysis. In our study, 9 randomized trials with a total of 1,263 patients were included. Meta-analyses showed that TLH was associated with lower risks of major complications (RR = 0.53, 95%CI 0.29-0.98, *P* = 0.042), total complications (RR = 0.59, 95%CI 0.42-0.82, *P* = 0.002) and postoperative complications (RR = 0.57, 95%CI 0.40-0.83, *P* = 0.003). However, there were no obvious differences in risks of intra-operative complications (RR = 0.98, 95%CI 0.62-1.55, *P* = 0.919) and mortality (RR = 0.96, 95%CI 0.66-1.40, *P* = 0.835). In conclusion, our results provide new evidence of a benefit for TLH over TAH in terms of major complications, total complications and postoperative complications in endometrial cancer patients.

Keywords: Endometrial cancer - total abdominal hysterectomy - total laparoscopic hysterectomy - meta-analysis

Asian Pacific J Cancer Prev, **14 (4)**, 2515-2519

Introduction

Endometrial cancer is the third most common cancer in women accounting for 6-9% of all cancers in female patients (Jemal et al., 2010; Jemal et al., 2011; Rowlands et al., 2011). Endometrial cancer mainly occurs in postmenopausal women and 90% of patients are older than 50 years (Tangjitgamol et al., 2010; Saso et al., 2011). Since postmenopausal bleeding is an early and obvious sign, most patients (75%) are diagnosed at an early stage (Salani et al., 2011; Saso et al., 2011). Standard treatment for patients with early-stage endometrial cancer is total abdominal hysterectomy (TAH) and bilateral salpingooophorectomy and/or pelvic and/or para-aortic lymph node dissection (El-Nashar and Mariani, 2011; Kehoe and Miller, 2011; Salani et al., 2011). Although TAH is an effective treatment, morbidity associated with laparotomy can be substantial (particularly wound complications) because of the high incidence of obesity and comorbidity in this population (El-Nashar and Mariani, 2011; Manchana, 2011). An alternative approach for patients with early endometrial cancer is total laparoscopic hysterectomy (TLH) (Carter, 2011; Frumovitz et al., 2011). Several prospective controlled studies showed that TLH was an effective, minimally invasive, safe alternative to TAH for benign indications (Mueller et al., 2010; Carter, 2011). However, previous randomized studies of TLH versus TAH in patients with endometrial cancer are limited, and more importantly, are not powered enough to give a precise estimate of the effects (Carter, 2011). Based on these considerations, in order to obtain a more consistent appraisal of the evidence regarding the effects of TLH to endometrial cancer, we conducted a meta-analysis of randomized trials quantitatively regarding clinical outcomes including complication rates and mortality rate.

Materials and Methods

Search strategy and eligibility criteria

Randomized controlled trials were identified from PubMed, EMBASE, CBM and Cochrane Review databases. The search terms used for the retrieval of relevant studies were: ("laparoscopic hysterectomy" or "laparoscopy") and ("abdominal hysterectomy" or "laparotomy") and "endometrial cancer" or "endometrial carcinoma") and ("RCT" or "randomized" or "randomized controlled trial"). There was no restriction by year of publication, language, or publication status applied. The reference lists of identified studies and relevant review

*[1]Department of Obstetrics and Gynecology, [2]Department of Neurology, the First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China *For correspondence: wanghuiling0518@126.com*

Table 1. Summary of the Pooled Results in This Meta-analysis

Comparison items	No. of included studies	Pooled RR		Heterogeneity		Model
		RR [95%CI]	*P* value	I^2 (%)	P_H [1]	
Major complications	8	0.53(0.29-0.98)	0.042	52.80%	0.038	Random
Mortality	6	0.96(0.66-1.40)	0.835	0%	0.749	Fixed
Total complications	9	0.59(0.42-0.82)	0.002	63.80%	0.005	Random
Intra-operative complications	7	0.98(0.62-1.55)	0.919	20.50%	0.273	Fixed
Postoperative complications	8	0.57(0.40-0.83)	0.003	52.20%	0.041	Random

[1] P_H, the *P* value of heterogeneity analysis

articles were searched for additional studies. Trials that met the following criteria were eligible for inclusion in this study: (i) randomized controlled trials, (ii) participants with a clinical diagnosis of endometrial cancer, (iii) assessing the effects of TLH versus TAH in women with early-stage endometrial cancer.

Data extraction and main endpoints

The details extracted were the study and patient population characteristics, the nature of the intervention and comparator, outcomes assessed, and study quality. The quality of randomized controlled trials included into this meta-analysis was assessed by the Jadad's score (Jadad et al., 1996). Randomized controlled trials with scores no less than 3 points were defined as high quality randomized controlled trials, while randomized controlled trials with scores less than 3 point were defined as lesser quality randomized controlled trials. The primary end-points were the major complication rate and mortality rate, while the second end-points were total complication rate, postoperative complication rate and intra-operative complication rate. The major complications included injuries of bowel, bladder, ureter, vessel, nerves; thrombo-embolic events such as DVT (Deep Venous Thrombosis) or pulmonary embolism; haematoma requiring surgical intervention; hemorrhage requiring transfusion and/or surgical intervention; wound dehiscence requiring surgical intervention or re-admission; wound infections including vaginal vault abscess, requiring surgical intervention and/or prolonged hospital stay and/or readmission and/or treatment; other major complications (Janda et al., 2010; Mourits et al., 2010).

Statistical analysis

In each study the relative risk (RR) with a 95% confidence interval (CI) was calculated for dichotomous outcomes. To assess the between-study heterogeneity more precisely, both the chi-square based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation attributable to heterogeneity were calculated (Cochran, 1954; Higgins et al., 2003). A significance level of less than 0.10 for the chi-square test was interpreted as evidence of heterogeneity (Higgins et al., 2003). When there was no statistical evidence of heterogeneity, a fixed effect model was adopted otherwise, a random effect model was chosen (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986). Publication bias was investigated by funnel plot and an asymmetric plot suggested possible publication bias (Stuck et al., 1998). In addition, funnel-plot asymmetry was assessed by the method of Egger's linear regression test (Egger et al., 1997). Statistical analyses were performed with the software program STATA (Version 12.0, StataCorp LP, College Station, TX, USA). All *P* values were two-sided and a *P* value of less than 0.05 was deemed statistically significant.

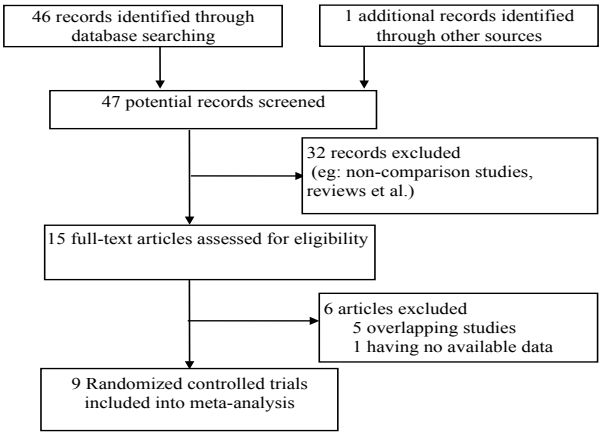

Figure 1. Flow Chart Demonstrating Selection of Studies for Inclusion in the Meta-analysis

Results

Characteristics of included studies

The initial search identified 47 citations, of which 32 referred to editorials, non-comparison studies or reviews, and 15 were examined in more detail (Figure 1). Six studies were further excluded including one study for no available data (Nicklin et al., 2011) and 5 overlapping studies (Tozzi et al., 2005; Zullo et al., 2005; Bijen et al., 2009; Bijen et al., 2011; Bijen et al., 2011). Finally, nine randomized controlled trials with a total of 1263 patients were included into this meta-analysis (Fram, 2002; Tozzi et al., 2005; Zorlu et al., 2005; Chen and Huang, 2007; Wang, 2008; Malzoni et al., 2009; Zullo et al., 2009; Janda et al., 2010; Mourits et al., 2010). The sample size in each trial was relatively small, ranging from 52 to 332 participants. The quality of randomized controlled trials was assessed by the Jadad's score, and 5 trials were high quality randomized controlled trials with scores no less than 3 points (Tozzi et al., 2005; Malzoni et al., 2009; Zullo et al., 2009; Janda et al., 2010; Mourits et al., 2010).

Meta-analysis

Table 1 summarized the main results of this meta-analysis. TLH were associated with lower risks of major complications (RR = 0.53, 95%CI 0.29-0.98, *P* = 0.042),

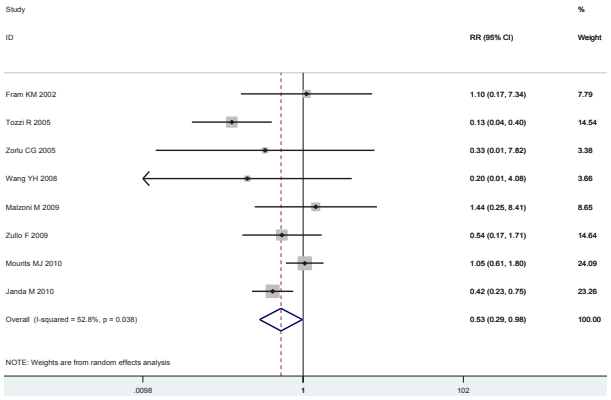

Figure 2. Forest Plot of Pooled RR with 95% CI for Comparing TLA with TAH for Early-stage Endometrial Cancer on the Assessment of Major Complications

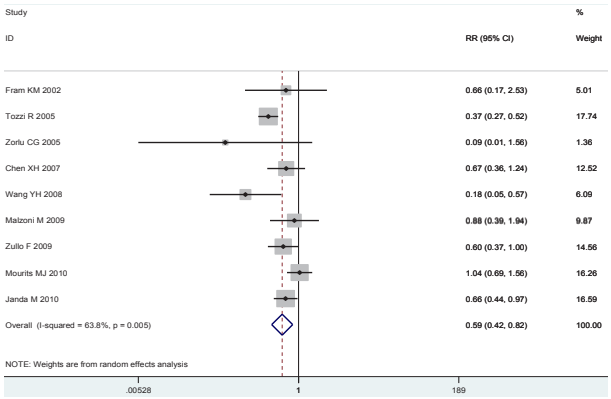

Figure 3. Forest Plot of Pooled RR with 95% CI for Comparing TLA with TAH for Early-stage Endometrial Cancer on the Assessment of Total Complications

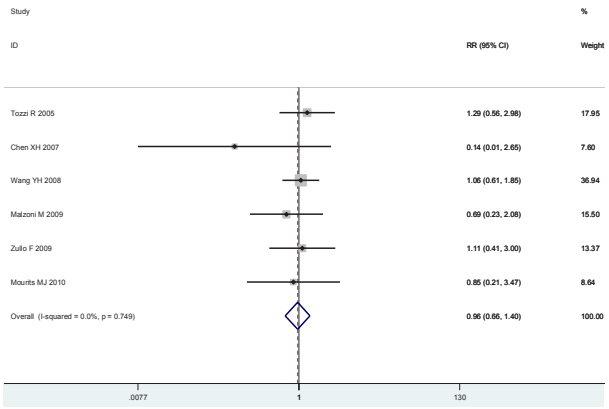

Figure 4. Forest Plot of Pooled RR with 95% CI for Comparing TLA with TAH for Early-stage Endometrial Cancer on the Assessment of Mortality

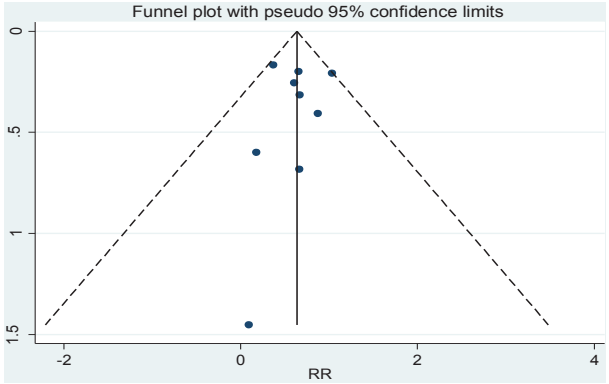

Figure 5. Funnel Plot to Assess Publication bias in the Meta-analysis of Comparing TLA with TAH for Early-stage Endometrial Cancer on the Assessment of Total Complications (*P* Egger's test = 0.947)

total complications (RR = 0.59, 95%CI 0.42-0.82, *P* = 0.002) and postoperative complications (RR = 0.57, 95%CI 0.40-0.83, *P* = 0.003) compared with the TAH group (Figure 2, Figure3). But there was no obvious difference in risks of intra-operative complications (RR = 0.98, 95%CI 0.62-1.55, *P* = 0.919) and mortality (RR = 0.96, 95%CI 0.66-1.40, *P* = 0.835) (Figure 4).

Assessment of publication bias

Funnel plot and Egger's test were performed to assess the publication bias in this meta-analysis. The Funnel plots' shape for the meta-analyses for the assessment of total complications was symmetrical and did not showed obvious evidence of asymmetry (Figure 5). The Egger's test also suggested obvious evidence of symmetry in the meta-analysis for the assessment of total complications (P Egger's test > 0.05) (Figure 5). Thus, the results above suggested that publication bias was not evident in this meta-analysis.

Discussion

Previous prospective controlled studies showed that TLH was an effective, minimally invasive and safe alternative to TAH for patients with endometrial cancer. Two meta-analyses have been published to give a comprehensive review on the effects of TLH compared with TAH (Ju et al., 2009; Palomba et al., 2009). However, previous randomized studies of TLH versus TAH in patients with endometrial cancer are limited, and more importantly, are not powered enough to give a precise estimate of the effects (Ju et al., 2009; Palomba et al., 2009). Two new randomized studies with large sample size were published to further assess the safety of TLH (Janda et al., 2010; Mourits et al., 2010). The outcomes from these two new randomized studies were also inconsistent from each other in terms of the safety of TLH (Janda et al., 2010; Mourits et al., 2010). Besides, previous meta-analyses didn't include studies published in Chinese, which could cause the selection bias (Ju et al., 2009; Palomba et al., 2009). Thus, in order to obtain a more consistent appraisal of the evidence regarding the effects of TLH to endometrial cancer, we conducted a meta-analysis of randomized trials quantitatively regarding clinical outcomes including complication rates and mortality rate.

Some possible limitations to this meta-analysis should be acknowledged. First, the eligibility criteria for inclusion of patients with endometrial cancer differed for each study, which might influence the obvious consistency of effects across the included studies and cause obvious between-study heterogeneity in this meta-analysis. Besides, to ensure uniformity in defining both patient characteristics for endometrial cancer and clinical efficacy measures,

a meta-analysis of individual patient data is needed (Simmonds et al., 2005). Second, the clinical outcomes of TAH or TLH and bilateral salpingooophorectomy and/or pelvic and/or para-aortic lymph node dissection differed, but we didn't perform subgroup analyses according to the combined treatment status such as salpingooophorectomy and/or pelvic and/or para-aortic lymph node dissection owing to the limited studies reported in the original papers (Ju et al., 2009; Palomba et al., 2009; Kehoe and Miller, 2011; Saso et al., 2011). Thus, further studies could compare TAH and TLH according to the different status of the combined treatment. Finally, owing to the lack of relative information, the risk of biases could not be well assessed and the outcomes from this study might be affected by risk of biases from those included studies. Besides, randomized controlled trials using longer term outcome assessments and more patient outcomes are urgently needed to identify the outcome from this meta-analysis (Janda et al., 2010; Mourits et al., 2010).

We included 9 RCTs (with a total of 1263 patients) into this meta-analysis. Meta-analyses showed that TLH was associated with lower risks of major complications (RR = 0.53, 95%CI 0.29-0.98, P = 0.042), total complications (RR = 0.59, 95%CI 0.42-0.82, P = 0.002) and postoperative complications (RR = 0.57, 95%CI 0.40-0.83, P = 0.003). But there was no obvious difference in risks of intra-operative complications (RR = 0.98, 95%CI 0.62-1.55, P = 0.919) and mortality (RR = 0.96, 95%CI 0.66-1.40, P = 0.835).

As to the complications, there was a lower risk of postoperative complications in patients undergoing TLH, but there was no difference in risks of both intra-operative and complications, confirming the results previous two meta-analyses (Ju et al., 2009; Palomba et al., 2009). However, previous meta-analyses didn't assess the safety of TLH in terms of major complications and total complications (Ju et al., 2009; Palomba et al., 2009). Our meta-analysis shows that TLH was associated with lower risks of major complications (RR = 0.53, 95%CI 0.29-0.98, P = 0.042), total complications (RR = 0.59, 95%CI 0.42-0.82, P = 0.002), which suggest TLH is safer than TAH for patients with endometrial cancer. Compared with those two previous meta-analyses suggesting TLH is as safe as TAH (Ju et al., 2009; Palomba et al., 2009), our meta-analysis further suggest TLH is safer than TAH for patients with endometrial cancer and obtain a more consistent appraisal of the evidence regarding the effects of TLH to endometrial cancer.

In conclusion, compared with TAH, TLH can benefit patients with endometrial cancer with lower risks of major complications, total complications and postoperative complications. Besides, randomized controlled trials using longer term outcome assessments and more patient outcomes are urgently needed to further identify the long term outcomes of TLH for patients with endometrial cancer.

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