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The necessity of radical hysterectomy (RH) for pure endometrial carcinoma combined with cervical involvement: a retrospective cohort study comparing RH with total hysterectomy (TH)

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Abstract

Objective: The purpose of this study was to explore the necessity of radical hysterectomy (RH) for patients with pure endometrial carcinoma (PEC) combined with cervical involvement by comparing with total hysterectomy (TH). **Methods:** A total of 162 patients who were diagnosed as PEC combined with cervical involvement of stage II and III by postoperative pathological examination between January, 2007 and December, 2017 were included in our study. Among of them, 91 were followed up till the end of this study and 71 were lost in the follow-up. In the 91 patients with complete follow-up information, 34 patients were treated with TH and 57 patients were treated with RH. The 5-year progression free survival rate, 5-year overall survival rate, recurrence rate and postoperative complications of patients were evaluated. **Results:** There were no significant differences in both the overall survival curve and progression free survival curve between patients with PEC receiving RH and those receiving TH (both $p > 0.05$). The analysis of postoperative complications showed that patients with RH treatment may have a higher probability of postoperative lymphocyst and urinary dysfunction. **Conclusions:** RH may not improve the prognosis of cervical involvement in patients with PEC. The postoperative complications of patients with PEC who treated with RH may increase.

Keywords: radical hysterectomy; total hysterectomy; pure endometrial carcinoma; cervical involvement

Introduction

Endometrial carcinoma (EC) is one of the most common gynecological carcinomas (GCs) in the world, and it is also the major cause of death for patients with GCs. Endometrial cancer is most prevalent in elderly and obese women with cardiovascular and metabolic diseases [1]. The treatment of EC is based on the stages of canceration and histological types. Clinical treatment methods mainly include total hysterectomy (TH), radical hysterectomy (RH), radiotherapy, and chemotherapy [2]. Most patients with endometrial cancer are diagnosed and treated early (80% in stage I), with a 5-year survival rate exceeding 95%. However, if there is regional transmission or distant disease, the 5-year survival rate is much lower (68% and 17%, respectively) [3].

Based on the National Comprehensive Cancer Network (NCCN) 2018 guidelines, both RH and TH were acceptable options for patients with pure endometrial carcinoma (PEC). In this case, there are many arguments about whether RH or TH should be used in patients with stage II PEC. According to Phelippeau's research, the types of hysterectomy did not make any difference to the overall survival (OS) rate [4]. This can be confirmed by the 3-year OS rates of patients with estrogen dependent EC, with 94.1% in RH group and 88.7% in TH group. Similarly, Takano's research also showed that RH and modified RH did not impact the five-year OS rates and progression-free survival (PFS) rates of patients with EC combined with a cervical involvement rates, with 83.6% in RH and 84% in TH for five-year OS rate, and 71.6% in RH and 66.4% in TH for five-year PFS rates [5]. Similar results were found

in Wright's study [6]. Besides, in Lee's study, he found it cannot conclusively refute or support the necessity of RH in the treatment for patients with cervical extension.

On the contrary, many researchers have argued that RH did improve the prognosis, and prevent local recurrences in patients with EC combined with cervical involvement. In Sartori's study, the researchers enrolled 203 patients with Stage II (IIa & IIb) EC, and analyzed the survival outcomes of the patients who received TH or RH treatments [8]. Their results indicated that the patients in the TH and RH groups had 5-year survival rates of 79% and 94%, and 10-year survival rates of 74% and 94%, respectively. The total recurrence and local recurrence rates were 7.4% and 2.9% in the RH group and 17.6% and 10.3% in the TH group. Similar results were also found in the Mariani and Cornelison's studies [9, 10].

In the mentioned studies above, the staging methods were based on the staging system developed by the International Federation of Obstetricians and Gynecologists (FIGO) in 1998, which had included the patients with EC combined with cervical glandular involvement (stage IIa) in the system. In the FIGO 2009 version, the stage IIa was re-categorized to stage I due to its relatively improved prognosis. Elshaikh assessed the subjects using the FIGO 2009 Staging System, and found that the survival rate of the patients with Stage II endometrial cancer in the RH group was higher than that in the TH group [11]. However, in Ozgul's study, he also used the FIGO 2009 staging system, and found that hysterectomy improved neither the disease free survival nor overall survival in patients with EC combined with cervical involvement.

In this study, we analyzed the prognosis of patients with PEC combined with cervical

involvement who were treated with RH or TH, and provided some evidence on that which type of surgery methods for treating patients with PEC combined with cervical involvement was effective.

Subjects and Methods

Subjects

This study was approved by the ethics committee of the Obstetrics and Gynecology Hospital of Fudan University. All patients signed the informed consent. A total of 162 patients who were diagnosed as PEC combined with cervical involvement of stage II and III by postoperative pathological examination between January, 2007 and December, 2017 were included in our study. Among of them, 91 of them were followed up till the end of this study and 71 were lost in the follow-up. In the 91 patients with complete follow-up information, 34 patients were treated with TH and 57 patients were treated with RH. Inclusion criteria: (a) patients with endometrial adenocarcinoma who were treated between January, 2013 and December, 2017; (b) patients who had cervical involvement by postoperative pathological examination; (c) patients who received RH or TH as their primary surgery. Exclusion criteria: (a) patients without cervical involvement; (b) patients treated without surgeries; (c) patients treated with secondary surgeries; (d) patients with carcinosarcoma or endometrial stroma sarcoma or stage II endometrial cancer diagnosed by postoperative pathological examination.

Entry methods

The choice of RH or TH was based on a discussion between the doctors and the patients, and considered the physical status of the patients, the optimal resections of the tumors, the follow-up treatment, and the patients' life quality after surgeries. The patients made the final decisions on the choice of treatment. The clinical data included the type of surgery, complications which were related with the surgery, adjuvant therapies, as well as the follow-up data that included the recurrent site and patient status of their last visit. The pathological data of FIGO stage, histological type, tumor grade, depth of myometrial invasion, cervical interstitial invasion, lymphatic vessel invasion and retroperitoneal lymph node invasion were analyzed. At least one pathologist performed a formal review of the pathological data. The pathologist analyzed the pathological reports to determine the cervical lesion and its stage.

Total hysterectomy (TH)

TH surgeries for patients in TH group were performed by a supervised, board-certified, gynecologic oncologist. Uterine support structures and vaginal canals were severed near the uterine attachment site. There was an extra fascial technique implemented that removed some of the vaginal wall without leaving residual cervical area [13].

Radical hysterectomy (RH)

RH surgeries for all patients in RH group were performed by a supervised, board-certified, gynecologic oncologist. Both the paravesical space and the pararectal space were extended, and the anterior, middle, and posterior uterine supports were separated and severed. Portions of the vaginal wall and pelvic connective tissues were

widely excised, and a regional pelvic node dissection was performed. The cardinal ligament was severed near the pelvic wall, and the anterior layer of the vesico-uterine ligament was separated and severed. The ureters were detached and displaced laterally, and the posterior layer was separated and severed. The rectovaginal ligament and the interspace ligament were severed. The paravaginal connective tissue and a portion of the vaginal wall (at least 3 cm) were then excised [14].

Definition of survival rates

The progression-free survival rate was measured from the date of the primary surgery to the date of a subsequent relapse, progression, or to the last contact for the disease-free patients. The overall survival rate was measured from the date of the primary surgery to the death or the last contact.

Statistical analysis

Statistical analysis was made by software SPSS17.0 (International Business Machines, corp., Armonk, NY, USA). The Kaplan–Meier method was used to calculate the survival distribution of patients. The significance of the survival distribution in each group was tested using the log-rank test. A *P*-value of less than 0.05 was considered to be statistically significant.

Results

General clinical data

In total, the clinical data from 250 patients with EC combined with cervical involvement between January, 2007 and December, 2017 were extracted from the

database of Obstetrics and Gynecology Hospital of Fudan University. Among them, 162 patients suffered from pure endometrioid carcinoma (PEC), in which 91 patients were followed up until the end of our study, and 71 patients were lost in the follow-up period. Among the 91 patients with a complete set of follow-up data, 34 patients were treated with TH and 57 patients were treated with RH.

Baseline characteristics

The median follow-up time for the TH group and RH group was 37 months and 35 months, respectively. There was no significant difference in the median ranges for the onset age and menopause age between the patients treated with TH and RH ($P > 0.05$) (**Table 1**). In addition, most of the patients who went to the hospital had presented with irregular vaginal bleeding and post-menopause vaginal bleeding.

As far as the surgery procedures were concerned, 10 patients received laparotomy and 24 patients received laparoscopy in the TH group, while 14 patients received laparotomy and 43 patients received laparoscopy in the RH group. Additionally, 28 patients accepted pelvic lymph node dissection and 8 patients accepted para-aortic lymph node dissection in TH group, while all the patients received pelvic lymph nodes dissection and 18 patients accepted para-aortic lymph nodes dissection in the RH group.

After the operation, in the TH group, 17 patients received radiotherapy, 16 patients did not accept radiotherapy, and 1 patient had an unknown status, and 15 patients received chemotherapy and 19 patients did not.

After the operation, in the RH group, 35 patients received radiotherapy, 21 patients

did not accept any radiotherapy, and 1 patient had an unknown status, and 30 patients received chemotherapy and 27 patients did not. In all patients, 35 patients received radiotherapy combined with chemotherapy, of which 25 patients were in the RH group and 10 patients were in the TH group.

Pathological findings

There were 29 patients with PEC in stage II cervical invasion and 5 patients with PEC in stage III cervical invasion in the TH group. There were 44 patients with PEC in stage II cervical invasion and 13 patients with PEC in stage III cervical invasion in the RH group. In terms of grade designation, there were 21 patients with grade 1 (G1), 9 patients with grade 2 (G2) and 4 patients with grade 3 (G3) in TH group, while there were 21 patients with G1, 27 patients with G2 and 7 patients with G3 in RH group. In the TH group, there were 21 patients with myometrial invasion less than 1/2 and 12 patients with myometrial invasion more than 1/2, while there were 34 patients with myometrial invasion less than 1/2 and 23 patients with myometrial invasion more than 1/2 in the RH group. The lymph-vascular space invasion (LVSI) was observed in 27 patients in TH group, and in 18 patients in the RH group. In the TH group, 3 patients had a metastasis on the pelvic lymph nodes, and 1 patient had a metastasis on the para-aortic lymph nodes. Meanwhile, in the RH group, 8 patients had a metastasis on the pelvic lymph nodes and none had a metastasis on the para-aortic lymph nodes.

Interestingly, it was found that grade 3, $\geq 1/2$ myometrial invasion, serosa invasion, pelvic lymph nodes metastasis and lymph-vascular invasion were the most frequent risk factors for recurrence of PEC (**Table 2**).

Survival outcomes

The 5-year overall survival rates in the TH group and RH group were 90.8% and 90.1%, respectively ($P = 0.846$). The 5-year progression free survival rates in the TH and RH group were 86.2% and 92.6% ($P = 0.358$). Although there was no significant difference in the progression free survival between the TH and RH group, we can observe that there was a trend that patients in the RH group had a higher progression free survival rate in comparison with the TH group (**Figure 1**). All causes of death were disease progression, and the causes of relapse were distant metastases.

Most of the postoperative complications were lymphocyst (**Table 3**). There were 10 and 15 patients with postoperative lymphocyst in the TH group and RH group, respectively. To be noticed, the incidence of urinary incontinence and dysuria in the RH group was significantly higher than that in the TH group.

Discussion

In the current study, we managed to investigate what impact the surgery type had on the survival outcomes for patients with EC. The results showed that an RH procedure may not have an effect on the prognosis of patients with stage II & III PEC combined with cervical involvement, and it may increase the chance of postoperative complications, especially the complications of the urinary system.

Previously, it has been widely recognized that endometrial cancer combined with cervical involvement should be treated similarly to cervical cancer. That is, cutting off the parametrical portion and part of vaginal tissue. This treatment could improve the

patients' prognosis, just as patients with cervical cancer. However, whether cervical involvement could predict parametrical and vaginal metastases is still unclear. In Watanabe's research, it was concluded that a parametrical spread could not only be predicted by cervical involvement alone, but also be predicted by other various lymph-vascular space invasions related to the patient's histopathologic factors [15]. However, the results of Yura's research suggested that a parametrical metastasis was positively related to cervical involvement by univariate analysis [16]. In Tamussino's research, it was found that patients with a cervical stroma involvement had a high probability (46%) of having a parametrical metastasis, and thus a radical hysterectomy was recommended for these patients [17]. On the other hand, despite NCCN's recommendation of a radical hysterectomy for patients with endometrial cancer combined with cervical involvement, whether radical hysterectomy could effectively prevent parametrical and vaginal metastases has remained controversial. The major metastasis pattern for cervical cancer is a direct invasion [18], so resection of parametrical tissues can effectively prevent a pelvic recurrence. However, the prevalent metastasis pattern for endometrial cancer is a lymph-vascular invasion. Even in cases of patients having a parametrical invasion, as discussed in Watanabe's research, most of the parametrical spread occurred in the lymphatic system and blood vessels [15]. Thus, the resection of the parametrical tissues may not prevent the relapse of an endometrial cancer. However, instead of preventing a local recurrence, another important purpose for radical hysterectomy is to verify the surgical stage of the patients, and to direct the relevant adjuvant therapy. According to NCCN 2018,

the major adjuvant treatment option for the patients in stage II is radiotherapy, and the major adjuvant treatment of patients in stage IIIb is chemotherapy. Only radical hysterectomy could verify patients in stage IIIb. However, the incidence of postoperative metastasis after parametrical hysterectomy is very low and only 1 patient in our research study was found to have a parametrical metastasis. Further investigation is also needed to determine whether radical hysterectomy should be a routine procedure performed for patients with endometrial cancer combined with cervical involvement.

When it came to the postoperative complications, it was found in our study that the patients who had received an RH procedure may have an increased probability of lymphocyst and urinary incontinence. Compared with simple hysterectomy, radical hysterectomy may cut off more lymphatic vessels and nerves, and thus also take a longer time. This may be the reason that radical hysterectomy may lead to higher probability of Lymphocyst and urinary incontinence. Also, the rate of postoperative infection or the volume of blood loss may also increase. In Miyamoto's study, similar results were confirmed [19]. There was a correlation between a longer operation time and more frequent development of severe adverse events, such as blood loss and lymphedema. This was observed in the patients who received modified radical hysterectomy.

In the Gynecologic Oncology Group (GOG) 99 study [20], patients were divided into high-intermediate risk group if they met the following criteria, including any age with grade 2 or 3 tumor, LVSI, and outer-third myometrial invasion, or at least 50 years

with any two of the risk factors above, or at least 70 years with any one of the risk factors above. In our study, it was found that grade 3, $\geq 1/2$ myometrial invasion, pelvic lymph nodes metastasis and lymph-vascular invasion were high risk factors in determining of patients deaths. Concerning lymph nodes metastasis, there are tremendous researches about its metastasis status related with endometrial cancer's prognosis. It was acknowledged that positive lymph nodes biopsy may predict a recent or later recurrence. However, it was controversial about whether to practice lymph nodes dissection for every patient. In fact, we can also evaluate the lymph nodes metastasis status by CT or MRI, but both of their sensitivity were not very satisfying. Then we may wonder if there would be some serum molecular factors indicating the lymph nodes metastasis. For the endometrial cancer, there were few studies about this topic. But for other tumors, people had begun to study. In Juan Li's review, she summarized 9 possible predictive factors for esophageal lymph nodes metastasis.

In Yue Xu's study, it was found that tumor-associated glycoprotein 72 was a useful predictor factor for lymph nodes metastasis in esophagogastric junction adenocarcinoma [21]. Similarly, in Dalma Udovicic-Gagula's research, Ki-67 and estrogen receptor β were potential indicators of regional lymph node positivity for primary cutaneous melanoma [22]. In endometrial carcinoma, there may also be serum predictors of lymph nodes metastasis, and this needs our further study.

The strength of our study was that we enrolled all of the available patients with a cervical invasion, which meant that some patients in stage III and IV were also

included only if they had cervical stroma involvement. The follow-up time was also long enough to draw a meaningful conclusion. However, this research was limited by its small sample size, retrospective nature and high loss rate. This may reduce the reliability of the results.

Conclusion

Our study researched the survival, recurrence and postoperative complications of patients with PEC combined with cervical involvement. We found that radical hysterectomy may not have an effect on improving the prognosis of these patients with PEC. Moreover, the occurrence of postoperative complications may be higher after radical hysterectomy. In conclusion, RH may be unnecessary for patients with PEC in stage II and III combined with cervical involvement.

Declarations

The authors declare that they have no conflicts of interest.

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Figures

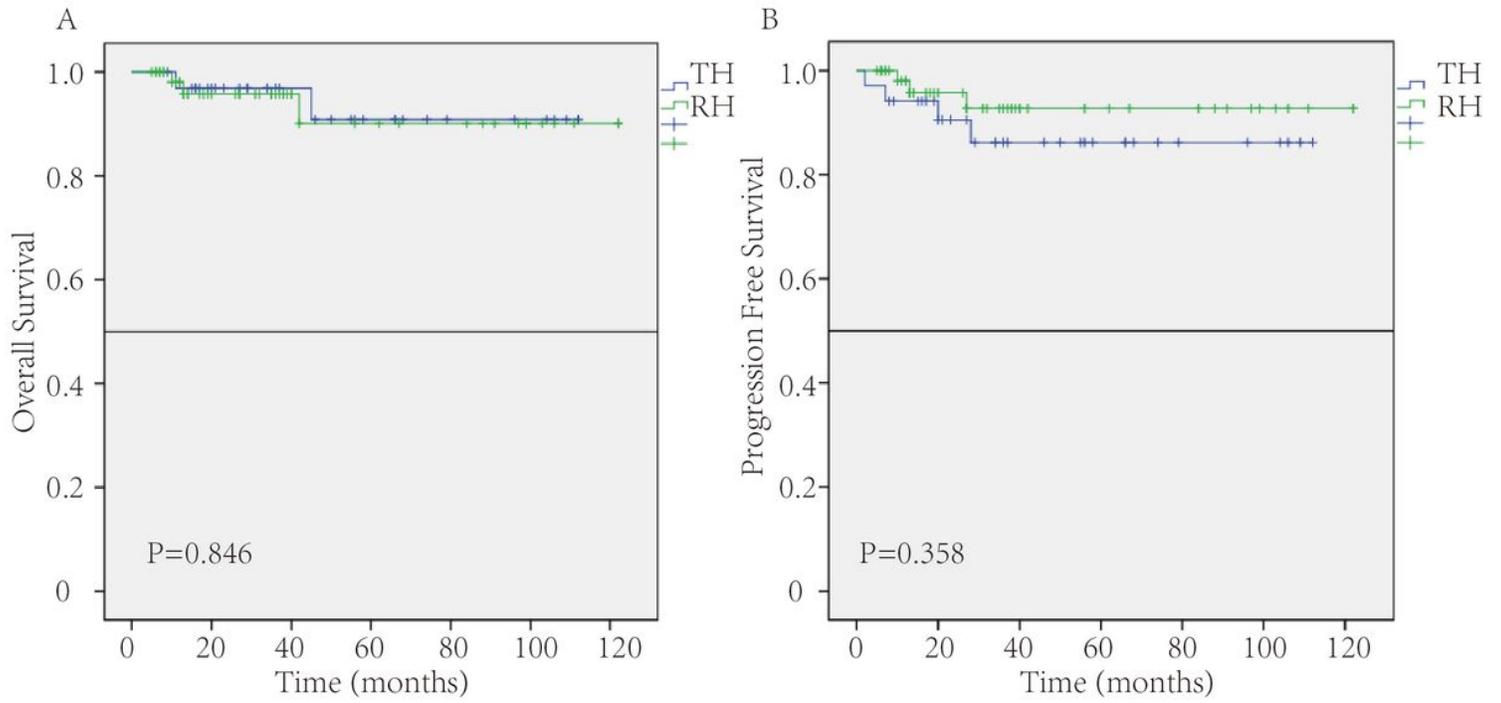


Figure 1

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