

Identification of risk factors for the prognosis of Chinese patients with endometrial carcinoma

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Abstract

This study aimed to retrospectively analyze risk factors for the prognosis of Chinese patients with endometrial carcinoma.

Total 600 patients who were admitted to the Department of Gynecology, the Fourth Hospital of Hebei Medical University and were pathologically diagnosed as endometrial carcinoma after surgery from January 1, 1997 to December 31, 2006 were selected, and the related factors affecting their prognosis were analyzed.

The survival of 600 patients with endometrial carcinoma was 2 to 136.5 months (average survival 57.39 ± 33.55 months), and 109 cases (18.2%) died from endometrial cancer. The overall survival rate of 1, 3, and 5 years after surgery was 96.8%, 89.9%, and 82.1%, respectively. Univariate analysis showed that age, menopausal status, pathological type, histological grade, pathological staging, tumor size, myometrial invasion, cervical involvement, ovarian metastasis, lymph node metastasis, and treatment method were the factors affecting the prognosis of endometrial carcinoma. Multivariate regression analysis showed that pathological type, histological grade, pathological staging, and cervical involvement were independent risk factors for the prognosis of endometrial carcinoma. The patients with high-grade and deep myometrial invasion, cervical involvement, full cavity tumor, and lymph node metastasis had a high incidence of ovarian metastasis.

Pathological type, histological grade, pathological staging, and cervical involvement are independent risk factors affecting the prognosis of Chinese patients with endometrial carcinoma.

Keywords: Chinese, endometrial carcinoma, prognosis, risk factor

1. Introduction

Endometrial carcinoma is one of the common malignant tumors in the female genital tract, accounting for 20% to 30% of the malignant tumors in the female genital tract. Endometrial carcinoma is the fourth most common cancer in women, and the incidence is second only to breast cancer, lung cancer, and intestinal cancer. Over the past 20 years, the incidence of endometrial carcinoma has increased significantly worldwide. However, due to the slow growth, late metastasis, and significant symptoms of endometrial carcinoma, most patients can be

diagnosed and treated in time. About 69% of endometrial cancer patients can be diagnosed when the tumor is confined to the uterus, so the overall survival rate is high.^[1] Endometrial carcinoma: molecular subtypes, precursors, and the role of pathology in early diagnosis.

Numerous studies have shown that prognostic factors in endometrial carcinoma include age, pathological type, histological grade, pathological staging, myometrial invasion, tumor location, tumor size, lymphovascular space invasion, cervical involvement, ovarian metastasis, lymph node metastasis, peritoneal lavage cytology, and hormone receptor status, and pathological staging and histological grade have been recognized as 2 important prognostic factors.^[2] However, it remains unclear whether these prognostic factors could predict the prognosis of endometrial cancer patients in Chinese. Therefore, in this study, we aimed to retrospectively analyze risk factors for the prognosis of Chinese patients with endometrial carcinoma. Total 600 patients with endometrial cancer who received surgical treatment for the first time in the Fourth Hospital of Hebei Medical University from January 1, 1997 to December 31, 2006 were enrolled, their clinical and follow-up data were analyzed retrospectively, and the related risk factors for the prognosis of endometrial carcinoma were identified.

2. Materials and methods

2.1. Subjects

This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University and all patients signed informed consent before enrollment into this study. A total of 600 endometrial cancer patients who received surgery for the first

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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time in the Fourth Hospital of Hebei Medical University from January 1, 1997 to December 31, 2006 were enrolled. Endometrial cancer was confirmed by surgical pathology. The survival was defined from the day of surgery to death or cutoff date. The deadline for follow-up was March 31, 2008. The inclusion criteria were as follows: 1) the first treatment of all cases was surgical treatment in our hospital; 2) pathologically diagnosed as endometrial carcinoma after surgery; and 3) the clinical data and follow-up data were complete. The exclusion criteria were as follows: 1) those who had received radiotherapy, chemotherapy, or hormone therapy before surgery were excluded; 2) those who had metastatic cancer and synchronous primary cancers of endometrium and ovary were excluded; and 3) those who had a history of other malignant tumors were excluded.

2.2. Data collection

The data of all patients were collected, including age, height, weight, complications (history of hypertension and diabetes), family history of malignant tumor in first-degree relatives, menstrual history, pregnancy history, surgical-pathological staging, pathological type, histological grade, myometrial invasion, cervical and ovarian metastasis, tumor location, tumor size, surgical method, and postoperative adjuvant therapy. Histological grading of endometrial carcinoma was judged as follows: G1 (low grade): non-squamous or mulberry-like solid growth area $\leq 5\%$; G2 (medium grade): non-squamous or mulberry-like solid growth area was 6% to 50%; and G3 (high grade): non-squamous or mulberry-like solid growth area $> 50\%$. Pathological staging of endometrial carcinoma was judged following the recommendation by International Federation of Gynecology and Obstetrics in October 1988. Ovarian metastasis in endometrial carcinoma was judged if the patients met 2 of the following criteria: (1) small ovary (diameter < 5 cm); (2) the bilateral ovaries were involved, and the ovaries were multinodular; (3) deep myometrial invasion in the uterus; (4) vascular invasion; and (5) fallopian tube involvement.

2.3. Follow-up

All patients were followed up by telephone, letters, and home visits to record the survival of patients: survival, death and causes of death, time of death, and postoperative treatment. The deadline for follow-up was March 31, 2008. Actually, 554 cases were followed up and 46 cases were lost to follow-up, and the follow-up rate was 92.3%.

2.4. Statistical analysis

Statistical analysis was performed using SPSS13.0 software. The survival rate was calculated by Kaplan–Meier method. The log-rank test was used for univariate analysis of survival-related factors, and Cox regression model was used for multivariate analysis. Data were compared with *t* test or χ^2 test. $P < .05$ was considered significant.

3. Results

3.1. General information

The onset age of 600 patients was distributed between 26 and 78 years, the average age at onset was 54.93 ± 8.36 years, and the median age was 55 years. Among them, 286 cases (47.7%) were

Table 1

Clinical data of 600 patients with endometrial carcinoma.

Clinical data		Cases	Percentage (%)
Age	< 55 yrs	286	47.7
	≥ 55 yrs	314	52.3
Clinical symptoms	Simple vaginal bleeding	488	81.4
	Abnormal vaginal discharge	67	11.2
	Vaginal bleeding + abnormal discharge	23	3.8
	Lower abdominal pain	14	2.3
	Asymptomatic or hypogastric mass	8	1.3
Complications	Hypertension	121	20.2
	Diabetes	32	5.3
	Hypertension + diabetes	26	4.3
	obesity	120	20.0
Family history of malignant tumor (first-degree relatives)	Gynecological malignancy	19	19.2
	Digestive system tumor	63	63.6
	Breast cancer	2	2.0
	Others	15	15.2
Menstrual history	Regular	569	94.8
	Irregular	31	5.2
Menopausal history	Premenopausal	215	35.8
	Postmenopausal	385	64.2
Surgical method	Total hysterectomy	144	24.0
	Subtotal hysterectomy	100	16.7
	Radical hysterectomy	356	59.3
Lymphadenectomy	Yes	240	40.0
	No	360	60.0
Treatment	Surgery	319	53.2
	Surgery + chemotherapy	196	32.7
	Surgery + radiotherapy	29	4.8
	Surgery + radiochemotherapy	56	9.3

< 55 years old and 314 cases (52.3%) were ≥ 55 years old (Table 1). About 85% of patients showed vaginal bleeding, including 194 cases (32.3%) with premenopausal vaginal bleeding and 316 cases (52.7%) with postmenopausal vaginal bleeding. There were 67 cases (11.2%) with simple abnormal vaginal discharge; 23 cases (3.8%) with vaginal bleeding and abnormal discharge, 14 cases (2.3%) with lower abdominal pain, and 8 cases (1.3%) with asymptomatic or only palpable lower abdominal mass (Table 1). There were 121 cases (20.2%) complicated with hypertension, 32 cases complicated with diabetes (5.3%), 26 cases (4.3%) complicated with hypertension and diabetes, and 120 cases (20.0%) complicated with obesity. Total 99 cases (16.5%) had first-degree relatives with history of malignant tumors. Among them, 19 cases (19.2%) had history of gynecological malignancies; 46 cases (46.5%) had history of esophageal cancer and gastric cancer, 9 cases had history of colorectal cancer (9.1%), and 8 cases (8.1%) had history of other gastrointestinal malignancies (including 6 cases of liver cancer and 2 cases of pancreatic cancer); 2 cases had history of breast cancer (2.0%); 9 cases had history of lung cancer (9.1%); 2 cases had history of urinary malignancy (2.0%) (Table 1). Among 600 patients, 569 cases (94.8%) had regular menstruation and 31 cases (5.2%) had irregular menstruation; 215 cases (35.8%) were pre-menopausal and 385 cases (64.2%) were menopausal. The menopausal age was 34 to 61 years, and the average menopausal age was 49.7 years. The menstruation span was 18 to 48 years, with an average of 33.9 years (Table 1).

3.2. Treatment methods

All the patients were initially treated with surgery, 144 cases (24.0%) underwent total hysterectomy, 100 cases (16.7%) underwent subtotal hysterectomy, and 356 cases (59.3%) underwent radical hysterectomy; 360 cases (60.0%) underwent pelvic lymphadenectomy and 240 cases (40.0%) did not undergo pelvic lymphadenectomy (Table 1). In addition, 319 cases (53.2%) did not receive postoperative adjuvant therapy, 196 cases (32.7%) received postoperative adjuvant chemotherapy, 29 cases (4.8%) received postoperative adjuvant radiotherapy, and 56 cases (9.3%) received postoperative radiotherapy combined with chemotherapy (Table 1).

3.3. Pathological status

For pathological stage, 424 cases (70.7%) were stage I, 81 cases (13.5%) were stage II, 89 cases (14.8%) were stage III, and 6 cases (1.0%) were stage IV.

For histological grading, 232 cases (38.6%) were Grade 1 (G1), 304 cases (50.7%) were Grade 2 (G2), and 64 cases (10.7%) were Grade 3 (G3).

For pathological types, there were 574 cases (95.7%) of endometrial carcinoma, including 541 cases (90.2%) of endometrial adenocarcinoma, 31 cases (5.2%) of adenoacanthoma, and 2 cases (0.3%) of adenosquamous carcinoma. There were 26 cases (4.3%) of non-endometrial carcinoma, including 7 cases (1.1%) of small cell carcinoma, 9 cases (1.5%) of mixed cell carcinoma, 1 case (0.2%) of squamous cell carcinoma, 3 cases of clear cell carcinoma (0.5%), 3 cases (0.5%) of undifferentiated carcinoma, and 3 cases (0.5%) of serous papillary adenocarcinoma.

For metastasis, 437 cases (72.8%) had no or shallow myometrial invasion, 163 cases (27.2%) had deep myometrial invasion, 43 cases (7.2%) had ovarian metastasis, and 132 cases (22.0%) had cervical involvement (Table 2).

3.4. Univariate analysis of prognosis factors of endometrial carcinoma

The overall survival rate of the patients at 1, 3, and 5 years after surgery was 96.8%, 89.9%, and 82.1%, respectively, and 109 cases (18.2%) died of endometrial carcinoma.

Table 2
Pathological data of 600 patients with endometrial carcinoma.

Pathological data		Cases	Percentage (%)
Surgical-pathological staging	Stage I	424	70.7
	Stage II	81	13.5
	Stage III	89	14.8
	Stage IV	6	1.0
Histological grade	G1	232	38.6
	G2	304	50.7
	G3	64	10.7
Pathological type	Endometrial carcinoma	574	95.7
	Non-endometrial carcinoma	26	4.3
Myometrial invasion	No/shallow myometrial	437	72.8
	Deep myometrial	163	27.2
Ovarian metastasis	No	557	92.8
	Yes	43	7.2
Cervical involvement	No	468	78.0
	Yes	132	22.0

The 5-year survival rate of patients under 55 years old or more than 55 years old was 86.5% and 78.0%, respectively, and the difference was statistically significant ($\chi^2=8.288$, $P<.05$).

The 5-year survival rate of 215 postmenopausal cases and 385 postmenopausal cases was 87.2% and 79.2%, respectively, and the difference was statistically significant ($\chi^2=8.207$, $P<.05$).

The 5-year survival rate of 574 cases of endometrial carcinoma and 26 cases of non-endometrial carcinoma was 85.2% and 21.6%, respectively, and the difference was statistically significant ($\chi^2=146.633$, $P<.001$).

The 5-year survival rate of 232 cases of grade G1, 304 cases of grade G2, and 64 cases of grade G3 was 93.6%, 83.7%, and 30.0%, respectively, and the difference was statistically significant ($\chi^2=170.911$, $P<.001$).

The 5-year survival rate of 421 cases of stage I, 81 cases of stage II, 89 cases of stage III, and 6 cases of stage IV was 90.9%, 74.9%, 50.3%, and 33.3%, respectively, and the difference was statistically significant ($\chi^2=105.619$, $P<.001$).

The 5-year survival rate of 437 cases with no/shallow myometrial invasion and 163 cases with deep myometrial invasion was 88.4% and 65.6%, respectively, and the difference was statistically significant ($\chi^2=41.841$, $P<.001$).

The 5-year survival rate of 468 cases without cervical involvement and 132 cases with cervical involvement was 88.2% and 57.1%, respectively, and the difference was statistically significant ($\chi^2=65.130$, $P<.001$).

The 5-year survival rate of 372 cases with tumors in the upper part of the uterine cavity, 40 cases with tumors in the lower part of the uterine cavity, and 188 cases with tumors in the full cavity was 83.7%, 78.7%, and 79.6%, respectively, and the difference was not statistically significant ($\chi^2=5.233$, $P>.05$).

The 5-year survival rate of 116 cases with tumor diameter <2 cm, 415 cases with tumor diameter ≥ 2 cm, and 69 cases with tumors in the full cavity was 88.3%, 83.7%, and 65.0%, respectively, and the difference was statistically significant ($\chi^2=13.729$, $P=.001$).

The 5-year survival rate of 43 cases with ovarian metastasis and 557 cases without ovarian metastasis was 34.7% and 85.7%, respectively, and the difference was statistically significant ($\chi^2=78.199$, $P<.001$).

The 5-year survival rate of 360 patients who underwent lymphadenectomy and 240 patients who did not undergo lymphadenectomy was 83.8% and 80.0%, respectively, and the difference was not statistically significant ($\chi^2=3.346$, $P>.05$).

The 5-year survival rate of 321 cases without lymph node metastasis and 39 cases with lymph node metastasis was 88.6% and 48.7%, respectively, and the difference was statistically significant ($\chi^2=39.772$, $P<.001$).

In particular, we examined the effect of surgical methods on the prognosis of 144 patients who underwent the total hysterectomy, 100 patients who underwent subtotal hysterectomy, and 356 patients who underwent radical hysterectomy, and their 5-year survival rate was 76.5%, 78.6%, and 85.4%, respectively. The survival curves showed that the difference was not statistically significant ($\chi^2=3.683$, $P>.05$) (Fig. 1).

Next, we examined the effect of treatment methods on the prognosis of 319 patients treated with surgery alone, 196 patients treated with surgery+chemotherapy, 29 patients treated with surgery+radiotherapy, and 56 patients treated with surgery+radiochemotherapy, and their 5-year survival rate was 56.0%, 73.8%, 83.4%, and 86.3%, respectively. The survival curves

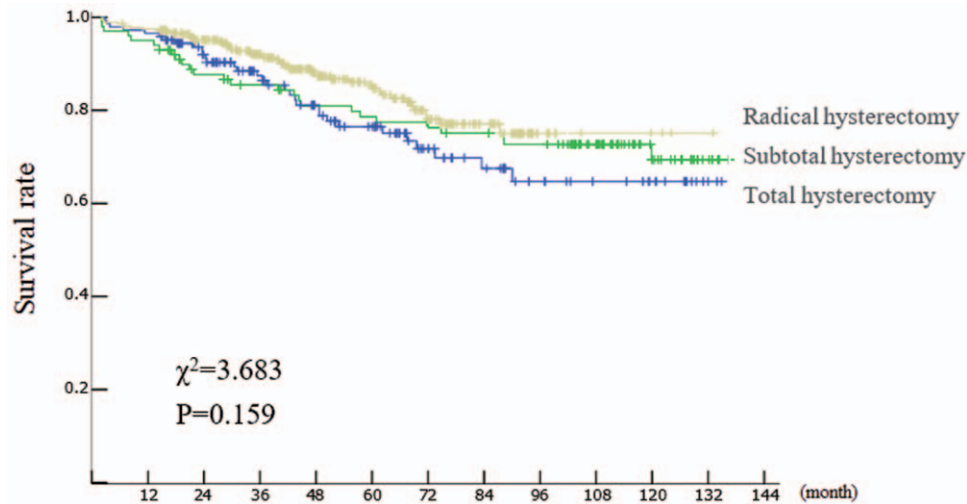


Figure 1. The survival curves of different groups with different surgical procedures for endometrial carcinoma.

showed that the difference was statistically significant ($\chi^2 = 26.063$, $P < .001$) (Fig. 2).

The Cox regression model was used to analyze prognostic factors with statistical significance in univariate analysis. The results showed that pathological type, histological grade, pathological staging, and cervical involvement were the independent risk factors of the prognosis of endometrial carcinoma (Table 3).

4. Discussion

Detailed clinicopathological data provide valuable information for predicting the prognosis of endometrial cancer patients and guiding the choice of treatment methods. In recent years, many studies on multivariate analysis of the prognostic factors in endometrial carcinoma have suggested that pathological staging and histological grade are 2 important independent prognostic factors.^[2] Hefler et al analyzed the data of 344 endometrial cancer patients and found that staging and age were independent

risk factors for the prognosis of endometrial carcinoma.^[3] However, whether age is an independent prognostic factor for endometrial carcinoma is still controversial. Ossewaarde et al believed that the survival rate of endometrial cancer patients at different ages was affected by other factors.^[2] Endometrial carcinoma is more common in postmenopausal women. Pellerin et al evaluated the clinical and follow-up data of 38 endometrial cancer patients under 45 years old. Compared with endometrial cancer patients over 45 years old, patients under 45 years old had lower staging, lower histological grade, and a better prognosis.^[4] Nakanishi et al reported similar results.^[5] However, another study showed no significant difference in clinical staging and histological type between endometrial cancer patients under 45 years old and elderly patients.^[6] The pathogenesis of endometrial carcinoma in postmenopausal women may be different from that in premenopausal women, and the prognosis is worse than that of postmenopausal women.^[7]

The results of this study showed that in the group younger than 55 years old and premenopausal group, histiocytic grade and the

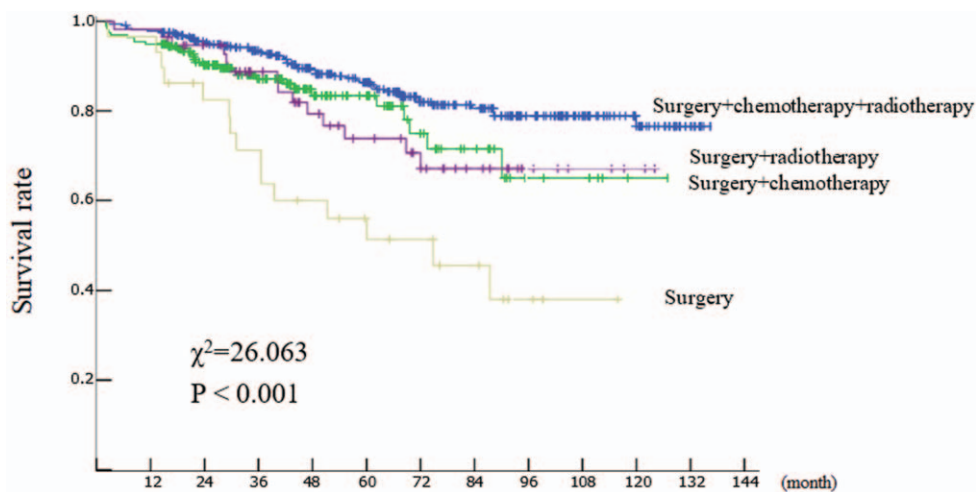


Figure 2. The survival curves of different groups with different treatment modalities for endometrial carcinoma.

Table 3**Independent prognostic factors of endometrial carcinoma by COX hazard model.**

Variable	B	SE	Wald	df	Sig.	Exp(B)
Pathological type	1.735	0.278	38.933	1	0.000	5.670
Cervical involvement	0.638	0.232	7.540	1	0.006	1.893
Pathological stage	0.502	0.123	16.559	1	0.000	1.652
Histological grade	0.816	0.182	20.092	1	0.000	2.262

incidence of deep myometrial invasion were low, and the 5-year survival rate was 86.5% and 87.2%, respectively; in the group over 55 years old and postmenopausal group, histiocytic grade and the incidence of deep myometrial invasion were high, and the 5-year survival rate was 78.0% and 79.2%, respectively. However, age and menopause were not independent prognostic factors of endometrial carcinoma, which may be related to different age, menopausal status, and clinicopathological characteristics.

The retrospective analysis of 181 cases of endometrial carcinoma by Steiner et al showed that histological type was an independent risk factor for prognosis.^[2] In this study, the 5-year survival rate of endometrioid carcinoma and non-endometrioid carcinoma was 85.2% and 21.6%, respectively, showing a significant difference in survival rate. In addition, non-endometrioid carcinoma had a high histiocytic grade and high incidence of deep myometrial invasion, similar to that reported in the literature.^[8] Therefore, pathological type is an independent risk factor for the prognosis of endometrial carcinoma.

Well-differentiated tumors tend to be confined to the endometrium, and even there is myometrial invasion, its effect on the prognosis is slight.^[9] In this study, the 5-year survival rate of grades G1, G2, and G3 was 93.6%, 83.7%, and 30.0%, respectively. Histological grade is an independent prognostic factor for endometrial carcinoma. The incidences of ovarian metastasis and lymph node metastasis in patients with low histological grade were both significantly lower than those in patients with high histological grade. Therefore, the histological grade can be used as an important indicator to judge the prognosis of endometrial carcinoma.

It was reported that the 3-year overall survival rate of endometrial cancer patients was 93.4% at stage I, 84.2% at stage II, 69.6% at stage III, and 30.3% at stage IV, respectively, and the staging was proposed as an independent prognostic factor for endometrial carcinoma.^[10] Heffler et al performed multivariate analysis to show that staging and age were independent risk factors for the prognosis of endometrial carcinoma.^[3] Our study showed that the 5-year survival rate of pathological stage I, II, III, and IV was 90.9%, 74.9%, 50.3%, and 33.3%, respectively, and the pathological stage was an independent risk factor for the prognosis of endometrial carcinoma, consistent with previous studies.^[3,10]

Many studies have confirmed that lymph node metastasis is a main prognostic factor and the basis of postoperative adjuvant therapy. It is generally believed that high-risk factors of lymph node metastasis are high histological grade, deep myometrial invasion, cervical involvement, and high-risk pathological types. The retrospective analysis of 175 cases of endometrial carcinoma by Kamura et al showed that deep myometrial invasion and tumor diameter can be used to evaluate the status of lymph node metastasis.^[11] In this study, the 5-year survival rate of patients

with and without lymph node metastasis was 48.7% and 88.6%, respectively, and lymph node metastasis was a prognostic factor in endometrial carcinoma.

Tumor size is a prognostic factor to affect lymph node metastasis and survival. Studies have shown that the patients with tumor <2 cm did not have lymph node metastasis, and the 5-year survival rate was 98%; when the tumor was larger than 2 cm, the lymph node metastasis rate was 18%, and the 5-year survival rate was 84%; when the tumors were full in the uterine cavity, the 5-year survival rate was only 64%.^[12] The study on 345 cases of endometrial carcinoma by Shah et al showed that tumor size was related to extrauterine disease, but was not an independent prognostic factor for endometrial carcinoma.^[13] Consistent with these previous studies, in this study, the 5-year survival rate was 88.3%, 83.7%, and 65.0%, respectively, for the tumor size <2 cm, ≥2 cm, and full of the uterine cavity. We found that tumor size was a prognostic factor of endometrial carcinoma, but was not an independent prognostic factor based on multivariate analysis.

Surgical treatment is the main treatment method for stage I endometrial carcinoma, but the choice of surgical methods and whether lymphadenectomy is necessary for early endometrial cancer is still controversial. Pelvic lymphadenectomy is of great clinical significance in defining staging, estimating prognosis, and guiding postoperative treatment. However, pelvic lymphadenectomy may increase postoperative complications in most endometrial cancer patients, and whether it can improve survival rate and prevent recurrence is still controversial. The retrospective analysis of 514 cases of stage I endometrial carcinoma by Benedetti Panici et al showed that for 264 cases with pelvic lymphadenectomy and 250 cases without lymphadenectomy, the 5-year disease-free survival rate was 81% and 81.7%, respectively, and the 5-year overall survival rate was 85.9% and 90.0%, respectively, and the differences were not significant, indicating that lymphadenectomy cannot improve the prognosis of patients.^[14] Interestingly, Xu et al reported that different surgical procedures for thyroid cancer also affected prognostic factors.^[15] In addition to surgery, adjunct therapies such as chemotherapy and radiotherapy are important for cancer treatment.^[16] In this study, we examined the effect of treatment methods on the prognosis of patients, and the survival of patients improved significantly after the combination of surgery with radiochemotherapy.

In conclusion, pathological type, histological grade, pathological staging, and cervical involvement are independent risk factors for the prognosis of endometrial cancer patients. The prognosis of endometrial carcinoma is closely related to the clinicopathological characteristics of patients. We should strictly evaluate the risk factors related to the prognosis of endometrial cancer patients, and formulate individualized treatment plans to achieve good outcomes.

Author contributions

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