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Oncological outcomes of minimally invasive surgery in non-endometrioid endometrial Cancer patients with varying prognostic risks: a retrospective cohort study based on the ESGO/ESTRO/ESP 2020 guidelines

Bin Liu[1†], Yan Liu[2†], Wenju Liu[3†], Cuibo Lin[1], Lin Lin[1], Weiting Chen[1], Wanzhen Lin[1], Wei Chen[1*] and Jie Lin[1*]

Abstract

Background Non-endometrioid endometrial carcinomas (NEEC) are characterized by their rarity and adverse prognoses. This study evaluates the outcomes of open versus minimally invasive surgery (MIS) in NEEC patients stratified by prognostic risks according to the 2020 ESGO-ESTRO-ESP risk classification guidelines.

Methods A retrospective analysis was performed on 99 NEEC patients who underwent initial surgery at Fujian University Cancer Hospital. Patients were categorized into two groups: those undergoing MIS and those undergoing open surgery. We compared disease-free survival (DFS) and overall survival (OS) between these groups. Cox regression analysis was employed to identify risk factors for DFS, which were further validated via bootstrap statistical methods.

Results The study included 31 patients in the MIS group and 68 in the open surgery group. The demographics and clinical characteristics such as age, body mass index, comorbidities, histological subtypes, and FIGO stage were similar between groups ($P>0.05$). The MIS group experienced ten recurrences (1 vaginal, 2 lymph nodes, 7 distant metastases), whereas the open surgery group had seven recurrences (1 vaginal, 3 lymph nodes, 1 pelvis, 2 distant metastases), yielding recurrence rates of 10.3% versus 25.6% ($P=0.007$). Besides lymphovascular space invasion (LVSI), surgical approach was also identified as an independent prognostic factor for DFS in high-risk patients ($P=0.037$, 95% CI: 1.062–7.409). The constructed nomogram demonstrated a robust predictive capability with an area under the curve (AUC) of 0.767. Survival analysis for high- and intermediate-risk patients showed no significant differences in OS between the two groups ($P_{high\ risk}=0.275$; $P_{intermediate-risk}=0.201$). However, high-risk patients in the MIS group exhibited significantly worse DFS ($P=0.001$).

†Bin Liu, Yan Liu and Wenju Liu have contributed equally to this work.

*Correspondence:
Wei Chen
youki0601@163.com
Jie Lin
linjie@fjzlhospital.com

Full list of author information is available at the end of the article

Conclusion This investigation is the inaugural study to assess the impact of surgical approaches on NEEC patients within the framework of the latest ESGO-ESTRO-ESP risk classifications. Although MIS may offer clinical advantages, it should be approached with caution in high-risk NEEC patients due to associated poorer DFS outcomes.

Keywords Non-endometrioid endometrial carcinomas, Minimally invasive surgery, Open surgery, Oncological outcome, Prognostic risk

Introduction

Endometrial cancer (EC) is the most prevalent gynecologic malignancy in developed countries, with an increasing incidence [1]. Non-endometrioid endometrial cancers (NEECs) account for 10-20% of all EC cases and are attributed to approximately 40% of EC-related mortalities [2, 3]. NEECs are associated with poor prognoses [4–6].

The use of MIS for tumor treatment has gained widespread recognition. Research has shown that MIS has similar intraoperative complications but fewer postoperative complications compared to open surgery in EC cases. According to the most recent guidelines from the National Comprehensive Cancer Network (NCCN), patients with early-stage NEEC have the option of undergoing either minimally invasive or open surgery [7].

Although previous studies have primarily focused on early-stage or low-risk cohorts in EC, numerous scholars have explored the feasibility of MIS for high-risk histological subtypes of EC patients [8]. Additionally, various studies have evaluated different surgical approaches for patients with NEEC according to FIGO staging, concluding that MIS is a viable option for stage I NEEC [9, 10]. However, these studies have not addressed variations in prognostic risks among NEEC patients. The 2020 ESGO/ESTRO/ESP Guidelines incorporate pathological conditions, uterine factors, postoperative stage, and other comprehensive elements to refine the classification of prognostic risk factors for NEEC patients, thereby enhancing the precision of prognosis predictions. The determination of the most appropriate surgical approach for NEEC patients, based on the ESGO/ESTRO/ESP 2020 Guidelines, remains unresolved.

In this study, we initially analyzed the general characteristics of 99 patients with NEEC, categorizing them into MIS and open surgery groups based on varying prognostic risks. Subsequently, we compared the survival outcomes between these two groups and analyzed the risk factors associated with recurrence. Additionally, we have developed a nomogram for clinical implementation aimed at predicting the risk of postoperative recurrence.

Materials and methods

Patients selection

A retrospective analysis was conducted on 138 patients with NEEC who underwent surgical treatment at Fujian Medical University Cancer Hospital between January 2011 and March 2018. Our study received approval from the Institutional Review Board of the Ethics Committee at the Cancer Hospital affiliated with Fujian Medical University (No. K2022-064-01) and was conducted in accordance with the Declaration of Helsinki. Given that this study was conducted retrospectively, the Ethics Committee agreed to waive the requirement for written informed consent and ensure patient privacy throughout the data analysis process.

We classified patients with NEEC into high and intermediate prognostic risk groups according to the 2020 ESGO-ESTRO-ESP endometrial prognostic risk classification, developed by the European Society of Gynaecological Oncology, the European Society for Radiotherapy and Oncology, and the European Society of Pathology. Patients with stage Ia NEEC were classified as intermediate prognostic risk, while all other cases were categorized as high-risk [11]. We excluded patients who (1) had recurrent disease and distant metastases; (2) underwent palliative surgery or optimal cytoreduction surgery for advanced cases; (3) received preoperative neoadjuvant chemotherapy or radiotherapy; (4) lacked complete follow-up information; (5) minimally invasive procedure was converted to open surgical intervention and (6) had endometrioid histology. Ultimately, 99 patients were included in the study. Of these, 68 underwent open surgical procedures and 31 underwent MIS procedures (Fig. 1).

Selection of surgical methods

All surgical procedures were performed by experienced gynecological oncologists who annually conducted at least 100 malignant tumor surgeries and over 50 laparoscopic procedures for a minimum of three years. Each patient provided written informed consent for the surgery (The patient was provided with comprehensive information regarding the advantages and disadvantages of both surgical methods prior to the operation, enabling them to make an informed and autonomous decision). Initial treatment for all NEEC patients included surgeries such as hysterectomy (radical, modified radical, and extrafascial). Furthermore, surgical resection encompassed sentinel lymph nodes, pelvic or para-aortic lymph nodes, and the greater omentum.

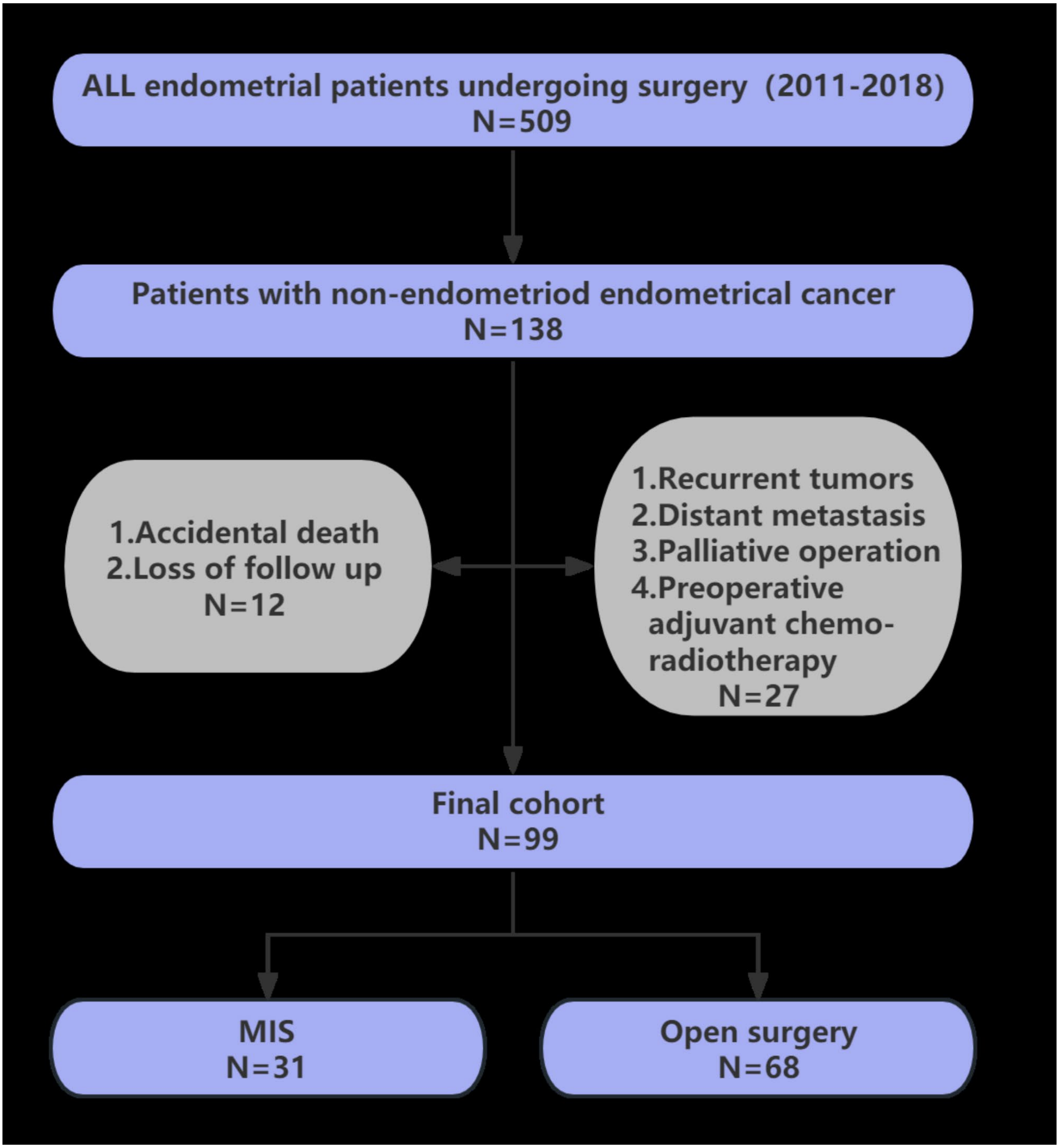

Fig. 1 Flowchat of this study

Data collection

Relevant medical and surgical histories were extracted from the electronic health records and operative logs. Data collected included age, body mass index (BMI), FIGO stage, grade, histologic type, tumor size, pathological risk factors, adjuvant treatments, and results from ultrasound and imaging studies. The initial locations of recurrence were classified as lymph node, vaginal, pelvic, and distant metastasis. The adjuvant therapy employed in our study was based on the NCCN guidelines and implemented according to the FIGO2009 staging system (Non-invasive stage Ia of serous and clear cell carcinoma can be follow-up, while a combination of radiotherapy and chemotherapy is necessary for any stage of other subtypes. Administering chemotherapy or radiation alone as adjuvant therapy following surgery is considered non-standard practice). The primary endpoints of this study were DFS and OS in patients diagnosed with NEEC, who underwent diverse surgical approaches. OS is defined as the time from initial cancer diagnosis to either the last follow-up or death due to cancer, while DFS refers to the period from cancer diagnosis to either the first recurrence or disease progression. The follow-up was conducted until January 2023.

Surgical technique

Preoperative planning and preparation: The diagnosis of NEEC was confirmed by preoperative pathological examinations in all patients, with no evidence of distant metastasis observed in imaging evaluations. Multidisciplinary team (MDT) discussions were held for patients with pre-existing complications such as diabetes, hypertension, and hyperlipidemia prior to surgery to ensure optimal control of blood glucose levels, blood lipids, and blood pressure within acceptable ranges for surgical intervention. All patients received routine vaginal (for those sexually active) and intestinal preparation before surgery. After vaginal sterilization and catheterization, a uterine manipulator was placed in those with a history of sexual activity.

Intraoperative procedure: The MIS utilized Olympus or STORz television laparoscopy systems and Johnson surgical instruments (The selection of the MIS system is conducted in a randomized manner, with arrangements made based on different operating rooms). Patients were positioned with a 30°head-down tilt and elevated hips. Trocar placements are illustrated in Fig. 2A. Pneumoperitoneum pressure was maintained within 10–14 mmHg. Cauterization was employed in MIS for the occlusion of fallopian tubes prior to the introduction of a uterine manipulator. Following this, a uterine manipulator is introduced, and the connective tissue is carefully sutured and dissected using an ultrasonic scalpel. The bipolar electrocoagulation device is utilized for accurate sealing of the periuterine and ovarian vessels. Pelvic lymph nodes and para-aortic lymph nodes are surgically removed with the assistance of an ultrasonic scalpel. After the surgical specimen was removed through the vagina, CO_2 was evacuated, and the pelvic cavity was lavaged with a large volume of physiological saline.

Open surgery involved a longitudinal incision around the navel in the mid-abdomen (Fig. 2B), protected with a film around the incision. The patient was positioned horizontally. The single-stage electric knife, with an approximate power of 70 W, is used for separation and cutting. Closure of the periuterine and ovarian vessels can be achieved using either a vascular clamp or silk ligature. When performing para-aortic lymph node resection, a tractor is utilized to fully expose the abdominal aorta and inferior vena cava up to the level of the renal vein.

Both surgical techniques employed Vchow sutures for suturing the vaginal stump.

In all patients, resection of the fallopian tubes and ovaries was performed.The procedure for radical hysterectomy included the removal of 3 cm of vaginal and paratrophic tissue, whereas modified radical hysterectomy

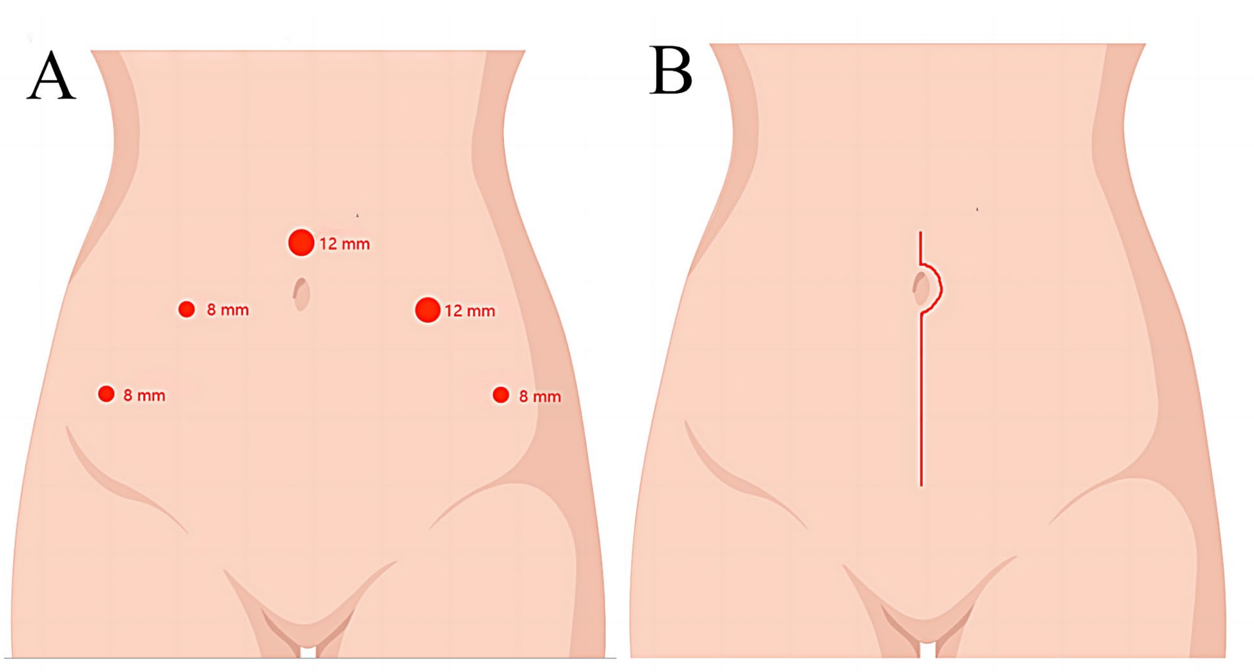

Fig. 2 Illustration of different surgical approaches. **A** Trocars positions of minimally invasive surgery. **B** Incision approach for open surgery

involved the removal of 2 cm. The extent of hysterectomy is determined based on preoperative imaging assessment. Extrafascial hysterectomy is performed in cases with early-stage lesions, whereas radical or modified radical resection is chosen for lesions that infiltrate more than half of the myometrium or invade the cervix. For patients with stage I disease as determined by preoperative clinical evaluation, sentinel lymph node biopsy was performed by injecting indocyanine green into the cervix. If the result was positive, paraaortic lymph node resection followed. Systemic lymphadenectomy was conducted in all other patients. Resection of the greater omentum was performed in all patients diagnosed with NEEC, except those preoperatively diagnosed with stage I clear cell carcinoma.

Statistical analysis

Continuous variables are presented as median (range), and categorical variables are expressed as frequency or percentage. To assess the association between two categorical variables, either the Chi-square test or Fisher's exact test is utilized. The Power Analysis and Sample Size software (Pass version 2021) was utilized to conduct a power analysis on the sample size employed in the study.

Multivariate Cox regression models are employed to evaluate prognostic factors associated with DFS, incorporating significant variables from univariate analyses into multivariate analyses. The model's robustness was further verified through adjustment for potential confounding factors, subsequent hierarchical analysis, and sensitivity analysis.

The first model adjusts for age and BMI. Given the non-estrogenic characteristics of non-endometrioid adenocarcinoma and its lack of association with menopause, we limited our study population to individuals under the age of 60 due to concerns regarding compromised immune function and decreased body tolerance in older patients and their potential impact on postoperative recurrence. Patients with a BMI greater than 25 were excluded from the analysis as obese individuals were more likely to opt for minimally invasive surgery. In Model 2, samples were excluded if they did not receive standardized adjuvant therapy following surgery, such as those with insufficient treatment duration or lacking radiotherapy or chemotherapy. Noncompliance with the National Comprehensive Cancer Network (NCCN) guidelines for standard postoperative adjuvant therapy may result inlead to short-term tumor recurrence. In light of previous research indicating the safety of minimally invasive surgery in early-stage cases, we excluded samples from the intermediate -risk in Model 3 and conducted a re-analysis specifically focusing on the impact of different variables on DFS within the high-risk group. Lastly, Given the limited sample size, we applied the bootstrap method (1,000 samplings) to validate significant factors. This involved multiple samplings, assessing model performance for each sample, and combining results to confirm or refine initial single-factor and multi-factor conclusions based on verification outcomes. Bootstrap, a resampling statistical technique involving repeated sampling from the original dataset with replacement, was used to generate bootstrap samples of the same size as the original dataset. By generating a large number of such bootstrap samples, we can build an empirical distribution of a statistic of interest.

The Kaplan-Meier and log-rank tests were used to compare OS and DFS between the MIS and open surgery groups across different prognostic risks. Nomograms were developed based on multiple logistic regression, with the model's predictive accuracy assessed using the receiver operating characteristic Bootstrap-Receiver operating characteristic (BS-ROC) curve and BS calibration curve following the BS validation method. Statistical significance was established at a P value of less than 0.05. Data analysis and visualization were conducted using the R package (version 4.1.0) and GraphPad Prism (version 8.0).

Results

Overall, 99 patients with NEEC were included in the final cohort. The patient selection process is illustrated in Fig. 1. Of these patients, 7 (7.1%) were diagnosed with carcinosarcoma, 18 (18.2%) with clear cell carcinoma, 18 (18.2%) with serous carcinoma, 51 (51.5%) with mixed histological types, and 5 (5.1%) with rare histological types. 60% of the NEEC patients underwent simultaneous pelvic and para-aortic lymph node dissection. The two patient groups were comparable in terms of lymph node dissection, depth of myometrial invasion, tumor grading, histological subtype, tumor size, endometrial thickness (transvaginal ultrasound), lymph node metastasis, lymphovascular space invasion (LVSI) positivity, and adjuvant treatment. The clinicopathological features of the patients are listed in Table 1. Given the varying rates of recurrence between the MIS and open surgery groups, a bilateral test with a significance level of 0.05 was conducted. The statistical power of the sample size was determined to be 0.79 using PASS 2021 software.

Out of the total, 31 patients (31.3%) underwent MIS procedures, while 68 (68.7%) received open surgery. The median age in the MIS group was 54 years (range: 51–62) and the median BMI was 21.7 kg/m² (range: 21.0-22.6), compared to the open surgery group, which had a median age of 58 years (range: 53–61) and a median BMI of 21.9 kg/m² (range: 21.1–22.9). Early-stage NEEC was diagnosed in 48 cases (48.5%) in the open surgery group and 26 cases (26.3%) in the MIS group. During a follow-up period of 61.30 months for the MIS group (range:

Table 1 Clinopathological characteristics of patients

Variable	MIS (*n*=31)	Open (*n*=68)	*P*-value
Age, year, median (range)	54(51,62)	58(53,61)	0.571
BMI, kg/m2,median (range)	21.7(21.0,22.6)	21.9(21.1,22.9)	0.709
Comorbidity,%			0.711
No	14(45.2%)	33(48.5%)	
Yes	17(54.8%)	35(51.5%)	
Histology,%			0.116
Carcinosarcoma	1(3.2%)	6(8.8%)	
Clear Cell	8(25.8%)	10(14.7%)	
Serous	9(29.0%)	9(13.2%)	
Mixed	13(41.9%)	38(55.9%)	
Other	0(0%)	5(7.4%)	
Endometrial thickness(TVUS), mm			0.944
<5	23(74.2%)	50(73.5%)	
≥5	8(25.8%)	18(26.5%)	
Different prognostic risks,%			0.473
Intermediate -risk	17(54.8%)	32(47.1%)	
High-risk	14(45.2%)	36(52.9%)	
FIGO stage,%			0.158
I-II	26(83.9%)	48(70.6%)	
III-IVA	5(16.1%)	20(29.4%)	
Type of hysterectomy,%			0.811
RH	27(87.1%)	58(85.3%)	
SH	4(12.9%)	10(14.7%)	
Depth of myometrial invasion,%			0.473
<50%	17(54.8%)	32(47.1%)	
≤50%	14(45.2%)	36(52.9%)	
LN metastasis,%			0.139
No	28(90.3%)	53(77.9%)	
Yes	3(9.7%)	15(22.1%)	
Tumor size,%			0.283
<5	18(58.1%)	47(69.1%)	
≥5	13(41.9%)	21(30.9%)	
LVSI positive,%			0.126
No	16(51.6%)	46(67.6%)	
Yes	15(48.4%)	22(32.4%)	
Cervical stromal invasion,%			0.607
No	23(74.2%)	47(69.1%)	
Yes	8(25.8%)	21(30.9%)	
Adjuvant therapy,%			0.969
No	9(29.0%)	20(29.4%)	
Yes	22(71.0%)	48(70.6%)	
Recurrences,%			0.007
No	21(67.7%)	61(89.7)	
Yes	10(32.3%)	7(10.3%)	
Survival state,%			0.702
survival	26(83.9%)	59(86.8%)	
death	5(16.1%)	9(13.2%)	

MIS minimally invasive surgery; *BMI* body mass index; *TVUS* transvaginal ultrasound; *FIGO* international federation of gynecology and obstetrics; *RH* radical hysterectomy; *SH* simple hysterectomy; *LVSI* lymphovascular space invasion

15.4-101.4) and 65.95 months for the open surgery group (range: 6.9-132.4), 17 patients (17.2%) experienced recurrence, as detailed in Table 2. Of these, 10 (25.6%) were from the MIS group and 7 (10.3%) from the open surgery group, indicating a significantly higher recurrence rate in the MIS group ($P=0.007$).

The MIS group reported ten recurrence cases (1 vaginal, 2 lymph nodes, and 7 distant metastases), whereas the open group reported seven recurrences (1 vaginal, 3 lymph nodes, 1 pelvic, and 2 distant metastases). Distant metastasis was the most prevalent type of recurrence in the MIS group (7 cases, 22.58%). Conversely, lymph node metastasis was the most common recurrence site in the open group (3 cases, 4.41%). The rate of distant metastasis in the MIS group was significantly higher than in the open group ($P=0.006$). However, there was no difference in the rates of other types of recurrences between the two groups. Further subgroup analysis revealed no significant differences in recurrence rates between the intermediate-risk groups of both surgical approaches. Nevertheless, within the high-risk group, the MIS group exhibited a significantly higher recurrence rate compared to the open group ($P=0.001$), as detailed in Table 2.

Patients were categorized into intermediate-risk and high-risk subgroups within two separate groups. We observed no statistically significant difference in OS between the intermediate-risk and high-risk subgroups ($P>0.05$) as shown in Fig. 3. However, among high-risk NEEC patients, the DFS in the MIS cohort was lower compared to the open surgery cohort ($P<0.05$), as depicted in Fig. 4.

Univariate analysis identified the surgical approach (odds ratio [OR] 3.347, 95% confidence interval [CI] 1.273–8.797, $P=0.014$) and LVSI positivity (OR 9.999, 95% CI 2.866–34.888, $P<0.001$) as risk factors for DFS in patients with NEEC. Multifactorial analysis confirmed these findings, showing that the surgical approach (OR 2.806, 95% CI 1.062–7.409, $P=0.037$) and LVSI positivity (OR 9.165, 95% CI 2.615–32.120, $P=0.001$) remained significant risk factors (Table 3). In stratified and sensitivity analyses, Model 1 was adjusted for age and BMI to exclude patients aged over 60 years and those with a BMI greater than 25. The findings indicate that LVSI, surgical approach, and cervical stromal invasion were determined to be significant risk factors for DFS ($P<0.05$) (Table S1).

Table 2 Oncologic outcomes of patients

Variable	MIS (*n*=31)	Open (*n*=68)	*P*-value
Recurrences total, %			0.007
Yes	10(32.25%)	7(10.24%)	
No	21(67.74%)	61(89.71%)	
Recurrences site,%			
Vaginal	1(3.23%)	1(1.47%)	0.846
Pelvis	0(0%)	1(1.47%)	0.685
Lymph node	2(6.45%)	3(4.41%)	0.948
Distant metastasis	7(22.58%)	2(2.94%)	0.006
Recurrences by different prognostic risks,%			
Intermediate-risk	0(0%)	2(2.94%)	0.846
High-risk	10(32.25%)	5(7.35%)	0.001
Median follow-up, months	61.30	65.95	

MIS minimally invasive surgery

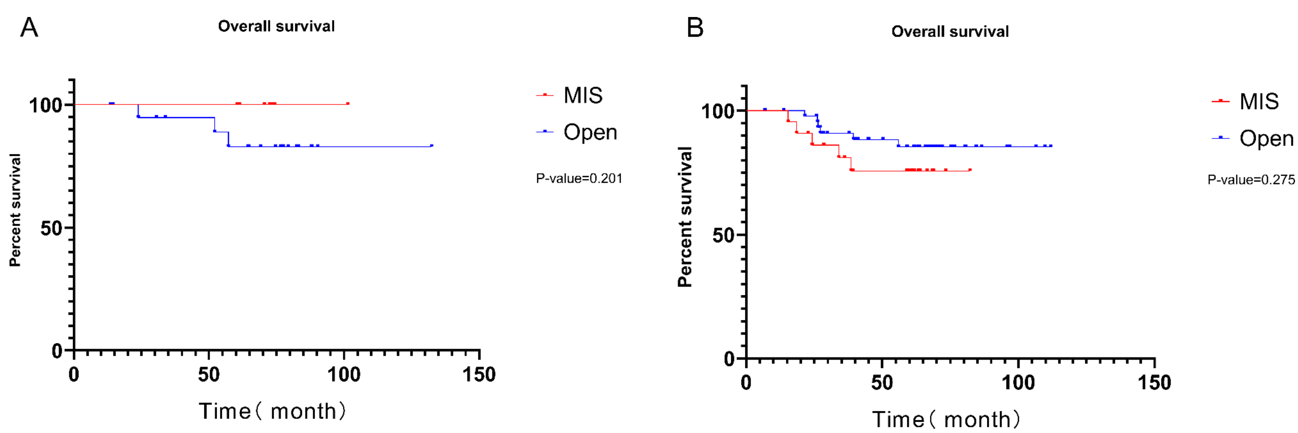

Fig. 3 The Kaplan-Meier curves comprehensively depict overall survival outcomes of the two surgical approaches. **A** Overall survival in intermediate-risk group. **B** Overall survival in high-risk group

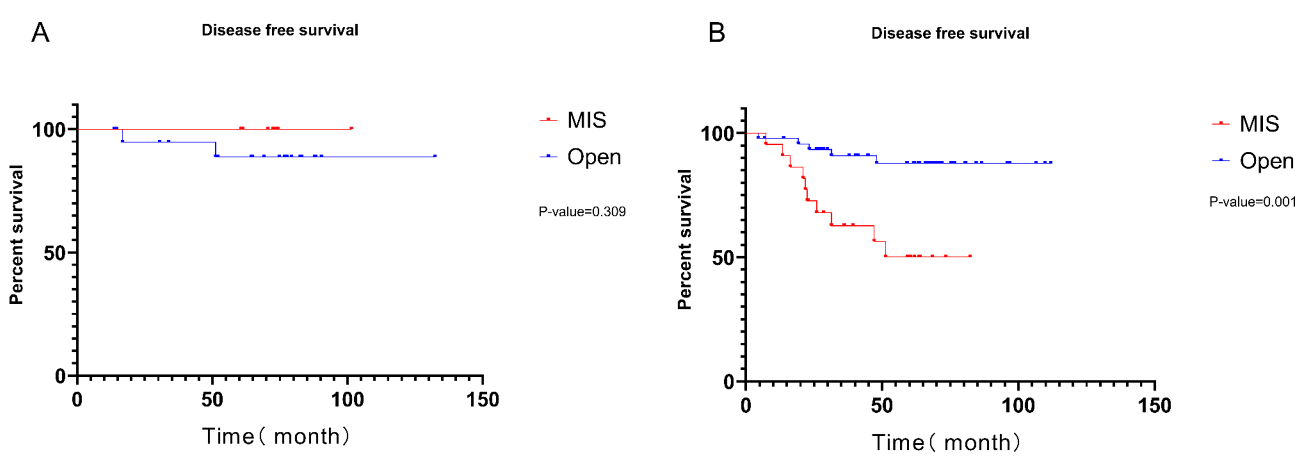

Fig. 4 The Kaplan-Meier curves comprehensively depict the outcomes of tumor progression of the two surgical approaches. **A** Disease free survival in intermediate-risk group. **B** Disease free survival in high-risk group

Table 3 Multivariate cox regression analysis of DFS

Characteris	DFS					
	Univariate	Analysis		Multivariate	Analysis	
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Age, **year** (< 55 vs.≥55)	0.681	0.263–1.765	0.430			
BMI, **kg/m2** (< 22 vs. ≥22)	1.879	0.715–4.942	0.201			
Comorbidity (Yes vs. No)	0.620	0.236–1.630	0.333			
Type of hysterectomy (RH vs. SH)	2.814	0.373–21.236	0.316			
Prognostic-risk groups	1.559	0.592–4.101	0.369			
Endometrial thickness(TVUS), **mm** (< 5 vs.≥5)	1.424	0.501–4.049	0.509			
Depth of myometrial invasion,**%** (< 50 vs.≥50)	2.042	0.755–5.527	0.160			
Tumor size, **cm** (< 5 vs.≥5)	2.520	0.971–6.539	0.057			
Surgical approach (Open vs. MIS)	3.347	1.273–8.797	0.014	2.806	1.062–7.409	0.037
Cervical stromal invasion depth (Yes vs. No)	1.887	0.717–4.965	0.198			
Histology (single vs.mix)	1.176	0.454–3.047	0.739			
LVSI positive (Yes vs. No)	9.999	2.866–34.888	0.000	9.165	2.615–32.120	0.001
Adjuvant therapy (Yes vs. No)	6.707	0.889–50.516	0.065			

DFS: disease-free survival; *MIS*: minimally invasive surgery; *BMI*: body mass index; *TVUS*: transvaginal ultrasound; *RH*: radical hysterectomy; *SH*: simple hysterectomy; *LVSI*: lymphovascular space invasion

Subsequently, we conducted a reanalysis of relapse in the subgroup of patients who received standard adjuvant therapy following surgery, which confirming our primary results (Table S2). Given the elevated rate of relapse observed in the high-risk subgroup of patients undergoing MIS, our stratified analysis among high-risk patients revealed that LVSI and surgical approach remained significantly associated with poor DFS ($P<0.05$) (Table S3). The obtained result underwent bootstrap statistical analysis and was further validated through 1000 random samplings, resulting in a C-index value of 0.835 with a 95% CI ranging from 0.696 to 0.909.

Simultaneously, we have developed a nomogram based on logistic regression models to accurately predict recurrence risk, utilizing clinical expertise and comprehensive multivariate analyses. (Fig. 5). Given the limited sample size and the absence of an external validation dataset, we employed 1,000 bootstrap resampling iterations to validate the multifactorial results and the nomogram, subsequently constructing BS-ROC curves and calibration curves. (Fig. 6). Our nomogram demonstrated exceptional predictive performance, evidenced by an area under the curve (AUC) of 0.767 (95% CI). The average absolute error of the calibration curve was 0.031, indicating that our nomogram's predictions closely align with actual outcomes.

Disscussion

Which surgical procedure, MIS or open surgery, is more beneficial for patients with high-risk NEEC? Our research is the first to evaluate the clinical-pathological features and prognostic outcomes of different surgical approaches for high-risk NEEC patients, adhering to the 2020 ESGO/ESTRO/ESP guidelines. The selection of MIS as a surgical approach for high-risk NEEC patients should be approached with caution due to the poorer DFS outcomes observed, despite similar OS rates reported in our study.

A substantial body of literature demonstrates that MIS achieves survival outcomes comparable to open surgery [12–14]. Due to its many advantages, including reduced blood loss, expedited recovery, and shorter hospital stays, MIS is widely utilized [15, 16]. However, in November 2018, the LACC trial revealed that MIS resulted in inferior outcomes compared to open surgery in cases of cervical cancer [17]. Our previous research identified a positive correlation between MIS and inferior DFS in EC patients with moderate to high prognostic risk, aligning with the findings from the LACC trial [18]. Additionally,

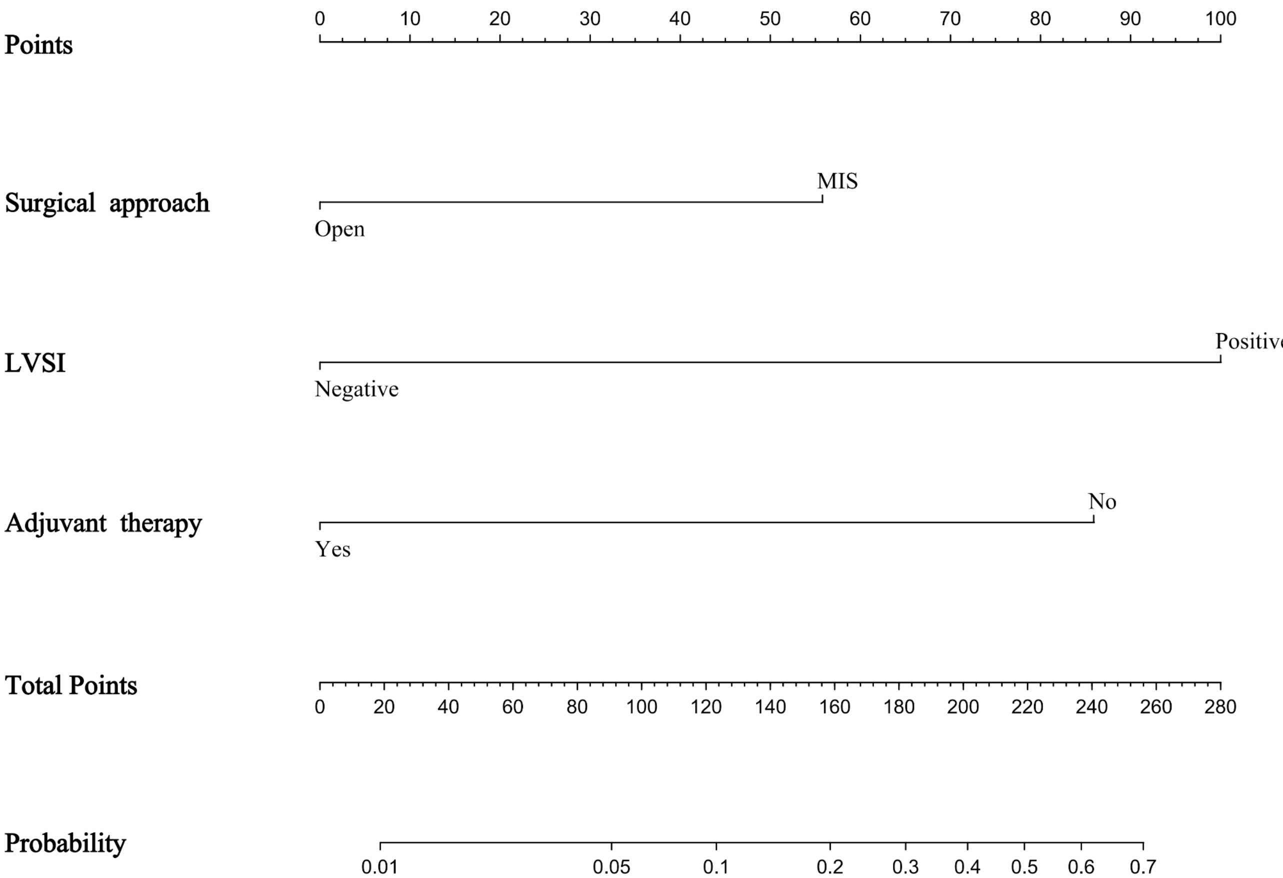

Fig. 5 A nomogram to predict the risk of recurrence in non-endometrioid endometrial cancer

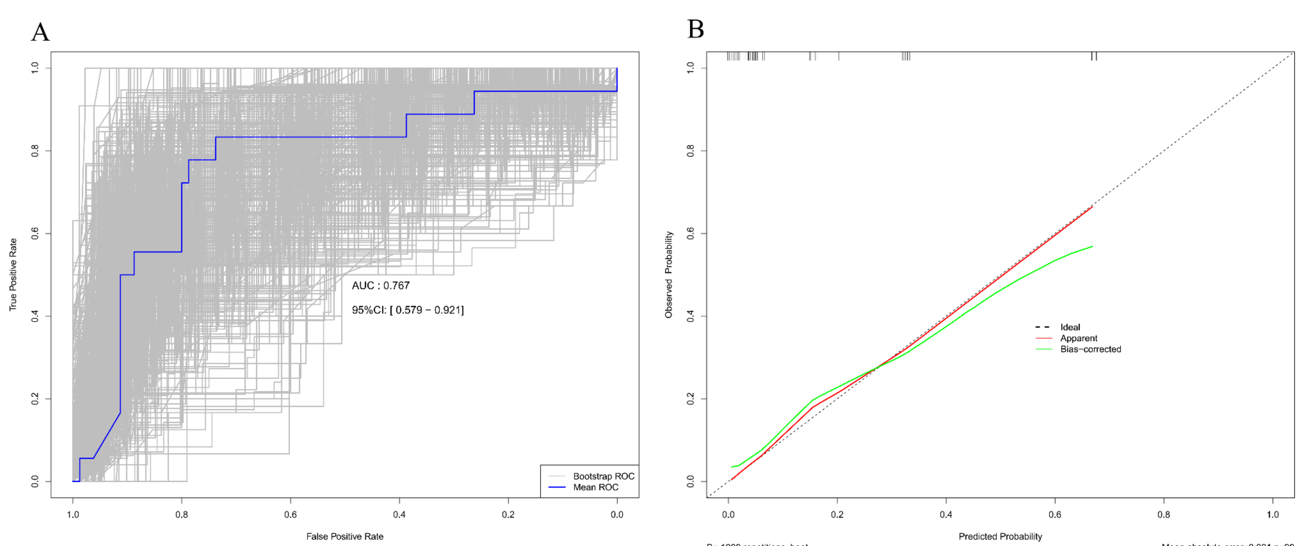

Fig. 6 Bootstrap-Receiver operating characteristics (BS-ROC) curve and Bootstrap calibration plot. **A** Bootstrap-Receiver operating characteristics (BS-ROC) curve. **B** Bootstrap calibration plot

the use of MIS in treating advanced stages of EC, such as NEEC, remains controversial [19, 20].

NEEC encompasses several aggressive subtypes, including uterine serous carcinoma (USC), carcinosarcoma, undifferentiated, clear cell, and squamous cell carcinoma [21, 22]. NEEC, characterized by its relatively low incidence, is noted for its high malignancy, high recurrence rate, and poor prognosis even with comprehensive treatment. There has been limited research focusing on the survival outcomes associated with different surgical approaches for high-risk NEEC. Pedra Nobreden et al. conducted a retrospective analysis of 147 stage I endometrial carcinosarcomas patients and reported that the two-year progression-free and disease-specific survival rates were similar between the open and MIS groups [9]. Another study indicated that MIS offered survival outcomes comparable to those of open surgery in patients with NEEC, regardless of disease stage [10]. The results of a recent meta-analysis indicate that minimally invasive surgery and open surgery yielded similar disease-free survival and overall survival rates in patients with high-risk endometrial cancer [23]. However, it is important to note that the study's categorization was based solely on FIGO staging, which included grade 3 endometrioid adenocarcinoma, without considering other pathological features such as myometrial invasion, tumor diameter, or lymphatic space invasion. This suggests that the high-risk group in the study may have encompassed cases from both our moderate- and high-risk groups, potentially leading to different conclusions than those drawn in our study. Nevertheless, the conclusion for the moderate-risk group in our study aligns with the findings of this meta-analysis. However, these studies share common limitations, such as short follow-up periods, limited application of FIGO staging, and ambiguous details regarding postoperative adjuvant therapy. Such confounding factors could potentially affect the impact of surgical methods on the recurrence and survival rates in NEEC patients. Unlike previous studies, we categorized patients with similar prognostic risks into a single group according to the 2020 ESGO/ESTRO/ESP guidelines, which could avoid certain aspects that impact survival outcomes.

Our study is inevitably influenced by selection bias and confounding factors due to its retrospective design. These factors include but are not limited to sample size, surgeons' expertise, technological variability in MIS equipment, and patient selection criteria. To mitigate the impact of these factors, we initially imposed stringent criteria for admission and exclusion, while also conducting a power analysis on the included sample size. The calculated power value of 0.79, based on the discrepancy in recurrence rates between two groups, was deemed sufficient for identifying significant differences in outcomes. Additionally, while surgical approach selection is influenced by patient preferences, it has been noted that obese patients often favor MIS, whereas elderly patients show a preference for open surgery. Model 1 was adjusted for age and BMI, and subsequently reanalyzed by excluding elderly or obese patients, yielding findings that align closely with the primary model. In an effort to address potential reverse causality, additional models (Model 2 and Model 3) were constructed for further analysis. Nevertheless, surgical method and LVSI continue to be significant risk factors for DFS. Lastly, due to the rarity of NEEC, our study was limited by a small sample size. To ensure the robustness of our findings, we employed bootstrap statistical methods for verification. By effectively mitigating potential biases caused by the small sample size and uneven distribution of samples, this approach fully demonstrates the robustness of the main model.

Given the uncertain role of molecular typing in predicting the prognosis of NEEC, we excluded molecular typing data from our analysis. In previous research, survival outcomes for the low-risk MIS group were comparable to those of the open surgery group. However, the intermediate-high-risk and high-risk MIS groups exhibited suboptimal DFS, which may be attributed to the unique tumor behaviors associated with NEEC. This finding aligns with those of our current study. As no statistically significant difference in postoperative adjuvant therapy administration was observed between the groups, and considering that previous research has indicated a potential survival benefit for high-risk EC types with such therapy, this factor was included in our prognostic prediction model analysis.

The preoperative evaluation of NEEC using vaginal ultrasound is considered inadequate [24], potentially due to the absence of abnormal endometrial hyperplasia as a pathological basis for NEEC and the predominance of postmenopausal women with atrophic endometrium among NEEC patients. Consequently, magnetic resonance imaging (MRI) is advised for more comprehensive preoperative imaging assessments [25].

The observed lower rate of DFS in the MIS group may be attributed to several factors. First, controversy persists over the use of uterine manipulators, which some studies suggest could increase recurrence risks post-surgery by facilitating malignant cell migration into blood vessels [26–28]. Studies showed uterine manipulators might "help" malignant tumor cells flow into the blood vessel, or even LVSI due to compression effects [29, 30]. Additionally, LVSI has been independently linked to poorer outcomes in uterine serous carcinoma [31–33], a finding corroborated by our research. Nonetheless, evidence indicating that uterine manipulators significantly affect prognosis remains inconclusive, with no clear association between surgical methods and LVSI incidence [34–37]. In this study, prior to the LACC study findings, the use of uterine manipulators in the MIS cohort was unavoidable, yet it did not result in a statistically significant difference in LVSI incidence compared to the open surgery group. Second, animal studies suggest that pneumoperitoneum may damage the peritoneum and promote tumor cell proliferation. Various pneumoperitoneum pressures have also been shown to alter the intraperitoneal environment favorably for tumor growth, necessitating further investigation in MIS contexts. Lastly, the steep Trendelenburg position during MIS could facilitate the migration of tumor cells from the vagina into the abdominal and pelvic cavities, particularly in EC patients with cervical involvement. Stolnicu et al. noted that vaginal recurrences in EC were linked to residual tumor cells in the vagina post-surgery [38]. However, both MIS and open surgery groups in our study demonstrated low vaginal recurrence rates, likely due to the prevalent use of radical hysterectomy (85.9%). Although radical hysterectomy has not shown to improve early-stage EC prognosis [39], its impact on NEEC remains unverified. In conclusion, the higher recurrence rate in the MIS group may be attributed to dynamic changes in circulating tumor cells and peritoneal contamination following vaginal opening during hysterectomy, particularly among high-risk patients.

In our study, the nomograms developed may assist in integrating multiple predictive variables to quantify the overall risk of outcomes, thereby aiding clinicians in formulating treatment plans. Surgical approaches, LVSI, and adjuvant therapy were identified as significant predictors. Similarly, the Mayo Clinic tumor center has utilized nomograms to predict the risks of lymph node metastases and LVSI status in EC patients. The presence of LVSI was identified as the most significant predictor for lymph node metastasis [40, 41], corroborating our findings.

This study still has certain limitations. Firstly, the retrospective design inherently introduced selection bias, as patient data were collected retrospectively and surgical approaches were not randomly assigned. However, we rigorously established the inclusion criteria and employed stratified analysis and sensitivity analysis to mitigate the impact of selection bias and confounding factors. Due to the single-center study, the equipment used for MIS is relatively standardized, thereby minimizing the potential impact of different surgical instruments on surgical accuracy. Although the surgical proficiency of the surgeon may influence clinical outcomes, our study intentionally excluded physicians with less than three years of experience in order to mitigate potential bias. Secondly, critical information such as specific prognostic biomarkers, molecular subgroups, and targeted therapies was incomplete and consequently not incorporated into our analysis. Due to the retrospective nature of this study and the rarity of this disease, external verification is currently not feasible. However, we utilized the Bootstrap statistical analysis method for internal validation through repeated data sampling. In future prospective and multicenter studies, efforts can be made to enable external validation in order to further assess how these factors affect NEEC tumor outcomes and improve statistical reliability. Thirdly, our study did not exclude patients with Lynch syndrome. Given that the prognosis for NEEC patients with Lynch syndrome is markedly better than for those without [42], this exclusion could have influenced our findings. Moreover, certain minimally invasive procedures were conducted at a later stage, resulting in an insufficient OS follow-up time. This limitation has implications for the evaluation of OS-related tumor outcomes and necessitates longer observation periods to further validate these findings.

Given that the risk factors included in the ESGO/ESTRO/ESP 2020 guidelines for risk stratification are predominantly obtained postoperatively, it is imperative to develop a preoperative risk assessment in conjunction with our research findings and supplementary methods to guide surgical approach selection. Firstly, preoperative imaging, such as magnetic resonance imaging (MRI), plays a pivotal role in evaluating tumor size, myometrial invasion, and potential lymph node involvement. Secondly, an endometrial biopsy is conducted to procure a tissue sample for histopathological examination. This biopsy can furnish information on tumor grade and histological subtype, as well as identify LVSI and Molecular Profiling—critical components of risk assessment. Furthermore, personalized treatment plans should be formulated through MDT discussions while taking into account the patient's overall health status, preferences, and specific tumor characteristics. For patients at high risk of postoperative recurrence, careful consideration of minimally invasive surgery is recommended.

Conclusion

Our study has certain limitations but provides valuable insights. It confirms that MIS does not lead to adverse tumor outcomes in NEEC patients with intermediate risk profiles. However, for high-risk NEEC patients, MIS is associated with an increased risk of recurrence. Consequently, MIS may not be the optimal treatment approach for high-risk NEEC cases. In clinical practice, this conclusion is applicable not only to high-risk NEEC cases but also to malignant tumors with high malignancy and advanced stages. Clinicians should thoroughly assess the surgical approach in conjunction with imaging or auxiliary detection methods. If potential abdominal and pelvic tumor exposure or metastasis risk is identified, a cautious selection of MIS is warranted as "life takes precedence over the aesthetics of incision." Certainly, prospective and multicenter studies with extended follow-up periods are essential for enhancing and validating our research findings. These endeavors will facilitate the identification of optimal indications for MIS.

Abbreviations

NEEC Non-endometrioid endometrial carcinomas
MIS Minimally invasive surgery

ESGO-ESTRO-ESP	European Society of Gynaecological Oncologythe, European Society for Radiotherapy and Oncology, European Society of Pathology
OS	Overall survival
DFS	Disease-free survival
LVSI	Lymphovascular space invasion
FIGO	International Federation of Gynecology and Obstetrics
EC	Endometrial cancer
LACC	Laparoscopic approach to cervical cancer
BMI	Body mass index
ROC	Receiver operating characteristic
LN	Lymph node
AUC	Area under the curve
USC	Uterine serous carcinoma
RH	Radical hysterectomy
SH	Simple hysterectomy
TVUS	Transvaginal ultrasound

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
BL, YL and WL have contributed equally to this work. BL, YL and WL contributed to the study conception and design, drafting of the manuscript and analysis and interpretation of the data. CL, LL, WTC and WL contributed to the acquisition of the data, interpretation of the analysis results, and critical revision of the manuscript for important intellectual content. WC, JL authored or reviewed drafts of the article, and approved the final draft.BL is responsible for the overall content as the guarantor. All authors read and approved the finamanuscript.

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Data availability
The dataset supporting the conclusions of this article is included within the article.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of Ethics Committee of the Cancer Hospital Affiliated with Fujian Medical University (NO.K2022-064-01). The retrospective nature of the study led to a waiver of participant consent by the institutional review board of Ethics Committee of the Cancer Hospital Affiliated with Fujian Medical University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Gynecology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, 420 Fuma Road, 350014 Fuzhou, Fujian, China
[2]Fujian Provincial Key Laboratory of Brain Aging and Neurodegenerative Diseases, School of Basic Medical Sciences, Fujian Medical University, Xue Yuan Road, 350108 Fuzhou, China
[3]Department of Gastrointestinal Surgical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, 420 Fuma Road, 350014 Fuzhou, Fujian, China

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