High-grade endometrial carcinoma limited to the endometrium or a polyp: is adjuvant treatment necessary?

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HIGHLIGHTS

- Our data indicate no benefit of adjuvant treatment on outcome for patients with serous intraepithelial carcinoma.
- Recurrence rate is low without adjuvant treatment (12%).
- Outcome following treatment for patients with recurrent serous intraepithelial carcinoma is excellent.

ABSTRACT

Objective High-grade endometrial carcinoma limited to the endometrium or a polyp is a rare clinical entity. Currently there is no consensus on standard treatment. Thus, the goal of this study was to evaluate the clinical outcomes of patients with type II endometrial carcinoma without myometrial infiltration or limited to a polyp.

Methods We retrospectively identified type II endometrial carcinoma (FIGO endometrioid grade 3, serous, clear cell, mixed and carcinosarcoma) with spread limited to the endometrium or a polyp from April 2013 to November 2017. Medical records were reviewed for the following information: age at diagnosis, patient characteristics, type of surgery, histology, stage according to FIGO 2009 classification, adjuvant treatments, and site of recurrence. Descriptive statistics and the Kaplan–Meier estimate were used for analysis.

Results A total of 25 patients with a type II stage IA adenocarcinoma were included. All were surgically staged with total hysterectomy, salpingo-oophorectomy, and lymph nodes assessment. The median age at diagnosis was 69 years. All patients had either disease limited to the endometrium (60%) or a polyp (40%). Only four patients had lymphovascular space invasion (16%). The median follow-up was 44 (range 2–67) months. Six patients (24%) received vault brachytherapy only and all others received no adjuvant treatment after surgery (n=19, 76%). Three patients (12%) experienced recurrences at 15, 21, and 55 months after surgery. Following systemic treatment all are alive and disease-free. The 3-year progression-free survival and overall survival were 91% and 100%, respectively.

Conclusion Expectant management with surveillance alone following surgery appears to be safe for patients with high-grade endometrial carcinoma limited to a polyp or the endometrium without myometrial invasion.

INTRODUCTION

Endometrial carcinoma is the most common gynecologic malignancy and the fourth most common cancer diagnosed in women. In 2020, 7400 new cases of endometrial cancer have been diagnosed in Canada and 1300 have died of the disease.[1] Mortality caused by endometrial cancer has increased three-fold over the last few decades.[2] One of the hypotheses explaining this increase in mortality is the increasing incidence of high-grade (type II) endometrial carcinoma. Type II endometrial carcinoma accounts for approximately 20% of all endometrial carcinoma but is responsible for approximately 40% of endometrial cancer deaths.[3] Type II subtypes include uterine serous carcinoma, grade 3 endometrioid, clear cell, carcinosarcoma, and mixed histology. The most common subtype is serous carcinoma which accounts for 11.4% of all endometrial carcinoma, and more than half of all high-grade endometrial carcinoma.[2]

It has been proposed that serous intraepithelial carcinoma is a precursor of uterine serous carcinoma. Both have an identical P53 mutation profile and can be associated with extrauterine disease, suggesting that serous intraepithelial carcinoma may be considered as an early form of uterine serous carcinoma rather than a precursor.[4] Histologically, serous intraepithelial carcinoma have no myometrial invasion, typically develop on an atrophic endometrium or polyp, and are characterized by high-grade cellular atypia, polymorphism, and detachment of cells.[5] Although it does not infiltrate the myometrium, it is still associated with extrauterine disease in 33%–67% of cases.[3]

Other type II endometrial carcinoma include carcinosarcoma (4.1%), clear cell (3.5%), mixed (4.5%), and grade 3 endometrioid (9.7%).[2] Those types of endometrial carcinoma are also considered high-risk and are treated similar to uterine serous carcinoma. Compared with low-grade endometrioid carcinoma, type II endometrial carcinoma have a higher propensity for lymphovascular space invasion, intra-peritoneal spread, and early distant metastasis. At the time of diagnosis about 60%–70% of patients will have disease outside the uterus.[6]

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The optimal management of early-stage type II endometrial carcinoma is based on histology and recurrence risk, but there is currently no standard treatment for stage IA without myometrial invasion or limited to a polyp. A recent update of the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) guidelines for the management of endometrial carcinoma suggested that high-grade endometrial carcinoma limited to a polyp or the endometrium should be classified as intermediate-risk of recurrence. Thus, there is no recommendation for brachytherapy as adjuvant treatment except if other risk factors, such as lymphovascular space invasion, are present.[7] There have been a few retrospective studies with a limited number of patients studying those precise cases.[8–17] At our center, most patients do not receive adjuvant treatment after surgery.

Thus, the goal of this study was to describe the characteristics of our patients with a type II endometrial carcinoma without myometrial infiltration or limited to a polyp. The secondary objective was to evaluate the clinical outcomes of patients observed after surgery (not receiving systemic adjuvant treatment) and compare these to the existing literature.

METHODS

Patient Eligibility

We retrospectively reviewed electronic files of patients who underwent surgery for endometrial carcinoma from April 2013 to November 2017 at our center. This project received approval from our research ethics committee. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested. Medical records were reviewed for the following information: age at diagnosis, patient demographics, type of surgery, histology, stage according to International Federation of Gynecology and Obstetrics (FIGO) 2009 classification, adjuvant treatments, and site of recurrence, if any. Only patients with high-grade histology (FIGO endometrioid grade 3, serous, clear cell, mixed, carcinosarcoma) without myometrial invasion or limited to a polyp were included. Patients with or without lymphovascular space invasion were included.

The initial diagnosis for all patients was made by office endometrial biopsy or dilatation and curettage. All surgical approaches were included (laparotomy or minimally invasive surgery). The surgery had to include at least a total hysterectomy with bilateral salpingo-oophorectomy, peritoneal washings, and sentinel lymph node (SLN) mapping, with or without pelvic and para-aortic lymphadenectomy, and omental biopsy. Statistical analysis included Kaplan–Meier estimates for 3-year pelvic progression-free survival and overall survival. Time-to-event was calculated from date of surgical staging.

Studies Inclusion

A literature review was undertaken to identify studies that reported outcomes of patients with stage IA serous endometrial carcinoma limited to the endometrium or a polyp. The literature search was conducted through PubMed. Our research query included "endometrial serous intraepithelial carcinoma", "serous uterine carcinoma PLUS polyp", and "serous endometrial carcinoma PLUS endometrium". Titles and abstracts were reviewed and we identified eight retrospective studies that compared adjuvant treatments and recurrence rates. No prospective studies were identified.

RESULTS

Patient Characteristics

Our retrospective cohort included 856 patients who underwent surgery for endometrial carcinoma. A total of 25 patients (2.9%) had a type II stage IA adenocarcinoma without myometrial invasion in 15 (60%) or limited to a polyp in 10 (40%). Fifteen patients (60%) had a diagnosis of serous intraepithelial carcinoma, 4 patients (16%) had mixed carcinoma with a high-grade component, 2 patients (8%) had clear cell, 3 patients (12%) had grade III endometrioid, and 1 patient (4%) had carcinosarcoma (Table 1). All patients had residual polyp or intraepithelial lesion on the final hysterectomy specimen. Only 4 (16%) patients had lymphovascular space invasion. The mean age at diagnosis was 69 (range 52–91) years. Median body mass index (BMI) was 30 kg/m^2, and 12 patients (48%) had a BMI below 30 kg/m^2.

All patients had pre-operative imaging studies. Up to 48% (n=12) of patients had a computed tomography scan of the abdomen and pelvis, 12 (48%) patients had an ultrasound of the abdomen and pelvis, and a pre-operative imaging study was not found for 1 patient (4%). Endometrial thickness was available in 18 patients (62.2%), and the mean thickness was 14 (range 5–30) mm. Pre-operative biopsy showed high-grade neoplasia in 18 (72%) patients, endometrial intraepithelial neoplasia in 4 (16%) patients, and endometrioid carcinoma grade 1 in 3 (12%) patients (Table 1).

Pre-operative CA-125 testing was also available for all patients. The median was 24 (range 5–326) units/mL. The patient with the elevated CA-125 level of 326 units/mL had a concomitant diagnosis of Child C cirrhosis with ascites. Otherwise, all values ranged from 5 to 44 units/mL.

In terms of surgical approach, 12 patients (48%) had robotic surgery, 10 patients (40%) had laparoscopic surgeries, and 3 patients (12%) underwent laparotomy (Table 1). All patients underwent total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, and 4 (16%) patients had omental sampling. As for lymph node evaluation, 3 (12%) patients had SLN only (all three had endometrial intraepithelial neoplasia on pre-operative biopsy), 19 (76%) patients had SLN and pelvic node dissection, and 3 (12%) patients had SLN with pelvic and para-aortic lymph node evaluation. Of the 25 patients in which SLN mapping was attempted, 23 (92%) patients had bilateral detection, and 2 (8%) patients had unilateral detection. For those two patients, complete lymph node dissection was performed, either unilateral or bilateral. All patients had negative surgical staging on final pathology.

Adjuvant Treatments

After surgery, most patients did not receive any adjuvant treatments (n=19 or 76%). Of the six patients (24%) who received vaginal vault brachytherapy only, two had presence of lymphovascular space invasion on final pathology. All cases were discussed at our multidisciplinary tumor board. The most frequent reasons for brachytherapy treatment recommendation were grade 3 endometrioid carcinoma (2/3 patients) and clear cell histology (1/2 patients). In addition, 2/4 patients with lymphovascular space invasion received vault brachytherapy.

Recurrences

At the time of the analysis, a total of 3 (12%) patients had recurrences (Online Supplemental Material 1). Two patients died of causes unrelated to endometrial carcinoma. The first patient died

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Table 1 Patients (n = 25) and tumor characteristics

Characteristic	n	%
Age at diagnosis (years)		
Median	69	
Range	55–91	
BMI (median) (kg/m2)	30	
<30	12	48
30–40	9	36
>40	4	16
Pre-operative imaging studies		
CT scan of abdomen and pelvis	12	48
Ultrasound of abdomen and pelvis	12	48
Unknown	1	4
Histology (on pre-operative endometrial biopsy)		
High-grade carcinoma	18	72
Endometrioid grade 1	3	12
Endometrial Intraepithelial neoplasia	4	16
Histology (on final pathology)		
Serous	15	60
Mixed	4	16
Grade 3 endometrioid	3	12
Clear cell	2	8
Carcinosarcoma	1	4
Polyp		
Yes	10	40
No	15	60
Lymphovascular space invasion		
Yes	4	16
No	21	84
CA-125 (units/mL)		
Median	24	
Range	5–326	
Surgical approach		
Robotic surgery	12	48
Laparoscopic surgery	10	40
Laparotomy	3	12
Surgical staging		
SLN + pelvic lymphadenectomy	19	76
SLN + pelvic and para-aortic lymphadenectomy	3	12
SLN only	3	12
Omentectomy	4	16
Follow-up (months)		
Median	44	
Range	2–67	

BMI, body mass index; CT, computed tomography; SLN, sentinel lymph node.

2 months after surgery from complications of Child C cirrhosis, a condition for which she was awaiting hepatic transplant. The second patient died 4 years after initial surgery from a cause unknown at the time of analysis, but she had no evidence of cancer recurrence at her last follow-up. The median follow-up was 44 (range 2–75) months. Two of 25 patients who recurred had not received adjuvant treatment after their initial surgery and one patient had received vault brachytherapy. Table 2 summarizes those three cases.

The 3-year progression-free survival and overall survival were 91% and 100%, respectively (Figure 1A,B).

Literature Review

To compare our results to the existing literature, we searched the literature and selected the eight largest series on endometrial cancer stage 1A limited to a polyp or the endometrium. All are retrospective series. Data are summarized in Table 3. In four of those series, most patients (51.3%–62.6%)[9 10 14 15] received adjuvant treatment. In six series, including ours, no impact of adjuvant treatment on outcome was reported, with recurrence rate and outcome comparable to our study. There are no prospective studies on type II endometrial carcinoma limited to the endometrium or to a polyp.

DISCUSSION

Summary of Main Results

In our study, the recurrence rate was 12% and all patients were alive and free of disease following salvage systemic chemotherapy treatment. The type of surgical staging did not appear to have an impact on recurrence. However, two of the three patients experiencing recurrence had lymphovascular space invasion on their final pathology report, and one had not received adjuvant brachytherapy.

Results in the Context of Published Literature

Our data are similar to older series in the literature (Table 3). A retrospective study published by Chang-Halpenny et al in 2013, showed a similar recurrence rate of 7.8% at 5 years. Most patients in that study did not receive adjuvant treatment (80%), a percentage comparable to our cohort.[8] Another study by Liang et al showed a lower recurrence rate (5.9%) at 3 years. Unlike our study, most patients did receive adjuvant treatment (76.5%), but there was no difference in the rate of recurrence whether patients received adjuvant treatment or not.[9] Lastly, a recent Canadian study showed a recurrence rate of 12.2% and a 5-year overall survival of 80.7%.[11] This cohort is very similar to ours as most patients did not receive any adjuvant treatment. In their retrospective study, the authors also demonstrated that recurrence rates were rare in the omentum and para-aortic area despite the low rate of para-aortic lymphadenectomy (0%) and omental biopsy (51%).

A large retrospective series from the National Cancer Database in the United States was recently published, and unlike our cohort, the 5-year overall survival was 9.4% higher in the chemoradiation group compared with the observation group (81.9% in the observation group compared with 91.3% in the chemoradiation group, p=0.001). Although it is a large cohort, it should be noted that cause of death and cancer-specific progression-free survival were not available, since the information could not be retrieved from the database. Also, more patients in the observation group had government insurance (compared with private insurance) which could explain the difference in overall survival.[10]

With regards to lymph node staging, a recent expert review has concluded that SLN evaluation is adequate for the staging of

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Table 2 Patients with recurrences

Patient	Histology	Polyp	LVSI	Adjuvant treatment	Site of recurrence	Time to recurrence (months)	Treatment	Outcome
1	Serous	Yes	Yes	No	Vaginal vault	55	ChemoTx EBRT BrachyTx	NED 75 months
2	Serous	Yes	No	No	Nodes	15	ChemoTx	NED 41 months
3	Mixed (serous 10%)	No	Yes	BrachyTx	Lungs	21	ChemoTx	NED 67 months

BrachyTx, brachytherapy; ChemoTx, chemotherapy; EBRT, external beam radiation therapy; LVSI, lymphovascular space invasion; NED, no evidence of disease.

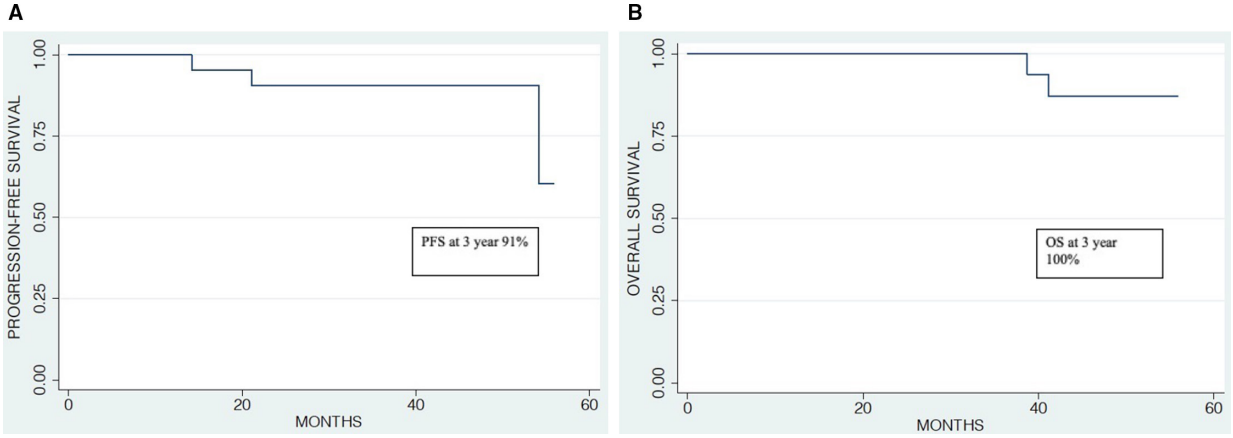

Figure 1 A: Kaplan–Meier for progression-free survival (PFS). B: Kaplan–Meier for overall survival.

uterine serous carcinoma. Indeed, the review confirms that accumulating data support the safety and effectiveness of SLN mapping for apparent early-stage uterine serous carcinoma.[18] A series published in 2017 compared survival of patients with SLN mapping versus complete lymphadenectomy and showed no difference in survival, suggesting that SLN alone does not appear to compromise prognosis in uterine serous carcinoma.[19] Lastly, in a recent study published by Jegatheeswaran et al, 36.6% of patients with high-grade endometrial carcinoma had complete surgical staging including para-aortic lymph node sampling and omentectomy but 50.1% had only SLN mapping and pelvic lymphadenectomy, indicating a trend towards omitting para-aortic lymphadenectomy and omental biopsy in high-grade uterine neoplasia.[20] Thus, the low rate of omental and para-aortic sampling in our study is in line with the trend towards less extensive surgical staging and increased use of SLN biopsies in high-risk endometrial cancer.

Study Strengths and Weaknesses

The strength our of study is that it is a single-center series with a uniform post-operative management and included only patients with disease limited to a polyp or without myometrial invasion. Our study is limited by its small size, its retrospective nature, and relatively short follow-up. However, due to the rarity of this entity, a large prospective study would be hard to conduct. Another limitation of our study is that only 16% of patients had omental sampling and 12% had para-aortic lymph node sampling, which is lower than in previous older studies. However, recent publications have shown that the detection of microscopic disease in normal-appearing omentum is rare in uterine serous carcinoma.[21] Although a recent study showed that the occurrence of omental metastases in patients with serous intraepithelial carcinoma varied from 5.1% to 9.8%,[22] adnexal involvement was found to be an important risk factor associated with omental involvement.[22] Hui et al also showed that when the omentum is involved, it is usually macroscopic disease or there is evidence of metastases elsewhere.[23]

Implications for Practice and Future Research

Although this study was not meant to be a thorough literature review, we identified the largest studies on endometrial carcinoma limited to a polyp or the endometrium. Smaller studies were not all included. Our review highlights the lack of prospective data and uniform management of those patients.

CONCLUSIONS

The findings of our study are concordant with other larger retrospective studies showing that expectant management with surveillance alone appears to be safe for patients with high-grade endometrial carcinoma limited to a polyp or the endometrium without myometrial invasion. Recurrence rate is low and salvage rate following treatment may favorably impact outcomes.

Contributors MCR and LDN gathered patients' data. JG did the statistical analyses. LDN wrote the first draft of the article and MP reviewed the article. All authors contributed to study design, data interpretation, critical review of article

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Table 3 Literature review

Study	Type	Inclusion criteria	Adjuvant treatment	Outcome	Conclusion
Nasioudis et al[10]	Retrospective cohort (n=1709) National Cancer Database (USA)	▶ Stage IA ▶ Serous carcinoma ▶ Limited to a polyp or the endometrium	▶ No adjuvant treatment (n=833, 48.7%) ▶ CT only (n=353, 20.7%) ▶ CT+RT (n=348, 20.4%), 80% brachy only ▶ RT only (n=175, 10.2%)	▶ Median F/U: 58.55 months ▶ 5-year OS 81.9% in observation group compared with 91.3% in CT+RT and 85% RT only (p=0.001) ▶ OS better in CT +RT group compared with observation (HR 0.55, CI 95% 0.35–0.88) and CT group (HR 0.64, CI 95% 0.35–0.8) ▶ PFS unknown (cause of death N/A in database)	No difference between CT and CT-RT Better OS if CT or CT+RT compared with observation
Mandato et al[12]	Retrospective cohort n=75, 66 patients with stage IA	▶ Retrospective data from 7 gynecology-oncology centers in Italy ▶ Patients with USC confined to a polyp of any stage (88% stage IA)	▶ No adjuvant treatment in 50 patients (66.7%) ▶ Adjuvant treatment in 25 patients, including 24.2% with FIGO IA – RT (4%) – CT (88%) – Brachy (8%) – 12% patients (n=9) upstaged to stage II-IV (all received adjuvant treatment)	▶ Median F/U 40 months ▶ 45% had complete surgical staging (including para-aortic LN and omentectomy), 45% had incomplete staging and 13.3% no staging ▶ Patients with stage IA complete staging and no adjuvant Tx had a risk of relapse of 5.2% ▶ Patients with stage IA, complete staging, and adjuvant treatment had a risk of recurrence of 12.5%	Complete surgical staging and HTN were associated with lower risk of relapse (especially compared with no staging) No impact of adjuvant treatment
Boyraz et al[13]	Retrospective cohort study n=182 patients n=20 for patients with USC confined to the endometrium	Patients with USC confined to the endometrium with or without metastatic disease	▶ 20 patients had stage IA confined to the endometrium ▶ Observation (70%) ▶ Brachy (20%) ▶ CT+brachy (5% ▶ CT (5%)	▶ Mean F/U 31 months ▶ 6 patients with disease confined to the uterus had adjuvant treatment (30%) ▶ OS and PFS similar for patients who received adjuvant treatment compared with observation (p=0.25 and p=0.30, respectively)	No impact of adjuvant treatment
Liang et al[9]	Retrospective cohort (n=85)	▶ Stage IA ▶ High-grade EC ▶ Limited to a polyp (57.6%) or without myometrial invasion (24.4%) ▶ LVSI excluded	▶ No adjuvant treatment (23.5%, 9 because of patient refusal) ▶ CT±RT (58.1%) ▶ Brachy (24.7%)	▶ Median F/U 46.5 months ▶ 5 recurrences: – 4 had received adjuvant therapy (3 CT +brachy and 1 brachy) ▶ PFS and OS rate at 3 years: 94.9% and 98.8%, respectively	No impact of adjuvant treatment on outcome
Mahdi et al[14]	Retrospective cohort study (n=115)	▶ Stage IA non-invasive USC ▶ Surgical staging including pelvic LNP (84%), omentectomy 57%	▶ Observation (37.4%) ▶ CT (18.3%) ▶ CT +brachy (23.5%) ▶ CT +RT (1.7%) ▶ CT +RT+brachy (0.9%) ▶ RT +brachy (4.4%)	▶ Mean F/U 52 months ▶ Mean PFS 53.2 and mean OS 68.9 months ▶ CT did not impact on mean PFS and OS (recurrences of 25.5% vs 26.9%, p=0.85)	No impact of adjuvant treatment Staging LNP had an impact on recurrence rate
van der Putten et al[11]	Retrospective cohort study (Stage IA without myometrial invasion n=41)	▶ USC stage I (at least 10% of serous) ▶ Surgical staging with at least a hysterectomy and salpingo-oophorectomy – Pelvic LNP in 66% – No omental biopsy in 51.2%	▶ Observation (73.1%) ▶ Brachy (5%) ▶ CT (2.4%) ▶ CT +RT (19.5%)	▶ 5-year disease-free survival of 80.7% ▶ Recurrence rate of 12.2% – 10% in observation and 18% in adjuvant treatment group (p=0.6) ▶ 72.2% of recurrences were distant ▶ Few para-aortic and omental recurrences	No impact of adjuvant treatment on outcomes
Chang-Halpenny et al[8]	Retrospective cohort (n=51)	▶ Stage IA ▶ Serous carcinoma or clear cell ▶ Limited to a polyp or endometrium ▶ 5 had myometrial invasion (9.8%)	▶ No adjuvant treatment (n=40, 80%) ▶ Adjuvant treatment if myometrial invasion, positive peritoneal washings, or incomplete staging – CT+RT (n=6, 12%) – CT (n=3, 6%) ▶ Brachy only (n=1, 2%)	▶ Median F/U 45.2 months ▶ 4 recurrences with carcinomatosis or pelvic lymph nodes (7.8%) ▶ 11 deaths: 3 from EC, 2 new gynecologic cancer, 6 from non-malignant conditions ▶ PFS and OS at 5 years: 93% and 80.6%, respectively	No impact of adjuvant treatment on outcome

Continued

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Table 3 Continued

Study	Type	Inclusion criteria	Adjuvant treatment	Outcome	Conclusion
Fader et al[15]	Retrospective cohort (n=54) *Entire cohort n=206	▶ Stage IA ▶ Serous carcinoma	▶ No adjuvant treatment (n=21, 38.9%) ▶ CT (n=28, 51.9%) ▶ Brachy (n=5, 9.3%)	▶ For the stage IA subgroup: ▶ Median F/U 27 months ▶ 6 recurrences (11.1%) ▶ OS or PFS not available ▶ For the entire cohort: substage (p=0.005) and CT (p=0.001) associated with better PFS ▶ Recurrences: 21.4% ▶ 31.1% in observation group ▶ 38.3% in RT group ▶ 10.5% in CT group (p=0.001)	Impact of adjuvant treatment (CT) on outcome for the entire cohort Not evaluable for the stage IA subgroup
Dallaire-Nantel et al	Retrospective cohort (n=25)	▶ Stage IA ▶ Type II endometrial carcinoma ▶ Limited to a polyp or the endometrium	▶ No adjuvant treatment (n=19, 76%) ▶ Brachy (n=6, 24%) ▶ No patients received CT	▶ Median F/U 44 months ▶ 3 recurrences (12%) ▶ PFS and OS at 3 years: 91% and 100%, respectively	No impact of adjuvant treatment on outcome

brachy, brachytherapy; CI, confidence interval; CT, chemotherapy; CT-RT, chemoradiation; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; F/U, follow-up; HR, hazard ratio; HTN, hypertension; LN, lymph node; LNP, pelvic lymph node; LVSI, lymphovascular space invasion; N/A, not available; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; Tx, treatment; USC, uterine serous carcinoma.

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