Adjuvant chemotherapy in early-stage endometrioid endometrial cancer with >50% myometrial invasion and negative lymph nodes

Francesco Multinu ,[1,2] Simone Garzon ,[1,3] Amy L Weaver,[4] Michaela E. McGree,[4] Enrico Sartori,[5] Fabio Landoni,[6] Paolo Zola,[7] Giorgia Dinoi,[1,8] Giovanni Aletti,[2,9] Matthew S Block,[10] Angiolo Gadducci,[11] Andrea Mariani[1]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2020-002094).

For numbered affiliations see end of article.

Correspondence to
Dr Andrea Mariani, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN 55905, USA; mariani.andrea@mayo.edu

FM and SG contributed equally.

FM and SG are joint first authors.
AG and AM are joint senior authors.

Received 24 September 2020
Revised 5 February 2021
Accepted 8 February 2021
Published Online First 19 February 2021

To cite: Multinu F, Garzon S, Weaver AL, *et al. Int J Gynecol Cancer* 2021;**31**:537–544.

HIGHLIGHTS

- Adjuvant chemotherapy was associated with improved oncologic outcomes, but the associations did not meet statistical significance.
- Stage II and advanced age were the strongest risk factors for poor prognosis.
- Adjuvant chemotherapy needs further investigation, especially in patients with grade 2–3 stage II endometrial cancer with myometrial invasion >50%.

ABSTRACT

Objective The role of adjuvant chemotherapy as an addition or alternative to radiotherapy for early-stage high-risk endometrioid endometrial cancer is controversial. This study aimed to investigate the role of adjuvant chemotherapy in early-stage high-risk endometrioid endometrial cancer.

Methods We identified patients with stage I or II endometrioid grade 2 or 3 endometrial cancer with myometrial invasion >50% and negative lymph nodes after pelvic with or without para-aortic lymphadenectomy at four institutions (USA and Italy). Associations between chemotherapy and cause-specific and recurrence-free survival were assessed with Cox proportional hazards models. Hematogenous, peritoneal, and lymphatic recurrences were defined as 'non-vaginal'.

Results We identified 329 patients of mean (SD) age 66.4 (9.8) years. The median follow-up among those alive was 84 (IQR 44–133) months. The 5-year cause-specific survival was 86.1% (95% CI 82.0% to 90.4%) and the 5-year recurrence-free survival was 82.2% (95% CI 77.9% to 86.8%). Stage II (vs stage IB) was associated with poorer cause-specific and recurrence-free survival. A total of 58 (90.6%) of 64 patients who had chemotherapy had 4–6 cycles of platinum-based regimen. In adjusted analysis, we did not observe a statistically significant improvement in cause-specific survival (HR 0.34; 95% CI 0.11 to 1.03; p=0.06) or non-vaginal recurrence-free survival (HR 0.36; 95% CI 0.12 to 1.08; p=0.07) with adjuvant chemotherapy. Sixteen of 18 lymphatic recurrences (88.9%; 3/5 pelvic, all 13 para-aortic) were observed in the 265 patients who did not receive adjuvant chemotherapy. Among stage II patients, no deaths (100% 5-year recurrence-free survival) were observed in the eight patients who received adjuvant chemotherapy compared with 66% 5-year recurrence-free survival in the 34 patients who did not.

Conclusion Although we observed that adjuvant chemotherapy was associated with improved oncologic outcomes in early-stage high-risk endometrioid endometrial cancer, the associations did not meet conventional levels of statistical significance. Further research is warranted in this relatively uncommon subgroup of patients.

INTRODUCTION

In 2020, a total of 65 620 new cases of endometrial cancer and 12 590 deaths were estimated in the USA.[1] Apparent early-stage endometrial cancer comprises most cases at diagnosis, and primary surgery with total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment is the standard of care.[2] Conversely, post-operative management of confirmed early-stage endometrioid endometrial cancer is not standardized.[2]

Adjuvant external beam radiotherapy and vaginal brachytherapy have improved locoregional control in early stages,[3–5] but have not improved distant recurrence or overall survival.[3] Therefore, chemotherapy has been investigated as an additional or alternative adjuvant treatment,[3 6] particularly for high-risk early-stage endometrioid endometrial cancer.[7–12] However, randomized trials investigating adjuvant chemotherapy[13–15] or chemoradiotherapy[6 15–18] have reported conflicting results. Therefore, it is unclear which patients with early-stage endometrioid endometrial cancer, if any, would benefit from adjuvant chemotherapy.

One reason the evidence is unclear is that early-stage endometrioid endometrial cancer is heterogeneous in a continuum for risk of recurrence and cancer-related death.[2] Risk has been associated with specific factors, including age, International

Table 1 Patient and tumor characteristics, extent of surgical staging, and adjuvant therapy in patients with stage I and II endometrioid grade 2 or 3 endometrial cancer with myometrial invasion >50%

Characteristics	Mayo Clinic (n=141)	Italian centers (n=188)	Total (n=329)
Age at surgery, mean (SD), years	69.1 (9.9)	64.4 (9.1)	66.4 (9.8)
Grade, n (%)			
2	99 (70.2)	107 (56.9)	206 (62.6)
3	42 (29.8)	81 (43.1)	123 (37.4)
FIGO stage,* n (%)			
IB	127 (90.1)	158 (84.0)	285 (86.6)
II	14 (9.9)	30 (16.0)	44 (13.4)
LVSI, n (%)			
No	94 (66.7)	89 (47.3)	183 (55.6)
Yes	35 (24.8)	61 (32.4)	96 (29.2)
Unknown	12 (8.5)	38 (20.2)	50 (15.2)
Para-aortic LND, n (%)			
No	56 (39.7)	170 (90.4)	226 (68.7)
Yes	85 (60.3)	18 (9.6)	103 (31.3)
Adjuvant therapy, n (%)			
None	39 (27.7)	38 (20.2)	77 (23.4)
VB only	35 (24.8)	12 (6.4)	47 (14.3)
EBRT ± VB	39 (27.7)	102 (54.3)	141 (42.9)
Chemotherapy ± VB	25 (17.7)	19 (10.1)	44 (13.4)
Chemotherapy and EBRT ± VB	3 (2.1)	17 (9.0)	20 (6.1)

*According to the 2009 FIGO staging system.
EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; LND, lymphadenectomy; LVSI, lymphovascular space invasion; VB, vaginal brachytherapy.

Federation of Gynecology and Obstetrics (FIGO) stage, myometrial invasion depth, tumor grade, and lymphovascular space invasion.[9] These factors are present in varying degrees in selected populations, defining different sub-groups with various risk levels and potential benefit from chemotherapy. The low prevalence of every single sub-group defined by each unique combination of risk factors limits the power of previous studies to exclude the role of adjuvant chemotherapy in those at high risk, which are investigated merged with sub-groups at lower risk to achieve sufficient study power.[6 13–18] On that basis, we specifically focused on a restricted group of patients with high-risk early-stage endometrioid endometrial cancer characterized by myometrial invasion >50% and grade 2 or 3. High-grade early-stage endometrioid endometrial cancer with deep myometrial invasion was reported to potentially benefit from adjuvant chemotherapy.[14]

We performed a multicenter retrospective study of patients with stage I or II endometrioid grade 2 or 3 endometrial cancer who had myometrial invasion >50% and negative lymph nodes. We aimed to compare oncologic outcomes between patients who received adjuvant chemotherapy and those who did not.

METHODS

We retrospectively identified all patients with FIGO stage I or II endometrioid endometrial cancer, grade 2 or 3, and myometrial invasion >50% who underwent pelvic ± para-aortic lymphadenectomy and had negative lymph nodes. Patients were identified from the endometrial cancer databases at four large institutions in the USA (Mayo Clinic in Rochester, Minnesota) and Italy (University of Pisa, University of Turin, and University of Brescia). At the Mayo Clinic patients were treated from January 1984 to December 2012 and, at the three Italian institutions, from January 1987 to December 2012. We excluded patients with synchronous invasive cancer, patients who underwent neoadjuvant therapy, those with unknown adjuvant therapy status, and patients who did not consent. Details regarding excluded patients among those identified at the Mayo Clinic are shown in Online supplemental figure 1.

The variables collected for analysis were patient age, FIGO grade and stage, lymphovascular space invasion, the extent of lymphadenectomy, type of adjuvant therapy, date and site of the first recurrence, vital status, date and cause of death, and date of the last follow-up. The first recurrence site was classified as vaginal if recurrence involved the vaginal cuff or as non-vaginal if recurrence was localized to the lymph node basins or peritoneum or was distant through hematogenous spread.

The inclusion criteria required that patients had undergone hysterectomy, bilateral salpingo-oophorectomy, and pelvic ± para-aortic lymphadenectomy. No patient underwent sentinel lymph node biopsy due to the fact that it was not standard of care at the time. The para-aortic area was evaluated according to institutional guidelines and the surgeon's discretion. Adjuvant therapy was administered following institutional guidelines and the preferences of the physician and patient. Pelvic external beam radiotherapy was performed with a beam of 15–18 mV and a daily fraction of 1.8 Gy up to a dose of 45–50.4 Gy given in 5–6 weeks. The sequential protocol for combined regimens (chemotherapy before radiotherapy) was used at the Italian centers and Mayo Clinic; the sandwich protocol (3 cycles of chemotherapy, radiotherapy, 3 cycles of chemotherapy) was used only at the Mayo Clinic.

Patient and pathologic characteristics and adjuvant therapy use were summarized with standard descriptive statistics and compared between Mayo Clinic and Italian centers. Primary outcomes were cause-specific survival (event=death due to disease), recurrence-free survival (event=first recurrence at any site), and non-vaginal recurrence-free survival (event=first recurrence is non-vaginal). Each outcome was estimated with the Kaplan–Meier method, restricting follow-up to the first 5 years after surgery. Univariate Cox proportional hazards regression models were fit to evaluate the association of each characteristic with each outcome. Cox models were stratified by center (Mayo Clinic vs Italian centers) to accommodate a separate hazard function.

Given the absent random assignment of adjuvant therapy, we evaluated the association of receiving chemotherapy with primary outcomes by fitting Cox proportional hazards models weighted using the inverse probability of treatment weighting. The propensity

Table 2 Univariate analysis of factors evaluated for an association with cause-specific survival (CSS), recurrence-free survival (RFS), and non-vaginal RFS within 5 years after surgery

	CSS (37 events)		RFS (51 events)		Non-vaginal RFS (42 events)	
Characteristic*	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age at surgery, years†	1.31 (0.93 to 1.86)	0.13	1.37 (1.01 to 1.84)	0.04	1.25 (0.90 to 1.73)	0.19
Age at surgery by quartile (Q), years						
Q1: <60.3 (n=82)	Reference		Reference		Reference	
Q2: 60.3 to <66.1 (n=83)	4.64 (1.54 to 14.00)		2.62 (1.08 to 6.39)		2.07 (0.83 to 5.21)	
Q3: 66.1 to <73.4 (n=82)	3.42 (1.06 to 10.98)		2.62 (1.05 to 6.54)		1.98 (0.76 to 5.16)	
Q4: ≥73.4 (n=82)	2.71 (0.81 to 9.08)		2.62 (1.05 to 6.56)		1.98 (0.76 to 5.18)	
Grade		0.10		0.17		0.17
2 (n=206)	Reference		Reference		Reference	
3 (n=123)	1.74 (0.91 to 3.33)		1.48 (0.85 to 2.58)		1.53 (0.83 to 2.83)	
FIGO stage‡		0.03		0.04		0.06
IB (n=285)	Reference		Reference		Reference	
II (n=44)	2.22 (1.07 to 4.60)		1.94 (1.01 to 3.71)		1.98 (0.97 to 4.03)	
LVSI§		0.38		0.09		0.15
No (n=183)	Reference		Reference		Reference	
Yes (n=96)	1.37 (0.68 to 2.79)		1.66 (0.93 to 2.99)		1.59 (0.85 to 2.98)	
Para-aortic LND		0.07		0.27		0.23
No (n=226)	Reference		Reference		Reference	
Yes (n=103)	0.41 (0.16 to 1.08)		0.65 (0.31 to 1.39)		0.60 (0.26 to 1.39)	
Adjuvant therapy		0.59		0.57		0.51
None (n=77)	Reference		Reference		Reference	
VB only (n=47)	0.74 (0.23 to 2.44)		1.22 (0.49 to 3.01)		1.30 (0.48 to 3.50)	
EBRT ± VB (n=141)	0.91 (0.42 to 1.97)		0.84 (0.42 to 1.66)		0.99 (0.46 to 2.13)	
Chemotherapy ± VB (n=44)	0.34 (0.08 to 1.57)		0.50 (0.16 to 1.55)		0.32 (0.07 to 1.47)	
Chemotherapy and EBRT ± VB (n=20)	0.35 (0.05 to 2.79)		0.49 (0.11 to 2.18)		0.66 (0.14 to 3.05)	

*Each characteristic was evaluated in a separate univariate stratified Cox proportional hazards regression model, stratified by the two center groups (Mayo Clinic and 3 Italian centers), to accommodate a separate hazard function for each of the two center groups because of their different patient populations.
†HR per 10-year increase in age.
‡According to the 2009 FIGO staging system.
§The 50 patients with unknown information for LVSI were not included in the univariate analysis.
EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; LND, lymphadenectomy; LVSI, lymphovascular space invasion; VB, vaginal brachytherapy.

score values for the inverse probability of treatment weighting were estimated using as covariates age, grade, FIGO stage, lymphovascular space invasion, and para-aortic lymphadenectomy. Detailed inverse probability of treatment weighting analysis is available in the Online supplemental material.

In an exploratory analysis to identify a sub-group of patients who may benefit more from chemotherapy, we evaluated the association between adjuvant chemotherapy and outcomes separately, according to the presence of risk factors, by fitting inverse probability of treatment weighting-adjusted Cox proportional hazards models stratified by center and using robust sandwich covariance estimates. Risk factors were those identified according to univariate analysis.

Analyses were performed with Statistical Analysis System (SAS) version 9.4 (SAS Institute), with statistical significance set at a two-tailed α level of 0.05. The study was approved by the Institutional Review Board of all centers, which waived the requirement for written informed consent.

RESULTS

We included 329 patients who met the inclusion criteria: 141 patients were treated at the Mayo Clinic and 188 at the three Italian institutions. Table 1 summarizes the characteristics of the patients and tumors, the extent of surgical staging, and adjuvant therapy administration. Adjuvant chemotherapy was used in 19.5%

(64/329) of patients. Details of chemotherapy regimens are reported in Online supplemental table 1. Of the 64 patients who received chemotherapy, most (98.4%) had a platinum-based regimen, 44 (68.8%) patients had chemotherapy ± vaginal brachytherapy, and 20 (31.2%) patients had chemotherapy and external beam radiotherapy ± vaginal brachytherapy. A total of 58 patients (90.6%) had 4–6 cycles of chemotherapy. Distribution over time of patient inclusion, rate of para-aortic lymphadenectomy, and adjuvant chemotherapy is reported in Online supplemental table 2.

Of the 329 patients, 59 died (37 patients died of disease) within the first 5 years. Among the remaining 270 patients, the median follow-up was 84 (IQR 44–133) months. Disease recurred in 51 patients (15.5%) within 5 years after surgery; the first recurrence was vaginal only in nine patients and non-vaginal in 42 (hematogenous or peritoneal only (or both) in 23; lymphatic only in 10 (all para-aortic); lymphatic and hematogenous or peritoneal in 7 (4 pelvic and 3 para-aortic); hematogenous and vaginal in 1; and lymphatic (pelvic), hematogenous, and vaginal in 1). Overall, 18 (5.5%) patients had lymphatic recurrence: 5 pelvic and 13 para-aortic. All 10 isolated lymphatic failures were para-aortic.

The 5-year cause-specific survival was 86.1% (95% CI 82.0% to 90.4%) and the 5-year recurrence-free survival was 82.2% (95% CI 77.9% to 86.8%). With univariate analysis, FIGO stage II (vs stage IB) was significantly associated with poorer cause-specific and recurrence-free survival, and older age with poorer recurrence-free survival; no other variable was significantly associated (Table 2).

Standardized differences of covariates in the adjusted cohort were less than the 0.20 threshold of desirability for four of the five characteristics (see Online supplemental table 3). To address the residual imbalance in age between groups, outcomes were compared between the group that received chemotherapy (± external beam radiotherapy ± vaginal brachytherapy) and the group that did not by fitting the Cox models with age as the time scale. Moreover, the analysis was stratified by the center groups (Mayo Clinic vs Italian centers) to accommodate a separate hazard function because of observed differences (Table 1). The inverse probability of treatment weighting-adjusted analysis of outcomes did not show a statistically significant association between the administration of adjuvant chemotherapy and cause-specific survival (HR 0.34; 95% CI 0.11 to 1.03; p=0.06), recurrence-free survival (HR 0.57; 95% CI 0.24 to 1.37; p=0.21), and non-vaginal recurrence-free survival (HR 0.36; 95% CI 0.12 to 1.08; p=0.07) (Table 3 and Figure 1).

Sixteen of 18 lymphatic recurrences (88.9%; 3/5 pelvic and all 13 para-aortic) were observed in the 265 patients who did not receive adjuvant chemotherapy; 6% of patients (16/265) had lymphatic recurrences compared with 3.1% (2/64) of patients who received chemotherapy (Table 3). Eleven of 13 para-aortic recurrences (84.6%) were observed in the 194 patients who had neither para-aortic lymphadenectomy nor adjuvant chemotherapy. Two para-aortic recurrences were reported in the 71 patients who had para-aortic lymphadenectomy but did not receive adjuvant chemotherapy (see Online supplemental table 4). Conversely, no para-aortic recurrences were observed among the 32 patients who did not undergo para-aortic lymphadenectomy but received chemotherapy (see Online supplemental table 4).

We evaluated the association between adjuvant chemotherapy and outcomes, stratifying according to the presence of significant (p<0.05) risk factors (stage II for cause-specific survival; stage II and older age for recurrence-free survival; Table 2). Online supplemental table 5 shows the Kaplan–Meier estimate of 5-year cause-specific survival and 5-year recurrence-free survival for the inverse probability of the treatment weighting-adjusted cohort according to the presence of risk factors and receipt of adjuvant chemotherapy. Among the 42 patients with stage II, no deaths (100% 5-year cause-specific survival) were observed in the eight patients who received

Table 3 Comparison of outcomes between patients who did or did not receive chemotherapy

Outcome	Received chemotherapy	No of events within 5 years	Without IPTW adjustment*		With IPTW adjustment*	
			HR (95% CI)	P value	HR (95% CI)	P value
Death due to disease	No (n=265)	34	Reference		Reference	
	Yes (n=64)	3	0.30 (0.09 to 1.01)	0.05	0.34 (0.11 to 1.03)	0.06
Recurrence						
Any	No (n=265)	45	Reference		Reference	
	Yes (n=64)	6	0.54 (0.22 to 1.33)	0.18	0.57 (0.24 to 1.37)	0.21
Non-vaginal	No (n=265)	38	Reference		Reference	
	Yes (n=64)	4	0.39 (0.14 to 1.13)	0.08	0.36 (0.12 to 1.08)	0.07
Lymphatic	No (n=265)	16	Reference		Reference	
	Yes (n=64)	2	0.40 (0.09 to 1.82)	0.23	0.34 (0.07 to 1.71)	0.19
Para-aortic	No (n=265)	13	Reference		Reference	
	Yes (n=64)	0	0.10 (0.01 to 2.09)	0.14	0.11 (0.01 to 2.21)	0.15
HP	No (n=265)	28	Reference		Reference	
	Yes (n=64)	4	0.54 (0.18 to 1.61)	0.27	0.52 (0.17 to 1.58)	0.25

*Each Cox proportional hazards regression model was fit using age as the time scale in order to more completely adjust for age and stratified by the two center groups (Mayo Clinic and 3 Italian centers) to accommodate a separate hazard function for each country given the different patient populations.
HP, hematogenous and/or peritoneal; IPTW, inverse probability of treatment weighting.

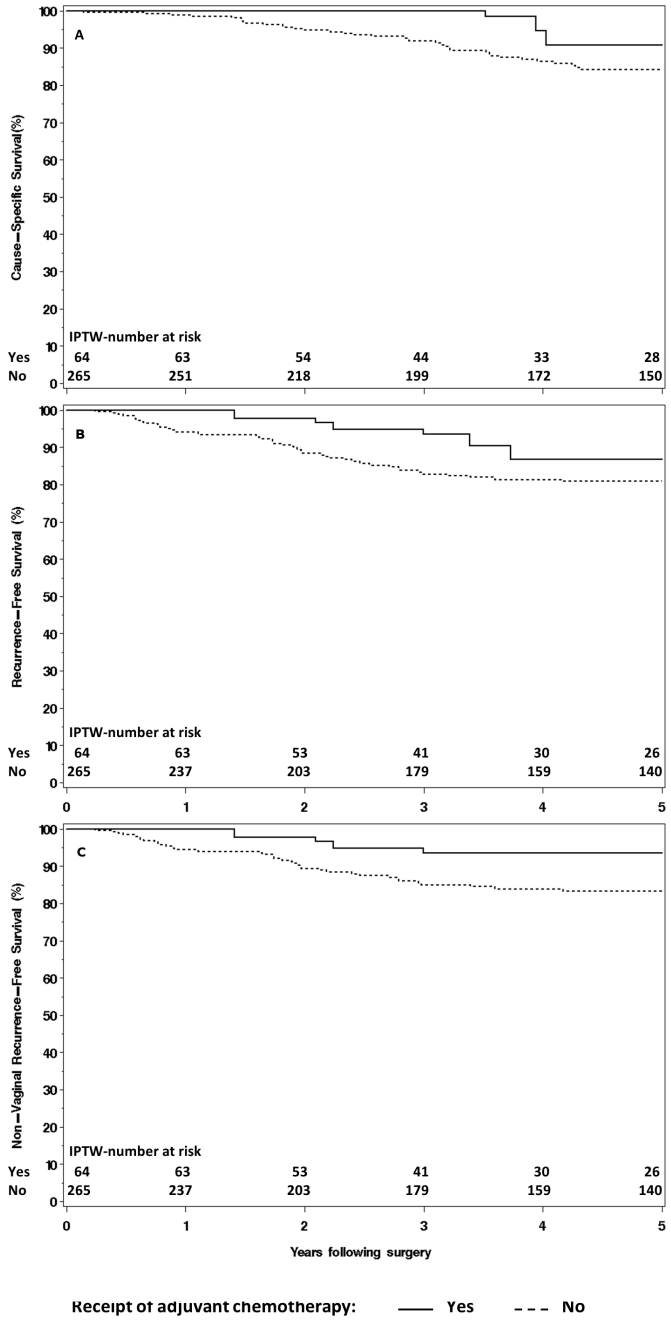

Figure 1 Inverse probability of treatment weighting (IPTW) for survival in patients who did or did not receive adjuvant chemotherapy. (A) Cause-specific survival. (B) Recurrence-free survival. (C) Non-vaginal recurrence-free survival.

adjuvant chemotherapy, compared with 66% 5-year cause-specific survival in the 34 stage II patients without adjuvant chemotherapy (Figure 2B).

DISCUSSION

Summary of Main Results

Although we observed that adjuvant chemotherapy was associated with improved cause-specific survival and non-vaginal recurrence-free survival in stage I or II endometrioid grade 2 or 3 endometrial cancer with myometrial invasion >50%, the associations did not meet conventional levels of statistical significance. Stage II and advanced age were the strongest risk factors for poor prognosis in early-stage grade 2 and 3 endometrioid endometrial cancer with deep myoinvasion.

Results in the Context of Published Literature

Although adjuvant external beam radiotherapy is commonly used in high-intermediate-risk and high-risk early-stage endometrial cancer,[19] it does not impact rates of distant recurrence and overall survival.[3] For this reason, adjuvant chemotherapy and chemoradiotherapy have been investigated in endometrial cancer sub-groups with a higher rate of distant recurrence and cancer-related mortality.[3 6] Nevertheless, previous studies including patients with high-risk early-stage endometrial cancer have reported conflicting results.[6 13–18]

Concerning adjuvant chemotherapy versus external beam radiotherapy, Maggi et al[13] and the Gynecologic Oncology Group (GOG)-249 trial[16] included patients who had high-risk early-stage endometrial cancer similar to patients in our study and observed comparable overall and recurrence-free survival. Similarly, Susumu et al[14] confirmed these results in patients with stage I, II, or IIIA endometrioid endometrial cancer with myometrial invasion >50%. Nevertheless, when they excluded stage I patients who were not high-intermediate risk as per the GOG-99 trial,[5] chemotherapy significantly improved overall and recurrence-free survival. It is noteworthy that chemotherapy seemed to prevent distant relapses more than external beam radiotherapy in the study by Maggi et al.[13] Moreover, including patients with either grade 1 or myometrial invasion ≤50% and administering only three cycles of chemotherapy may have obscured the benefit of chemotherapy in the GOG-249 trial.[16]

With regard to chemoradiotherapy versus external beam radiotherapy, the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-3 trial observed improved 5-year overall and recurrence-free survival in the chemoradiotherapy group.[6] However, the exploratory analysis did not confirm these results in stage I or II diseases. Similarly, Kuoppala et al[18] did not report improved 5-year overall and recurrence-free survival. Conversely, the study by Hogberg et al[17] showed significantly improved recurrence-free and cause-specific survival among patients with stage I or II endometrioid endometrial cancer who received chemoradiotherapy.[17] These benefits were confirmed in a subsequent meta-analysis including five randomized controlled trials.[15]

These conflicting results may be related to the heterogeneity of the study populations, differences in treatment protocols, and a study power calculated for the entire study population but not for each sub-group of endometrial cancer.[20 21] Moreover, many trials are designed to detect a minimum improvement of 10%, but less may be acceptable.[22] A Cochrane systematic review reported an absolute reduction of 4% for death and 5% for distant recurrence after chemotherapy.[15]

Nevertheless, conversely to that suggested by Susumu et al[14] and Hogberg et al,[17] our study results did not show a statistically significant benefit of adjuvant chemotherapy in patients with stage I or II endometrioid grade 2 or 3 endometrial cancer with myometrial invasion >50% and negative nodes in improving cause-specific survival (HR 0.34; 95% CI 0.11 to 1.03; p=0.06),

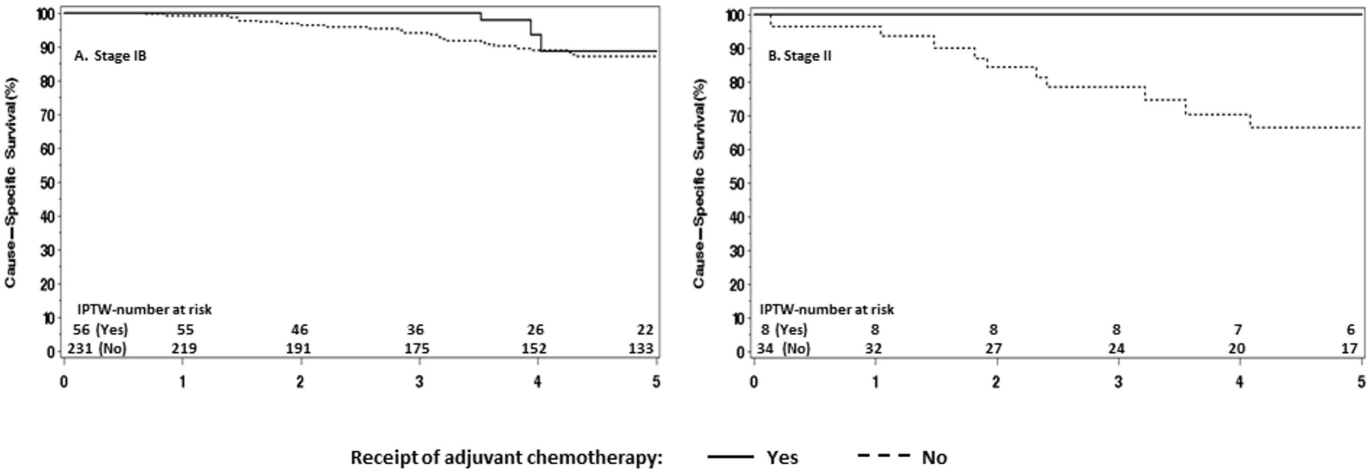

Figure 2 Inverse probability of treatment weighting (IPTW) for cause-specific survival according to receipt of adjuvant chemotherapy. (A) Patients with FIGO stage IB. (B) Patients with FIGO stage II.

recurrence-free survival (HR 0.57; 95% CI 0.24 to 1.37; p=0.21), and non-vaginal recurrence-free survival (HR 0.36; 95% CI 0.12 to 1.08; p=0.07). This study is the first to focus on this specific sub-group of patients with early-stage high-risk endometrial cancer. The multicenter design allowed identifying a high number of patients with homogeneous risk, with a higher number of recurrences than the previous series.[9 10] Moreover, more than 90% of patients who received chemotherapy had platinum-based regimens with 4–6 cycles.

Nevertheless, although our study aimed to overcome the limitations of previous evidence and provide targeted indications for clinical practice, the sample size was not sufficient to confirm a protective effect with the chosen level of statistical significance. In fact, stage I and II, grade 2 and 3 endometrioid endometrial cancer with myometrial invasion >50% is a relatively rare sub-group of patients. Thus, consistent with previous studies,[13 14] only a small percentage of patients treated each year met the inclusion criteria for this investigation, leading to a study of nearly 30 years. This sub-group accounted for 5.2% of the overall Mayo Clinic population who underwent surgical treatment for endometrial cancer (170/3267 before applying exclusion criteria), which is consistent with an estimated prevalence in the literature of 6.1%.[23] The low prevalence explains the relatively limited number of such patients reported in the literature. It is also noteworthy that the sample size is further restricted when focusing only on patients with surgical staging, as in our study. Surgical staging with lymph node assessment is essential to classify these patients appropriately.

Regarding non-vaginal recurrences, the limited numbers do not allow us to draw definitive conclusions on a possible protective effect of chemotherapy for specific recurrence sites such as para-aortic recurrences. Concerning the exploratory analysis, we did not identify a sub-group that may benefit from adjuvant chemotherapy. However, adjuvant chemotherapy may deserve further investigation in our stage II sub-group. Indeed, in stage II endometrial cancer, distant recurrences and overall survival are not improved by external beam radiotherapy; however, it is still unclear which sub-group of stage II may benefit from adjuvant chemotherapy.[24]

Strengths and Weaknesses

Despite the advantages, a multicenter design also has some limitations. Adjuvant chemotherapy remains heterogeneous, impeding definitive conclusions on the most appropriate regimen. The long time interval and the multicenter origin of data did not allow a complete centralized pathology review, although it was conducted at each center to confirm diagnoses. Differences in adopting para-aortic lymphadenectomy between Italian centers and the Mayo Clinic prohibit definitive conclusions regarding the impact on prognosis (9.6% of patients underwent para-aortic lymphadenectomy at the Italian centers and 60.3% at the Mayo Clinic). Therefore, the trend in improved outcomes related to para-aortic lymphadenectomy may reflect other differences between centers. Moreover, the observed effect of para-aortic lymphadenectomy may be partly due to selection bias; patient and tumor characteristics may have influenced the surgeon's decision. Finally, treatment trends over time have to be considered (see Online supplemental table 2). The use of para-aortic lymphadenectomy at the Mayo Clinic increased in the last years of the study period due to a more standardized surgical approach introduced in 2004. Chemotherapy was administered, particularly at the Mayo Clinic, mostly in the second half of the time interval. This distribution may reduce selection bias, being associated more with a change in clinical practice than patients' characteristics. However, simultaneously, it may introduce unknown confounders associated with oncologic outcomes. Non-random assignment of patients to adjuvant therapy introduces potential selection bias and possible confounders. However, the propensity score methodology allowed for a reduction in the imbalance of measured covariates between the two groups, limiting the risk of biases and strengthening results.

Implications for Practice and Future Research

Our study results do not conclusively support the use of adjuvant platinum-based chemotherapy in patients with stage I or II endometrioid grade 2 or 3 endometrial cancer and myometrial invasion >50%, given that the p value did not meet the conventional level of statistical significance. However, we do feel that our study is not without merit, and studies involving cohorts from other institutions are warranted to evaluate the reproducibility of our findings.

Increasing the sample size may help to achieve statistically significant results; however, the effect size (ie, HR) may change in a larger or different cohort and, as a consequence, statistical significance may still not be obtained. Therefore, a post hoc power calculation using the currently observed effect size does not add useful information to our analysis and was not conducted.[25] In particular, in this cohort there is a suggestion that especially women with stage II endometrial cancer may warrant more investigations on the role of adjuvant chemotherapy. In the future, additional information provided by integrated clinicopathologic and molecular risk profiling may further guide the adjuvant treatment.[26 27]

CONCLUSION

The role of adjuvant chemotherapy as an addition or alternative to radiotherapy is controversial in early-stage high-risk endometrioid endometrial cancer. In our study, although the numbers were relatively large for a highly selected sub-group of patients, we still did not observe a statistically significant improvement of oncologic outcomes with the use of adjuvant chemotherapy in patients with stage I or II endometrioid grade 2 or 3 endometrial cancer with deep myoinvasion and negative lymph nodes. Further research is warranted in this relatively rare sub-group of patients.

Author affiliations
[1]Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota, USA
[2]Division of Gynecologic Oncology, IEO, European Institute of Oncology IRCCS, Milan, Lombardia, Italy
[3]Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of Insubria, Varese, Lombardia, Italy
[4]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA
[5]Department of Obstetrics and Gynecology, University of Brescia, Brescia, Lombardia, Italy
[6]Department of Medicine and Surgery, Clinic of Obstetrics and Gynecology, San Gerardo Hospital, University of Milan-Bicocca, Monza, Lombardia, Italy
[7]Department of Surgical Sciences, University of Turin, Torino, Piemonte, Italy
[8]Division of Gynecologic Oncology, Department of Women and Child Health, Catholic University of the Sacred Heart, Roma, Lazio, Italy
[9]Department of Hematology and Hemato-Oncology, European Institute of Oncology, Milano, Lombardia, Italy
[10]Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA
[11]Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Toscana, Italy

Twitter Francesco Multinu @Fmultinu

Contributors Conception and design of the study: FM, AM, AG, and SG. Data collection, analysis, and interpretation: ALW, MM, SG, FM, AM, AG, ES, FL, and PZ. Writing, review, and editing the manuscript: all authors.

Funding This publication was made possible by the Clinical and Translational Science Awards (CTSA) Program through grant number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). This work was partially supported by the Italian Ministry of Health with Ricerca Corrente and 5×1000 funds.

Disclaimer The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Competing interests MSB received institutional (not personal) research support from Bristol-Myers Squibb Co, Merck & Co, Genentech, Pharmacyclics, Transgene, Immune Design, and Marker Therapeutics outside the present work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. 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.

ORCID iDs
Francesco Multinu http://orcid.org/0000-0001-8535-4059
Simone Garzon http://orcid.org/0000-0002-5840-699X

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2 National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology - uterine neoplasms*. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2019.
3 Creutzberg CL, van Putten WLJ, Koper PCM, *et al*. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. *Lancet* 2000;355:1404–11.
4 Creutzberg CL, Nout RA, Lybeert MLM, *et al*. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e631–8.
5 Keys HM, Roberts JA, Brunetto VL, *et al*. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004;92:744–51.
6 de Boer SM, Powell ME, Mileshkin L, *et al*. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. *Lancet Oncol* 2019;20:1273–85.
7 Bosse T, Peters EEM, Creutzberg CL, *et al*. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – a pooled analysis of PORTEC 1 and 2 trials. *Eur J Cancer* 2015;51:1742–50.
8 Creutzberg CL, van Putten WLJ, Wárlám-Rodenhuis CC, *et al*. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma trial. *JCO* 2004;22:1234–41.
9 Morrow CP, Bundy BN, Kurman RJ, *et al*. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol* 1991;40:55–65.
10 Mariani A, Webb MJ, Keeney GL, *et al*. Hematogenous dissemination in corpus cancer. *Gynecol Oncol* 2001;80:233–8.
11 Gadducci A, Cavazzana A, Cosio S, *et al*. Lymph-vascular space involvement and outer one-third myometrial invasion are strong predictors of distant haematogeneous failures in patients with stage I-II endometrioid-type endometrial cancer. *Anticancer Res* 2009;29:1715–20.
12 Gadducci A, Cosio S, Fabrini MG, *et al*. Patterns of failures in endometrial cancer: clinicopathological variables predictive of the risk of local, distant and retroperitoneal failure. *Anticancer Res* 2011;31:3483–8.
13 Maggi R, Lissoni A, Spina F, *et al*. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer* 2006;95:266–71.
14 Susumu N, Sagae S, Udagawa Y, *et al*. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2008;108:226–33.
15 Johnson N, Bryant A, Miles T, *et al*. Adjuvant chemotherapy for endometrial cancer after hysterectomy. *Cochrane Database Syst Rev* 2011:CD003175.
16 Randall ME, Filiaci V, McMeekin DS, *et al*. Phase III trial: adjuvant pelvic radiation therapy versus vaginal brachytherapy plus

paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer. *J Clin Oncol* 2019;37:1810–8.
17 Hogberg T, Signorelli M, de Oliveira CF, *et al*. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. *Eur J Cancer* 2010;46:2422–31.
18 Kuoppala T, Mäenpää J, Tomas E, *et al*. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. *Gynecol Oncol* 2008;110:190–5.
19 Colombo N, Creutzberg C, Amant F, *et al*. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *Int J Gynecol Cancer* 2016;26:2–30.
20 Randall M. Management of high-risk endometrial cancer: are we there yet? *Lancet Oncol* 2019;20:1192–3.
21 Eifel PJ. High intermediate risk endometrial cancer. What is it? *Int J Gynecol Cancer* 2019;29:1084–5.
22 ANZGOG and PORTEC Group, Blinman P, Mileshkin L, *et al*. Patients' and clinicians' preferences for adjuvant chemotherapy in endometrial cancer: an ANZGOG substudy of the PORTEC-3 intergroup randomised trial. *Br J Cancer* 2016;115:1179–85.
23 Farrell R, Dixon SC, Carter J, *et al*. Lymphadenectomy in early-stage intermediate-/high-risk endometrioid endometrial cancer: clinical characteristics and outcomes in an Australian cohort. *Int J Gynecol Cancer* 2017;27:1379–86.
24 Narasimhulu DM, Cope A, Riaz IB, *et al*. External beam radiotherapy versus vaginal brachytherapy in patients with stage II endometrial cancer: a systematic review and meta-analysis. *Int J Gynecol Cancer* 2020;30:797–805.
25 Lenth RV. *Technical report no. 378, "post hoc power: tables and commentary"*. Iowa City, Iowa: Department of Statistics and Actuarial Science, University of Iowa, 2007. https://stat.uiowa.edu/sites/stat.uiowa.edu/files/techrep/tr378.pdf
26 Talhouk A, McConechy MK, Leung S, *et al*. Confirmation of promise: a simple, genomics-based clinical classifier for endometrial cancer. *Cancer* 2017;123:802–13.
27 Wortman BG, Bosse T, Nout RA, *et al*. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: evaluation of the pilot phase of the PORTEC-4a trial. *Gynecol Oncol* 2018;151:69–75.