Díaz-cazáres *et al. J Cancer Metastasis Treat* 2023;9:13
DOI: 10.20517/2394-4722.2022.127

Journal of Cancer Metastasis and Treatment

Original Article

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Impact of timing of adjuvant radiotherapy on locoregional control in patients with high-risk endometrial cancer

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How to cite this article: Díaz-cazáres O, Olimón C, Valles A, Sánchez I, Balderrama R, Fuentes J, Rodríguez J, Saavedra C, Ayala-Hernández LE, Villalvazo-Anaya A, Mireles-Ramirez MA, Chávez AH, Bayardo LH, Gutiérrez-Valencia E. Impact of timing of adjuvant radiotherapy on locoregional control in patients with high-risk endometrial cancer. *J Cancer Metastasis Treat* 2023;9:13. https://dx.doi.org/10.20517/2394-4722.2022.127

Received: 8 Nov 2020 **First Decision:** 8 Mar 2023 **Revised:** 30 Mar 2023 **Accepted:** 15 Apr 2023 **Published:** 25 Apr 2023

Academic Editor: Gunnar Kristensen **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Aim: High-risk endometrial cancer has a higher risk of regional and distant recurrence. We sought to examine our institutional experience regarding the timing of adjuvant radiotherapy and local failure (LF), locoregional failure (LRF), distant failure (DF), and overall survival (OS).

Methods: We retrospectively reviewed a database of patients with high-risk endometrial cancer treated with sequential chemotherapy followed by adjuvant external beam radiation therapy (EBRT) with or without brachytherapy from 2012 to 2019.

Results: One hundred thirty-one patients were identified. The median age at diagnosis was 65 (range 32-81). The most prevalent FIGO stages were IIIB (28.2%, *n* = 37), IIIC1 (19.8%, *n* = 26), and IIIA (17.6%, *n* = 23). Of the patients, 29% (*n* = 38) had positive lymph nodes and 71% (*n* = 93) had negative lymph nodes. The most prevalent histology was endometrioid (71%, *n* = 93), serous (12.2%, *n* = 16), clear cell (9.2%, *n* = 12), and other (7.6%, *n* = 10). Moreover, 100% (*n* = 131) of the patients completed EBRT. The mean EBRT dose was 49.6 Gy (range 45-50.4). The median number of days between surgery and EBRT was 212.4 days (range 103-219). The mean brachytherapy dose was 14.7 Gy (range 12-30). The cumulative incidence of LF was 6.1%, LRF was 19%, DF was 19%, and the median survival was 33.4 months. For patients who completed EBRT 180 days after surgery, LRF (HR 3.55 [1.23-10.2], *P* = 0.013), LF (HR 1.91 [0.4-8.9], *P* = 0.429), DF (HR 0.91 [0.41-2], *P* = 0.806), and OS (HR 0.92 [0.33-2.6], *P* = 0.87).

Conclusion: In our cohort of patients with high-risk endometrial cancer treated with chemotherapy followed by radiotherapy, delaying RT was associated with an increased risk of LRF but no differences in DF or OS.

Keywords: Locally advanced endometrial cancer, high-risk endometrial cancer, adjuvant radiotherapy, adjuvant chemotherapy, timing of radiotherapy

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in middle- and high-income countries and the second most common gynecological malignancy in low-income countries, following cervical cancer[1]. High-risk endometrial cancer is more aggressive[2] and has a higher rate of regional and distant metastasis than local recurrence[3,4]. For this reason, multimodal adjuvant therapy has been explored[5]. The role of adjuvant external beam radiotherapy in patients with high-risk endometrial cancer has been established, demonstrating a decrease in regional relapse[6]. In addition, the benefit of systemic therapy in reducing the risk for DF has been demonstrated in this group of patients[7]. Although different sequencing approaches, such as concomitant, sequential, or "sandwich", are recommended in relation to adjuvant radiotherapy (RT), the superiority of one over another has not been established[8,9]. Consequently, the optimal timing of external beam radiation therapy (EBRT) following surgery and chemotherapy for high-risk endometrial cancer has rarely been studied. We aim to report the clinical implications of delaying adjuvant EBRT after chemotherapy in patients with high-risk endometrial cancer reporting the following outcomes: local failure (LF), locoregional failure (LRF), distant failure (DF), and overall survival (OS). In low- and middle-income countries, access to radiotherapy in public health care centers is limited, and treatment delays can be significant. Hence, a sequential strategy for treating patients with high-risk endometrial cancer seems appropriate, avoiding delays in adjuvant treatment by starting systemic therapy first, followed by adjuvant radiotherapy[10].

METHODS

After receiving approval from the institutional ethics board (R-2022-1301-035), we retrospectively reviewed a database of patients with high-risk endometrial cancer from two cancer centers in Mexico: Centro Médico Nacional de Occidente and Unidad Medica de Alta Especialidad 71. Stage IB with high-grade endometrioid histology, stage II, stage III-IVA without residual disease, and non-endometrioid histology regardless of the clinical stage were considered for analysis. Patients received sequential chemotherapy (4-6 cycles) given intravenously 4-6 weeks after surgery, followed by EBRT. Chemotherapy was carboplatin AUC5 and paclitaxel 175 mg/m^2 followed by adjuvant EBRT with or without brachytherapy from 2012 to 2019. Given that chemotherapy started 4-6 weeks after surgery, and there were 3 weeks between each chemotherapy cycle, and a 2- to 4-week interval between the adjuvant chemotherapy and the start of EBRT is advisable to avoid unacceptable toxicity, the cutoff for analyzing clinical outcomes was 180 days (the minimum time

between surgery and EBRT ranged from 119 to 175 days). The number of fractions and dose of EBRT were determined at the discretion of the treating physician. Commonly the patients were followed every 3 months during the first year after treatment, then every 4 months during the second year, followed by every 4-6 months during the third year and onward. LF was defined as recurrence in the vaginal vault, LRF was defined as any pelvic and/or paraaortic recurrence, and DF was defined as any recurrence outside the pelvis and paraaortic lymph nodes. Relapses were determined by imaging (CT scan or MRI) and biopsy if needed. The probabilities of LF, LRF, and DF from the date of surgery were calculated using the cumulative incidence function. Patients who died without presenting any failure were considered competitive risk events.

Cumulative incidence curves between groups (EBRT: ≤ 180 days or > 180 days) were compared with Gray's test. Estimated subdistribution hazard ratios (HRs) and their associated 95% confidence intervals were computed with the Fine-Gray proportional subdistribution hazards regression model. Overall survival probabilities from the date of surgery were calculated with the Kaplan-Meier approach. Patients who were alive until September 30, 2021 (last database revision) were considered censored events. Differences between curves (EBRT: ≤180 days or >180 days) were compared with the log-rank test. We used Matlab (R2021b; MathWorks, Inc., Natick, MA, USA) to refine the data set, and the statistical analysis was done in R version 4.1.2. $P < 0.05$ was considered significant. The patient selection criteria for the final analysis are described in Figure 1.

RESULTS

The population consisted of 131 patients. Most of the patients were younger than 60 years old ($n = 66$, 50.4%), followed by 60-70 years old ($n = 50$, 38.2%). A minority of the patients were older than 70 years ($n = 15$, 11.4%).

Most of the patients had FIGO stage III disease, with IIIB the most prevalent (28.2%), followed by IIIC1 (19.8%) and IIIA (17.6%); among those with stage III disease, IIIC2 was the least frequent (6.9%). Moreover, 26.7% of the population was in early-stage disease, 16% had stage IB disease, and 10.7% had IIA disease. Only one patient had IIB disease (0.8%).

Regarding nodal status, 71% of patients had a negative nodal status, and 29% had positive nodes. The endometrioid histology was the most frequent ($n = 93$), followed by serous ($n = 16$), clear cell ($n = 12$), mixed ($n = 2$), and other ($n = 8$). Ninety patients had lymphovascular invasion, whereas only 41 patients had no lymphovascular invasion. The majority of patients had grade 3 disease (51.2%), followed by grade 2 (36.6%) and grade 1 (12.2%). Most of the population (83.2%) had a 50% or greater invasion grade, and a small group had less than a 50% invasion grade (16.8%). Patient demographic data are summarized in Table 1.

All patients underwent surgery (hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection), followed by 4-6 cycles of chemotherapy at 4-6 weeks and completed EBRT. One hundred twenty-seven patients (96.9%) received brachytherapy. The mean time from surgery to EBRT was 212.4 days, with a standard deviation of 103.5 days. From surgery to brachytherapy start, the mean time was 294.9 days ($\sigma = 145.8$ days), and from surgery to brachytherapy end, the mean time was 299.3 days ($\sigma = 145.9$ days). The EBRT dose ranged from 45 Gy to 50.4 Gy, with a mean of 49.6 Gy, and the brachytherapy dose ranged from 12 Gy to 30 Gy, with a mean of 14.7 Gy. Treatment characteristics are summarized in Table 2. The cumulative incidence of failure percentages was tied between LRF and DF (19% each). LF was less common (6.1%). Median survival was 33.4 months for the entire population, and median follow-up was

Table 1. Demographic data classified according to the time elapsed from surgery to EBRT

Characteristic	EBRT ≤ 180 days (*n* = 54)	EBRT > 180 days (*n* = 77)	*P*-value
Age at diagnosis (years)			0.59
< 60	30 (56%)	36 (47%)	
60-70	18 (33%)	32 (41.5%)	
> 70	6 (11%)	9 (11.5%)	
FIGO			0.68
IB	8 (15%)	13 (17%)	
IIA	7 (13%)	7 (9%)	
IIB	0 (0%)	1 (1%)	
IIIA	9 (16.5%)	14 (18%)	
IIIB	19 (35%)	18 (23%)	
IIIC1	8 (15%)	18 (23%)	
IIIC2	3 (5.5%)	6 (8%)	
Nodal status	14 (26%)	24 (31%)	0.56
Present	40 (74%)	53 (69%)	
Absent			
Histology			0.7
Endometrioid	41 (76%)	52 (67.5%)	
Serous	4 (7%)	12 (15.5%)	
Clear cell	5 (9%)	7 (9%)	
Mixed	1 (2%)	1 (1%)	
Other	3 (5.5%)	5 (6.5%)	
Lymphovascular invasion			0.26
Present	34 (63%)	56 (73%)	
Absent	20 (37%)	21 (27%)	
Grade			0.17
1	5 (9%)	11 (14%)	
2	25 (46%)	23 (30%)	
3	24 (44%)	43 (56%)	
Grade of invasion			0.23
< 50%	12 (22%)	10 (13%)	
≥ 50%	42 (78%)	67 (87%)	

P-values were obtained by applying Chi-squared test or Fisher's exact test.

1521 days. The cumulative incidence of LF for patients was divided between those whose time interval between surgery and EBRT start was up to 180 days or more [Figure 2] and was not statistically significant ($P = 0.429$). LRF was also divided between those patients whose time between surgery and EBRT start was up to 180 days or more. In this case, HR was 3.55, which was deemed statistically significant ($P = 0.013$) [Figure 3]. DF by days between surgery and EBRT start had a low HR (0.91) and was not statistically significant (0.806) [Figure 4]. No difference in OS was demonstrated between the groups ($P = 0.87$) [Figure 5].

DISCUSSION

High-risk endometrial cancer has a higher risk of local, regional, and distant failure. Hence, it is associated with a higher number of cancer-related deaths. Because of this, the role of multimodal adjuvant therapy has been studied[11]. Hogberg *et al.* analyzed two clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) with 534 patients (19.8% with stage III, 49% with grade 3, and 28% with non-endometrioid), 267 of whom received EBRT and 267 of whom received EBRT and sequential chemotherapy in an adjuvant setting[12]. Vaginal brachytherapy was added in the case of cervical stromal involvement.

Table 2. Treatment characteristics *n* = 131

Treatment			
Surgery	131		100%
Chemotherapy	131		100%
EBRT			
Start	131		100%
Complete	131		100%
Brachytherapy			
Start	127		100%
Complete	127		100%
Time between treatments			
Treatment	Mean (days)	Standard deviation (days)	Median (days)
Surgery-EBRT start	212.4	103.5	219
Surgery-Brachytherapy start	294.9	145.8	301
Surgery-Brachytherapy end	299.3	145.9	304
Dose			
Treatment		Mean (Gy)	Range (Gy)
EBRT		49.6	[45, 50.4]
Brachytherapy		14.7	[12, 30]

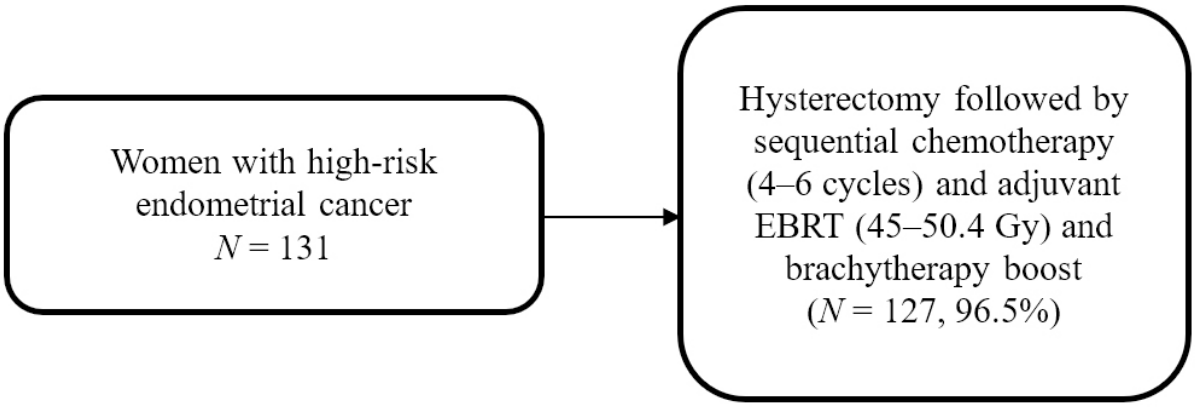

Figure 1. Methodology for selecting patients included in the final LF, LRF, DF, and OS analysis.

Although chemotherapy is the main adjuvant strategy for high-risk endometrial cancer as per the GOG-258 trial, an unacceptable risk of locoregional recurrence was proven in patients treated with chemotherapy alone *vs.* the combined modality (vaginal 7% *vs.* 2%, pelvic/paraaortic 22% *vs.* 11%). Given that locoregional recurrences can undergo salvage treatment in a small percentage of patients, and given the morbidity this represents, we believe a combined sequential modality as adjuvant treatment is necessary to prevent locoregional relapses, as a sequential strategy improved cancer-specific survival in a combined analysis of NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III without a significant increase in the incidence of adverse grade 3-5 effects compared to EBRT alone (63% *vs.* 58%)[12,13].

In the NSGO/EORTC trial, the combined modality therapy was superior in terms of progression-free survival (PFS; HR 0.64 [95%CI: 0.41-0.99], $P = 0.04$). However, MaNGO found a nonsignificant difference in PFS (HR 0.61 [0.33-1.12], $P = 0.10$). Both trials showed a significant improvement in cancer-specific survival ($P = 0.01$) and PFS ($P = 0.009$) and a trend toward significance in improvement in OS ($P = 0.07$),

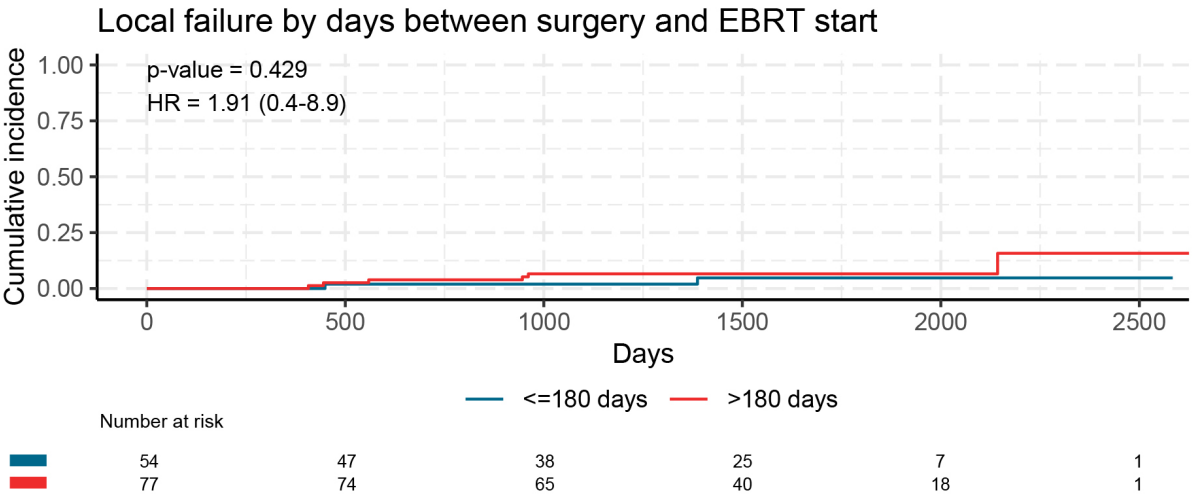

Figure 2. Cumulative incidence of local failure by days between surgery and EBRT start (< 180 days *vs.* > 180 days).

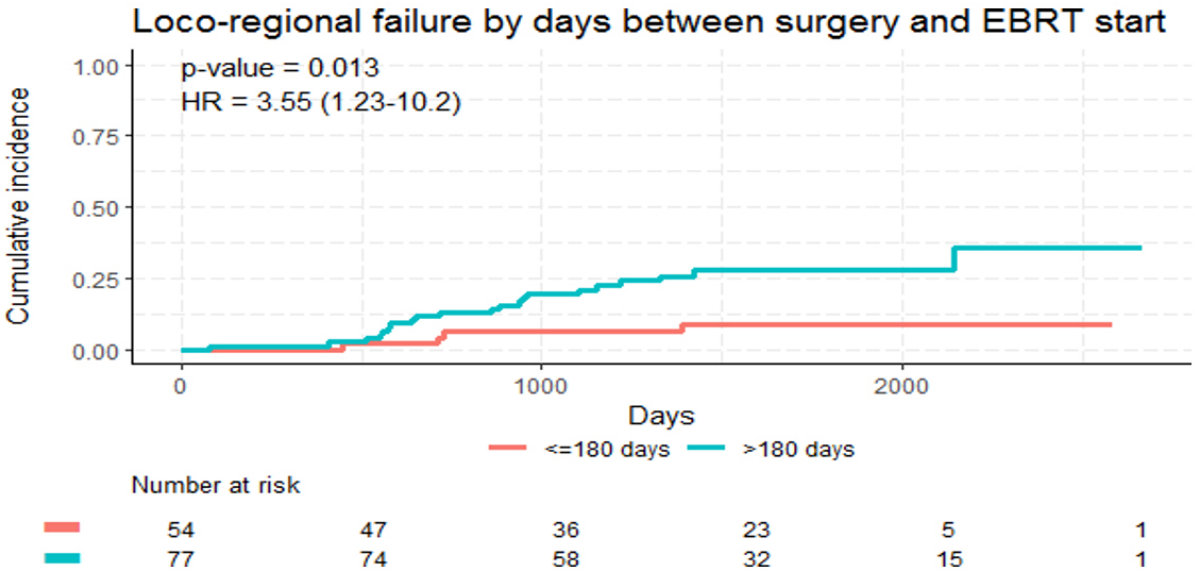

Figure 3. Cumulative incidence of locoregional failure by days between surgery and EBRT start (< 180 days *vs.* > 180 days).

favoring the chemotherapy and sequential radiotherapy group[12]. Therefore, the previous data suggest that combined adjuvant treatment reduces the rates of regional and distant failure.

The role of adjuvant radiotherapy in patients with endometrial cancer has been demonstrated in the presence of factors correlated with a higher risk of pelvic recurrences, such as nodal involvement, high-grade endometrial histology, > 50% depth of myometrial invasion, extrauterine extension, and non-endometrial histology[14]. According to Luo *et al.*, postoperative EBRT improved disease-free survival by decreasing by 5% the rate of vaginal recurrences compared with observation[15].

Overall, adjuvant treatment delays in patients with endometrial cancer are associated with socioeconomic status and lack of public awareness of the signs and symptoms of endometrial cancer. Moreover, it has been

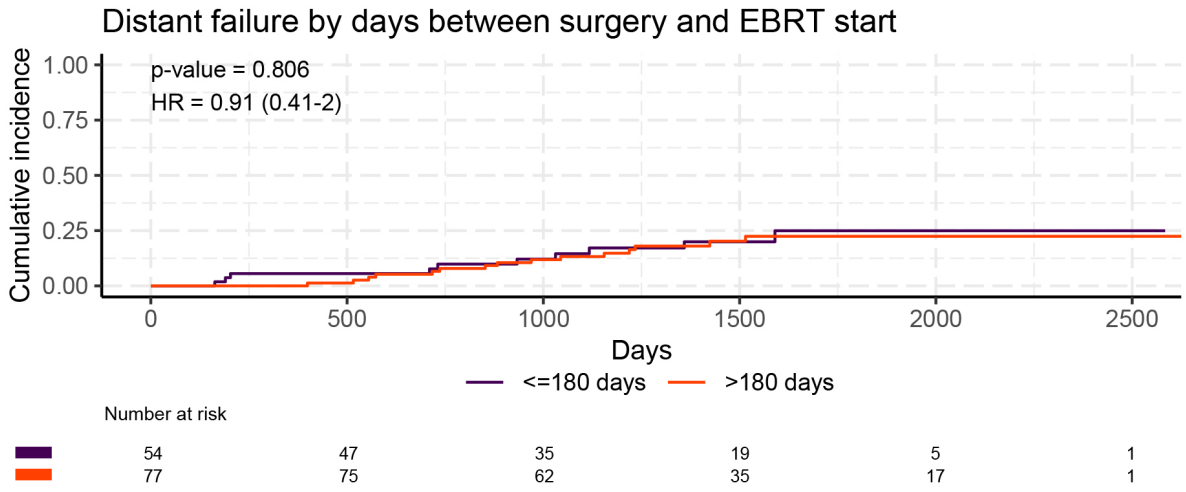

Figure 4. Cumulative incidence of distant failure by days between surgery and EBRT start (< 180 days *vs.* > 180 days).

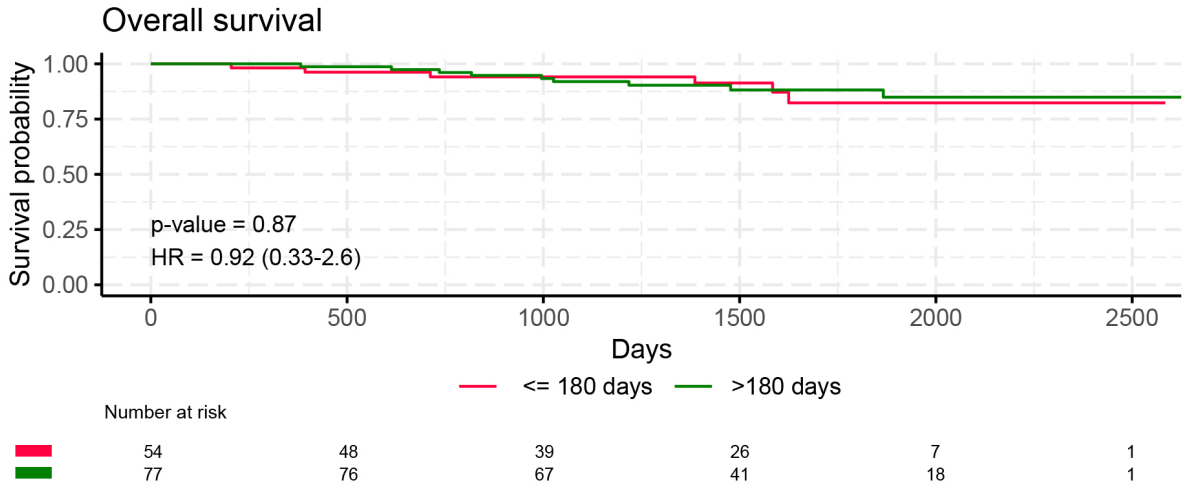

Figure 5. Overall survival (< 180 days *vs.* > 180 days).

reported that there is little awareness among general practitioners of symptoms associated with endometrial cancer, conditioning delays in the timely referral of these patients[16,17].

It has been reported that the type of surgery (robotic, laparoscopic, laparotomy), multidisciplinary boards, and the type of center influence the time of EBRT start and influence oncological outcomes[18]; the time until the start of EBRT could represent quality criteria for endometrial cancer care for institutions[19]. Also, racial differences and type of health service (private, public) may influence time-to-treatment intervals, with Hispanic and African American women having longer delays than Caucasian women[15,20].

The time interval from surgery to radiotherapy in patients with early-stage endometrial cancer is a prognostic factor for OS. Luo *et al.* analyzed 349,404 patients with primary uterine carcinoma and reported that a time interval less than or equal to 86 days is associated with better OS compared to more than 86 days ($P < 0.0001$), although they analyzed patients with early-stage endometrial cancer, and stage II and non-endometrial histology patients were included[15]. Neron *et al.* reported the impact of time to radiotherapy as a prognostic factor in endometrial cancer and found that a time interval of < 8 weeks is associated with a

trend toward a decrease in the local recurrence rate, with no impact on OS, metastasis-free survival, or event-free survival[19]. Fifty-six patients (17%) had chemotherapy concomitantly, but patients who had adjuvant chemotherapy before radiotherapy were excluded[19]. However, the time interval between radiotherapy after surgery has been poorly studied in patients with high-risk endometrial cancer.

The present study analyzed the implication of delaying adjuvant EBRT < 180 *vs.* >180 days in patients with high-risk endometrial cancer who have received 4 to 6 cycles of adjuvant chemotherapy. This treatment strategy is used in many public centers in low- and middle-income countries as a bridge to mitigate the time between surgery and EBRT plus or minus brachytherapy. It is interesting that our results showed similar rates of DF (19%) compared to the literature and similar rates of LRF (19%) and LF (10.7%) compared to the GOG-258 trial[13], which included patients with FIGO III-IVA and I-II with non-endometrial histology who received either adjuvant chemoradiotherapy or chemotherapy alone. Nonetheless, the rates of LF and LRF were higher compared to some previous series as described in PORTEC-3, which reported 5-year failure-free survival of 75.5% (70.3-79.9%) in the chemoradiotherapy group *vs.* 68.6% (63.1%-73.4%) in the radiotherapy group (HR 0.71 [0.53-0.95], $P = 0.022$)[21].

We believe this increase in LF and LRF could be explained by the characteristics of patients included in this study and the timing between surgery and EBRT, which is commonly seen in regions where radiotherapy is not widely available. Patients must travel long distances or move to different cities to receive radiotherapy.

One of the suggested disadvantages of receiving 4-6 cycles of chemotherapy and delaying EBRT is that this sequential approach may decrease the local control and regional control that EBRT offers. One trial conducted by Lu *et al.* that included 51 patients reported no significant differences between adjuvant chemoradiation given sequentially or as "sandwich" treatment in 5-year OS, local progression-free survival, or distant metastasis-free survival between the sequential and "sandwich" groups: 87% *vs.* 77% ($P = 0.37$), 89% *vs.* 100% ($P = 0.21$), and 78% *vs.* 85% ($P = 0.79$), respectively[22]. Nonetheless, another retrospective multi-institutional study with 179 stage IIIC patients found better 5-year OS (74% *vs.* 56%, $P = 0.03$) with a "sandwich" treatment strategy than a sequential approach[23].

In conclusion, in the present study of patients with high-risk endometrial cancer, delaying adjuvant EBRT after chemotherapy > 180 days was associated with an increased risk of locoregional failure but not distant failure or overall survival.

DECLARATIONS

Authors' contributions

Conceptualization, collection of data, manuscript review and editing, final approval of manuscript: Díaz-cazáres O

Collection of data, manuscript review and editing, final approval of manuscript: Olimón C, Valles A, Rodríguez J, Saavedra C, Villalvazo-Anaya A, Mirele-Ramirez MA

Review and editing, manuscript drafting, final approval of manuscript: Sanchez I, Fuentes J, Bayardo LH, Ayala-Hernández LE, Chávez AH

Manuscript review and editing, final approval of manuscript: Balderrama R

Statistical analysis, manuscript review and editing, final approval of manuscript: Ayala-Hernández LE

Conceptualization, study design, statistical analysis, manuscript review and editing, manuscript drafting, final approval of manuscript: Gutiérrez-Valencia E

Availability of data and materials
Not applicable.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Financial support and sponsorship
None.

Ethical approval and consent to participate
This retrospective study was reviewed and approved by the institutional ethics board (R-2022-1301-035).

Consent for publication
Not applicable.

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