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Scientific Article

Addition of Postoperative Radiation Therapy After Preoperative Chemotherapy and Surgery in Patients With Locally Advanced Endometrial Cancer Is Associated With Improved Outcomes

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Abstract

Purpose: Our purpose was to examine outcomes of patients with locally advanced endometrial cancer who undergo neoadjuvant chemotherapy followed by surgery (PreCT) with/without postoperative adjuvant radiation therapy. A secondary analysis of down staging and margin clearance was made with reference to those receiving upfront surgery and then adjuvant chemotherapy (PostCT).

Methods and Materials: The National Cancer Database was queried for FIGO (The International Federation of Gynecology and Obstetrics) stage III/IV locally advanced endometrial cancer cases who underwent definitive surgery from 2010 to 2016 and received chemotherapy as part of their treatment. Cases were classified into 2 cohorts: preoperative chemotherapy +/- postoperative chemotherapy cohort (PreCT) and postoperative chemotherapy cohort (PostCT) for reference for margin assessment. Cases who received preoperative radiation therapy were excluded while those who received postoperative radiation were included in the analysis. Primary endpoints were overall survival (OS), surgical margin status, rate of downstaging, and effect of adjuvant radiation therapy on OS among the PreCT cohort. Univariable (UVA) and multivariable (MVA) Cox regression analyses were performed.

Results: A total of 13,369 cases were identified with 1059 in PreCT and 12,310 in PostCT cohorts. PreCT had lower OS than PostCT (UVA: hazard ratio [HR], 2.18; $P < .001$; MVA: HR, 1.873; $P < .001$). PreCT cases with negative margins, who presumably had unresectable tumors initially, also had worse OS compared with PostCT with negative margins (UVA: HR, 2.20; $P < .001$; MVA: HR, 1.84; $P < .001$); however, PreCT with negative margins had similar survival to PostCT with positive margins (UVA: HR, 0.825; $P < .001$; MVA: $P = .885$). The addition of radiation after surgery in the PreCT cohort was associated with improved survival (5-year OS 20.5% compared with 50%, respectively; UVA: HR, 0.450; $P < .001$; MVA: HR, 0.337; $P < .001$). Although fewer cases in PreCT had negative margins compared with PostCT (72% compared with 84%, $P < .001$), approximately 19% of cases in PreCT had lower pathologic T-stage compared with clinical T-stage and 11% had lower N-stage.

Conclusions: Neoadjuvant chemotherapy was given in cases with worse oncologic prognostic factors, many of whom were likely unresectable at outset, compared with those who received postoperative chemotherapy. Although neoadjuvant chemotherapy is associated with tumor downstaging, survival is lower than with primary surgery probably because of these baseline differences. The addition of adjuvant radiation after surgery in cases who received preoperative chemotherapy is associated with improved survival.

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Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Endometrial cancer (EC) remains the most common gynecologic malignancy in the United States, with incidence and mortality increasing despite developments in treatment.[1,2] Approximately 20% of women present with locally advanced EC (LAEC), often defined as FIGO (The International Federation of Gynecology and Obstetrics) stage III or IV, which is associated with higher mortality than early-stage EC.[2] Guidelines recommend upfront surgery followed by risk-adjusted adjuvant therapy for operable LAEC.[3-5] However, many patients with LAEC are inoperable because of the extent of disease at presentation.[6,7] Guidelines recommend preoperative therapy followed by reassessment of surgical feasibility,[3,5] though the optimal approach remains unclear.[8] Few studies have investigated the benefit of preoperative chemotherapy (PreCT) followed by interval cytoreductive surgery (ICS). Small studies comparing PreCT and ICS to primary surgery followed by adjuvant chemotherapy have shown similar outcomes.[9,10] These encouraging studies are often limited by small sample sizes, short follow-up, and single-institution practice patterns.

A recent National Cancer Database (NCDB) analysis evaluated outcomes for LAEC cases who underwent PreCT and surgery compared with surgery followed by postoperative chemotherapy (PostCT) and found that the PreCT cohort had lower overall survival (OS) compared with PostCT but superior survival compared with those who received chemotherapy alone.[11] Because the gold standard for resectable LAEC is PostCT rather than PreCT, the study compared cases who were likely unresectable at the outset to those who were resectable and underwent postoperative therapy. However, the extent of resection, tumor response to PreCT, and the role of radiation therapy were not investigated. In our study, we analyzed cases with LAEC in the NCDB to explore the effect of PreCT on tumor downstaging and the rate of negative surgical margins and to investigate the effect of adjuvant radiation.

Methods and Materials

Patient cohort

The NCDB was queried for cases with FIGO stage III/IV EC from 2010 to 2016 with serous, clear cell, or endometrial histology who underwent surgery and had known chemotherapy and radiation sequencing (Fig. 1 and E1). This study received exempt status from our institutional review board.

The cohort was divided into 2: a cohort that received PreCT and a cohort that received PostCT. Because the study aimed to investigate the benefit of preoperative therapy, cases who received only PreCT were combined with those who underwent Pre- and PostCT; this cohort was called "PreCT." The comparison of PreCT negative margins versus PostCT positive margins, while not strictly valid (these being different cohorts), is done to highlight the benefit of PreCT in presumed unresectable advanced endometrial cancer and as a means of assessing benefit of negative margins in PreCT. Cases who received preoperative radiation therapy were excluded from analysis, as preoperative radiation therapy would have significant effect on management and outcomes, confounding analysis. Cases were further stratified by whether they did or did not receive adjuvant radiation (Fig. 1).

Variables analyzed and outcomes

Variables that may act as confounders were extracted or generated (Fig. 1). The primary endpoints of the analysis were OS, rate of presurgical downstaging, surgical margin status, and effect of adjuvant radiation therapy on OS among the PreCT cohort. The PostCT cohort was used for reference or baseline in the analysis. The rate of presurgical downstaging was determined by comparing American Joint Committee on Cancer 7th edition pathologic to American Joint Committee on Cancer clinical stage for both T- and N-stage. The control for this analysis was comparing the pathologic and clinical stage in cases who received no preoperative treatment and hence should not have downstaging.

Statistical analysis

Patient, disease, and treatment characteristics were reported using medians and interquartile ranges for continuous variables and counts/percentages for categorical variables. Patient, disease, and treatment characteristics were compared between cohorts with Fisher's exact or χ^2 test. OS was estimated by using the Kaplan-Meier method. Univariable (UVA) and multivariable (MVA) Cox regression analyses assessed the associations between OS and predictive factors of patient, disease, and treatment characteristics. In MVA analysis, the backward model selection method was used with a UVA P value $<$ .15 to enter. Hazard ratios (HRs) and 95% confidence intervals are reported. UVA logistic analysis and MVA logistic analysis with the backward model selection were used to evaluate the association between margin status and predictive factors. All analyses were conducted by using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.1.0 (R Foundation, Vienna, Austria).

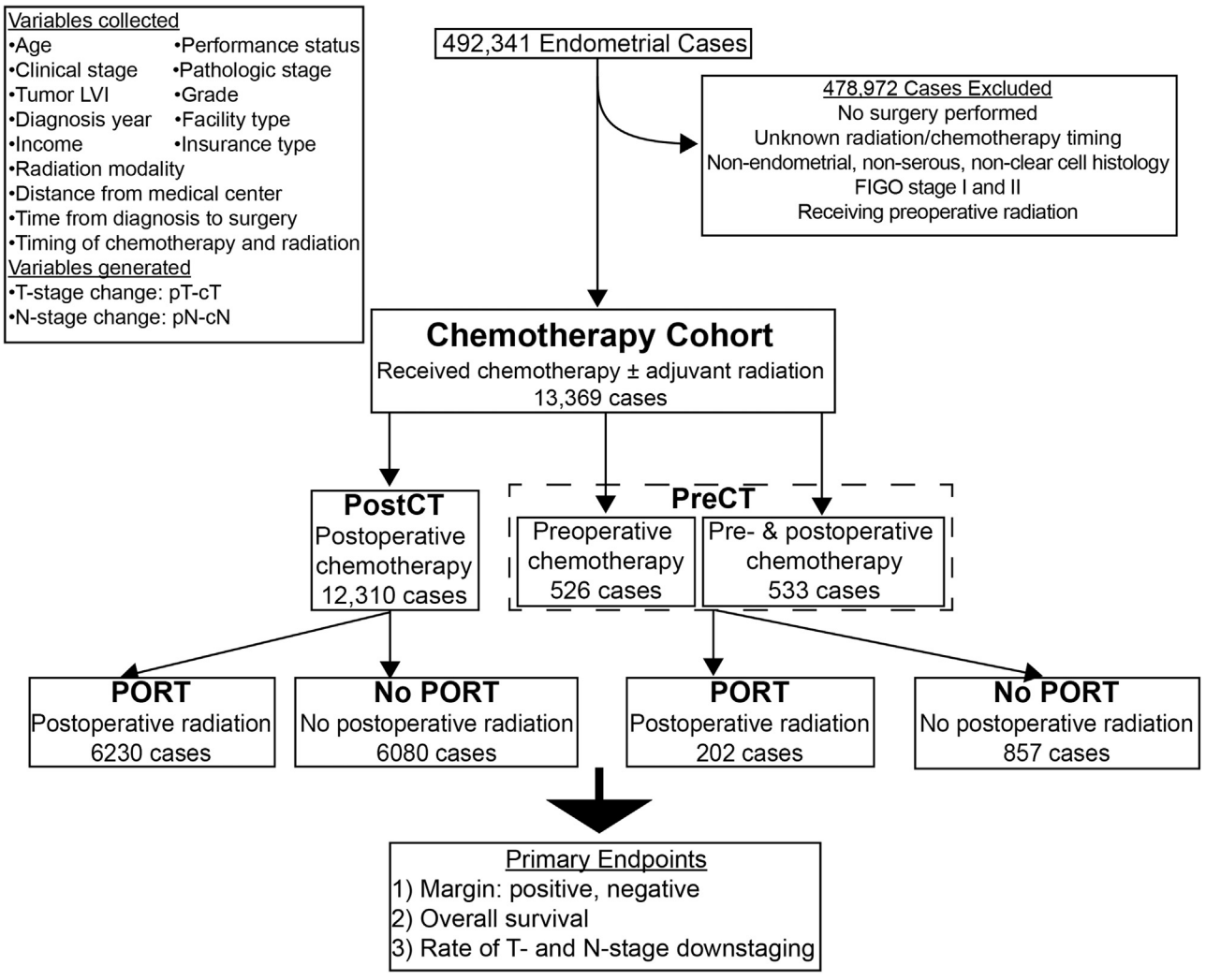

Figure 1 Schema of case allocation.

Results

Our total cohort consisted of 13,369 cases, median age of 63 (interquartile range, 57-70). The PreCT cohort included 1059 cases (526 who received PreCT and 533 who received both Pre- and PostCT) and 12,310 PostCT cases.

Demographics

Clinically node-positive, pathologically node-negative, higher clinical and pathologic T-stage, nonendometrial histology, lack of adjuvant radiation therapy, and positive surgical margins were more common in PreCT than in PostCT cases (Table 1). Charlson/Deyo performance status and age were similar between Pre- and PostCT cohorts. The number of cases treated with PostCT was similar in 2010 to 2013 and 2014 to 2016, while more cases were treated in the PreCT paradigm in 2014 to 2016 compared with 2010 to 2013.

Survival

In the combined cohort, higher grade, age >70 years, and positive surgical margins had the greatest effect on OS (HR, 4.852; 4.059-5.799; $P < .001$; HR, 2.761; 2.405-3.170; $P < .001$; HR, 2.615; 2.425-2.820; $P < .001$ on UVA, respectively) (Table 2; Fig. E2A). Adjuvant radiation therapy portended better OS for the entire cohort, with a 5-year OS of 65% compared with 43% without adjuvant therapy (UVA: HR, 0.453; 0.424-0.484; MVA: HR, 0.620; 0.556-0.691; $P < .001$). In the PreCT cohort, the addition of adjuvant radiation was associated with improved 5-year survival, from 21% to 52% (UVA: HR, 0.450; 0.343-0.590; MVA: HR, 0.337; 0.215-0.526; $P < .001$). Similarly, the addition of adjuvant radiation in the PostCT cohort was associated with improved 5-year survival, from 46% to 66% (UVA: HR, 0.478; 0.446-0.512; MVA: HR, 0.635; 0.568-0.711; $P < .001$) (Table 2; Fig. E3). This benefit was similar in magnitude on UVA whether the radiation was external beam or brachytherapy for both Pre- and PostCT (Table 2).

Table 1 Demographic details of cases included in the study

	PreCT (N = 526)		Pre- and PostCT (N = 533)		PreCT (N = 1059)		PostCT (N = 12,310)		*P* value all 3 cohorts	*P* value Pre- and PostCT
	#	%	#	%	#	%	#	%		
TNM pathologic N-stage										
Node negative	178	59.1%	142	50.9%	320	55.2%	3831	36.0%	< .001	< .001
Node positive	123	40.9%	137	49.1%	260	44.8%	6800	64.0%		
TNM clinical N-stage										
Node negative	235	60.4%	260	60.2%	495	60.3%	6994	77.8%	< .001	< .001
Node positive	154	39.6%	172	39.8%	326	39.7%	1997	22.2%		
Change in TNM N-stage										
Same stage	237	81.2%	205	72.7%	442	77.0%	5161	61.5%	< .001	
Increase stage	30	10.3%	47	16.7%	77	13.4%	3142	37.4%		< .001
Decrease stage	25	8.6%	30	10.6%	55	9.6%	89	1.1%		
TNM pathologic T-stage										
T1, T2	135	28.2%	136	27.6%	271	27.9%	5071	42.2%	< .001	< .001
T3, T4	343	71.8%	356	72.4%	699	72.1%	6951	57.8%		
TNM clinical T-stage										
T1, T2	77	26.5%	71	23.4%	148	24.9%	3787	62.3%	< .001	< .001
T3, T4	214	73.5%	232	76.6%	446	75.1%	2287	37.7%		
Change in TNM T-stage										
Same stage	169	64.3%	182	66.2%	351	65.2%	4256	71.8%	< .001	< .001
Increase stage	47	17.9%	34	12.4%	81	15.1%	1538	26.0%		
Decrease stage	47	17.9%	59	21.5%	106	19.7%	132	2.2%		
Lymphovascular invasion										
No	209	49.5%	182	42.6%	391	46.1%	4081	36.1%	< .001	< .001
Yes	213	50.5%	245	57.4%	458	53.9%	7236	63.9%		
Histology										
Serous	263	50.0%	291	54.6%	554	52.3%	3478	28.3%	< .001	< .001
Clear cell	28	5.3%	32	6.0%	60	5.7%	602	4.9%		
Endometrial	235	44.7%	210	39.4%	445	42.0%	8230	66.9%		
Grade										
Well diff.	27	6.8%	37	9.3%	64	8.1%	1322	13.2%	< .001	< .001
Moderately diff.	63	15.9%	50	12.5%	113	14.2%	2457	24.6%		
Poorly diff.	246	62.3%	234	58.6%	480	60.5%	5199	52.0%		
Anaplastic	59	14.9%	78	19.5%	137	17.3%	1013	10.1%		
Radiation boost										
No boost	496	94.7%	484	91.3%	980	93.0%	10,015	82.4%	< .001	< .001
External beam	6	1.1%	14	2.6%	20	1.9%	520	4.3%		
Brachytherapy	22	4.2%	32	6.0%	54	5.1%	1615	13.3%		
Radiation										
No radiation	437	83.4%	420	79.2%	857	81.3%	6080	49.7%	< .001	< .001
External beam	63	12.0%	82	15.5%	145	13.8%	4637	37.9%		
Brachytherapy	24	4.6%	28	5.3%	52	4.9%	1513	12.4%		

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Table 1 (*Continued*)

	PreCT (N = 526)		Pre- and PostCT (N = 533)		PreCT (N = 1059)		PostCT (N = 12,310)		*P* value all 3 cohorts	*P* value Pre- and PostCT
	#	%	#	%	#	%	#	%		
Surgical margins										
Negative	320	72.6%	305	71.6%	625	72.1%	9033	84.1%	< .001	< .001
Positive	121	27.4%	121	28.4%	242	27.9%	1704	15.9%		
Facility type										
Academic/research	294	56.9%	295	57.1%	589	57.0%	6037	50.1%	< .001	< .001
Other	223	43.1%	222	42.9%	445	43.0%	6020	49.9%		
Age										
<49	37	7.0%	47	8.8%	84	7.9%	1219	9.9%	.169	.116
50-70	340	64.6%	353	66.2%	693	65.4%	7865	63.9%		
>70	149	28.3%	133	25.0%	282	26.6%	3226	26.2%		
Year of diagnosis										
2010-2013	216	41.1%	190	35.6%	406	38.3%	6108	49.6%	< .001	< .001
2014-2016	310	58.9%	343	64.4%	653	61.7%	6202	50.4%		
Insurance										
Private/managed care	192	36.5%	235	44.1%	427	40.3%	5659	46.0%	< .001	.001
Medicare/Medicaid	311	59.1%	270	50.7%	581	54.9%	6038	49.0%		
Not insured/unknown	23	4.4%	28	5.3%	51	4.8%	613	5.0%		
Facility location										
New England	21	4.1%	36	7.0%	57	5.5%	674	5.6%	.002	.020
Middle Atlantic	77	14.9%	79	15.3%	156	15.1%	1778	14.7%		
South Atlantic	111	21.5%	93	18.0%	204	19.7%	2437	20.2%		
East North Central	93	18.0%	104	20.1%	197	19.1%	2359	19.6%		
East South Central	30	5.8%	22	4.3%	52	5.0%	674	5.6%		
West North Central	37	7.2%	56	10.8%	93	9.0%	1263	10.5%		
West South Central	55	10.6%	30	5.8%	85	8.2%	756	6.3%		
Mountain	17	3.3%	17	3.3%	34	3.3%	589	4.9%		
Pacific	76	14.7%	80	15.5%	156	15.1%	1527	12.7%		
Days from diagnosis to definitive surgery										
≤30	33	6.4%	23	4.4%	56	5.4%	6975	57.6%	< .001	< .001
31-60	25	4.9%	22	4.2%	47	4.5%	4017	33.2%		
61-90	35	6.8%	70	13.3%	105	10.1%	792	6.5%		
91-120	95	18.4%	168	32.0%	263	25.3%	173	1.4%		
≥120	327	63.5%	242	46.1%	569	54.7%	160	1.3%		
Days from diagnosis to first surgery										
≤30	50	9.7%	57	10.9%	107	10.3%	7204	59.5%	< .001	< .001
31-60	26	5.0%	27	5.1%	53	5.1%	3866	31.9%		
61-90	34	6.6%	67	12.8%	101	9.7%	752	6.2%		

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Table 1 (*Continued*)

	PreCT (N = 526)		Pre- and PostCT (N = 533)		PreCT (N = 1059)		PostCT (N = 12,310)		*P* value all 3 cohorts	*P* value Pre- and PostCT
	#	%	#	%	#	%	#	%		
91-120	91	17.7%	159	30.3%	250	24.0%	160	1.3%		
≥120	314	61.0%	215	41.0%	529	50.9%	135	1.1%		
Charlson/Deyo score										
0	397	75.5%	397	74.5%	794	75.0%	9006	73.2%	.537	.370
1	102	19.4%	105	19.7%	207	19.5%	2653	21.6%		
2	24	4.6%	23	4.3%	47	4.4%	494	4.0%		
≥3	3	0.6%	8	1.5%	11	1.0%	157	1.3%		
Household income by ZIP										
<$38,000	118	22.4%	103	19.3%	221	20.9%	2022	16.4%	< .001	< .001
$38,000- $47,999	135	25.7%	124	23.3%	259	24.5%	2761	22.5%		
$48,000- $62,999	125	23.8%	137	25.7%	262	24.7%	3404	27.7%		
≥$63,000	148	28.1%	169	31.7%	317	29.9%	4107	33.4%		
Distance from treatment center										
<5	104	19.8%	93	17.4%	197	18.6%	2769	22.5%	.011	.013
5-20	206	39.2%	214	40.2%	420	39.7%	4948	40.2%		
20-40	83	15.8%	85	15.9%	168	15.9%	1962	15.9%		
>40	132	25.1%	141	26.5%	273	25.8%	2623	21.3%		
Adjuvant radiation therapy										
Not given	437	83.1%	420	78.8%	857	80.9%	6080	49.4%	< .001	< .001
Adjuvant radiation given	89	16.9%	113	21.2%	202	19.1%	6230	50.6%		

Abbreviations: PostCT = postoperative chemotherapy; PreCT = preoperative chemotherapy; TNM = tumor, node, metastases.

Five-year OS was higher for the Post- than the PreCT cohort (55% vs 26%; UVA: HR, 2.18; 1.985-2.411; MVA: HR, 1.873; 1.535-2.285; $P < .001$; Fig. 2B). PreCT with negative margins had lower OS compared with PostCT with negative margins (UVA: HR, 0.455; 0.397-0.521; MVA: HR, 0.554; 0.421-0.729; $P < .001$; Fig. 2A). PreCT with negative margins had better OS than PostCT with positive margins upon UVA (5-year OS 36% and 32%, respectively; HR, 0.825; 0.714-0.954; $P = .009$; Fig. 2C) but not upon MVA ($P = .885$).

Margin analysis and downstaging

Fewer cases in PreCT had negative margins (72%) than in PostCT (84%) ($P < .001$; Table 1). However, a significant proportion of PreCT were downstaged based on N-stage (11%) and T-stage (19%) (Table 3). Control analysis (PostCT cohort) revealed lower pathologic stage in 1% of cases based on N-stage and 2% based on T-stage. Because no downstaging should have occurred in PostCT, these numbers offer us a control cohort on which to assess the downstaging seen in the PreCT cohort. PreCT cases who were downstaged based on T-stage were then more likely to have negative surgical margins compared with those who were not downstaged (86% and 69%, respectively, $P = .001$); PreCT cases who were downstaged based on N-stage trended toward having more negative margins (82% and 72%, respectively, $P = .11$). Downstaging of T-stage for PreCT was associated with better survival (UVA: HR, 0.612; 0.431-0.869; $P = .023$; MVA: HR, 0.366; 0.198-0.0679; $P = .006$) (Table 3). However, downstaging of N-stage for the PreCT cohort was not associated with a survival difference ($P = .151$).

Discussion

Patients with LAEC who cannot undergo upfront surgical resection pose a significant clinical challenge, and there is limited evidence guiding clinical practice. Several retrospective studies have reported better OS and progression-free survival among patients with LAEC who have

Table 2 Cox regression of survival with HR for UVA and MVA, only variable with $P \leq .05$

	Survival-UVA				Survival-MVA			
	R				R			
	All	All-neg margin	PreCT	PostCT	All	All-neg margin	PreCT	PostCT
TNM pathologic N-stage								
Node negative	R	R	R	R	R	R	R	R
Node positive	1.2	1.2	1.5	1.2	1.4	1.6	1.8	1.8
TNM clinical N-stage								
Node negative	R	R	R	R	R		R	
Node positive	1.6	1.6	1.4	1.5	1.2		2.1	
Change in TNM N-stage								
Same stage	R	R		R				R
Increase stage	0.73	0.80		0.77				0.81
Decrease stage	1.0	1.2		0.78				0.77
TNM pathologic T-stage								
T1, T2	R	R	R	R	R	R		R
T3, T4	2.2	1.9	1.8	2.2	1.8	1.7		1.9
TNM clinical T-stage								
T1, T2	R	R		R		R		
T3, T4	2.0	1.8		2.00		1.1		
Change in TNM T-stage								
Same stage	R	R	R	R			R	
Increase stage	1.1	1.1	0.91	1.2			0.80	
Decrease stage	1.3	1.3	0.61	1.3			0.37	
Lymphovascular invasion								
No	R	R	R	R	R	R		R
Yes	1.6	1.5	1.6	1.6	1.4	1.3		1.4

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Histology									
	Serous	2.4	2.5	1.6	2.4	1.1			1.1
	Clear cell	2.6	2.8	2.2	2.5	1.5			1.5
	Endometrial	R	R	R	R	R			R
Grade									
	Well diff.	R	R	R	R	R	R		R
	Moderately diff.	2.0	1.9	1.7	2.1	1.7	1.6		1.8
	Poorly diff.	4.9	4.3	3.7	4.8	3.5	3.5		3.7
	Anaplastic	6.0	5.5	5.5	5.8	3.9	3.7		3.9
Radiation boost									
	No boost	R	R	R	R				
	External beam	0.77	0.52	0.47	0.82				
	Brachytherapy	0.55	0.52	0.30	0.59				
Radiation									
	No radiation	R	R	R	R				
	External beam	0.46	0.52	0.42	0.49				
	Brachytherapy	0.44	0.52	0.56	0.43				
Surgical margins									
	Negative	R	-	R	R	R	-		R
	Positive	2.6	-	1.9	2.6	1.5	-		1.5
Facility type									
	Academic/research	R							
	Other	0.98							
Age									
	≤49	R	R	R	R	R	R	R	R
	50-70	1.6	1.7	1.6	1.6	1.4	1.7	1.2	1.4
	≥70	2.8	3.2	2.4	2.8	2.1	2.6	2.4	2.0
Year of diagnosis									
	2010-2013								
	2014-2016								

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Insurance						
	Private/managed care	R	R	R	R	
	Medicare/Medicaid	1.7	1.7	1.3	1.7	
	Not insured/unknown	1.2	1.1	0.97	1.2	
Facility location						
	New England	R	R		R	
	Middle Atlantic	1.1	1.1		1.1	
	South Atlantic	1.4	1.4		1.4	
	East North Central	1.2	1.2		1.1	
	East South Central	1.3	1.4		1.3	
	West North Central	1.1	1.1		1.1	
	West South Central	1.1	1.0		1.1	
	Mountain	1.1	1.0		1.2	
	Pacific	1.1	1.1		1.1	
Days from diagnosis to definitive surgery						
	≤30	R	R	R	R	R
	31-60	0.86	0.96	2.5	0.85	2.7
	61-90	0.98	1.1	3.8	0.86	7.9
	91-120	1.5	1.5	3.1	0.84	3.8
	≥120	1.8	1.8	3.1	0.87	4.0
Days from diagnosis to first surgery						
	≤30	R	R	R	R	
	31-60	0.87	0.96	1.6	0.86	
	61-90	1.0	1.1	3	0.88	
	91-120	1.5	1.5	2.4	0.87	
	≥120	1.9	1.9	2.6	0.70	
Charlson/Deyo score						
	0	R	R		R	
	1	1.1	1.1		1.1	
	2	1.2	1.2		1.3	

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≥3	1.4	1.3		1.5				
Household income by ZIP								
<$38,000	1.3	1.2		1.3	1.2			
$38,000-$47,999	1.1	1.1		1.1	1.2			
$48,000-$62,999	1.1	1.0		1.1	1.1			
≥$63,000	R	R		R	R			
Distance from treatment center								
<5	R							
5-20	0.97							
20-40	0.98							
>40	1.0							
Chemotherapy timing								
PostCT	R	R	-	-	R	R	-	-
PreCT	2.2	2.2	-	-	1.8	1.8	-	-
Adjuvant radiation								
Not given	R	R	R	R	R	R	R	R
Radiation therapy given	0.45	0.52	0.45	0.48	0.62	0.60	0.34	0.64

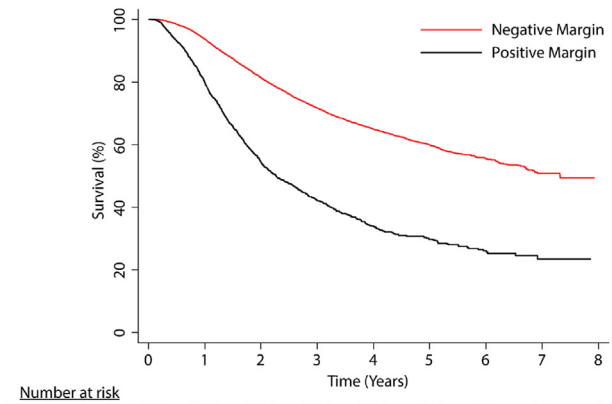
Abbreviations: HR = hazard ratio; MVA = multivariable analysis; OS = overall survival; PostCT = postoperative chemotherapy; PreCT = preoperative chemotherapy; R = reference; TNM = tumor, node, metastases; UVA = univariable analysis.
All-neg margin are all cases in the cohort with negative margins.

undergone optimal cytoreductive surgery than among those with suboptimal surgery.[12,13] However, many patients with LAEC are inoperable because of the extent of disease at presentation.[6,7] Consensus guidelines recommend preoperative therapy followed by reassessment of surgical feasibility,[3,5] though the optimal approach remains unclear because of lack of evidence.[8] Furthermore, the role of additional therapies after surgery in these situations is even more controversial.

We analyzed the NCDB to better understand outcomes for cases with LAEC who received PreCT compared with a control cohort consisting of those undergoing surgery followed by PostCT. Because receiving PreCT before undergoing surgery is deviation from the standard approach of upfront surgical resection, these cases were likely unresectable. Cases who received preoperative radiation were excluded, because radiation may have a significant effect on tumor downstaging and confound the effect of PreCT. Furthermore, patients receiving concurrent PreCT and radiation would have received a lower dose of chemotherapy compared with those receiving chemotherapy alone. We included patients who received postoperative radiation therapy and analyzed the role of postoperative radiation.

Despite the PreCT cohort having more adverse oncologic factors and lower survival than PostCT, PreCT cases who obtained negative surgical margins had similar survival to those who obtained positive surgical margins and underwent PostCT. Analysis of baseline characteristics confirmed that the PreCT cohort had worse oncologic factors in our study. Many of the cases who received PreCT were likely unresectable at presentation, even among those who eventually achieved negative surgical margins, because receiving PreCT is a deviation from standard practice. The finding of lower survival among those receiving PreCT in our study contrasts with 2 small retrospective studies of patients with stage IV EC, which reported similar survival among those who underwent neoadjuvant chemotherapy followed by ICS and those who had upfront surgery.[9,14] In our study, PreCT cases

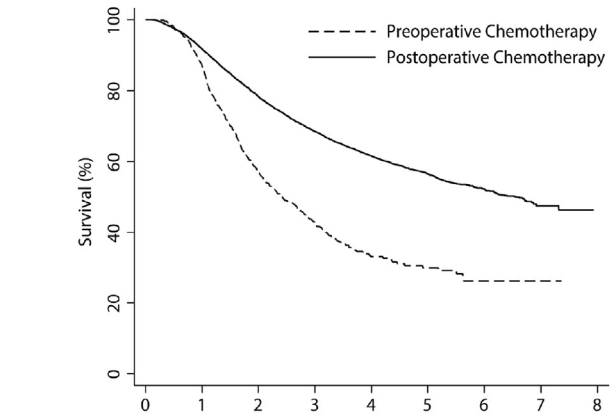
(A)



Number at risk

Negative Margin	7987	6965	5092	3409	2200	1240	560	148	0
Positive Margin	1632	1224	727	439	267	152	63	20	0

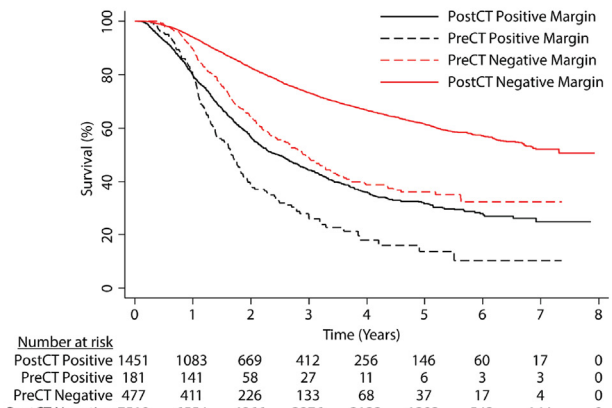
(B)



Number at risk

Preoperative	658	552	284	160	79	43	20	7	0
Postoperative	8961	7637	5535	3688	2388	1349	603	161	0

(C)



Number at risk

PostCT Positive	1451	1083	669	412	256	146	60	17	0
PreCT Positive	181	141	58	27	11	6	3	3	0
PreCT Negative	477	411	226	133	68	37	17	4	0
PostCT Negative	7510	6554	4866	3276	2132	1203	543	144	0

(D)

	5-year survival	P-value	Hazard Ratio (95% CI)	Pairwise Comparison P-value
PostCT, positive margins	32%	< 0.001	Reference	< 0.001, < 0.001, 0.009, < 0.001, < 0.001
PreCT, positive margins	15%		1.587 (1.319 - 1.910)	
PreCT, negative margin	36%		0.825 (0.714 - 0.954)	
PostCT, negative margin	62%		0.381 (0.351 - 0.412)	

Figure 2 Survival of chemotherapy cohort with respect to margins (A), timing of chemotherapy (B), and both timing and margins (C). Pairwise comparison in (D).

Table 3 Margin analysis for chemotherapy cohorts by comparing AJCC stage after surgery to the stage before surgery

	T-stage					N-stage			
Staging change	PreCT		PostCT		Staging change	PreCT		PostCT	
Increase	71	16%	1351	26%	Increase	68	14%	2821	38%
+ Margins	24	34%	242	18%	+ Margins	16	24%	246	9%
- Margins	47	66%	1109	82%	- Margins	52	76%	2575	91%
Same	288	65%	3815	72%	Same	364	75%	4506	61%
+ Margins	89	31%	567	15%	+ Margins	105	29%	781	17%
- Margins	199	69%	3248	85%	- Margins	259	71%	3725	83%
Decrease	86	19%	118	2%	Decrease	51	11%	77	1%
+ Margins	12	14%	15	13%	+ Margins	9	18%	21	27%
- Margins	74	86%	103	87%	- Margins	42	82%	56	73%
Total	445	5284			Total	483		7404	
+ Margins	125	28%	824	16%	+ Margins	130	27%	1048	14%
- Margins	320	72%	4460	84%	- Margins	353	73%	6356	86%

Abbreviations: AJCC = American Joint Committee on Cancer; PostCT = postoperative chemotherapy; PreCT = preoperative chemotherapy.

who obtained negative surgical margins had better survival than those who obtained positive surgical margins and underwent adjuvant chemotherapy, but this difference did not persist upon MVA. This finding is consistent with several retrospective reports of better survival with more complete surgical excision.[7,13,15,16] Interestingly, PreCT cases with negative surgical margins still had lower survival than PostCT with negative margins, suggesting that achieving complete resection does not obviate other adverse risk factors in the PreCT cohort.

The addition of adjuvant radiation therapy was associated with improved survival in cases who received PreCT. The 5-year OS improved from 20% to 50% in the PreCT cohort (UVA: HR, 0.450; MVA: HR, 0.337). This suggests that patients who receive neoadjuvant chemotherapy have the best survival if they receive all 3 modalities. To our knowledge, this is the first report of improved outcomes with addition of radiation therapy after surgery among those who received PreCT and surgery.

Several randomized prospective studies investigated the benefit of radiation therapy in the adjuvant setting for LAEC after surgical resection.[17-19] Notably, GOG 258 (Gynecologic Oncology Group) did not show a survival benefit to adjuvant radiation among resectable patients, whereas several NCDB studies (including the present study) showed that cases who received adjuvant radiation had improved survival.[20] It is important to note that patients who received PreCT were excluded from GOG 258, and it is unclear if the lack of benefit extends to those undergoing PreCT. However, our study suggests the benefit of adjuvant radiation is greater for the PreCT cohort than for the PostCT cohort (HR, 0.34 for PreCT and HR, 0.64 for PostCT, relative to no adjuvant radiation) and hence may be more important for those undergoing preoperative therapy than for patients who underwent definitive surgery upfront.

There are concerns that LAEC responds poorly to chemotherapy or radiation and that administering neoadjuvant therapy could cause disease progression by delaying primary surgery. A study of 39 patients with LAEC who received neoadjuvant chemotherapy followed by ICS reported that 41% of patients progressed during neoadjuvant chemotherapy,[21] while another study with 33 patients reported that only 12% progressed.[22] Conway et al[15] analyzed patients who underwent neoadjuvant therapy because of unresectable disease and excluded patients who were unresectable because of performance status and found that 68% of patients could undergo surgery after neoadjuvant chemotherapy (29%) or radiation (48%). Our findings agree with the later studies and suggest that LAEC responds to chemotherapy. We assessed response to neoadjuvant therapy by comparing clinical and pathologic stage. PreCT cases were downstaged 19% for T-stage and 11% for N-stage. The control cohort analysis suggests that lower pathologic stage is expected in only 1% to 2% of cases. Despite significant downstaging, PreCT had a lower rate of negative surgical margins than PostCT in our study (72.1% and 84.1%, respectively).

The response rate to neoadjuvant therapy in our study was generally lower than reported in other studies, as evident from downstaging; however, cases in our study were generally more advanced. Vargo et al[23] analyzed 33 patients who underwent neoadjuvant radiation followed by ICS; all patients achieved negative margins, and 58% no longer had cervical invasion. However, 52% were FIGO stage II, and only 48% were FIGO stage III, whereas our study excluded FIGO stage II patients and hence represents a more

advanced cohort. Several other retrospective studies of neoadjuvant therapy have similarly focused on FIGO stage II patients.[23-29] Furthermore, approximately half of our cases were treated outside an academic institution, so they likely reflect greater patient heterogeneity.

Nevertheless, some single institution studies with similar inclusion criteria to our study reported promising results with neoadjuvant therapy, which suggests a more favorable response in select LAEC cases. Iheagwara et al[24] analyzed 34 patients with type II EC, >68% with LAEC, who underwent neoadjuvant chemoradiation and reported that 94% were downstaged, with 95% obtaining negative margins, 15% having complete pathologic response, and 35% having residual microscopic disease. Brodeur et al[30] analyzed 30 otherwise operable patients who received neoadjuvant radiation therapy (37% FIGO stage II and 63% stage III) and reported a 15% complete pathologic response rate, with 90% obtaining negative margins. A multi-institutional retrospective clinical study of 102 patients with LAEC (32% FIGO stage III and 68% FIGO stage IV) who received neoadjuvant chemotherapy reported that 72% had partial response on imaging, 78% proceeded to ICS, and 60% had complete debulking.[16] The NCDB report on preoperative chemotherapy by Chambers et al[11] did not examine the role of margins or downstaging, despite margin status being a predictor of survival.

Our study benefits from inclusion of a large and heterogeneous LAEC patient cohort that was treated in various clinical settings. Furthermore, we examined the role of radiation and correlated the treatment intervention to both margin status and assessed tumor response to preoperative treatment. These factors have a significant effect on prognosis but are often not accounted for in retrospective studies. The decision to pursue neoadjuvant chemotherapy or primary surgery is complex and can result in significant selection bias in database studies. We identified more adverse prognostic factors in the neoadjuvant cohort and attempted to account for this imbalance via MVA. Nevertheless, selection bias persists, in part because of variables that were either not collected or insufficiently detailed, such as cause of death, chemotherapy type/dosing/timing, and radiation dose/fields. The effect of PreCT on tumor downstaging is, however, not affected by this selection bias.

Conclusions

PreCT in LAEC is associated with downstaging; however, survival was lower compared with those who received PostCT, likely because of more adverse patient/tumor factors in the PreCT cohort. Despite this imbalance, those who received PreCT and obtained negative margins had similar survival to those who obtained positive margins and then received adjuvant chemotherapy. Addition of adjuvant radiation therapy is associated with improved OS among cases who received PreCT. These findings suggest that neoadjuvant therapy can downstage LAEC with potential improvement in survival and should be investigated further in prospective studies.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101126.

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