Risk-Adapted Adjuvant Therapy in High-Risk Early-Stage Endometrioid Endometrial Cancer: Implications for Military Women's Health

MHSRS-26-5265

Kathleen M. Darcy PhD[1-3], Samantha J. Leite MD[1,4], Chunqiao Tian PhD[1,2], Sara M. Drayer MD FACOG LCDR MC USN[1], Christopher M. Tarney MD FACOG LTC MC USA [1,3], S. Ahmed M. Hussain MD FACOG Maj MC USAF[1], Jordyn Tumas MD[1,4], Kelley Ferguson[1,4], Taylor Deskins MPH[1,2], Leslie M. Randall MD[1,4,5], John K. Chan MD[6], Daniel S. Kapp PhD MD[7], Kristen P. Bunch DO MBA FACOG, LTC MC USA [1], Nicholas W. Bateman PhD[1-3], Thomas P. Conrads PhD[1,3,8], G. Larry Maxwell MD FACOG COL USA (retired)[1,3,8]

1. Gynecologic Cancer Center of Excellence, Murtha Cancer Center Research Program, Department of Surgery, Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Bethesda MD, USA. 2. The Henry M Jackson Foundation for the Advancement of Military Medicine, Inc. Bethesda, MD, USA. 3. Department of Gynecologic Surgery and Obstetrics, Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Bethesda MD, USA. 4. Department of Obstetrics and Gynecology, Inova Fairfax Hospital, Falls Church, MD, USA. 5. Inova Shar Cancer Institute, Falls Church, VA, USA. 6. Palo Alto Medical Foundation, California Pacific Medical Center, Sutter Health, San Francisco, CA, USA. 7. Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, USA. 8. Women's Health Integrated Research Center, Inova Women's Service Line, Inova Health System, Falls Church, VA, USA.

Background

- Patients with high-risk stage I-II endometrioid endometrial carcinoma (EEC) represent a heterogeneous group with variable recurrence risk.
- Current guidelines permit adjuvant radiotherapy (RT) alone or combined chemotherapy plus radiotherapy (CT+RT), yet prior randomized trials included non-endometrioid histologic subtypes and advanced-stage disease and did not isolate lymphovascular space invasion (LVSI) as a modifier of chemotherapy benefit.
- Consequently, the survival impact of systemic escalation in biologically defined high-risk early-stage EEC remains uncertain.

Objectives

- To evaluate whether adjuvant CT+RT provides an overall survival benefit when added to RT in patients with high-risk stage I-II EEC.
- To identify biologically defined subgroups most likely to benefit from treatment escalation.

Why This Matters to the MHS

- Endometrial cancer incidence and mortality continue to rise among U.S. women.
- Avoiding unnecessary chemotherapy reduces toxicities, healthcare utilization, and patient burden.
- Risk-adapted therapy improves survivorship, readiness, and quality of life.
- Pathology-based treatment selection supports delivery of high-value, evidence-based oncology care.

Methods

- **Study Design**: Retrospective National Cancer Database Cohort Study (2004-2020).
- **Inclusion Criteria**: Patients with high-risk stage I-II EEC, defined as stage I tumors with ≥50% myometrial invasion, high-grade histology, LVSI positivity, or stage II disease. All patients received RT alone or CT+RT.
- **Primary Endpoint:** Overall Survival (OS)
- **Statistical Approach**:
  - Propensity Score Modeling based on inverse probability of treatment weighting (IPTW)
  - Weighted Kaplan-Meier analyses and Cox proportional hazards models
  - Prespecified subgroup and sensitivity analyses.

Results: Survival benefit from chemotherapy plus radiation is confined to tumors with both grade 3 histology and LVSI positivity.

Figure 1. Flow Diagram and Framework

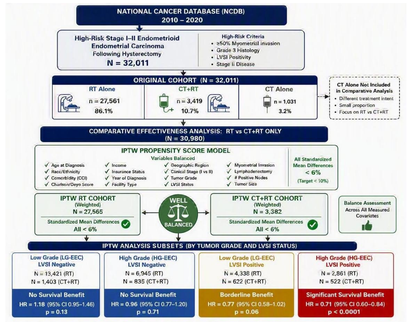
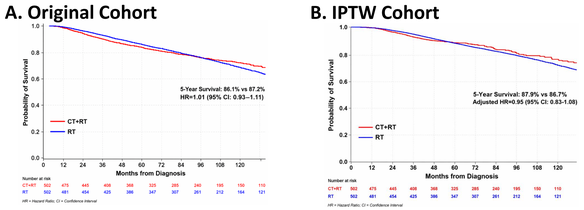


Figure 3. Subgroup Analysis (CT-RT vs. RT)

Within Individual IPTW-Subsets	Adjusted HR (95% CI)	P-value
Age Group		
<50 years	0.99 (0.57 - 1.70)	0.957
50 - 59 years	1.07 (0.82 - 1.39)	0.631
60 - 69 years	1.02 (0.82 - 1.26)	0.889
≥70 years	0.84 (0.66 - 1.06)	0.144
Comorbidity Score		
0	0.99 (0.84 - 1.15)	0.848
≥1	0.87 (0.68 - 1.11)	0.250
Race/Ethnicity		
Non-Hispanic White	0.96 (0.83 - 1.12)	0.622
Non-Hispanic Black	0.84 (0.60 - 1.16)	0.283
Others	0.75 (0.48 - 1.19)	0.224
Stage		
IA	0.81 (0.63 - 1.04)	0.101
IB	0.98 (0.80 - 1.19)	0.823
II	0.94 (0.77 - 1.16)	0.572
Tumor Grade		
Low-Grade	1.00 (0.82 - 1.22)	0.981
High-Grade	0.83 (0.73 - 0.95)	0.005
Lymphovascular Space Invasion		
Negative	1.12 (0.93 - 1.35)	0.219
Positive	0.74 (0.62 - 0.87)	0.0003
Tumor Grade/LVSI		
LG-EEC/LVSI-	1.18 (0.91 - 1.54)	0.207
HG-EEC/LVSI-	0.96 (0.79 - 1.16)	0.655
LG-EEC/LVSI+	0.77 (0.59 - 1.01)	0.058
HG-EEC/LVSI+	0.71 (0.60 - 0.84)	<0.0001
Lymphadenectomy		
No	0.96 (0.68 - 1.38)	0.840
Yes	0.94 (0.81 - 1.09)	0.400
Overall	0.95 (0.83 - 1.08)	0.418

Figure 2. Survival for CT+RT vs. RT before and after IPTW.



Key Finding: No Improvement in Survival with **CT+RT** vs. **RT** only. Routine escalation did not improve survival.

Figure 4. Overall Survival within Subgroups

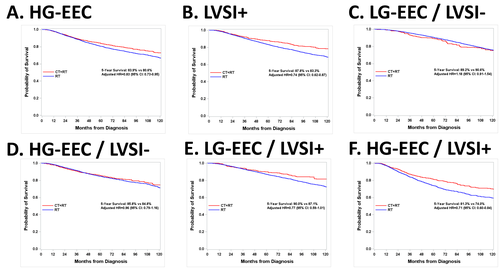


Figure 5. Five-Year Survival, Absolute Risk Reduction (AAR) and Number Needed to Treat (NNT) by Grade and LVSI Status

	5-Year OS (%) by Treatment after IPTW			
	CT+RT (95% CI)	RT (95% CI)	ARR (95% CI)	NNT (95% CI)
Overall	87.9 (85.9 to 89.6)	86.7 (86.2 to 87.2)	1.2 (-0.7 to 3.0)	-
By Tumor Grade				
LG-EEC	89.3 (86.7 to 91.4)	89.3 (88.8 to 89.8)	0.0 (-2.4 to 2.4)	-
HG-EEC	83.9 (81.9 to 85.7)	80.6 (79.4 to 81.6)	3.3 (1.1 to 5.6)	30 (18 to 91)
By LVSI Status				
LVSI-	88.2 (85.3 to 90.5)	88.9 (88.4 to 89.5)	-0.7 (-3.4 to 1.9)	-
LVSI+	87.8 (85.5 to 89.8)	83.3 (82.4 to 84.1)	4.5 (2.2 to 6.9)	22 (14 to 45)
By Tumor Grade and LVSI				
LG-EEC / LVSI -	89.2 (85.1 to 92.2)	90.6 (90.0 to 91.2)	-1.4 (-5.0 to 2.1)	-
LG-EEC / LVSI +	90.0 (86.9 to 92.4)	87.1 (86.2 to 88.0)	2.9 (0.0 to 5.7)	-
HG-EEC / LVSI -	85.8 (83.0 to 88.1)	84.8 (83.5 to 86.0)	1.0 (-1.8 to 3.8)	-
HG-EEC / LVSI+	81.3 (78.3 to 83.9)	74.0 (71.8 to 76.0)	7.3 (3.8 to 10.8)	14 (9 to 26)

Take-Home Message: Most high-risk early-stage EEC patients can avoid chemotherapy without compromising survival.

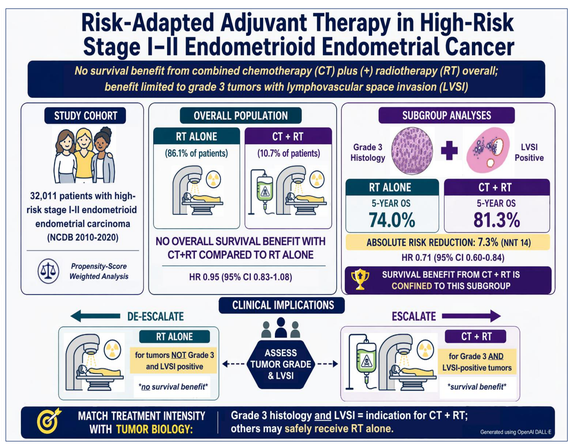
- Not all high-risk early-stage EEC is biologically equivalent. Routine CT escalation does not improve survival overall.
- Grade 3 + LVSI identifies the treatment-responsive subgroup. Patients with both features experience the greatest benefits from CT+RT (absolute risk reduction [AAR] 7.3% and number needed to treat [NNT] = 14)
- Risk-adapted therapy can reduce overtreatment while preserving outcomes. Pathology-guided treatment selection supports high value care across the MHS.

Abbreviations: OS, overall survival; IPTW, inverse probability of treatment weighting; EEC, endometrioid endometrial carcinoma; LG, low grade (grade 1-2); HG, high grade (grade 3-4); LVSI, lymphovascular space invasion; CT+RT, chemotherapy and radiation; RT, radiation; ARR, absolute risk reduction; NNT, number needed to treat; CI, confidence interval.

Figure 5. Risk-Adapted Treatment Schema

Findings	Result
Overall CT+RT vs RT	HR 0.95 (NS)
High Grade Tumors	HR 0.83, p=0.005
LVSI+ Tumors	HR 0.74, p=0.0003
Grade 3 + LVSI+	HR 0.71, p<0.0001
5-Year OS Benefit	81.3% vs 74.0%
Absolute Survival Gain (ARR)	7.3%
Number Needed to Treat (NNT)	14

Pathology Group	Recommended Strategy
Grade 1-2 / LVSI-	RT alone
Grade 1-2 / LVSI+	RT alone (consider individualization)
Grade 3 / LVSI-	RT alone (consider individualization)
Grade 3 / LVSI+	CT+RT favored



Clinical Bottom Line: Routine chemotherapy escalation is not supported for most high-risk stage I–II patients with EEC.

MHS Impact

- Supports precision oncology using routinely available pathology findings.
- Reduces overtreatment in approximately 88% of high-risk EEC patients who lack both grade 3 histology and LVSI positivity.
- Preserves long-term survivorship, functional capacity, and military readiness.
- Improves stewardship of oncology resources by targeting chemotherapy to patients most likely to benefit.
- Provides an immediately implementable framework applicable throughout the MHS.

Conclusions

- In high-risk stage I-II EEC, routine escalation to combined CT+RT did **not** improve overall survival compared with RT alone.
- Treatment benefit was biologically heterogeneous and was restricted to patients with both **grade 3 histology and LVSI positivity**.
- In this subgroup, CT+RT improved 5-year overall survival from **74.0% to 81.3%** (ARR 7.3%; NNT=14) and reduced mortality by 29% (HR 0.71, 95% CI 0.60-0.84).
- Patients lacking both adverse features derived little or no survival benefit from chemotherapy escalation.
- Grade 3 histology combined with LVSI defines a practical, pathology-based threshold for treatment intensification.
- These findings support risk-adapted, high-value oncology care across the Military Health System by aligning treatment intensity with demonstrated clinical benefit.

 Funding: Funding for this project was provided from awards HU0001-23-2-0038 and HU0001-24-2-0047 (Co-PIs: Christopher M. Tarney and G. Larry Maxwell) to the Gynecologic Cancer Center of Excellence Program from the Uniformed Services University of the Health Sciences from the Defense Health Program, and administered by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.