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Prognostic Value of PORTEC-3 Molecular Markers by Disease Risk in a Real-World Early Endometrial Cancer Cohort

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Objective

- Explore whether PORTEC-3 study results that show differential outcomes by molecular subtype in endometrial cancer (EC) patients with early-stage high risk disease also hold true in EC patients with “intermediate risk” and "low risk" early-stage disease in a Tempus next generation sequenced (NGS) real-world data (RWD) patient population.
- Understand baseline population prognostic factor differences between the PORTEC-3 and Tempus populations

Conclusions

- Marker prognostic ranking was consistent between the PORTEC-3 high risk cohort and all risk levels in RWD despite absolute RFS differences likely due to differences in baseline characteristics and outcome assessments.
- The consistent poor prognosis of p53abn patients, good prognosis of POLEm albeit with limited power, and moderate prognosis of NSMP and dMMR patients in RWD support use of these markers to inform treatment decisions across disease risk levels in an early EC setting.

Plain language summary

Why did we perform this research?

Risk for endometrial cancer recurrence after initial treatment varies by cancer stage, grade, and histology. Risk may be further associated with “molecular subtypes”, or specific combinations of genetics and protein levels.[1] A patient’s subtype can inform the best treatment approach to balance benefit/risk in the early disease setting. In a previous clinical trial, PORTEC-3, researchers developed a categorization of four molecular subtypes (POLEm, p53abn, NSMP, and dMMR/MSI-H) in early-stage high-risk endometrial cancer patients.[2] We sought to reproduce these findings in a different population and at different risk levels which may extend the findings to more patients.

How did we perform this research?

We looked at how these molecular subtypes related to recurrence risk using a cohort of high-risk patients identified from historical medical record databases (real-world data patients, i.e. RWD).[3] We also looked at how these molecular subtypes related to the risk of cancer recurrence in medium and low risk patients.

What were the findings of this research?

We found that these four molecular subtypes in this RWD patient population shared the same cancer recurrence risk ranking (POLEm at least risk, dMMR/MSI-H and NSMP at similar intermediate risk, and p53abn at greatest risk) as the PORTEC-3 patients. These results were consistent across the high, medium, and low risk levels defined by cancer stage, grade, and histology.

What are the implications of this research?

By confirming prior research findings, we have increased the confidence in the use of these molecular subtypes as prognostic of cancer recurrence risk and provided support for their use in a broader population.

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References:
1. Information on the original molecular subtype work may be found here: https://www.nature.com/articles/nature12113
2. Information on the PORTEC-3 study may be found here: https://ascopubs.org/doi/full/10.1200/JCO.20.00549
3. Information on how Tempus categorized cancer risk using stage, grade, and histology may be found here: https://pubmed.ncbi.nlm.nih.gov/35200562/

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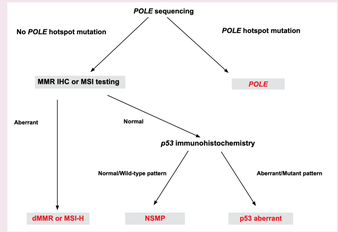
Introduction

- Molecular classification of EC proposed by The Cancer Genome Atlas in 2013 has improved prognostic assessment of patients.[1]
- PORTEC-3 assessed these molecular markers in early-stage high risk patients.[2]
- We examined the prognostic value of these markers in a RWD cohort of early-stage high risk patients and extended the analysis to intermediate and low risk patients to inform treatment decisions across disease risk levels.

Methods

- We performed a retrospective study of EC patients from the Tempus de-identified, multimodal real-world database with primary cancer diagnosis 2016-2022.
- Stage I-III patients who received total hysterectomy with bilateral salpingo-oophorectomy and NGS Tempus xT assays were stratified into high, intermediate, and low risk disease levels based on tumor characterization and categorized into POLE mutated (POLEm), mismatch repair-deficient (dMMR), p53-abnormal (p53abn), or no specific molecular profile (NSMP) PORTEC-3 subtypes.[3]
- Recurrence-free survival (RFS), defined as time from surgery to earliest disease recurrence, progression, metastasis or death, was assessed using Kaplan-Meier methods for the combination of risk level and molecular subtype. We compared RFS trends across molecular subtypes at 5-years in PORTEC-3 and 18-months in RWD due to limited follow-up.

Figure 1. Molecular subtype algorithm



Results and interpretation

Figure 2. Study schematic

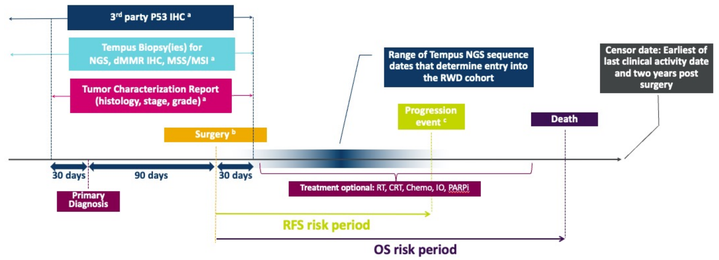


Figure 3. Tempus recurrence free survival curves

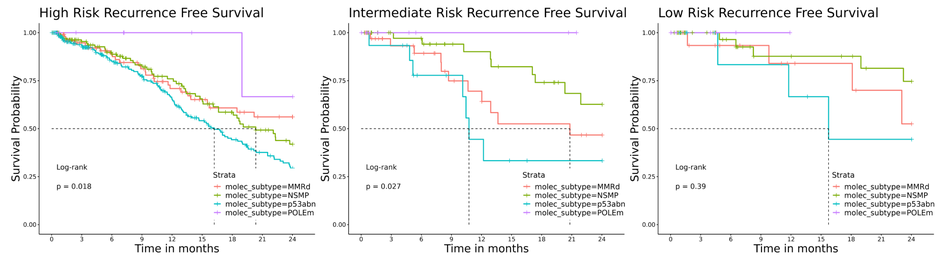


Table 1. Analysis population consort table

Criteria	N patients (% previous)
Tempus sequenced patients with primary curated endometrial cancer; ≥ 18y at primary diagnosis	3,043
Primary diagnosis between 2016-2022	2,639 (87%)
No additional cancers up to 5 years before surgery	2,474 (94%)
Surgery no later than 90 days from primary diagnosis	1,290 (52%)
Valid histology between primary diagnosis & surgery	1,290 (100%)
Stage 1-3 between primary diagnosis & surgery	1,038 (80%)
xT biopsy no later than 30 days after surgery	740 (71%)

Table 2. Population baseline characteristics

	PORTEC-3	Tempus High Risk	Tempus Intermediate Risk	Tempus Low Risk
No. of patients	410	546	110	84
Age, years (mean (range))	61.2 (26.7 – 80.5)	65 (31 – 88)	69.4 (61 – 84)	53 (33 – 63)
Histotype				
Endometrioid	274 (67)	216 (40)	95 (86)	76 (90)
Serous carcinoma	65 (15.9)	140 (26)		
Clear-cell carcinoma	39 (9.5)	26 (4.8)		
Mixed carcinoma	19 (4.6)	NA		
Carcinosarcoma		86 (16)	8 (7.3)	4 (4.8)
Other	13 (3.2)	78 (14)	7 (6.4)	4 (4.8)
Stage				
I	127 (30.9)	139 (25.0)	110 (100.0)	84 (100)
II	105 (25.6)	51 (9.3)		
III	178 (43.4)	356 (65)		
LVSI – present *				
Present (N1, N2)	255 (62.2)	237 (43.4)		
Absent (N0)	155 (37.8)	246 (45.1)	90 (82)	55 (65)
Unable to be determined (NX)	--	43 (7.9)	17 (15)	19 (23)
Unknown	--	20(3.7)	3 (2.7)	10 (12)
Molecular Subtype				
p53abn	93 (22.7)	260 (48)	16 (15)	10 (12)
MMRd	137 (33.4)	116 (21)	41(37)	23 (27)
NSMP	129 (31.5)	160 (29)	45 (41)	45 (54)
POLEm	51 (12.4)	20 (1.8)	8 (7.3)	6 (7.1)

Table 3. RFS in PORTEC-3 (5-year and 18-month) and Tempus RWD (18-month)

Risk:	PORTEC-3 (N=410)			Tempus (N=740)					
	High			High (N=546)		Intermediate (N=110)		Low (N=84)	
	N (%)	5y RFS %	18m RFS % (95% CI)*	N (%)	18m RFS % (95% CI)	N (%)	18m RFS % (95% CI)	N (%)	18m RFS % (95% CI)
POLEm	51 (12)	98	98 (87, 100)	10 (2)	100 (NA, NA)	8 (7)	100 (NA, NA)	6 (7)	100 (NA, NA)
NSMP	129 (31)	74	91 (85, 95)	160 (29)	59 (47, 68)	45 (41)	74 (53, 87)	45 (54)	88 (66, 96)
dMMR	137 (33)	72	87 (81, 92)	116 (21)	61 (47, 72)	41 (37)	53 (29, 72)	23 (27)	84 (49, 96)
P53abn	93 (23)	48	71 (60, 79)	260 (48)	44 (36, 52)	16 (15)	33 (8, 62)	10 (12)	44 (7, 78)

*Extracted from published Kaplan Meier curves via R package IPDfromKM (https://cran.r-project.org/web/packages/IPDfromKM/index.html).

Key results

- Of the 740 eligible RWD patients, 546 (74%), 110 (15%) and 84 (11%) were high, intermediate, and low risk and 286 (39%), 250 (34%), 180 (24%) and 24 (3%) were P53abn, NSMP, dMMR and POLEm, respectively.
- Similar to RFS trends at 5 years reported in PORTEC-3, the p53abn subtype consistently had the lowest 18-month RFS, although the degree of separation from other subtypes varied across risk levels.
- NSMP and dMMR subtypes had 18-month RFS within 4% of each other for high and low risk levels, consistent with PORTEC-3.
- The POLEm subtype had 100% 18-month RFS across risk levels, but low prevalence.

Limitations

- Direct comparison of absolute RFS risks by landmark timepoints between PORTEC-3 and Tempus sequenced real world populations is not possible due to key baseline differences. Tempus patients tended to have a lower percentage of endometrioid patients, higher percentage of serous patients, few stage 2 patients, and a higher proportion of p53abn patients, relative to the PORTEC-3 population. Trial-based vs. real-world outcome assessment also likely differed.
- The clinical determinants for ordering Tempus NGS are yet to be fully understood. Therefore, extrapolation of these results beyond this population should be done with caution.
- Sample size was limited in the POLEm and low risk populations.

Acknowledgements

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Disclosures

Jessica Dow is a current Tempus employee and Sahiti Kolli is a former Tempus employee; the remainder of the authors are Astrazeneca employees who also hold stock in the company.

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3. Mitric C, Bernardini MQ. Endometrial Cancer: Transitioning from Histology to Genomics. Current Oncology. 2022; 29(2):741-757