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Adjuvant Treatment in Early Stage Endometrial Cancer: Context-Dependent Impact of Somatic *CTNNB1* Mutation on Recurrence-Free Survival

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Abstract

Objective: *CTNNB1* mutation is associated with decreased recurrence-free survival in early stage, grades 1–2 endometrioid endometrial cancer patients. The objective of this study was to determine if adjuvant therapy modifies this risk of disease recurrence.

Methods: A retrospective, stage I endometrial cancer cohort from MD Anderson Cancer Center was assessed. Clinical and pathological characteristics and type of adjuvant therapy (cuff brachytherapy, pelvic radiation, chemotherapy) were obtained by review of medical records. *CTNNB1* exon 3 sequencing was performed. Summary statistics were calculated, and recurrence-free survival was measured using the Kaplan-Meier product-limit estimator.

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Competing Interests

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Results: The analysis included 253 patients, 245 with information regarding adjuvant therapy. Most patients had tumors of endometrioid histology (83%) with superficial myometrial invasion (79%) and no lymphatic/vascular space invasion (68%). Tumor *CTNNB1* mutations were present in 18% of patients. Patients receiving adjuvant therapy were more likely to have higher grade tumors, non-endometrioid histology, deep myometrial invasion, and lymphatic/vascular invasion. For patients with low risk features not receiving adjuvant therapy, the presence of *CTNNB1* mutation did not significantly impact recurrence-free survival (11.3 years wildtype vs 8.1 years mutant, p=0.65). The cohort was then limited to intermediate risk tumors, defined as endometrioid histology of any grade with deep myometrial invasion and/or lymphatic/vascular space invasion. When recurrence-free survival was stratified by *CTNNB1* mutation status and adjuvant therapy, patients with *CTNNB1* mutations and no adjuvant therapy had the shortest recurrence-free survival at 1.6 years, followed by patients with *CTNNB1* mutation who received adjuvant therapy (4.0 years), and wildtype *CTNNB1* with and without adjuvant therapy (8.5 and 7.2 years, respectively) (comparison for all four groups, p=0.01).

Conclusion: In patients with intermediate risk endometrioid endometrial cancers, the use of adjuvant therapy was associated with an improvement in recurrence-free survival for patients with tumor mutations in *CTNNB1*.

Precis

The *CTNNB1* mutation status of an early stage endometrioid endometrial cancer may help to inform adjuvant therapy decisions.

INTRODUCTION

The majority of endometrial cancer patients diagnosed at an early stage will be cured of their disease [1]. However, there is a small subset of women who will ultimately have a recurrence, and, once endometrial cancer recurs, especially outside the vaginal cuff, it is more frequently considered to be incurable [2]. Furthermore, as the incidence of endometrial cancer continues to rise, the absolute number of patients with recurrent endometrial cancer and the annual mortality also continue to increase [3].

Identifying which early stage patients are at highest risk of recurrence has been difficult, particularly for patients with cancers with endometrioid histology who are generally considered to have good outcomes. For this reason, adjuvant treatment recommendations from the National Cancer Center Network are somewhat ambiguous [4]. Depending on the presence or absence of risk factors, options may include observation, vaginal brachytherapy, or pelvic radiation therapy for Stage I disease. Currently, risk factors include deep myometrial invasion (more than 50% of the myometrial thickness), lymphatic/vascular invasion, and grade 3 disease [5–7]. The 2020 European consensus statement now includes molecular classification in their prognostic group stratification method [8], and the most recent National Comprehensive Cancer Network guidelines similarly include molecular classification in the recommended pathology evaluation [4]. Aside from a comment on *POLE* mutations in the European guidelines, the inclusion of molecular testing into these guidelines is not accompanied with specific recommendations on how to incorporate the results of specific tests with treatment decisions regarding adjuvant therapy.

Our group has previously shown that among women with International Federation of Obstetrics and Gynecology (FIGO) stage I or II, grade 1 or 2 endometrial endometrioid cancer, those whose tumors harbor a somatic *CTNNB1* mutation have a poorer recurrence-free survival [9]. In this study, of those mutations with at least 10% frequency in the cohort, *TP53* mutation was the only other gene mutation associated with a difference in survival outcomes. These prognostic findings have been supported by other retrospective studies which similarly showed an association of increased risk of recurrence with these tumor molecular alterations [10–14].

Current adjuvant treatment strategies do not consider presence or absence of tumor gene mutations associated with increased risk of recurrence in early stage disease. Therefore, we do not yet know whether traditional adjuvant treatment strategies would be effective in preventing recurrences in these subsets of patients that have been genomically characterized. The primary objective of this study was to determine whether women whose tumors harbor a somatic *CTNNB1* mutation have longer recurrence-free survivals if they receive traditional adjuvant therapy strategies compared with those who do not. We focused on *CTNNB1* gene mutation, as it is more common than *TP53* mutation in patients with endometrial cancers that are early stage and low grade (26% vs 9%) [9].

METHODS

This was a retrospective cohort study of patients who received care at the University of Texas MD Anderson Cancer Center for endometrial cancer. Patients who had sequencing of their tumor performed for the *CTNNB1* gene in any setting, since the year 2000, were included. Patients were also included if they have FIGO stage I disease after primary surgical management, and all histologies were included. Clinical and pathological characteristics were obtained by review of the electronic medical record and the hysterectomy pathology reports. Patients were excluded if they did not have surgical management of their endometrial cancer or if they did not have any follow-up contact with our institution after surgery. Patients with a concurrent cancer requiring adjuvant therapy, a history of cancer that then recurred after their endometrial cancer diagnosis, or progression of disease during adjuvant therapy were excluded.

Pathology was reviewed at our institution by a gynecologic pathologist to confirm the histologic diagnosis. Somatic tumor testing was performed in one of three ways: as standard of care using a next-generation sequencing panel of the exon 3 hot spot testing, in a research setting using next generation sequencing, or in a research setting using Sanger sequencing for exon 3 of the *CTNNB1* gene. Somatic alterations of the *CTNNB1* gene are most commonly found in exon 3 [15], and as such this is frequently the only exon evaluated on hot spot next generation sequencing panels. Germline testing was not included in this analysis.

Summary statistics were used to describe the demographic and clinical characteristics of the study population and by adjuvant therapy status. Associations of demographic and clinical characteristics by adjuvant therapy were conducted using t-test, rank-sum test, chi-squared test, or Fisher’s exact test depending on the underlying distribution of the data. Recurrence-

free survival was estimated using the Kaplan-Meier product-limit estimator. Recurrence-free survival was measured from the date of surgery to the earliest of date of the last clinic visit, date of first recurrence, or date of death. Patients alive and recurrence-free were censored at the date of last clinic visit. All statistical analysis were performed using Stata/MP v15.0 (College Station, TX). This study was approved by the University of Texas MD Anderson Cancer Center Insitututional Review Board (Protocol LAB01–718). 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.

RESULTS

Two hundred fifty-three patients were included in this analysis, 245 of whom had information about adjuvant therapy available. Clinical and demographic characteristics of the study population are listed in Table 1. The mean age of patients in the study cohort was 60 years, 83% of whom had endometrioid tumors and only 25% of whom had grade 3 tumors. The median follow-up was 4.7 years (range 0.02–18.6 years). When the study population was stratified by receipt of any adjuvant therapy, significantly more patients in the adjuvant therapy group had mixed and non-endometrioid histologies ($p<0.001$), grade 3 tumors ($p<0.001$), deep myometrial invasion ($p<0.001$), and lymphatic/vascular space invasion ($p<0.001$) (Table 1). Mean tumor size was also larger in those who received adjuvant therapy ($p<0.01$; Table 1). There was no significant difference between the two adjuvant therapy groups regarding *CTNNB1* mutation status (21% versus 14% in the no adjuvant therapy and adjuvant therapy groups, respectively; $p=0.18$). Among those who received adjuvant therapy, the majority received vaginal cuff brachytherapy alone (Table 2). The use of pelvic radiation (with or without brachytherapy) and chemotherapy (with or without radiation) was less common. Clinical and demographic characteristics were then stratified by the presence or absence of a *CTNNB1* mutation (Table 3). Patients whose tumors harbored *CTNNB1* mutations were younger at diagnosis (52.5 vs 61.3 years, $p < 0.001$) and more frequently had lower grade tumors (grade 1 endometrioid 31% vs 11%, $p < 0.001$). There were no other clinical or demographic differences between the groups.

We first investigated the impact of *CTNNB1* mutation status in patients who did not receive adjuvant therapy and did not meet intermediate risk criteria [4, 5, 7] – those with tumors showing grade 1 or 2 endometrioid histology, absent lymphatic/vascular space invasion, and superficial or no myometrial invasion (Table 4). There was no difference in recurrence-free survival between the patients whose tumors harbored somatic *CTNNB1* mutations and those with tumors that were wildtype for the gene (8.1 versus 11.3 years, respectively, $p=0.65$).

We next limited the analysis to women with any grade endometrioid tumor who had at least one of the intermediate risk factors: lymphatic/vascular space invasion or deep myometrial invasion at least 50% myometrial invasion. Results from this recurrence-free survival analysis are summarized in Table 5. Patients with a somatic *CTNNB1* mutation had shorter recurrence-free survival than those who were wildtype for the gene (2.4 versus 8.5 years, respectively; $p=0.01$). We then further stratified these groups into the presence or absence of adjuvant therapy. Patients with tumors with a somatic *CTNNB1* mutation and did not receive adjuvant therapy had the shortest recurrence-free survival at 1.6 years. Patients

harboring a somatic mutation but who received adjuvant therapy had a recurrence-free survival of 4.0 years. Patients whose tumor was wildtype for the *CTNNB1* gene and who did and did not receive adjuvant therapy had recurrence-free survivals of 8.5 and 7.2 years, respectively (comparison for all four groups: p=0.01) (Table 5).

DISCUSSION

Summary of Main Results

Our results suggest that adjuvant therapy may be beneficial for women with stage I endometrioid endometrial cancer whose tumors demonstrate intermediate risk features and harbor a *CTNNB1* mutation. In women not receiving adjuvant treatment whose tumors had only low risk features, outcomes were not statistically significantly different for those with and without somatic *CTNNB1* mutations. Qualitatively, there were no differences in the adjuvant therapy strategies administered for those with and without somatic mutations. It is noteworthy that this study started with a large number (n=253) of stage I patients with molecular data available. However, once survival outcomes for specific subgroups were evaluated, the patient numbers dramatically decrease in each relevant comparison group. While the patient numbers in our study are small, these data suggest that the survival impact of tumor *CTNNB1* mutation is context-dependent, becoming most evident in the setting of stage I, intermediate risk disease. Validation of these data in an independent patient population is necessary before they could be implemented into clinical practice.

Results in the Context of Published Literature

We first identified *CTNNB1* gene mutation as a possible prognostic from our re-evaluation of TCGA endometrial cancer data which focused only on endometrioid carcinomas [16]. In this analysis, Cluster II was characterized by significantly worse survival, activation of the Wnt/β-catenin pathway, a preponderance of *CTNNB1* mutations, and the lowest number of gene mutations overall compared to the other three endometrioid clusters [16]. The fact that few mutations overall were present in this cluster led us to believe that *CTNNB1* mutation was the primary driver of the poor survival. This suspicion was confirmed in a subsequent analysis employing targeted next generation sequencing [9] in which only *CTNNB1* and *TP53* mutations were associated with worse recurrence-free survival in low grade, early stage endometrioid carcinomas. Importantly, *CTNNB1* and *TP53* gene mutations only infrequently overlap in the same endometrial cancer [9, 16], thus we believe these gene mutations are independent drivers of poor prognosis.

The optimal method of assessing *CTNNB1* mutation status for endometrial cancer is uncertain. Most of the activating mutations associated with worse survival in endometrial cancer occur in exon 3 [16], so this is a relatively simple and straight-forward sequencing assay for the clinical laboratory. Classically, *CTNNB1*-mutant cancers are associated with nuclear localization of β-catenin protein [17, 18]. It is unclear if immunohistochemistry for β-catenin can be used as a surrogate of gene sequencing. We previously found that a relatively high proportion of *CTNNB1*-mutant endometrial cancers had relatively poor nuclear localization of the protein by immunohistochemistry [19]. Others have advocated for the immunohistochemistry approach as a more cost-effective method [12].

Other molecular markers that may be relevant to low grade, early stage endometrial tumors include mismatch repair deficiency, p53 alterations, and L1 cell adhesion molecule (L1CAM) expression. All of these alterations can be evaluated using immunohistochemistry. Although mismatch repair deficiency is critical for identification of potential germline mutation carriers, the reports surrounding the prognostic value of mismatch repair deficiency in early stage endometrial cancer have been mixed [20–22]. However, these are included in most molecular classification algorithms [4, 8, 23], and given the responsiveness of these tumors to immunotherapy [24, 25] and potentially to radiation therapy [26, 27], we anticipate that this molecular finding may soon guide frontline treatment decisions. Although less common, *TP53* mutations in endometrioid tumors have also been associated with worse survival outcomes [9, 28]. Less is known about L1CAM, but recent studies suggest its expression in early stage endometrioid tumors may be associated with worse survival outcomes [29, 30]. The impact of adjuvant treatment on these outcomes remains largely unknown.

Our data mirror findings seen with other histologic features. The largest landmark trials for early stage high intermediate risk endometrial cancer are GOG-99, PORTEC-1, and PORTEC-2 [5–7]. These studies solidified the recommendation that administering adjuvant therapy in the form of cuff brachytherapy to women whose tumors show high intermediate risk factors is associated with a decreased risk of local recurrence. Interestingly, none of these studies demonstrated an improvement in overall survival. Data regarding systemic therapy for intermediate risk are limited, and even adjuvant hormonal therapy has not been found to add much benefit [31]. Thus, systemic therapy for women without high risk disease is not currently recommended [4].

Molecular profiling for endometrial cancer has been well-described by the Cancer Genome Atlas [32] and more recently by Clinical Proteomic Tumor Analysis Consortium [33]. Its direct application to patient care has been limited, however. In an attempt to make molecular subtyping more feasible in the clinical setting, several modified algorithms have been proposed [21, 23]. As a first application of prospectively using molecular profiling to inform adjuvant treatment decisions in early stage endometrial cancer, results from PORTEC-4a will be available soon. In this novel randomized clinical trial, patients with high intermediate risk disease are randomized to receive either vaginal brachytherapy or an adjusted adjuvant therapy regimen (observation, vaginal brachytherapy, or external beam radiation therapy) based on molecular features of their tumors [34]. Specifically, the study is incorporating *POLE* mutations, mismatch repair deficiency, *TP53* mutation, *CTNNB1* mutation, L1CAM expression, or substantial lymphatic/vascular space invasion into their risk assessment. In patients with tumors that are mismatch repair proficient, the presence of a *CTNNB1* mutation results in vaginal brachytherapy, but in the absence of a *CTNNB1* women are triaged to observation alone. This ground-breaking adjuvant therapy algorithm is based on the knowledge that patients whose tumors have *CTNNB1* mutations have shorter recurrence-free survival. However, it is still unknown whether adjuvant brachytherapy is an adequate strategy to mitigate the increased risk of recurrence. We look forward to the results from PORTEC-4a to help inform future clinical trials.

Strengths and Weaknesses

Strengths of our study include the relatively large number of stage I, low grade endometrial cancer patients whose tumors had sequencing of the *CTNNB1* gene performed. Patients had relatively long term follow-up, and information about adjuvant therapy was available. Our study also had limitations, largely due to its retrospective nature. We cannot rule out any potential bias that could have been present in decisions about adjuvant therapy allocation. However, the fact that *CTNNB1* mutation testing was performed after treatment outcomes were known, as well as the similar rates of *CTNNB1* mutations in both therapy groups, was reassuring. Additionally, our study represents patients who were seen at a large, tertiary care cancer center and may not be reflective of patients in other settings. These findings will need to be validated in other populations before implementation into routine clinical care. We also do not have full next generation sequencing data available for all of the patients in this cohort, as a subset only had Sanger sequencing of the *CTNNB1* gene. Thus, we cannot rule out an impact of another alteration in our findings. However, our prior data showed that, in general, in this population of patients, concurrent alterations were not more frequent in the tumors with *CTNNB1* mutations, with the exception of *KRAS* and *TP53*, both of which were less common in tumors with *CTNNB1* mutations [9]. Last, the absolute numbers of patients with tumor somatic *CTNNB1* mutations in this study were low, which limits our power to do other potentially useful sub-analyses or multivariable analyses. However, baseline clinical and demographic characteristics suggested that *CTNNB1* mutations were not associated with higher risk features; if anything, these tumors tended to be lower grade and endometrioid histology. Thus, we do not think that *CTNNB1* mutations are serving as surrogates for other higher risk histologic features known to be associated with a higher risk of recurrence. However, we hope that future large, prospective studies will be better situated to investigate these related questions.

Implications for Practice and Future Research

Interventional trials evaluating adjuvant therapy approaches should incorporate *CTNNB1* mutation status into risk stratification protocols to better delineate the role of adjuvant therapy in this important patient population and to identify which treatment approaches may be most beneficial. If our findings are replicated in future studies, we envision that *CTNNB1* mutation status would be another tumor feature, along with lymphatic/vascular space invasion, tumor grade, and deep myometrial invasion, that should be considered when contemplating adjuvant treatment for early stage, endometrioid endometrial cancer.

Conclusions

Our data suggest that some of the additional risk conferred by the presence of a somatic *CTNNB1* in patients with intermediate risk characteristics may be overcome with traditional adjuvant therapy approaches for early stage endometrial cancer. Although the numbers of patients included in this study are small, these dataprovide further support for the use of molecular typing in the upfront treatment setting.

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REFERENCES

1. Dowdy SC, et al. , Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. Gynecol Oncol, 2012. 127(1): p. 5–10. [PubMed: 22771890]
2. Creutzberg CL, et al. , Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol, 2003. 89(2): p. 201–9. [PubMed: 12713981]
3. Siegel RL, et al. , Cancer Statistics, 2021. CA Cancer J Clin, 2021. 71(1): p. 7–33. [PubMed: 33433946]
4. Network NCC Uterine Neoplasms (Version 4.2021). 2021 September 3, 2021 October 20, 2021]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
5. Keys HM, 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(3): p. 744–51. [PubMed: 14984936]
6. Creutzberg CL, et al. , Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet, 2000. 355(9213): p. 1404–11. [PubMed: 10791524]
7. Nout RA, et al. , Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet, 2010. 375(9717): p. 816–23. [PubMed: 20206777]
8. Concin N, et al. , ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer, 2021. 31(1): p. 12–39. [PubMed: 33397713]
9. Kurnit KC, et al. , CTNNB1 (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. Mod Pathol, 2017. 30(7): p. 1032–1041. [PubMed: 28281553]
10. Myers A, et al. , beta-Catenin mutations in recurrent FIGO IA grade I endometrioid endometrial cancers. Gynecol Oncol, 2014. 134(2): p. 426–7. [PubMed: 24952365]
11. Moroney MR, et al. , Molecular markers in recurrent stage I, grade 1 endometrioid endometrial cancers. Gynecologic oncology, 2019. 153(3): p. 517–520. [PubMed: 30910249]
12. Costigan DC, et al. , Clinicopathologic and immunohistochemical correlates of CTNNB1 mutated endometrial endometrioid carcinoma. International Journal of Gynecological Pathology, 2020. 39(2): p. 119–127. [PubMed: 30702464]
13. Ruz-Caracuel I, et al. , Clinicopathological features and prognostic significance of CTNNB1 mutation in low-grade, early-stage endometrial endometrioid carcinoma. Virchows Arch, 2021.
14. Yano M, et al. , Impact of TP53 immunohistochemistry on the histological grading system for endometrial endometrioid carcinoma. Mod Pathol, 2019. 32(7): p. 1023–1031. [PubMed: 30742011]
15. Gao C, et al. , Exon 3 mutations of CTNNB1 drive tumorigenesis: a review. Oncotarget, 2018. 9(4): p. 5492–5508. [PubMed: 29435196]
16. Liu Y, et al. , Clinical significance of CTNNB1 mutation and Wnt pathway activation in endometrioid endometrial carcinoma. J Natl Cancer Inst, 2014. 106(9).
17. Rubinfeld B, et al. , Stabilization of beta-catenin by genetic defects in melanoma cell lines. Science, 1997. 275(5307): p. 1790–2. [PubMed: 9065403]
18. Morin PJ, et al. , Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. Science, 1997. 275(5307): p. 1787–90. [PubMed: 9065402]
19. Kim G, et al. , Nuclear β-catenin localization and mutation of the CTNNB1 gene: a context-dependent association. Mod Pathol, 2018. 31(10): p. 1553–1559. [PubMed: 29795437]

20. Backes FJ, et al. , Mismatch repair deficiency identifies patients with high-intermediate-risk (HIR) endometrioid endometrial cancer at the highest risk of recurrence: A prognostic biomarker. Cancer, 2019. 125(3): p. 398–405. [PubMed: 30561762]
21. Stelloo E, et al. , Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res, 2016. 22(16): p. 4215–24. [PubMed: 27006490]
22. Diaz-Padilla I, et al. , Mismatch repair status and clinical outcome in endometrial cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol, 2013. 88(1): p. 154–67. [PubMed: 23562498]
23. Talhouk A, et al. , Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer, 2017. 123(5): p. 802–813. [PubMed: 28061006]
24. Le DT, et al. , Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science, 2017.
25. Oaknin A, et al. , Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol, 2020. 6(11): p. 1766–1772. [PubMed: 33001143]
26. Reijnen C, et al. , Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer. Gynecol Oncol, 2019. 154(1): p. 124–130. [PubMed: 31103324]
27. León-Castillo A, et al. , Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol, 2020: p. Jco2000549.
28. Nout RA, et al. , Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3K-AKT, Wnt/beta-catenin and P53 pathway activation. Gynecol Oncol, 2012. 126(3): p. 466–73. [PubMed: 22609107]
29. Bosse T, et al. , L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results. Eur J Cancer, 2014. 50(15): p. 2602–10. [PubMed: 25126672]
30. Smogeli E, et al. , L1CAM as a prognostic marker in stage I endometrial cancer: a validation study. BMC Cancer, 2016. 16: p. 596. [PubMed: 27488577]
31. Martin-Hirsch PP, et al. , Adjuvant progestagens for endometrial cancer. Cochrane Database Syst Rev, 2011(6): p. Cd001040. [PubMed: 21678331]
32. Cancer Genome Atlas Research, N., et al. , Integrated genomic characterization of endometrial carcinoma. Nature, 2013. 497(7447): p. 67–73. [PubMed: 23636398]
33. Dou Y, et al. , Proteogenomic Characterization of Endometrial Carcinoma. Cell, 2020. 180(4): p. 729–748.e26. [PubMed: 32059776]
34. Wortman BG, 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(1): p. 69–75. [PubMed: 30078506]

Highlights

- Tumor *CTNNB1* mutation correlated with shorter recurrence-free survival in intermediate risk patients
- In intermediate risk endometrial cancer with *CTNNB1* mutation, adjuvant therapy may improve survival
- In low risk endometrial cancer patients, the presence of *CTNNB1* mutation did not impact survival

Table 1.

Clinical and demographic characteristics of the study population overall, and when stratified by presence or absence of adjuvant therapy receipt.

Characteristic	Overall[a] (n=253)	No Adjuvant Treatment (n = 145)	Any Adjuvant Treatment (n = 100)	P-value
Mean age at diagnosis in years (SD)	59.8 (12.5)	58.6 (12.8)	61.1 (11.7)	0.09
Mean tumor size in cm (SD) [b]	4.3 (2.5)	4.0 (2.6)	4.7 (2.4)	0.01
Histology, n (%)				<0.001
Endometrioid	210 (83%)	138 (95%)	66 (66%)	
Mixed	31 (12%)	3 (2%)	26 (26%)	
Non-endometrioid	12 (5%)	4 (3%)	8 (8%)	
Histologic grade, n (%) [c]				<0.001
Grade 1	37 (15%)	35 (24%)	2 (2.0%)	
Grade 2	151 (60%)	97 (68%)	50 (50%)	
Grade 3	63 (25%)	11 (8%)	48 (48%)	
Deep (≥50%) myometrial invasion, n (%) [d]	53 (21%)	13 (9%)	38 (38%)	<0.001
Lymphatic/vascular space invasion, n (%) [e]	79 (32%)	19 (14%)	58 (58%)	<0.001
***CTNNB1* mutation present, n (%)**	45 (18%)	30 (21%)	14 (14%)	0.18

[a] Adjuvant treatment data missing for n=8 patients

[b] Tumor size data missing for n=13 patients

[c] Histologic grade data missing for n=2 patients

[d] Depth of myometrial invasion data missing for n=3 patients

[e] Lymphatic/vascular space invasion data missing for n=6 patients

SD, standard deviation.

Table 2.

Type of adjuvant therapy administered among patients who received adjuvant therapy.

Adjuvant Therapy	***CTNNB1* Wildtype (n=43)**	***CTNNB1* Mutant (n=5)**
Cuff Brachytherapy	25	3
Pelvic Radiation (with or without brachytherapy)	14	2
Chemotherapy with or without Radiation Therapy	4	0

Table 3.

Clinical and demographic characteristics of the study population overall, and when stratified by presence or absence of *CTNNB1* mutation.

Characteristic	Overall (n=253)	*CTNNB1* wildtype (n = 208)	*CTNNB1* mutant (n = 45)	P-value
Mean age at diagnosis in years (SD)	59.8 (12.5)	61.3 (11.9)	52.5 (12.5)	< 0.001
Mean tumor size in cm (SD) [a]	4.3 (2.5)	4.3 (2.5)	4.0 (2.6)	0.92
Histology, n (%)				0.10
Endometrioid	210 (83%)	168 (81%)	42 (93%)	
Mixed	31 (12%)	28 (13%)	3 (7%)	
Non-endometrioid	12 (5%)	12 (6%)	0 (0%)	
Histologic grade, n (%) [b]				< 0.001
Grade 1	37 (15%)	23 (11%)	14 (31%)	
Grade 2	151 (60%)	124 (60%)	27 (60%)	
Grade 3	63 (25%)	59 (29%)	4 (9%)	
Deep (≥50%) myometrial invasion, n (%) [c]	53 (21%)	43 (21%)	10 (23%)	0.79
Lymphatic/vascular space invasion, n (%) [d]	79 (32%)	70 (34%)	9 (21%)	0.09

[a] Tumor size data missing for n=13 patients

[b] Histologic grade data missing for n=2 patients

[c] Depth of myometrial invasion data missing for n=3 patients

[d] Lymphatic/vascular space invasion data missing for n=6 patients

SD, standard deviation.

Table 4.

Recurrence-free survival for low risk endometrial cancer patients (grade 1 or 2 endometrioid histology, no lymphatic/vascular space invasion, less than 50% myometrial invasion) who did not receive any adjuvant therapy. CI, confidence interval; NE, not evaluable.

***CTNNB1* mutation status**	**N**	**Events**	**Median Recurrence-Free Survival, in years (CI)**	**P-value**
Wildtype	91	19	11.3 (5.3 – NE)	
Mutant	27	6	8.1 (2.8 – NE)	
				0.65

Table 5.

Recurrence-free survival for intermediate risk endometrial cancer patients (any grade endometrioid, plus lymphatic/vascular space invasion *or* deep myometrial invasion) stratified by *CTNNB1* mutation status and receipt of adjuvant therapy. CI, confidence interval; NE, not evaluable.

***CTNNB1* mutation status**	**Median RFS in years (CI)**	**p-value**	**Adjuvant therapy?**	**N**	**Events**	**Median RFS in years (CI)**	**p-value**
Wildtype	8.5 (3.2 – NE)		No	19	6	7.2 (1.0 – NE)	
			Yes	41	13	8.5 (2.2 – NE)	
Mutant	2.4 (0.2 – NE)		No	6	5	1.6 (0.2 – NE)	
			Yes	5	2	4.0 (2.4 – NE)	
		0.01					0.01