**APPLICATION OF THE PROACTIVE MOLECULAR RISK CLASSIFIER FOR
ENDOMETRIAL CANCER (ProMisE) TO PATIENTS CONSERVATIVELY
TREATED: OUTCOMES FROM AN INSTITUTIONAL SERIES**

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OBJECTIVE

To test the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) and determine the frequency of specific/prognostic molecular alterations within a cohort of endometrial cancer (EC) women conservatively treated by combined hysteroscopic resection and progestin therapy.

STUDY DESIGN

We used blocks of formalin-fixed paraffin-embedded tissue from the primary tumors of patients enrolled into the ECCo trial (EudraCT 2010-018581-23) between 2007 and 2016. In order to assign EC resectoscopic specimens to one of four ProMisE subgroups, testing involved sequential assessment of i) immunohistochemistry (IHC) for mismatch repair (MMR) proteins MLH1, MSH2, MSH6 and PMS2; ii) sequencing for POLE/POLD1 exonuclease domain mutations (EDMs); iii) p53 IHC.

RESULTS

Molecular analysis methods were used in 25 patients (stage IA, G1-2 endometrioid EC), of whom 15 (60%) represented fully evaluable cases. Seven cases (46.7%) had abnormal MMR IHC, POLE/POLD1 EDMs were found in 3 cases (20%), and abnormal p53 IHC in 1 case (6.6%). Three patients (20%) had more than one molecular feature. Among 10 (40%) ‘unclassifiable’ patients, six failures in achieving complete molecular categorization were due to the low tumor volume. Molecular classification of the 15 fully evaluable cases yielded the following ProMisE subtypes: 7 (46.7%) MMR IHC abnormal, 1 (6.6%) POLE EDM, 0 (0%) p53 IHC abnormal, 7 (46.7%) p53 IHC wild-type.

Case #	Tumor diameter (cm)/grade	MMR IHC abn	POLE – POLD1 mutation; AF (%)	p53 IHC	Oncologic outcomes [§]	Relapse (months)	2 nd cancer (months)	Current status	Germline LS genetic testing
1	≤2/G1	-	-	wt	CR	-	-	NED	negative
2	≤2/G1	-	-	wt	CR	-	-	NED	negative
3	≤2/G1	MSH6; PMS2	-	wt	Persistence	-	-	NED	n/a
4	≤2/G1	PMS2	-	abn	CR	-	Intestinal (105)	DOD*	PMS2 mut
5	>2/G1	-	-	wt	CR	41	Ovarian (41)	NED	negative
6	≤2/G1	-	-	wt	CR	-	-	NED	negative
7	>2/G2	MSH2; MSH6	POLE: p.A341 T (c.1021 G > A); 13.5	wt	Progression [†]	-	-	NED	n/a
8	≤2/G1	MSH2; MSH6	-	wt	CR	-	-	NED	n/a
9	≤2/G1	-	POLE: p.V411 L (c.1231 G > T); 30.7	wt	CR	-	-	NED	negative
10	≤2/G1	MSH6	POLD-1: p.D402 N (c.1204 G > A); 35.4	wt	CR	-	Breast (84)	NED	MSH6 mut
11	≤2/G1	MSH2; MSH6	-	wt	CR	-	-	NED	n/a
12	≤2/G1	-	-	wt	CR	-	-	NED	negative
13	≤2/G1	-	-	wt	CR**	8	Ovarian (8)	NED	negative
14	≤2/G1	MSH2	-	wt	CR	11	-	AWBC	negative
15	≤2/G1	-	-	wt	CR	-	-	NED	negative

Abn: abnormal; AF: allelic frequency; AWBC: alive with breast cancer; CR: complete regression; DOD: died of disease; IHC: immunohistochemistry; LS: Lynch syndrome; MMR: mismatch repair; mut: mutation; n/a: not available; NED: no evidence of disease; wt: wild-type.

[§]At 6 months; [†]Definitive surgery at 3 months; *Right-sided colon cancer; **After re-treatment of persistent disease at 6 months.

CONCLUSION

Although larger series are needed to further assess the feasibility of a molecular categorization in a fertility-sparing setting, data presented are promising. In women with early stage low-volume disease, operative hysteroscopy could be advantageous to provide samples allowing complete genetic risk assessment.