抄読会　2026 年 01 月 19 日

Central Pathology Review of Endometrial Hyperplasia and Adenocarcinoma Before and After Treatment With the Levonorgestrel Intrauterine Device–Results From the feMMe Phase 2 Randomized Clinical Trial.

Baxter E, Robledo KP, Cummings M, et al. Am J Surg Pathol. 2026;50(2):259-266.

要旨

子宮体癌は増加傾向にあり、その標準的治療は子宮および両側付属器の摘出であるが、endometrioid carcinoma, grade 1 (EmC)の患者では黄体ホルモン製剤を用いた妊孕性温存治療が考慮されることがある。これまで複数の後ろ向き研究で黄体ホルモン製剤未治療の endometrial hyperplasia (EmH)と EmC の鑑別の再現性が低いことが示されているが、黄体ホルモン製剤治療後の診断者間 bias を研究は 1 つあるのみであり、治療前後の両方の検体を用いた診断者間 bias を評価した研究は存在しない。本報告は feMMe phase 2 randomized clinical trial (levonorgestrel intrauterine device の EmH と EmC に対する治療効果をみた study)における治療前、治療後 3 ヶ月と 6 ヶ月に採取された子宮内膜生検の施設診断と中央診断における診断者間 bias を評価した。

中央診断は症例の臨床情報と feMMe の試験結果は盲検された上で、2 名の婦人科病理医による HE 標本のみの評価で行われた。診断者間 bias は Cohen kappa 計数を用いて評価され、≤0.20 は不一致、0.21-0.39 は最小限一致、0.40- 0.59 は低一致、0.60-0.79 は中一致、0.80-0.90 は高一致、>0.90 はほぼ完全一致とした。

各時点での施設診断と中央診断の結果を table 1 に示す。治療前標本が入手できた 143 例中 105 例(73%)の診断が一致し、Cohen kappa 計数は 0.50 と低一致性を示すに留まった。治療後 3 ヶ月標本が入手できた 134 例中 107 例(80%)の診断が一致し、Cohen kappa 計数は 0.72 と中等度の一致性を示した。治療後 6 ヶ月標本が入手できた 127 例中 98 例(77%)の診断が一致し、Cohen kappa 計数は 0.64 と中等度の一致性を示した。内訳を見てみると、治療前の施設診断は癌腫を増殖症と低く診断する傾向がみられ、治療後 3 ヶ月と 6 ヶ月時点では病変を見逃す傾向がある。この原因は table 2 で示されているように採取法や閉経の有無と相関がない。診断不一致の例は fig.1-3 に示されている。

Take Home Message

1. 黄体ホルモン治療前の婦人科病理医と施設病理医の診断一致率は低く、特に施設診断は低めに診断される傾向がある。
2. 黄体ホルモン治療後の一致性は治療前よりも良くなるが、施設病理医は残存病変を見逃す傾向が見られる。

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TABLE 1. Diagnostic Agreement Between Trial Site Pathologists and Central Review of feMMe Trial Tissue Specimens

	Central review diagnosis						
Site diagnosis	**NED**	**EH**	**EHA**	**G1 EAC**	**G2 EAC**	**Other**	**Total**
Baseline							
NED	0	0	0	0	0	0	*0*
EH	0	0	0	0	0	0	0
EHA	2	1	37	20	2	0	62
G1 EAC	0	1	4	68	8	0	81
G2 EAC	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Total	2	2	41	88	10	0	143
Three months post-LNG-IUD							
NED	48	9	3	1	0	0	61
EH	1	5	2	0	0	0	8
EHA	2	3	9	2	0	0	16
G1 EAC	0	2	0	43	0	1*	46
G2 EAC	0	0	0	1	2	0	3
Other	0	0	0	0	0	0	0
Total	51	19	14	47	2	1	134
Six months post-LNG-IUD							
NED	60	9	2	4	0	0	75
EH	1	8	3	1	0	0	13
EHA	1	3	3	1	0	0	8
G1 EAC	0	0	0	24	4	0	28
G2 EAC	0	0	0	0	3	0	3
Other	0	0	0	0	0	0	0
Total	62	20	8	30	7	0	127

*Case diagnosed as serous or clear cell endometrial cancer on central review.

EH indicates endometrial hyperplasia without atypia; EHA, endometrial hyperplasia with atypia; G1 EAC, grade 1 endometrioid adenocarcinoma; G2 EAC, grade 2 endometrioid adenocarcinoma; NED, no evidence of disease.

TABLE 2. Characteristics of Concordant and Discordant Cases

	Baseline			Three months post LNG-IUD			Six months post LNG-IUD		
	Concordant (n = 105) (%)	**Discordant (n = 38) (%)**	***P***	**Concordant (n = 107) (%)**	**Discordant (n = 27) (%)**	***P***	**Concordant (n = 98) (%)**	**Discordant (n = 29) (%)**	***P***
Sampling method									
Pipelle	11 (10)	6 (16)	0.60	55 (51)	13 (48)	0.50	28 (29)	5 (17)	0.42
Curette	89 (85)	31 (82)		47 (44)	11 (41)		65 (66)	22 (76)	
Unknown	5 (5)	1 (2)		5 (5)	3 (11)		3 (3)	2 (7)	
Other	0 (0)	0 (0)		0 (0)	0 (0)		2 (2)	0 (0)	
Age (y)									
Mean ± SD	54.1 ± 13.8	52.3 ± 13.2	0.47	54.1 ± 13.7	54.7 ± 12.6	0.86	55.1 ± 13.0	54.4 ± 13.3	0.79
Menopausal status									
Pre	42 (40)	17 (45)	0.70	45 (42)	10 (37)	0.67	39 (40)	11 (38)	1.00
Post	63 (60)	21 (55)		62 (58)	17 (63)		59 (60)	18 (62)	
BMI (kg/m^2)									
Mean ± SD	47.4 ± 9.2	49.7 ± 9.3	0.20	46.4 ± 9.2	47.1 ± 6.8	0.66	46.2 ± 9.0	45.2 ± 6.8	0.52

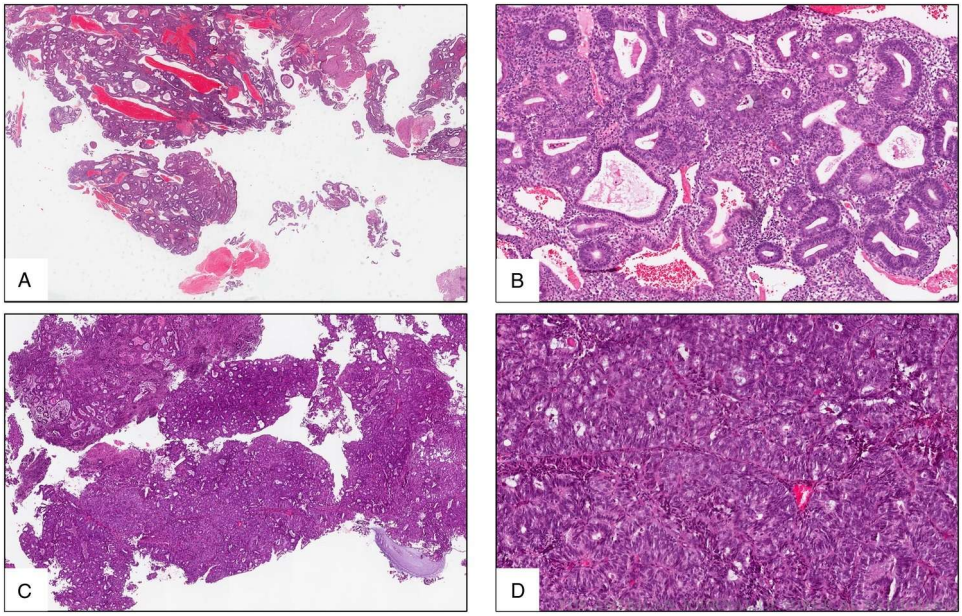

Fig. 1. Hematoxylin and eosin staining of cases that were discordant between trial site pathologists and central review regarding baseline diagnosis. (A, B) Case 73 was diagnosed as grade 1 endometrioid adenocarcinoma by the site pathologist and was downgraded to endometrial hyperplasia on central review. (C, D) Case 61 was diagnosed as grade 1 endometrioid adenocarcinoma by the site pathologist and was upgraded to grade 2 endometrioid adenocarcinoma on central review. Slides are shown at (A, C) low power and (B, D) high power.

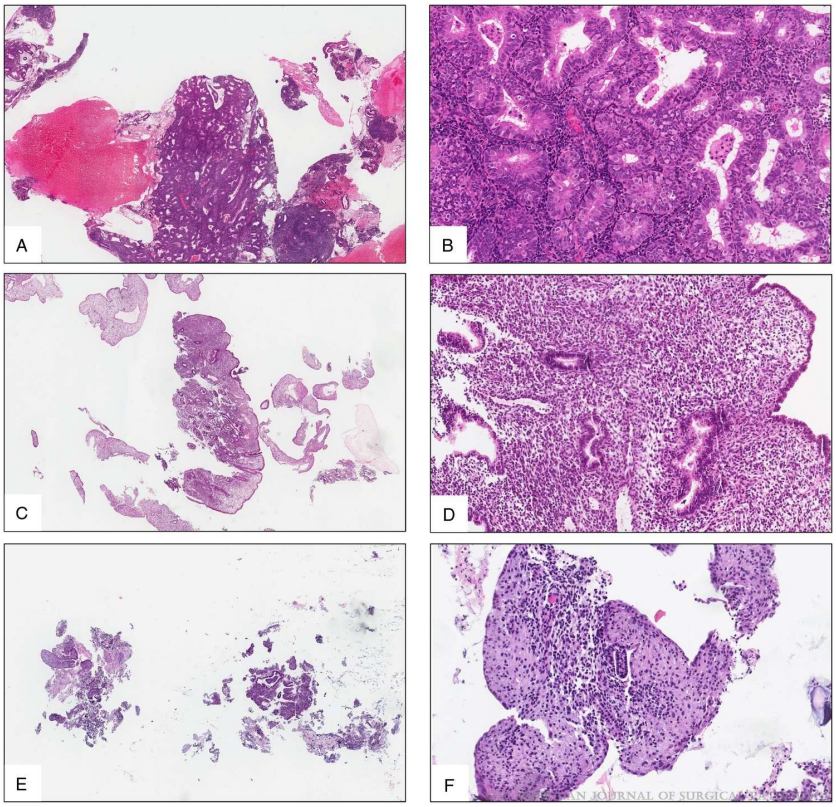

Fig.2. Hematoxylin and eosin staining of a case that was discordant between trial site pathologists and central review post-treatment. Case 75 was diagnosed at (A, B) baseline as endometrial hyperplasia with atypia by both the site pathologist and central review. (C, D) At 3 months and (E, F) 6 months post-treatment, site-reported diagnosis was persistent endometrial hyperplasia with atypia, which was downgraded to no evidence of disease on central review at both time points. Slides are shown at (A, C, E) low power and (B, D, F) high power.

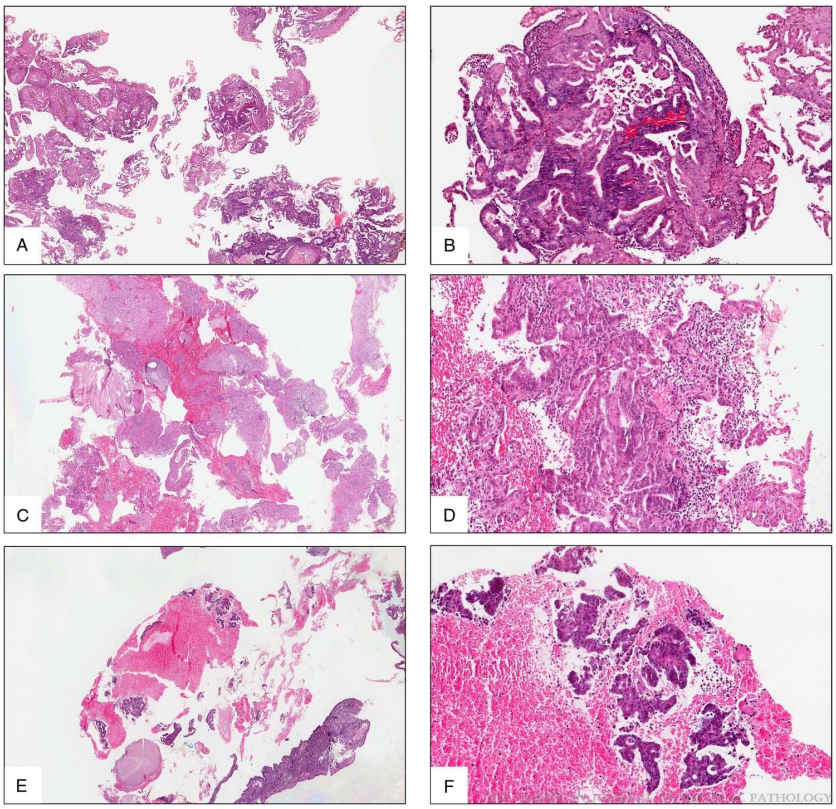

Fig.3. Hematoxylin and eosin staining of a case that was discordant between trial site pathologists and central review post-treatment. Case 46 was diagnosed at (A, B) baseline and (C, D) 3 months post-treatment as grade 1 endometrioid adenocarcinoma by both the site pathologist and central review. (E, F) At 6 months post-treatment, site-reported diagnosis was no evidence of disease, which was upgraded to grade 1 endometrioid adenocarcinoma on central review. Slides are shown at (A, C, E) low power and (B, D, F) high power.