the calculated predictive probability values were significantly different between the LNM-positive and -negative groups ($P = 1.39 \times 10^{-10}$), and high diagnostic accuracy of 83.6% area under the curve (AUC) was obtained. The LNM diagnosis requires essentially minimize the time difference between the diagnosis and hysterectomy. Therefore, reverse transcription-polymerase chain reaction enabled quantification from RNA in one step within 30 min, for intraoperative diagnosis.

Conclusion This diagnostic method uses rapid nucleic acid amplification for intraoperative quantification of biomarkers in the primary tissue. Furthermore, the predictive model combined with various clinical variables can be used to discriminate LNM with high accuracy and facilitate individualization of the surgical treatment.

2022-RA-809-ESGO UNDERLYING CAUSES AND PROGNOSIS OF MISMATCH REPAIR DEFICIENCY IN ENDOMETRIAL CANCER OTHER THAN *MLH1* PROMOTER HYPERMETHYLATION

[1]Merve Kaya, [2]Cathalijne Post, [3]Carli M Tops, [4]Ellen Stelloo, [3]Maartje Nielsen, [5]Melanie E Powell, [6]Alexandra Leary, [7]Linda R Mileshkin, [8]Paul Bessette, [2]Stephanie M de Boer, [9]Ina M Jürgenliemk-Schulz, [10]Ludy Lutgens, [11]Jan J Jobsen, [12]Elzbieta M van der Steen-Banasik, [2]Remi A Nout, [2]Nanda Horeweg, [4]Tom van Wezel, [4]Vincent Smit, [2]Carien L Creutzberg, [4]Tjalling Bosse. *[1]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; [2]Department of Radiation Oncology, Leiden University Medical Center, Leiden, Netherlands; [3]Department of Clinical Genetics, Leiden University Medical Center, Leiden, Netherlands; [4]Department of Pathology, Leiden University Medical Center, Leiden, Netherlands; [5]Department of Clinical Oncology, Barts Health NHS Trust, London, UK; [6]Department of Medical Oncology, Gustave Roussy, Villejuif, France; [7]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [8]Department of Obstetrics and Gynaecology, University of Sherbrooke, Sherbrooke, QC, Canada; [9]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, Netherlands; [10]Department of Radiation Oncology, MAASTRO Clinic, Maastricht, Netherlands; [11]Department of Radiation Oncology, Medical Spectrum Twente, Enschede, Netherlands; [12]Department of Radiation Oncology, Radiotherapy Group, Arnhem, Netherlands*

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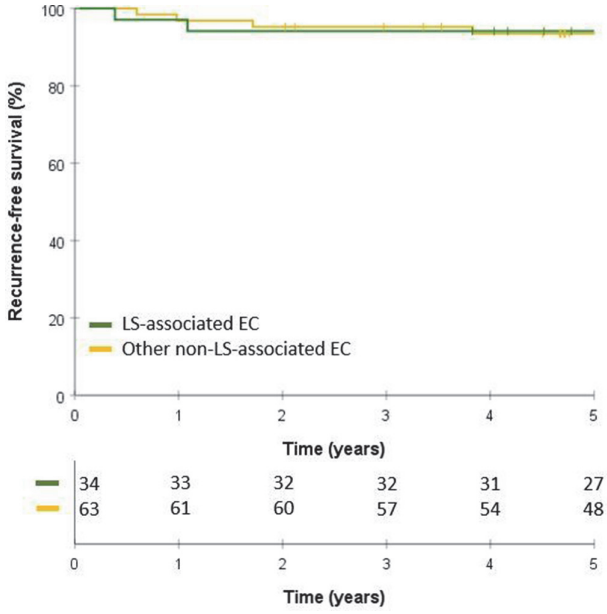
Introduction/Background The vast majority of mismatch repair-deficient (MMRd) endometrial carcinomas (EC) are due *MLH1* promoter hypermethylation. Here, we aimed to investigate the prevalence, prognosis and underlying causes (including Lynch syndrome (LS)) of MMRd EC other than *MLH1* promoter hypermethylation.

Methodology From the 409 MMRd ECs that were identified by MMR-immunohistochemistry (IHC) in the PORTEC-1,-2 and -3 trials, 97 cases did not have *MLH1* promoter hypermethylation. These 97 cases were analyzed by matched tumor-normal tissue targeted next-generation sequencing (NGS) for the presence of MMR and *POLE* mutations (class 4/5 variants). Furthermore, microsatellite instability (MSI) testing was performed. Differences in 5-year recurrence-free survival (RFS) were analysed using the Kaplan-Meier method and log-rank test. On a subset of cases NGS is pending and results will be added for the meeting.

Results In 34 cases (35%) a germline MMR mutation (LS-associated) was identified of which 8 (24%) had a second somatic hit. Upon excluding LS-associated ECs, a somatic alteration in MMR genes was observed in 52% (n=33), including double somatic hits in 35% (n=22). In the remaining 48% of cases (n=30) no MMR mutation was found of which the majority (n=22) was confirmed MSI. Rereview of all (discrepant) MMR-IHC did not reveal misinterpretation of MMRd status. Somatic *POLE* mutations were identified in 7/97 cases (7%). The 5-year RFS did not differ significantly between LS-associated and non-LS-associated MMRd EC (5-year RFS 94.1% [95% CI 86.5–100%] vs 93.5% [95% CI 87.5–99.9%], respectively; p=0.72; figure 1).



Abstract 2022-RA-809-ESGO Figure 1 Kaplan-Meier survival curves for recurrence-free survival for patients with LS-associated EC (germline mutation in MMR gene) and other non-LS-associated MMRd EC. All Cases with MMRd phenotype without *MLH1* promoter hypermethylation are included in this analysis, including cases with a concurrent *POLE* mutation (*POLE*mut-MMRd EC). *P* value reflect 2-sided log-rank test. Abbreviations: EC, endometrial cancer; LS, Lynch syndrome; MMR, mismatch repair; MMRd, mismatch repair-deficient;

Conclusion Identification of an underlying cause for unmethylated MMRd is feasible in the majority of EC cases applying matched tumor-normal tissue NGS. A significant proportion was confirmed to be LS-associated or sporadic MMRd, while only a small subset remained unresolved. Although this distinction did not carry prognostic relevance, identification of definitive sporadic causes may release patients and relatives from burdensome LS-surveillance.

2022-RA-815-ESGO ENDOMETRIAL CANCER INCIDENCE IN PATIENTS WITH ATYPICAL ENDOMETRIAL HYPERPLASIA ACCORDING TO MODE OF MANAGEMENT

[1,2]Anas Barakat, [1]Aemn Ismail, [1,2]Supratik Chattopadhyay, [1]Quentin Davies. *[1]Gynaecology Oncology Department, University Hospitals of Leicester NHS Trust, LEICESTER, UK; [2]Leicester Cancer Research Centre, University of Leicester, Leicester, UK*

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Introduction/Background It is well established that around one-third of patients with atypical Endometrial hyperplasia (AEH) develop endometrial cancer (EC). The aim of the study is to determine the incidence of EC in AEH patients in UHL and to explore the reasons why AEH patients opted for conservative management.

Methodology A retrospective cohort study including 119 patients recruited from the University Hospitals of Leicester from 01/01/2015 to 01/01/2020 with a diagnosis of AEH by pipelle or endometrial biopsy. Patients were divided into two groups according to the management modality: primary surgery (n=99) and conservative treatment (n=20).

Results EC was diagnosed in 34.4% of patients with AEH managed by primary surgery. Moreover, the incidence of EC in patients with AEH managed conservatively is 25%. The main reason for opting for conservative management was that patients were unfit for surgery when assessed in the high-risk Anaesthetic Clinic (35%).

Conclusion Total hysterectomy is the safest first line of treatment in AEH due to the high risk of concurrent EC and progression to EC. Currently, there is no reliable follow up intervention to distinguish between concurrent EC and progression of AEH. Adequate discussion and counselling are essential when discussing conservative management for women with atypical complex endometrial hyperplasia. Moreover, counselling patients regarding high risk of developing concurrent endometrial cancer and/or progression to endometrial cancer should be done.

2022-RA-825-ESGO THE IMPACT OF AGE ON PROGNOSIS IN WOMEN WITH ENDOMETRIAL CANCER: A POOLED ANALYSIS OF THE PORTEC-1, -2 AND -3 RANDOMISED TRIALS

[1]Famke Charlotte Wakkerman, [1]Stephanie M De Boer, [2]Melanie E Powell, [3]Alexandra Leary, [4]Anthony Fyles, [5]Linda R Mileshkin, [6]Naveena Singh, [7]Remi A Nout, [8]Ina M Jürgenliemk-Schulz, [9]Jan J Jobsen, [10]Ludy CHW Lutgens, [11]Elsbieta M van der Steen-Banasik, [7]Jan-Willem M Mens, [12]Annerie Slot, [13]Hans W Nijman, [14]Vincent THBM Smit, [14]Tjalling Bosse, [1]Carien L Creutzberg, [1]Nanda Horeweg. *[1]Department of Radiation Oncology, Leiden University Medical Center, Leiden, Netherlands; [2]Department of Clinical Oncology, Barts Health NHS Trust, London, UK; [3]Department of Medical Oncology, Gustave Roussy, Villejuif, France; [4]Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada; [5]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia; [6]Department of Pathology, Barts Health NHS Trust, London, UK; [7]Department of Radiotherapy, Erasmus MC Cancer Institute, Rotterdam, Netherlands; [8]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, Netherlands; [9]Department of Radiotherapy, Medisch Spectrum Twente, Enschede, Netherlands; [10]Maastricht Radiation Oncology Clinic, Maastricht, Netherlands; [11]Radiotherapiegroep, Arnhem, Netherlands; [12]Radiotherapeutic Institute Friesland, Leeuwarden, Netherlands; [13]Department of Gynaecologic Oncology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [14]Department of Pathology, Leiden University Medical Center, Leiden, Netherlands*

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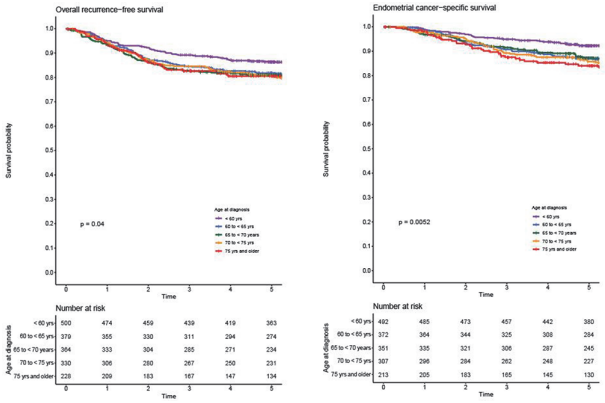
Introduction/Background Numerous studies showed that elderly women with endometrial cancer (EC) have a higher risk of recurrence and cancer-related death. It is unclear whether ageing is a risk factor by itself, or whether other risk factors become increasingly common at older age. We addressed to this using the large PORTEC collection of molecularly classified EC with long-term follow-up data.

Methodology Data of 1801 women participating in the randomised PORTEC trials were pooled and analysed. PORTEC-1 included 714 women with intermediate-risk EC, PORTEC-2 427 with high-intermediate risk EC, and PORTEC-3 660 with high-risk EC. Overall recurrence-free and EC-specific survival were estimated using Kaplan-Meier's method. Prognostic value of age (continuous) was determined by multivariable Cox regression analyses with correction for all significant risk factors identified by univariable analyses.



Abstract 2022-RA-825-ESGO Figure 1 Clinical outcomes by age of women with endimetrial cancer participanting in the PORTEC-1, -2 and -3 trial

Abstract 2022-RA-825-ESGO Table 1 The relation of age with clinicopathological and molecular variable of EC

Age groups	<60	60-<65	65-<70	70-<75	≥75	All	p-value
	n = 500 (%)	n = 379 (%)	n = 364 (%)	n = 330 (%)	n = 228 (%)	n = 1801 (%)	
Received adjuvant therapy							**< 0.0001[b]**
None	107 (21.4)	71 (18.7)	69 (19.0)	81 (24.5)	44 (19.3)	372 (20.7)	
External beam RT	250 (50.0)	173 (45.6)	194 (53.3)	158 (47.9)	112 (49.1)	887 (49.3)	
Chemoradiation	127 (25.4)	87 (23.0)	55 (15.1)	42 (12.7)	16 (7.0)	327 (18.2)	
Brachytherapy	16 (3.2)	48 (12.7)	46 (12.6)	49 (14.8)	56 (24.6)	215 (11.9)	
Stage							**< 0.0001[b]**
I	303 (60.6)	266 (70.2)	286 (78.6)	274 (83.0)	202 (88.6)	1331 (73.9)	
II	70 (14.0)	40 (10.6)	34 (9.3)	21 (6.4)	7 (3.1)	172 (9.6)	
III	127 (25.4)	73 (19.3)	44 (12.1)	35 (10.6)	19 (8.3)	298 (16.5)	
Histograde							**< 0.0001[b]**
Endometrioid gr 1-2	318 (63.6)	265 (69.9)	237 (65.1)	237 (71.8)	175 (76.8)	1232 (68.4)	
Endometrioid gr 3	113 (22.6)	62 (16.4)	72 (19.8)	45 (13.6)	29 (12.7)	321 (17.8)	
Serous	30 (6.0)	27 (7.1)	25 (6.9)	30 (9.1)	13 (5.7)	125 (6.9)	
Clear cell	24 (4.8)	15 (4.0)	12 (3.3)	10 (3.0)	5 (2.2)	66 (3.7)	
Other	15 (3.0)	10 (2.6)	18 (4.9)	8 (4.9)	6 (2.6)	57 (3.2)	
Myometrial invasion[1]							**< 0.0001[a]**
< 50%	231 (46.4)	127 (33.6)	106 (29.1)	90 (27.3)	50 (21.9)	604 (33.6)	
≥ 50%	267 (53.6)	251 (66.4)	258 (70.9)	240 (72.7)	178 (78.1)	1194 (66.4)	
Lymphovascular space invasion[2]							**< 0.0001[a]**
Absent	288 (64.6)	243 (70.6)	239 (73.3)	242 (80.7)	169 (84.5)	1181 (73.1)	
Present	158 (35.4)	101 (29.4)	87 (26.7)	58 (19.3)	31 (15.5)	435 (26.9)	
Molecular class[3]							**< 0.0001[b]**
POLE mut	62 (18.2)	21 (7.8)	11 (4.1)	17 (7.2)	5 (2.7)	116 (9.0)	
MMRd	108 (31.8)	82 (30.6)	75 (28.1)	59 (25.1)	61 (33.5)	385 (29.8)	
p53abn	26 (7.6)	43 (16.0)	41 (15.4)	39 (16.6)	30 (16.5)	179 (13.9)	
NSMP	144 (42.4)	122 (45.5)	140 (52.4)	120 (51.1)	86 (47.3)	612 (47.7)	
5-year RFS (SE)	86.5 (1.5)	81.8 (2.0)	81.0 (2.1)	80.6 (2.2)	80.5 (2.7)	82.6 (0.9)	**0.040[c]**
Mean RFS (95%CI)	15.0 (14.5-15.5)	13.8 (13.2-14.5)	13.9 (13.2-14.5)	13.6 (12.9-14.4)	12.5 (11.2-13.7)	14.2 (13.9-14.5)	
5-year CCS	92.3 (1.2)	87.3 (1.7)	87.1 (1.8)	85.7 (2.0)	84.1 (2.6)	88.0 (0.8)	**0.005[c]**
Mean CCS (95%CI)	15.8 (15.4-16.2)	14.8 (14.3-15.3)	15.1 (14.5-15.6)	15.7 (15.0-16.4)	13.1 (12.0-14.3)	16.2 (15.9-16.5)	

Definition of abbreviations: RT = radiotherapy, *POLE* mut = DNA polymerase-episilon mutated, MMRd = mismatch-repair deficient, p53abn = p53 abnormal, NSMP = no-specific molecular profile, RFS = overall recurrence-free survival. CSS = endometrial cancer specific survival.
Significance of the relation of age as a contious variable across groups was tested using the a) Mann-Whitney U test, b) Kruskal-Wallis test
Survival across 5 age categories was estimated accoding to Kaplan-Meier's method and tested using the c) log-rank test
1) 3 missing, 2) 185 missing, 3) 509 missing.

Results Median follow-up was 12.3 years for PORTEC-1, 10.5 years for PORTEC-2 and 6.1 years for PORTEC-3. Overall recurrence-free and EC-specific survival significantly decreased with age (figure 1). The relation of age with clinicopathological and molecular variables of EC is shown in table 1. Women ≥60 years had significantly less often *POLE*mut (5.7% vs. 18.2%) and more often p53abn EC (16.1% vs. 7.6%, p<0.0001). In multivariable analysis, age was an independent risk factor for overall recurrence with a hazard ratio (HR) of 1.03 per year (95%CI 1.02–1.05; p<0.0001), corrected for stage, histotype and grade, myometrial invasion, lymphovascular space invasion (LVSI), molecular class and received adjuvant treatment. Likewise, age had independent prognostic value for EC-specific survival with an HR of 1.05 per year (95%CI 1.02–1.07; p<0.0001), corrected for stage, histotype and grade, LVSI and molecular class.

Conclusion The molecular profile of elderly women was less favourable. The risk of recurrence and EC-related death continuously increases with age, especially from 60 years onwards. Our study showed that age is a significant and independent prognostic risk factor.