27 THERAPEUTIC ROLE OF PELVIC AND PARA-AORTIC LYMPHADENECTOMY IN APPARENT EARLY STAGE EPITHELIAL OVARIAN CANCER

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Introduction The therapeutic role of pelvic and para-aortic lymphadenectomy in surgical staging of apparent early-stage epithelial ovarian cancer (aeEOC) is still unclear. Recently, ESGO-ESMO consensus established that re-staging lymphadenectomy is not recommended if patients are already due to receive adjuvant chemotherapy for high-risk eEOC. The aim

of this study was to evaluate the potential therapeutic role of systematic lymphadenectomy in patients with eEOC.

Methods Multi-center retrospective cohort study with CE approval, comparing women with aeEOC who underwent no lymphadenectomy (NL) versus lymph node sampling (SL) versus adequate systematic bilateral pelvic and para-aortic lymphadenectomy (AL) (defined as ≥ 20 lymph-nodes).

Inclusion criteria epithelial ovarian carcinoma; no bulky (≥ 10 mm short axis) pelvic or para-aortic lymph nodes at CT-scan; complete intra-peritoneal staging and at least 3 cycles of platinum-based adjuvant chemotherapy.

Results 639 of 2,559 patients with FIGO stage IA-IIIa1 ovarian cancer, met inclusion criteria. 360 (56.3%) underwent AL, 150 (23.5%) SL and 129 (20.2%) NL (table 1). AL patients were younger ($p < 0.001$), experienced a higher number of grade 3–5 post-operative complications ($p = 0.008$) and had a longer time to start chemotherapy ($p = 0.034$). There was no difference in intra-operative complications. Median follow-up was 63 months (range, 5–342). The 5-year disease-free survival (DFS) was 79.7% vs. 76.5% vs. 68.3% ($p = 0.006$) (figure 1), and 5-year overall survival (OS) was 92.3% vs. 94.5% vs. 89.8% ($p = 0.165$) (figure 2) in women who received AL vs. SL vs. NL, respectively. Lymphadenectomy represented independent factor for DFS improvement, HR 0.52 (95%CI 0.37–0.73) ($p < 0.001$).

Abstract 27 Table 1 Patients' and surgery characteristics

Characteristic	All cases n = 639	Adequate lymphadenectomy (≥ 20 LN) n = 360	Lymph node sampling (1-19 LN) n = 150	No lymphadenectomy n = 129	p value
Mean age, years (± SD)	56 (± 11.3)	54 (± 10.6)	56 (± 11.3)	60 (± 12.1)	< 0.001
Histology*					0.106
Serous	312 (48.8%)	172 (47.8%)	80 (53.3%)	60 (46.5%)	
Endomet	164 (25.7%)	100 (27.8%)	34 (22.7%)	30 (23.3%)	
Clear	105 (16.4%)	58 (16.1%)	28 (18.7%)	19 (14.7%)	
cell	16 (2.5%)	7 (1.9%)	2 (1.3%)	7 (5.4%)	
Indiffer	10 (1.6%)	7 (1.9%)	1 (0.7%)	2 (1.6%)	
nated	25 (3.9%)	13 (3.6%)	5 (3.3%)	7 (5.4%)	
Mixed	4 (0.6%)	1 (0.3%)	0 (0%)	3 (2.3%)	
Other					0.025
Grade**					
G1	35 (5.5%)	18 (5%)	3 (2%)	14 (10.9%)	
G2	145 (22.7%)	83 (23.1%)	33 (22%)	29 (22.5%)	
G3	456 (71.4%)	256 (71.1%)	114 (76%)	86 (66.7%)	0.005
FIGO stage					
IA	134 (21.0%)	68 (18.9%)	35 (23.3%)	31 (24.1%)	
IB	25 (3.9%)	16 (4.4%)	5 (3.3%)	4 (3.1%)	
IC1	137 (21.4%)	71 (19.7%)	37 (24.7%)	29 (22.5%)	
IC2	58 (9.1%)	34 (9.4%)	15 (10%)	9 (7.0%)	
IC3	43 (6.7%)	25 (7.0%)	7 (4.7%)	11 (8.6%)	
IIA	64 (10.0%)	36 (10%)	18 (12%)	10 (7.6%)	
IIB	120 (18.8%)	64 (17.8%)	21 (14%)	35 (27.1%)	
IIIA1	58 (9.1%)	46 (12.8%)	12 (8%)	0 (0%)	
Total number of lymph nodes removed, median (range)	32 (1-149)	48 (20-149)	11 (1-19)	-	< 0.001
Median number of pelvic lymph nodes removed, (range)	18 (0-85)	28 (0-85)	5 (0-19)	-	< 0.001
Median number of para-aortic lymph nodes removed, (range)	14 (0-82)	20.5 (0-82)	4 (0-19)	-	< 0.001
Number of surgeries***					0.008
One	426 (66.7%)	229 (63.6%)	101 (67.3%)	96 (74.4%)	
Two	200 (31.3%)	128 (35.6%)	47 (31.3%)	25 (19.4%)	
Surgical approach at time of lymphadenecto my					< 0.001
Laparot	368 (57.6%)	292 (81.1%)	76 (50.7%)	-	
Minimal	142 (22.2%)	68 (18.9%)	74 (49.3%)	-	
lyminisive					
Number of patients with intra-operative complications	19 (3.0%)	12 (3.3%)	4 (2.7%)	3 (2.3%)	0.904
Number of patients with G3-5 early post-operative complications	27 (4.2%)	23 (6.4%)	2 (1.3%)	2 (1.6%)	0.008
Median time to start chemotherapy, days (range)*	36 (8-169)	36 (8-169)	39 (10-160)	33 (8-97)	0.034
Chemotherapy regimen					0.145
Carbopl	237 (37.1%)	135 (37.5%)	47 (31.3%)	55 (42.6%)	
atin					
Carbopl	402 (62.9%)	225 (62.5%)	103 (68.7%)	74 (57.4%)	
atin/Paclitaxel					

* 3 pts (0.5%) missing; ** 3 pts (0.4%) missing; *** 13 pts (2.0%) missing; * re-staging pts excluded and 44 pts missing. LN: lymph nodes; SD: standard deviation; FIGO: International Federation of Gynecology and Obstetrics; LPT: laparotomy; G: grade

At risk							
No lymph nodes removed	129	69	26	13	10	5	3
1-19 lymph nodes removed	150	78	23	11	6	4	0
≥ 20 lymph nodes removed	360	213	74	32	6	1	1

Abstract 27 Figure 1 Disease-free survival in patients undergoing adequate vs sampling vs no lymphadenectomy

At risk							
No lymph nodes removed	129	89	35	17	12	6	4
1-19 lymph nodes removed	150	104	28	13	7	4	0
≥ 20 lymph nodes removed	360	244	84	33	7	1	1

Abstract 27 Figure 2 Overall survival in patients undergoing adequate vs sampling vs no lymphadenectomy

Conclusion Pelvic and para-aortic lymphadenectomy in surgical staging of eEOC improves DFS for the price of increasing post-operative complications and time to chemotherapy but does not affect OS.

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28 PREVALENCE AND PROGNOSIS OF LYNCH SYNDROME AND SPORADIC MISMATCH REPAIR DEFICIENCY IN THE COMBINED PORTEC-1,-2 AND -3 ENDOMETRIAL CANCER TRIALS

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Introduction Here we aimed to evaluate the prevalence and prognosis of Lynch Syndrome (LS)-associated endometrial cancer (EC) in relation to sporadic mismatch repair deficient EC (MMRd-EC) in the combined PORTEC-1,-2 and 3 trials comprising 1336 ECs.

Methods MMR-status was determined by MMR-immunohistochemistry (MLH1/PMS2/MSH6/MSH2). MMRd-ECs with detected promoter hypermethylation of MLH1 were classified as sporadic (methylated MMRd-EC). For unmethylated MMRd-EC cases tumor and normal tissue next-generation sequencing was performed. ECs with MMR germline mutations were classified as LS-associated (LS MMRd-EC). Unmethylated MMRd-ECs without MMR germline mutations were classified as MMRd-EC due to other causes (other MMRd-EC). Overall and recurrence-free survival were estimated and compared using Kaplan-Meier method and pairwise log-rank test.

Results Among the 1336 ECs, 926 were MMR proficient. Of the 410 MMRd-EC, 376 could be fully triaged; 281 (75%)

were methylated MMRd-ECs; 37 (10%) LS MMRd-ECs, and 58 (15%) other MMRd-ECs. The overall LS prevalence was 2.8%. Overall 5-year survival for LS MMRd-EC was 89% (95%CI 79–100%; $p=0.055$), other MMRd-EC 96% (92–100%; $p=0.001$), both compared to methylated MMRd-EC 79% (74–84%); 5-year recurrence-free survival was 92% (84–100%; $p=0.123$), 95% (89–100%; $p=0.002$), compared to 79% (74–84%), respectively.

Conclusion The prevalence of LS in the PORTEC EC trial population was 3% and within the MMRd group 10%. LS MMRd-EC seems to have a better overall and recurrence-free survival than sporadic MMRd-EC caused by hypermethylation. Further research into the underlying causes of non-hypermethylated somatic MMRd-EC is ongoing.

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29 COMPREHENSIVE MOLECULAR ASSESSMENT OF MISMATCH REPAIR DEFICIENCY IN LYNCH-ASSOCIATED OVARIAN CANCERS USING NEXT-GENERATION SEQUENCING (NGS) PANEL

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Objectives Abnormalities in mismatch repair (MMR) gene may be the result of pathogenic germline (Lynch syndrome) and somatic mutations as well as epigenetic events. We aimed to examine the cause of MMR defects (MMRd) in non-serous/non-mucinous ovarian cancer (OC) through targeted mutational sequencing.

Methods Women with non-serous/mucinous OC (N = 215) were prospectively recruited from three cancer centers in Ontario, Canada. Tumors were assessed for MMR protein expression by immunohistochemistry. Matched MMRd tumor-normal samples were run on a custom NGS panel to identify germline and somatic mutations, copy number variants, rearrangements and promoter methylation in MMR and associated genes.

Results Of 215 women enrolled in our study, 185 (86%) had OC and 30 (14%) had synchronous OC and endometrial cancer. Twenty-eight (13%) cases were MMRd, 11 of which were synchronous. Using the NGS panel, Lynch syndrome (LS) was detected in 39% of MMRd cases (11/28; 7 OC and 4 synchronous): 7 MSH6, 2 MLH1, 1 PMS2, and 1 MSH2. An explanation for the observed MMR phenotype was available for 18/20 deficient cases, including 9/10 MLH1/PMS2- (7 somatic methylation, 1 bi-allelic somatic deletion, 1 germline mutation), 0/1 PMS2-, 6/7 MSH6- (6 germline mutations) and 2/2 MSH2/MSH6- (1 germline mutation, 1 bi-allelic somatic mutation). Concordance between clinical and research panel sequencing results was 90%.

Conclusions Use of our custom NGS panel allows for the streamlined assessment of hereditary and somatic causes of MMR deficiency in OC and may be an attractive screening strategy for LS in this population.

Abstract 28 Figure 1 Kaplan-Meier survival curves for recurrence-free survival in the fully triaged MMRd patients