Supplementary Online Content

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Demographic and clinical characteristics of the study population and associated tumors according to patient group.

Characteristic	HPV Positive HGD/EAC patients (n=37, 26.1%)	HPV Negative HGD/EAC patients (n=105, 73.9%)	P-value [a]
Sex (M/F)	33 (89.2%) 4 (10.80%)	93 (88.6%) 12 (11.4%)	0.92
Age, mean (SD) in years Range	65.2 (SD +/- 12.4) Min=33.0, Max=89.0	66.2 (SD +/- 12.0) Min=32.0, Max=90.0	0.65
BMI, mean (SD)	27.7 (SD+/-5.7)	27.0 (SD+/-5.1)	0.53
Ever smoked	24/37 (64.9%)	77/105 (73.3%)	0.33
>10 pack years[b]	22/24 (91.7%)	69/76 (90.8%)	0.90
>20 pack years[b]	15/24 (62.5%)	48/76 (63.2%)	0.95
Alcohol intake	26/36 (72.2%)	75/105 (71.4%)	0.93
Excess Alcohol[c]	8/35 (22.9%)	18/105 (17.1%)	0.45
Low pRb	18/37 (48.7%)	35/105 (33.3%)	0.10
Low CD1	22/37 (59.5%)	54/105 (51.4%)	0.40
Ki-67 positive	31/37 (83.8%)	79/105 (75.2%)	0.28

High MCM2	15/37 (40.5%)	70/105 (66.7%)	0.005

[a] Differences between HPV positive versus HPV negative cases regarding baseline characteristics were assessed using two-sample t-test for all numerical data and chi-square analysis for binary measurements.

[b] A pack-year=smoking one packet of cigarettes per day for a year.

[c] Excess alcohol intake=for men >21 units per week, for women >14 units per week.

Abbreviations: BMI; body mass index, CD1; cyclin D1, EAC; esophageal adenocarcinoma, EMR; endoscopic mucosal resection, HGD; high-grade dysplasia, HPV; human papillomavirus, MCM; minichromosome maintenance protein, PPI; proton-pump inhibitors, pRb; retinoblastoma protein, NSAID's; non-steroidal anti-inflammatory drugs, RFA; radiofrequency ablation, SD; standard deviation

eFigure 1. Flow diagram showing HPV DNA and biomarker status of enrolled study patients.
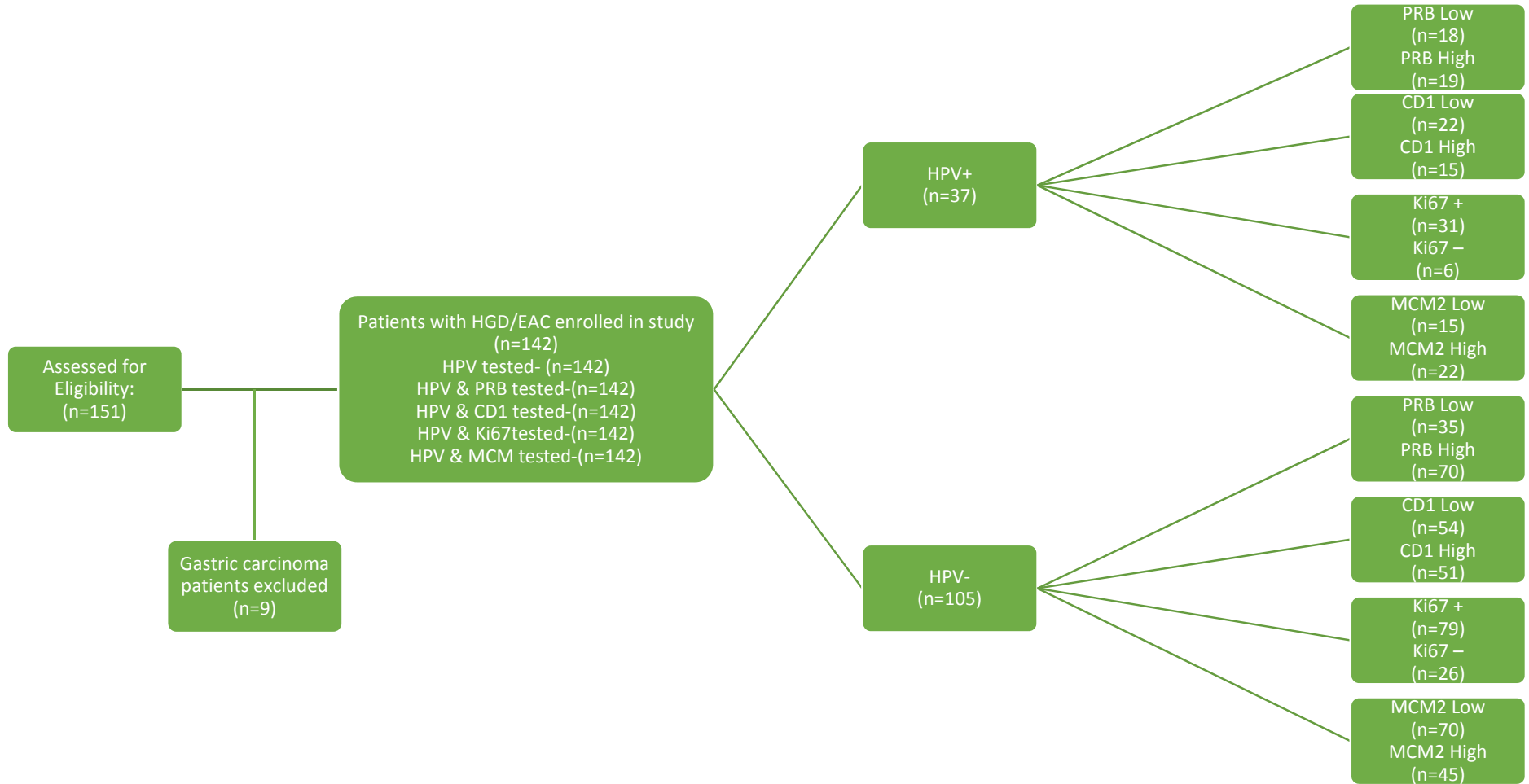
eFigure 2. Positive nuclear staining patterns for A) pRb, B) Cyclin D1, C) MCM2, D) Ki-67. Magnification X 20
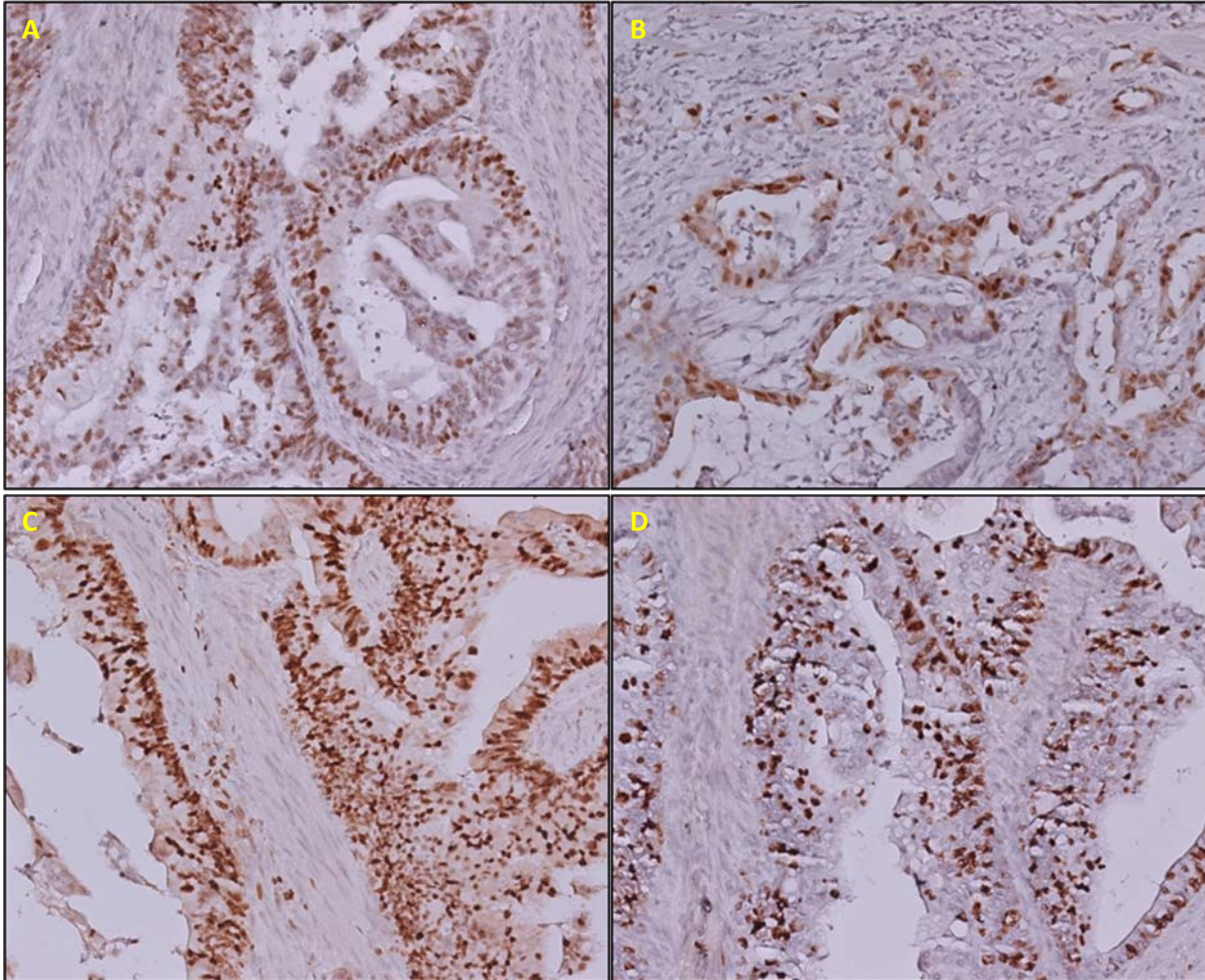
eTable 2. Comparison of Survival, Disease Relapse, Progression and Site of Failure in low pRb or high pRb expression patients stratified by HPV status.

	HPV + No. (%CI)		HPV- No. (%CI)		
	Low pRb (4)	High pRb (3)	Low pRb (2)	High pRb (1)	p-value
Disease-free survival, mean (SD), mo	41.2 (31.2)	39.5 (37.0)	25.5 (27.6)	23.4 (24.6)	0.03
Overall survival, mean (SD), mo	42.9 (30.5)	44.5 (35.8)	30.2 (25.9)	29.6 (25.2)	0.08
Survival status (alive at last follow-up)	12(66.7)	14 (73.7)	16 (45.7)	42 (60.0)	0.19
Recurrence or progression	4 (22.2)	5 (26.3)	20 (57.1)	41 (58.6)	0.006
Recurrence	2 (11.1)	4 (21.1)	13 (37.1)	33 (47.1)	0.02
Local-regional failure	1 (5.6)	5 (26.3)	7 (20.0)	25 (35.7)	0.05
Distant metastases	3 (16.7)	0 (0)	13 (37.1)	16 (22.9)	0.02
Death due to OAC	2 (11.1)	3 (15.8)	15 (42.9)	23 (32.9)	0.049

Abbreviations: EAC; esophageal adenocarcinoma, HPV; human papillomavirus, mo; months N/A; not applicable, pRb; retinoblastoma protein, SD; standard deviation.

eTable 3. Comparison of Survival, Disease Relapse, Progression and Site of Failure in low CD1 or high CD1 expression patients stratified by HPV status

	HPV + No. (%CI)		HPV- No. (%CI)		
	Low CD1 (4)	High CD1 (3)	Low CD1 (2)	High CD1 (1)	p-value
Disease-free survival, mean (SD), mo	38.9 (33.2)	42.5 (35.7)	26.3 (24.0)	21.7 (27.0)	0.02
Overall survival, mean, mo	43.1 (33.1)	44.6 (33.6)	32.3 (22.2)	27.1 (28.2)	0.05
Survival status (alive at last follow-up)	16 (72.7)	10 (66.7)	35 (64.8)	23 (45.1)	0.07
Recurrence or progression	4 (18.2)	5 (33.3)	31 (57.4)	30 (58.8)	0.004
Recurrence	2 (9.1)	4 (26.7)	21 (38.9)	25 (49.0)	0.01
Local-regional failure	2 (9.1)	4 (26.7)	19 (35.2)	13 (25.5)	0.14
Distant metastases	2 (9.1)	1 (6.7)	12 (22.2)	17 (33.3)	0.049
Death due to OAC	2 (9.1)	3 (20.0)	16 (29.6)	22 (43.1)	0.024

Abbreviations: EAC; esophageal adenocarcinoma, HPV; human papillomavirus, mo; months N/A; not applicable, CD1; Cyclin D1, SD; standard deviation

eTable 4. Comparison of Survival, Disease Relapse, Progression and Site of Failure in low MCM2 or high MCM2 expression patients stratified by HPV status

	HPV + No. (%CI)		HPV- No. (%CI)		
	Low MCM2 (4)	High MCM2 (3)	Low MCM2 (2)	High MCM2 (1)	p-value
Disease-free survival, mean (SD), mo	42.5 (35.7)	38.9 (33.2)	25.3 (23.6)	23.5 (26.5)	0.03
Overall survival, mean, mo	44.6 (33.6)	43.1 (33.1)	32.8 (24.0)	28.3 (26.0)	0.06
Survival status (alive at last follow-up)	10 (66.7)	16 (72.7)	22 (62.9)	36 (51.4)	0.27
Recurrence or progression	5 (33.3)	4 (18.2)	18 (51.4)	43 (61.4)	0.003
Recurrence	4 (26.7)	2 (9.1)	12 (34.3)	34 (48.6)	0.007
Local-regional failure	4 (26.7)	2 (9.1)	10 (28.6)	22 (31.4)	0.23
Distant metastases	1 (6.7)	2 (9.1)	8 (22.9)	21 (30.0)	0.08
Death due to OAC	3 (2.5)	2 (9.1)	10 (28.6)	28 (40.0)	0.035

Abbreviations: EAC; esophageal adenocarcinoma, HPV; human papillomavirus, mo; months N/A; not applicable, MCM; Minichromosomal maintenance protein SD; standard deviation.

eTable 5. Comparison of Survival, Disease Relapse, Progression and Site of Failure in Ki-67 positive or negative patients stratified by HPV status

	HPV + No. (%CI)		HPV- No. (%CI)		
	Ki67 + (4)	Ki67 – (3)	Ki67 + (2)	Ki67 – (1)	p-value
Disease-free survival, mean (SD), mo	37.6 (34.7)	53.2 (27.6)	25.9 (27.0)	18.8 (19.7)	0.009
Overall survival, mean, mo	41.6 (33.6)	54.8 (28.9)	31.1 (26.9)	25.8 (19.3)	0.03
Survival status (alive at last follow-up)	22 (71.0)	4 (66.7)	44 (55.7)	14 (53.9)	0.45
Recurrence or progression	9 (29.0)	0 (N/A)	42 (53.2)	19 (73.1)	0.001
Recurrence	6 (19.4)	0 (N/A)	32 (40.5)	14 (53.9)	0.01
Local-regional failure	6 (19.4)	0 (N/A)	19 (24.1)	13 (50.0)	0.01
Distant metastases	3 (9.7)	0 (N/A)	23 (29.1)	6 (23.1)	0.08
Death due to OAC	5 (16.1)	0 (N/A)	27 (34.2)	11 (42.3)	0.048

Abbreviations: EAC; esophageal adenocarcinoma, HPV; human papillomavirus, mo; months N/A; not applicable, SD; standard deviation.