Clinical Outcomes of HPV-associated and Unassociated Endocervical Adenocarcinomas Categorized by the International Endocervical Adenocarcinoma Criteria and Classification (IECC)

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汇报人：刘坦坦

1.3 腺癌和前驱病变

原位腺癌 8140/2

腺癌 8140/3

子宫颈管腺癌，普通型 8140/3

黏液性癌，非特殊型（NOS） 8480/3

胃型 8482/3

肠型 8144/3

印戒细胞型 8490/3

绒毛状腺癌 8263/3

子宫内膜样腺癌 8380/3

透明细胞癌 8310/3

浆液性癌 8441/3

中肾管癌 9110/3

混合性腺癌-神经内分泌癌 8574/3

2014版，女性生殖器官肿瘤分类

International Endocervical Adenocarcinoma Criteria and Classification (IECC): A new pathogenetic classification for invasive adenocarcinomas of the endocervix

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- IECC: International Endocervical Adenocarcinoma (ECAs) Criteria and Classifi cation.
- Morphological features (luminal mitoses and apoptosis) linked to etiology (i.e. HPV infection): HPV-associated (HPVA) and HPV-unassociated (NHPVA) adenocarcinomas.
- Subclassification:

  HPVA: cytoplasmic features;

  NHPVAs: established criteria.

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HPV-associated adenocarcinoma (HPVA)

1. 普通型宫颈腺癌：<50%细胞胞浆内出现黏液；
2. 黏液腺癌，NOS
3. 肠型黏液腺癌：杯状细胞成分≥50%；
4. 印戒细胞型黏液腺癌：印戒细胞成分≥50%；
5. 浸润性复层产生黏液的癌（iSMILE/iSMC）：复层柱状细胞巢，周边栅栏状排列，含有黏液；
6. 绒毛腺管状腺癌：外生性纤长乳头+普通型细胞形态

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Non-HPV-associated adenocarcinoma (NHPVA)

1. 胃型腺癌
2. 子宫内膜样腺癌
3. 浆液性癌
4. 透明细胞癌
5. 中肾管癌
6. 浸润性腺癌，NOS: WHO/IECC 无法分类

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- Results：

  HPVA: usual-type, 95% HPV-positive;

  NHPVA: Gastric type, 100% HPV-negative.

- Limitation:

  limited clinical data.

Introduction

- In this report, we aim to further explore clinical outcomes in ECAs classifi ed by IECC.

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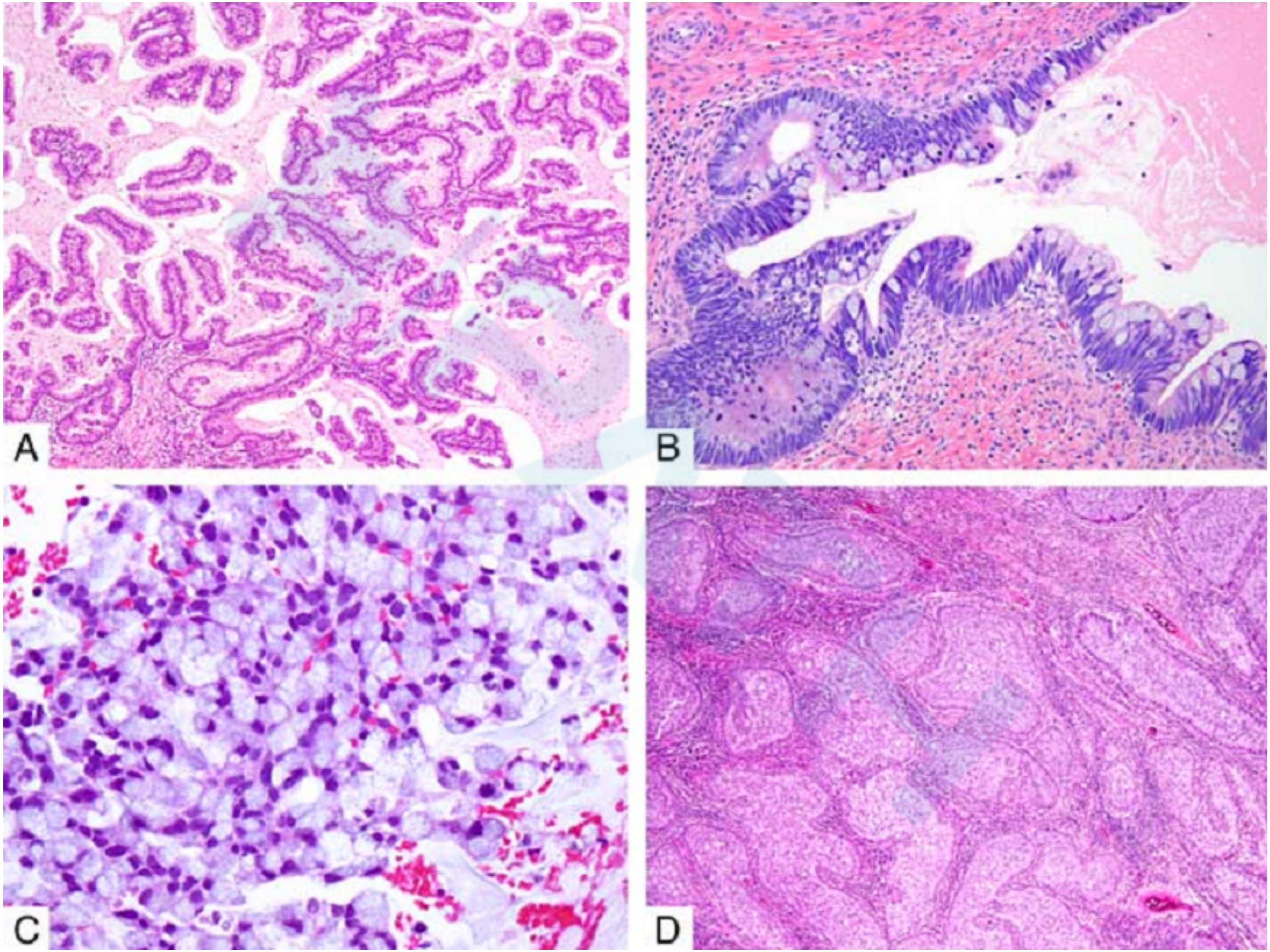
MATERIALS AND METHODS

- 7 institutions around the world: 205/409 invasive ECAs (Excluded: types of tumors; sites; treatment);
- Classifi ed: IECC; Grading: FIGO grading system;
- HPV status: HPV in situ hybridization (RNAscope Probe HPV-HR18);
- Clinical data and follow-up;
- Statistical analysis:

  OS: overall survival; DFS: disease-free survival;

  PFS: progression-free survival.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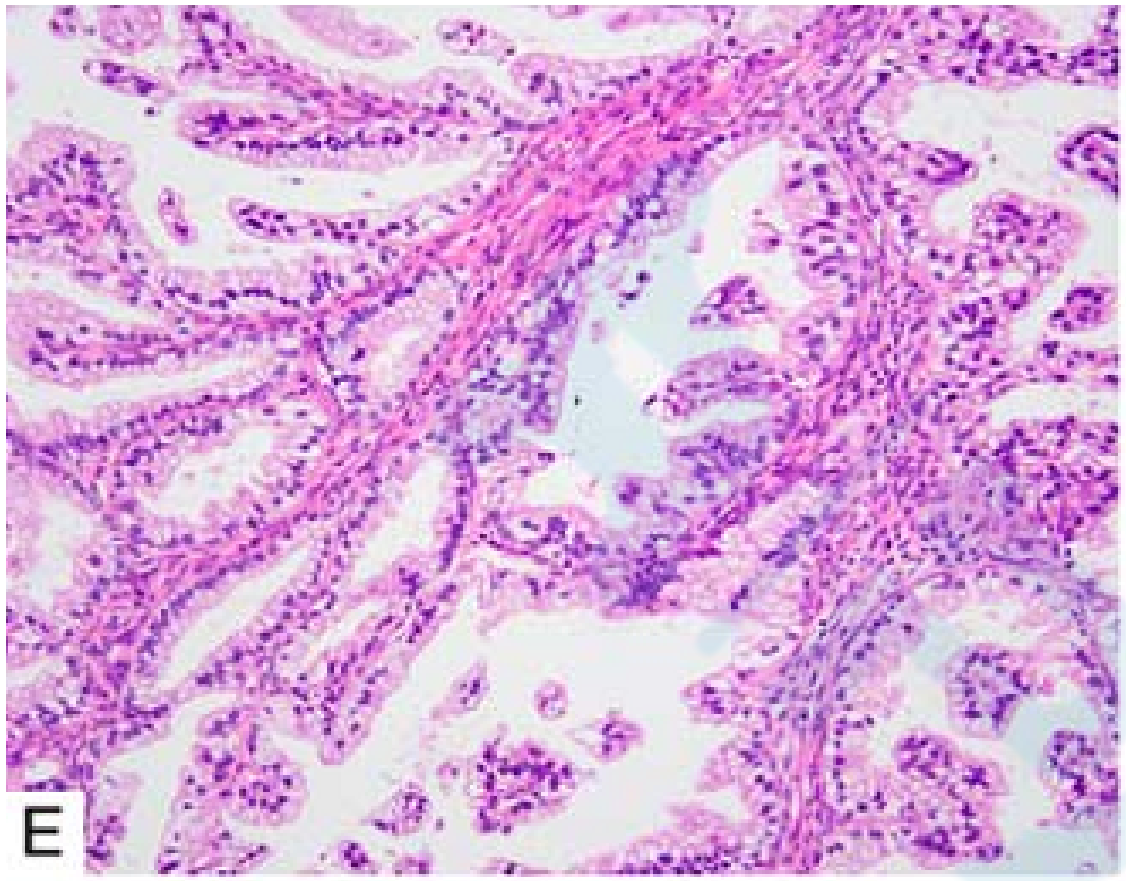
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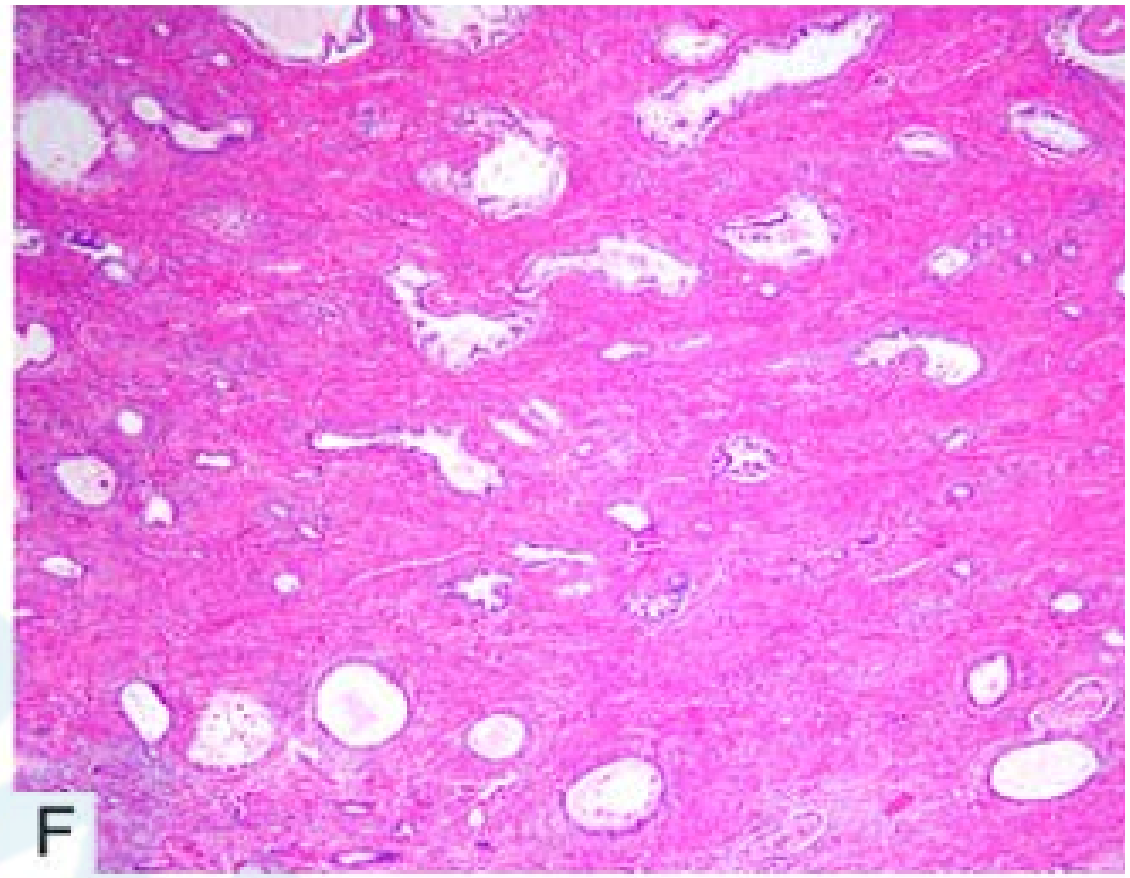
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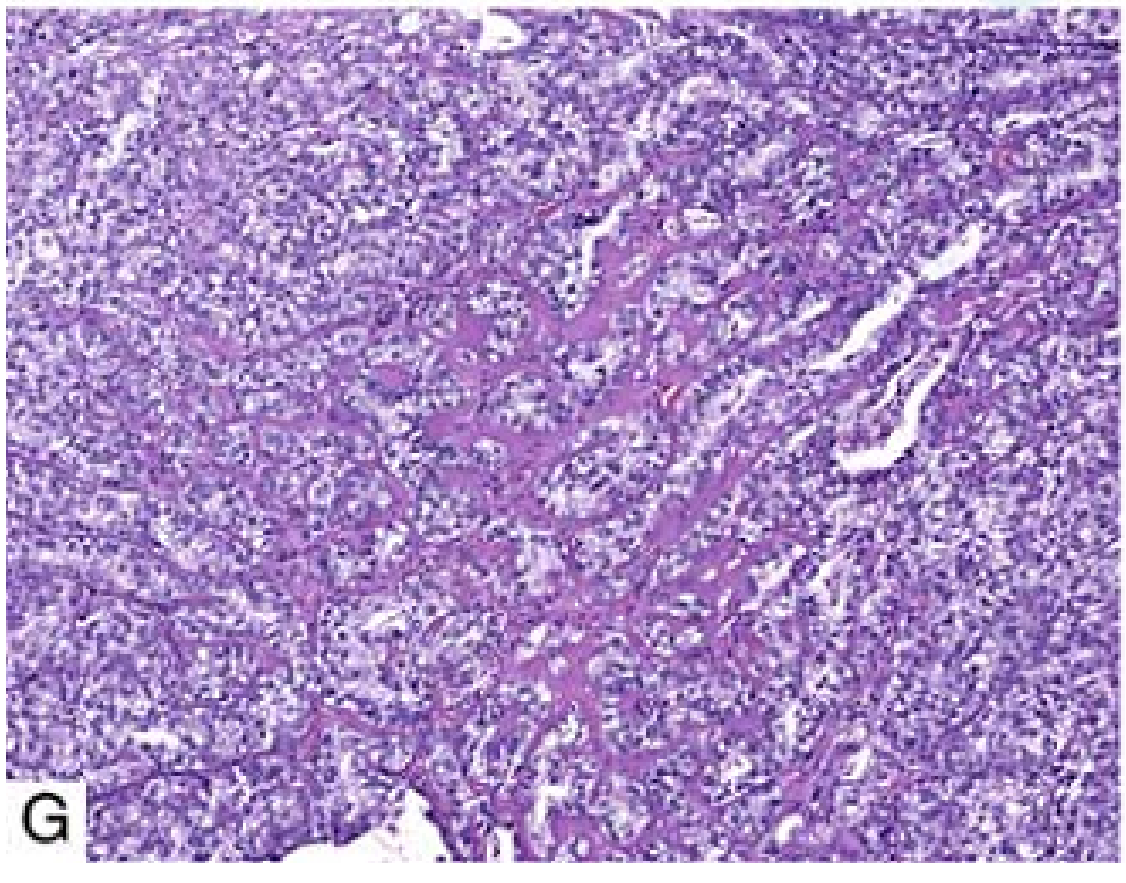
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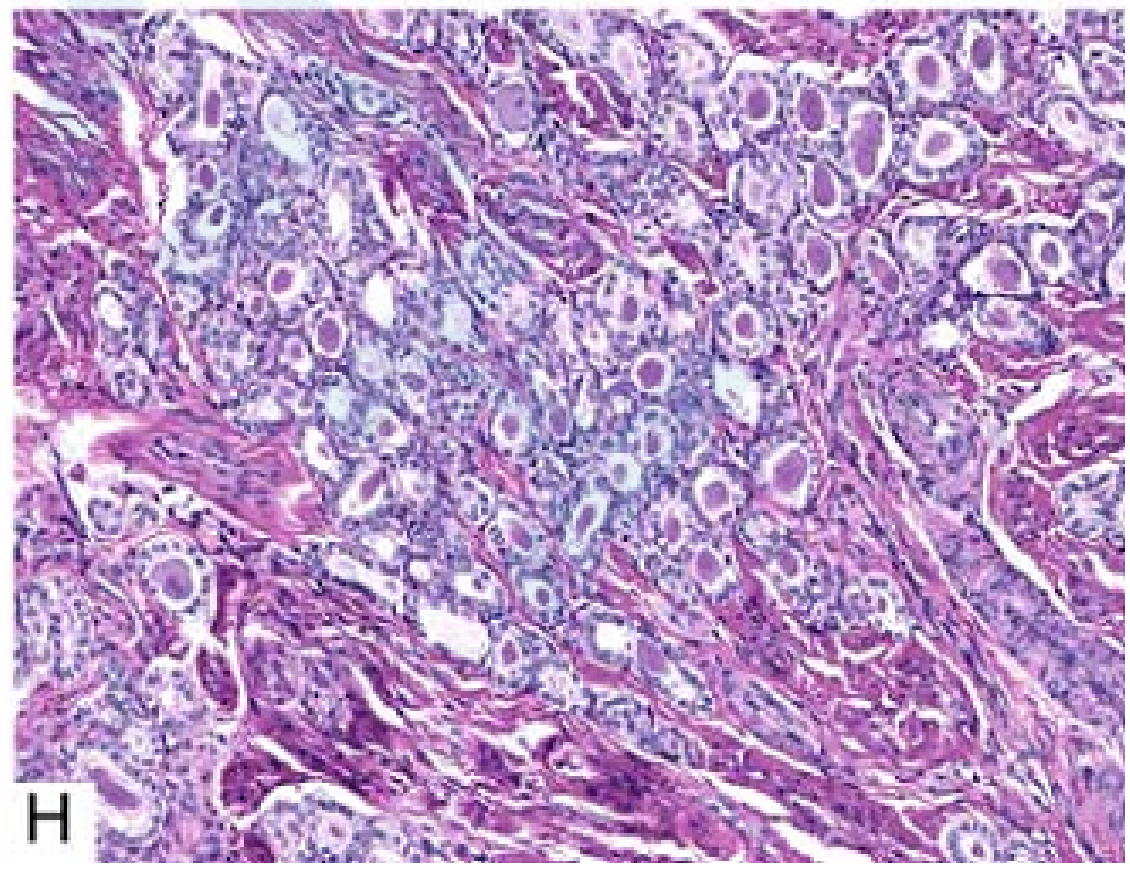
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RESULTS——TABLE 1

Distribution of Cohort: IECC Subtypes, Patient Age, Tumor Size, FIGO Stage, Presence of LVI, LNM, and Local and Distant Recurrences

1. HPVA type: usual-type (71.7%), mucinous HPVAs of various subtypes (mucinous NOS, iSMILE, and intestinal type);
   NHPVA type: gastric-type (11.7%), CCC (3.4%).
2. NHPVA *vs* HPVA: larger, older patients, more frequent LVI, LNM and recurrence;
3. 62.5% gastric type: Stage II or higher;
   83.7% usual-type ECAs: Stage I.

RESULTS——TABLE 2

TABLE 2. Univariate Analysis of OS, DFS, and PFS in the IECC Cohort With Respect to IECC Subtype, Microscopic Grade, Presence of LVI, LNM, Treatment, and Local (Pelvic) and Distant (Extrapelvic) Recurrences

Test	OS	*P*	HR	CI	DFS	*P*	HR	CI	PFS	*P*	HR	CI
HPVA vs. NHPVA	****	<0.0001	0.06	0.017-0.17	****	<0.0001	0.18	0.07-0.41	***	0.0002	0.20	0.08-0.47
HPVA usual vs. HPVA mucinous	NS	0.08	0.18	0.02-1.19	NS	0.28	0.48	0.12-1.82	*	0.04	0.20	0.03-0.98
HPVA mucinous vs. NHPVA gastric	NS	0.10	0.40	0.13-1.19	NS	0.34	0.63	0.2432-1.620	NS	0.67	0.78	0.25-2.41
Grade 3: HPVA vs. NHPVA	****	<0.0001	0.02	0.005-0.16	**	0.0097	0.16	0.03-0.63	NS	0.41	0.52	0.11-2.44
Grade 1 vs. 2 vs. 3: HPVA	NS	0.57			NS	0.59			NS	0.38		
Grade 1 vs. 2 vs. 3: NHPVA	NS	0.22			NS	0.3			NS	0.99		
LVI: HPVA vs. NHPVA	**	0.003	0.21	0.07-0.61	*	0.02	0.42	0.19-0.88	NS	0.06	0.49	0.23-1.04
LNM: HPVA vs. NHPVA	NS	0.26	0.37	0.06-2.04	NS	0.46	0.62	0.16-2.28	NS	0.28	0.56	0.20-1.59
Surgical treatment: HPVA vs. NHPVA	NS	0.73	2.8	0.007-10	**	0.06	0.009	0.0003-0.26	**	0.007	0.01	0.0004-0.30
Surgical + oncologic treatment: HPVA vs. NHPVA	****	<0.0001	0.13	0.04-0.36	***	0.0002	0.18	0.07-0.44	*	0.03	0.41	0.18-0.93
Pelvic recurrence: HPVA vs. NHPVA	***	0.0005	0.05	0.01-0.28	**	0.005	4.58	1.90-11.06	*	0.01	0.21	0.06-0.69
Distant recurrence: HPVA vs. NHPVA	NS	0.09	3.404	0.82-14.08	NS	0.58	1.39	0.43-4.46	NS	0.48	1.03	0.35-3.03

*,**,***Strength of association between variable and outcome.
****Stronger association than*.
NS indicates not significant.

HPVA > NHPVA (ie, survival was superior in the setting of HPVAs), including patients treated with surgery followed by adjuvant therapy; usual-type HPVA > mucinous HPVA; FIGO grade 3 HPVA > NHPVA; HPVA > NHPVA, both with lymphovascular invasion; and HPVA > NHPVA in patients with

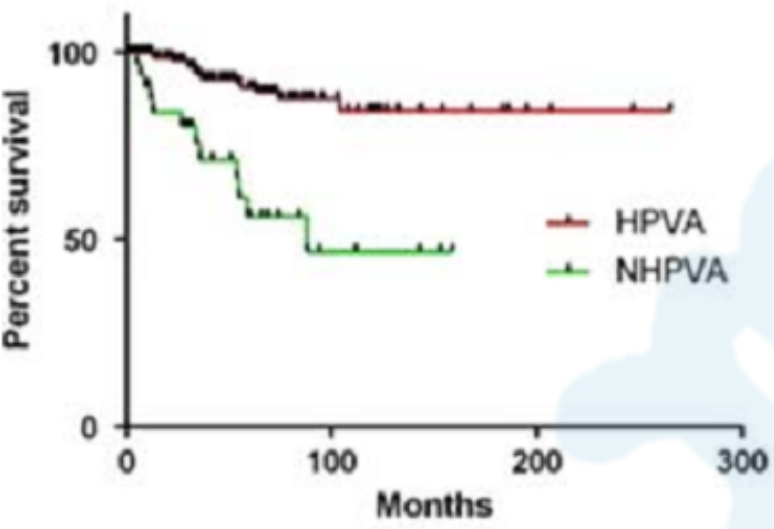
RESULTS——TABLE 3

TABLE 3. Multivariate Analysis of OS, DFS, and PFS in the IECC Cohort With Respect to the Covariates Age, FIGO Stage, Grade, Tumor Size, and Silva Pattern in HPVAs, NHPVAs and the Entire Cohort

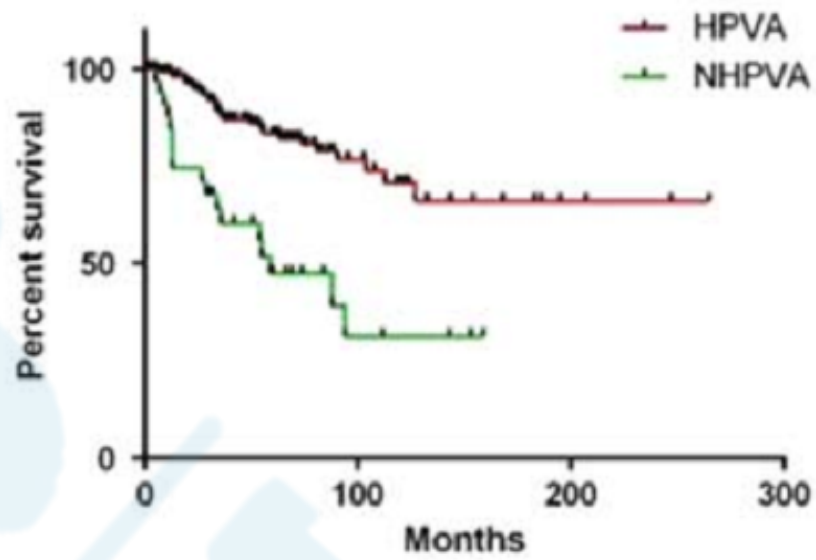
	OS			DFS			PFS		
Covariate	***P***	**HR**	**CI**	***P***	**HR**	**CI**	***P***	**HR**	**CI**
All (HPVA and NHPVA)									
HPV status	0.060	0.14	0.03-0.95	0.064	0.14	0.02-1.02	0.81	1.3	0.14-11
Age (y)	0.95	1	0.96-1.05	0.77	1.01	0.96-1.05	0.97	1	0.96-1.04
Stage (I/II vs. III/IV)	0.056	7.73	1.32-33.8	0.044	8.43	1.47-37.3	0.65	1.45	0.3-7.09
Grade (1 vs. 2 vs. 3)	0.34	3.42, 3.51	0.21-520, 0.27-494	0.39	2.55, 2.98	0.16-393, 0.23-416	0.067	0.37	0.13-1.08
Size	0.10	1.03	0.99-1.07	0.067	1.04	1-1.08	0.48	0.99	0.96-1.02
Silva pattern (A/B vs. C)	0.09	3.5	0.4-458	0.18	2.29	0.24-304	—	—	—
HPVA only									
Age (y)	0.83	1.01	0.96-1.05	0.63	1.02	0.96-1.06	0.96	1	0.96-1.04
Stage (I/II vs. III/IV)	0.072	6.98	1.17-30	0.056	7.48	1.31-32	0.73	1.32	0.27-6.4
Grade (1 vs. 2 vs. 3)	0.95	0.33, 0.3	0-64, 0-65	0.99	0.32, 0.33	0-63, 0-74	0.072	0.38	0.13-1.1
Size	0.19	1.03	0.99-1.07	0.10	1.03	0.99-1.08	0.44	0.99	0.96-1.02
Silva pattern (A/B vs. C)	0.086	4.14	—	0.18	2.58	—	—	—	—
NHPVA only									
Age (y)	0.032	1.06	1-1.1	0.052	1.09	1-1.18	0.51	1.02	0.96-1.1
Stage (I/II vs III/IV)	0.022	8×10^{9}	—	0.0044	5×10^{22}	—	1	9×10^{8}	—
Grade (1 vs. 2 vs. 3)	0.54	0.35, 1.17	0.02-5.5, 0.18-7.4	0.098	0, 0.74	0.09-6.06	0.44	0.4	0.04-4.03
Size	0.0022	1.1	1.01-1.19	0.0035	1.1	1.01-1.2	0.27	1.04	0.97-1.1
Silva pattern (A/B vs. C)	—	—	—	—	—	—	—	—	—

NHPVAs: statistically signifi cant associations between OS and age, stage and tumor, as well as between DFS and stage and tumor size;
HPVAs: nearly signifi cant statistical associations between patient Stage and DFS, between Silva invasion pattern and OS.

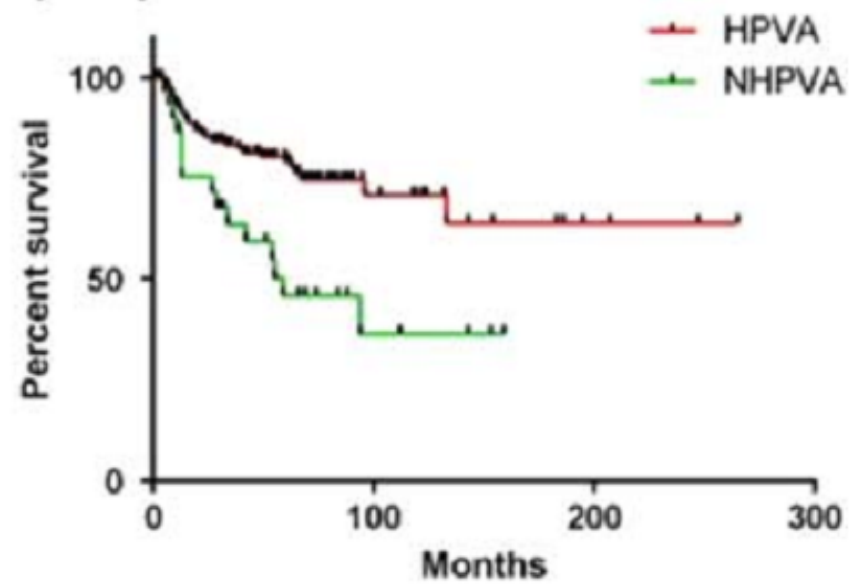
Survival curves in HPVA versus NHPVA (OS, DFS, PFS)



Overall survival

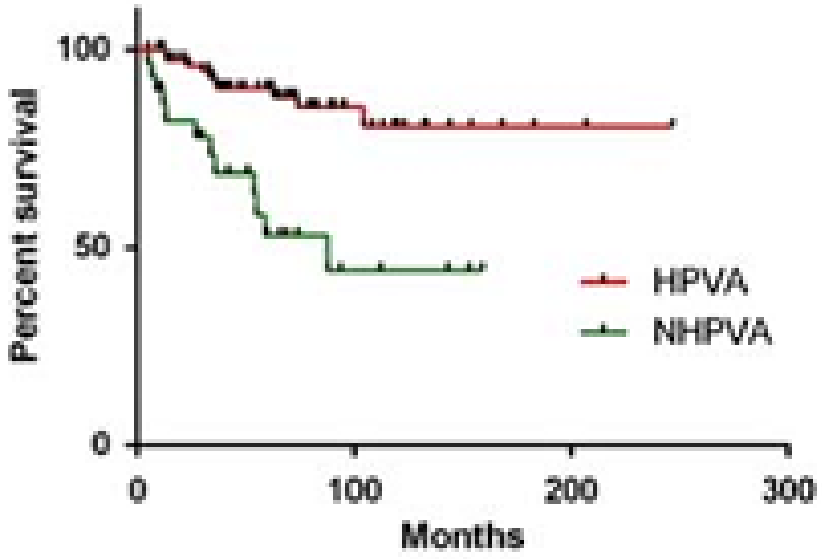


Disease free survival

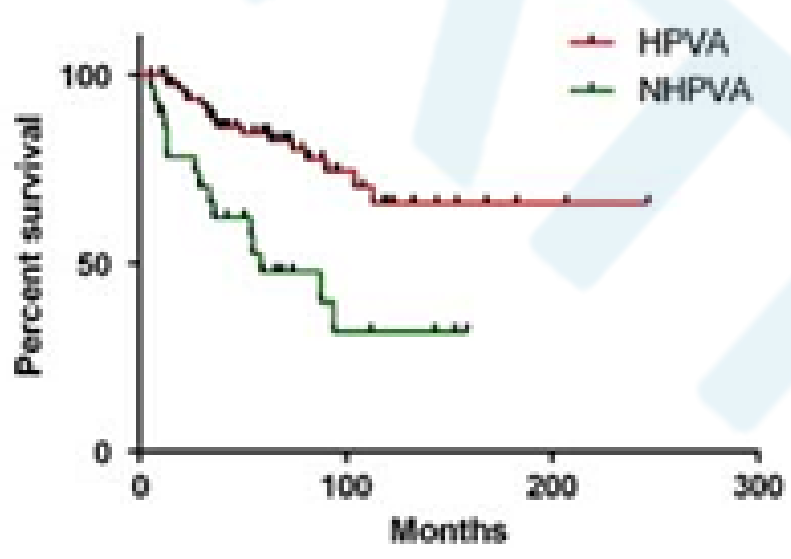


Progression free survival

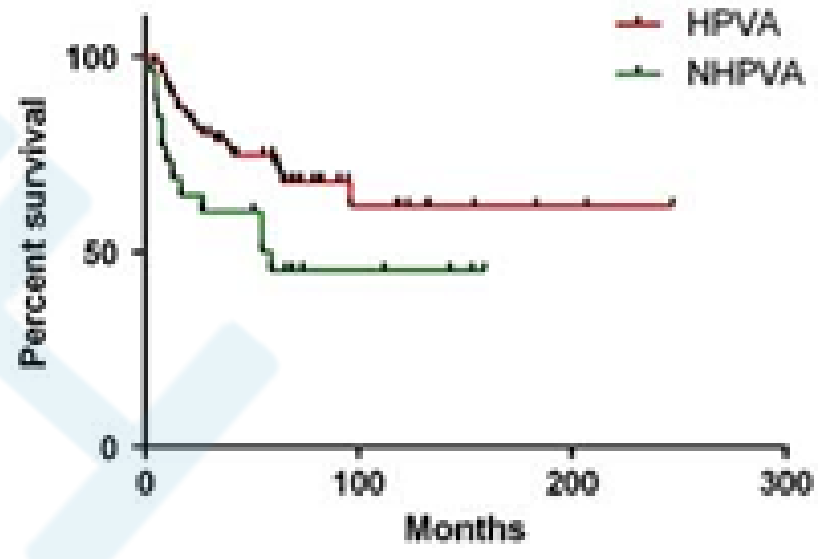
Survival curves in HPVA versus NHPVA with surgical and adjuvant treatment (OS, DFS, PFS)



Overall survival

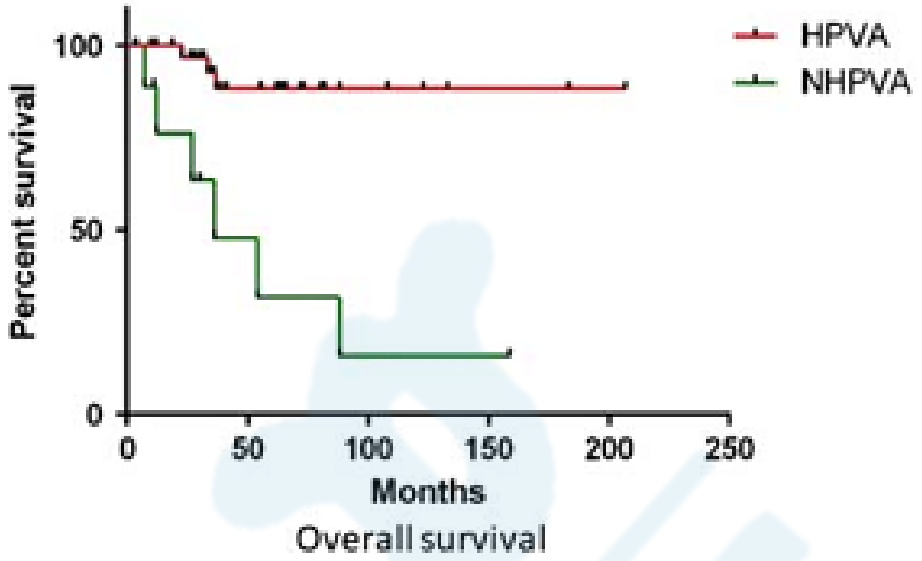


Disease free survival

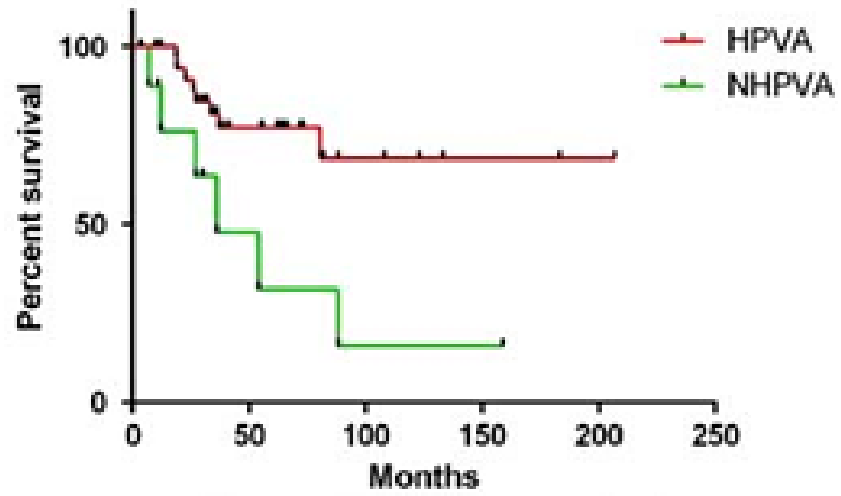


Progression free survival

Survival curves in grade 3 HPVA vs NHPVA (OS, DFS)

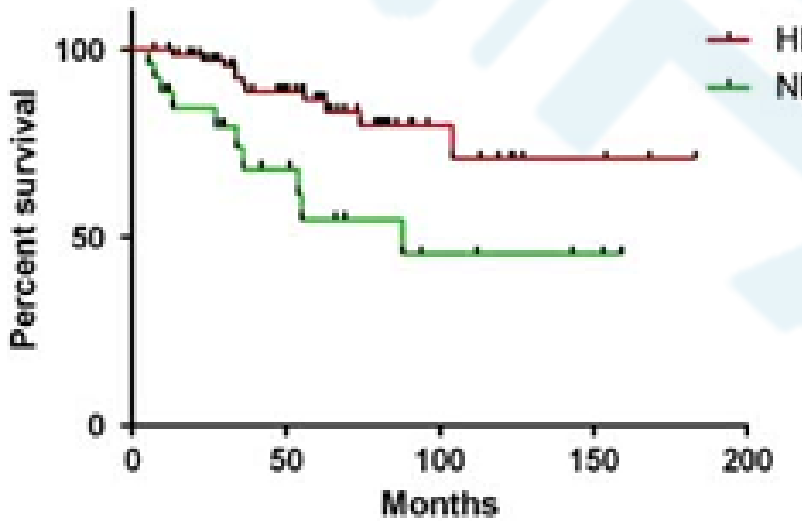


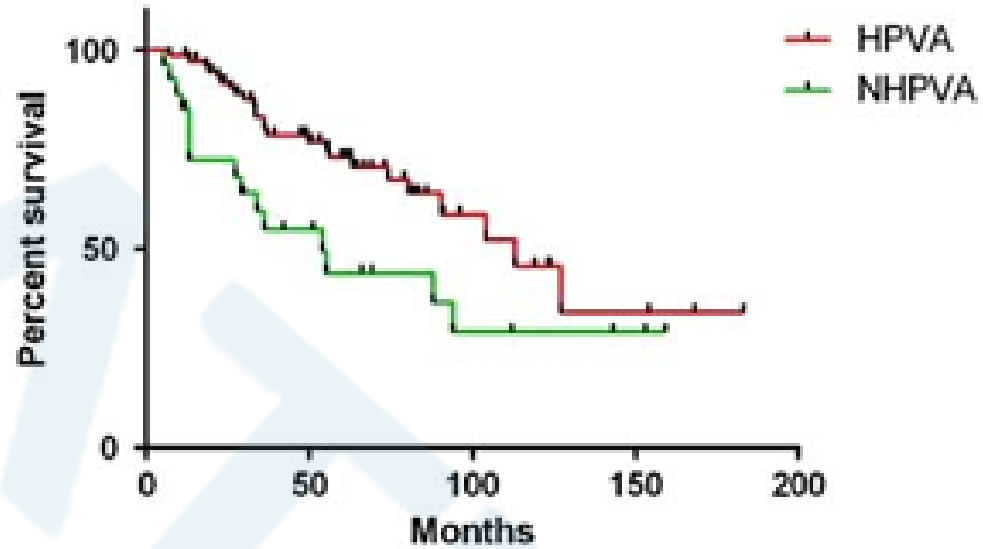
Overall survival



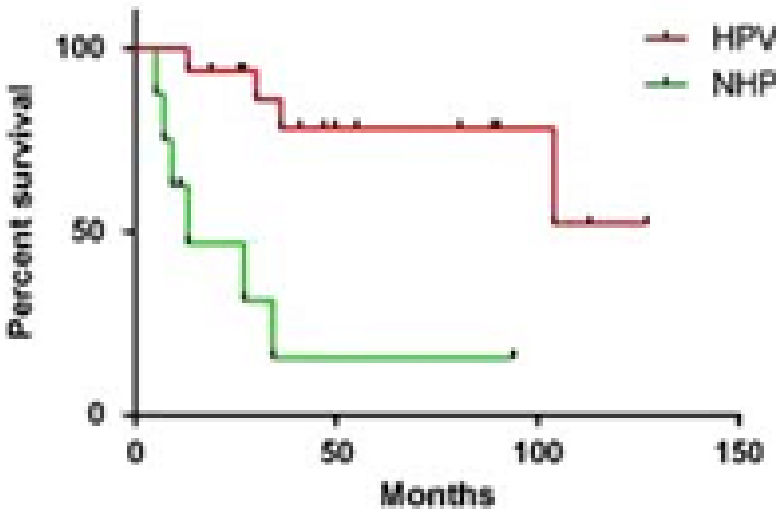
Disease disease free survival

Survival curves in HPVA vs NHPVA with LVI

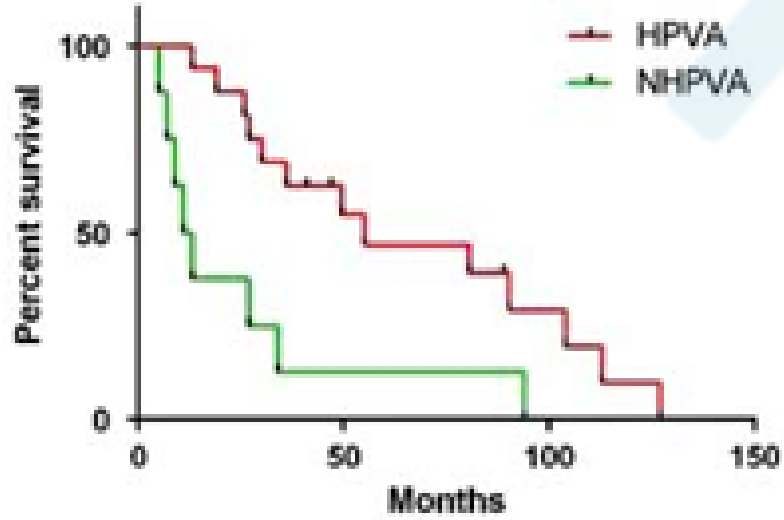




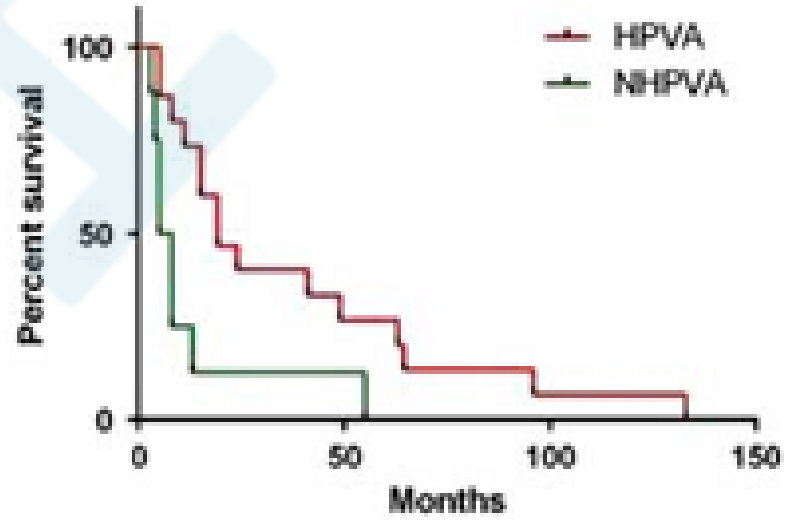
Survival curves in HPVA vs NHPVA with local (pelvic) recurrences (OS, DFS, PFS)



Overall survival



Disease free survival



Progression free survival

DISCUSSION

- The 2014 WHO classifi cation: morphologic (specifi cally cytoplasmic) features; lack pathogenesis or clinical outcomes.
- IECC: HPVA and NHPVA; p16/HPV status; superior agreement; good reproducibility; prediction of HPV status.

DISCUSSION

Clinical and demographic parameters differ：

- NHPVAs: larger tumors, older patients, FIGO Stage II or more advanced (>50% of cases).
- Multivariate analysis of NHPVAs:
  1. OS: age, stage and tumor size;
  2. DFS: stage and tumor size.
- Multivariate analysis of HPVAs:
  1. None of the variable reached clinical signifi cance for OS;
  2. OS: stage and Silva pattern.

DISCUSSION

Prognostic parameters assessed on histologic examination differ:

- LNM with the pattern of stromal invasion of HPVAs with superior results:

  ①Silva system: Silva A(nondestructive invasion), Silva B (limited destructive invasion) and Silva C(diffuse destructive invasion)

  ②Silva A and Silva B: not associated with LNM;

  ③Silva C: associated with LNM (＞25% of cases)

- NHPVAs: Silva C type, more frequently associated with LVI and LNM, rendering the Silva classifi cation irrelevant

  for prognostication.

DISCUSSION

- HPVAs have superior OS, DFS, and PFS compared with NHPVAs on univariate analysis.

- Similar results have been reported by other investigators:

  ① gastric-type ECAs: decreased 5-year; a signifi cant risk for disease recurrence.

  ② NHPVAs: higher frequencies of destructive invasive patterns LVI and advanced stage; worse PFS and DSS.

DISCUSSION

- Survival did not differ between HPVAs and NHP-VAs in patients who underwent surgery alone；
- Signifi cant differences with a combination of surgery and adjuvant therapy.

HPVAs: adjuvant therapy

DISCUSSION

- Clinical outcomes between mucinous HPVA and gastric-type NHPVA:

  ——mucinous HPVA: heterogenous collection of subvariants(mucinous NOS, intestinal, signet-ring cell,and iSMILE);

  ——mucinous HPVAs: a worse PFS than usual-type HPVAs, but a better OS compared with gastric-type NHPVAs;

  ——mucinous HPVAs should be separated from both nonmucinous HPVAs and NHPVAs.

DISCUSSION

- Microscopic grade is not an important prognostic parameter in ECAs:

  ① No statistically signifi cant differences in OS and DFS among FIGO grades 1, 2 and 3.

  ② HPVAs: silva invasion pattern is relative to OS.

  ③ NHPVAs: no apparent associations between features and clinical outcomes.

Conclusion

- IECC classifi cation:

  1. categorizes ECAs on the basis of HPV status;

  2. clinical relevance along with stage, tumor size, and Silva pattern.

     HPVAs: stage, Silva pattern.

     NHPVAs: age, stage, and tumor size.

- HPVAs: adjuvant therapy;
- Separation of HPVAs from NHPVAs, as well as mucinous HPVAs from nonmucinous HPVAs;

Conclusion

- Silva pattern might be viewed as an surrogate for HPVA grade:

  —FIGO grading of HPVAs and NHPVAs is not informative；

  —Silva system performs well for HPVAs, but is not applicable to NHPVA.

THANK YOU !