

Understanding HPV-Independent Endocervical Adenocarcinoma

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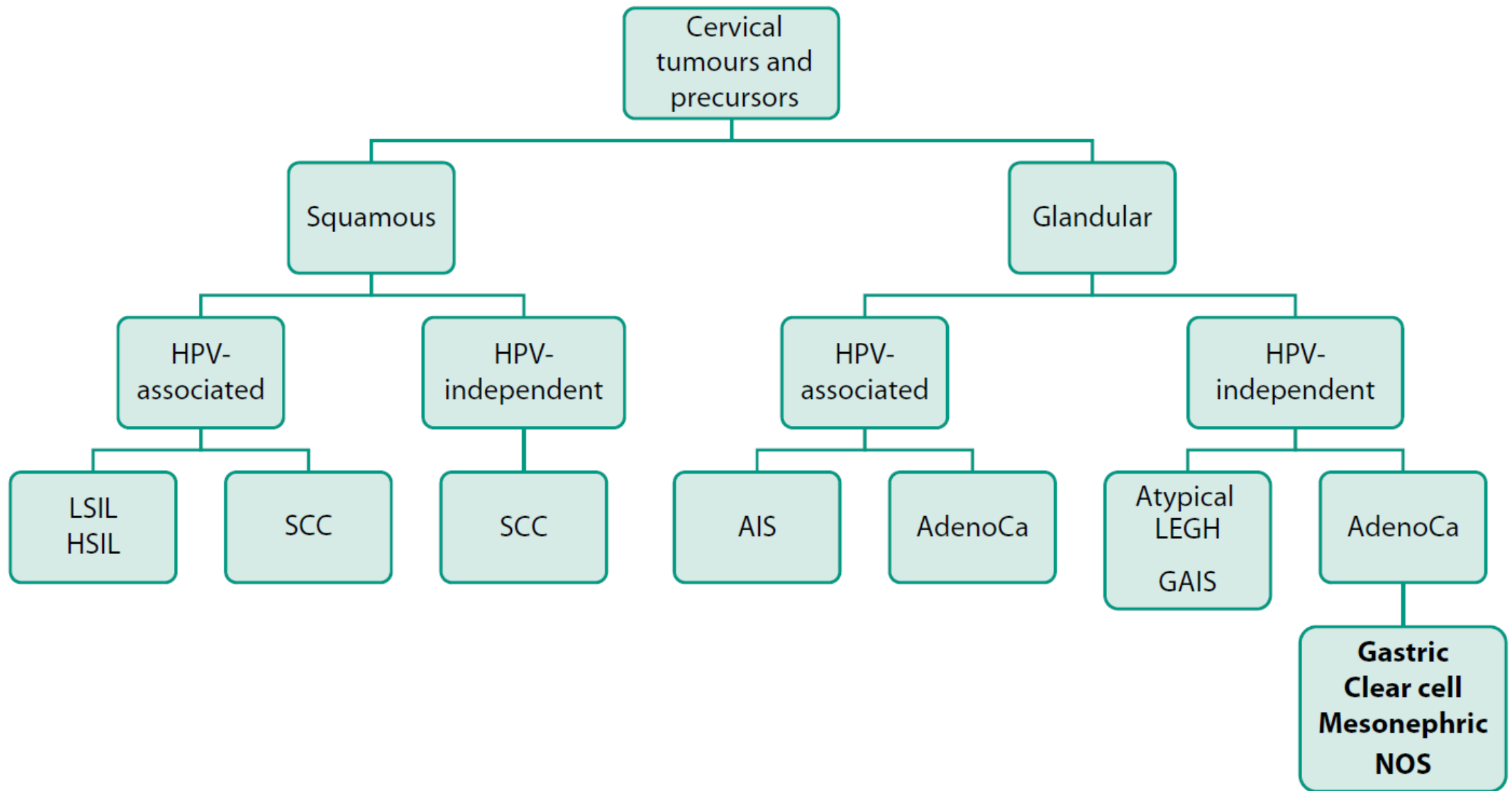
Background

- Persistent infection with oncogenic human papillomavirus (HPV) is a prerequisite in most cervical cancers.
- Increasing recognition of HPV-independent cervical cancers, especially adenocarcinoma

WHO's global strategy for the elimination of cervical cancer

- Vaccination of 90% of girls by age 15
- Screening of 70% of women by a high-performance test
- Management of 90% of women with preinvasive and invasive cervical disease

- Reduction in the prevalence of **HPV-associated** adenocarcinomas
- Increase in the proportion of **HPV-independent** adenocarcinomas



HPV-negative cervical cancers

HPV-independent cervical cancers
(true negative)

False negative HPV test results

- Loss of HPV DNA L1 fragments during host genome integration
- Low viral load
- Sampling error – necrosis/inflammation
- Technical factors concerning various HPV tests – non-nucleic acid signal amplification methods: less sensitive

Histological misclassification

- Extension of endometrial cancer to cervix
- Distant metastases from other HPV-negative primary cancers

Gastric-type endocervical adenocarcinoma

- Higher incidence in Asian countries, particularly in Japan:
 - 20-25% of all endocervical adenocarcinoma (10-15% in the western population)
- Clinical presentation
 - Median age 49.5 years (HPV-associated tumors 42 years)
 - Symptoms:
 - Watery, mucoid vaginal discharge, abnormal uterine bleeding, abdominal pain
 - Atypical glandular cells on a cervical smear
 - Incidental histological finding during LEEP or hysterectomy
 - Clinical signs:
 - Bulky and indurated cervix without a well-demarcated mass
 - More likely to involve the parametrium and vaginal tissue than HPV-associated adenocarcinoma

Stolnicu S, *et al.* Am J Surg Pathol 2019;43:466-74.

Aggarwal IM, *et al.* The Obstetrician & Gynaecologist 2023;25:47-58.

Gastric-type vs. usual HPV-associated endocervical adenocarcinoma

Clinical-pathological-radiological findings

Characteristics	Gastric-type adenocarcinoma	HPV-associated adenocarcinoma
Appearance	Multicystic (solid-cystic pattern with inner solid components, deep stromal infiltration, indistinct borders)	Mass-forming or polypoid
Location	Superior cervix close to the internal os	Lower endocervix or ectocervix
Precursor lesions	LEGH	Adenocarcinoma in situ
p16 IHC	Negative or focal	Diffusely positive

Usual HPV associated vs. gastric-type endocervical adenocarcinoma

Extent and spread

Study	N (HPVA/Gastric)	FIGO stage \geq II		Tumor size		LVSI		Deep stromal invasion	
		HPVA	Gastric	HPVA	Gastric	HPVA	Gastric	HPVA	Gastric
Kojima 2007	53 (37/16)	25%	44%	> 4 cm: 32%	> 4 cm: 50%	62%	75%	29%	31%
Karamurzin 2015	178 (139/39)	11%	59%	-	-	13%	48%	-	-
Stolnicu 2019	171 (147/24)	16%	54%	20 mm	40 mm	50%	83%	-	-

Kojima A, *et al.* Am J Surg Pathol 2007;31:664-72.
 Karamurzin YS, *et al.* Am J Surg Pathol 2015;39:1449–57.
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Usual HPV associated vs. gastric-type endocervical adenocarcinoma Extent and spread

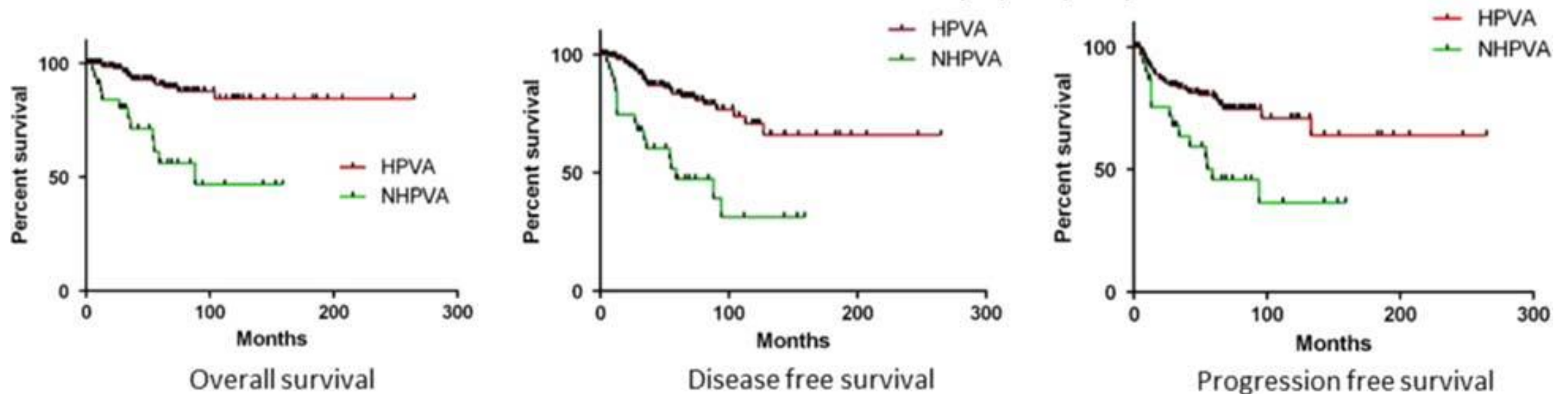
Study	LN metastasis		Parametrial extension		Vaginal extension		Lower uterine segment extension		Ovarian metastasis	
	HPVA	Gastric	HPVA	Gastric	HPVA	Gastric	HPVA	Gastric	HPVA	Gastric
Kojima 2007	29%	31%	19%	38%	8%	31%	16%	44%	3%	6%
Karamurzin 2015	8%	50%	-	-	-	-	-	-	0%	35%
Stolnicu 2019	12%	16.7%	-	-	-	-	-	-	-	-

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Usual HPV associated vs. gastric-type endocervical adenocarcinoma Recurrence

Recurrence	HPVA	Gastric
Local	8.8%	33.3%
Distant	5.4%	8.3%

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



Gastric-type endocervical adenocarcinoma Management

- Currently, no separate management guidelines