Human oncoviruses: Mucocutaneous manifestations, pathogenesis, therapeutics, and prevention

Papillomaviruses and Merkel cell polyomavirus

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Learning objectives
After completing this learning activity, participants should be able to recognize mucocutaneous manifestations of cancers associated with human papillomavirus and Merkel cell polyomavirus and describe risk factors, key pathogenic events, prevention, and therapies for these cancers.

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In 1964, the first human oncovirus, Epstein–Barr virus, was identified in Burkitt lymphoma cells. Since then, 6 other human oncoviruses have been identified: human papillomavirus, Merkel cell polyomavirus, hepatitis B and C viruses, human T-cell lymphotropic virus-1, and human herpesvirus-8. These viruses are causally linked to 12% of all cancers, many of which have mucocutaneous manifestations. In addition, oncoviruses are associated with multiple benign mucocutaneous diseases. Research regarding the pathogenic mechanisms of oncoviruses and virus-specific treatment and prevention is rapidly evolving. Preventative vaccines for human papillomavirus and hepatitis B virus are already available. This review discusses the mucocutaneous manifestations, pathogenesis, diagnosis, treatment, and prevention of oncovirus-related diseases. The first article in this continuing medical education series focuses on diseases associated with human papillomavirus and Merkel cell polyomavirus, while the second article in the series focuses on diseases associated with hepatitis B and C viruses, human T-cell lymphotropic virus-1, human herpesvirus-8, and Epstein–Barr virus. (J Am Acad Dermatol 2019;81:1-21.)

Key words: anal cancer; cervical cancer; human papillomavirus; Merkel cell carcinoma; Merkel cell polyomavirus; oncovirus; oropharyngeal cancer; penile cancer; vaginal cancer; vulvar cancer.

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Abbreviations used:

cSCC:	cutaneous squamous cell carcinoma
EV:	epidermodysplasia verruciformis
FDA:	US Food and Drug Administration
HPV:	human papillomavirus
pRB:	retinoblastoma protein
HR:	high risk
LT:	large T antigen
MC:	Merkel cell
MCC:	Merkel cell carcinoma
MCPyV:	Merkel cell polyomavirus
OPSCC:	oropharyngeal squamous cell carcinoma
PIN:	penile intraepithelial neoplasia
SCC:	squamous cell carcinoma
SCCA:	squamous cell carcinoma of the anal canal
ST:	small T antigen
UV:	ultraviolet
VaIN:	vaginal intraepithelial neoplasia
VIN:	vulvar intraepithelial neoplasia

PAPILLOMAVIRUSES

Key points

- **E6 and E7 are the primary human papillomavirus oncoproteins, inhibiting the functions of p53 and retinoblastoma protein, respectively**
- **Human papillomaviruses 16 and 18 are the most common human papillomavirus types associated with malignancy**
- **Human papillomaviruses 5 and 8 are the most common human papillomavirus types associated with cutaneous squamous cell carcinoma in patients with epidermodysplasia verruciformis**
- **Administration of the human papillomavirus nonavalent vaccination is recommended for males and females 9-45 years of age to prevent condyloma acuminata and cervical, vulvar, vaginal, and anal cancers**

		HPV Type	Disease (% attributed cases)
Alpha	mucosal high-risk	HPV16	Cervical squamous cell carcinoma (~50) Cervical adenocarcinoma (~35) Oropharyngeal cancer (~25)
		HPV18	Cervical squamous cell carcinoma (~20) Cervical adenocarcinoma (~35)
		HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Cervical squamous cell carcinoma (~30)
	mucosal low-risk	HPV6, 11	Benign genital lesions Respiratory papillomatosis
		HPV13, 32	Oral focal epithelial hyperplasia
	cutaneous benign	HPV2, 3, 27, 57	Skin warts
Mu		HPV1	Skin warts
Beta	cutaneous	HPV5, 8	First beta HPV types isolated from SCC of EV individuals
		HPV9, 12, 14, 15, 17, 19-25, 36-38, 47, 49, 75, 76, 80, 92, 93, 96, 98-100, 104, 105, 107, 110, 111, 113, 115, 118, 120, 122, 124, 143, 145, 150-52, 159	Likely associated with SCC in EV patients as well as immuno-compromised and immuno-competent individuals
Gamma		HPV4, 48, 50, 60, 65, 88, 95, 101, 103, 108, 109, 112, 115, 116, 119, 121, 123, 126-142,144, 146-149, 153-158, 161-170	Unknown

Fig 1. Many of the identified human papillomavirus (HPV) types that belong to different genera (ie, α, β, γ, and μ) of the HPV phylogenetic tree are shown. In addition, the main diseases that have been associated with different HPV types are described on the left. Adapted from Tommasino,[13] with permission from Elsevier.

Human papillomavirus

Human papillomavirus (HPV) is associated with multiple mucocutaneous diseases.[1,2] The fully characterized HPV types, presently up to 225, are organized into 5 HPV genera (α, β, γ, ν, and μ).[2-4] α-HPV targets mucosa and the skin, while other genera infect only skin (Fig 1).[3,5] HPV is the most common sexually transmitted infection and the primary causative agent of nearly all cervical cancers.[1,2,6] Additional HPV-associated malignancies include vulvar, vaginal, penile, anal, oropharyngeal, and cutaneous squamous carcinomas (Table I).[7,8]

Structure and life cycle. HPV is a nonenveloped ~8-kb double-stranded circular DNA virus.[9] The HPV genome has an early-coded region (E1, E2, and E4-E7), a late-coded region (capsid proteins L1 and L2), and a noncoding region containing the origin of replication and transcription factor–binding sites (Table II).[3,9,10] HPV infects basal keratinocytes of stratified epithelium after transmission across a disrupted epithelial barrier.[10,11] As basal cells differentiate, E1 and E2 enhance viral genome replication while capsid protein expression also increases. Approximately 2 to 3 weeks after infection, E4 guides a nonlytic release of fully coated progeny virions from superficial, terminally differentiated keratinocytes.[3,9,12-14]

Pathogenesis and carcinogenesis. Knowledge regarding HPV carcinogenesis stems primarily from the study of cervical cancer and the most highly carcinogenic HPV types of the α genus, HPVs 16 and 18.[9] The α-HPV genus is divided into 2 groups based upon oncogenic potential (Fig 1): low risk and high risk (HR).[15] Regardless of HPV type, most infections are subclinical and cleared within 1 to 2 years.[2] Only a small portion of HR HPV infections leads to precancerous lesions, and <1% of these lesions becomes malignant.[16]

The oncogenic potential of HR HPV is largely because of E6 and E7, whose primary carcinogenic mechanisms are inhibition of tumor suppressor proteins p53 and retinoblastoma protein (pRB), respectively.[17-19] E6 binds the cellular ubiquitin ligase E6-associated protein to form a complex of E6/E6-associated protein/p53. Polyubiquitination of p53 ensues, targeting it for proteasome degradation.[17,20] HR E6 also targets PDZ (PSD/Dlg/ZO) domains, resulting in the loss of cell-to-cell contact inhibition and cell polarity.[17,21,22] E7 uses its Leu-X-Cys-X-Glu domain to bind pRB, prompting cullin 2 ubiquitin ligase to target pRB for proteasome destruction. pRB is then unable to inhibit the e2F transcription factors (e2F1 to e2F3).[17,20] E7 also targets pRB-related pocket proteins p107 and p130, as well as cyclin-dependent kinase inhibitors p21 and p27, all of which are cell cycle regulators.[17,18,20]

Persistent HPV infection alone is not sufficient to induce cervical cancer development; genomic integrity must also be compromised.[23] The HPV genome integrates into the host genome in most cervical cancers, and nearly always in HPV 18–associated cancers.[12,24,25] Integration typically occurs at chromosomal fragile sites, frequently disrupting the open-reading frame of E2 and less commonly that of E1, E4, or E5.[12,23] E2 inhibits the expression of E6 and E7, and its disruption enables uninhibited E6 and E7 oncoprotein activity.[24]

Cervical cancer

Cervical cancer is the fourth most common cancer in women and the second most common cause of cancer death in women. Approximately 265,672 women die from the disease annually.[26] More than 99% of cervical cancers are attributable to HPV infection, with HPV 16 and 18 accounting for >70% of cervical cancer and the majority of high-grade precursor lesions.[16,26] Cervical cancer typically occurs in women ≥35 years of age, while HPV infection occurs earlier in life (peak age of 25). The progression of precursor lesions to cervical cancer usually takes ≥10 years.[16,27-29]

The most common site of persistent HPV infection and cervical cancer development is the transformation zone between the columnar epithelium of the endocervix and squamous epithelium of the ectocervix.[30] Persistent infection can cause cervical intraepithelial neoplasia, which may progress to cervical cancer.[31] Cervical intraepithelial neoplasia and cervical cancer screening uses cytology and HPV testing (Table I) to guide the use of invasive diagnostic and treatment options, such as colposcopy, cone biopsy excision, and loop electrosurgical excision.[32] Unnecessary cervical excisions must be avoided in young women because these procedures increase the risk of preterm birth and mid-trimester pregnancy loss.[33]

Vulvar and vaginal cancer

Vulvar and vaginal squamous cell carcinoma (SCC) comprise 5.6% and 4.7% of female genital tract cancers, respectively.[34] Vulvar SCC typically occurs in postmenopausal women and is HPV-positive approximately 18% to 75% of the time.[35,36] Vaginal SCC arises from vaginal intraepithelial neoplasia (VaIN) and vulvar SCC arises from vulvar intraepithelial neoplasia (VIN). Usual-type VIN (Fig 2) is associated with HPV and gives rise to warty and basaloid vulvar SCC. Differentiated-type VIN develops from chronic vulvar conditions (lichen

Table I. Human papillomavirus–associated cancers with respective characteristics, epidemiology, screening, and treatment

HPV-associated cancer	Typical age group	Risk factors	Presentation	Histology	Precursor lesion	Precursor and carcinoma in situ treatment	Screening methods	Potential treatment modalities for invasive cancer
Cervical	Most common in ages 35-44 (median age 50)[134]	Early onset of sexual activity, high number of sexual partners, smoking, HIV infection, low socioeconomic status, multiparity, long-term OCP use, immunosuppression, and in utero DES exposure (adenocarcinoma only)[135,136]	Early: asymptomatic; advanced: dyspareunia, vaginal bleeding/discharge (often postcoital), pelvic/back pain, and inguinal lymphadenopathy[137]	Approximately 80% SCC, 20% adenocarcinoma[138] (both HPV-related)[139]	CIN1 (LSIL) (spontaneously regresses in 70-90% of cases), CIN2, and CIN3 (HSIL) (12% of untreated CIN3 progresses to cancer)[33,140]	CIN1: observe; CIN2: excise or active surveillance in women <30 years of age; CIN3: always excise[33,140]	Avg risk women: Papanicolaou smear every 3 y ages 21-65 or Papanicolaou smear every 3 years ages 21-29 then Papanicolaou smear plus HPV testing every 5 y ages 30-65	Surgery (ie, cone bx, trachelectomy, or hysterectomy); lymph node evaluation/dissection; RT: BRT/brachytherapy; systemic therapy[138]
Anal	Majority age ≥55[141]	Receptive anal intercourse, smoking, chronic immunosuppression, Crohn's disease, h/o genital warts[142,143]	Rectal bleeding, anal discharge, pruritus, pain, sensation of mass, tenesmus, fecal incontinence, change in stool caliber, and inguinal lymphadenopathy[142]	90% SCC (only HPV-related CA), other 10% include adenocarcinoma, BCC, melanoma, and GIST[144]	AIN 1 (LSIL), AIN 2 and AIN 3 (HSIL)	WLE, topical 5-FU, imiquimod, infrared coagulation, CO_2 laser, and electrocautery[145]	DARE, anal Papanicolaou smear, high-resolution anoscopy	Surgery (eg, local excision, abdominoperineal resection); lymph node evaluation/groin dissection; RT; systemic therapy[146]
Oropharyngeal	Average age of 62, but incidence is rising in younger population[147]	Male to female (2:1), smoking, alcohol, chewing tobacco, chewing betel quid, and Plummer–Vinson syndrome[148,149]	Dysphagia, odynophagia, otalgia, voice hoarseness, stridor, persistent sore throat or cough, mass in neck, and cervical lymphadenopathy[149,150]	SCC (only HPV-related CA), lymphoma[151]	No clinically apparent lesions currently identified[53]	Not applicable	No screening procedures	Tx algorithm determined by HPV status; surgery (resection); lymph node evaluation/dissection; systemic therapy (including second-line options: nivolumab, pembrolizumab, and afatinib)[53]
Penile	Elderly men (median age 60)[152]	Lack of neonatal circumcision, poor genital hygiene, PUVA phototherapy, lichen sclerosis, chronic balanitis, low socioeconomic status, and HIV infection[152]	Nodular, ulcerative, or exophytic fungating lesions on penis or foreskin[153]	90% SCC (only HPV-related CA), other 10% include melanoma, BCC, and adenocarcinoma[154]	PIN 1 (erythroplasia of Queyrat), PIN 2 (Bowen disease), and PIN 3 (bowenoid papulosis)	Appropriate treatment modalities may include surgery (eg, WLE, glansectomy, and Mohs micrographic surgery), lymph node evaluation/biopsy/dissection, topical therapy (imiquimod and 5-FU), and laser therapy (CO_2, Nd:YAG, and KTP)[155]	No screening procedures	Surgery (eg, WLE, glansectomy, Mohs micrographic surgery, partial/total penectomy); lymph node evaluation/dissection; laser therapy (CO_2, Nd:YAG, and KTP); RT; systemic therapy[155]
Vulvar	Postmenopausal women[156]	Smoking, HIV infection, lichen sclerosus, and h/o cervical cancer[157]	Vulvar mass or ulcer, pain, pruritus, occasional bleeding or discharge[156]	90% SCC (only HPV-related CA), melanomas, adenocarcinomas, BCCs, verrucous, carcinomas, and sarcomas[156]	Usual type VIN (HPV-related, precursor to warty and basaloid SCC), differentiated VIN (non–HPV-related; lichen sclerosus, lichen simplex chronicus; precursor to keratinizing SCC)[37,158]	WLE[159]	No screening procedures	Surgery (eg, WLE, modified local resection, and modified radical vulvectomy); lymph node evaluation/dissection; EBRT; systemic therapy[159]

Vaginal	Women ages 35-90 (most common in ages 60-79)[160]	Early onset of intercourse, ≥5 lifetime sexual partners, chronic vaginitis, smoking, HIV infection, h/o cervical cancer, low socioeconomic status, previous hysterectomy, h/o genital warts, and in utero DES exposure[160]	Often asymptomatic, painless vaginal bleeding or discharge (most common presentation), urinary and rectal sx also possible depending on tumor location[160]	85% SCC (only HPV-related CA), 15% adenocarcinoma[161]	VAIN 1-3	Laser vaporization, WLE, brachytherapy, topical 5-FU, imiquimod, and PDT with 5-aminolevulinic acid[162]	No screening procedures	Surgery and RT ± pelvic dissection (early stages); surgery includes upper vaginectomy or vulvovaginectomy ± hysterectomy; RT only (later stages), and role of CT unclear[163]
Cutaneous squamous cell carcinoma	EV: ≥30 y[58]; OTRs: risk increases with time posttransplant[164]; immunocompetent: ≥50 y	UV exposure, increased age, fair-skin, light-colored eyes, red hair, immunosuppression, EV, organ transplant (heart/lung > kidney > liver), and select genetic syndromes[164,165]	Nonhealing skin lesion, usually in sun-exposed areas; ulceration can occur; often asymptomatic but may be painful or bleed	SCC (many histologic subtypes)	Actinic keratosis, SCC in situ (Bowen disease)	Excision, cryotherapy, curettage and electrodessication, topical tx (imiquimod, 5-FU, ingenol mebutate, diclofenac, and retinoids)	Regular skin examinations	Standard excision, Mohs micrographic surgery, curettage and electrodessication, cryotherapy (for small cSCC), or RT for nonsurgical candidates (avoid RT in EV)[70,166]; EV and OTR: topical and systemic retinoids, photodynamic therapy, adjunct topicals (5-FU or imiquimod) may be useful[58,68]; EV: cidofovir, cimetidine, and interferon use has also been reported[58]

5-FU, Fluorouracil; *AIN*, anal intraepithelial neoplasia; *APR*, abdominoperineal resection; *Avg*, average; *BCC*, basal cell carcinoma; *CA*, cancer; *CIN*, cervical intraepithelial neoplasia; *CT*, chemotherapy; *cSCC*, cutaneous squamous cell carcinoma; *DARE*, digital anal rectal examination; *DES*, diethylstilbestrol; *EV*, epidermodysplasia verruciformis; *EBRT*, external beam radiation therapy; *GIST*, gastrointestinal stromal tumor; *H/O*, history of; *HPV*, human papillomavirus; *HSIL*, high-grade squamous epithelial lesion; *KTP*, potassium titanyl phosphate; *ILND*, inguinal lymph node dissection; *LEEP*, loop electrosurgical procedure; *LN*, lymph node; *LSIL*, low-grade squamous intraepithelial lesion; *Mets*, metastasis; *OCP*, oral contraceptive pill; *OTR*, organ transplant recipient; *PDT*, photodynamic therapy; *PIN*, penile intraepithelial neoplasia; *PUVA*, psoralen plus ultraviolet A light phototherapy; *RT*, radiation therapy; *SCC*, squamous cell carcinoma; *Tx*, treatment; *SLNB*, sentinel lymph node biopsy; *UV*, ultraviolet exposure; *VAIN*, vaginal intraepithelial neoplasia; *VIN*, vulvar intraepithelial neoplasia; *WLE*, wide local excision; *YAG*, yttrium aluminum garnet.

Table II. Human papillomavirus viral proteins and their functions

Viral protein	Function
E1	DNA helicase; controls genome replication and amplification[13,25]
E2	Transcriptional regulator of E6 and E7; also regulates replication, and genome partitioning[13,25]
E4	Helps evade epithelial defenses; also destabilizes cytokeratin network to aid in viral progeny release[13,25]
E5	Minor viral oncoprotein; stimulates mitogenic signals of growth factors[9,13]
E6	Major viral oncoprotein; inactivates p53, PDZ-containing proteins, and other proteins; activates hTERT[13,17,25]
E7	Major viral oncoprotein; inactivates pRB, CKIs, and other proteins[13,20]
L1	Major capsid protein; main component of FDA-approved recombinant vaccines[72]
L2	Minor capsid protein; main component of investigational recombinant vaccines[72]

CKI, Cyclin-dependent kinase; *FDA*, US Food and Drug Administration; *hTERT*, human telomerase reverse transcriptase; *pRB*, retinoblastoma protein.

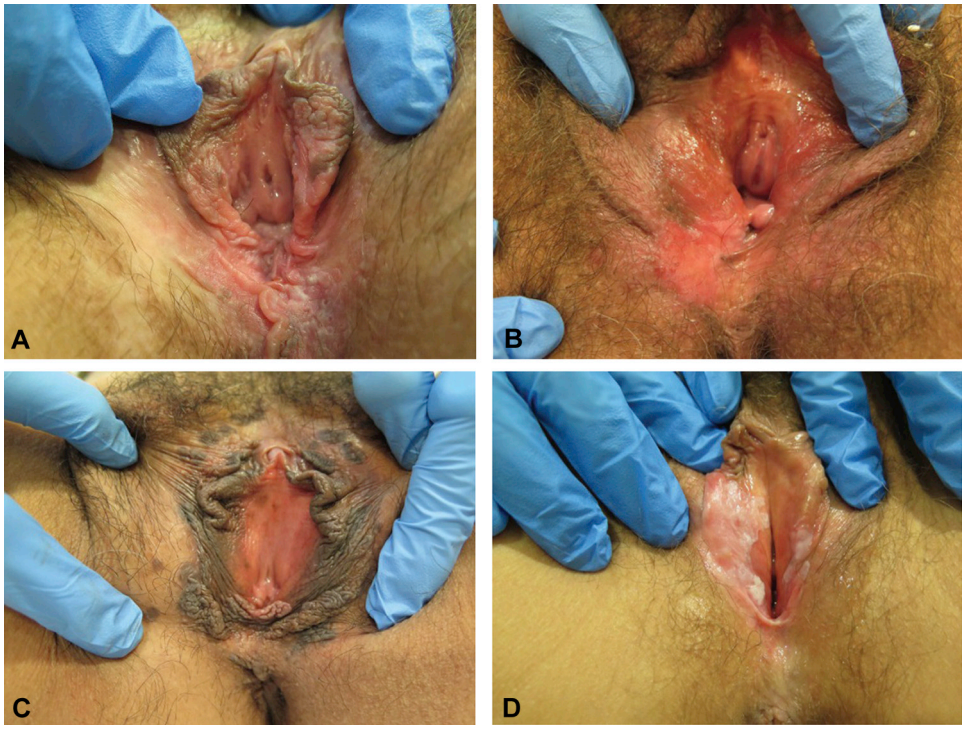

Fig 2. Usual-type vulvar intraepithelial neoplasia. **A**, Vulvar multifocal lesions: white and brown plaque on the inner surface of the left labium minus; white and brown papules on the perineum. **B**, Unifocal white, red, and brownish plaque on the right posterior part of the vulva, in the context of diffuse vulvar erythema, with excoriations caused by scratching. **C**, Multifocal bilateral brown papules on the labia majora from the anterior part of vulva to the perineum. **D**, White papule on the inner surface of the posterior right labium minus in the context of confluent bilateral white macules on the vaginal vestibule. Reprinted from Preti M, Igidbashian S, Costa S, et al. VIN usual type—from the past to the future. Ecancermedicalscience 2015;9:531. This work is licensed under a Creative Commons license.

sclerosus and lichen planus) and gives rise to HPV-independent SCC.[37]

Penile cancer

Penile SCC, although uncommon in the United States, is especially prominent in Africa and South America.[38,39] Penile SCC is subdivided into warty, basaloid, keratinizing, and verrucous subtypes.[38,40] Keratinizing and verrucous SCCs are unrelated to HPV while warty and basaloid SCCs are often associated with HPV.[38,40] Warty and basaloid SCCs arise from penile intraepithelial neoplasia (PIN), which contains clonally integrated HPV 60% to 100% of the time.[41] PIN progresses through dysplastic stages: I (mild), II (moderate), and III (severe), correlating with erythroplasia of Queyrat, Bowen disease, and bowenoid papulosis, respectively (Fig 3, Table III).[40,42] A high index of suspicion should be maintained for PIN

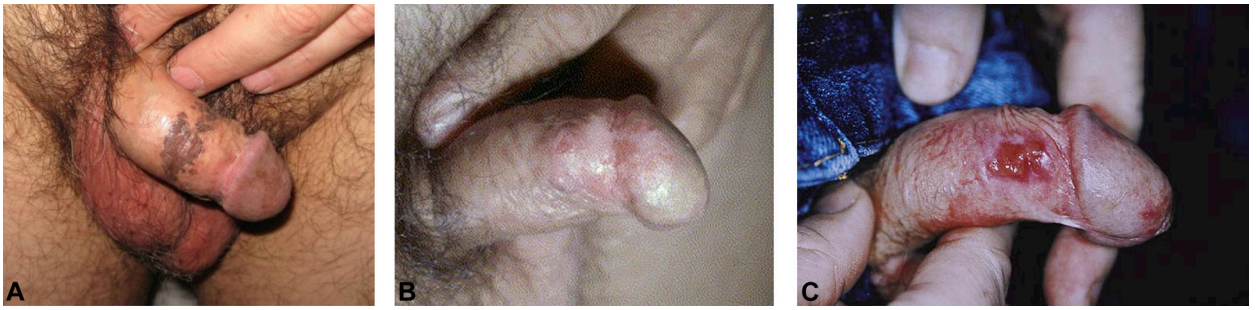

Fig 3. Penile intraepithelial neoplasia. **A**, Bowenoid papulosis. **B**, Erythroplasia of Queyrat. **C**, Bowen disease. *A*, Used with permission from Marcucci C, Sabban EC, Friedman P, Peralta R, Calb I, Cabo H. Dermoscopic findings in bowenoid papulosis: report of two cases. Dermatol Pract Concept 2014;4:61-3. *B*, Used with permission from Micali G, Nasca MR, Innocenzi D, Schwartz RA. Penile cancer. J Am Acad Dermatol 2006;54:369-91. *C*, Used with permission from Thai KE, Sinclair RD. Treatment of Bowen's disease of the penis with imiquimod. J Am Acad Dermatol 2002;46:470-1.

Table III. Characteristics of penile intraepithelial neoplasia*

	Bowenoid papulosis	Erythroplasia of Queyat	Bowen disease
Age at diagnosis, y	<40	>40	>40
Location	Penile shaft, glans, or prepuce	Glans and prepuce	Follicle-bearing skin of the genitals
Size, mm	2-10	10-15	10-15
Gross appearance	Multiple small well-demarcated smooth brown, red, or pink papillomatous papules or patches	One or more moist velvety shiny red patches	Single scaly red or slightly pigmented plaque

*Reprinted with permission from Crispen and Mydlo.[40]

because it is often misdiagnosed as benign conditions, such as lichen planus and balanitis.[40] Early diagnosis allows for management with minimally invasive surgery or even topical therapies and may circumvent the need for penile amputation.[43,44]

Anal cancer

Seventy percent to 90% of squamous cell carcinoma of the anal canal (SCCA) is caused by HPV.[45,46]

Populations that are particularly at risk for SCCA are men who have sex with men, HIV-infected persons, and women with vulvar or cervical cancer.[47] Screening methods for anal intraepithelial neoplasia and SCCA are currently being evaluated in clinical trials and include Papanicolaou smear of the transformation zone, high-resolution anoscopy, and digital anorectal examination.[48,49] Anal cancer screening is currently recommended for patients who are infected with HIV and women with cervical dysplasia or cancer.[46,48]

Oropharyngeal carcinoma

The incidence of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) has drastically increased over the past few decades while the incidence of tobacco-associated and HPV-negative OPSCC has decreased.[50] Risk factors for oral HPV infection (prevalence of 6.9%) include earlier and increased participation in oral sex, a greater number of lifetime sexual partners (oral or vaginal), and smoking.[51,52] Oral sex is not required to transmit HPV, and "deep kissing" may serve as a route of transmission.[52]

Knowledge regarding the transition from HPV infection to OPSCC is lacking, and clinically apparent precursor lesions have not been identified.[53] The presence of HPV, however, correlates with a better overall survival and response to treatment, regardless of regimen.[51,54-56] Deescalated radiation treatment protocols for HPV-positive OPSCC are being investigated to minimize treatment-related morbidity, such as dysphagia and xerostomia (ClinicalTrials.gov identifiers NCT02908477 and NCT03416153). One chemoradiation trial yielded good oncologic control with low rates of dysphagia and mucositis.[56]

Cutaneous squamous cell carcinoma

β-HPVs are strongly associated with cutaneous SCC (cSCC) in individuals with epidermodysplasia verruciformis (EV), an autosomal recessive genodermatosis characterized by profound susceptibility to HPV infection predominantly caused by mutations in *EVER1* and

Table IV. Current preventative human papillomavirus vaccines approved by the US Food and Drug Administration

Brand name	Valency	Year of FDA approval	FDA-approved indications	L1 protein production	HPV types covered	Cross-immunity HPV types	WHO vaccination schedule[74]
Cervarix	Bivalent	2009	CIN 1-3, cervical cancer, cervical AIS in females 9-25 years of age[167]	Baculovirus insect cell expression system	16 and 18	31, 33, and 45	For ages 9-14: 3 doses (0, 2, and 6 months) or 2 doses (0 and 6-12 months); for ages 15-26: 3 (0, 2, and 6 months)*
Gardasil	Quadrivalent	2006	CIN 1-3, cervical cancer, cervical AIS, condyloma acuminata, VIN 2 and 3, VaIN 2 and 3 in females 9-26 years of age; condyloma acuminata, AIN, and anal cancer in males 9-26 years of age[168]	*Saccharomyces cerevisiae*	6, 11, 16, and 18	31, 33, and 45	Same schedule used for all HPV vaccinations
Gardasil 9	Nonavalent	2014	Cervical, vulvar, vaginal, and anal cancer; condyloma acuminata, CIN 1-3, VIN 2 and 3, VaIN 2 and 3, AIN 1-3 in females 9-45 years of age; anal cancer, AIN 1-3, and condyloma acuminata in males 9-45 years of age[75]	*Saccharomyces cerevisiae*	6, 11, 16, 18, 31, 33, 45, 52, and 58	Not yet known	For ages 9-14: same schedule as other HPV vaccinations; for ages 15-45: 3 (0, 2, and 6 months)

AIN, Anal intraepithelial neoplasia; *AIS*, adenocarcinoma in situ; *CIN*, cervical intraepithelial neoplasia; *FDA*, US Food and Drug Administration; *HPV*, human papillomavirus; *VaIN*, vaginal intraepithelial neoplasia; *VIN*, vulvar intraepithelial neoplasia; *WHO*, World Health Organization.

*If the interval between doses is shorter than 5 months, then a third dose should be given at least 6 months after the first dose. A 3-dose schedule remains necessary for those known to be immunocompromised or infected with HIV.

Table V. New and investigative immunotherapy and targeted therapy for HPV-related cancers*

Therapeutic agent	Mechanism of action	Indications for HPV-related cancers approved by the FDA	Completed and ongoing clinical trials
Antiangiogenic agents			
Bevacizumab	Humanized anti-VEGF 2 IgG1	Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease[169]	Multiple ongoing clinical trials for treatment of HPV-related cancers with anti-VEGF medications: bevacizumab, pazopanib, cediranib, and sunitinib[170]
Immune checkpoint inhibitors			
Pembrolizumab	Anti—PD-1 humanized IgG4	Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy (accelerated approval)[171]	Phase Ib trial results: objective response rate was 32% in HPV-induced HNSCC patients vs 14% in HPV-unrelated cancers; significant improvement in overall response rate in PD-L1—positive tumor (22%) vs PD-L1—negative tumors (4%) (NCT01848834)[172]; ongoing trials for multiple cancers: anal, cervical, penile, vulvar, and HNSCC
Nivolumab	Anti—PD-1 human IgG4	Recurrent or metastatic HNSCC with disease progression on or after a platinum-based therapy[173]	Phase III trial results: significant improvement in overall survival; tumor PD-L1 expression level of $\geq$1% or p16$^+$ tumors may improve treatment response (NCT02105636)[174]; ongoing trials for multiple cancers: HNSCC, anal, cervical, and vulvar
Cemiplimab	Anti—PD-1 human IgG4	Awaiting FDA priority review for locally advanced and metastatic cSCC[175]	Ongoing trial for treatment of locally advanced and metastatic cSCC (NCT03492489)
Avelumab	Anti—PD-1 human IgG1	No current indications	Ongoing phase II trial will evaluate avelumab with valproic acid for treatment of HPV p16$^+$ cervical cancer, HNSCC, penile SCC, vaginal SCC, and vulvar SCC (NCT03357757)
Ipilipumab	Anti—CTLA-4 human IgG1K	No current indications	Ongoing trials for multiple cancers: cervical, HNSCC, penile, vaginal, and vulvar
Therapeutic vaccines			
ADXS11-001	Live-attenuated listeria monocytogenes vaccine that secretes proteins that activate both the innate and adaptive immune responses[176]	No current indications	ADXS11-011 yielded promising results in phase I-II trials[177]; ongoing phase I-III trials for multiple cancers: cervical, HNSCC, and anal
VGX-3100	Synthetic DNA plasmid vaccine with genes E6 and E7 of HPV 16 and HPV 18, resulting in an adaptive immune response[178]	Currently not approved by FDA; waiver granted by European Medicines Agency for treatment of CIN in the pediatric population[179]	Phase 2b trial demonstrated regression of CIN 2/3 to CIN1 or normal pathology in 48.2% of VGX-3100 recipients[178]; ongoing trials for VIN, CIN, and AIN

Continued

Table V. Cont'd

Therapeutic agent	Mechanism of action	Indications for HPV-related cancers approved by the FDA	Completed and ongoing clinical trials
HPV-targeted T cell therapies			
Tumor-infiltrating T cells	Infusion of tumor-infiltrating T cells with activity against E6 and E7; infusion preceded by lymphocyte-depleting chemotherapy and followed by administration of aldesleukin[180]	No current indications	Phase II trial completed for metastatic or locally advanced refractory/recurrent HPV-16$^+$ or HPV-18$^+$ cancer; cervical cancer results: 3/18 complete response, 2/18 partial response; noncervical cancer results: 2/11 partial response, 0/11 complete response (NCT01585428)
Genetically engineered E6 TCR T Cells	T cells engineered with a T-cell receptor that targets an HLA-A2$^+$ restricted epitope of HPV 16 E6[181]	No current indications	Completed phase I/II study for metastatic or refractory/recurrent HPV-16$^+$ cancer; regression of metastatic HPV$^+$ carcinoma occurred in 2 patients; no dose-limited toxicity (NCT02280811)

AIN, Anal intraepithelial neoplasia; *CIN*, cervical intraepithelial neoplasia; *cSCC*, cutaneous squamous cell carcinoma; *CTLA-4*, cytotoxic T-lymphocyte associated protein 4; *FDA*, US Food and Drug Administration; *HLA*, human leukocyte antigen; *HNSCC*, head and neck squamous cell carcinoma; *HPV*, human papillomavirus; *Ig*, immunoglobulin; *PD-1*, programmed cell death-1; *PD-L1*, programmed death ligand 1; *SCC*, squamous cell carcinoma; *TCR*, T-cell receptor; *VEGF*, vascular endothelial growth factor; *VIN*, vulvar intraepithelial neoplasia.
*This table is not inclusive but highlights some significant therapeutic agents.

EVER2 genes.[57-60] EV first manifests during childhood with polymorphic cutaneous lesions, including pityriasis versicolor–like macules and flat, wart-like papules that can become malignant.[61] By the fourth or fifth decade of life, approximately 50% of patients with EV develop cutaneous malignancies, predominately Bowen type carcinoma in situ and cSCC, in sun-exposed areas.[58] A similar syndrome called acquired EV can develop in patients with cell-mediated immune deficiencies, such as organ transplant recipients and HIV-infected individuals.[62,63]

HPVs 5 and 8 are present in 90% of EV cSCC, but additional β-HPV types have also been found (Fig 1).[15,57,64] β-HPVs are also associated with 75% to 90% of cSCC in organ transplant recipients.[65,66] Although controversial, β-HPVs appear linked to cSCC in the general population. In 1 study, 47% of cSCC in the general population tested positive for β-HPV, and a recent metaanalysis suggests that β-HPV infection in immunocompetent individuals carries a 42% increased risk for cSCC.[65,67]

Despite a strong association between β-HPV and cSCC, a clear causal relationship has not been established. β-HPV has been implicated in the initiation of cSCC but does not appear essential for tumor maintenance.[68] E6 and E7 have been implicated as the primary oncoproteins in β-HPV, and proposed carcinogenic mechanisms include increased susceptibility to ultraviolet (UV) light–induced oncogenesis, inhibition of PDZ domain protein syntenin-2, and increased accumulation of DNA damage in stem cell–like cells.[67,69]

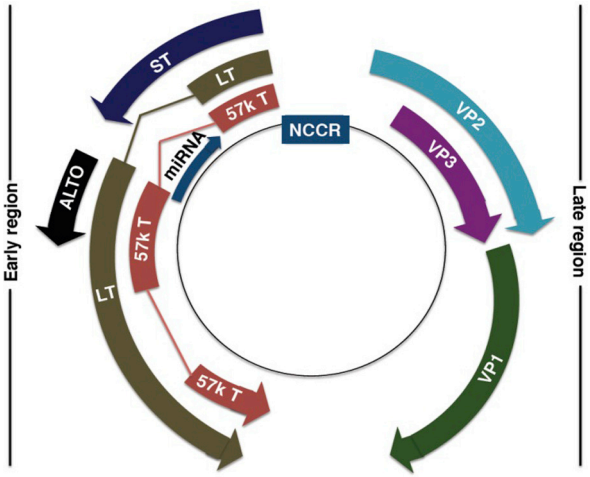

Fig 4. Merkel cell polyomavirus genome organization. Noncoding control region (NCCR): bipartite origin of replication. Early gene region: large T antigen (LT), small T antigen (ST), 57kT antigen (57kT), alternative T antigen open reading frame (ALTO), and microRNA (miRNA). Late gene region: capsid proteins (VP1-3). (Used with permission from Stakaitytė et al.[92] This work is licensed under a Creative Commons license.)

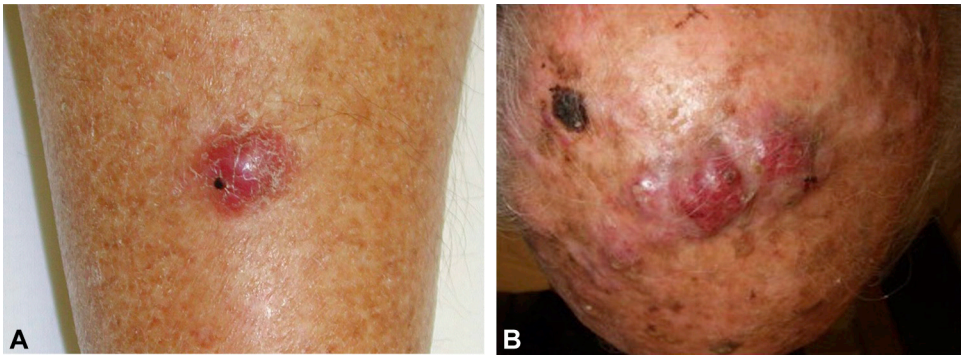

Fig 5. Merkel cell carcinoma (MCC). **A**, Typical MCC nodule present on the leg of a patient. **B**, MCC in a patient with metastatic renal carcinoma. *A*, Image credit to Howard Peach, Leeds Teaching Hospitals National Health Service Trust, United Kingdom. Used with permission from Stakaitytė et al.[92] This work is licensed under a Creative Commons license. *B*, Used with permission from Han et al.[115]

The presence of HPV does not currently affect cSCC treatment strategy, but additional preventative and treatment options for organ transplant and EV patients exist (Table I). Radiation therapy, however, should be avoided in patients with EV because it can enhance the deleterious effects of HPV.[70]

Vaccines and immunotherapy

Three recombinant vaccines based upon L1 protein (bivalent, quadrivalent, and nonavalent) are available to prevent infection from specific HR HPV types (Table IV).[71,72] The nonavalent vaccine (Gardasil 9; Merck & Co, Inc, Kenilworth, NJ) is the only vaccine currently available in the United States, while the others are still used in certain countries.[73] All 3 vaccines are similarly effective in preventing cervical cancer, even though the nonavalent vaccine provides direct protection against more cervical cancer–inducing HPV types.[74] The nonavalent vaccine is also indicated to prevent vulvar, vaginal, and anal cancer and associated precursors, as well as condyloma acuminata.[75] Future indications may include skin cancer prevention because reports of quadrivalent vaccination preventing keratinocyte carcinomas in immunocompetent patients have been published.[76]

Therapeutic vaccines and L2-based preventative vaccines are being investigated (Table V).[9] L2 sequences are highly conserved across HPV types, giving L2-based vaccines the potential to protect against many HPV types. In addition, many immunotherapies and targeted therapies for HPV-related malignancies are being investigated, and several are approved by the US Food and Drug Administration (Table V).

MERKEL CELL POLYOMAVIRUS

Key points

- **Merkel cell polyomavirus is nearly ubiquitous among skin flora but rarely causes Merkel cell carcinoma**
- **Merkel cell polyomavirus small T antigen and truncated large T antigen promote Merkel cell carcinoma oncogenesis**
- **Merkel cell carcinoma typically presents in white patients as a painless, rapidly expanding red to violaceous nodule in areas exposed to ultraviolet light**
- **Merkel cell carcinoma is highly aggressive, and treatment strategies are still evolving**

Merkel cell polyomavirus

Merkel cell polyomavirus (MCPyV) is a nonenveloped double-stranded DNA virus of the α-polyomavirus genus that is associated with Merkel cell carcinoma (MCC) development.[77] MCPyV was first discovered in 2008 by Feng et al[78] and is the only 1 of 14 human polyomaviruses linked with skin cancer.[79,80] MCPyV can be found in multiple anatomic locations and is nearly ubiquitous among skin flora.[81-83] Transmission likely occurs through contact with infected individuals who cutaneously shed MCPyV virions or with a fomite harboring previously shed virions.[83] Infection occurs early in life, with 60% to 80% of children testing positive for antibodies by 4 to 5 years of age.[84] Most MCPyV carriers are asymptomatic, harboring the virus in an innocuous state, and only a small portion develop MCC.[85]

Structure and genome. Most MCC cells contain a clonally integrated copy of the MCPyV genome.

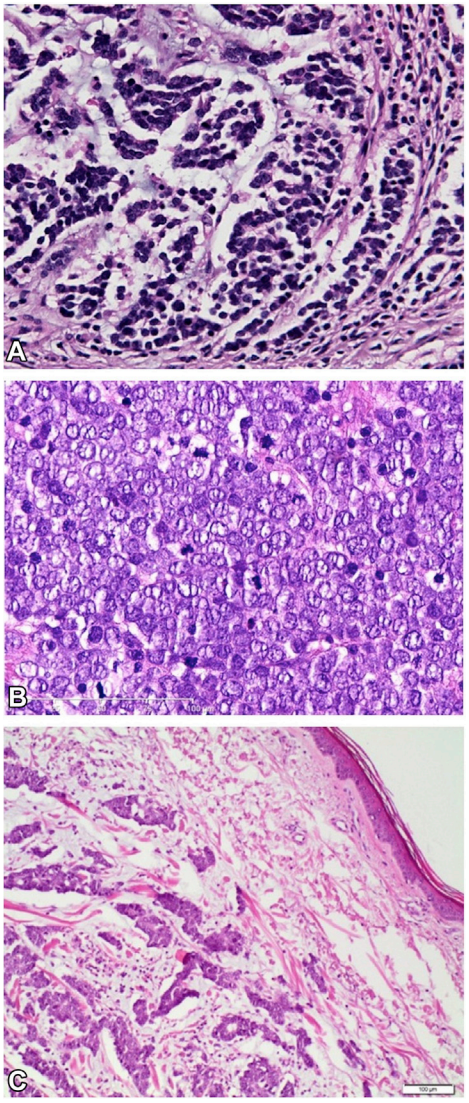

Fig 6. Merkel cell carcinoma (MCC) histology. **A**, Small-cell variant, histologically indistinguishable from bronchial small-cell carcinoma. **B**, Intermediate variant of MCC showing vesicular, basophilic nuclei with prominent nucleoli and high mitotic activity. **C**, Trabecular variant is rare and normally only seen as a small component of a mixed variant. Used with permission from Jaeger et al.[121] This work is licensed under a Creative Commons license.

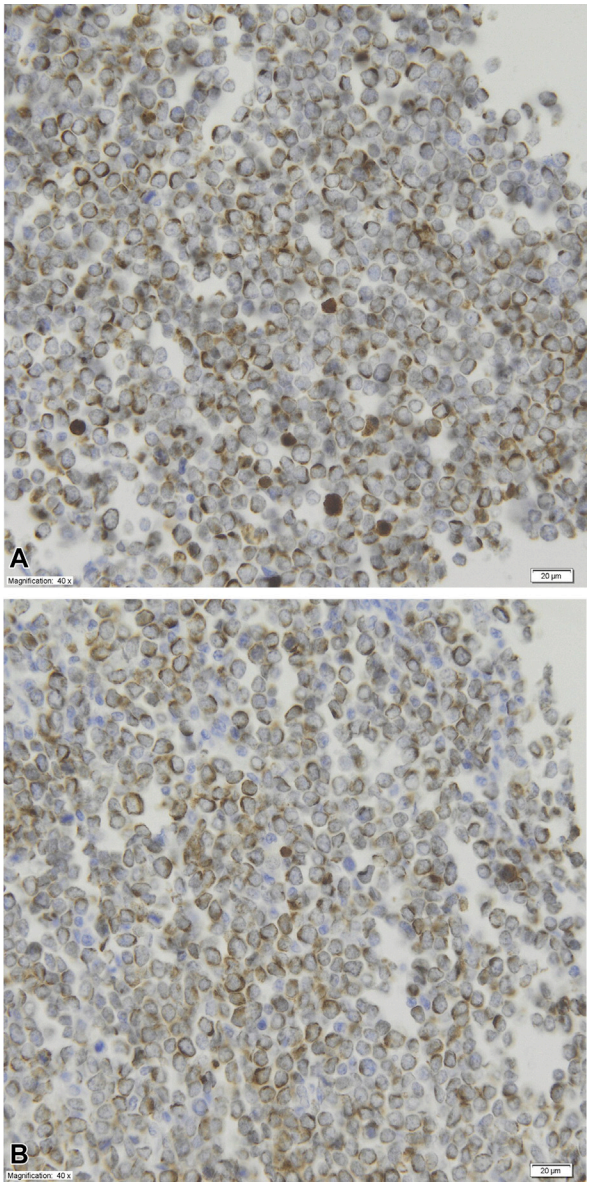

Fig 7. Merkel cell carcinoma (MCC). Typical paranuclear dot-like staining pattern in MCC. Pattern can be revealed either with pan-cytokeratin AE1/3 (**A**) and more specifically with cytokeratin 20 (**B**). Used with permission from Czapiewski and Biernat.[114]

Table VI. Immunohistochemistry of Merkel cell carcinoma and other tumors*

Tumor	CK20	CK7	Chromogranin A	NSE	TTF-1	S100	CD45 (LCA)	MASH-1	Vimentin
Merkel cell carcinoma	+	−	+/−	+	−	−	−	−	−
Small cell carcinoma of the lung	−	+	+/−	+/−	+	−	−	+	−
Melanoma	−	−	−	+/−	−	+	−	−	+
Lymphoma	−	−	−	−	−	−	+	−	+

CD45, Cluster of differentiation 45; *CK*, cytokeratin; *LCA*, leukocyte common antigen; *MASH-1*, mammalian achaete-scute homolog 1; *NSE*, neuron-specific enolase; *TTF-1*, thyroid transcription factor 1.

*Adapted from Schrama and Becker[103] and Becker JC, Assaf C, Vordermark D, et al. Brief S2k guidelines—Merkel cell carcinoma. J Dtsch Dermatol Ges 2013;11[suppl 3]:29-36.

Table VII. Some potential cells of origin for Merkel cell carcinoma and their shared markers/features with Merkel cell carcinoma*

	Markers/features	References
Merkel cell carcinoma	CK20$^+$, NSE$^+$, PAX5$^+$, NFP$^+$, TdT$^+$, TTF-1$^-$, CD45$^-$, and S100$^-$	Zur Hausen et al[123] and Ratner et al[182]
Merkel cells	CK20$^+$ and electron microscope morphology	Tang and Toker[183] and Moll et al[184]
Pro/pre-B and pre-B cells	PAX5$^+$ and TdT$^+$	Gore et al[185] and Adams et al[186]
Dermal fibroblasts	Major target of MCPyV infection, support productive viral transcription and replication	Liu et al[187]

CK20, Cytokeratin 20; *LCA*, leukocyte common antigen; *MCPyV*, Merkel cell polyomavirus; *NFP*, neurofilament protein; *NSE*, neuron-specific enolase; *PAX5*, paired box gene 5; *TdT*, terminal deoxynucleotidyl transferase; *TTF-1*, thyroid transcription factor 1.
*Reprinted with permission from Liu et al.[79]

Stage		Primary Tumor	Lymph Node	Metastasis
0		In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I	Clinical*	≤ 2 cm maximum tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
I	Pathological**	≤ 2 cm maximum tumor dimension	Nodes negative by pathologic exam	No distant metastasis
IIA	Clinical	> 2 cm tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIA	Pathological	> 2 cm tumor dimension	Nodes negative by pathological exam	No distant metastasis
IIB	Clinical	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIB	Pathological	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by pathologic exam	No distant metastasis
III	Clinical	Any size / depth tumor	Nodes positive by clinical exam (no pathological exam performed)	No distant metastasis
IIIA	Pathological	Any size / depth tumor	Nodes positive by pathological exam only (nodal disease not apparent on clinical exam)	No distant metastasis
		Not detected ("unknown primary")	Nodes positive by clinical exam, and confirmed via pathological exam	No distant metastasis
IIIB	Pathological	Any size / depth tumor	Nodes positive by clinical exam, and confirmed via pathological exam OR in-transit metastasis***	No distant metastasis
IV	Clinical	Any	+/- regional nodal involvement	Distant metastasis detected via clinical exam
IV	Pathological	Any	+/- regional nodal involvement	Distant metastasis confirmed via pathological exam
* Clinical detection of nodal or metastatic disease may be via inspection, palpation, and/or imaging				
**Pathological detection/confirmation of nodal disease may be via sentinel lymph node biopsy, lymphadenectomy, or fine needle biopsy; and pathological confirmation of metastatic disease may be via biopsy of the suspected metastasis				
***In transit metastasis: a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion				

Fig 8. Tumor node metastasis criteria and stage groupings for new 8th edition American Joint Committee on Cancer Merkel cell carcinoma staging system. Used with permission from Harms et al.[112]

Clonal integration appears to be a driving force in MCC development, as the MCPyV genome is found as a nonintegrated episome in MCPyV carriers without MCC.[78,86-88] The MCPyV genome consists of 3 regions: a noncoding regulatory region, an early coding region, and a late coding region (Fig 4).[9] The early coding region is expressed upon MCPyV cellular entry and consists of large T antigen (LT), small T antigen (ST), and the alternative LT open reading frame.[89-91] The T antigens are oncoproteins required for MCC development and cell survival.[79] The late-coding region includes major capsid protein VP1 (cellular binding/entry) and minor capsid proteins VP2 (increases infectivity) and VP3 (no role in MCC).[81,87,92,93]

MCC transformation. During MCC development, the virus undertakes 2 mutations: one mutation enables clonal integration and one causes truncation of LT.[94] The rarity of both mutations occurring accounts for the low incidence of MCC despite the high incidence of MCPyV infection.[9] LT truncation is necessary for oncogenesis and results from a deletion or stop mutation, possibly because of UV radiation.[95] Truncation occurs at the C-terminus,

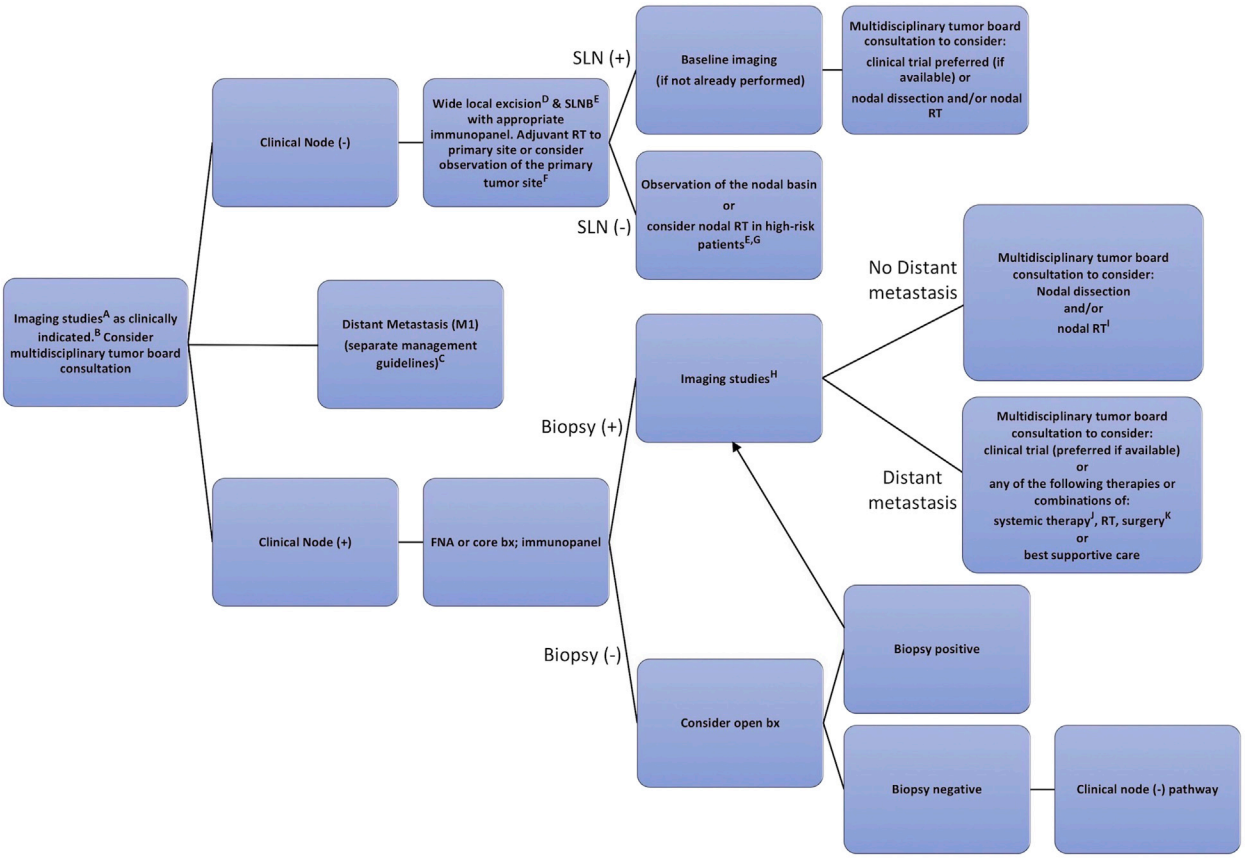

Fig 9. Recommended treatment strategy for confirmed Merkel cell carcinoma (MCC). Adapted with permission from the National Cancer Center Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Merkel cell carcinoma V.1.2018. © 2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data become available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. [A]Brain magnetic resonance imaging (MRI) with contrast and neck/chest/abdomen/pelvis computed tomography (CT) with contrast or whole body fluorodeoxyglucose positron emission tomography (FDG PET)/CT may be useful to identify and quantify regional and distant metastases. Some studies indicate that whole body FDG PET/CT may be preferred in some clinical circumstances. If whole body FDG PET/CT is not available, CT or MRI with contrast may be used. Imaging may also be useful to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, small cell lung cancer), especially in cases where CK-20 is negative. [B]Imaging is encouraged whenever metastatic or unresectable disease is suspected based on history and physical examination (H&P) findings. The most reliable staging tool to identify subclinical nodal disease is sentinel lymph node biopsy (SLNB). [C]Readers should reference complete NCCN guidelines (MCC-4) for information regarding management of distant metastasis (M1). [D]See Priniciples of Excision (MCC-C) of complete NCCN guidelines. In selected cases in which complete surgical excision is not possible, surgery is refused by the patient, or surgery would result in significant morbidity, radiation monotherapy may be considered (see Principles of Radiation Therapy [MCC-B] of complete NCCN guidelines). [E]In the head and neck region, risk of false-negative SLNBs is higher because of aberrant lymph node drainage and the frequent presence of multiple SLN basins. If SLNB is not performed or is unsuccessful, consider irradiating nodal beds for subclinical disease (see Principles of Radiation Therapy MCC-B of complete NCCN guidelines). [F]Consider observation of the primary site in cases where the primary tumor is small (eg, <1 cm) and widely excised with no other adverse risk factors such as lymphovascular

disrupting a p53 binding site and genes essential for viral replication.[79,87,90,96,97] During truncation, the N-terminus is preserved up to and including the MCPyV T unique region, retaining LT's ability to sequester and inactivate pRB.[9,78,90,92,97] ST, unlike LT, promotes oncogenesis in its native form.[98] ST acts in the mammalian target of rapamycin pathway to dysregulate cap-dependent cellular protein translation by promoting hyperphosphorylation and inactivation of 4E-BP1, the major regulator of eukaryotic cap-dependent translation.[99]

Merkel cell carcinoma

MCC is a rare primary neuroendocrine cutaneous carcinoma with an incidence of 0.79 per 100,000 population.[100] MCC is more aggressive than melanoma and has a disease-associated mortality of 46%.[101] The tumor was first described in 1972 as a "trabecular carcinoma of the skin."[102] The presence of neurosecretory granules led to the belief that Merkel cells (MCs), or cutaneous mechanoreceptors in the basal layer of the epidermis, were the cells of origin, and the tumor was redefined as MCC in the early 1980s.[103-105]

Presentation and risk factors. Common characteristics of MCC can be summarized by the acronym AEIOU: *a*symptomatic, *e*xpanding (rapidly) nodule, *i*mmunosuppressed, *o*lder, and *U*V exposure.[106] MCC typically occurs as a painless red to violaceous nodule in sun-exposed areas on the head and neck or limbs (Fig 5).[106,107] The lesion may initially be overlooked because of the benign appearance similar to a cyst or fibroma.[87,108] MCC expands rapidly over a few months and occasionally ulcerates.[106,109-111] MCC occurs primarily in non-Hispanic whites (96.4% of cases), with a median age of 76 years, and 97% of cases occur after 50 years of age.[112]

Although the majority of MCC arises in immunocompetent patients, it occurs at greater rates in immunocompromised patients.[9,113,114] Spontaneous MCC regression has been noted in some transplant recipients after the cessation of immunosuppressive medications,[115,116] and the presence of a strong intratumoral CD8 and CD4 lymphocyte response is an independent predictor of survival.[78,115]

UV exposure is a significant risk factor for MCC and may contribute by causing immunosuppression and mutagenesis. The majority of MCCs in Australia, the country with the highest MCC incidence, are MCPyV-negative and may arise from a UV-driven pathway.[117] The incidence of MCPyV-negative MCC, however, may have previously been overestimated, as MCPyV-detection techniques used in a recent study detected MCPyV DNA in nearly 100% of MCC.[118]

Histology. MCC consists of trabecular aggregates of small, round monomorphic blue cells with scant cytoplasm.[114] Cells demonstrate a high mitotic rate and contain apoptotic bodies with occasional necrosis.[113] MCC occurs in the reticular dermis or subcutis, rarely involving the papillary dermis or epidermis.[103,114,119] Three histologic subtypes exist based upon cellular appearance and arrangement: trabecular (the least common), intermediate (the most common), and small cell (Fig 6). Intermediate and small cell subtypes are more clinically aggressive than the trabecular subtype.[120,121]

Immunohistochemical staining distinguishes MCC from other tumors, including melanoma, metastatic small cell lung cancer, lymphoma, neuroblastoma, and metastatic carcinoid (Table VI).[113,122] CK20 staining reveals a paranuclear dot-like pattern (Fig 7).[114] MCC is also positive for neuroendocrine markers such as chromogranin A, synaptophysin, and neuron-specific enolase, and negative for TTF-1, CK7, PS100, and CD45.[85]

The theory that MCC arises from MCs is now being disputed for several reasons: MCs are epidermal while MCC is primarily dermal, MCs are postmitotic, and MCs and MCC have differing phenotypic

invasion or immunosuppression. [G]Consider RT when there is a potential for anatomic (eg, previous history of surgery including wide local excision), operator or histologic failure (eg, failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB. Consider RT in cases of profound immunosuppression. [H]Whole body PET with fused axial imaging (CT or MR) or neck/chest/abdomen/pelvis CT with contrast, with or without brain MRI, may be useful to identify and quantify regional and distant metastases. Some studies indicate that whole body PET with fused axial imaging may be preferred in some clinical circumstances. [I]Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest survival benefit for adjuvant chemotherapy (see Principles of Systemic Therapy [MCC-D] of complete NCCN guidelines). [J]Under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered. *Bx*, Biopsy; *RT*, radiation therapy; *SLN*, sentinel lymph node; *SLNB*, sentinel lymph node biopsy.

expression profiles.[123] Suggested alternatives for MCC cellular origin include pre/pro-B cells, epidermal and dermal stem cells, and dermal fibroblasts (Table VII).[78,124]

Prognosis and staging. The American Joint Committee on Cancer 8th edition staging criteria consider clinical and pathologic criteria separately (Fig 8).[112] The 5-year overall survival rates for local, nodal, and distant disease are 51%, 35%, and 14%, respectively.[112] Metastasis is common, occurring in 40% to 50% of patients, and can even result from superficial tumors.[113,125] Liver, lung, and bone are most commonly involved.[125] Positive prognostic factors include tumor size ≤2 cm, tumor-infiltrating immune cells, absence of lymphatic invasion, primary tumor on upper limb, female sex, and nodular growth pattern.[103,113] Some studies have indicated that MCPyV-positive tumors have a more favorable outcome, while others have not.[104]

Management

MCPyV-positive and -negative MCC should be treated according to the same National Comprehensive Cancer Network guidelines (Fig 9).[126] However, quantitation of MCPyV oncoprotein antibodies may be considered during initial workup because results may impact follow-up—seronegative patients may have a higher risk of recurrence, and in seropositive patients, a rising titer may be an early indicator of recurrence. The mainstay for nonmetastatic MCC management is wide local excision with sentinel lymph node biopsy.[126] Baseline imaging is recommended for a positive sentinel lymph node biopsy, clinically positive nodes, or metastatic disease. Nodal radiation or lymphadenectomy are necessary for pathology-proven nodal disease and can be used for clinically detected nodal disease. Nodal radiation may be considered in high-risk patients without proven nodal disease.[126]

Mohs micrographic surgery may be an appropriate alternative to wide local excision in some cases, and a recent review demonstrated these methods to have equivalent overall survival and initial tumor clearance rates in early stage MCC without nodal disease.[127] Another recent review indicated that local and regional radiation monotherapy may be a reasonable treatment for inoperable stage I, II, or III disease.[128]

Avelumab, a fully human anti-PD-L1 monoclonal antibody, is the only treatment for metastatic MCC that is approved by the US Food and Drug Administration. Avelumab demonstrated a treatment response in 33% of patients in a phase II clinical trial with a median overall survival of 11.3 months.[129,130] Pembrolizumab and nivolumab are anti-PD-L1 antibodies that are also being studied for use in metastatic MCC.[131-133]

In conclusion, HPV and MCPyV both contribute to a high oncologic disease burden globally. HPV is etiologically linked to multiple types of cancer, while MCPyV is linked to 1 highly aggressive cancer. HPV vaccination and cancer screening already play a large role in the prevention of cervical cancer and are now being investigated and implemented for other cancers. Effective treatment methods for MCC, especially advanced MCC, are currently limited, underscoring the importance of early clinical recognition and treatment.

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Answers to CME examination

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1. d
2. b
3. a
4. d