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Evidence-Based Clinical Practice Guidelines for Extramammary Paget Disease

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IMPORTANCE Extramammary Paget disease (EMPD) is a frequently recurring malignant neoplasm with metastatic potential that presents in older adults on the genital, perianal, and axillary skin. Extramammary Paget disease can precede or occur along with internal malignant neoplasms.

OBJECTIVE To develop recommendations for the care of adults with EMPD.

EVIDENCE REVIEW A systematic review of the literature on EMPD from January 1990 to September 18, 2019, was conducted using MEDLINE, Embase, Web of Science Core Collection, and Cochrane Libraries. Analysis included 483 studies. A multidisciplinary expert panel evaluation of the findings led to the development of clinical care recommendations for EMPD.

FINDINGS The key findings were as follows: (1) Multiple skin biopsies, including those of any nodular areas, are critical for diagnosis. (2) Malignant neoplasm screening appropriate for age and anatomical site should be performed at baseline to distinguish between primary and secondary EMPD. (3) Routine use of sentinel lymph node biopsy or lymph node dissection is not recommended. (4) For intraepidermal EMPD, surgical and nonsurgical treatments may be used depending on patient and tumor characteristics, although cure rates may be superior with surgical approaches. For invasive EMPD, surgical resection with curative intent is preferred. (5) Patients with unresectable intraepidermal EMPD or patients who are medically unable to undergo surgery may receive nonsurgical treatments, including radiotherapy, imiquimod, photodynamic therapy, carbon dioxide laser therapy, or other modalities. (6) Distant metastatic disease may be treated with chemotherapy or individualized targeted approaches. (7) Close follow-up to monitor for recurrence is recommended for at least the first 5 years.

CONCLUSIONS AND RELEVANCE Clinical practice guidelines for EMPD provide guidance regarding recommended diagnostic approaches, differentiation between invasive and noninvasive disease, and use of surgical vs nonsurgical treatments. Prospective registries may further improve our understanding of the natural history of the disease in primary vs secondary EMPD, clarify features of high-risk tumors, and identify superior management approaches.

Supplemental content

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Extramammary Paget disease (EMPD) is an epithelial malignant neoplasm in apocrine gland–rich skin, including the vulva, scrotum, and penis.[1] Extramammary Paget disease mimics inflammatory conditions, thereby delaying diagnosis. The cell of origin is unknown, with apocrine origin presumed, but intraepidermal keratinocytes and Toker cells are also implicated.

Although most EMPD is confined to the epidermis (intraepidermal EMPD [epiEMPD]), it can also invade the dermis and penetrate soft tissues (invasive EMPD [invEMPD]). Invasive EMPD can metastasize to regional lymph nodes (LNs) and other organs (metastatic EMPD). This type is distinct from secondary EMPD, which may evolve synchronously or asynchronously with an underlying adenocarcinoma. Mutational differences between secondary EMPD and associated underlying adenocarcinomas have been reported.[2]

The clinical practice guidelines presented are based on a systematic review of the literature. Recommendation statements focus on diagnosis and workup of EMPD and management of primary EMPD, including metastatic disease.

Methods

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (eFigure, eMethods, and eTable 1 in the Supplement). For guideline development, experts in EMPD from all key stakeholder specialties were identified (by N.K., J.L.O., B.W., and M.A.) through publication history, clinical expertise, and peer nomination. Secondary review was performed (M.A.) to ensure that all invitees had expertise in collaborative cancer research (eg, participation in National Comprehensive Cancer Network guideline groups or other oncology collaborative groups) and recognition as thought leaders in EMPD or related malignant neoplasms. Key questions included the following: "What are the best practices for diagnosis and risk assessment of EMPD?" and "How is primary EMPD, including metastatic disease, best managed?" Data extraction was performed for 23 493 cases of EMPD from 483 reports from January 1990 to September 18, 2019, meeting inclusion criteria (by N.K., J.L.O., B.W., J.X.W., V.H., and M.B.D.). A consensus meeting was held by teleconference in May 2020. Draft recommendations were iteratively reviewed until consensus was reached. Principles of EMPD management are summarized in the **Box**.

Clinical Presentation and Workup for EMPD

Recommendation 1

Physical examination should include examination of pubic, inguinal, genital, perineal, perianal, and axillary regions and associated regional LNs. Further examination may be tailored based on sex, presence of invasive disease, review of systems, and presence of discontinuous lesions (Grade C; category 2A).

The mean (SD) age of patients with EMPD was 70.7 (3.3) years (9951 of 18 600 women [53.5%]; **Table 1**).[3-6] The most common sites of lesions were the vulva (44.8% [8325 of 18 600]) and penis-scrotum (27.0% [5017 of 18 600]); 92.0% of lesions (17 112 of 18 600) were in regions normally covered by underwear. Men were 12.5-fold more likely to have perineal and perianal involvement.[7] Only

Box. Principles of EMPD Management

Principles of EMPD Management[a]

Overall Considerations

- The primary goal of the treatment of EMPD is complete excision with clear surgical margins and preservation of function and cosmesis. Refractory or localized intraepidermal disease may be treated with clinical margin clearance or topical therapy. All treatment decisions should be individualized based on clinical presentation, medical history, and patient preference.
- No specific systemic therapy for advanced disease can be recommended. Distant metastases are uncommon.

Screening

- Age-appropriate malignant neoplasm screening should be performed at baseline to distinguish between primary and secondary EMPD (Grade A). Additional screening should be guided by EMPD anatomical location, review of systems, physical examination, and laboratory tests or imaging findings. EMPD may precede an associated internal malignant neoplasm by 5 years.
- Routine use of sentinel LN biopsy in the workup of EMPD is not recommended (Grade C).

Intraepidermal EMPD

- The decision regarding the extent of resection to obtain tumor-free margins should be individualized. If tumor-free margins are desired, margin-controlled surgery (eg, MMS or CCPDMA) with en face sectioning is preferred (Grade B).
- Primary nonsurgical therapy (eg, imiquimod and photodynamic therapy) or other modalities (eg, carbon dioxide laser) may be considered in cases in which the morbidity from surgery is high (Grade D). Recurrences are common, and close surveillance is recommended to monitor for recurrence and adverse effects.

Invasive EMPD

- Surgical resection with curative intent is recommended (Grade B). Margin-controlled surgery (eg, MMS or CCPDMA) with en face sectioning is preferred; however, preoperative mapping biopsies combined with wide local excision can be considered as an alternative approach.
- Adjuvant nonsurgical therapies may be considered for noninvasive disease at the margins where continued surgical resection may incur excess morbidity (Grade D).
- Radiotherapy with curative intent may be indicated in cases in which surgery is not advised or feasible (Grade B). Radiotherapy can be considered in the adjuvant setting after surgery for persistent or recurrent EMPD (Grade C).

Metastatic EMPD

- Metastatic EMPD may be treated with chemotherapy, targeted therapy, or immune checkpoint inhibitors. Multidisciplinary tumor board consultation or clinical trial enrollment is recommended (Grade C).

Principles of Radiotherapy in EMPD[a]

Overall Considerations

- Consultation with a radiation oncologist familiar with EMPD is recommended given the rare nature of the malignant neoplasm.
- When radiotherapy is selected, protracted fractionation is associated with improved function and cosmesis and should be considered, especially for poorly vascularized areas.
- Contraindications to radiotherapy include prior radiotherapy of the target volume and genetic conditions that predispose patients to increased radiosensitivity (eg, ataxia telangiectasia).

(continued)

Box. (continued)

Radiotherapy should be used with caution in patients with connective tissue diseases.

Primary Radiotherapy

- In select cases for which surgical intervention is not possible or preferred and for which topical treatments are not preferred, primary radiotherapy may be used (Grade C).
- Data on dosing are limited. Reported dosing ranges from 30 to 70 Gy divided into at least 1.8 to 2.5 Gy per fraction. Mean recurrence rates are more than 30% (Grade C).

Adjuvant Radiotherapy

- Tumor bed: data on dosing are limited. Reported dosing ranges from 50 to 70 Gy with approximately 1.8 to 2.5 Gy per fraction. Margins are respective of tumor location and potential for wide subclinical spread (Grade C).
- Lymph node basin: data on dosing are limited. Reported dosing ranges from 50 to 70 Gy with 1.8 to 2.5 Gy per fraction (Grade C).
- Recurrent tumor: dosing is poorly defined but may assist with surgery for curative intent (Grade C).

Abbreviations: CCPDMA, complete circumferential peripheral and deep margin assessment; EMPD, extramammary Paget disease; LN, lymph node; MMS, Mohs micrographic surgery.

[a] All statements are consensus category 2A.

4.4% of patients (100 of 2298 within studies reporting) presented with multiple lesions. The mean (SD) time from patient-reported onset to diagnosis was 35.7 (13.8) months. The mean (SD) lesion diameter was 7.0 (2.7) cm. Most studies (62 of 92) reported recurrent lesions. Previous misdiagnoses included tinea cruris, candidiasis, eczema, fistula, and hemorrhoids.

Common clinical findings were erythema (35.8% [823 of 2298]), erosion or ulceration (15.1% [347 of 2298]), hypopigmentation (11.2% [258 of 2298]), nodules (10.1% [231 of 2298]), and "eczematous" presentation (8.3% [191 of 2298]). Symptoms included pruritus (28.1% [645 of 2298]; more common in the scrotum than the vulva) and pain (5.4% [123 of 2298]; typically cutaneous but also dysuria).

Lymph node examination was reported in 896 cases, and 194 (21.7%) had lymphadenopathy (likely an overestimate given consensus opinion). Compared with positive results from sentinel LN biopsy (SLNB), lymphadenopathy was associated with LN metastasis and worse overall survival. Sentinel LN biopsy is discussed further in recommendation 6.[8]

Table 1. Demographic Characteristics of Included Cases

Characteristic	Cases, No. (% of total) (N = 23 493)
Cases reporting demographic data, total No.	18 600
Age, mean (SD), y	70.7 (3.3)
Sex	
Female	9951 (53.5)
Male	8649 (46.5)
Race and ethnicity[a]	
American Indian or Alaska Native	0
Asian and Pacific Islander	6659 (35.8)
Black or African American	260 (1.4)
White	11 662 (62.7)
Location of EMPD	
Vulvar	8333 (44.8)
Penoscrotal	5022 (27.0)
"Genital"	1786 (9.6)
Perianal	1228 (6.6)
Inguinal	391 (2.1)
Perineal	372 (2.0)
Axillary	167 (0.9)
Other[b]	1321 (7.1)
Cases within studies clearly reporting type, total No.	13 509
EMPD type	
Primary EMPD	11 064 (81.9)
Secondary EMPD	2441 (18.1)
Lesion diameter, mean (SD), cm	7.0 (2.7)
Case reporting clinical finds, total No.	2298
Clinical findings	
Erythema	823 (35.8)
Erosion or ulceration	347 (15.1)
Hypopigmentation	258 (11.2)
Nodules	231 (10.1)
Eczematous	191 (8.3)

Abbreviation: EMPD, extramammary Paget disease.

[a] Asian cases are likely underrepresented as some studies from Asia did not specify ethnicity.

[b] Other included pubic, abdominal, thigh, thoracic, gluteal, sacral, perioral, scalp, and upper cutaneous lip. One study reported cases in patients with prior immunosuppressive therapy[3]; this occurrence is possibly underreported. Three studies reported a family history of cancer[4-6]; this occurrence is possibly underreported.

Recommendation 2

A biopsy should be performed for refractory or atypical intertriginous, genital erythematous, or papulosquamous lesions. Multiple biopsies may better characterize large, complex tumors, particularly nodular or thickened areas (Grade B; category 2A).

For large patches or plaques, multiple broad biopsies may be required to collect sufficient skin samples for pathologic analysis. Nodular or thickened areas may represent invasive disease,[9,10] for which biopsy to the level of adipose tissue is advised.

Histopathologically, EMPD cells are larger than keratinocytes, have pale to finely granular cytoplasm, and are arranged as single cells or cell clusters in the epidermis alone (epiEMPD) or in the dermis or deeper (invEMPD). One-third of reported cases were epiEMPD (32.1% [4255 of 13 259]), whereas the remainder were invEMPD. This finding likely represents publication bias given expert consensus that epiEMPD is more common. Twenty-six studies noted depth of invasion: 10.2% (61 of 597) were microinvasive (defined as ≤1 mm dermal invasion), 70.2% (419 of 597) were frank dermal, and 19.6% (117 of 597) were subcutaneous or deeper. The mean (SD) depth (reported in 5 studies [202 cases]) was 3.0 (1.0) mm. Among invEMPD cases reporting depth, 59.2% (190 of 321) were confined to the upper dermis, with the remainder in the reticular dermis. More than one-third of EMPD cases (39.0% [404 of 1036]) had adnexal involvement. Hair follicle involvement and eccrine gland involvement were common, with a mean depth of 1.6 mm (range, 0.5-3.3 mm) among cases with hair follicle involvement and 2.4 mm (range, 0.8-3.2 mm) among cases with eccrine gland involvement.[11]

Invasive EMPD was associated with being 60 years of age or older[12] and recurrence.[13] Invasive EMPD was associated with worse outcomes, including nodal metastasis,[12,14,15] distant metastasis,[16] and decreased overall survival.[17] Lymphovascular invasion occurred in 18.1% (198 of 1094) of cases (20 studies). Perineural invasion was rare. Lymphovascular invasion was associated with LN metastasis.[18,19]

Recommendation 3

A diagnostic immunohistochemical panel for EMPD consisting of cytokeratin 7 (CK7)–positive, CK20-positive or CK20-negative, p63-negative, SOX10-negative, and carcinoembryonic antigen (CEA)–positive results is recommended. This panel can exclude histologic mimics. CK20 and/or CDX2 positivity may potentially indicate secondary EMPD (Grade A; category 2A).

Histologic mimickers of EMPD include tumors exhibiting pagetoid spread, such as squamous cell carcinoma in situ (p63 positive), melanoma in situ (SOX10 positive), and, less commonly, sebaceous carcinoma (p63 positive or negative and adipophilin positive) (eTable 2 in the Supplement). Site-specific markers include gross cystic disease fluid protein (GCDFP15; genital EMPD with apocrine involvement) and CDX2 and CK20 (perianal disease).[20,21] Once diagnosis is confirmed, a suggested profile to screen for secondary EMPD includes CK7-positive, CK20-positive, CDX2-positive, GCDFP15-negative, and GATA3-negative results.[22] Overexpression of *ERBB2* (formerly *HER2*)[12,13,23-25] and protein kinase B[26-31] may be associated with invasive disease and LN metastasis, but some studies are conflicting.[32]

Recommendation 4

US Preventive Services Task Force age-appropriate and anatomical location–directed baseline malignant neoplasm screening should be performed to identify secondary EMPD. Laboratory tests and imaging should be guided by EMPD anatomical location, review of systems, physical examination, and laboratory test results or imaging findings. Extramammary Paget disease may precede an associated internal malignant neoplasm by 5 years (Grade A; category 2A).

Among primary EMPD cases including information on metastasis, 19.7% of patients (1859 of 9435) presented with nodal metastasis, 2.5% (240 of 9435) presented with distant metastasis, 0.07% (7 of 9435) presented with satellite metastasis, and 0.7% (69 of 9435) presented with unspecified information on metastasis. Specified sites of distant metastasis included hepatic (61.3% [19 of 31]), skeletal (41.9% [13 of 31]), pulmonary (35.5% [11 of 31]), adrenal (16.1% [5 of 31]), thyroid (12.9% [4 of 31]), gallbladder (6.5% [2 of 31]), and peritoneal (6.5% [2 of 31]) metastasis. Metastasis after presentation is discussed in recommendation 12.

Secondary EMPD was reported in 18.1% of patients (2441 of 13 509 with studies reporting the type of EMPD). In 12 cases, the underlying malignant neoplasm was not adenocarcinoma. Common adenocarcinomas were colorectal (215, including 59 anal and 47 rectal), breast (83), prostate (46), urothelial or bladder (44), gastric (18), endometrial or ovarian (13), renal (5), and adnexal (39, including sweat gland). Surveillance, Epidemiology, and End Results Program data demonstrated that secondary malignant neoplasms in EMPD were elevated, with an excess absolute risk of 97.4 malignant neoplasms per 10 000 person-years.[33,34] The interval between EMPD and internal malignant neoplasm diagnosis was specified in 438 cases. Eighty-nine cases (20.3%) arose within 1 year after EMPD diagnosis. The remaining asynchronous cases occurred after a mean (SD) of 5.4 (2.0) years and, therefore, have an uncertain association with EMPD.

Low true-positive rates and relatively high false-positive rates for prostate-specific antigen (PSA) and CEA do not support screening by laboratory testing for all EMPD cases. Although PSA is commonly reported (11 studies), the PSA level was elevated in 15.7% of patients (11 of 70) in 1 study, although none had prostate cancer.[12] In another study, 4 of 15 occult malignant neoplasms in a 132-patient cohort were detected by PSA testing.[35] The clinical implications of a lead-time diagnosis in the latter study are unknown. Carcinoembryonic antigen is also commonly reported (10 studies), and the level was elevated in 1 study in 16.7% of patients (10 of 60), with 70.0% (7 of 10) having metastases.[36] Three additional studies reported similar findings.[37-39] Pooled analysis suggests false-positive rates of 41%. One report showed that initial CEA levels above 20 ng/mL (to convert to micrograms per liter, multiply by 1.0) indicated a worse disease course.[39] Other blood tests, such as alpha-fetoprotein,[40,41] cancer antigen 19-9,[35] cell-free DNA,[42] and CYFRA21-1 (cytokeratin 19 fragment),[43,44] have been performed, with the last showing some promise in monitoring treatment response.[44]

Additional organ-specific studies included colonoscopy (20 studies), cystoscopy (18), sigmoidoscopy (6), endoscopy (6), mammography (6), Papanicolaou test (5), and bone scan (4). Given the prolonged lag time between EMPD diagnosis and identification of an underlying malignant neoplasm, universal screening protocols are impractical and not cost-effective. Particularly when lesions are ill defined or invasive disease is identified, a review of systems and a consideration of the anatomical region of involvement should guide test selection, such as anoscopy or colonoscopy for perianal EMPD, colposcopy and urine cytologic screening for vulvar EMPD, and urine cytologic screening and uroscopy for penile disease. Transvaginal ultrasonography and other imaging modalities may assist with ruling out intra-abdominal malignant neoplasms. One group reported high detection rates of occult malignant neoplasms (11.4% [15 of 132]) within the first year of diagnosis using PSA testing (prostate carcinoma, 4 cases), urine cytologic screening (urothelial carcinoma, 3 cases), and mammography (breast carcinoma, 2 cases).[35] Although another group proposed more extensive patient testing with invEMPD, subgroup analysis did not reveal a higher risk of secondary malignant neoplasms in patients with invEMPD compared with epiEMPD.[45] Investigational diagnostic techniques include reflectance confocal microscopy[46-48] and optical coherence tomography.[49] There is no validated staging system specific for EMPD.[50]

Recommendation 5

Advanced imaging (computed tomography, positron emission tomography/computed tomography, and magnetic resonance imaging) may be used to screen for metastases if internal malignant neoplasms or lymphadenopathy are found on initial screening. It is particularly recommended to assess for regional lymphadenopathy when palpable lymphadenopathy or histologically invasive disease is present. The anatomical site may determine the preferred modality (Grade C; category 2A).

Computed tomography (44 studies, typically chest, abdomen, and pelvis), ultrasonography (20 studies, typically abdominal and/or pelvic), plain radiography (19 studies, typically chest radiograph),

positron emission tomography/computed tomography (11 studies), and magnetic resonance imaging (9 studies) were used to identify metastasis or underlying malignant neoplasms. Internal malignant neoplasms were, in some cases, found incidentally on imaging (18.8% [3 of 16]).[38,51] Imaging may assist in identifying advanced contiguous malignant neoplasms (secondary EMPD extending from an adjacent contiguous cutaneous adenocarcinoma), advanced disease after a positive focused malignant neoplasm screening workup, histologically invasive disease, or lymphadenopathy. The rate of contiguous malignant neoplasms in 1 study was 23.0% (37 of 161),[35] which was higher than in other reports.[52]

Recommendation 6

Broad, routine use of SLNB in EMPD is not recommended. There is no evidence that a positive sentinel LN results in treatment that changes disease-specific survival. Lymphadenopathy detected on physical examination should be investigated by imaging and biopsy or fine needle aspirate (Grade C; category 2A).

Sentinel LN biopsy was used in 20 studies, particularly scrotal EMPD studies.[12] In 21.7% of cases (137 of 630), SLNB findings were positive. Tumor invasion to the reticular dermis or subcutis were associated with positive SLNB (40.7% positivity rate [22 of 54] vs 0% for epiEMPD).[15,16] Tumor size and presence of nodules was not associated with positivity.[53] Sentinel LN biopsy methods included isosulfan blue dye injection,[18,54,55] radioisotope lymphoscintigraphy with blue dye,[15,18,55] and indocyanine green fluorescence.[55,56] One study compared indocyanine green fluorescence–navigated SLNB with isosulfan blue dye injection and radioisotope lymphoscintigraphy, with the former proving more sensitive.[55] In 1 study, there was no difference in overall survival between SLNB-positive (16 of 107 cases [15.0%]) and SLNB-negative patients.[18] The utility of identifying microscopic nodal disease is presently unknown. Because of the relatively higher proportion of reported SLNB-positive cases, use of SLNB in invasive EMPD and scrotal EMPD may be considered to assist with prognosis and determining further workup. However, in contrast to frank nodal disease detected by clinical examination or imaging, it is unclear whether adjuvant therapy or LN dissection for SLNB-positive cases improves disease-specific survival. A randomized clinical trial, a prospective database study, or a well-designed cohort study would be useful in guiding future recommendations for SNLB.

Management: epiEMPD and invEMPD

Management of EMPD varies based on patient factors, tumor characteristics, and medical specialty. A management algorithm is presented in **Figure 1**. Primary EMPD is commonly removed by surgery. Of the 10 178 cases treated surgically, 9225 (90.6%) were treated with wide local excision (WLE), 400 (3.9%) with Mohs micrographic surgery (MMS), 506 (5.0%) with complete circumferential peripheral and deep margin assessment (CCPDMA), 34 (0.3%) with WLE plus photodynamic therapy, and 13 (0.1%) with WLE plus radiotherapy. The recurrence rate for WLE alone was 37.0% (507 of 1371); for margin-controlled surgery, 18.7% (120 of 642); and for MMS, 11.2% (22 of 197) (**Table 2**).

The mean (SD) surgical margin was 1.9 (1.0) cm. With the use of case-level data modeled for different anatomical sites, surgical margins for 95% tumor clearance were 4 cm for penoscrotal or vulvar sites and 3.5 cm for perianal and axillary sites. Techniques for margin assessment included mapping biopsies,[4,57-63] particularly at perianal and vulvar sites. Reported clinical utility is mixed.[9,57,58,64,65] Lymph node dissection was performed in 3.7% of surgical cases (380 of 10 178), typically at the time of tumor excision. The indication for LN dissection vs targeted removal of clinically or radiologically identified affected LNs is unclear based on the reported cases. There is no definitive evidence that LN dissection or resection of LN metastasis improves overall survival; however, surgery within the LN basin may be considered based on clinical judgment. Cases reported in the literature did not clarify the indication for LN dissection.

Intraepidermal EMPD

Recommendation 7

Decisions regarding the extent of resection of epiEMPD for tumor-free margins should be individualized. Because progression-free survival is 1 to 3 years, various operative strategies may be considered (Grade D; category 2A). If tumor-free margins are desired, margin-controlled surgery (eg, MMS or CCPDMA) with en face sectioning is preferred (Grade B; category 2A). If complex reconstruction is performed, consider delaying reconstruction until negative margins are confirmed and selecting reconstructive options that permit surveillance for recurrence (Grade D; category 2A).

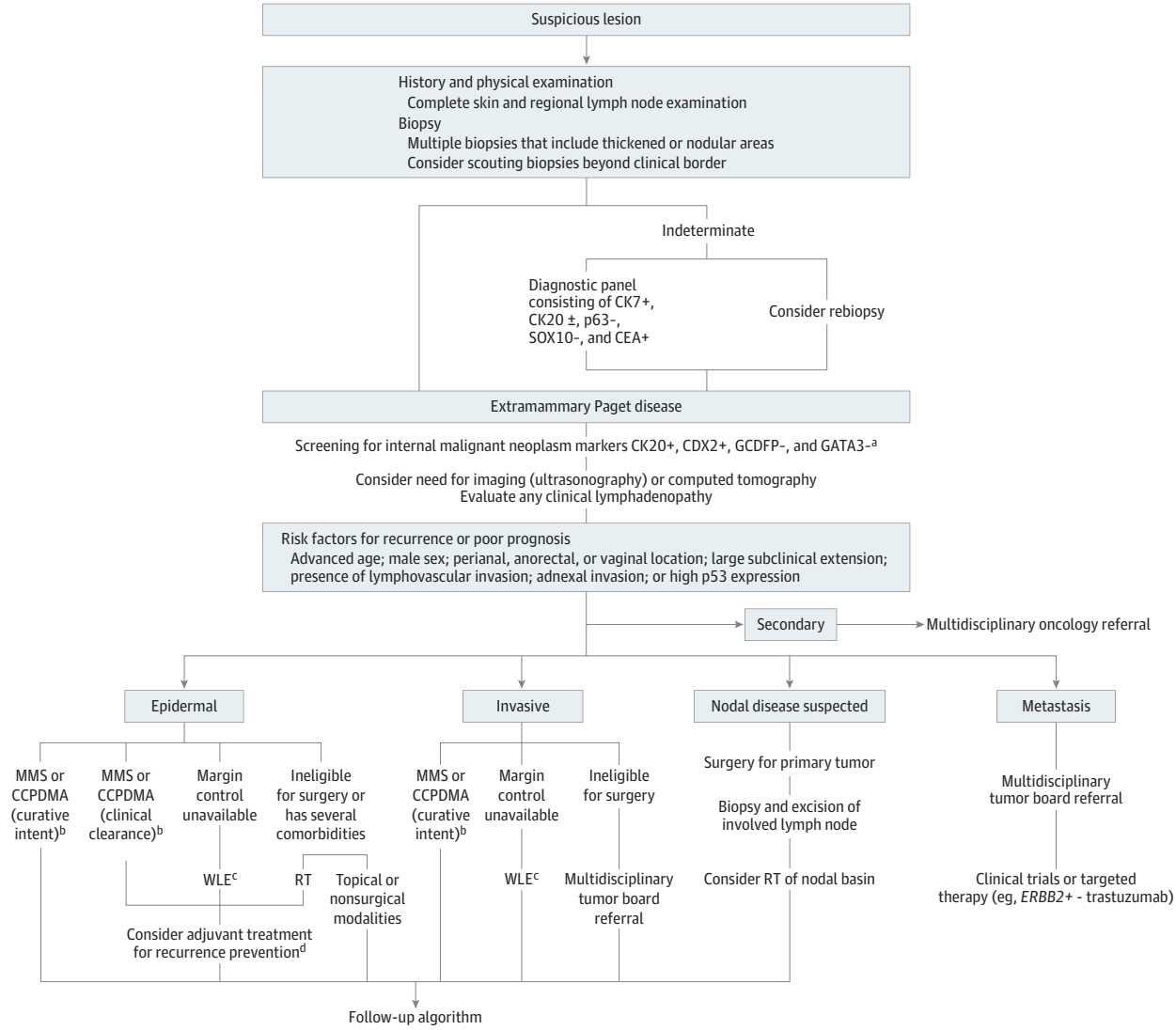
The median (SD) progression-free survival for epiEMPD was 20.4 (12.8) months.[66-69] Given the large size, chronicity, anatomical location, and patient-specific factors, excision of epidermal disease may induce unnecessarily high morbidity. Patient-centered discussion of treatment options, including observation, is important to guide management. If the decision is made to obtain complete tumor-free margins, margin-controlled techniques, such as MMS or CCPDMA, may have lower recurrence rates. Multidisciplinary surgical care must be considered when there is clinical perirectal and periurethral involvement. Immunohistochemistry (CK7[70,71] and CEA[72]) and periodic acid-Schiff with diastase staining[73] have been used with MMS to improve margin analysis. Recurrent epiEMPD can be retreated with surgery, which appears not to increase mortality (based on clinical experience of the guidelines group). For nonsurgical candidates, noninvasive therapies may be an option, albeit with likely higher recurrence rates (see recommendations 8 and 10).

Recommendation 8

Primary noninvasive therapy (eg, imiquimod and photodynamic therapy) or other modalities (carbon dioxide laser therapy) may be considered when morbidity from surgery is high. Adjuvant nonsurgical therapies (eg, imiquimod) may be considered for epiEMPD at the margins when continued surgery may incur excess morbidity (Grade D; category 2A). Surveillance is recommended to monitor for recurrence and adverse effects (Grade C; category 2A).

Fifty-four studies described nonsurgical therapies. Primary treatment with imiquimod (276 cases) resulted in a 30% complete response rate, 35.4% recurrence rate (35 of 99), and a mean time of 8.8 months (range, 4.25-18.0 months) to recurrence. Common imiquimod regimens were 1 to 3 times per week for 0.75 to 4 months

Figure 1. Management Algorithm for Extramammary Paget Disease (EMPD)



Positive markers are indicated by a plus sign, while negative markers are indicated by a minus sign. CCPDMA indicates complete circumferential peripheral and deep margin assessment; CEA, carcinoembryonic antigen; CK, cytokeratin; MMS, Mohs micrographic surgery; RT, radiotherapy; and WLE, wide local excision.

[a] Screening for internal synchronous malignant neoplasm is advised based on the anatomical site involved. Screening paradigms are not standardized. Some experts, however, suggest that patients with vulvar EMPD should receive urine cytologic screening, colonoscopy, and pelvic ultrasonography, while those with penoscrotal EMPD may undergo these investigations along with additional screening for prostate cancer. In the absence of specific staging criteria for EMPD, vulvar EMPD can be staged according to National Comprehensive Cancer Network guidelines on vulvar carcinoma.

[b] Intraepidermal EMPD has a small association with disease-specific survival. Expert opinion of the panel indicated that clearance of the immediate tumor area rather than exhaustive clearance may be appropriate for very large tumors, where subclinical spread is likely extensive and surgery is likely morbid. If clinical clearance is chosen, close observation and adjuvant treatment with topical immunotherapy should be considered. Radiotherapy may also be considered when margin control is indeterminate or for positive margins. Curative intent implies exhaustive tumor removal. Margin-control and tissue-sparing techniques are recommended as first-line treatment.

[c] Wide local excision may be supplemented with scouting biopsies to identify the degree of subclinical spread (respective of anatomical site).

[d] Adjuvant therapy may be most helpful in settings where surgery is not possible, margin control is not available, or clearance of the margins is not desired or possible.

(25 studies), with some more frequent and prolonged courses. For photodynamic therapy (263 cases), typically using topical aminolevulinic acid or methyl aminolevulinate with 3 to 4 hours of incubation (with or without occlusion) with red light for 3 to 8 treatments spaced 1 to 4 weeks apart (21 studies), the recurrence rate was 34.2% (13 of 38), with a median time to recurrence of 10 months (range, 3-30 months). Data for treatment with fluorouracil, carbon dioxide laser, and combination topical therapies are limited. Limitations of primary topical therapy include poor compliance due to skin irritation and possible residual or recurrent discontinuous tumor after treatment, which may complicate future treatment and monitoring.

Table 2. Outcomes With Margin-Controlled Surgery and Standard Excision for All Reported Cases of Extramammary Paget Disease

Outcome	WLE alone	Margin control[a]	MMS
Recurrence rate, No./total No. (%)	507/1371 (37.0)	120/642 (18.7)	22/197 (11.2)
Recurrence-free interval, median (range), mo	24.3 (4.0-152.0)	33.5 (24.0-40.8)	32.5 (31.0-35.9)
Overall survival, No./total No. (%)	766/992 (77.2)	517/559 (92.5)	46/51 (90.2)
Follow-up, median (range), mo	41.0 (11.0-216.0)	36.0 (21.0-64.9)	43.5 (26.0-59.2)

Abbreviations: MMS, Mohs micrographic surgery; WLE, wide local excision.

[a] Margin control refers to use of either complete circumferential peripheral and deep margin assessment or MMS.

Invasive EMPD

Recommendation 9

Surgical resection with curative intent is recommended for invEMPD. Margin-controlled surgery (eg, MMS or CCPDMA) with en face sectioning is preferred; however, preoperative mapping biopsies combined with WLE can be considered as an alternative approach (Grade B; category 2A).

Primary topical or nonsurgical therapy is considered second-line treatment when curative surgery is not possible. Patients receiving palliative treatment may benefit from topical or nonsurgical therapies (Grade D; category 2A).

Invasive EMPD has higher rates of recurrence,[74] metastasis,[14,16] and death.[36,75-77] Recurrence and mortality rates are lower with MMS or CCPDMA than with WLE. Epidermal EMPD and invEMPD can present within the same lesion. Surgical clearance of at least the invasive portion is preferred. If removal of epiEMPD would lead to excess morbidity, adjuvant nonsurgical approaches may be used with close follow-up.

Radiotherapy

Recommendation 10

Radiotherapy with curative intent may be indicated when surgery is inadvisable or infeasible (Grade B; category 2A). Radiotherapy can be considered in the adjuvant setting after surgery for persistent or recurrent EMPD (Grade C; category 2A).

Radiation treatment fields should account for subclinical extension, especially when there is curative intent. Where possible, treatment should extend 3.5 cm beyond the clinical border to encompass the tumor in 95% of cases. The decision to treat draining nodal basins should be individualized. Field design should consider injury to adjacent tissues.

Overall, 37 studies reported radiotherapy (commonly, electron beam, photons, and brachytherapy) in at least 1 case. Radiotherapy was the primary treatment modality in 7.5% of cases (263 of 3507) involving the primary tumor bed with or without the nodal basin.[36,78] Doses ranged from 30 to 64 Gy in 20 to 33 fractions. The recurrence rate was 30.6% (11 of 36).[17,79,80] Radiotherapy was used for patients with recurrent cases[81] and elderly patients with high potential surgical morbidity.[82] In the adjuvant setting, radiotherapy was used in 8.5% of cases (296 of 3466).[83-85] Dosing ranged from 45 to 64.8 Gy (median dose, 50 Gy) and 59 to 70.2 Gy (median dose, 60 Gy) in 25 to 39 fractions (median fraction, 33) to the primary tumor and LN bed, respectively. The recurrence rate was 34.8% (16 of 46).[83]

Management: Metastatic Disease

Recommendation 11

Patients with metastatic EMPD may be considered for chemotherapy, targeted therapy, or immune checkpoint inhibitors. Multidisciplinary tumor board consultation or trial enrollment is recommended (Grade C; category 2A).

A total of 189 of 1270 cases (14.9%) were treated with chemotherapy. Combination regimens were not superior to sequential single-agent cytotoxic therapy (commonly weekly docetaxel).[86,87] Combination chemotherapy may be appropriate for patients with good performance status, especially when a radiographic response is required.[66] Use of single-agent docetaxel[86] and low-dose fluorouracil with cisplatin has been reported in the treatment of locally advanced EMPD, but data are limited to case series.[88] Other approaches include next-generation sequencing (*PI3K* [phosphatidylinositol 3-kinase] inhibitors), fluorescence in situ hybridization (*ERBB2* inhibitors), and molecular techniques to evaluate for mismatch repair or microsatellite instability or high mutational burden (immune checkpoint inhibitors).[2,29,89-93]

Follow-up

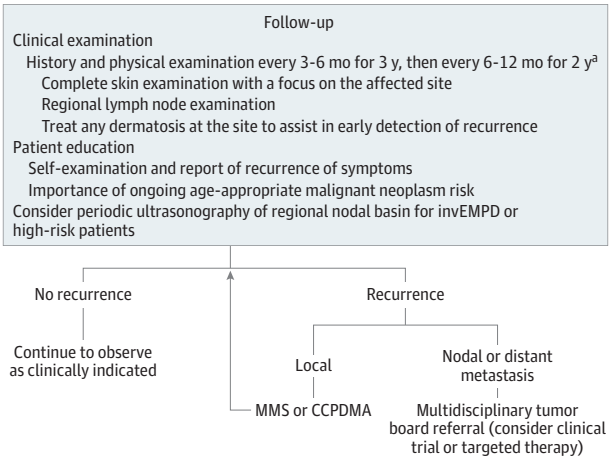
Recommendation 12

Physical examination, including LN examination, is recommended every 3 to 6 months for 3 years and then every 6 to 12 months until at least 5 years after diagnosis. Monitoring for internal malignant neoplasms or metastatic EMPD with imaging based on anatomical location may be considered for aggressive or invasive disease. To our knowledge, there are no data to recommend the optimal frequency or type of imaging (Grade D; category 2A).

A clinical algorithm to guide follow-up is presented in **Figure 2**. The mean (SD) follow-up was 53.5 (21.4) months. The mean (SD) recurrence rate after treatment was 27.5% (2.3%) (6189 of 22 505 cases). Local recurrence was most common (65.2% [542 of 831]), followed by distant metastasis (23.7% [197 of 831]) and regional nodal metastasis (11.1% [92 of 831]). Distant metastases were to the liver, bone, lung, skin, brain, peritoneum or retroperitoneum, axilla, and distant LN. The mean (SD) time to recurrence was 36.9 (24.0) months. The mean (SD) overall survival of patients with EMPD was 107.5 (63.0) months. A shorter interval of less than 6 months between examinations is recommended for those with extensive or aggressive disease.

To our knowledge, no longitudinal studies have established surveillance of EMPD. Recommendations are based on the literature and the approximately 20% probability of developing an internal

Figure 2. Follow-up Algorithm for Extramammary Paget Disease



CCPDMA indicates complete circumferential peripheral and deep margin assessment; invEMPD, invasive extramammary Paget disease; and MMS, Mohs micrographic surgery.

[a] Recurrent tumors treated with surgery may be considered for adjuvant radiotherapy.

malignant neoplasm within 5 years after diagnosis. Shorter intervals are suggested immediately after initial EMPD diagnosis. Circulating tumor-associated serum markers do not play an established role in EMPD surveillance. Owing to the variety of individual cases and little guidance beyond the expert opinion of the panel, it is most appropriate for physicians to exercise their clinical judgment to ensure follow-up examinations and monitoring by imaging that best suits the clinical situation.

Conclusions

The diagnosis of EMPD is predicated on a high index of suspicion because misdiagnosis as inflammatory skin disease is common. Immunohistochemical stains may exclude histologic mimics. Management of EMPD, whether intraepidermal or invasive, focuses on removal with clear histologic margins whenever possible. Tissue-conserving, margin-controlled surgery techniques, such as MMS or CCPDMA, are preferred when available. Nonsurgical treatments can be considered for epiEMPD if surgical therapy is not appropriate. Sentinel LN biopsy, adjuvant radiotherapy, and LN dissection are not routinely recommended because of insufficient evidence and morbidity. Metastatic EMPD or secondary EMPD is best managed with multidisciplinary consultation. Additional prospective data are needed to define the features of high-risk tumors and to further clarify the management of this highly recurrent and potentially aggressive cancer.

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