**Materials and Methods**

**Search Strategy**

The systematic review was conducted and reported in accordance with the PRISMA statement [13] and registered with the PROSPERO international prospective register. We searched without date limits in June 2019 using PubMed, Google Scholar, ScienceDirect, the ongoing trials registry/database of the US National Institutes of Health ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Reference lists from key trials and previous systematic review were manually scanned for additional results [9–12, 14]. The following search criteria were used: (“paget"[MeSH] OR "paget"[All Fields]) AND ("imiquimod"[All Fields] OR "imiquimod"[MeSH] OR "laser"[All Fields] OR "laser"[MeSH] OR "5-fu"[All Fields] OR "5-fu"[MeSH] OR "fluorouracil"[All Fields] OR "fluorouracil"[MeSH] OR "5-ALA"[All Fields] OR "5-ALA"[MeSH] OR "aminolevulinic"[All Fields] OR "aminolevulinic "[MeSH] OR "PDT"[All Fields] OR "PDT "[MeSH] OR "photodynamic"[All Fields] OR "photodynamic "[MeSH]).

**Eligibility Criteria**

Studies that met the following criteria were included: (i) relevance – original study of any design evaluating nonsurgical treatments for EMPD; and (ii) participants – patients of both sexes of any age with a clinical and histological diagnosis of early EMPD. We excluded: (i) case series with fewer than 3 patients due to risk of publication bias; (ii) studies that did not report at least one outcome; (iii) studies evaluating combined surgical and nonsurgical treatments; and (iv) studies focusing on metastatic disease.

**Outcomes**

Our primary outcome was defined as the complete remission of clinical symptoms and/or no residual disease on posttreatment biopsy. In this category, we also included publications that used the terms “complete response” (“CR”) or “symptom-free,” etc. Our secondary outcome was clinical regression by 50% or more. In this category, we also included publications that used the terms “marked improvement” or “minimal disease,” etc. Additional secondary outcomes were recurrence following complete remission and adverse events.

**Study Selection and Data Extraction**

Three reviewers (I.S., R.K., and Y.N.) independently screened titles and abstracts, followed by the full text of studies considered potentially eligible. The first author (I.S.) extracted data onto an electronic form, and the other two authors (R.K. and Y.N) checked the extracted data, including first author name, year of publication, number of participants, age, sex, initial versus recurrent treatment, tumor site, primary and secondary outcomes, and length of follow-up. Tumor site was categorized as genitalia when the penis, scrotum, or vulva was involved and as pubis/groin when the pubis, groin, or inguinal area was involved. Additional categories were perineum/perianal area, axilla, and face.

Risk of bias across cohort studies was assessed with the Newcastle Ottawa Quality Assessment Scale (NOS) by two authors (I.S. and R.K.). Any disagreement was resolved by discussion. Further discrepancies were resolved by a fourth author (A.L.) [15].

**Data analysis**

Complete and partial response rates, and recurrence rates were pooled using statistical software (Comprehensive Meta-Analysis, version 3.0, [Meta-Analysis@Meta-Analysis.com](file:///D%3A%5CDownloads%5CMeta-Analysis%40Meta-Analysis.com)). Analyses were performed using a random-effect model of DerSimonian and Lard, because we had expected considerable clinical heterogeneity. Heterogeneity was assessed by visually examining the forest plot for nonoverlapping CIs and via the χ2 test, with p < 0.1 indicating statistical significance and *I*2 >50% indicating substantial heterogeneity.