

Local Management of Anogenital Warts in Nonimmunocompromised Adults: A Network Meta-analysis of Randomized Controlled Trials

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To the Editor,

Anogenital warts (AGWs) remain a therapeutic challenge due to the complexity of their management and the high recurrence rates commonly observed (1, 2). This study aimed to evaluate the efficacy of topical and ablative treatments for AGW management through an updated network meta-analysis (NMA), building upon the work of Bertolotti et al. (3).

A systematic literature search of two databases was conducted from inception to August 2025. A total of 81 randomized controlled trials (RCTs) involving 11,083 participants were included, evaluating local treatments for AGWs. Eligible studies were parallel-group RCTs enrolling immunocompetent adults treated with at least one provider-administered or self-applied intervention. Studies in paediatric or immunocompromised populations were excluded. Full methodological details, including the search strategy, study selection (included and excluded studies), flow diagram and supplementary references, are provided in Appendices S1–S7.

The primary outcome was complete clearance of AGWs without recurrence, analysed using a network meta-analytic approach.

Results are presented as a forest plot (Fig. 1) and Surface Under The Cumulative Ranking (SUCRA) rankings (Fig. 2). Treatments were ranked using the SUCRA, with values ranging from 0 to 1, reflecting the probability that a given treatment occupies a particular rank, with values closer to one indicating greater efficacy.

All treatments demonstrated significantly greater efficacy than placebo, except for cidofovir and interferons administered intralesionally or topically (excluding interferon- α cream).

Among ablative therapies, surgical excision was the most effective (RR 9.59; 95% CI 4.71–19.50; SUCRA 0.843), followed by electrocoagulation (RR 8.49; 95% CI 4.16–17.35; SUCRA 0.792), aminolevulinic acid-photodynamic therapy (ALA-PDT) (RR 8.54; 95% CI 4.09–17.87; SUCRA 0.792), and CO₂ laser (RR 6.90; 95% CI 3.69–12.91; SUCRA 0.690).

Among topical agents, 5-fluorouracil (RR 5.21; 95% CI 2.79–9.71; SUCRA 0.493) and imiquimod 5 %

(RR 5.13; 95% CI 3.09–8.51; SUCRA 0.478) showed moderate efficacy. Podophyllotoxin appeared more effective in gel form than in cream or solution, while cidofovir ranked tenth overall.

Our findings confirm those of Bertolotti et al., identifying surgical excision as the most effective ablative option, and align with previous literature recognizing the high efficacy of electrosurgery and CO₂ laser (3, 4). Compared with the 2024 French guidelines – which recommend cryotherapy, imiquimod

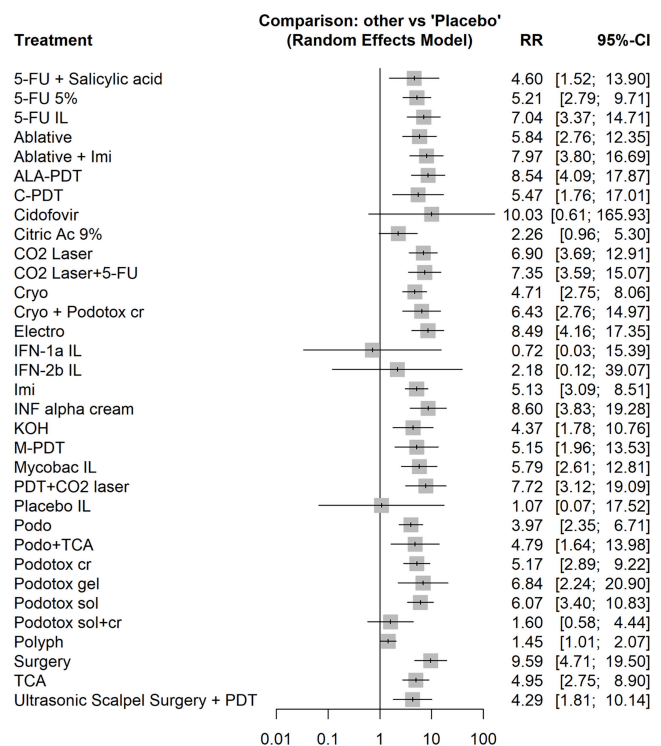


Fig. 1. Forest plot of the estimates of relative risk between each treatment and the reference placebo for complete lesion response. Data presented as RR (95% CI). 5-FU: 5 fluoro-uracil, 5-FU IL: 5 fluorouracil intra intralesional, ablative ablative treatment (surgery or electrosurgery or CO₂ laser or cryotherapy), Cryo: cryotherapy, Electro electrosurgery, IFN B: interferon B, Imi: imiquimod, INF cream: interferon cream, Mycobac IL: mycobacterium intra intralesional, PDT: photodynamic therapy, podo: podophyllin 20–25%, Podotox cr: podophyllotoxin cream, Podotox sol: podophyllotoxin solution, podotox gel: podophyllotoxin 0.5 % gel, podotox sol+cr: podophyllotoxin 0.5 % solution + cream, polyph: polyphenon, KOH: potassium hydroxide, TCA: trichloroacetic acid, Vit c: vitamin C, Cryo+Podo: cryotherapy+podophyllin, Cryo+Podotox: cryotherapy+podophyllotoxin, INF alfa 2-b: Interferon alfa 2-b.

SUCRA			
1 Surgery	0,843515152	18 5-FU 5%	0,493969697
2 Electro	0,795727273	19 Podotox cr	0,492848485
3 ALA-PDT	0,792575758	20 Imi	0,478787879
4 INF alpha cream	0,767454545	21 Podo+TCA	0,474939394
5 Ablative + Imi	0,752787879	22 5-FU + Salicylic acid	0,459757576
6 PDT+CO ₂ laser	0,721969697	23 TCA	0,456363636
7 CO ₂ Laser+5-FU	0,721757576	24 Cryo	0,421181818
8 CO ₂ Laser	0,690454545	25 KOH	0,405090909
9 5-FU IL	0,689454545	26 Ultrasonic Scalpel Surgery + PDT	0,404242424
10 Cidofovir	0,683393939	27 Podo	0,320939394
11 Podotox gel	0,641272727	28 IFN-2b IL	0,31830303
12 Cryo + Podotox cr	0,624757576	29 Citric Ac 9%	0,193272727
13 Podotox sol	0,597424242	30 Placebo IL	0,177424242
14 Ablative	0,569121212	31 IFN-1a IL	0,129030303
15 Mycobac IL	0,558787879	32 Podotox sol+cr	0,128575758
16 C-PDT	0,532727273	33 Polyph	0,100121212
17 M-PDT	0,506727273	34 Placebo	0,055242424

Fig. 2. Surface Under the Cumulative Ranking Curve (SUCRA) Analysis Representing probabilities of treatment ranking. SUCRA: surface under the cumulative ranking curve; ablative treatment: surgery or electrosurgery or CO₂ laser or cryotherapy, 5-FU: 5 fluoro-uracil, TCA: trichloroacetic acid, PDT: photodynamic therapy, KOH: potassium hydroxide, INF-1a: interferon-1a, INF-2b: interferon-2β.

5%, or podophyllotoxin as first-line options (1) – our results offer a complementary therapeutic perspective. In our analysis, cryotherapy achieved recurrence-free clearance in 47% of cases, consistent with the 44–87% range reported in European guidelines (2). Jung et al. suggested that imiquimod 2% may be more effective than 5%. However, one of the two RCTs evaluating 2% imiquimod used a twice-daily regimen, which deviates from standard practice (typically three times per week) and may have biased outcomes. Moreover, the assumption that lower concentrations improve tolerability is not supported by our previous NMA or Jung's analysis, both of which found no reduction in adverse events with lower doses (5, 6).

Formulation and dosage significantly influence the efficacy of podophyllotoxin. The 0.5% solution was more effective than the cream, confirming the findings of Werner et al. (RR 1.26; 95% CI 1.07–1.48) (7). Although our NMA suggested a trend favouring the 0.5% solution over imiquimod 5% (SUCRA 0.597 vs 0.478), Werner et al. did not find a significant difference between the two. No head-to-head study has compared the 0.5% gel and solution, but our results indicate higher efficacy for the gel (SUCRA 0.641), warranting further investigation.

A complementary NMA focusing on tolerability (6) showed that imiquimod 5% was better tolerated than podophyllotoxin, cryotherapy or 5-FU, while cidofovir emerged as the most tolerated topical agent. Overall, topical therapies were associated with fewer adverse events than ablative procedures. These results should be interpreted with caution. Surgical excision is less appropriate for patients with multiple lesions and carries greater risks of scarring and postoperative complications. CO₂ laser and PDT are limited by high cost, restricted availability, and technical challenges related to lesion localization. From a health-economics perspective, Agbeci et al. reported

that the podophyllotoxin 0.5% solution is the most cost-effective first-line option (8).

This study has several limitations: it focuses exclusively on local treatments and six-month clearance, does not assess long-term recurrence, lacks endpoints for safety or cost-effectiveness and includes some heterogeneity among trials.

In conclusion, this NMA indicates that surgical excision, PDT and electrosurgery offer the highest likelihood of achieving recurrence-free clearance in AGWs. Among first-line options recommended by the French guidelines, podophyllotoxin 0.5 % stands out for its efficacy, while imiquimod 5 % provides a balanced profile combining efficacy and tolerability. Further studies are warranted to confirm these observations.

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Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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