2nd EDITION

PRACTICAL TRAINING

HUMAN PAPILLOMAVIRUS

PRACTICAL CASES

MODULE 4. MANAGEMENT OF HPV PRESENCE AND HPV-INDUCED LESIONS

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INTRODUCTION

Human papillomavirus (HPV) detection in cervical mucous or infection (HPV integration in the cellular genome) is very common. In Spain, three out of every ten women under the age of 30 and one out of ten women over 30 are HPV-positive at any given time. At some point in their lives, eight or nine of every ten Spanish women will be HPV-positive[1]. In Spain, approximately one hundred thousand intraepithelial cervical lesions are diagnosed each year[2]. This imposes a significant burden on both public and private health care systems, costing €147,284,811[3].

OBJECTIVES

The objective of this module is to understand the current guidelines for managing various HPV-associated clinical situations and the cervical lesions resulting from HPV integration (infection).

1. PRESENCE OF HPV: MANAGEMENT

» HPV determination tests should never be carried out before 30 years of age. As mentioned before, HPV is very prevalent in women under 30 in Spain. There are also high rates of spontaneous clearance in that population. Performing determination in that group has low positive predictive value for intraepithelial cervical lesions and cervical cancer[3]. As a reminder, and as specified in Module 3 of this course, the technique used to determine the presence of HPV must be validated. HPV determination results influence management actions, so we need to ensure that this result is reliable, and comes from a validated technique.

» After 30 years of age, with a positive HPV determination, it is recommended to perform cytology as a decision-driving strategy[4,5] and then proceed according to the cytology result (see more below). If determination is negative, tests for the presence of HPV should be annual, never less.

» "Evidence-based medicine" does not provide recommended measures to facilitate eliminating HPV present in the cervix. Because of the well-established increased risk of cervical cancer in smokers[6], the first advice to give an HPV-positive smoker is to cease smoking. Professional help through *ad hoc* smoking cessation classes[7] is essential.

» A vaginal gel based on *Coriolus versicolor* demonstrated benefits for cervical re-epithelialization, balancing vaginal microbiota, and improving vaginal immunity[8-9]. A clinical trial[10] was then designed whose secondary endpoint was to evaluate the gel's efficacy in facilitating clearance of HPV present in the cervix. Recently presented[11] data currently in preparation for publication show a clear trend in patients with high-risk HPV: 63% in the treatment group cleared their HPV after 6 months of treatment, compared to 40% in the control group (Fig. 1). This trend must be confirmed in a similarly-designed study currently underway[12] that will allow for more case studies. On the other hand, intermediate results presented from a real-life prospective study show HPV clearance at 6 months in 54% of patients. Additionally, 83% of patients who do not clear the virus at 6 months manage to do so by extending treatment to 12 months[13]. These data are consistent with the results from independent observational studies[14] that show the capacity for high-risk HPV clearance at 6 months with the gel ranges between 50% and 70% of patients.

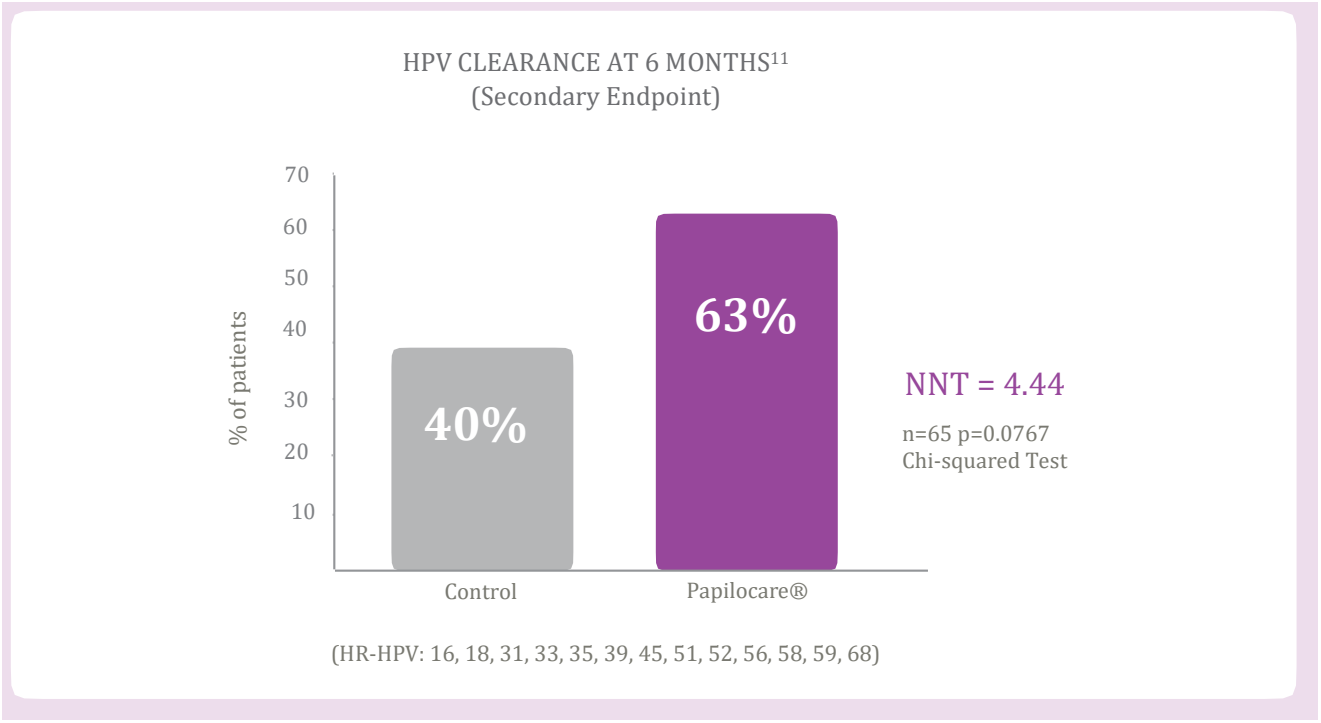

Figure 1. Results of Paloma Clinical Trial on High-Risk HPV Clearance

2. HPV-INDUCED LESIONS: MANAGEMENT

The following recommendations are based on those formulated in the *2014 Spanish Cervical Cancer Screening Guidelines*[4] and in the *2014 SEGO Oncoguide for Cervical Cancer Prevention*[5]. These references obtained a broad consensus from eight Spanish scientific societies, and should be considered required guidelines. In both publications, the supporting literature base can be consulted.

Health care practice is governed by specific recommendations[15] that allow preventive cytology screens from the time sexual relations are initiated (16 is the average age in Spain)[16]. For this reason, it is necessary to also establish management recommendations for anomalous cytology results in women under 30 (below).

Additionally, the management indications for women in special situations, menopause or pregnancy are also included:

» **Cytological result: "Atypical Squamous Cells of Undetermined Significance" (ASC-US).**
- Under 30 years of age: cytology in one year and follow-up according to result. If normal, test every three years.
- Over 30 years of age: HPV determination.
  a) HPV-positive: colposcopy.
  b) HPV-negative: cytology and HPV test (co-test) in three years.

» **Cytological result: "Atypical Squamous Cells cannot rule out a High-grade lesion" (ASC-H).**
- Follow-up for women under or over 25-30 years of age with this cytological result have demonstrated the same risk of developing a High-grade Squamous Intraepithelial Lesion (HSIL) for both age groups.
- Recommendation: colposcopy. If negative, conduct co-test in one year.

» **Cytological result: "Low-grade Squamous Intraepithelial Lesion" (LSIL).**
- Colposcopy is required, proceeding according to results.
- In menopausal women, it is acceptable to perform an HPV test to rule out cases where hypotrophy could have caused over-diagnosis of LSIL.
  a) HPV-positive: colposcopy.
  b) HPV-negative: co-test in 3 years.
- In pregnant women, the preferred option is to perform a colposcopy, but it is acceptable to postpone to six weeks after birth.

» **Cytological result: "High-grade Squamous Intraepithelial Lesion" (HSIL).**

- Colposcopy is required in all age groups, proceeding according to results. If negative, perform another cytological-colposcopic check-up in 6 months.

» **Cytological result: "Atypical Glandular Cells" (AGC).**

- From endocervical cells: colposcopy.
- From endometrial cells: endometrial biopsy.
- The presence of benign endometrial cells in the vaginal tract does not require any further exploration, except in post-menopausal women, in which case the endometrial study is required.

» **Histological diagnosis: "Low-grade cervical intraepithelial neoplasia" (CIN1).**

CIN1 is not a precancerous lesion, it is the histological response to infection with HPV. The possibility of a woman with a CIN1 diagnosis developing cancer does not exceed 30%, so the preferred action is appropriate monitoring and testing.

- With previous cytology of ASC-US or LSIL: co-test (if > 30 years old) or cytology-colposcopy at one year or when postpartum if pregnant.
- With previous cytology of ASC-H, AGC, or HSIL:
  a) Co-test (if > 30 years old) or cytology-colposcopy at one year or when postpartum if pregnant.
  b) Review previous cytological material.
  c) Excisional treatment is reserved for those at risk of loss to follow-up or repeated atypical cytology. Never perform in pregnant women.

» **Histological diagnosis: "High-grade cervical intraepithelial neoplasia" (CIN2/3).**

One of every three high-grade intraepithelial lesions progresses to cancer, so treating these lesions is necessary, except:

- If it is a small lesion, controllable via colposcopy, without endocervical affectation, with possible follow-up.
- During pregnancy when there is:
  a) No colposcopic suspicion of invasion.
  b) Possibility of cytological-colposcopic check-up every three months.

Furthermore, it is essential to insist on having cytology read by a trusted, accredited laboratory that has the required quality controls, and that the colposcopy adheres to current methods and image classifications[4].

Finally, with regard to management, it is important to also mention the results of the aforementioned clinical trial[11] in which the effect of the vaginal gel on low-grade HPV-induced cervical lesions was assessed as the primary endpoint. At 6 months, the treatment group showed a significantly greater percentage of patients whose "Atypical Squamous Cells of Undetermined Significance" (ASC-US) and "Low-grade Squamous Intraepithelial Lesion" (LSIL) cytological alterations were normalized, with concordant colposcopy, in comparison to the control group for both the total population (85% *vs.* 65%, $p < 0.031$) and the high-risk virus population (88% *vs.* 56%, $p < 0.003$).

Similarly, a clear trend was observed (73% *vs.* 43%, p = 0.0959) in the very high-risk sub-population (infected by any combination of HPV 16, 18 and 31) that did not reach significance due to the low number of cases[17] (Fig. 2).

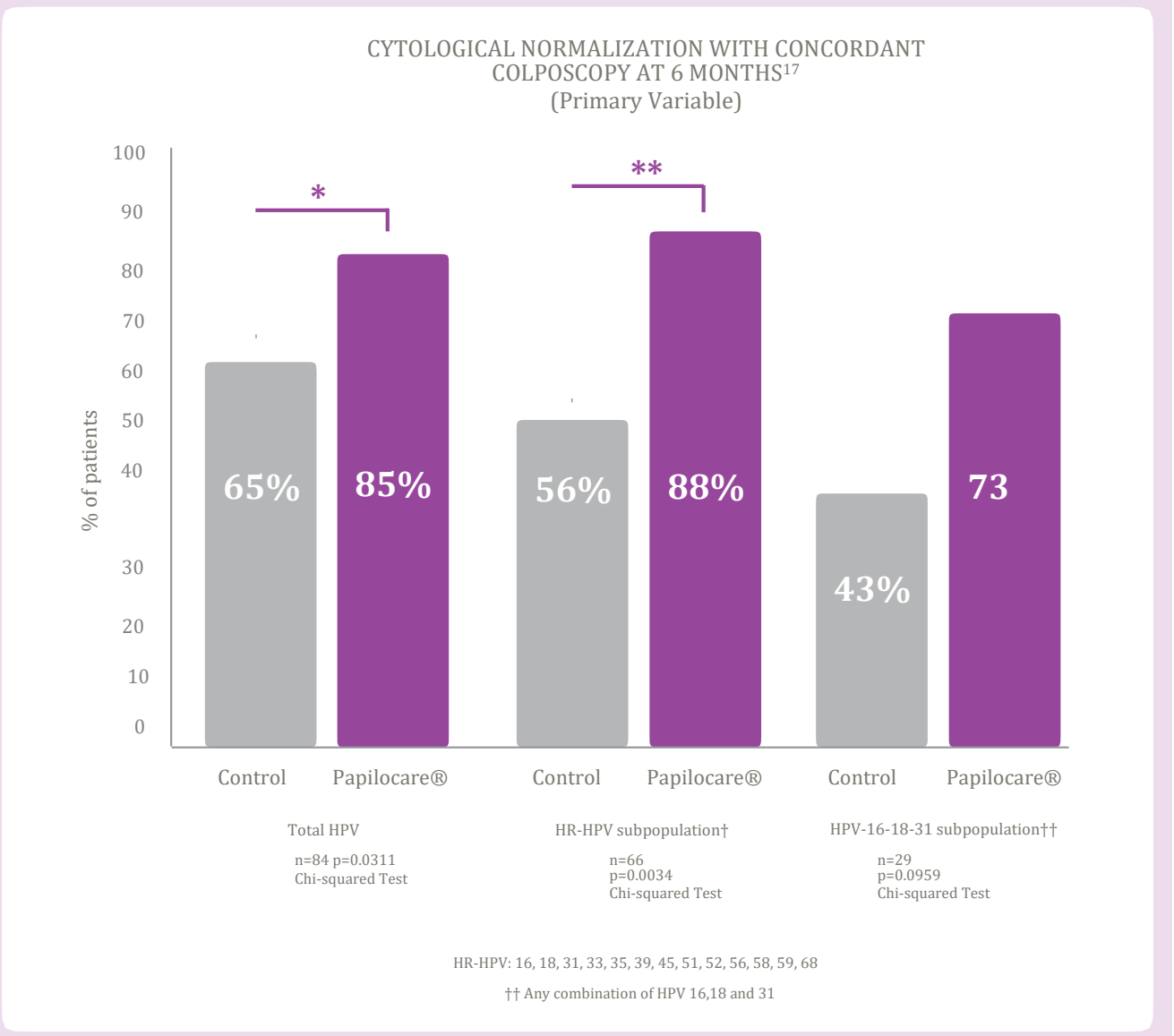

Figure 2. Results of the Paloma Clinical Trial on the normalization of HPV-induced cervical lesions.

On the other hand, in an intermediate analysis of the prospective observational study[13] it was observed that 65% of patients present normalization of low-grade cytological alterations with concordant colposcopy after 6 months of treatment with the gel. Of those with remaining alterations at 6 months, 94% normalize when the treatment is extended to 12 months (Fig.3).

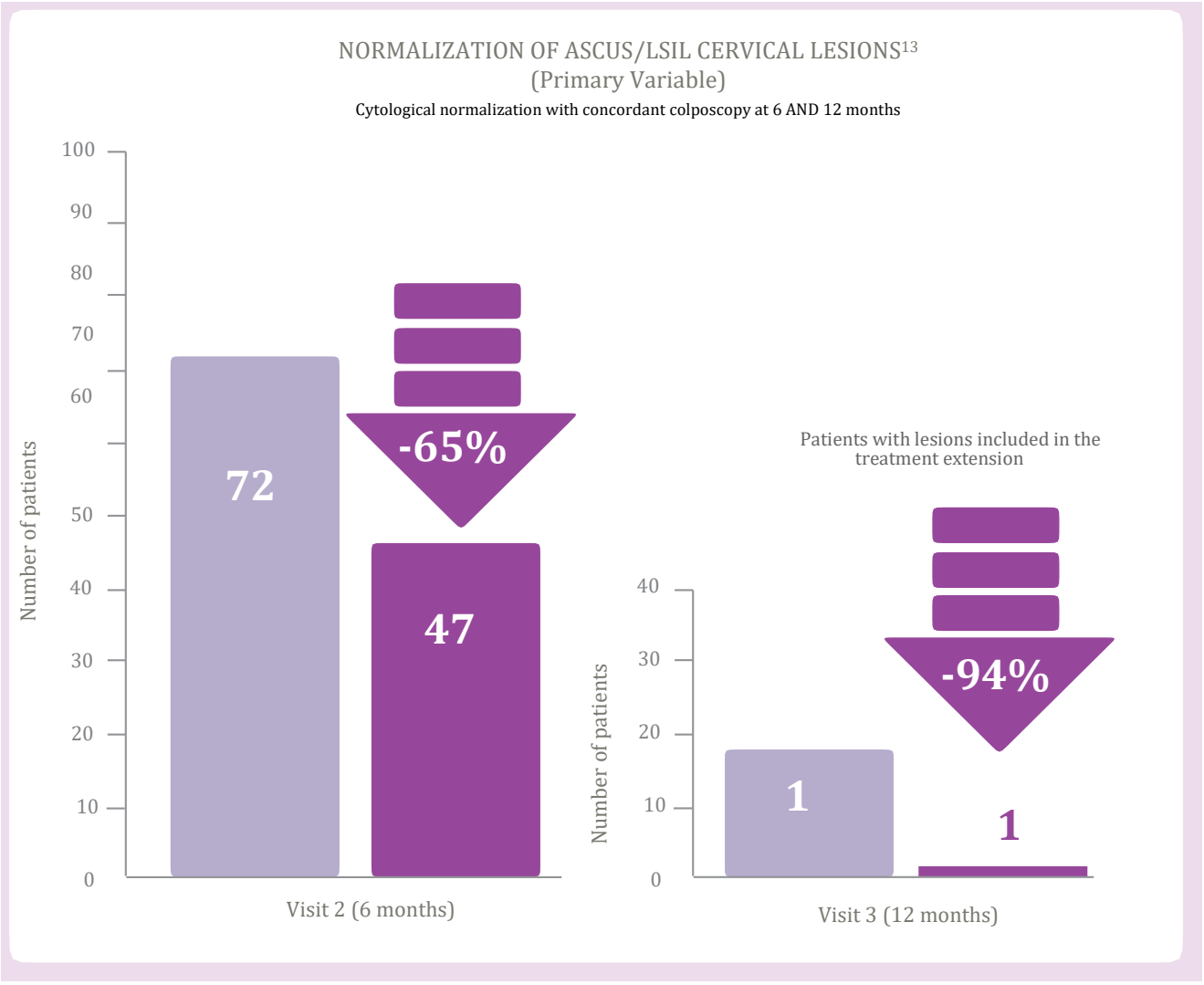

Figure 3. Intermediate Results from PapilOBS Study.

3. CONCLUSIONS

Determining whether the patient is an HPV carrier is appropriate after age 30. HPV is very common and transient under age 30, making testing inefficient.

For patients with HPV presence and low-grade cytological-colposcopic alterations, use of a *Coriolus versicolor*-based vaginal gel is recommended. This recommendation is based on early clinical trial data availability, real-world use, a robust benefit-risk ratio, and the lack of alternatives in routine clinical practice.

Appropriately managing HPV-dependent lesions and following protocols established by the relevant scientific societies is essential. Working efficiency is jeopardized by the uncontrolled use of unvalidated diagnostic techniques, lack of accreditation, and a lack of basic quality control techniques (cytology, colposcopy).

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