DECEMBER 2016

RECOMMENDATIONS AND GUIDELINES

/Summary

MANAGEMENT OF WOMEN WITH ABNORMAL CERVICAL CYTOLOGY

e-cancer.fr

INSTITUT NATIONAL DU CANCER

The French National Cancer Institute (INCa) is the health and scientific expertise agency in the field of cancer care responsible for coordinating cancer control in France.

The French National Cancer Institute (INCa) is the preeminent health and science agency in charge of cancer control in France.

The scientific coordination of these guidelines was conducted by the French National Cancer Institute.

The following collaborators contributed to this project, in the set-up of the workgroup and/or during the review process: Société française de colposcopie et de pathologie cervico-vaginale (SFCPCV), Collège national des gynécologues et obstétriciens français (CNGOF), Fédération nationale des collèges de gynécologie médicale (FNCGM), Société française de cytologie clinique (SFCC), Société française de pathologie (SFP), Centre national de référence des papillomavirus humains (CNR HPV), Société française de microbiologie (SFM), Collège de la médecine générale (CMG), Collège national des sages-femmes (CNSF) and Association des coordinateurs de structures de dépistage (ACORDE). A few patients also expressed their point of view as independent expert reviewers.

It is recalled that the guidelines cannot envisage all clinical scenarios and cannot therefore be seen as a substitute for the physician's judgement and responsibility to their patient.

It has received financial support from Unicancer within the framework of the guideline programme.

Citation: © *Management of women with abnormal cervical cytology, summary*, Collection recommandations et référentiels, INCa, December 2016.

It is available to download on website **e-cancer.fr**

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ABBREVIATIONS

Abbreviations based on 2014 Bethesda terminology

AGC: Atypical glandular cells
AIS: Endocervical adenocarcinoma in situ
ASC-H: Atypical squamous cells that cannot exclude HSIL
ASC-US: Atypical squamous cells of undetermined significance
HSIL: High-grade squamous intraepithelial lesion
LSIL: Low-grade squamous intraepithelial lesion
NILM : Negative for Intraepithelial Lesion or Malignancy

Other abbreviations

ANAES: Former French national health intervention evaluation agency (Agence nationale d'accréditation et d'évaluation en santé)
HAS: French national authority for health (Haute autorité de santé)
HPV: Human papillomavirus
INCa: French National Cancer Institute (Institut national du cancer)
MDT: Multidisciplinary team meeting

Abbreviations relative to the French classification of colposcopy quality

ZT1: Transformation zone type 1 (squamocolumnar junction fully seen)
ZT2: Transformation zone type 2 (squamocolumnar junction seen but endocervical)
ZT3: Transformation zone type 3 (squamocolumnar junction not fully seen)

FIGURES

INTRODUCTION

In France, it is estimated that 2,757 new cases of cervical cancer, with 1,092 deaths resulting from the disease, were diagnosed in 2015. Thanks to cervical smear screening, the incidence and mortality of invasive cervical cancer have been decreasing in France for more than 30 years[1]. This screening consists, for women aged 25-65, of performing a cervical cytology test every 3 years after 2 normal cytologies one year apart[2].

The French 2014-2019 Cancer Plan has among its objectives to launch a mass screening program for cervical cancer in order to fight against unequal access to and use of screening[3]. It is estimated that the implementation of the mass screening program will lead to approximately 235,000 abnormal cytology tests per year (cytology tests not NILM (Negative for Intraepithelial Lesion or Malignancy) according to Bethesda terminology), among which 31,000 precancerous or cancerous lesions will be identified. However, there will not be enough gynecologists to manage these patients, thus new health professionals (such as general practitioners and midwives) will be involved in the management of these women[4]. The guidelines are thus crucial to guarantee adequate management strategies for all patients.

Previous guidelines were formulated in 2002 by the National health intervention evaluation agency (ANAES)[5]. Since then, new HPV tests have been developed and $p16^{INK4A}$/Ki67 dual-staining has been evaluated in some studies. These tests could be of use for the triage of women with abnormal cytology, that is, the identification of women who require additional examinations due to a risk of progression of the lesion to cancer and women for whom monitoring is sufficient. Finally, the new data accrued since 2002 provide a better evaluation of the monitoring, diagnostic and therapeutic strategies and of obstetrical treatment morbidity. An update of the 2002 guidelines was thus necessary.

Among its missions, the French National Cancer Institute (INCa) is required to produce evidence-based guidelines for professionals. These updated guidelines are published in this context and detail indications for the use of the different diagnostic and therapeutic options in order to avoid excessive conizations and minimize overtreatment (Action 1.3 of the French 2014-2019 Cancer Plan)[6].

This summary report presents the key elements of the full clinical practice guideline report, available online in French at the French National Cancer Institute website: www.e-cancer.fr.

[1] Les cancers en France – Edition 2015, available at: http://www.e-cancer.fr/Actualites-et-evenements/Actualites/Publication-de-l-edition-2015-des-Cancers-en-France.

[2] http://www.e-cancer.fr/Professionnels-de-sante/Depistage-et-detection-precoce/Depistage-du-cancer-du-col-de-l-uterus/Le-depistage-par-frottis-cervico-uterin.

[3] Plan cancer 2014-2019 (février 2014), Objectif 1 – favoriser des diagnostics plus précoces ; faire reculer les inégalités face au cancer du col utérin et réduire son incidence ; available at the following address: http://www.e-cancer.fr/Plan-cancer/Plan-cancer-2014-2019-priorites-et-objectifs/Les-17-objectifs-du-Plan2/Objectif-1-Favoriser-des-diagnostics-plus-precoces.

[4] État des lieux et recommandations de la HAS pour le dépistage du cancer du col de l'utérus en France (July 2010), report available at the following address: http://www.e-cancer.fr/Professionnels-de-sante/Depistage-et-detection-precoce/Depistage-du-cancer-du-col-de-l-uterus/Le-depistage-par-frottis-cervico-uterin.

[5] Conduite à tenir devant une femme ayant un frottis cervico-utérin anormal (2002 ANAES guidelines): http://www.has-sante.fr/portail/upload/docs/application/pdf/frottis_final_-_recommandations.pdf.

[6] http://www.e-cancer.fr/content/download/64344/577264/file/Plan-cancer-2014-2019-obj1.pdf.

OBJECTIVES

These national guidelines are intended for use by health professionals who manage patients with abnormal cytology: gynecologists, colposcopists, pathologists, virologists, microbiologists, midwives and general practitioners.

Patients concerned by these guidelines are those eligible for the French cervical cancer screening program, who are immunocompetent and aged 25-65[7]. Based on current knowledge, the management will be similar for immunized and non-immunized women. Immunosuppressed women are not concerned by these guidelines.

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. These guidelines make no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaim any responsibility for their application or use in any way.

GUIDELINES

Guidelines for each situation are presented in the following figures. Some general messages are presented below.

HPV testing can be performed:

- by reflex HPV testing using the initial Pap smear, if it was a liquid-based;
- using a second sample if the initial Pap smear was conventional. In this case, repeat cytology is not necessary. HPV testing can be performed in a medical biology laboratory, so that a second consultation can be avoided.

General guidelines are:

- after a negative HPV test, cytology at 3 years is recommended;
- after a negative dual-staining test, cytology at 12 months is recommended;
- after normal cytological findings (after the initial abnormal cytology), cytology at 12 months is recommended;
- after a positive HPV test (for all high-risk genotype types) or positive dual-staining test or abnormal cytology (performed after the initial abnormal cytology), colposcopy is recommended. A biopsy should be performed during this colposcopy if an abnormality is detected;
- when (satisfactory (ZT1 or ZT2) or unsatisfactory (ZT3)) colposcopy is performed, a vaginal examination should be systematic.

Post-treatment monitoring guidelines have not been updated in this document. The current guidelines are those of the 2002 ANAES guidelines[8].

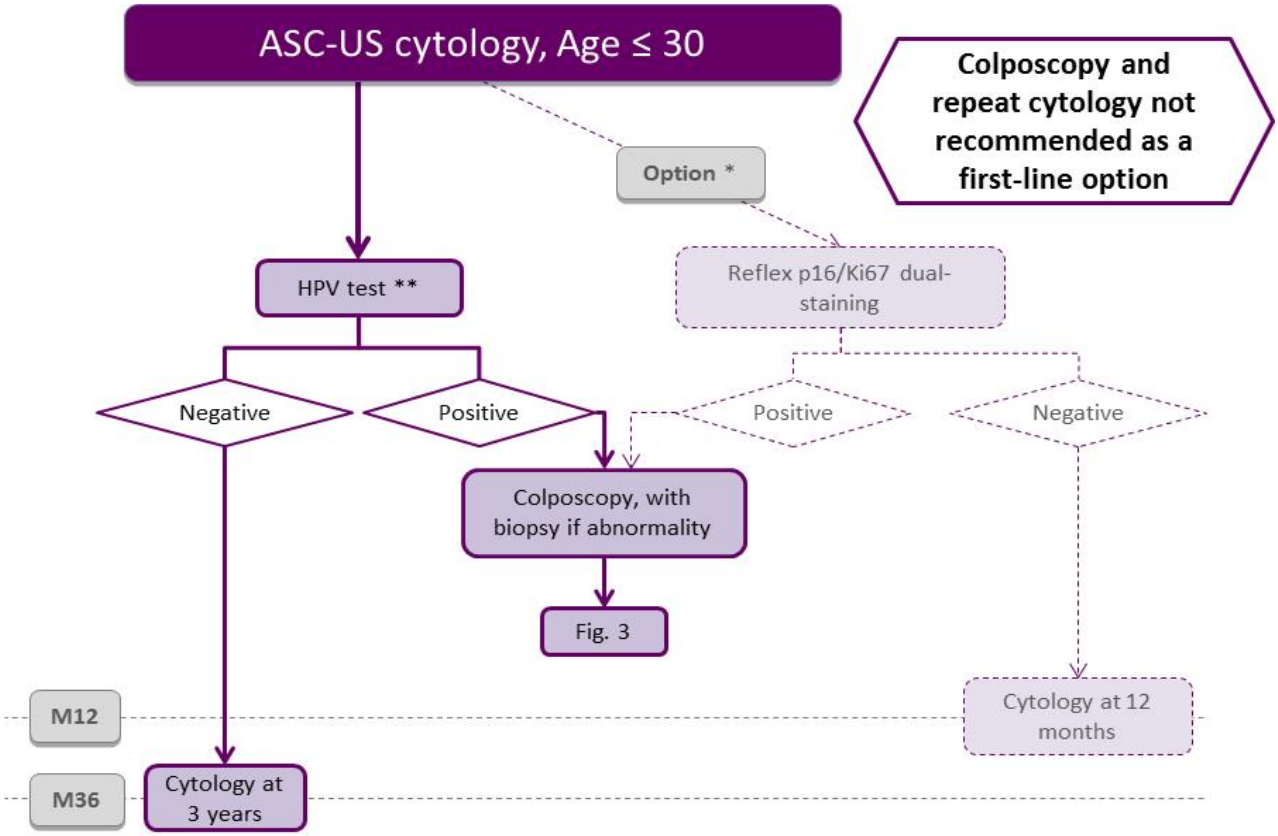
[7] Recommandations pour le dépistage du cancer du col de l'utérus en France – fiche de synthèse, HAS, 2010: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-11/fiche_de_synthese_recommandations_depistage_cancer_du_col_de_luterus.pdf.

[8] Conduite à tenir devant une femme ayant un frottis cervico-utérin anormal (2002 ANAES guidelines): http://www.has-sante.fr/portail/upload/docs/application/pdf/frottis_final_-_recommandations.pdf.

DIAGNOSTIC MANAGEMENT OF ABNORMAL CYTOLOGY

CYTOLOGY WITH ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE (ASC-US)

Figure 1: Initial ASC-US cytology (1): first-line management of women aged 25-30 years

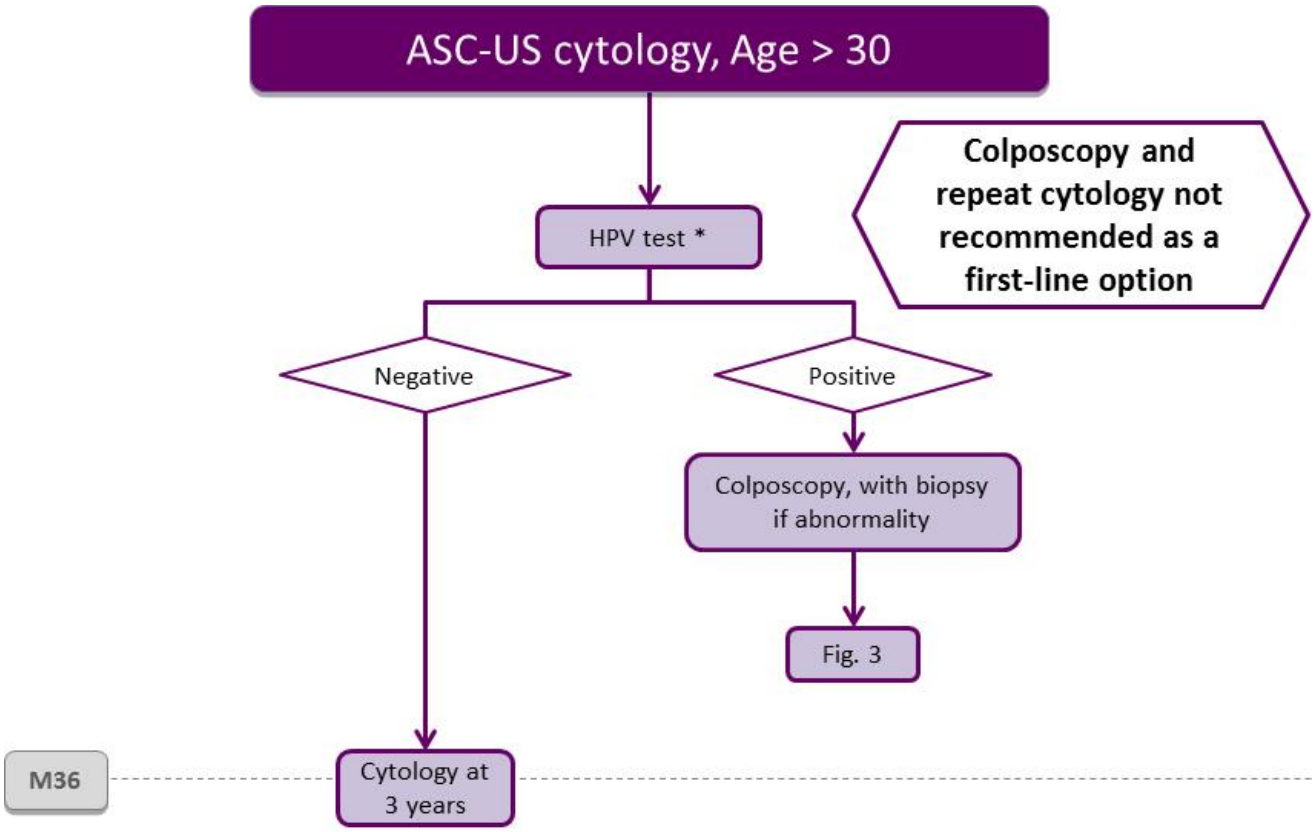


*: only possible with initial liquid-based Pap smear [9].

** : by reflex HPV testing if initial liquid-based initial Pap smear, using a second sample in a specific medium if initial conventional Pap smear.

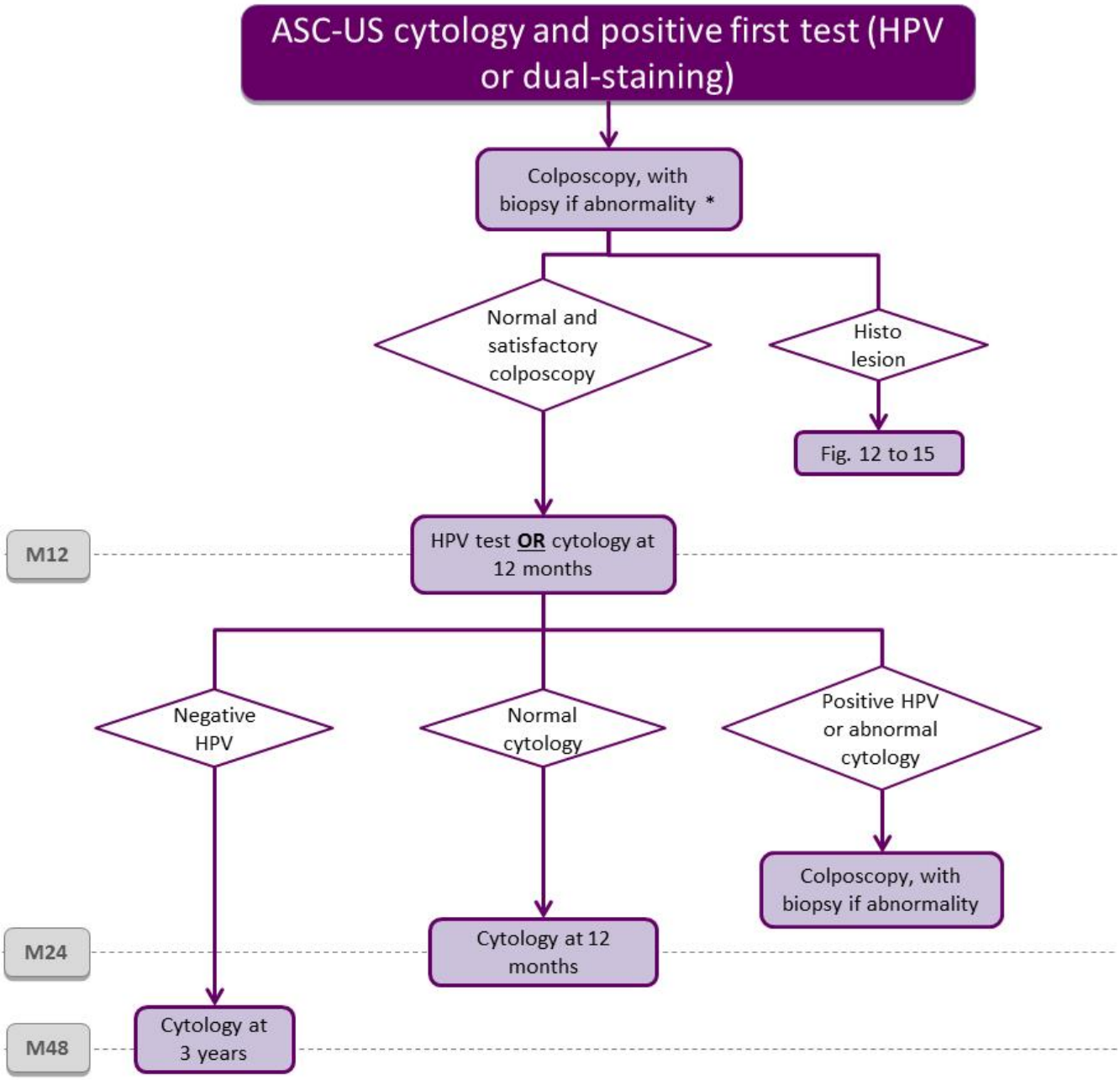
[9] This option is proposed in keeping with minority divergent opinions expressed in the workgroup and confirmed by the independent reviewers.

Figure 2: Initial ASC-US cytology (2): first-line management of women aged 30 years or older



* : by reflex HPV testing if initial liquid-based initial Pap smear, using second sample in a specific medium if initial conventional Pap smear.

Figure 3: Initial ASC-US cytology (3): management after positive HPV or dual-staining test

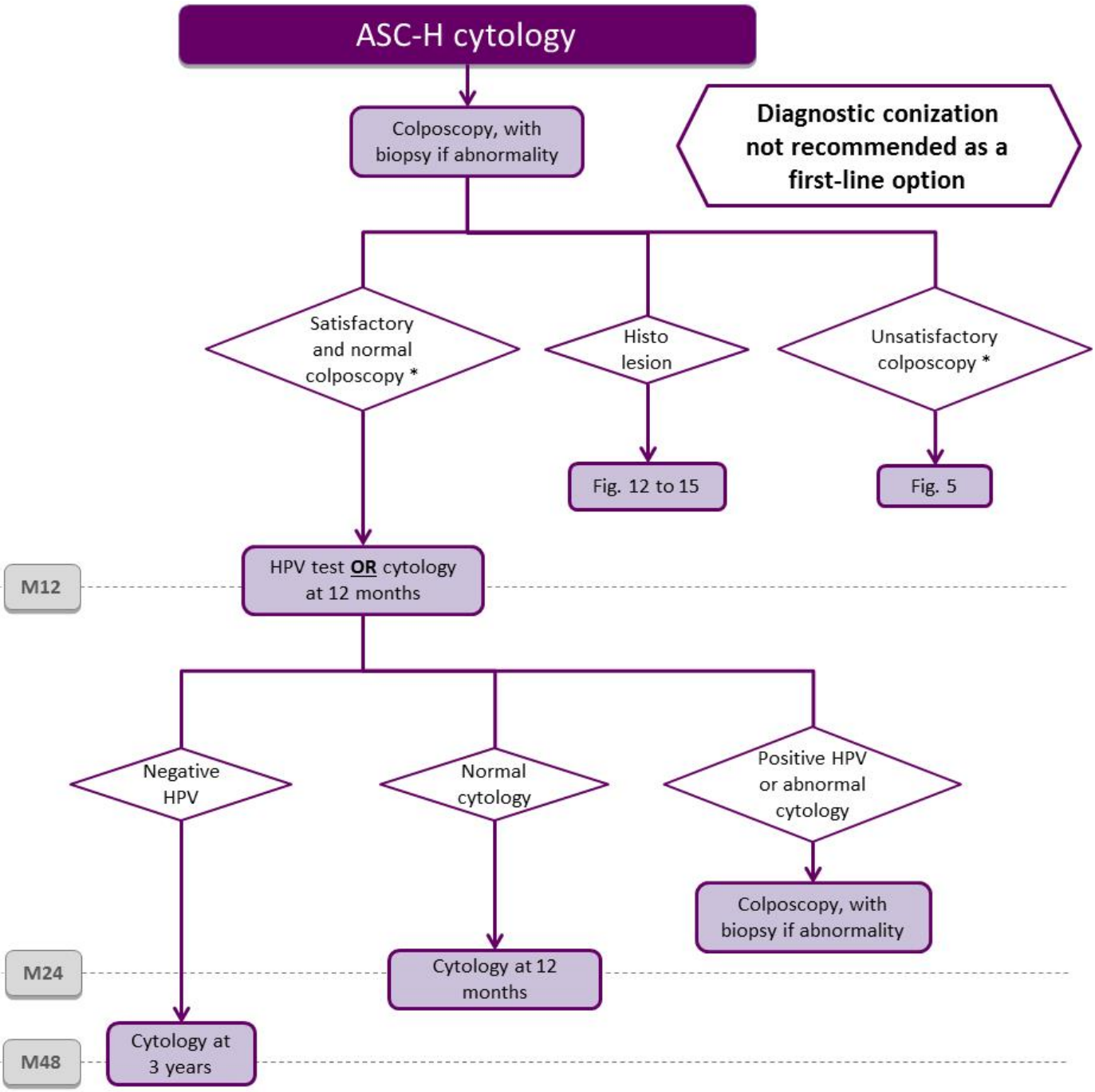


Histo lesion = histological lesion on biopsy.

* If colposcopy was unsatisfactory (ZT3), follow-up colposcopy after preparation and/or endocervical curettage should be proposed (not during pregnancy). Diagnostic conization is not recommended as a first-line option.

CYTOLOGY WITH ATYPICAL SQUAMOUS CELLS THAT CANNOT EXCLUDE HIGH-GRADE SUQAMOUS INTRAEPITHALIAL LESION (ASC-H)

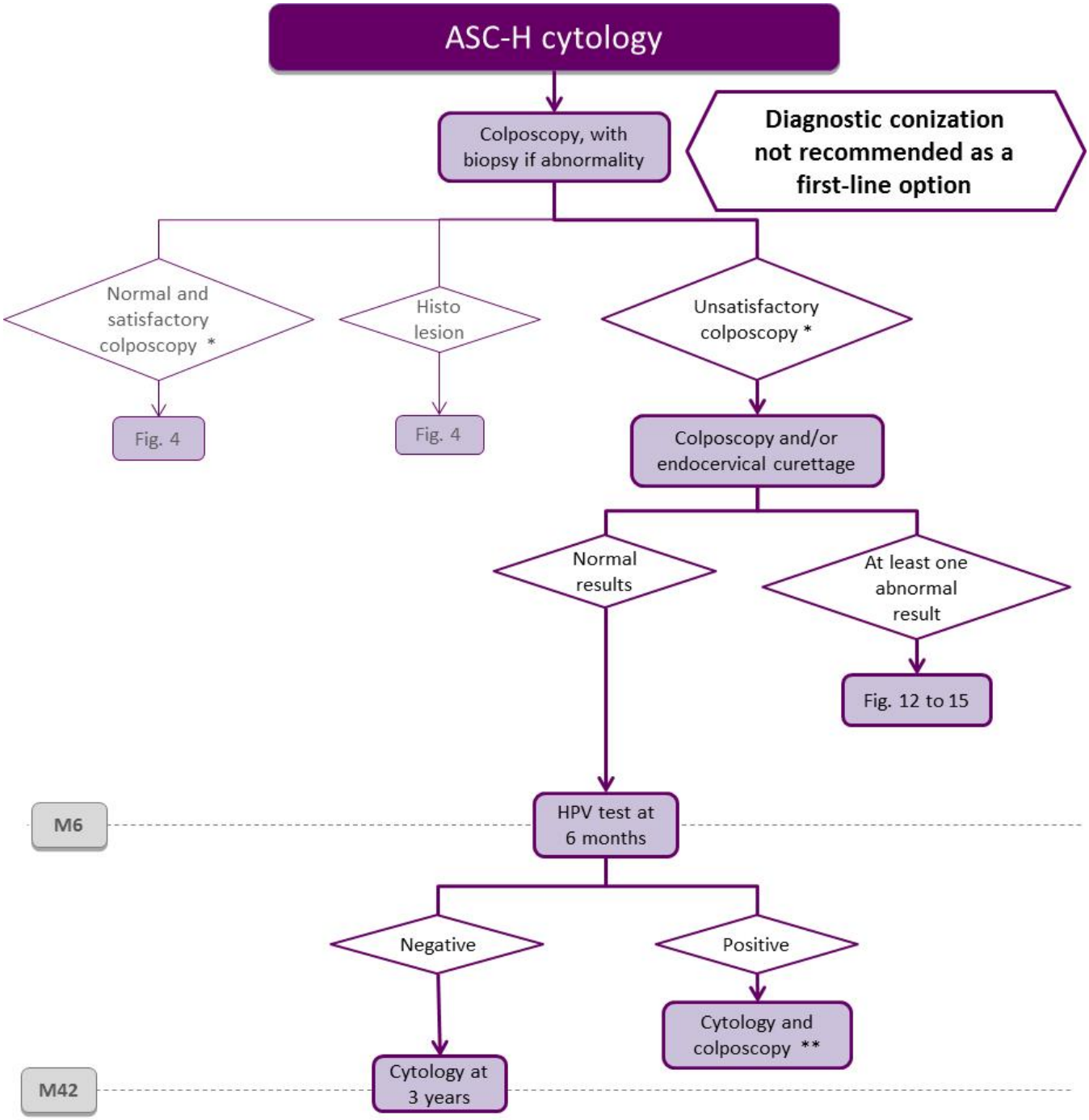
Figure 4: Initial ASC-H cytology (1): first-line management



Histo lesion = histological lesion on biopsy.

* If colposcopy is satisfactory (ZT1 or ZT2) and normal or unsatisfactory (ZT3), vaginal examination should be systematic.

Figure 5: Initial ASC-H cytology (2): management after unsatisfactory colposcopy



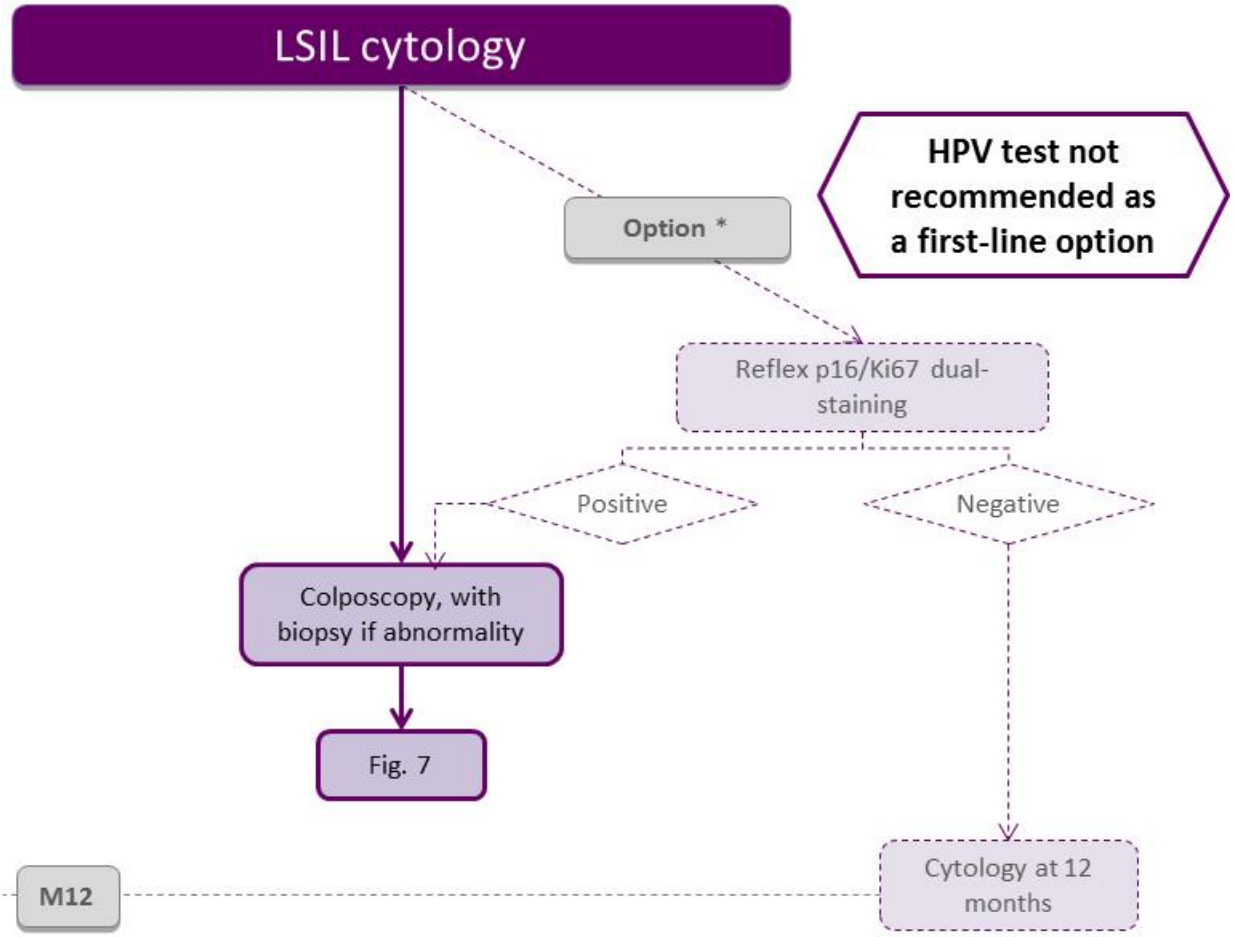
Histo lesion = histological lesion on biopsy

* If colposcopy is satisfactory (ZT1 or ZT2) and normal or unsatisfactory (ZT3), vaginal examination should be systematic.

** If abnormal cytology and unsatisfactory colposcopy persist, diagnostic conization may be proposed.

CYTOLOGY WITH LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL)

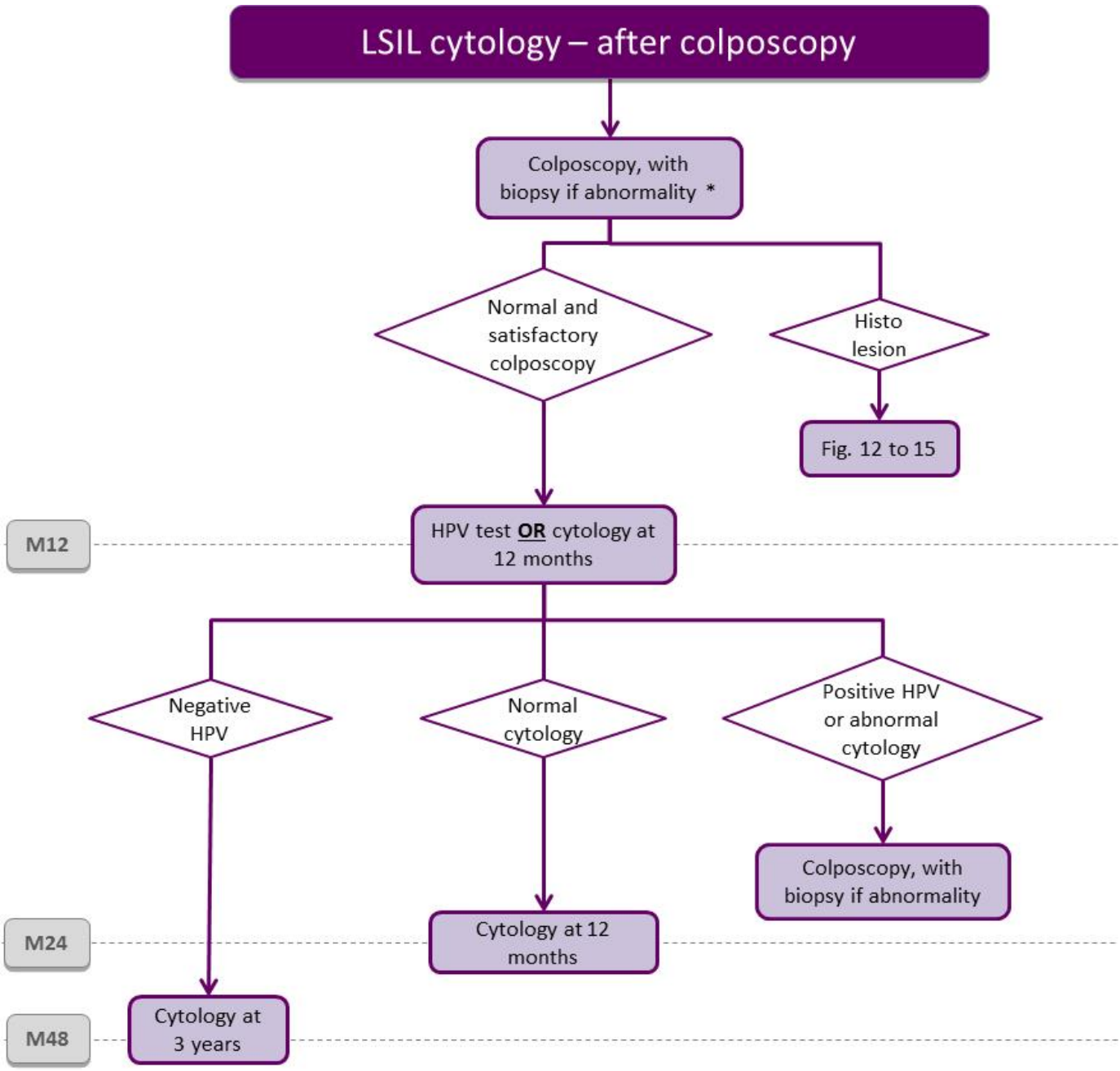
Figure 6: Initial LSIL cytology (1): first-line management



When colposcopy and dual-staining cannot be performed, cytology at 12 months, with follow-up at 24 months, may be proposed. If the second cytology is abnormal, colposcopy is necessary.

* only possible with initial liquid-based Pap smear.

Figure 7: Initial LSIL cytology (2): management after colposcopy

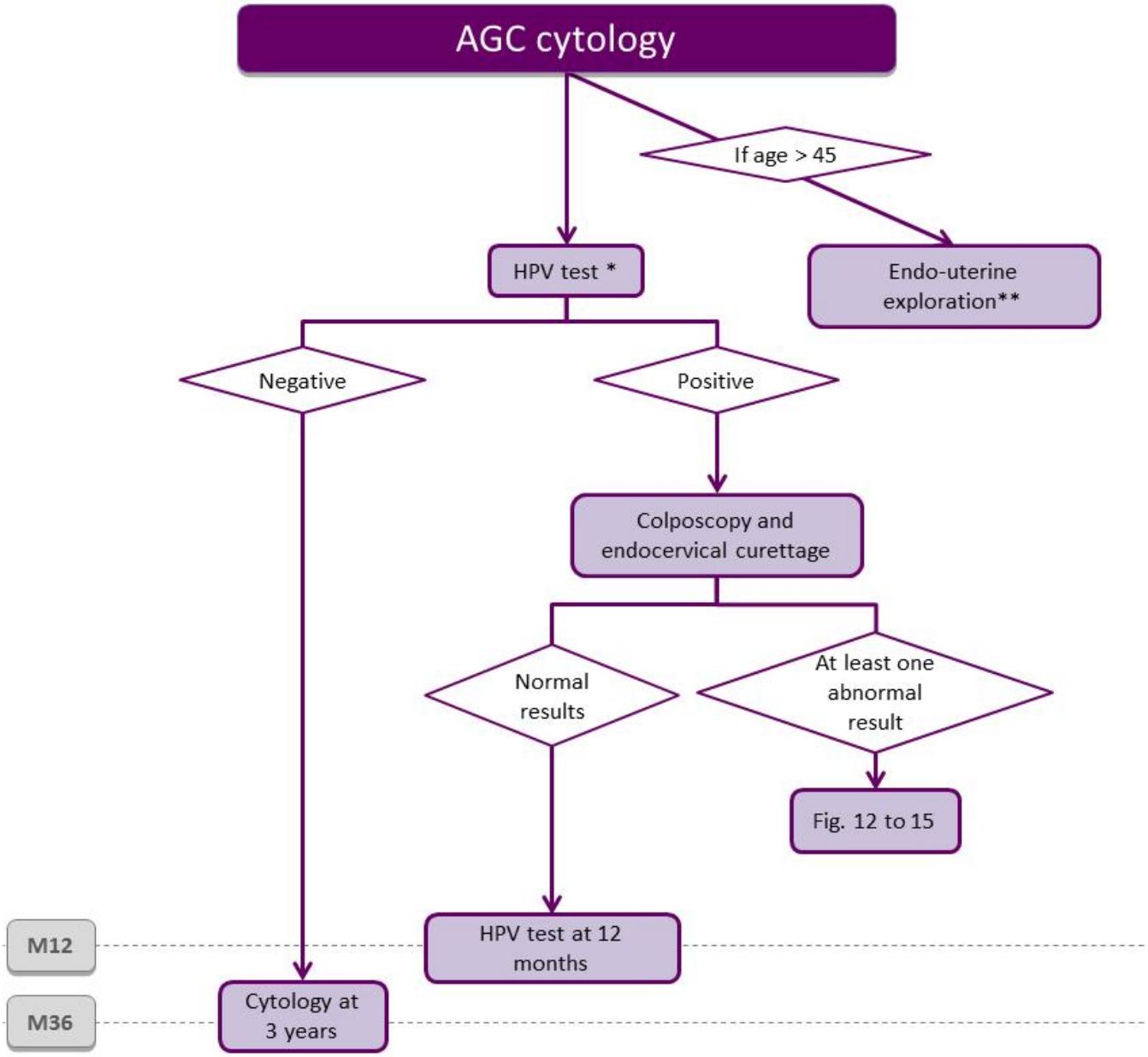


Histo lesion = histological lesion on biopsy

* If colposcopy was unsatisfactory (ZT3), follow-up colposcopy after preparation and/or endocervical curettage should be proposed (not during pregnancy). Diagnostic conization is not recommended as a first-line option.

CYTOLOGY WITH ATYPICAL GLANDULAR CELLS (AGC)

Figure 8: Initial AGC cytology

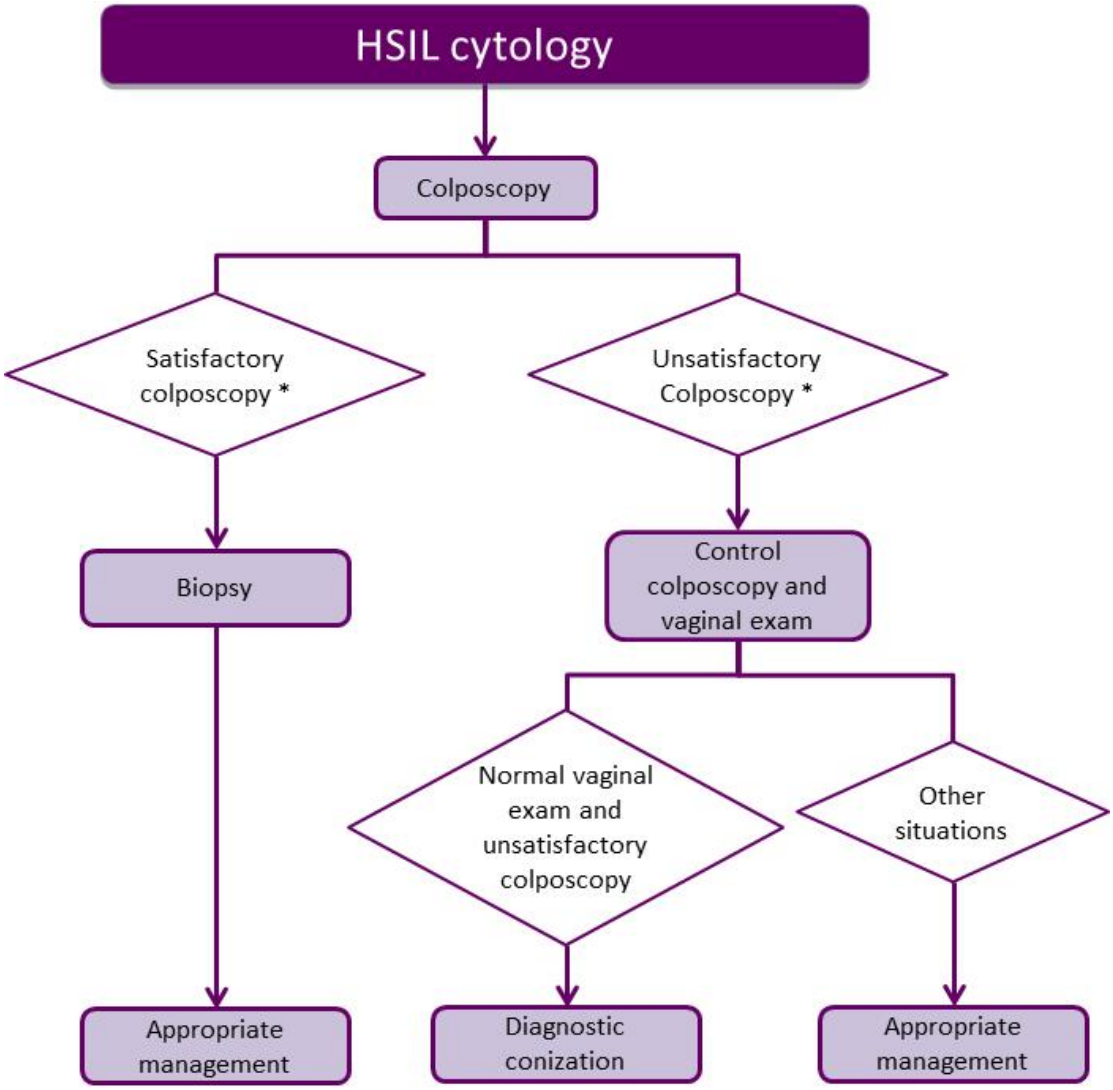


* : by reflex HPV testing if initial liquid-based initial Pap smear, using second sample in a specific medium if initial conventional Pap smear

** pelvic ultrasonography and endometrial biopsy should be performed in addition to HPV test.

CYTOLOGY WITH HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)

Figure 9: Initial HSIL cytology



This figure has been proposed by the workgroup based on the 2002 recommendations of ANAES[10].

colpo = colposcopy

* If colposcopy is satisfactory (ZT1 or ZT2) and normal or unsatisfactory (ZT3), vaginal examination should be systematic.

[10] Conduite à tenir devant une femme ayant un frottis cervico-utérin anormal (2002 ANAES guidelines): http://www.has-sante.fr/portail/upload/docs/application/pdf/frottis_final_-_recommandations.pdf

ABNORMAL CYTOLOGY DURING PREGNANCY

Figure 10: ASC-US or LSIL cytology identified during pregnancy

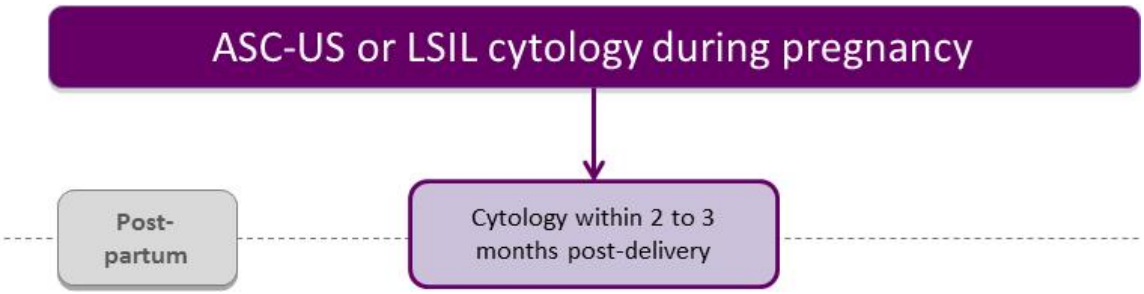
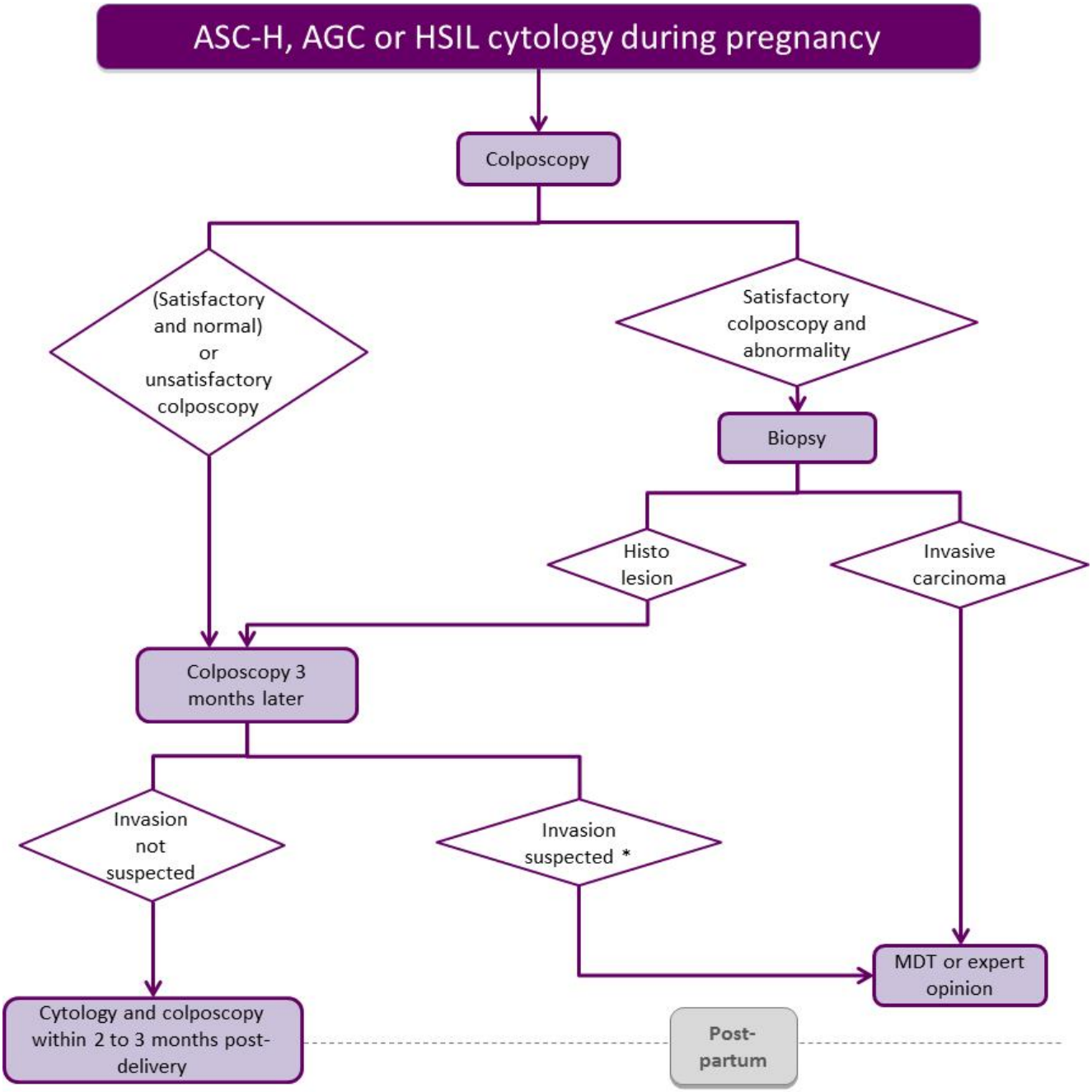


Figure 11: ASC-H, AGC or HSIL cytology identified during pregnancy



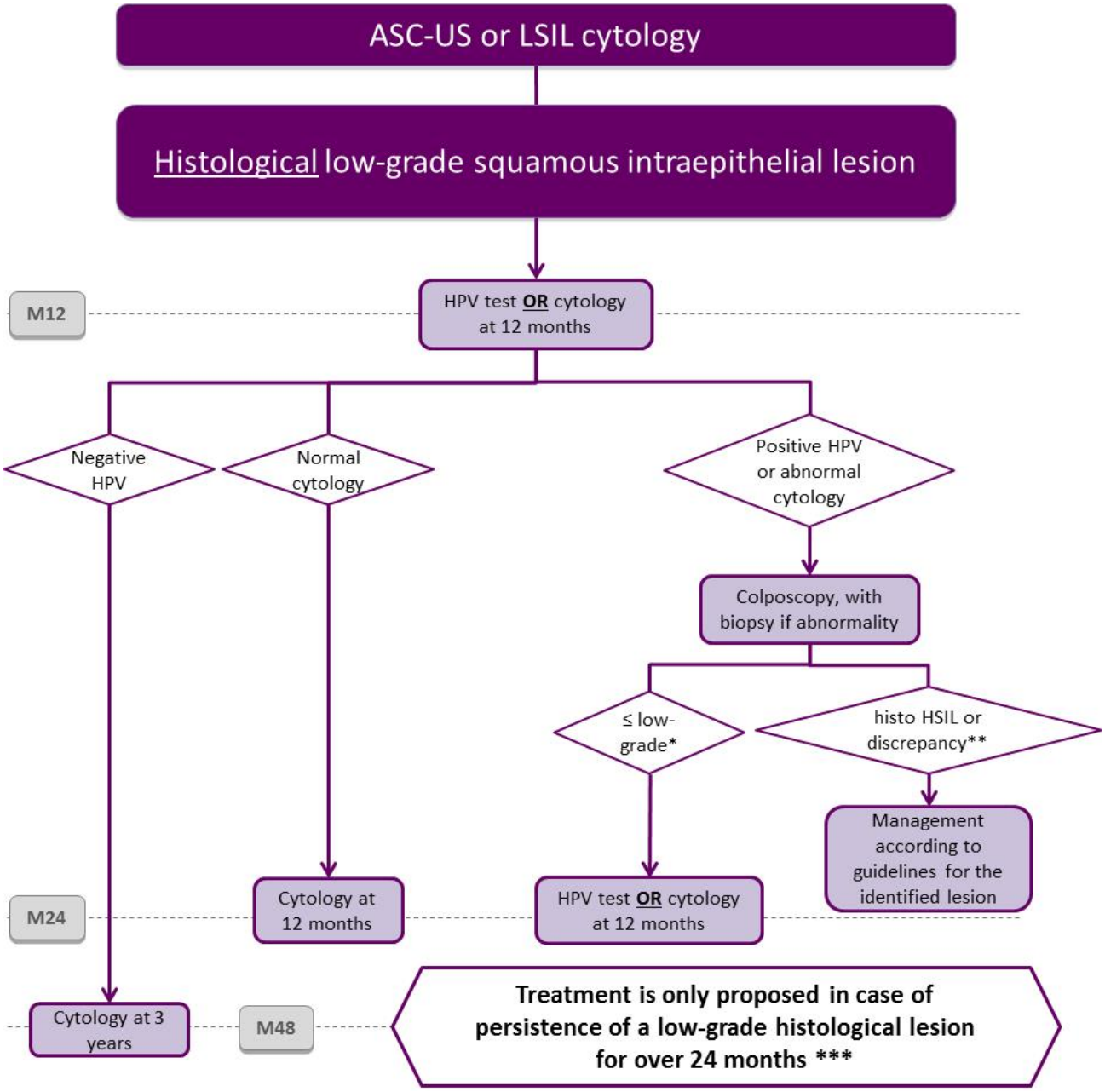
Histo lesion = histological squamous intraepithelial lesion on biopsy.

* A second biopsy is recommended.

THERAPEUTIC INDICATIONS

HISTOLOGICAL LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Figure 12: Histological low-grade squamous intraepithelial lesion after initial ASC-US or LSIL cytology



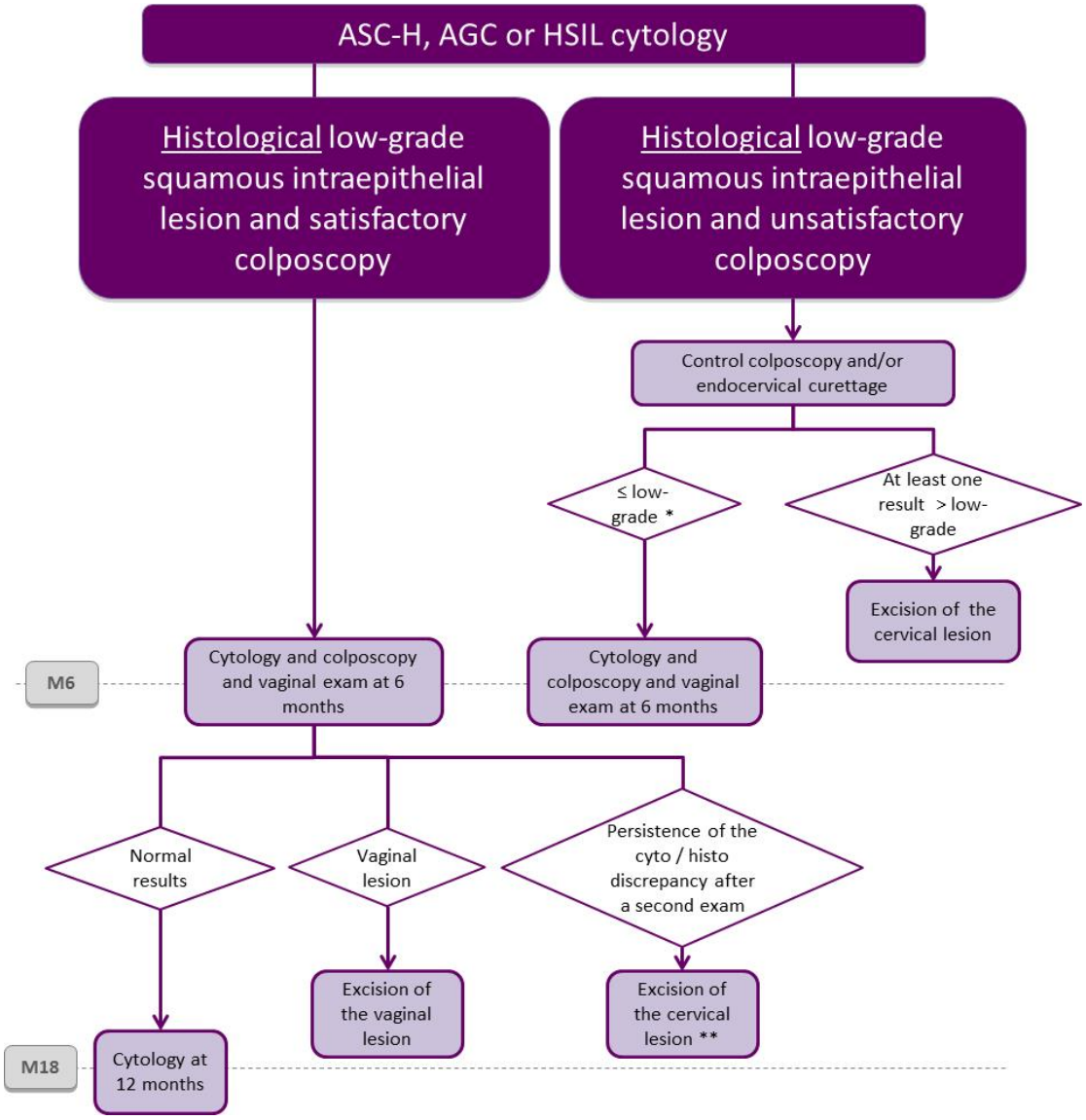
histo HSIL = histological high-grade squamous intraepithelial lesion on biopsy.

*≤ low-grade = satisfactory and normal colposcopy or histological low-grade squamous intraepithelial lesion.

** discrepancy = high-grade cytology and low-grade biopsy.

*** a destruction method will preferentially be proposed (because of absence of obstetric complications). Conization is not systematic and monitoring can be continued.

Figure 13: Histological low-grade squamous intraepithelial lesion after initial ASC-H, AGC or HSIL cytology



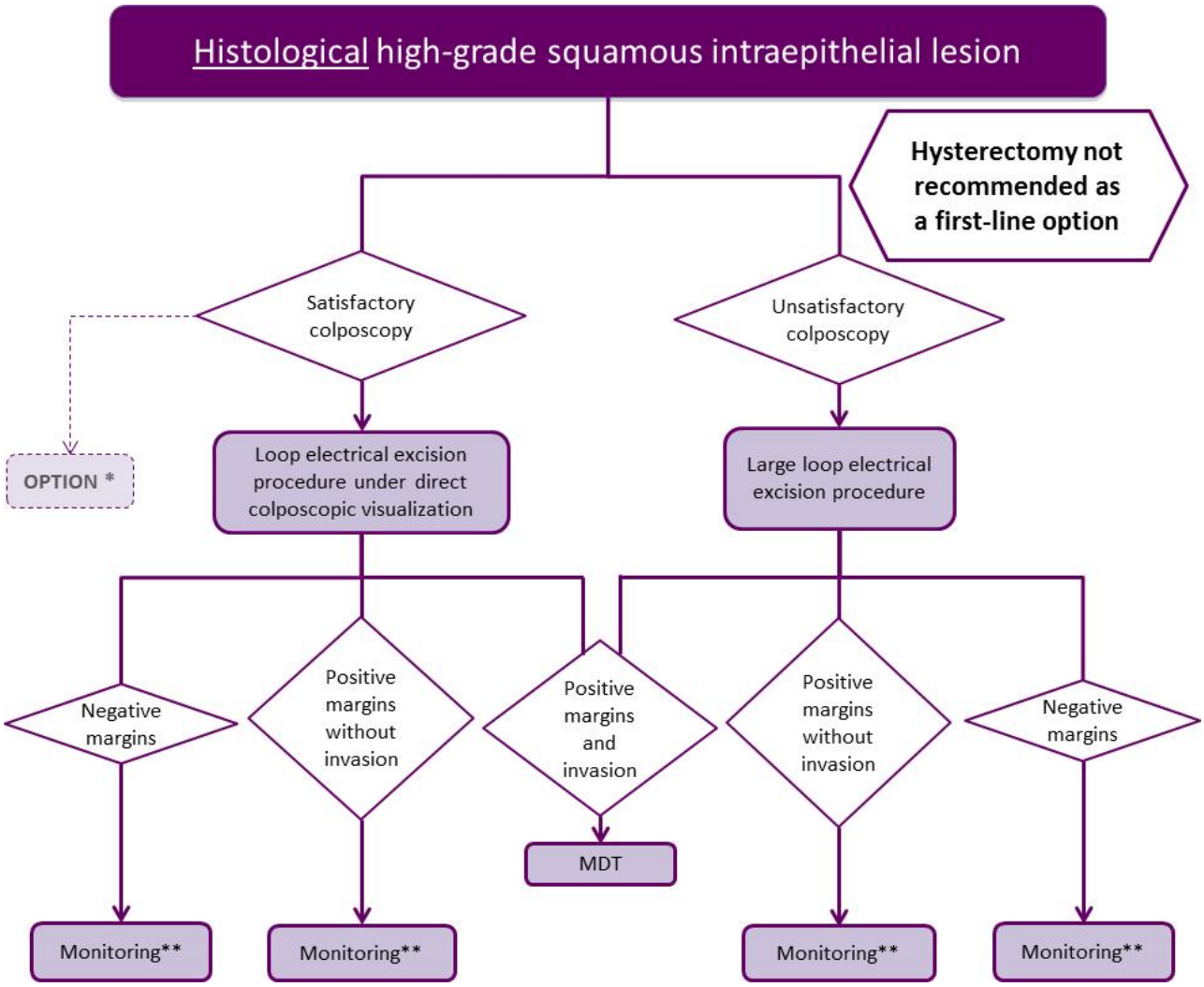
Cyto = cytology; histo = histology

* ≤ low-grade = satisfactory and normal colposcopy or histological low-grade squamous intraepithelial lesion.

** recommended using loop electrical excision procedure under direct colposcopic visualization.

HISTOLOGICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Figure 14: Histological high-grade squamous intraepithelial lesion

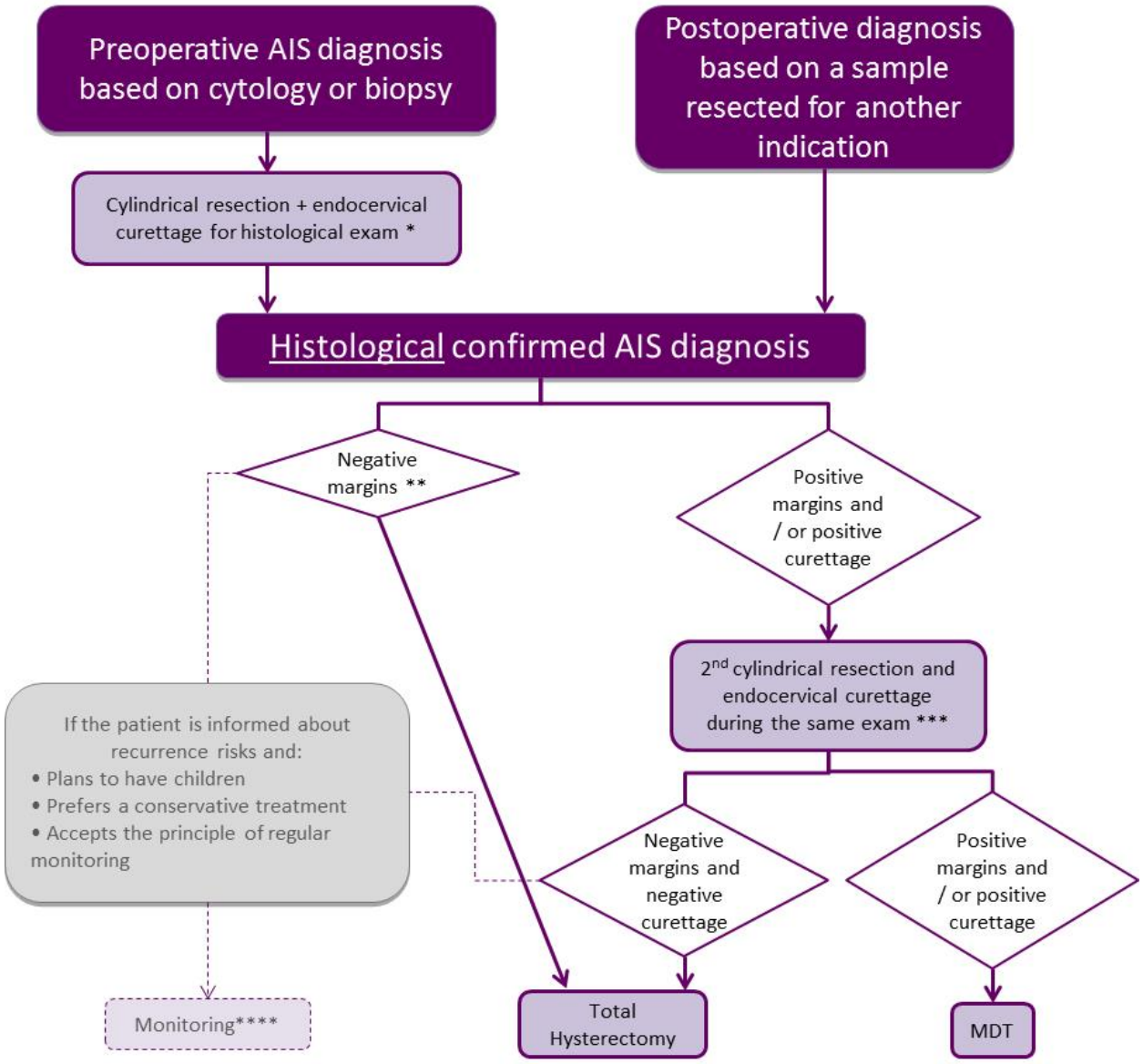


* Option: If the colposcopic appearance of the lesion is not invasive, if the lesion is small and if the squamocolumnar junction is seen, destruction or an abstention-monitoring approach may be proposed to a willing patient aged 30 and younger, who accepts the principle of regular monitoring (cytology and colposcopy +/- biopsy every 6 months for 2 years maximum).

** Note: Post-treatment monitoring guidelines have not been updated in this document. The current guidelines can be obtained in the 2002 ANAES guidelines.

ADENOCARCINOMA *IN SITU* (AIS)

Figure 15: Histologically confirmed adenocarcinoma *in situ*



*cylindrectomy by loop electrical excision procedure or cold-knife conization. Hysterectomy is not recommended because of the underlying risk of undiagnosed and untreated invasive lesion.

** negative margin = no lesion at the (lateral, endo and exocervical) edges of the sample. There is no definition of the minimal distance between the lesion and the edges of the sample.

*** in order to ensure the absence of invasive residual lesion.

**** Note: Post-treatment monitoring guidelines have not been updated in this document. The current guidelines can be obtained in the 2002 ANAES guidelines.

METHODS

GUIDELINE PRODUCTION METHODS

The details of the production methods are presented in the full report (in French) available online at the French National Cancer Institute website.

In brief, guideline production is based on:

- A critical appraisal of the best scientific data available, summarized in conclusions of the literature with corresponding levels of evidence;
- The professional experience and consensus of the expert group (expert agreement).

A systematic literature review of the studies published between January 2002 and January 2016 was carried out using the MEDLINE database. The literature search, the methodological analysis and the scientific data synthesis were conducted by the French National Cancer Institute. The guidelines were formulated by the multidisciplinary workgroup under the coordination of the French National Cancer Institute. The guidelines were then peer reviewed in March 2016 by independent experts with quantitative (notation) and qualitative (comments) assessments. Their comments were incorporated in the final version after a final meeting of the multidisciplinary workgroup.

GUIDELINE GRADING

Two levels are used for grading guidelines:

- By default, a guideline is the clinical approach that is unanimously recognized by experts as being the criterion-standard clinical approach;
- If an approach is deemed to be acceptable on the basis of data analysis but is not unanimously recognized as a criterion-standard clinical approach, the indication is given that it is subject to discussion / can be proposed ("option" in the guidelines).

LEVEL OF EVIDENCE

The levels of evidence correspond to the literature data notation, on which the guidelines are based. They are based on the type and quality of the studies available and on the consistency of their results. The levels of evidence used for these guidelines are presented in the full report.

WORKGROUP CREATION AND CONFLICT OF INTEREST PREVENTION

These guidelines were produced in association with a multidisciplinary workgroup representative of the modes of practice concerned by the management of patients with abnormal cervical cytology.

The experts of this external workgroup were appointed by the French National Cancer Institute, after analyzing their declaration of interest, further to a call for experts on the French National Cancer Institute website and on the suggestions of Société française de colposcopie et de pathologie cervico-vaginale, Collège national des gynécologues et obstétriciens français, Fédération nationale des collèges de gynécologie médicale, Société française de cytologie clinique, Société française de pathologie, Centre national de référence des papillomavirus humains, Société française de microbiologie, Collège de la médecine générale, Collège national des sages-femmes and Association des coordinateurs de structures de dépistage[11].

[11] http://www.e-cancer.fr/Institut-national-du-cancer/Deontologie-et-transparence-DPI/Prevention-et-gestion-des-conflits-d-interet

The workgroup composition and conflict of interest forms are available on the INCa website[12]. The list of the workgroup members is presented in the full report.

QUALITY CRITERIA OF RECOMMENDED TESTS

The workgroup members considered it important to reiterate some principles in order to guarantee the quality of tests or examinations. These principles are based on the opinion of the relevant French scholarly associations for each test.

These criteria are presented in a specific document available on the INCa website (in French).

WORKGROUP COMPOSITION, COORDINATION AND LIST OF INDEPENDENT REVIEWERS

WORKGROUP COMPOSITION

LIST OF MEMBERS WHO CONTRIBUTED TO THE FORMULATION OF THE GUIDELINES

BERGERON Christine, pathologist, Laboratoire Cerba, Cergy Pontoise (scientific coordinator) – *(except for the 2 options in respect of dual-staining for triage of ASC-US or LSIL cytologies)*

COCHAND-PRIOLLET Béatrix, pathologist, Hôpital Cochin, Paris (scientific coordinator), ***included in the workgroup in May 2015***

DALSTEIN Véronique, molecular biologist, CHU, Reims (scientific coordinator)

MERGUI Jean-Luc, gynecologist, Hôpital Pitié Salpétrière / Private practice (scientific coordinator)

BRUN Jean-Luc, gynecologist, CHU, Bordeaux

CARCOPINO Xavier, gynecologist, Hôpital Nord, Marseille

CARTIER Isabelle, pathologist, Laboratoire Cartier, Paris

[12] http://www.e-cancer.fr/Institut-national-du-cancer/Deontologie-et-transparence-DPI/Declarations-publiques-d-interets-DPI/Declarations-publiques-d-interets-DPI/%28show%29/Media/Docman/e-cancer-Espace-INCa/Declarations-publiques-d-interets-DPI/Groupes-de-travail-recommandations/Conduite-a-tenir-devant-une-femme-ayant-un-frottis-cervico-uterin-anormal/%28current%29/96686

COURTADE-SAIDI Monique, pathologist, CHU, Toulouse

FENDER Muriel, public health physician, Association EVE, Illkirch

GAILLOT Alain, pathologist, Cabinet Sipath-Unilabs, Clermont-Ferrand

GARRIGUE Isabelle, virologist, CHU, Bordeaux

GRAESSLIN Olivier, gynecologist, CHU, Reims ***included in the workgroup in June 2015***

HEARD Isabelle, gynecologist, Institut Pasteur, Paris

LAUDE Hélène, virologist, Institut Pasteur, Paris ***included in the workgroup in May 2015***

LEVEQUE Jean, gynecologist, CHU / Centre Eugène Marquis, Rennes

MOUSTEOU Françoise, gynecologist, Private practice, Cagnes-sur-Mer

SENGCHANH Somany, screening center medical coordinator, Centre de Coordination des Dépistages des Cancers, CHRU, Tours

RESIGNATION FROM THE WORKGROUP

These resignations were submitted before the first guideline formulation meeting.

DARAÏ Emile, gynecologist, Paris, resignation in March 2015

DI PATRIZIO Paolo, general practitioner, Dombasle sur Meurthe, resignation in March 2015

HALFON Philippe, virologist, Marseille, resignation in March 2015

VACHER-LAVENU Marie-Cécile, pathologist, Paris (scientific coordinator until her resignation), resignation in March 2015

GANTOIS Adrien, midwife, Private practice, Le-Pré-Saint-Gervais, resignation in October 2014

FRENCH NATIONAL CANCER INSTITUTE

Coordination by "Best Practices Department, Guidelines and Medicines Division"

MOROIS Sophie, project manager (since March 2015)

ROUE Tristan, project manager (since January 2016)

PLANCHAMP François, project manager (until December 2014)

DE PERETTI Camille, archivist

DUPERRAY Marianne, head of Department (since June 2016)

SCEMAMA Olivier, head of Department (between September 2014 and December 2015)

VERDONI Laetitia, head of Department (until May 2014)

DAHAN Muriel, head of Division (since October 2016)

BELORGEY Chantal, head of Division (between January 2015 and June 2016)

MAZEAU-WOYNAR Valérie, head of Division (until October 2014)

LIST OF INDEPENDENT EXPERT REVIEWERS

The list of independent expert reviewers is available in the complete report (in French) available online on the French National Cancer Institute website.

/Summary
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WITH ABNORMAL CERVICAL CYTOLOGY

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