

# Utérus - col

*Ce référentiel, dont l'utilisation s'effectue sur le fondement des principes déontologiques d'exercice personnel de la médecine, a été élaboré par un groupe de travail pluridisciplinaire de professionnels des réseaux régionaux de cancérologie de Lorraine (ONCOLOR), d'Alsace (CAROL), de Bourgogne (ONCOBOURGOGNE), de Champagne-Ardenne (ONCOCHA) et de Franche-Comté (ONCOLIE), en tenant compte des recommandations nationales, et conformément aux données acquises de la science au **17 mai 2013**.*

## ■ Généralités

---

- ▶ Le référentiel ne concerne que les carcinomes épidermoïdes et les adénocarcinomes du col de l'utérus. Tous les dossiers sont à présenter en RCP avant toute décision thérapeutique.
- ▶ Pour les lésions pré-cancéreuses, se référer aux recommandations du Collège National des Gynécologues Obstétriciens Français ([CNGOF](#)).
- ▶ Deux cas particuliers seront précisés :
  - le cas du **cancer sur col**
  - **restand**
  - la prise en charge du cancer du col **pendant la grossesse**.
- ▶ L'INCa et la Ligue contre le cancer mettent à disposition des patientes et de leurs proches un Guide Cancer Info sur « Les traitements du cancer invasif du col de l'utérus » (version de juin 2011). Il est [consultable](#) ou [téléchargeable](#) sur le site Cancer info.

## ■ Anatomicopathologie

---

- ▶ Ce référentiel ne concerne que les carcinomes épidermoïdes et les adénocarcinomes du col utérin. Pour les histologies particulières (neuroendocrines, mélanome...), discussion pré-thérapeutique en RCP.

## Lésions infracliniques

---

- ▶ **Le diagnostic repose sur l'examen histologique de la pièce de conisation. Le frottis ou la biopsie ne sont pas suffisants pour poser une indication d'hystérectomie ou orienter la prise en charge thérapeutique.**
- ▶ Éléments histologiques nécessaires à la prise de décision thérapeutique :
  - affirmation du diagnostic de cancer infiltrant
  - profondeur maximale de l'infiltration tumorale (mm)
  - degré d'extension latérale des lésions infiltrantes (mm) en précisant le diamètre maximal
  - présence ou absence d'embolies vasculaires
  - qualité des limites d'exérèse chirurgicale
  - apport de l'immunohistochimie dans le diagnostic différentiel d'une origine de l'endomètre versus endocol.

## Lésions macroscopiques

---

- ▶ Éléments histologiques sur la biopsie nécessaires à la prise de décision thérapeutique :
  - affirmation du diagnostic de cancer infiltrant
  - précision de son type dans la classification OMS 2003.

### **Référence**

Deville P, Tavassoli Fattaneh A.

Pathology and Genetics of Tumours of the Breast and Female Genital Organs (World Health Organization Classification of Tumors)

*International Agency for Research on Cancer, IARC Press Lyon 2003.*

## ■ Bilan initial

---

- ▶ Il comporte :
  - un **examen gynécologique** et des biopsies.
    - Si l'examen est difficile ou la tumeur volumineuse, un examen gynécologique sous anesthésie générale est recommandé avec cystoscopie ± rectoscopie ± biopsies d'endomètre
    - L'examen gynécologique par les différents intervenants aboutit à la stadification et à un schéma des lésions.

- **imagerie recommandée :**
  - **IRM pelvienne et lombo-aortique** : l'IRM lombo-aortique peut être remplacée par un scanner abdominal selon disponibilités locales
  - **TEP TDM à partir du stade IB2** : en option pour les stades IB1, notamment si la tumeur mesure plus de 2 cm ; si pas de PET, scanner thoracique.
- ▶ **dosage du SCC** si carcinome épidermoïde (optionnel).

## □ Classification FIGO (2009)

### Stade I

- ▶ La classification FIGO reste basée sur l'**examen clinique** ; l'atteinte ganglionnaire est à préciser à part.

Cancer strictement limité au col		
<b>Stade IA</b>	cancer invasif identifié seulement au microscope et envahissement du stroma : profondeur maximum de 5 mm, largeur maximum de 7 mm	
	<b>IA1</b>	profondeur ≤ 3 mm, largeur ≤ 7 mm
	<b>IA2</b>	3 mm < profondeur ≤ 5 mm et largeur ≤ 7 mm
<b>Stade IB</b>	cancer clinique limité au col visible en macroscopie ou cancer microscopique de dimension supérieure au IA	
	<b>IB1</b>	T ≤ 4 cm
	<b>IB2</b>	T >4 cm

## Stade II

---

<b>Cancer étendu au-delà du col mais n'atteignant pas la paroi pelvienne ni le tiers inférieur du vagin</b>		
<b>Stade IIA</b>	jusqu'aux deux tiers supérieurs du vagin  Taille T ≤ 4 cm	
<b>IIA1</b>		
	<b>IIA2</b>	Taille T >4 cm
<b>Stade IIB</b>	paramètres (proximaux)	

## Stade III

---

<b>Cancer étendu jusqu'à la paroi pelvienne et/ou au tiers inférieur du vagin (y compris hydronéphrose)</b>	
<b>Stade IIIA</b>	atteinte vaginale jusqu'au tiers inférieur
<b>Stade IIIB</b>	fixation à la paroi pelvienne (ou hydronéphrose ou rein muet)

## Stade IV

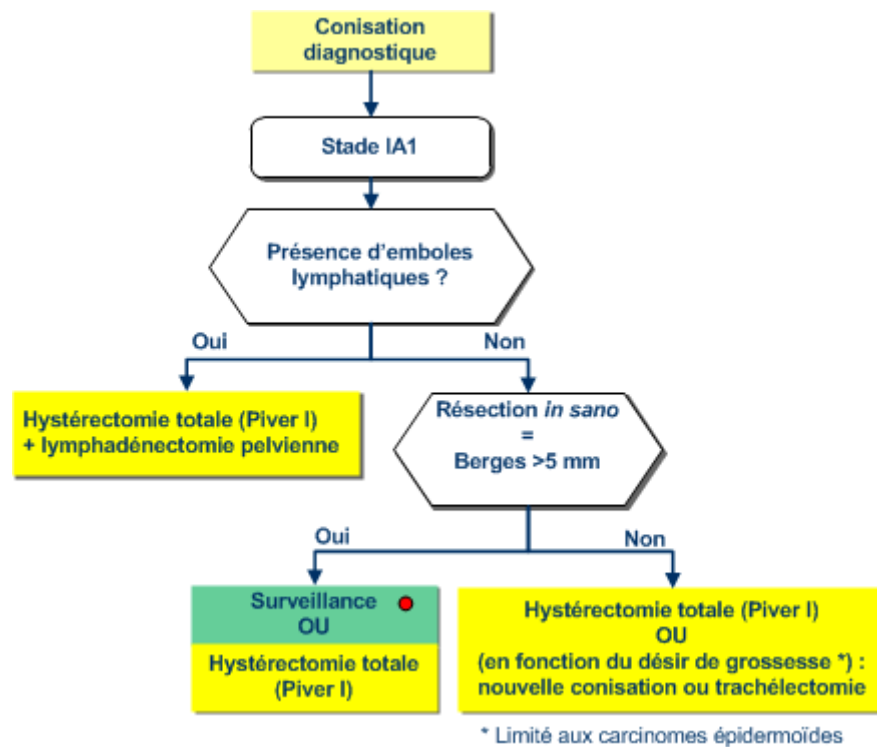
---

<b>Cancer étendu au-delà du petit bassin ou à la muqueuse vésicale et/ou rectale</b>	
<b>Stade IVA</b>	organe adjacent
<b>Stade IVB</b>	à distance, y compris ganglions lombo-aortiques

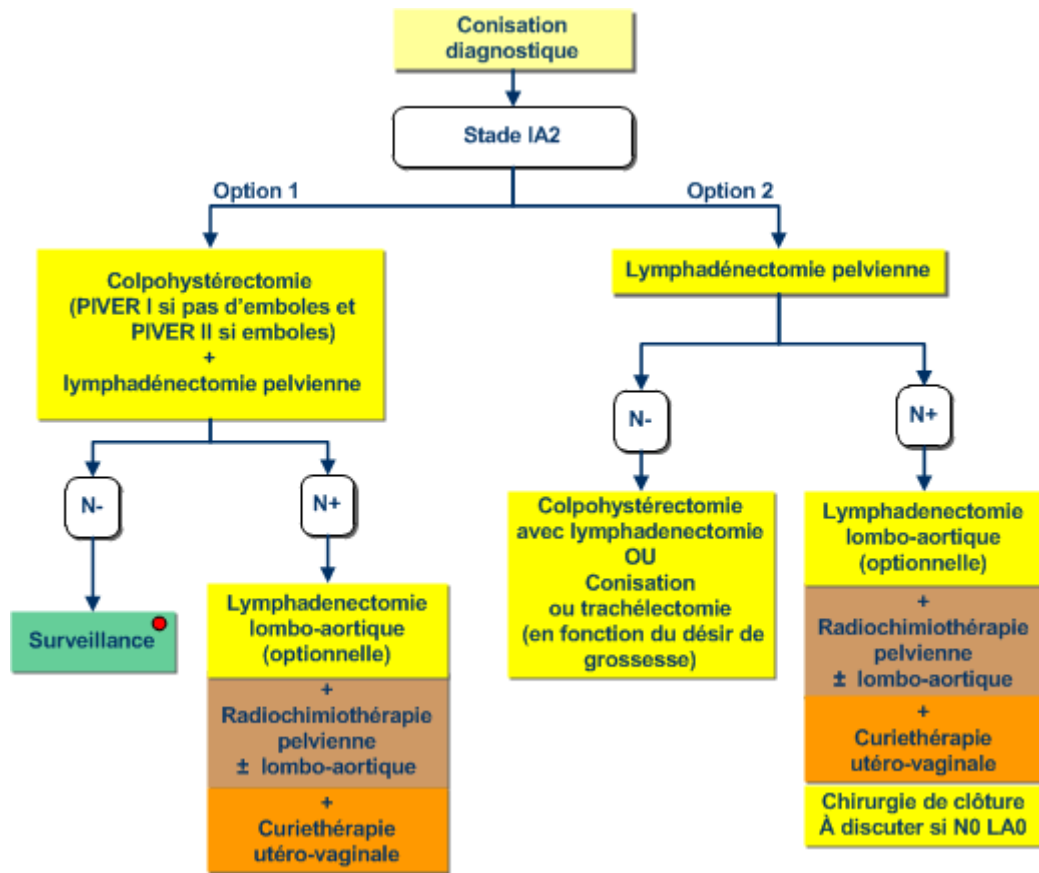
## ■ Prise en charge

- ▶ Le dossier du patient doit être présenté **avant toute prise en charge thérapeutique** (ou bien avant l'acte chirurgical)
- ▶ La prise en charge est fonction du stade FIGO et doit être faite par une équipe expérimentée.

### Stade IA1



## Stade IA2



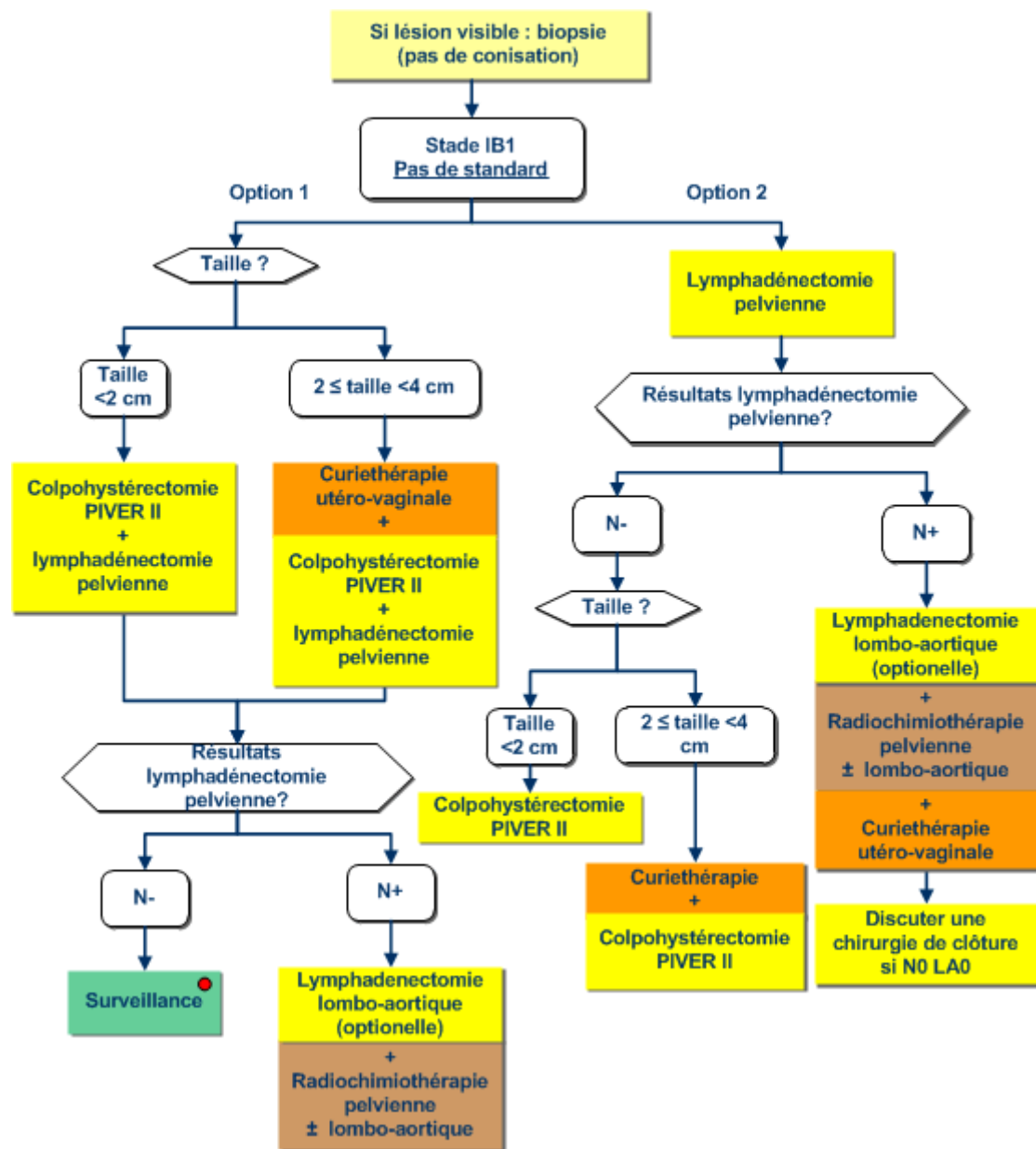
### Légende

*N0 et N1 : classification radioclinique*

*N + et N- : classification histologique*

*Np : adénopathie visible sur PET-Scan*

# Stade IB1



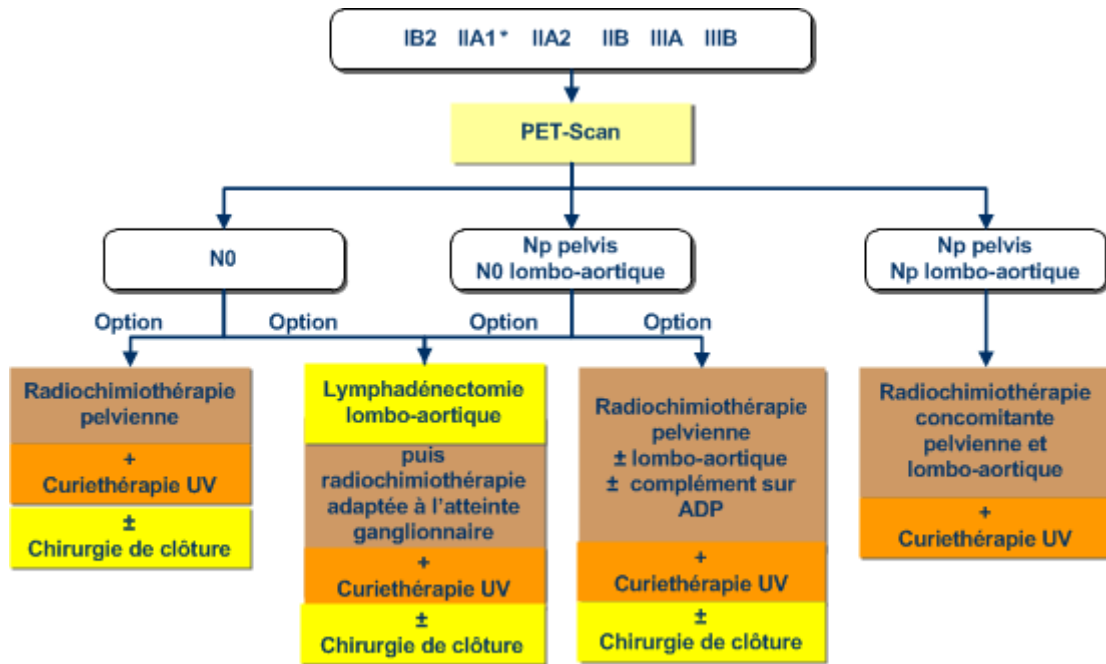
## Légende

N0 et N1 : classification radioclinique

N + et N- : classification histologique

Np : adénopathie visible sur PET-Scan

## Stade IB2, IIA1, IIA2, IIB, IIIA et IIIB



\* IIA1 <2 cm : une curietherapie UV suivie d'une chirurgie peut s'envisager

### **Légende**

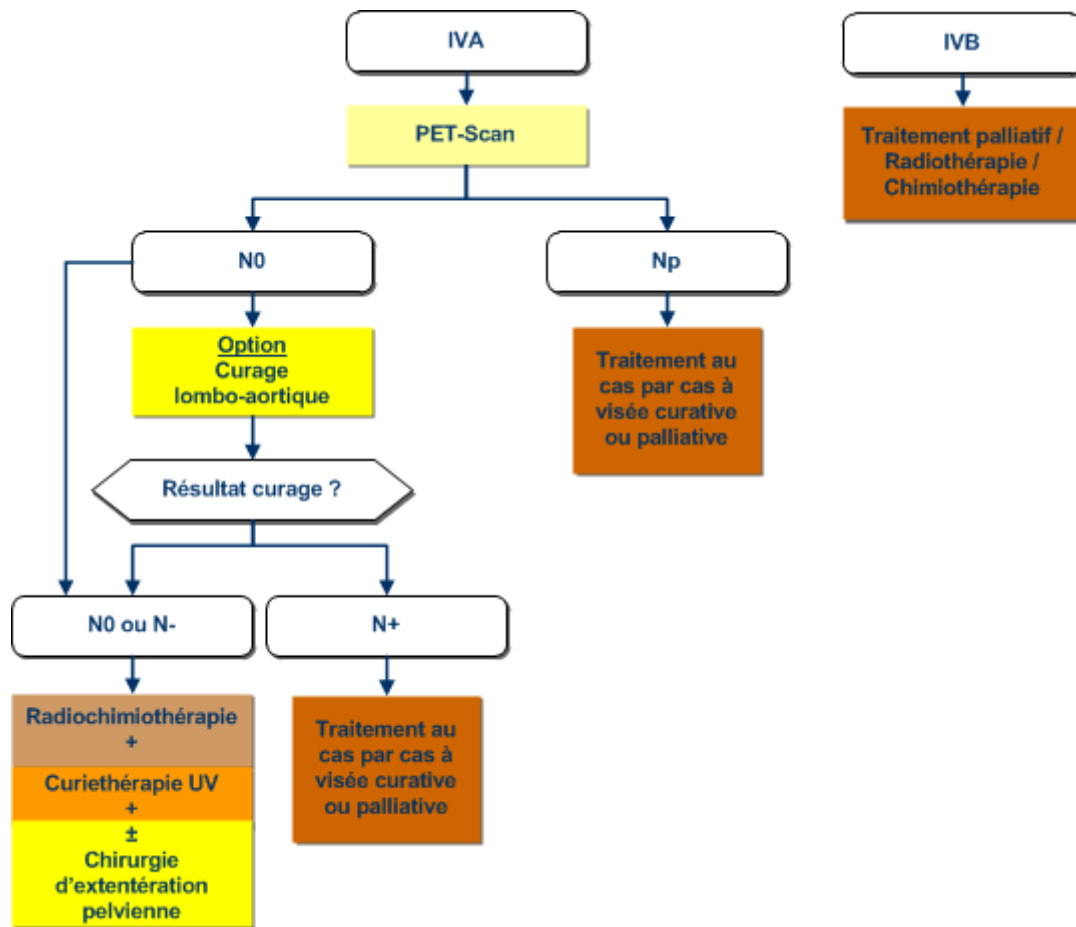
*N0 et N1 : classification radioclinique*

*N + et N- : classification histologique*

*Np : adénopathie visible sur PET-Scan*



## Stade IVA et IVB



### **Légende**

*N0 et N1 : classification radioclinique*

*N + et N- : classification histologique*

*Np : adénopathie visible sur PET-Scan*

## ■ Chirurgie

---

- ▶ Elle repose sur :
  - la conisation
  - l'hystérectomie totale
  - la colpohystérectomie totale avec annexectomie bilatérale et lymphadénectomie pelvienne.
  
- ▶ Le type d'hystérectomie pourra être défini selon la classification de **Piver** (types I à V)

### Cas particulier

- ▶ Pour des patientes ayant une tumeur de stade très précoce (IA1 ou IA2...) et ayant encore un désir de grossesse : curage percœlioscopique premier, suivi d'une trachélectomie si N(-).

### Conservation ovarienne

- ▶ Possible pour les stades  $\leq$  IB1.
- ▶ Nécessite une transposition ovarienne si une curiethérapie utéro-vaginale préopératoire est prévue.
- ▶ Elle s'envisage jusqu'à 40 ans ; au-delà, les risques de non fonctionnement après transposition sont importants.

## ■ Classification des hystérectomies selon Piver

---

<b>Type I</b>	hystérectomie extra fasciale
<b>Type II</b>	section du paramètre à l'aplomb de l'uretère dont la dissection est limitée ; colpectomie du tiers supérieur du vagin
<b>Type III</b>	exérèse large du paramètre au plus près de la paroi pelvienne ; colpectomie de la moitié supérieure du vagin
<b>Type IV</b>	dissection complète de l'uretère jusqu'à la pénétration vésicale ; colpectomie des trois quarts
<b>Type V</b>	exentération partielle (résection urétérale ou vésicale partielle)

## Référence

Piver MS, Rutledge F, Smith JP.

Five classes of extended hysterectomy for women with cervical cancer.

*Obstet. Gynecol.* 1974; 44(2): 265-72.

# Radiothérapie

---

## Radiothérapie externe

---

### Pelvis

- ▶ Dose totale : 45 Gy sur T.
- ▶ 45 à 50 Gy sur N0 ; 1,8 à 2 Gy par séance, 5 séances par semaine.
- ▶ Complément sur paramètre : 6 à 10 Gy, 1,8 à 2 Gy par séance, 5 séances par semaine.
- ▶ Complément sur Np = 6 à 16 Gy, 1,8 à 2 Gy par séance, 5 séances par semaine.

### Lombo-aortique

- ▶ Dose totale : 45 à 50 Gy ; 1,8 à 2 Gy par séance, 5 séances par semaine.
- ▶ Complément sur Np : 6 à 16 Gy, 1,8 à 2 Gy par séance, 5 séances par semaine.

## Curiethérapie

---

- ▶ Le volume cible inclut l'exo et l'endocol, les culs de sac vaginaux, les paramètres proximaux, le tiers supérieur du vagin ; elle doit donc être réalisée impérativement en préopératoire.
- ▶ Le **délai** entre radiothérapie externe et curiethérapie doit être **le plus court possible** (1 à 2 semaines) ; l'étalement total (RTE + Curiethérapie) doit si possible être inférieur à 55 jours.
- ▶ Une cure de **chimiothérapie concomitante** peut être réalisée.
- ▶ Elle est préférentiellement réalisée à **bas débit de dose ou débit pulsé**. Elle nécessite donc une hospitalisation de quelques jours en secteur spécialisé.
- ▶ La **dose délivrée est fonction de la dose de radiothérapie externe reçue auparavant** : soit 60 Gy si la curiethérapie est réalisée directement en préopératoire, soit 15 Gy environ si elle est faite en complément de la radiothérapie externe.
- ▶ Des **recommandations européennes** ont été publiées par le sous-groupe Gynéco du GEC ESTRO en terme de technique (dosimétrie en 3 dimensions sur scanner ou IRM recommandée), de définition des volumes et de doses à délivrer sur la tumeur et les organes critiques.

- ▶ Une **curiethérapie interstitielle** peut être ajoutée si nécessaire, ainsi qu'un complément vaginal.

### Références

Haie-Meder C, Pötter R, Van Limbergen E, *et al.*

Recommendations for Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV.

*Radiother Oncol. 2005;74:235-45.*

Pötter R, Haie-Meder C, Van Limbergen E, *et al.*

Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy- 3D dose

*Radiother Oncol. 2006 Jan;78(1):67-77. Epub 2006 Jan 5.*

## **Chimiothérapie**

---

- ▶ Les dossiers seront discutés au cas par cas en RCP.
- ▶ On privilégiera la participation aux essais thérapeutiques chaque fois que possible.

### **Traitement initial : radiochimiothérapie concomitante**

---

- ▶ Il existe une supériorité thérapeutique de l'administration concomitante de cisplatine pendant la radiothérapie par rapport à la radiothérapie seule.

**Indications** : stades IB2 à IVA ; N+

**Recommandations** : cisplatine (CDDP) 40 mg/m<sup>2</sup> hebdomadaire x 5 à 6

**Option** : CDDP 50 mg/m<sup>2</sup> J1 + 5-Fluorouracile (5-FU) 750 mg/m<sup>2</sup> J1 à J5 , reprise à J21

**Surveillance** : toxicité hématologique, rénale et digestive per- et post-thérapeutique.

### Références

Vale C, Tierney JF, Stewart LA, Brady M, *et al.*

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer :

A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials.

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration.

*J Clin Oncol. 2008 Dec 10;26(35):5802-12.*

Haie-Meder C *et al.*

Association radio-chimiothérapie chez les patientes atteintes d'un carcinome du col utérin.

*Bull Cancer 2005; 92(12): 1032-8.*

## Tumeurs métastatiques ou en rechute

---

- ▶ **Pas de standard.**
- ▶ **Recommandations** : utilisation de sels de platine si possible.
- ▶ **Difficultés** :
  - altération de la fonction rénale (sonde JJ) et de l'état général
  - toxicité souvent hématologique, rénale et neurologique
  - récurrence dans la zone irradiée
  - risque fistulaire et infectieux.
- ▶ **Soit cisplatine (CDDP) seul** : 50 à 100 mg/m<sup>2</sup> J1-J21.
- ▶ **Soit du CDDP en association** avec d'autres produits : soit topotécan 0,75 mg/m<sup>2</sup> J1 à J3 - J21, soit paclitaxel 135 mg/m<sup>2</sup> J1 sur 24h - J21.

## ▣ Le traitement du cancer du col restant

---

- ▶ Les principes de traitement sont identiques à ceux définis pour les cancers sur utérus intact.
- ▶ La **toxicité digestive** attendue de la radiochimiothérapie est supérieure à celle du traitement de l'utérus en place.
- ▶ Le **traitement radiocuriethérapique exclusif ou une association radiochirurgicale** sont possibles.
- ▶ Sur col restant, la curiethérapie peut soulever des **problèmes techniques** particuliers.

## ▣ Principes généraux de la prise en charge du cancer du col pendant la grossesse

---

- ▶ Le **diagnostic** lésionnel précis peut nécessiter une conisation, toujours possible (± cerclage).
- ▶ Le **traitement** immédiat ou différé doit tenir compte :
  - du stade et de l'évolutivité de la tumeur
  - de la maturité fœtale, à préciser avec l'équipe obstétrico-pédiatrique
  - du consentement éclairé de la mère.
- ▶ Un **avis** peut être demandé auprès d'une **équipe de référence**.
- ▶ Les **stades IA** peuvent être surveillés jusqu'à l'extraction fœtale, de préférence par césarienne.

- ▶ Pour les **autres stades**, la décision est prise en fonction de l'âge gestationnel :
  - 1<sup>er</sup> trimestre : évacuation utérine suivie du traitement standard
  - 2<sup>ème</sup> trimestre : sacrifice de la grossesse en fonction du stade tumoral, de l'évolutivité, de l'âge gestationnel
  - 3<sup>ème</sup> trimestre : attendre la maturité fœtale (35 S/A). Césarienne suivie du traitement standard.
- ▶ Pour plus de détails, voir les recommandations du Collège National des Gynécologues Obstétriciens Français (CNGOF) : [French recommendations on the management of invasive cervical cancer during pregnancy](#); 16/12/2008.

## ▣ Surveillance

---

### Examens cliniques et gynécologiques

---

- ▶ Interrogatoire et examen clinique, gynécologique avec toucher rectal :
  - tous les 4 à 6 mois pendant 2 ans
  - tous les 6 mois les 3 années suivantes
  - puis 1 fois par an.

### Examens paracliniques

---

- ▶ Scanner TAP annuel en option.
- ▶ Utérus en place : IRM à 6 mois puis annuelle pendant 2 ans + frottis annuel (en l'absence de radiothérapie ou curiethérapie).
- ▶ Le risque de séquelles urinaire et urétérale à distance doit être intégré dans la surveillance.
- ▶ Dosage SCC si élevé initialement.
- ▶ Examens orientés en fonction des signes d'appel cliniques (imagerie, biopsie), du stade initial de la maladie, du risque de récurrence et du traitement initial (comorbidités).

### Particularités

---

- ▶ Valeur très limitée des frottis après radiocuriethérapie (diagnostic différentiel difficile entre cellules dystrophiques et cellules tumorales) ; réaliser une biopsie en cas de lésion suspecte.
- ▶ Hormonothérapie substitutive de la ménopause n'est pas contre-indiquée.

## ■ Essais cliniques

---

- ▶ **TRIDICOL** : Optimisation de la distribution de doses en 3 dimensions de la curiethérapie utéro-vaginale à débit pulsé des cancers du col localement avancés.
  - Etablissement participant en Bourgogne : Centre Georges François Leclerc (Dijon).
  - Etablissement participant en Lorraine : Institut de Cancérologie de Lorraine (Vandœuvre-lès-Nancy).
  
- ▶ **HCL ERRIC** : Apport de la tomographie par émission de positons (TEP/TDM) au fluodesoxyglucose (FDG) et de l'imagerie par résonnance magnétique (IRM) de diffusion dans l'évaluation de la réponse tumorale après traitement par radiochimiothérapie et curiethérapie des cancers du col utérin opérables de stade IB2, IIA, IIB.
  - Etablissement participant en Bourgogne : Centre Georges François Leclerc (Dijon).

# **FRENCH RECOMMENDATIONS ON THE MANAGEMENT OF INVASIVE CERVICAL CANCER DURING PREGNANCY.**

**Morice P<sup>1</sup>, Narducci F<sup>2</sup>, Mathevet P<sup>3</sup>, Marret H<sup>4</sup>, Darai E<sup>5</sup>, Querleu D<sup>6</sup>**

**On the behalf of the French Working Group on Gynecological Cancers in Pregnancy,  
SFOG<sup>7</sup>, SFCP<sup>8</sup> and CNGOF<sup>9</sup>.**

**Date of publication : 16 dec.2008**

**Running head: Cervical cancer in pregnancy**

<sup>1</sup> *Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France*

<sup>2</sup> *Centre Oscar Lambret, 3 rue Frédéric Combemale, 59020 Lille, France*

<sup>3</sup> *Hôpital Edouard Herriot, Place d'Arsonval, 69437 Lyon, France*

<sup>4</sup> *Hôpital Bretonneau, 2 Boulevard Tonnellé, 37044 Tours, France*

<sup>5</sup> *Hôpital Tenon, 20 rue de la Chine, 75020 Paris, France*

<sup>6</sup> *Institut Claudius Regaud, 20-24 rue du Pont Saint Pierre, 31052 Toulouse, France*

<sup>7</sup> *Société Française d'Oncologie Gynécologique*

<sup>8</sup> *Société Française de Chirurgie Pelvienne*

<sup>9</sup> *Collège National des Gynécologues Obstétriciens Français*

Correspondence and proofs : Philippe Morice, M.D., Department of Surgery,  
Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France.  
Phone: 33.1.42.11.54.41. Fax: 33.1.42.11.52.13. Email: morice@igr.fr

**Key words:** cervical cancer, chemoradiation, neoadjuvant chemotherapy, pregnancy, preservation, staging procedures.



*Abstract:*

*Background:* Cervical cancer is one of the most frequently diagnosed cancers during pregnancy but the management of such cases remains unclear. A Working Group was set up in 2007 in France to propose national recommendations for the management of pregnant patients with invasive cervical carcinoma.

*Methods:* The recommendations are based on this literature review conducted by the members of the Working Group.

*Results:* Management of cervical cancer during pregnancy depends on 5 factors : stage of the disease (and the tumor size), nodal status, histologic subtype of the tumor, term of the pregnancy and on whether the patient wishes to continue her pregnancy. In patients with early stage disease diagnosed during the first 2 trimesters of pregnancy, there is an increasing tendency to preserve the pregnancy while awaiting fetal maturity in patients with absence of nodal involvement. The delivery (when the fetal maturity is attained) should be then performed using a caesarian section.

*Conclusions:* This article proposes recommendations for the management of pregnant patients with invasive cervical cancer. These recommendations have been validated by the 3 main scientific societies of gynecologic oncology, pelvic surgery and obstetrics and gynecology in France.

Cervical cancer is one of the most frequently diagnosed cancers during pregnancy along with breast cancer, lymphoma and melanoma (1). However, the real incidence of invasive cervical cancer remains unknown because studies of a large cohort of pregnant patients focusing on the incidence of malignancies have never been performed. The management of such patients also remains unclear because all the published series are retrospective, some of them including both invasive and preinvasive lesions whereas others mixed cases of cancer diagnosed during the pregnancy or during the post-partum period.

To date, the management of pregnant patients with cervical cancer diagnosed during the first 2 trimesters of pregnancy usually signified the interruption of the pregnancy and treatment of the cervical tumor. However, recent papers indicate an increasing tendency to preserve the pregnancy while awaiting fetal maturity before treating the cervical cancer in patients with early stage disease. This is a crucial point in patients who will be definitely deprived of future fertility after the treatment of their cervical cancer. The incidence of cervical lesions discovered in pregnant patients is unknown.

In order to clarify many of the remaining unanswered questions on the incidence and management of invasive disease in pregnancy, a Working Group was set up in 2007 to examine this issue. This group will be studying gynecological cancers (ovary and cervix) and breast cancer but also melanoma and hematological diseases. The aims of the group are two-fold : 1. to evaluate the true incidence of cancer during pregnancy, and for this purpose, national registration of cases observed is being organized in France. 2. to define national recommendations in order to harmonize the management of patients with invasive cancer. Recommendations about the management of invasive cancer were recently finalized, under the auspices of 3 French scientific learned societies. This is the first time that national recommendations concerning the management of cervical cancer in pregnancy have been finalized. They will be presented in this paper. These recommendations excluded the management of pre-invasive lesions which was more consensual and for which several recommendations were recently published (2,3).

### ***Methodology***

A literature review of papers published on this subject was conducted by the members of the Working Group. The data were identified through a Medline search for papers published in English or in French. The main search terms were “cervical cancer”, “cervical disease”, “pregnancy” and “pregnant patients”.

There is no randomized trial or large studies in the literature enabling us to define a consensual approach based on level-A Evidence-Based Medicine. Most of the published papers were retrospective studies or case reports. Consequently, the recommendations in the present paper are sometimes an arbitrary but a consensual choice of the panel of experts based

on the literature review and their own experience. The reference list at the end of this review does not include all the reviewed papers, but only those selected to corroborate the choice, or justify the remarks of the panel of experts.

The tumor classification used in the present paper was the 1995 FIGO classification (4) and the term of the pregnancy was calculated in weeks of gestation (WG).

### ***General Comments***

Management of cervical cancer during pregnancy depends on 5 factors : stage of the disease (and the tumor size), nodal status (if known), histologic subtype of the tumor, term of pregnancy and patient (and couple's) desire to preserve the pregnancy (if such a decision is oncologically safe). If the possibility of interrupting the pregnancy is mentioned by the patient (or physicians), she should be clearly informed by the clinicians during the oncological management about literature datas suggesting : 1. that the prognosis of cervical cancer is not worsened if the disease occurs during pregnancy (5-14) and 2. delaying treatment while awaiting fetal maturity in patients with early stage disease diagnosed during the first 2 trimesters of pregnancy does not seem to have a (major) impact on survival (15-21).

- Evaluation of the tumor is based on clinical examination and abdomino-pelvic Magnetic Resonance Imaging (22). A chest X ray can be performed (with fetal protection) after the 1<sup>st</sup> trimester in cases of locally advanced disease (stage  $\geq$  IB2).

- Management of the disease depends primarily on the term of the pregnancy, particularly if this tumor is diagnosed before or after the period when fetal maturity can be considered attained. Discussion about cancer management should therefore involve different physicians including the gynecological oncologist, radiation therapist, medical oncologist, radiologist and pathologist to define the optimal oncological management. But it should also include obstetrician and neonatologist to obtain the best compromise between the maternal and fetal prognosis. If a delivery is discussed before 36 WG, during the oncological management, this delivery should be performed in a unit adapted for the management of potentially severe prematurity.

### ***If the tumor is diagnosed at a term when fetal maturity could be considered attained***

It is possible to preserve the fetus without delaying the treatment of the cervical cancer which should be performed, according to the standards of care, after the delivery. The term of delivery should be defined according to the term at the time of the diagnosis and to whether or not the tumor needs to be treated urgently (stage of the disease and tumor size). The delivery should be (optimally) performed using a caesarian section (23-26).

During this caesarian section, nodal staging surgery (pelvic nodes with or without para-aortic nodes for tumors measuring  $> 4$  cm or positive pelvic nodes) is recommended.

Such staging procedure needs to be carried out by surgeons experienced in performing this oncologic surgical procedure. Ideally, the obstetrician and gynecological oncologist should be present during this caesarian section.

In multiparous woman and in patients who do not wish to preserve their fertility, with stage IB1 disease, a radical hysterectomy can be associated with nodal surgery at the time of the caesarian section (12,27-29).

***If the tumor is diagnosed before the term when fetal maturity is attained (between 26 to 30 WG) in a patient wishing to preserve the fetus (tumor with a usual histologic subtype and exclusion of small cell carcinoma or a similar aggressive tumor)***

**A. In stage IB1 disease diagnosed before 18 to 22 WG (term when pelvic laparoscopic lymphadenectomy is still technically feasible).**

**1. Stage IB1 and tumor size < 2 cm.**

The pregnancy is not being interrupted at this point. An initial laparoscopic pelvic lymphadenectomy is recommended (30). As this is a crucial procedure, it should be performed by surgeons trained to such procedure in pregnant patients.

**-Absence of nodal involvement :** In this case, the patient is followed up without immediate treatment of the cervical tumor. This follow-up procedure should include a clinical examination and imaging (MRI every 4 to 8 weeks, but there is no consensus among experts concerning the frequency of MRI) (22). In the absence of disease progression, curative treatment of the cervical tumor should begin as soon as fetal maturity was attained (5-15). The delivery route should be caesarian section (23) and the cervical tumor should be treated according to the standards of care. A radical hysterectomy can be performed at the time of caesarian section (27-29).

**- Presence of nodal involvement :** In this case, interruption of the pregnancy should be recommended to the patient and the standard management is chemoradiation therapy (after the uterus is empty). The radiation therapy fields depend on the highest level of nodal involvement (pelvic nodes alone or pelvic & para-aortic nodes). The status of para-aortic nodes can be determined by performing a laparoscopic para-aortic lymphadenectomy or Positron Emission Tomography imaging (carried out after pregnancy interruption). The choice between these two procedures will depend on the team administering treatment and on whether the surgeons have experience with laparoscopic para-aortic lymphadenectomy.

**2. Stage IB1 disease with a tumor size between 2 and 4 cm.**

It is impossible to define a standard management policy in such a situation and each case should be discussed separately. Because the risk of nodal involvement is significantly higher than in patients with a tumor measuring < 2 cm, pregnancy interruption is the first

option that should be discussed with the patient (particularly if the tumor is discovered during the 1<sup>st</sup> trimester). If the patient refuses this option, management could be similar to that of patients with a tumor measuring < 2 cm.

**B. In stage IB1 disease diagnosed after 18 to 22 WG (for which laparoscopic lymphadenectomy is not technically feasible, even in the hands of experienced surgeons)**

**1. Stage IB1 and tumor size < 2 cm.**

Careful follow-up should be conducted including clinical and radiological imaging (in the absence of “suspicious” lymph nodes on initial imaging). The clinician should explain to the patient the oncological uncertainty in such a situation, namely the potential risk of increasing the recurrence rate while awaiting fetal maturity. Curative treatment of the cervical tumor should be initiated once fetal maturity has been attained. The presence of a malignant tumor is not a contraindication to the use of neonatal corticoids to increase fetal chest maturity. The delivery route should be a caesarian section and the cervical tumor should be treated according to the standards of care. A radical hysterectomy with pelvic lymphadenectomy can be performed at the time of caesarian section.

**2. Stage IB1 with a tumor size between 2 and 4 cm.**

It is impossible to define a standard management policy in such a situation, therefore each case should be discussed individually. If the term when the tumor is diagnosed is very close to the term when fetal maturity is attained, the management can be similar to that of patients with a tumor measuring < 2 cm.

Particularly if the tumor size is close to 4 cm, the other option that could be discussed is the use of neoadjuvant chemotherapy (31,32). However, the patient should be informed of the uncertainty regarding the oncological and fetal outcomes of such management.

**C. In patients with a tumor measuring > 4 cm**

The standard management in France in such patients is based on chemoradiation therapy. If the tumor is discovered before 20 to 22 WG (no consensus between experts regarding this term), chemoradiation therapy should be delivered either after the uterus is empty (using a hysterotomy or another procedure-(33)) or with the fetus *in utero* if its expulsion seems to be impossible (bulky cervical cancer) (7,14,34,35). This chemoradiation therapy should be delivered (in terms of doses, type of concomitant chemotherapy and radiation therapy fields ) according to the usual standards in such a situation.

If the tumor is diagnosed after 22 WG (in the absence of extra-cervical spread detected at the radiological examination), chemoradiation can be started after the caesarean delivery which should be performed once fetal maturity has been attained (provided such management will not delay the start of tumor treatment for more than 6 to 8 weeks). During this caesarean

section, para-aortic staging surgery is recommended (if such surgery is performed by a surgeon who has experience performing this procedure).

Another option could be discussed in such a situation in patients wishing to preserve the viability of their fetus: the use of neoadjuvant chemotherapy. This treatment was not retained by our working group as a standard management in this context but was reported as case report in the literature (36-41). It should only be discussed if the tumor is diagnosed after 18 to 20 WG. The patient should receive a clear explanation regarding : 1. the potential risk of rapid progression (potentially lethal for the patient) of the disease reported in several cases after such management in the literature (37,41) and 2. the uncertainty concerning the long-term effects of neoadjuvant chemotherapy on the fetus.

***Patients with a more aggressive histologic subtype (small cell carcinoma or a similar unusual tumor) diagnosed during the 1<sup>st</sup> or 2<sup>nd</sup> trimester of pregnancy***

In such situation, each case should be discussed individually, but pregnancy preservation is not recommended because treatment of the tumor is regarded as an oncological emergency.

**Acknowledgements to members of Working Group :**

Pr Aubard (Limoges) ; Pr Baldauf (Strasbourg) ; Pr Bonnier (Marseille) ; Pr Canis (Clermont Ferrand); Dr Chauveau (Clamart) ; Dr Duvillard (Villejuif) ; Pr Fernandez (Clamart) ; Pr Frydman (Clamart) ; Pr Goffinet (Paris) ; Dr Haie-Meder (Villejuif) ; Pr Lécuro (Paris) ; Pr Lefranc (Paris) ; Dr Lhommé (Villejuif) ; Dr Pautier (Villejuif) ; Pr S. Uzan (Paris) ; Dr C. Uzan (Villejuif) ; Dr Rouzier (Paris)

## References

1. Moran BJ, Yano H, Al Zahir N, Farquharson M. Conflicting priorities in surgical intervention for cancer in pregnancy. *Lancet Oncol* 2007; 8: 536-544.
2. Salleret L, Mathevet P. Precancerous cervical lesions during pregnancy : diagnostic and treatment. *J Gynecol Obstet Biol Reprod* 2008.
3. Wright TC, Massad S, Dunton CJ et al. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol* 2007; 197: 340-345.
4. International Federation of Gynecology and Obstetrics. Modifications in the staging for stage I vulvar and stage I cervical cancer. *Int J Gynaecol Obstet* 1995; 50: 215-216.
5. Zemlickis D, Lishner M, Degendorfer P et al. Maternal and fetal outcome after invasive cervical cancer in pregnancy. *J Clin Oncol* 1991; 9: 1956-1961.
6. Baltzer J, Regenbrecht ME, Kopcke W, Zander J. Carcinoma of the cervix and pregnancy. *Int J Gynaecol.Obstet* 1990; 31: 317-323.
7. Creasman WT, Rutledge FN, Fletcher GH. Carcinoma of the cervix associated with pregnancy. *Obstet Gynecol* 1970; 36: 495-501.
8. Hopkins MP, Morley GW. The prognosis and management of cervical cancer associated with pregnancy. *Obstet Gynecol* 1992; 80: 9-13.
9. Jones WB, Shingleton HM, Russell A et al. Cervical carcinoma and pregnancy. A national patterns of care study of the American College of Surgeons. *Cancer* 1996; 77: 1479-1488.
10. Lee RB, Neglia W, Park RC. Cervical carcinoma in pregnancy. *Obstet Gynecol* 1981; 58: 584-589.
11. Manuel-Limson GA, Ladines-llave CA, Sotto LS, Manalo AM. Cancer of the cervix in pregnancy: a 31-year experience at the Philippine General Hospital. *J Obstet Gynaecol Res* 1997; 23: 503-509.
12. Sood AK, Sorosky JI, Krogman S et al. Surgical management of cervical cancer complicating pregnancy: a case-control study. *Gynecol Oncol* 1996; 63: 294-298.
13. Nevin J, Soeters R, Dehaeck K et al. Advanced cervical carcinoma associated with pregnancy. *Int J Gynecol Cancer* 1993; 3: 57-63.
14. Sood AK, Sorosky JI, Mayr N et al. Radiotherapeutic management of cervical carcinoma that complicates pregnancy. *Cancer* 1997; 80: 1073-1078.
15. Van Der Vange V, Weverling GJ, Ketting BW et al. The prognosis of cervical cancer associated with pregnancy: a matched cohort study. *Obstet Gynecol* 1995; 85: 1022-1026.
16. Sorosky JI, Squatrito R, Ndubisi BU et al. Stage I squamous cell cervical carcinoma in pregnancy: planned delay in therapy awaiting fetal maturity. *Gynecol Oncol* 1995; 59: 207-210.
17. Van Vliet W, Van Loon AJ, Ten Hoor KA, Boonstra H. Cervical carcinoma during pregnancy: outcome of planned delay in treatment. *Eur J Obstet Gynecol Reprod Biol* 1998; 79: 153-157.
18. Nguyen C, Montz FJ, Bristow RE. Management of stage I cervical cancer in pregnancy. *Obstet Gynecol Surv.* 2000; 55: 633-643.
19. Takushi M, Moromizato H, Sakumoto K, Kanazawa K. Management of invasive carcinoma of the uterine cervix associated with pregnancy: outcome of intentional delay in treatment. *Gynecol Oncol* 2002; 87: 185-189.
20. Germann N, Haie-Meder C, Morice P et al. Management and clinical outcomes of pregnant patients with invasive cervical cancer. *Ann Oncol* 2005; 16: 397-402.
21. Lee JM, Lee KB, Kim YT et al. Cervical cancer associated with pregnancy: results of a multicenter retrospective Korean study (KGOG-1006). *Am J Obstet Gynecol* 2008; 198: 92.e1-6. Epub 2007 Oct 1.

22. Zanetta G, Pellegrino A, Vanzulli A et al. Magnetic Resonance imaging of cervical cancer in pregnancy. *Int J Gynecol Cancer* 1998; 8: 265-269.
23. Sood AK, Sorosky JI, Mayr N et al. Cervical cancer diagnosed shortly after pregnancy: prognostic variables and delivery routes. *Obstet Gynecol* 2000; 95: 832-838.
24. Copeland LJ, Saul PB, Sneige N. Cervical adenocarcinoma: tumor implantation in the episiotomy sites of two patients. *Gynecol Oncol* 1987; 28: 230-235.
25. Khalil AM, Khatib RA, Mufarrij AA et al. Squamous cell carcinoma of the cervix implanting in the episiotomy site. *Gynecol Oncol* 1993; 51: 408-41
26. Cliby WA, Dodson MK, Podratz KC. Cervical cancer complicated by pregnancy: episiotomy site recurrences following vaginal delivery. *Obstet Gynecol* 1994; 84: 179-182.
27. Monk BJ, Montz FJ. Invasive cervical cancer complicating intrauterine pregnancy: treatment with radical hysterectomy. *Obstet Gynecol* 1992; 80: 199-203.
28. Thompson JD, Caputo TA, Franklin EW, III, Dale E. The surgical management of invasive cancer of the cervix in pregnancy. *Am J Obstet Gynecol* 1975; 121: 853-863.
29. Sivanesaratnam V, Jayalakshmi P, Loo C. Surgical management of early invasive cancer of the cervix associated with pregnancy. *Gynecol Oncol* 1993; 48: 68-75.
30. Alouini S, Rida K, Mathevet P. Cervical cancer complicating pregnancy: implications of laparoscopic lymphadenectomy. *Gynecol Oncol* 2008;108: 472-7.
31. Giacalone PL, Laffargue F. Cisplatin neoadjuvant chemotherapy in a pregnant woman with invasive carcinoma of the uterine cervix. *BJOG* 1996; 103: 932-934.
32. Caluwaerts S, Van Calsteren K, Mertens L et al. Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer diagnosed during pregnancy: report of a case and review of the literature. *Int J Gynecol Cancer*. 2006;16: 905-908.
33. Ostrom K, Ben-Arie A, Edwards C et al. Uterine evacuation with misoprostol during radiotherapy for cervical cancer in pregnancy. *Int J Gynecol Cancer* 2003; 13: 340-343.
34. Prem KA, Makowski EL, McKelvey JL. Carcinoma of the cervix associated with pregnancy. *Am J Obstet Gynecol* 1966; 95: 99-108.
35. Benhaim Y, Haie-Meder C, Lhomme C et al. Chemoradiation therapy in pregnant patients treated for advanced stage cervical carcinoma during the 1st trimester of the pregnancy : report of 2 cases. *Int J Gynecol Cancer* 2007; 17: 270-274.
36. Jacobs AJ, Marchevsky A, Gordon RE et al. Oat cell carcinoma of the uterine cervix in a pregnant woman treated with cis-diamminedichloroplatinium. *Gynecol Oncol* 1980; 9: 405-410.
37. Tewari K, Cappuccini F, Gambino A et al. Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy. *Cancer* 1998; 82: 1529-1534
38. Marana HR, De Andrade JM, Da Silva Mathes AC et al. Chemotherapy in the treatment of locally advanced cervical cancer and pregnancy. *Gynecol Oncol* 2001; 80: 272-274.
39. Palaia I, Pernice M, Graziano M et al. Neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer during pregnancy: a case report. *Am J Obstet Gynecol* 2007; 197: e5-e6.
40. Karam A, Feldman N, Holschneider CH. Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy. *Nat Clin Pract Oncol* 2007; 4: 375-380.
41. Benhaim Y, Pautier P, Bensaid C et al. Neoadjuvant chemotherapy for advanced stage cervical cancer in a pregnant patient: Report of 1 case with rapid tumor progression. *Eur J Obstet Gynecol Reprod Biol* 2008; 136: 267-268.