

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

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**On the behalf of the French Working Group on Gynecological Cancers in Pregnancy,
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Running head: Cervical cancer in pregnancy

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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 1st 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 1st 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 1st or 2nd 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.

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