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### ► To cite this version:

Nathalie Rives, Blandine Courbière, Thierry Almont, Diana Kassab, Claire Berger, et al.. What should be done in terms of fertility preservation for patients with cancer? The French 2021 guidelines. European Journal of Cancer, 2022, 173, pp.146-166. 10.1016/j.ejca.2022.05.013 . hal-03927595

**HAL Id: hal-03927595**

**<https://hal.science/hal-03927595>**

Submitted on 6 Jan 2023

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Review

## What should be done in terms of fertility preservation for patients with cancer? The French 2021 guidelines

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## KEYWORDS

Oncofertility;  
Practice guidelines;  
France;  
Supportive care

**Abstract** *Aim:* To provide practice guidelines about fertility preservation (FP) in oncology.

*Methods:* We selected 400 articles after a PubMed review of the literature (1987–2019).

*Recommendations:* Any child, adolescent and adult of reproductive age should be informed about the risk of treatment gonadotoxicity.

In women, systematically proposed FP counselling between 15 and 38 years of age in case of treatment including bifunctional alkylating agents, above 6 g/m<sup>2</sup> cyclophosphamide equivalent dose (CED), and for radiation doses on the ovaries  $\geq 3$  Gy.

For postmenarchal patients, oocyte cryopreservation after ovarian stimulation is the first-line FP technique.

Ovarian tissue cryopreservation should be discussed as a first-line approach in case of treatment with a high gonadotoxic risk, when chemotherapy has already started and in urgent cases.

Ovarian transposition is to be discussed prior to pelvic radiotherapy involving a high risk of premature ovarian failure.

For prepubertal girls, ovarian tissue cryopreservation should be proposed in the case of treatment with a high gonadotoxic risk.

In pubertal males, sperm cryopreservation must be systematically offered to any male who is to undergo cancer treatment, regardless of toxicity. Testicular tissue cryopreservation must be proposed in males unable to cryopreserve sperm who are to undergo a treatment with intermediate or severe risk of gonadotoxicity.

In prepubertal boys, testicular tissue preservation is:

- recommended for chemotherapy with a CED  $\geq 7500$  mg/m<sup>2</sup> or radiotherapy  $\geq 3$  Gy on both testicles.

- proposed for chemotherapy with a CED  $\geq 5.000$  mg/m<sup>2</sup> or radiotherapy  $\geq 2$  Gy.

If several possible strategies, the ultimate choice is made by the patient.

## 1. Introduction

In Europe and the United States, the survival of patients with cancer has increased considerably over the last few decades due to diagnostic and therapeutic advances [1,2]. Notably, the 5-year survival rate for cancers in children, adolescents and young adults exceeds 80% [3]. As the

prognosis for cancer improves, the long-term side-effects of treatment become increasingly important. Impaired fertility is among the adverse effects that have the greatest impact on the quality of life in patients of childbearing age, regardless of gender [4,5]. Gonadal function disorders are also a major issue for partners of patient with cancer, survivors of childhood cancers and their parents

[6]. In France, fertility preservation (FP) is targeted explicitly at objectives 7 and 8 of the last cancer plan, notably Action 8.1, which aims to ‘Ensure access to FP [7]. According to the article L.2141-11 of the French Public Health Code, FP for cancer is free of charge. In order to prevent unequal access to care, the national territory is covered by a network of 29 comprehensive regional CECOS centres organised in the federation.

FP is a very evolving field. Over the last 5 years, new technical possibilities have developed, widening the field of indications for FP (especially in women and children). Thus, more than 130 births of healthy children have been obtained after the orthotopic auto-transplantation of ovarian tissue after puberty [8] and the first cases of spontaneous pregnancies and live births after the transplantation of ovarian tissue preserved during childhood have also been reported [9,10].

At present, measures to enable people with cancer to preserve fertility potential could be proposed to a majority of them. However, several recent surveys have indicated that many patients, both men and women, are still inadequately counselled about the deleterious effects of cancer treatments and that an even smaller number are offered an FP proposal [11,12]. Moreover, when FP is offered, there is often a lack of consensus in advice and referral standards, leading to the heterogeneity of practice [12,13].

## 2. Objectives and targets

These recommendations are intended for healthcare professionals involved in cancer patients care and the management of adverse effects on fertility induced by cancer or its treatment. The aim of these recommendations is to enable optimal and homogeneous FP practice throughout the country for children, adolescents, and adults treated for cancer. The clinical questions considered in these guidelines are the following:

- Q1: Who should receive advice on FP?
- Q2: What medical or surgical treatments help reduce infertility risk?
- Q3 - Which FP methods are used for adults and children?
- Q4: How is fertility monitored in the post-cancer period?

This work, accredited by the French National Cancer Institute (INCa), was coordinated by the « Association Francophone des Soins Oncologiques de Support » with the support of the « Association Française d’Urologie ».

## 3. Methods

### 3.1. Panel composition

The INCa convened an Expert Panel consisting of experts in clinical medicine and research relevant to FP in patients with cancer, including adult and paediatric

oncology, obstetrics-gynaecology, andrology, reproductive endocrinology, public health, psychosocial oncology and bioethics. Two patient representatives were also part of the Panel. Panel members are listed in [Appendix A](#).

### 3.2. Literature review and analysis

We conducted a systematic literature review based on a comprehensive bibliographic strategy on PubMed® over a broad period (1987–2019) using FP-related keywords. The AGREE II tool [14] was used to analyse the relevance of existing clinical practice guidelines [15–22]. The literature data were completed by suggestions from the Expert Panel, particularly on studies that were not indexed in Medline® [Fig. 1].

### 3.3. Study selection

Exclusion criteria were males >60 years and females >40 years; studies dealing with laboratory techniques; *in vitro* studies; animal studies; case reports and duplicates, non-English or non-French articles.

### 3.4. Review

This work has been submitted to a multidisciplinary review panel accounting for 32 about 100 members (list included in [Appendix A](#)), which enabled the potentially divergent opinions of experts to be collected, thereby ensuring adequate quality of data. The members of the working group finally reviewed the comments collected in order to finalise the document in a dedicated meeting.

### 3.5. Level of evidence and grading of guidelines

The level of evidence depended on the type and quality of the available studies, as well as the consistency of their results. It is specified for each of the methods/interventions considered.

[Table 1](#) summarises the grading classification used in these guidelines.

### 3.6. Conflicts of interest

The Expert Panel was assembled in accordance with INCa’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines.<sup>1</sup> All members of the Expert Panel completed INCa’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or

<sup>1</sup> “Policy” found at <https://dpi.sante.gouv.fr/dpi-public-webapp/app/home>

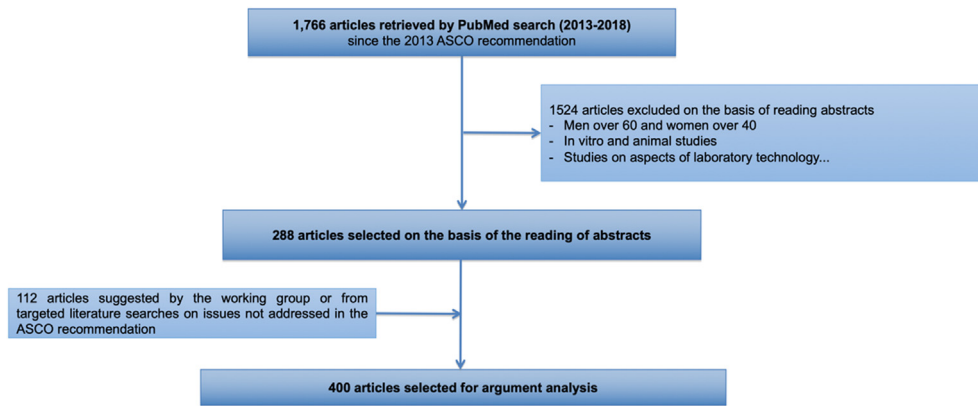


Fig. 1. Flowchart for selection of articles.

advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

## 4. Recommendations

### 4.1. Guidelines for FP in female patients

#### Q1: Who should receive advice on fertility preservation (information and action)?

##### ◆ Treatment effects – **Chemotherapy** [23–27]

**G1.** It is recommended to inform any female child, adolescent (and their legal representatives) and woman of reproductive age of the risk level in respect of gonadotoxicity and/or premature ovarian failure (POF) according to the chemotherapy regimen envisaged from the diagnostic delivery and/or therapeutic proposal consultation stage (**Grade A**).

**G2.** Any female child, adolescent and woman of reproductive age required to undergo a chemotherapy regimen can receive specialist information on the impact of these treatments on her ovarian reserve (**Grade A**).

**G3.** It is recommended to systematically propose FP consultation for any female patient under 38 years of age required to undergo a treatment protocol including bifunctional alkylating agents of high ovarian toxicity (**Grade A**). Between the ages of 38 and 40, it is recommended to discuss the indication of FP on a case-by-case basis (**EC**).

**G4.** FP is not necessary for girls under 15 years of age receiving less than 6 g/m<sup>2</sup> CED (cyclophosphamide equivalent dose). (**Grade C**).

From 6 g/m<sup>2</sup> CED and/or after 15 years of age, it is recommended to refer the patient to a specialist in reproductive medicine to discuss FP on a case-by-case basis (**EC**).

**G5.** It is recommended to preserve the fertility of female children, adolescents and young adults required to receive busulfan and thiotepa at myeloablative doses (**Grade A**).

**G6.** FP is not generally necessary in the case of treatment with dacarbazine and temozolomide, which are monofunctional alkylating agents of very low gonadotoxicity (**Grade B**). An FP strategy may be discussed on a case-by-case basis, according to the initial ovarian reserve in particular (**EC**). Long-term ovarian function monitoring is recommended (**EC**).

**G7.** It is recommended to inform the patient of the low risk of gonadotoxicity in the case of chemotherapy regimens without alkylating agents (**Grade A**). An FP strategy may be discussed on a case-by-case basis according to the initial ovarian reserve (**EC**). Long-term ovarian function monitoring is recommended (**EC**).

**G8.** Based on the data from the literature to date, it is not possible to recommend or not recommend a clinical approach in the case of immunotherapy or targeted therapies.

An FP strategy may be discussed on a case-by-case basis, particularly according to the foreseeable treatment duration (**EC**).

##### ◆ Treatment effects – **Radiotherapy** [28–40]

**G9.** For any woman of reproductive age requiring a primary pelvic radiotherapy treatment, an ovarian reserve assessment is recommended regardless of the planned radiation dose (**EC**).

**G10.** Before initiating craniospinal, abdominal, pelvic or lower limb root radiotherapy, it is recommended to conduct uterine and ovarian dosimetry to discuss FP indications (**EC**).

**G11.** Before total body radiation, systematic specialised FP consultation is recommended to provide information on gonadotoxic and uterine risks (**EC**).

**G12.** It is recommended to inform the patient of the low risk of gonadotoxicity in the case of scheduled radiation of the ovaries with a cumulative dose of less than or equal to 3 Gy (**EC**). An FP strategy may be discussed

Table 1

Grading classification according to the HAS. HAS, Haute Autorité de Santé (National Authority for Health).

Level of scientific evidence provided by the literature (HAS grid)		Guideline grade
Level 1	High-power randomised comparative trials Meta-analysis of randomised comparative trials Decision analysis based on well-conducted studies	<b>A</b> Established scientific evidence
Level 2	Low-power randomised comparative trials Well-conducted non-randomised comparative studies Cohort studies	<b>B</b> Scientific presumption
Level 3	Case-control studies.	<b>C</b>
Level 4	Comparative studies with significant bias Retrospective studies Case series Descriptive epidemiological studies (transversal, longitudinal).	Weak level of evidence
Expert consensus	In the absence of studies, the guidelines are based on consensus among the experts of the working group, after consulting the review group. A lack of grading does not mean that the guidelines are not relevant or useful. However, it should encourage the initiation of supplementary studies.	<b>EC</b> Expert consensus

on a case-by-case basis according to the initial ovarian reserve at a specialist consultation (**EC**). Long-term ovarian function monitoring is recommended (**EC**).

**G13.** For scheduled radiation doses on the ovaries greater than 3 Gy, specialised FP consultation is recommended to propose and adapt preservation techniques according to the radiation dose to be administered, any associated treatments, and the patient's age (**Grade B**).

**G14.** For women with a previous history of pelvic radiotherapy and who have not received oncofertility counselling prior to treatment, specialist counselling is recommended after the treatments (**EC**).

**G15.** In the case of cerebral radiotherapy including the hypothalamus-pituitary region, FP techniques are not recommended due to the lack of impact on ovarian reserve (**EC**).

**G16.** In the case of pelvic radiotherapy, it is recommended to provide information on uterine effects and on long-term obstetrical risks (**EC**).

*Q2. Which medical or surgical treatments help reduce infertility risk?*

◆ Medical treatments – **GnRH Agonists** [41–49]

**G17.** GnRH agonists cannot be recommended as an FP method (**Grade A**).

**G18.** No data are available to recommend the use of GnRH agonists either to protect the ovarian reserve from the effects of chemotherapy or to improve chances of spontaneous pregnancy (**Grade A**).

◆ Surgical treatments – **Ovarian transposition** [50–52]

**G19.** It is recommended to discuss ovarian transposition prior to pelvic radiotherapy involving a high risk of POF at least to preserve endocrine ovarian function (**Grade C**).

**G20.** In the context of FP prior to pelvic radiotherapy, associating ovarian tissue cryopreservation

with transposition of the contralateral ovary may be discussed (**EC**).

**G21.** It is not recommended to perform ovarian transposition in the case of risk of ovarian metastasis (**EC**).

◆ Surgical treatments – **Uterine transposition** [38,53–55].

**G22.** In the case of pelvic radiotherapy, there is not enough evidence to recommend or not recommend uterine transposition outside a research protocol (**EC**).

*Q3 - Which FP methods are used for adults and children?*

◆ Oocyte cryopreservation – embryo cryopreservation: pre-requisites for oocyte stimulation with a view to oocyte vitrification [56–76].

**G23.** It is recommended to inform the patient of the procedure in respect of the FP technique(s) envisaged with, for each, the risks and limitations of the technique, as well as the expected chances of pregnancy, taking future scientific progress into account (**EC**).

**G24.** Assessment of the ovarian reserve with a plasma anti-Mullerian hormone (AMH) assay and an ultrasound antral follicle count is required to adapt the gonadotrophin doses in the case of ovarian stimulation. The procedures for prescribing and conducting these investigations are decided in tandem between the oncology teams and the FP centre (**EC**).

**G25.** The preferred ovarian stimulation regimen is the antagonist type regimen with GnRH-agonist triggering final oocyte maturation (**EC**). Dual triggers associating GnRH agonists and hCG may be discussed in certain scenarios in order to increase the number of mature oocytes (**EC**).

**G26.** Ovarian stimulation must be started before the start of the gonadotoxic treatments after consulting with the oncologists and checking that there are no contraindications to ovarian stimulation (**EC**).

**G27.** Ovarian stimulation may be started at any stage of the cycle and may be repeated if permitted by the interval prior to starting the gonadotoxic treatment (**Grade C**).

**G28.** Thromboprophylaxis must be proposed from the start of ovarian stimulation in thromboembolic risk cases (**Grade A**).

- ◆ Oocyte cryopreservation – **embryo cryopreservation: biological aspects and chances of having a baby** [26,77–81]

**G29.** Oocyte cryopreservation after ovarian stimulation is an FP technique to be discussed as the first-line approach for postmenarchal patients who have reached puberty in the case of moderate to medium-toxicity chemotherapy, i.e. without high-dose alkylating agents (**Grade A**).

**G30.** It is recommended to perform oocyte cryopreservation before 38 years of age (**Grade C**). Between the ages 38 and 40, it is recommended to discuss the indication of oocyte cryopreservation on a case-by-case basis based on ovarian reserve markers (**EC**). In young postmenarchal adolescents, the technique must be discussed on a case-by-case basis according to maturity and the acceptability of the vaginal puncture procedure for the girl (**EC**).

**G31.** In cases of treatment regimens envisaging high ovarian toxicity, the choice between oocyte cryopreservation after oocyte stimulation and ovarian tissue cryopreservation must be discussed on a case-by-case basis (**EC**).

**G32.** Oocyte cryopreservation must be preferred over embryo cryopreservation so as to favour the preservation of the woman's fertility and not that of the couple (**EC**).

**G33.** As a precaution, oocyte cryopreservation is not indicated if the patient is undergoing chemotherapy, to prevent the cryopreservation of mature oocytes carrying chemo-induced DNA mutations (**EC**).

**G34.** Obtaining cryopreserved oocytes does not dispense the need for an analysis of the benefit of associating another additional FP technique. A second FP phase involving ovarian tissue cryopreservation could be discussed in the case of therapeutic intensification. Similarly, additional oocyte cryopreservation could be discussed in certain conditions after cancer treatment. This analysis includes the number of oocytes already cryopreserved, the patient's age, the type of treatment envisaged in the case of therapeutic intensification (**EC**).

- ◆ Anti-estrogenic therapies for oestrogen-sensitive tumours [57,69,82–89].

**G35.** There is not enough scientific evidence to recommend or not recommend anti-oestrogen therapy during ovarian stimulation in the context of breast cancer (**EC**).

**G36.** Any co-prescription of anti-oestrogen therapy during ovarian stimulation for breast cancer must be assessed (**EC**).

- ◆ Ovarian tissue cryopreservation/autograft [90–119].

**G37.** In prepubertal females, it is recommended to propose ovarian tissue cryopreservation in the case of treatment with a high gonadotoxic risk (**Grade C**).

**G38.** In postpubertal females, ovarian tissue cryopreservation is to be discussed as a first-line approach in the case of treatment with a high gonadotoxic risk (**Grade A**).

**G39.** In postpubertal females, the choice between oocyte and/or ovarian tissue cryopreservation must be discussed on a case-by-case basis in the case of treatment with a high gonadotoxic risk (**Grade C**).

**G40.** It is recommended not to perform ovarian tissue cryopreservation after 36 years (**Grade B**).

Between the ages 36 and 38 years, ovarian tissue cryopreservation may, however, be discussed on a case-by-case basis after accounting for the balance between poor chances of birth and the other techniques that may be proposed to the patient (**Grade B**).

**G41.** It is recommended to perform ovarian tissue cryopreservation when chemotherapy has already started and the future treatment involves a high gonadotoxic risk (**Grade B**).

**G42.** Ovarian tissue cryopreservation is a technique that can be proposed in urgent cases when treatment with a high gonadotoxic risk cannot be deferred (**Grade A**).

**G43.** The theoretical risk of reintroducing residual disease after ovarian tissue autografting must not result in contraindication of ovarian tissue cryopreservation if it is medically indicated, due to the possibilities of future reuse with advances in research (in vitro follicle growth, artificial ovary, etc.) (**EC**).

**G44.** In the case of cancer with a risk of an ovarian site, screening for residual disease, if possible, by molecular biology or any other suitable discriminatory technique, must be conducted on the medulla and/or at least one fragment of ovarian cortex when freezing ovarian tissue and/or before envisaging ovarian tissue grafting (**EC**).

**G45.** In the case of leukaemia, it is recommended to remove ovarian tissue not at the time of diagnosis but on remission and before pre-allogeneic haematopoietic stem cell transplantation conditioning (**Grade C**).

**G46.** It is recommended that ovarian tissue grafting is indicated and performed by experienced teams (**EC**).

- ◆ *In vitro* Oocyte maturation [8,120–126].

**G47** Oocyte cryopreservation after *in vitro* oocyte maturation (IVM) may be a strategic option for patients who have reached puberty and are under 38 years of age with a good ovarian reserve where ovarian stimulation is

contraindicated or if there is no time before oncology treatment in the case of intermediate gonadotoxic risk (**Grade C**).

**G48.** It is not recommended to propose IVM isolated from oocytes retrieved *in vivo* on ovarian tissue in the case of treatment with a high gonadotoxic risk unless this is the only possible FP strategy of woman (**EC**).

◆ Combination of different FP techniques [127–134].

**G49.** It is sometimes possible to associate different FP techniques; it is recommended to inform the patient of this possibility (**Grade C**). In the case of several possible strategies, the ultimate choice is made by the patient after the benefits and limitations of each technique and their possible combinations have been explained to her (**EC**).

**G50.** If it is decided to associate oocyte cryopreservation and ovarian tissue cryopreservation in the context of treatment with a high gonadotoxic risk, it is advised to envisage a primary laparoscopy for surgical ovarian tissue extraction prior to ovarian stimulation for oocyte cryopreservation (**EC**).

**G51.** IVM on oocytes retrieved *ex vivo* on ovarian tissue may be conducted before and after puberty in addition to ovarian tissue cryopreservation (**Grade C**).

Q4: How is fertility monitored in the post-cancer period? [135–166]

**G52.** For women of reproductive age, it is recommended to assay the AMH level before the start of treatment and then 12–24 months after the end, in order to assess the degree of follicular loss (**Grade A**).

**G53.** For women of reproductive age who have undergone cancer treatment with a gonadotoxic risk, the regular monitoring of ovarian function is recommended by a multidisciplinary team, particularly including a reproductive medicine specialist (**EC**).

**G54.** In the case of a previous history of cancer during childhood or adolescence using gonadotoxic agents, specialised consultation in reproductive medicine is recommended when the patient reaches adulthood to assess the impact of the treatments on ovarian function and the uterus (**EC**).

**G55.** Due to the possibility of spontaneous pregnancy, effective contraception is recommended for women of reproductive age who do not wish to get pregnant, even in the case of a previous history of highly gonadotoxic treatment and/or of POF (**EC**).

**G56.** In the case of a high risk of POF, one or more ovarian stimulation cycles for oocyte cryopreservation could be proposed at an interval from the end of the gonadotoxic treatment (**EC**). The eligibility criteria shall be the resumption of spontaneous menstrual cycles in the presence of a detectable AMH level.

**G57.** As a precaution, oocyte cryopreservation must be performed at an interval from the mutagenic effects

of chemotherapy (**EC**). The oncologist's prior approval shall be essential before procedure set-up.

**G58.** It is recommended to carry out the long-term follow-up of children and women of reproductive age who have undergone FP in order to assess the rates of use and birth rates both after spontaneous pregnancy and reuse of cryopreserved oocytes and/or cryopreserved ovarian tissue (**EC**).

**G59.** It is recommended to carry out the long-term monitoring of ovarian function and fertility in children and women of reproductive age who have been administered new cancer therapies (**EC**).

#### 4.2. Guidelines for FP in male patients

Q1: Who should receive advice on FP (information and action)? [15,167–220]

**G60.** All male FP requests must be accompanied by details of the therapeutic strategy envisaged (estimated cumulative doses per chemotherapy drug and radiotherapy). This information must be provided to the oncologist to forward to the reproductive medicine specialist; in particular for radiotherapy, the estimated testicular dose must be specified (**EC**).

**G61.** Sperm cryopreservation must be systematically offered to any male who has reached puberty who is to undergo cancer treatment, regardless of toxicity (**Grade A**).

**G62.** Testicular tissue cryopreservation must be proposed to all prepubertal boys who are to undergo chemotherapy treatment for which the estimated CED is greater than or equal to 5000 mg/m<sup>2</sup> (**Grade A**).

**G63. In the case of chemotherapy,** testicular tissue cryopreservation is recommended for all prepubertal boys who are to undergo chemotherapy treatment for which the estimated CED is greater than or equal to 7500 mg/m<sup>2</sup> (**Grade A**). Testicular tissue cryopreservation must be proposed to all pubertal males who have not undergone sperm cryopreservation and who are to undergo chemotherapy treatment for which the estimated CED is greater than or equal to 5000 mg/m<sup>2</sup> (**Grade A**).

**G64. In the case of radiotherapy,** it is recommended, for prepubertal boys and pubertal males (who have not undergone sperm cryopreservation), to preserve testicular tissue in the case of radiotherapy  $\geq 3$  Gy on both testicles and discuss it for any radiotherapy exposing both testicles to doses  $> 2$  Gy (**EC**).

**G65.** For males who have reached puberty, sperm cryopreservation is proposed in cases of total or partial unilateral or bilateral orchiectomy, radical pelvic surgery (prostate, bladder and rectum) or seminal tract surgery or in the case of retroperitoneal lymph node dissection or the case of retroperitoneal surgery (prostate, bladder and rectum  $\pm$  colon) (**Grade A**).



In some cases, partial orchiectomy may be discussed but a resumption of spermatogenesis is not guaranteed; FP is therefore necessary beforehand (**Grade C**).

**G66.** For prepubertal boys, testicular tissue cryopreservation must be proposed in the case of unilateral or bilateral orchiectomy on a single anatomical or functional testicle (**Grade A**).

◆ Specific scenarios

**G67.** In the case of progression or recurrence in a male who has reached puberty having undergone unsatisfactory FP, it is recommended to reconsider additional FP procedures (**EC**).

**G68.** In prepubertal boys, isolated retroperitoneal lymph node dissection can lead to ejaculation or retrograde ejaculation in adulthood. This surgical treatment is not an indication of testicular tissue cryopreservation (**EC**).

*Q2: Which FP methods are used for pubertal adolescents, adults and prepubertal boys?*  
[168,184,192–194,203,221–306]

**G69.** The patient and his legal representative (if the patient is a minor) must be informed of the different FP options as soon as the disease diagnosis has been delivered in order to optimise the procedure and not delay oncology care (**Grade A**).

**G70.** Sperm cryopreservation, the gold standard FP for men, is recommended from puberty (**Grade A**).

**G71.** Testicular tissue cryopreservation is recommended primarily for prepubertal boys (**Grade A**).

**G72.** Given the lack of evidence in respect of efficacy, protective hormone therapy is not recommended (**Grade A**).

**G73.** The use of testicular protection prior to the start of radiotherapy involving the pelvis (in particular, lombo-aortic, pelvic or upper extremity lower limb irradiation) does not dispense with the FP techniques mentioned above (**Grade A**).

**G74.** Due to the potential mutagenic risks associated with radio and/or chemotherapy treatment, sperm cryopreservation must be performed before the start of treatment (**Grade C**).

Given the risk of sperm cryopreservation failure due to severe sperm parameter alterations (severe oligozoospermia, necrozoospermia, azoospermia), ejaculation disorders or collection failure:

- sperm cryopreservation should be performed preferentially before the surgical procedure in the case of orchiectomy;
- sperm cryopreservation must be necessarily performed before the surgical procedure in the case of retroperitoneal lymph node dissection or radical pelvic surgery (**Grade C**).

**G75.** The conditions to be met insofar as possible before sperm cryopreservation are as follows (**EC**):

- provide for at least 2 sperm collections if possible;

- drink 1.5 L of water the day before the appointment;
- abstain from sex or ejaculation for between 2 and 7 days;
- prescribe health safety tests in accordance with the regulatory provisions in force (HIV1/HIV2, HCV, HBV, HBs Ag, antiHBe antibody, antiHBs antibody and syphilis serologies in France) in order to have results that are less than 3 months old on the day of the consultation appointment, unless previously agreed otherwise;
- in the case of known or potential viral risk, refer the patient to a centre capable of providing care in a viral context;
- the patient should have a medical prescription, a valid form of ID, his national health insurance card and top-up health insurance where applicable.

**G76.** In the case of adolescents, sperm cryopreservation must be proposed from 11 years of age after conducting a physical examination checking that the pubertal development corresponds to at least Tanner stage III or is accompanied by a testicular volume greater than 5 ml. However, it is necessary to conduct a prior assessment of psychosexual maturity (**Grade C**).

All adolescent patients with cancer referred for sperm cryopreservation must be seen alone and accompanied by their legal representative or their guardian carrying a form of ID (preference is given, if possible, to the presence of the father or a male representative) (**EC**).

The practical sperm collection and cryopreservation procedures are specified to the patient. It should be taken into consideration that the patient may not have any experience with masturbation (**EC**).

The information provided must enable the adolescent to dissociate fertility, sexuality and virility (**EC**).

Providing an information booklet beforehand may facilitate this approach.<sup>2</sup>

**G77.** The working group would like to point out that the patient undergoing sperm cryopreservation must be informed of the age limit for Medically Assisted Reproduction (MAP) cover, which is currently recommended by the French Biomedicine Agency advisory board at 59 years for men in France and recently validated by the French Regulations.

**G78.** Sperm collection for the purposes of FP is performed essentially by masturbation, with an associated pharmacological erection treatment if required. Penile vibratory stimulation or endorectal electrostimulation is a possible alternative to failure to ejaculate by masturbation (**Grade C**).

Sperm collection by surgical testicular sperm extraction (**Grade C**):

- is recommended in the event of failure to collect or preserve sperm (confirmed azoospermia),
- must be proposed in the presence of severe alterations of spermiatic parameters (severe oligozoospermia, necrozoospermia) compromising subsequent use in MAP.

<sup>2</sup> [https://www.ligue-cancer.net/article/25977\\_le-cecos-cest-quoi](https://www.ligue-cancer.net/article/25977_le-cecos-cest-quoi)

Onco-testicular sperm extraction (TESE) is the most widely reported technique in studies; research to be encouraged to confirm the benefit of micro-TESE in the field of cancer.

**G79.** Testicular tissue cryopreservation is recommended for prepubertal boys before starting a treatment with intermediate or high toxicity for future fertility (**Grade A**).

**G80.** Testicular tissue cryopreservation should be offered in pubertal adolescents before therapeutic intensification in the absence of satisfactory sperm cryopreservation (**Grade A**).

**G81.** In cases where testicular tissue cryopreservation is indicated, the results of health safety tests in accordance with the regulatory provisions in force which are less than 3 months old (HIV1/HIV2, HCV, HBV, HBs Ag, antiHbc antibody, antiHBs antibody and syphilis serologies) must be submitted to the laboratory on the day of the consultation appointment or no later than the day before the surgical procedure, unless previously agreed otherwise (**EC**).

**G82.** It is recommended to perform bilateral testicular biopsy for testicular tissue cryopreservation (**Grade B**).

**G83.** The patient and his or her legal representative must be informed that subsequent use of cryopreserved testicular tissue is currently under research (**EC**).

*Q3: How is fertility monitored in the post-cancer period?*

[15,185,189–191,196,201,202,222,224,225,231,307–327]

**G84.** After cancer treatment, it is recommended to provide age-adapted fertility monitoring for all males under 60 years of age (prepubertal boys, adolescents, adults) (**Grade C**).

**G85.** For prepubertal boys, it is recommended to monitor pubertal development (Tanner classification stage, growth curve, testicular volume, plasma LH, FSH, testosterone and inhibin levels) annually or twice yearly if the test results change (**Grade C**).

This monitoring will enable (**EC**):

- set-up of hormone replacement therapy in the case of endocrine deficiency or a blocking treatment in the case of early puberty;
- assessment of psychosexual maturation during adolescence with a view to:
  - discussing with the patient any questions pertaining to relationships, future relationships and parenthood to prevent withdrawal from and avoidance of romantic relationships;
  - offering a semen analysis when sufficient psychological maturation has been reached.

If the patient has undergone testicular tissue or sperm cryopreservation, a consultation in reproductive medicine is a legal requirement from 18 years of age.

If the patient has not undergone testicular tissue or sperm cryopreservation, a consultation in reproductive medicine is recommended from 18 years of age (**EC**).

**G86.** Aside from any wish on the part of the adolescent and young adult to become a father, it is recommended to assess the resumption of spermatogenesis and testicular endocrine function after the treatments: a first semen analysis and testicular endocrine function investigation (plasma LH, FSH, testosterone and inhibin levels) are indicated in the year following the end of treatments (**Grade C**).

In the case of semen analysis and/or testicular endocrine function impairment, a consultation with a reproductive medicine specialist is recommended to investigate fertility impairment and set up periodic follow-up to define the treatment options when the patient wishes to become a father (**EC**).

Due to the risk of impairment of sperm nuclear quality, contraception is recommended for 18–24 months after the end of treatment in pubertal males (**Grade C**).

**G87.** When a patient whose sperm has been frozen prior to cancer treatment wishes to become a father, it is recommended to update the fertility investigation of both members of the couple to estimate the chances of spontaneous pregnancy or the need to use MAP. Comparing sperm characteristics pre- and post-treatment will aid the decision, observing an interval of at least 18–24 months from the end of treatments for any use of fresh sperm (see G86) (**EC**).

The reproductive medicine specialist should contact the practitioner responsible for cancer follow-up to obtain information on the patient's clinical status, treatments administered and prognosis, with a view to adapting the treatment (**EC**).

**G88.** When a patient whose sperm has not been frozen prior to cancer treatment wishes to become a father, it is recommended to investigate the couple's fertility, taking into account the type of cancer, type of treatment and the time that has elapsed since the end of treatment (**Grade C**).

The reproductive medicine specialist should contact the practitioner responsible for cancer follow-up to obtain information on the patient's clinical status, treatments administered and prognosis, with a view to adapting the treatment (**EC**).

The treatment of the patient's wish to become a father must account for the possibility of delayed spermatogenesis recovery. However, the partner's age and ovarian reserve must be taken into consideration in the decision-making process (**EC**).

In the case of non-obstructive azoospermia, there is no formal evidence contraindicating TESE testicular sperm retrieval (**Grade C**).

**G89.** The patient shall be informed of other ways in which to fulfil his wish to become a father (sperm and embryo donation, as well as adoption) (**EC**).

## Additional resources

Data Supplements and Thesaurus can be found at <http://www.e-cancer.fr/>.

## Funding

These Guidelines were accredited by the National Cancer Institute, through CEO ruling No. 2021-01, dated 16/03/2021, and supported by Unicancer Group.

## Authors contributions

EH and TA were major contributors in writing the manuscript. All authors made substantial contributions to conception, design and in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

## Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors thank the following for their participation in the review process: the Association Francophone des Soins Oncologiques de Support (AFSOS), the Association Française d'Urologie (AFU), the Association Interdisciplinaire post-Universitaire de Sexologie (AIUS), the Federation of Centers for the Study and Conservation of Eggs and Sperm (CECOS), the National College of French Gynecologists and Obstetricians (CNGOF), the Reference Center for Teratogenic Agents (CRAT), the Adolescent and Young Adult Onco-hematology Group (GO-AJA), the Research and Study Group on Cryopreservation of the Ovary and Testis (GRECOT), the French-Speaking Society of Andrology (SALF), the French Society of Endocrinology (SFE), the French Society of Pediatrics (SFP), the French Society of Radiotherapy Oncology (SFRO), UNICANCER-GETUG, the League against Cancer, the Laurette Fugain association, the France Lymphome Espoir association and the Association des COordinateurs de REseaux de CAncérologie (ACORESCA).

The authors thank the National Cancer Institute, through CEO ruling No. 2021-01 (dated 16/03/2021) and Unicancer Group for supporting the recommendations.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2022.05.013>.

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