



**Who should be informed about the potential infertility risk?**

We strongly recommend that healthcare providers inform all CAYA cancer patients and their parents/caregivers/partners about the expected risk of infertility, which may vary in magnitude based on the specific treatment planned (very low- to moderate-quality evidence).

**Who should be counselled about fertility preservation?**

We strongly recommend that healthcare providers<sup>1</sup> discuss fertility preservation options and alternative family planning with CAYA cancer patients and their parents/caregivers/partners if planned treatment will include alkylating agents<sup>2</sup> (high-quality evidence), radiotherapy to volumes exposing the testes (moderate quality evidence), HSCT (expert opinion), cisplatin (low-quality evidence) orchiectomy (expert opinion), and/or cranial radiotherapy (very low-quality evidence).

If planned treatment will not include gonadotoxic modalities<sup>3</sup>, referral to a specialist to discuss fertility preservation options and family planning may be considered upon the request for additional information of the CAYA cancer patient and their parents/caregivers/partners (no studies).

**What methods for reproductive preservation are appropriate to offer in counselling?<sup>4</sup>**

*Male CAYA cancer patients at potential risk of infertility: high-dose alkylating agents (CED ≥ 4000 mg/m<sup>2</sup>), radiotherapy to volumes exposing the testes, or HSCT*

We strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal<sup>5</sup> CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).

When masturbation or penile vibration is not successful due to failure to ejaculate, we strongly recommend offering sperm cryopreservation via electro-ejaculation or testicular sperm extraction to pubertal and postpubertal<sup>5</sup> CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).

We moderately recommend offering harvesting of testicular tissue for cryopreservation to prepubertal CAYA cancer patients in this treatment group, only as part of clinical trials or approved protocols (very low-quality evidence, existing guidelines).<sup>6</sup>

We moderately recommend offering harvesting of testicular tissue for cryopreservation to pubertal and postpubertal<sup>5</sup> CAYA cancer patients in this treatment group who cannot undergo other fertility preservation options, only as part of clinical trials or approved protocols (very low-quality evidence, existing guidelines).<sup>6</sup>

We do not recommend offering hormone suppression during alkylating agent chemotherapy to pubertal and postpubertal<sup>5</sup> CAYA cancer patients (existing guidelines).

*Male CAYA cancer patients at potential risk of infertility: low-dose alkylating agents (CED < 4000 mg/m<sup>2</sup>), cisplatin or orchiectomy*

We strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal<sup>5</sup> CAYA cancer patients in this treatment group (very low quality evidence, existing guidelines).

When masturbation or penile vibration is not successful due to failure to ejaculate, we moderately recommend offering sperm cryopreservation via electro-ejaculation or testicular sperm extraction only to pubertal and postpubertal<sup>5</sup> CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment<sup>7</sup> in the future (very low-quality evidence, existing guidelines).<sup>8</sup>

No recommendation can be formulated for offering harvesting of testicular tissue for cryopreservation to prepubertal, pubertal and postpubertal<sup>5</sup> CAYA cancer patients in this treatment group (insufficient evidence).

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|---|
| We do not recommend offering <u>hormone suppression</u> during alkylating agent chemotherapy to pubertal and postpubertal <sup>5</sup> CAYA cancer patients (existing guidelines).  |
| <i>Male CAYA cancer patients at potential risk of infertility: cranial radiotherapy</i>   |
| We strongly recommend offering <u>sperm cryopreservation via masturbation or penile vibration</u> to pubertal and postpubertal <sup>5</sup> CAYA cancer patients in this treatment group (very low- quality evidence, existing guidelines).   |
| When masturbation or penile vibration is not successful due to failure to ejaculate, we moderately recommend offering <u>sperm cryopreservation via electro-ejaculation or testicular sperm extraction</u> only to pubertal and postpubertal <sup>5</sup> CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment <sup>7</sup> in the future (very low-quality evidence, existing guidelines). <sup>8</sup> |
| We do not recommend offering <u>harvesting of testicular tissue for cryopreservation</u> to prepubertal, pubertal and postpubertal <sup>5</sup> CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).  |
| <i>Male CAYA cancer patients not at risk of infertility: other treatments</i>   |
| We moderately recommend offering <u>sperm cryopreservation via masturbation or penile vibration</u> to pubertal and postpubertal <sup>5</sup> CAYA cancer patients in this treatment group based on their wishes and shared decision-making with their healthcare provider (very low-quality evidence, existing guidelines).  |
| When masturbation or penile vibration is not successful due to failure to ejaculate, we moderately recommend offering <u>sperm cryopreservation via electro-ejaculation or testicular sperm extraction</u> only to pubertal and postpubertal <sup>5</sup> CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment <sup>7</sup> in the future (very low-quality evidence, existing guidelines). <sup>8</sup> |
| We do not recommend offering <u>harvesting of testicular tissue for cryopreservation</u> to prepubertal, pubertal and postpubertal <sup>5</sup> patients in this treatment group (very low-quality evidence, existing guidelines).  |

Abbreviations: CAYA, childhood, adolescent, and young adult; CED, cyclophosphamide equivalent dose; HSCT, hematopoietic stem cell transplantation.

Note: Patients who will be treated with bilateral orchiectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations.

<sup>1</sup> The panel agreed that the choice of who should discuss fertility preservation and family planning options with the CAYA cancer patients and their families depends more on the provider's knowledge, patient's disease state and local access to fertility specialists than identifying a particular discipline to assume this role. Possibilities include paediatric oncologist, (paediatric) endocrinologist, fertility specialist, specialised nurse or other relevant healthcare provider. Of critical importance is that a system is in place to identify who is responsible for having the discussion.

<sup>2</sup> Alkylating agents: cyclophosphamide, procarbazine, busulfan, ifosfamide, mechlorethamine (nitrogen mustard), melphalan, chlorambucil, thiothepa, carmustin (BCNU), lomustine (CCNU), dacarbazine, temozolomide. A calculation formula for the cyclophosphamide equivalent dose can be found in Green et al. *Pediatr Blood Cancer*. 2014;61(1):53-67.

<sup>3</sup> Therapies that do not include alkylating agents, radiotherapy to volumes exposing the testes, cisplatin, orchiectomy, and/or cranial radiotherapy.

<sup>4</sup> The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision

<sup>5</sup> Pubertal patients are defined as  $\geq$  tanner stage II.

<sup>6</sup> The panel agreed that transplantation of cryopreserved testicular tissue should only be offered in the context of research, recognizing the experimental nature and the insufficient evidence available about its feasibility to restore fertility and the potential risk of reintroduction of malignant cells during auto-transplantation of testicular tissue.

<sup>7</sup> Patients needing high-dose alkylating agents (CED  $\geq$  4000 mg/m<sup>2</sup>) and/or radiotherapy to volumes exposing the testes in the future.

<sup>8</sup> For patients not at risk of cancer recurrence, we do not recommend.

**FIGURE:** Recommendations for preservation of reproductive fertility for male patients with childhood, adolescent, and young adult cancer

| Male patients with CAYA cancer patients before age 25 years   |   |  |  |   |  |                                    |  |  |  |  |
|---|---|--|--|---|--|------------------------------------|--|--|--|--|
| Strong recommendation <sup>1</sup> to inform all patients with CAYA cancer and their parents, caregivers, and partners about the expected risk of infertility |   |  |  |   |  |                                    |  |  |  |  |
| Counselling and methods for preservation of male reproductive fertility   | At potential risk of infertility  |  |  |   |  |                                    | Not at risk of infertility   |  |  |  |
|   | High-dose alkylating agents <sup>2</sup> , radiotherapy to testes, or HSCT                |  | Low-dose alkylating agents <sup>2</sup> , cisplatin, or orchiectomy                                      |   | Cranial radiotherapy   |                                    | Other treatment groups <sup>4</sup>  |  |  |  |
|   | Pubertal <sup>3</sup> or Postpubertal   | Prepubertal  | Pubertal <sup>3</sup> or Postpubertal  | Prepubertal                               | Pubertal <sup>3</sup> or Postpubertal  | Prepubertal                        | Pubertal <sup>3</sup> or Postpubertal  | Prepubertal  |  |  |
|   | Counselling about options for fertility preservation and alternative family planning      | Strong recommendation <sup>5</sup>   | Strong recommendation <sup>5</sup>   | Strong recommendation <sup>5</sup>        | Strong recommendation <sup>5</sup>   | Strong recommendation <sup>5</sup> | Strong recommendation <sup>5</sup>   | Moderate recommendation <sup>6</sup> only if requested   | Moderate recommendation <sup>6</sup> only if requested |  |
|   | Sperm cryopreservation via masturbation or penile vibration                               | Strong recommendation <sup>7</sup>   |  | Strong recommendation <sup>7</sup>        |  | Strong recommendation <sup>7</sup> |  | Moderate recommendation <sup>7</sup> for only patients at high risk of cancer recurrence <sup>8</sup> or if requested <sup>9</sup> |  |  |
| Sperm cryopreservation via electro-ejaculation or TESE  | Strong recommendation <sup>7</sup>  |  | Moderate recommendation <sup>7</sup> for only patients at high risk of cancer recurrence <sup>8,10</sup> |   | Moderate recommendation <sup>7</sup> for only patients at high risk of cancer recurrence <sup>8,10</sup> |                                    | Moderate recommendation <sup>7</sup> for only patients at high risk of cancer recurrence <sup>8,10</sup> |  |  |  |
| Harvesting of testicular tissue for cryopreservation <sup>11</sup>  | Moderate recommendation <sup>7</sup> only as part of clinical trials or approved protocol | Moderate recommendation <sup>7</sup> only as part of clinical trials or approved protocols | No recommendation (insufficient evidence)  | No recommendation (insufficient evidence) | Not recommended <sup>7</sup>   | Not recommended <sup>7</sup>       | Not recommended <sup>7</sup>   | Not recommended <sup>7</sup>   | Not recommended <sup>7</sup>                           |  |
| Hormone suppression during alkylating agent chemotherapy  | Not recommended <sup>12</sup>   |  | Not recommended <sup>12</sup>  |   |  |                                    |  |  |  |  |

Abbreviations: CAYA, childhood, adolescent, and young adult; HSCT, hematopoietic stem cell transplantation; TESE, testicular sperm extraction.

Note: The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.

Patients who will be treated with bilateral orchiectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations.

<sup>1</sup> This recommendation is based on very low- to moderate-quality evidence.

<sup>2</sup> High-dose alkylating agents defined as a cyclophosphamide equivalent dose (CED) of  $\geq 4000$  mg/m<sup>2</sup> and low-dose alkylating agents defined as CED  $< 4000$  mg/m<sup>2</sup>; A CED calculation can be found in Green et al. *Pediatr Blood Cancer*. 2014;61(1):53-67.

<sup>3</sup> Pubertal patients are defined as  $\geq$  tanner stage II (testicular volume of  $\geq 4$ cc).

<sup>4</sup> Therapies that do not include alkylating agents, radiotherapy to volumes exposing the testes, HSCT, cisplatin, orchiectomy, and/or cranial radiotherapy. Includes patients who will be treated with major surgery to spinal cord/sympathetic nerves/pelvis.

<sup>5</sup> This recommendation is based on very low- to high-quality evidence.

<sup>6</sup> This recommendation is based on expert opinions; no studies were identified.

<sup>7</sup> This recommendation is based on a combination of very low-quality evidence, evidence cited in high-quality existing evidence-based guidelines and expert opinions.

<sup>8</sup> Patients who may need high-dose alkylating agents (CED  $\geq 4000$  mg/m<sup>2</sup>), radiotherapy to volumes exposing the testes and/or HSCT in the future for cancer recurrence.

<sup>9</sup> Based on patient's wishes and shared decision-making with the healthcare provider.

<sup>10</sup> For patients who are not at risk of cancer recurrence, we do not recommend.

<sup>11</sup> The panel agreed that transplantation of cryopreserved testicular tissue should only be offered in the context of research, recognizing the experimental nature and the insufficient evidence available about its feasibility to restore fertility and the potential risk of reintroduction of malignant cells during auto-transplantation of testicular tissue.

<sup>12</sup> This recommendation is based on evidence cited in high-quality existing evidence-based guidelines and expert opinions.

## Publication

Mulder RL, Font-Gonzalez A, Green DM, Loeffen EAH, Hudson MM, Loonen J, Yu R, Ginsberg JP, Mitchell RT, Byrne J, Skinner R, Anazodo A, Constine LS, de Vries A, JahnuKainen K, Lorenzo A, Meissner A, Nahata L, Dinkelman-Smit M, Tournaye H, Haupt R, van den Heuvel-Eibrink MM, van Santen HM, van Pelt AMM, Dirksen U, den Hartogh J, van Dulmen-den Broeder E, Wallace WH, Levine J, Tissing WJE, Kremer LCM, Kenney LB, van de Wetering MD; PanCareLIFE Consortium. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. 2021;22(2):e57-e67.