International Guideline Harmonization Group
for Late Effects of Childhood Cancer

IGHG Hypothalamic-pituitary dysfunction surveillance recommendations 2021

General recommendations
CAYA cancer survivors with a history of: • Radiation therapy exposing the HP region (high-quality evidence for GHD, moderate-quality evidence for ACTHD, low-quality evidence for TSHD, LH/FSHD, CPP). • A CNS tumor near or within the HP region (high-quality evidence for all HP disorders and expert opinion) • Surgery near or within the HP region (expert opinion) • Hydrocephalus or cerebrospinal fluid shunt (low-quality evidence and expert opinion for GHD and CPP) and their health-care providers should be aware of the risk of HP dysfunction (i.e., GHD, TSHD, LH/FSHD, ACTHD or CPP) (strong recommendation). CAYA cancer survivors with a history of: • Exposure to high dose radiation therapy to the HP region° • Surgery near or within the HP region • A CNS tumor near or within the HP region should be referred to an (pediatric) endocrinologist, whenever feasible, or followed by a multidisciplinary team including an (pediatric) endocrinologist due to the high risk of developing HP dysfunction (expert opinion, strong recommendation).
Who needs surveillance for HP dysfunction?
Surveillance for HP dysfunction <u>is recommended</u> for CAYA cancer survivors with a history of: • Radiation therapy exposing the HP region† Note: this also applies for radiation therapy to a non-CNS/solid tumor of the head and neck • A CNS tumor near or within the HP region† • Surgery near or within the HP region† (strong recommendation).
Surveillance for GHD <u>is reasonable</u> for CAYA cancer survivors with a history of: • TBI (very low-quality evidence and expert opinion) • Hydrocephalus or cerebrospinal fluid shunt (low-quality evidence and expert opinion) Surveillance for CPP†† <u>is reasonable</u> for CAYA cancer survivors with a history of: • Hydrocephalus or cerebrospinal fluid shunt (low-quality evidence and expert opinion) (moderate recommendation).
When should surveillance for HP dysfunction be initiated?
<u>All</u> at-risk* CAYA cancer survivors, caregivers and/or parents should be counselled about signs and symptoms of HP dysfunction and offer psychosocial support if preferred, and late effects health care providers should be educated on the risk and consequences of HP dysfunction, to prevent delay in diagnosis and treatment (expert opinion, strong recommendation).
Initiation of surveillance for HP dysfunction <u>is recommended:</u> • For any HP dysfunction: 1 year after completion of radiation therapy even in the absence of symptoms‡, or from diagnosis in CAYA cancer survivors with CNS tumors or surgery near or within the HP region (expert opinion, strong recommendation). • For GHD and CPP††: from occurrence of hydrocephalus or cerebrospinal fluid shunt (expert opinion, strong recommendation)

At what frequency should surveillance for HP dysfunction be performed?

Surveillance with physical examination, including height and pubertal status is recommended every 6 months for at-risk* pre- and peri-pubertal CAYA cancer survivors, and every year for at risk* adult CAYA cancer survivors (expert opinion, strong recommendation).

Annual laboratory surveillance for HP dysfunction is recommended for all at-risk* CAYA cancer survivors (expert opinion, strong recommendation).

For how long should surveillance for HP dysfunction be performed?

Surveillance for HP dysfunction (*i.e.,* ACTHD, GHD, LH/FSHD and TSHD) is reasonable for at-risk* CAYA cancer survivors for at least 15 years after cancer diagnosis or from treatment exposure (moderate-quality evidence and expert opinion, moderate recommendation).º
However, HP dysfunction may still occur after 15 years. Continuation of surveillance should be a shared decision between survivor and healthcare provider considering available healthcare resources (expert opinion, moderate recommendation).

Surveillance for CPP is recommended for at-risk* childhood cancer survivors until age 8 years in girls and 9 years in boys (expert opinion, strong recommendation).

What surveillance modality should be used for HP dysfunction for all at-risk* CAYA cancer survivors?

For all at-risk* CAYA cancer survivors**,** the following evaluation is recommended:

- A relevant patient and familial clinical history
- A physical examination assessing signs and symptoms suggestive of HP dysfunction
- FT4 measurement
- TSH measurement
- Morning cortisol measurement

(existing guidelines and expert opinion, strong recommendation).

For all at-risk* CAYA cancer survivors, the following evaluation is not recommended:

- TRH test or nocturnal TSH surge for the diagnosis of TSHD

(very low-quality evidence and expert opinion, strong recommendation).

For pre- and peri-pubertal at-risk* CAYA cancer survivors, additional monitoring recommended include:

- Height velocity (*i.e.,* height plotted on a growth chart) in relation to parental height, and
- Pubertal development and pubertal progression (*i.e.,* Tanner stage)¶

(high-quality evidence and expert opinion, strong recommendation).

For adult at-risk* CAYA cancer survivors, additional evaluation that is reasonable includes:

- IGF-I measurement, with the understanding that an IGF-I level >0 SDS does not rule out the diagnosis of GHD

(expert opinion, moderate recommendation).

For adult at-risk* CAYA cancer survivors, additional evaluation recommended include:

- In males: measurements of morning testosterone§ (assay measuring free testosterone if overweight) and LH
- In females: measurements of estradiol, FSH and LH

(existing guidelines and expert opinion, strong recommendation).

What should be done when abnormalities are identified?
Referral to an (pediatric) endocrinologist is recommended: • For pre- and peri-pubertal CAYA cancer survivors experiencing decline in height velocity or lack of acceleration of height velocity in case of signs of puberty or with a height SDS below their target height range SDS, which cannot be explained by other causes (expert opinion, strong recommendation). • For all CAYA cancer survivors with clinical symptoms or laboratory results suggestive for HP dysfunction (expert opinion, strong recommendation).
Referral to an (pediatric) endocrinologist is recommended: • For all CAYA cancer survivors with low morning cortisol (expert opinion, strong recommendation). These survivors should be counselled regarding risks associated with untreated ACTHD. Ideally, an interim management plan should be agreed upon by the referring provider and the endocrinologist who is receiving the referral until provocative testing has established adequate ACTH axis function. This plan may involve initiating hydrocortisone replacement at maintenance or stress doses depending on the level of suspicion and the survivor's clinical presentation.
CAYA cancer survivors with (a suspicion for) HP dysfunction should be counseled regarding the benefits of hormonal replacement therapy‖ (or treatment in case of CPP) on overall health, as well as the risks associated with untreated HP dysfunction, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

Abbreviations: ACTHD= adrenocorticotropic hormone deficiency, CAYA= childhood and young adult, CCP= central precocious puberty, CNS= central nervous system, FT4= free thyroxine, FSH= follicle stimulating hormone, GHD= growth hormone deficiency, HP= hypothalamic-pituitary, IGF-I= insulin-like growth factor, LH= luteinizing hormone, SDS= standard deviation score, LH/FSHD= luteinizing hormone/follicle-stimulating hormone deficiency, TBI= total body irradiation, TRH= thyrotropin releasing hormone, TSH= thyroid stimulating hormone, TSHD= thyroid stimulating hormone deficiency.

In this table, recommendations for surveillance of HP dysfunction are given. If clinical symptoms or laboratory findings suggest HP dysfunction (for example signs of puberty not appropriate for the age or low FT4), the CAYA cancer survivor should be referred to a (pediatric) endocrinologist for further counseling and to discuss the benefits and harms of starting specific treatment.

† Concerning radiation therapy exposing the HP region; there is high-quality evidence for GHD, moderate-quality evidence for ACTHD, and low-quality evidence for TSHD, LH/FSHD and CPP. Concerning surgery near or within the HP region; there is high-quality evidence for all HP disorders, supported with expert opinion. Concerning surgery near or within the HP region; there is expert opinion for all HP disorders.

º The panel agreed that the risk for HP dysfunction increases, with higher doses of radiation therapy. When the RT dose exceeds 30 Gy, there is a higher risk for HP disorders including ACTHD, LH/FSHD and TSHD.

†† Surveillance for CPP should include monitoring for onset of puberty in CCS below age 8 years (girls, based on thelarche) or 9 years (boys, based on testicular enlargement).

*At-risk CAYA cancer survivors include survivors treated with radiation therapy exposing the HP region, with CNS tumors or surgery near or within the HP region. For GHD and CPP, history of hydrocephalus or cerebrospinal fluid shunt may also be a risk factor.

º In CAYA cancer survivors treated with neurosurgery outside the HP region only, one-time surveillance post-surgery suffices in the absence of other risk factors.

‡ Monitoring height and pubertal status at six months after RT is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Clinicians involved in the follow-up care of CAYA cancer survivors should be aware that CPP may already present in the first year after RT exposure, necessitating early referral.
¶ Boys exposed to gonadotoxic therapy (*i.e.,* alkylating agents and radiotherapy to the testes) may have testes small for pubertal stage while in puberty. Instead, morning testosterone (before 10.00 AM) should be used as screening modality as testicular volume may be unreliable.
§ Measuring morning testosterone before 10.00 AM, preferably by tandem mass spectroscopy and not in an immunoassay.
‖ Thyroid hormone replacement therapy should be started only after evaluation of function of the hypothalamic-pituitary-adrenal axis.

Publication

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