Conclusions and levels of evidence for gonadotoxicity surveillance for male CAYA cancer survivors

Who needs surveillance?	
Impaired spermatogenesis risk in CAYA cancer survivors (evidence from systematic search)**	
Increased risk after *cyclophosphamide* vs. no cyclophosphamide	Level C
Increased risk after higher *cyclophosphamide* dose vs. lower dose	Level B
Increased risk after *mechlorethamine* vs. no mechlorethamine[†]	Level C
Increased risk after higher *mechlorethamine* dose vs. lower dose	Level C
Increased risk after *procarbazine* vs. no procarbazine[‡]	Level C
Increased risk after higher *procarbazine* dose vs. lower dose	Level C
Risk after *dacarbazine* vs. no dacarbazine	No studies
No increased risk after higher *dacarbazine* dose vs. lower dose	Level C
Risk after *temozolomide*	No studies
Risk after *other alkylating agents*[¶]	No studies
Risk after *platinating agents*[#]	No studies
Risk after *cytosine arabinoside*	No studies
No increased risk after *radiotherapy potentially exposing the testes given as TBI* vs. no radiotherapy	Level C
Risk after higher dose of *radiotherapy potentially exposing the testes* vs. lower dose	No studies
Risk after *unilateral orchiectomy*	No studies
Impaired spermatogenesis risk in cancer survivors (evidence from supplemental search)**	
Increased risk probable after *busulfan and cyclophosphamide for HSCT*	Expert opinion[§]
Increased risk probable after *fludarabine and melphalan for HSCT*	Expert opinion[§]
Increased risk probable after *ifosfamide >60 g/m^2*	Expert opinion[§]
Unclear risk after *cisplatin*	Expert opinion[§]
Probably no increased risk after *radiotherapy potentially exposing the testes to <2-3 Gy*	Expert opinion[§]
Increased risk probable after *radiotherapy potentially exposing the testes to >2-3 Gy*	Expert opinion[§]
Increased risk probable after *radiotherapy potentially exposing the testes given as TBI*	Expert opinion[§]
Probably no increased risk after *unilateral orchiectomy*	Expert opinion[§]
Testosterone deficiency risk in CAYA cancer survivors (evidence from systematic search)	
No increased risk after *cyclophosphamide* vs. no cyclophosphamide	Level C
Risk after higher *cyclophosphamide* dose vs. lower dose	No studies
Risk after *chlorambucil* vs. no chlorambucil	No studies
No increased risk after higher *chlorambucil* dose vs. lower dose[†]	Level C
No increased risk after *procarbazine* vs. no procarbazine	Level C
No increased risk after higher *procarbazine* dose vs. lower dose[∞]	Level C
Risk after *dacarbazine*	No studies
Risk after *temozolomide*	No studies
Risk after *other alkylating agents*[‖]	No studies
No increased risk after *platinating agents*[#] vs. no platinating agents	Level C
Risk after higher *platinating agents*[#] dose vs. lower dose	No studies
Risk after cytosine arabinoside	No studies
No increased risk after *radiotherapy potentially exposing the testes given as TBI or pelvic/abdominal radiation* vs. no radiotherapy	Level C
Risk after higher dose of *radiotherapy potentially exposing the testes* vs. lower dose	No studies
Risk after *unilateral orchiectomy*	No studies
Testosterone deficiency risk in cancer survivors (evidence from supplemental search)	
Probably no increased risk after *cyclophosphamide*	Expert opinion[§]
Probably no increased risk after *busulfan and cyclophosphamide for HSCT*	Expert opinion[§]
Probably no increased risk after *fludarabine and melphalan for HSCT*	Expert opinion[§]
Probably no increased risk after *procarbazine and mechlorethamine*	Expert opinion[§]
Probably no increased risk after *ifosfamide*	Expert opinion[§]
Probably no increased risk after *cisplatin*	Expert opinion[§]

Probably no increased risk after *radiotherapy potentially exposing the testes to <12 Gy*	Expert opinion[§]
Increased risk probable after *radiotherapy potentially exposing the testes to ≥12 Gy*	Expert opinion[§]
Increased risk probable after *radiotherapy potentially exposing the testes given as TBI*	Expert opinion[§]
Physical sexual dysfunction risk in CAYA cancer survivors (evidence from systematic search)	
Risk after *surgery to the spinal cord / sympathetic nerves / pelvis*	No studies
Risk after *radiotherapy potentially exposing the testes / pelvis*	No studies
Risk in *patients who are hypogonadal (decreased testosterone)*	No studies
Physical sexual dysfunction risk in cancer survivors (evidence from supplemental search)	
Probably increased risk after *surgery to the spinal cord / sympathetic nerves / pelvis*	Expert opinion[§]
Probably increased risk after *radiotherapy potentially exposing the testes / pelvis*	Expert opinion[§]
Probably increased risk in *patients who are hypogonadal (decreased testosterone)*	Expert opinion[§]
What surveillance modality should be used?	
Diagnostic value endocrine measurement to detect impaired spermatogenesis in CAYA cancer survivors	
Fair diagnostic value of inhibin B to detect azoospermia	Level B
Fair diagnostic value of FSH to detect azoospermia	Level B
Fair diagnostic value of inhibin B/FSH ratio to detect azoospermia	Level C
Diagnostic value endocrine measurement to detect testosterone deficiency in CAYA cancer survivors	
Diagnostic value of LH to detect testosterone deficiency	No studies
At what frequency should surveillance be performed?	
Impaired spermatogenesis risk in CAYA cancer survivors	
Likelihood or timing of changes (deterioration or improvement) in spermatogenesis parameters	No studies
Testosterone deficiency risk in CAYA cancer survivors	
Likelihood or timing of changes (deterioration or improvement) of testosterone levels	No studies

Abbreviations: CAYA, childhood adolescent and young adult; FSH, follicle stimulating hormone; HSCT, haematopoietic stem cell transplant; Level A, high level of evidence; Level B, moderate/low level of evidence; Level C, very low level of evidence; LH, luteinising hormone; TBI, total body irradiation.

* Inclusion criteria systematic literature search: 1) male childhood, adolescent and young adult cancer survivors; 2) ≥75% diagnosed with cancer prior to age 25 years; 3) ≥50% of patients with a follow-up of ≥2 years after cancer diagnosis; 4) impaired spermatogenesis defined as azoospermia or oligozospermia and testosterone deficiency defined as decreased testosterone; 5) sample size ≥20 patients; 6) study controlled for important confounding factors such as treatment or age. For the key question 'who needs surveillance' we performed a supplemental literature search. We only performed and reported the supplemental search when there was no evidence available in the systematic search or if there was evidence not supporting an effect. If there were no studies available we reported this as 'no studies'.
** This refers to risk of permanently impaired spermatogenesis
[†] Given as part of multi-agent treatment including procarbazine
[‡] Given as part of multi-agent treatment including mechlorethamine
[¶] Busulfan, chlorambucil, ifosfamide, melphalan, thiotepa, carmustine (BCNU), lomustine (CCNU).
[#] Carboplatin, cisplatin.
[§] Expert opinion based on studies of the supplemental literature search that did not fulfill the inclusion criteria and/or of very low quality
[∞] Given as part of multi-agent treatment including chlorambucil
[‖] Busulfan, mechlorethamine, ifosfamide, melphalan, thiotepa, carmustine (BCNU), lomustine (CCNU).