Conclusions of evidence tables from the systematic literature search for gonadotoxicity surveillance for male CAYA cancer survivors

Impaired spermatogenesis – Who needs surveillance

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with cyclophosphamide? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **higher cumulative cyclophosphamide dose** was **significantly** associated with azoospermia or severe oligo-asthenozoospermia **as compared to survivors treated without and with lower doses of cyclophosphamide** in a low quality multivariable analysis without correction for radiotherapy (no effect measure reported).	*Lopez Andreu 2000*
In male survivors of childhood cancer, **higher cyclophosphamide equivalent dose** was **significantly** associated with azoospermia and oligospermia **as compared to survivors treated with lower cyclophosphamide equivalent doses** in a multivariable analysis (azoospermia OR 1.22; 95% CI 1.11-1.34; oligospermia OR 1.14; 95% CI 1.04-1.25).	*Green 2014*
Overall conclusion	
Risk after cyclophosphamide vs. no cyclophosphamide: Some evidence suggests that male childhood cancer survivors treated with cyclophosphamide have an increased risk of impaired spermatogenesis.	*1 study* **Level C**
Risk after higher cyclophosphamide dose vs. lower dose: Evidence suggests that male childhood cancer survivors treated with higher doses of cyclophosphamide have a higher risk of impaired spermatogenesis.	*2 studies* **Level B**

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with mechlorethamine? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **higher number of MOPP cycles** was **significantly** associated with a decreased sperm concentration as **compared to survivors treated without and a lower number of MOPP cycles** in a multivariable analysis (beta -6.25 ($p<0.05$)).	*van Beek 2007*
Overall conclusion	
Risk after mechlorethamine vs. no mechlorethamine: Some evidence suggests that male childhood cancer survivors treated with mechlorethamine (given as part of multi-agent treatment including procarbazine) have an increased risk of impaired spermatogenesis.	*1 study* **Level C**
Risk after higher mechlorethamine dose vs. lower dose: Some evidence suggests that male childhood cancer survivors treated with higher doses of mechlorethamine (given as part of multi-agent treatment including procarbazine) have a higher risk of impaired spermatogenesis.	*1 study* **Level C**

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with procarbazine? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **higher number of MOPP cycles** was **significantly** associated with a decreased sperm concentration as **compared to survivors treated without and a lower number of MOPP cycles** in a multivariable analysis (beta -6.25 (p<0.05)).	*van Beek 2007*
Overall conclusion	
Risk after procarbazine vs. no procarbazine: Some evidence suggests that male childhood cancer survivors treated with procarbazine (given as part of multi-agent treatment including mechlorethamine) have an increased risk of impaired spermatogenesis.	*1 study* **Level C**
Risk after higher procarbazine dose vs. lower dose: Some evidence suggests that male childhood cancer survivors treated with higher doses of procarbazine (given as part of multi-agent treatment including mechlorethamine) have a higher risk of impaired spermatogenesis.	*1 study* **Level C**

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with dacarbazine? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **higher number of EBVD/ABVD cycles** was **not significantly** associated with sperm concentration as **compared to survivors treated with a lower number of EBVD/ABVD cycles** in a multivariable analysis (p>0.05, no effect measure reported).	*van Beek 2007*
Overall conclusion	
Risk after dacarbazine vs. no dacarbazine: No studies reported on the risk of dacarbazine vs. no dacarbazine on impaired spermatogenesis in male childhood cancer survivors.	*0 studies* **No studies**
Risk after higher dacarbazine dose vs. lower dose: Some evidence suggests that there is no significant effect of dacarbazine dose on impaired spermatogenesis in male childhood cancer survivors.	*1 study* **Level C**

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with radiotherapy potentially exposing the testes? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **total body irradiation (10-12 Gy)** was **not significantly** associated with azoospermia **as compared to survivors treated without total body irradiation (but treated with cyclophosphamide, or busulfan, or both, or cyclophosphamide and total nodal irradiation)** in a multivariable regression analysis (association significant in a univariable regression analysis (OR 30.0; 95% CI 2.8-322.1)).	*Wilhelmsson 2014*
Overall conclusion	
Risk after radiotherapy potentially exposing the testes vs. no radiotherapy: Some evidence suggests that there is no significant effect of radiotherapy potentially exposing the testes (given as total body irradiation) on spermatogenesis in male childhood cancer survivors.	*1 study* **Level C**
Risk after higher dose of radiotherapy potentially exposing the testes vs. lower dose: No studies reported on the effect of radiotherapy dose on impaired spermatogenesis in male childhood cancer survivors.	*0 studies* **No studies**

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with temozolomide? What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with other alkylating agents? What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with platinum agents? What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with cytosine arabinoside? What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of impaired spermatogenesis in male CAYA cancer survivors treated with unilateral orchiectomy?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with cyclophosphamide? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **cyclophosphamide** was **not significantly** associated with a lower (but not necessarily abnormal) testosterone level as **compared to survivors treated without cyclophosphamide** in a multivariable regression analysis (no effect measure reported).	*Tromp 2011*
In male survivors of childhood cancer, **cyclophosphamide** was **not significantly** associated with a lower (but not necessarily abnormal) testosterone level as **compared to survivors treated without cyclophosphamide** in a multivariable regression analysis (no effect measure reported).	*Siimes 1993*
Overall conclusion	
Risk after cyclophosphamide vs. no cyclophosphamide: Some evidence suggests that there is no significant effect of cyclophosphamide on testosterone deficiency in male childhood cancer survivors.	*2 studies* **Level C**
Risk after higher cyclophosphamide dose vs. lower dose: No studies reported on the effect of cyclophosphamide dose on testosterone deficiency in male childhood cancer survivors.	*0 studies* **No studies**

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with chlorambucil? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, a **higher amount of ChlVPP chemotherapy** was **not significantly** associated with Leydig cell dysfunction as **compared to survivors treated with a lower amount of ChlVPP chemotherapy** in a multivariable regression analysis (no effect measure reported).	*Mackie 1996*
Overall conclusion	
Risk after chlorambucil vs. no chlorambucil: No studies reported on the risk of chlorambucil vs. no chlorambucil on testosterone deficiency in male childhood cancer survivors.	*0 studies* **No studies**
Risk after higher chlorambucil dose vs. lower dose: Some evidence suggests that there is no significant effect of chlorambucil dose (given as part of multi-agent treatment including procarbazine) on testosterone deficiency in male childhood cancer survivors.	*1 study* **Level C**

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with procarbazine? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **procarbazine** was **not significantly** associated with a lower (but not necessarily abnormal) testosterone level as **compared to survivors treated without procarbazine** in a multivariable regression analysis (no effect measure reported). In male survivors of childhood cancer, a **higher amount of ChlVPP chemotherapy** was **not significantly** associated with Leydig cell dysfunction as **compared to survivors treated with a lower amount of ChlVPP chemotherapy** in a multivariable regression analysis (no effect measure reported).	*Tromp 2011* *Mackie 1996*
Overall conclusion	
Risk after procarbazine vs. no procarbazine: Some evidence suggests that there is no significant effect of procarbazine on testosterone deficiency in male childhood cancer survivors. **Risk after higher procarbazine dose vs. lower dose:** Some evidence suggests that there is no significant effect of procarbazine dose (given as part of multi-agent treatment including both chlorambucil and procarbazine) on testosterone deficiency in male survivors of childhood cancer.	*1 study* **Level C** *1 study* **Level C**

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with platinum agents? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **cisplatin/carboplatin** were **not significantly** associated with a lower (but not necessarily abnormal) testosterone level **as compared to survivors treated without cisplatin/carboplatin** in multivariable regression analyses (no effect measure reported).	*Tromp 2011*
Overall conclusion	
Risk after platinum agents vs. no platinum agents: Some evidence suggests that there is no significant effect of platinum agents on testosterone deficiency in male childhood cancer survivors. **Risk after higher platinum agent dose vs. lower dose:** No studies reported on the effect of platinum agent dose on testosterone deficiency in male childhood cancer survivors.	*1 study* **Level C** *0 studies* **No studies**

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with radiotherapy potentially exposing the testes? What is the risk after higher doses?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, **total body irradiation and pelvic/abdominal radiotherapy** were **not significantly** associated with a lower (but not necessarily abnormal) testosterone level **as compared to survivors treated without total body irradiation and pelvic/abdominal radiotherapy** in a multivariable regression analysis (association total body irradiation significant in a univariable linear regression analysis (beta -3.53)).	*Tromp 2011*
Overall conclusion	
Risk after radiotherapy potentially exposing the testes vs. no radiotherapy: Some evidence suggests that there is no significant effect of radiotherapy potentially exposing the testis on testosterone deficiency in male childhood cancer survivors.	*1 study* **Level C**
Risk after higher dose of radiotherapy potentially exposing the testes vs. lower dose: No studies reported on the effect of radiotherapy dose on testosterone deficiency in male childhood cancer survivors.	*0 studies* **No studies**

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with dacarbazine?
What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with temozolomide?
What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with other alkylating agents
What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with cytosine arabinoside?
What is the risk after higher doses?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of testosterone deficiency in male CAYA cancer survivors treated with unilateral orchiectomy?

No studies identified in childhood, adolescent and young adult cancer survivors.

Physical sexual dysfunction – Who needs surveillance?

What is the risk of physical sexual dysfunction in male CAYA cancer survivors treated with surgery to the spinal cord, sympathetic nerves or pelvis?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of physical sexual dysfunction in male CAYA cancer survivors treated with radiotherapy potentially exposing the testes or pelvis?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of physical sexual dysfunction in male CAYA cancer survivors with hypogonadism?
No studies identified in childhood, adolescent and young adult cancer survivors.

Impaired spermatogenesis – What surveillance modality should be used?

What is the diagnostic value of inhibin B compared to FSH to detect impaired spermatogenesis in male CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors In male survivors of childhood cancer, the **sensitivity** of inhibin B, FSH and inhibin B:FSH ratio to detect azoospermia was 100%, 78.1% and 75.3%, respectively. In male survivors of childhood cancer, the **specificity** of inhibin B, FSH and inhibin B:FSH ratio to detect azoospermia was 45.0%, 74.1% and 74.5%, respectively. In male survivors of childhood cancer, the **negative predictive value (NPV)** of inhibin B, FSH and inhibin B:FSH ratio to detect azoospermia was 100%, 84.6% and 83.5%, respectively. In male survivors of childhood cancer, the **positive predictive value (PPV)** of inhibin B, FSH and inhibin B:FSH ratio to detect azoospermia was 52.1%, 65.1% and 63.8%, respectively. In male survivors of childhood cancer, the **area under the receiver operating characteristics (ROC) curve** of inhibin B, FSH and inhibin B:FSH for azoospermia was 0.72, 0.83 and 0.83, respectively.	*Green 2013*
In male survivors of childhood cancer, the **sensitivity** of inhibin B and FSH to detect azoospermia was 91% and 96%, respectively. In male survivors of childhood cancer, the **specificity** of inhibin B and FSH to detect azoospermia was 90% and 96%, respectively. In male survivors of childhood cancer, the **NPV** of inhibin B and FSH to detect azoospermia was 98% and 99%, respectively. In male survivors of childhood cancer, the **PPV** of inhibin B and FSH to detect azoospermia was 66% and 50%, respectively.	*Romerius 2010*
10)In male survivors of childhood cancer, the **PPV** of inhibin B, FSH and inhibin B+FSH to detect azoospermia was 42.3%, 61.5% and 66.7%, respectively.	*Rendtorff 2012*
In male survivors of childhood cancer, the **area under the ROC curve** of inhibin B, FSH and inhibin B+FSH for low sperm concentration was 0.83, 0.73 and 0.78, respectively.	*Lähteenmäki 2008*
In male survivors of childhood cancer, the **sensitivity** of inhibin B and FSH to detect non-azoospermia was 80% and 80% respectively. In male survivors of childhood cancer, the **specificity** of inhibin B and FSH to detect non-azoospermia was 100% and 80%, respectively. In male survivors of childhood cancer, the **area under the ROC curve** of inhibin B and FSH for non-azoospermia was 0.74 and 0.80, respectively.	*Jahnukainen 2011*
In male survivors of childhood cancer, the **sensitivity** of FSH to detect non-azoospermia was 56%. In male survivors of childhood cancer, the **specificity** of FSH to detect non-azoospermia was 81%. In male survivors of childhood cancer, the **area under the ROC curve** of FSH for non-azoospermia was 0.79.	*Wilhelmsson 2014*
Overall conclusion	
Diagnostic value inhibin B: If a cut-off level of 31 ng/L is used, 100% of the patients who actually have azoospermia will have a true positive test result, and none will have a false negative test result. In addition, 45% of the patients who do not actually have azoospermia will have a true negative test result, but 55% will have a false positive test result (suggesting that they have azoospermia when in fact they do not).	*4 studies* **Level B**
Diagnostic value FSH: If a cut-off level of 11.5 IU/L is used, 78% of the patients who actually have azoospermia will have a true positive test result, and 22% will have a false negative test results.	*5 studies* **Level B**

In addition, 74% of the patients who do not actually have azoospermia will have a true negative test result, but 26% will have a false positive test result (suggesting that they have azoospermia when in fact they do not). **Diagnostic value inhibin B / FSH ratio:** If a cut-off level of 2.52 pg/mIU is used, 75% of the patients who actually have azoospermia will have a true positive test result, and 25% will have a false negative test results. In addition, 75% of the patients who do not actually have azoospermia will have a true negative test result, but 25% will have a false positive test result (suggesting that they have azoospermia when in fact they do not).	*1 study* **Level C**

Diagnostic value inhibin B to detect azoospermia

	Definition	Number of patients / Number who received gonadotoxic therapy	Sensitivity	Specificity	NPV	PPV	AUC
Green 2013	≤31 ng/L	275 / 275	100%	45%	100%	52%	0.72
Romerius 2010	<50 ng/L	129 / 85	91%	90%	98%	66%	-
Rendtorff 2012	<80 ng/L	42/ NS	-	-	-	42%	-
Jahnukainen 2011*	>122 ng/L	47 / 31	80%	100%	-	-	0.74
Lähteenmäki 2008†	NS	23 / 18	-	-	-	-	0.83

* Diagnostic value for non-azoospermia
† Diagnostic value for low sperm concentration (<20 x10^6/mL)

Diagnostic value FSH to detect azoospermia

	Definition	Number of patients / Number who received gonadotoxic therapy	Sensitivity	Specificity	NPV	PPV	AUC
Green 2013	>11.5 IU/L	275 / 275	78%	74%	85%	65%	0.83
Romerius 2010	>10.9 IU/L	129 / 85	96%	96%	99%	50%	-
Rendtorff 2012	>10 IU/L	42 / NS	-	-	-	62%	-
Jahnukainen 2011*	<5 IU/L	47 / 31	80%	80%	-	-	0.80
Wilhelmsson 2014*	<10 IU/L	31 / 31	56%	81%	-	-	0.79
Lähteenmäki 2008†	NS	23 / 18	-	-	-	-	0.73

* Diagnostic value for non-azoospermia
† Diagnostic value for low sperm concentration (<20 x10^6/mL)

Diagnostic value inhibin B and FSH to detect azoospermia

	Definition	Number of patients / Number who received gonadotoxic therapy	Sensitivity	Specificity	NPV	PPV	AUC
Green 2013	Ratio: ≤2.52 pg/mIU	275 / 275	75%	75%	84%	64%	0.83
Rendtorff 2012	<80 ng/L >10 IU/L	42 / NS	-	-	-	67%	-
Lähteenmäki 2008[†]	NS	23 / 18	-	-	-	-	0.78

[†] Diagnostic value for low sperm concentration (<20 x10^6/mL)

Abbreviations: AUC, area under the receiver operating characteristics (ROC) curve; NPV, negative predictive value; NS, not specified; PPV, positive predictive value

Testosterone deficiency – What surveillance modality should be used?

What is the diagnostic value of LH to detect testosterone deficiency in male CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

Impaired spermatogenesis – At what frequency should surveillance be performed?

What is the likelihood of change (improvement or deterioration) of spermatogenesis parameters in male CAYA cancer survivors treated with potentially gonadotoxic therapy? What is the timing of such change?
No studies identified in childhood, adolescent and young adult cancer survivors.

Testosterone deficiency – At what frequency should surveillance be performed?

What is the likelihood of change (improvement or deterioration) of testosterone levels in male CAYA cancer survivors treated with potentially gonadotoxic therapy? What is the timing of such change?
No studies identified in childhood, adolescent and young adult cancer survivors.