Conclusions of evidence for fertility preservation in male patients with CAYA cancer

Who should be informed about potential risk of infertility?	
Satisfaction with information reported by cancer patients diagnosed before age 25 years and their parents	**Quality of evidence**
Not all pre- and post-pubertal patients and their parents are satisfied with the content of fertility preservation information provided Satisfaction about completeness of information positively impacts the decision to preserve fertility	⊕⊕⊖⊖ LOW[1]
Desire for information reported by cancer patients diagnosed before age 25 years and their parents	**Quality of evidence**
Post-pubertal patients strongly desire information about the effects of cancer treatment on fertility (median score 9) and options for fertility preservation (median score 10) (scale 1-10, includes male and female)	⊕⊕⊖⊖ LOW[2]
Most pre-pubertal patients and their parents desire information on testicular biopsy irrespective of infertility risk before treatment	⊕⊕⊖⊖ LOW[3]
Desire for information reported by healthcare providers of cancer patients diagnosed before 25 years	**Quality of evidence**
Some patients and their parents desire information about fertility preservation but paediatric oncologists report difficulties initiating discussions on this topic	⊕⊖⊖⊖ VERY LOW[4]
Who should be counselled about fertility preservation?	
Risk of impaired spermatogenesis in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Increased risk after *alkylating agents* vs. no alkylating agents	⊕⊕⊕⊕ HIGH[5-7]
Increased risk after *increasing doses of alkylating agents*	⊕⊕⊕⊕ HIGH[5-7]
Increased risk after *cyclophosphamide* vs. no cyclophosphamide	⊕⊕⊕⊕ HIGH[5-7]
Increased risk after *increasing doses of cyclophosphamide*	⊕⊕⊕⊕ HIGH[5-7]
Increased risk after *procarbazine* and *mechlorethamine* (given as part of multi-agent treatment) vs. no procarbazine and mechlorethamine	⊕⊖⊖⊖ VERY LOW[5]
Increased risk after *increasing doses of procarbazine* and *mechlorethamine* (given as part of multi-agent treatment)	⊕⊖⊖⊖ VERY LOW[5]
Unknown risk after *dacarbazine*	No studies
No significant effect of *dacarbazine dose*	⊕⊖⊖⊖ VERY LOW[5]
Unknown risk after busulfan, chlorambucil, ifosfamide, melphalan, thiotepa, carmustine (BCNU), lomustine (CCNU)	No studies
Unknown risk after *antimetabolites*	No studies
Unknown risk after *platinum compounds*	No studies
Increased risk after *radiotherapy to volumes exposing the testes* vs. no radiotherapy to the testes	⊕⊖⊖⊖ VERY LOW[5,6]
Unknown risk after *higher vs. lower doses of radiotherapy to volumes exposing the testes*	No studies
Unknown risk after *gonadotoxic chemotherapy combined with radiotherapy to volumes exposing the testes*	No studies
Unknown risk after *unilateral orchiectomy combined with radiotherapy to volumes exposing the testes*	No studies
Unknown risk after novel agents (tyrosine kinase inhibitors, demethylating agents, oxaliplatin)	No studies
Increased risk after *older age at cancer treatment* vs. younger age	⊕⊕⊖⊖ LOW[7-9]

Risk of testosterone deficiency in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Increased risk after *alkylating agents* vs. no alkylating agents	⊕⊕⊖⊖ LOW[5,6,10]
Increased risk after *increasing doses of alkylating agents*	⊕⊕⊖⊖ LOW[5,6,10]
Increased risk after *cyclophosphamide* vs. no cyclophosphamide	⊕⊕⊖⊖ LOW[5,6,10]
Increased risk after *increasing doses of cyclophosphamide*	⊕⊕⊖⊖ LOW[6,10]
No significant effect of *procarbazine* vs. no procarbazine*	⊕⊖⊖⊖ VERY LOW[5]
No significant effect of *procarbazine* and *chlorambucil dose* (given as part of multi-agent treatment)	⊕⊖⊖⊖ VERY LOW[5]
No significant effect of *antimetabolites**	⊕⊕⊖⊖ LOW[5]
Unknown risk after *higher vs. lower antimetabolite doses*	No studies
No significant effect of *platinum compounds* vs. no platinum compounds*	⊕⊖⊖⊖ VERY LOW[5]
Unknown risk after *higher vs. lower platinum compound doses*	No studies
Increased risk after *radiotherapy to volumes exposing the testes* vs. no radiotherapy to the testes	⊕⊕⊕⊕ HIGH[5,6,10,11]
Increased risk after increasing doses of *radiotherapy to volumes exposing the testes*	⊕⊕⊖⊖ LOW[10]
Unknown risk after *gonadotoxic chemotherapy combined with radiotherapy to volumes exposing the testes*	No studies
Unknown risk after *unilateral orchiectomy combined with radiotherapy to volumes exposing the testes*	No studies
No significant effect of *imatinib**	⊕⊖⊖⊖ VERY LOW[12]
Unknown risk after *other novel agents* (tyrosine kinase inhibitors, demethylating agents, oxaliplatin)	No studies
No significant effect of *age at cancer treatment*	⊕⊕⊕⊖ MODERATE[10,13,14]
Risk of hypogonadism (combined outcomes) in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Increased risk after *alkylating agents* vs. no alkylating agents	⊕⊖⊖⊖ VERY LOW[15,16]
Increased risk after *alkylating agents* and *platinum compounds* vs. alkylating agents only	⊕⊖⊖⊖ VERY LOW[15]
Increased risk after *radiotherapy to volumes exposing the testes* vs. no radiotherapy to the testes	⊕⊕⊕⊖ MODERATE[15,16]
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW[16]
No significant effect of *age at cancer treatment*	⊕⊖⊖⊖ VERY LOW[15]
Risk of hypogonadotropic hypogonadism in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW[17]
Increased risk after *increasing doses of cranial radiotherapy*	⊕⊕⊕⊖ MODERATE[18]
Likelihood of pregnancy/live birth in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Decreased likelihood after *cyclophosphamide* vs. no cyclophosphamide	⊕⊕⊖⊖ LOW[19,20]
Decreased likelihood after *increasing doses of cyclophosphamide*	⊕⊕⊖⊖ LOW[19,20]
Decreased likelihood after *high-dose ifosfamide* vs. no ifosfamide	⊕⊕⊖⊖ LOW[19,20]
No significant effect of *busulfan* vs. no busulfan	⊕⊕⊖⊖ LOW[20]
No significant effect of *lomustine* vs. no lomustine	⊕⊕⊖⊖ LOW[20]
No significant effect of *mechlorethamine* vs. no mechlorethamine	⊕⊕⊖⊖ LOW[19]
Decreased likelihood after *procarbazine* vs. no procarbazine	⊕⊕⊖⊖ LOW[19,20]
No decreased likelihood after *cytarabine* vs. no cytarabine	⊕⊕⊖⊖ LOW[19]
Decreased likelihood after *cisplatin* vs. no cisplatin	⊕⊕⊖⊖ LOW[20]

Decreased likelihood after *radiotherapy to volumes exposing the testes (>7·5 Gy)* vs. no radiotherapy to the testes	⊕⊕⊖⊖ LOW[19]
No significant effect of radiotherapy to volumes exposing *the pituitary-hypothalamic axis* vs. no radiotherapy to the pituitary-hypothalamic axis	⊕⊕⊖⊖ MODERATE[19,21]
Risk of ejaculation disorders in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Unknown risk after orchiectomy, retroperitoneal lymph node dissection or genitourinary surgery	No studies
Risk of obstructive azoospermia after orchiectomy in male cancer survivors diagnosed before age 25 years	**Quality of evidence**
Unknown risk after retroperitoneal lymph node dissection or genitourinary surgery	No studies
What male reproductive preservation methods are appropriate to offer in counselling?	
Pregnancy outcomes and live births in partners of male cancer patients diagnosed before age 25 years	**Quality of evidence**
2 live births after 13 *inseminations of cryopreserved sperm produced via masturbation* (although unknown if sperm were obtained from a cancer patient)	⊕⊖⊖⊖ VERY LOW[22]
Unknown pregnancy outcomes (including live births) after *sperm cryopreservation via vibration or electro-ejaculation*	No studies
3 live births after *testicular sperm extraction combined with intracytoplasmic sperm injection* in 2 out of 9 patients (22%)	⊕⊖⊖⊖ VERY LOW[23]
Unknown pregnancy outcomes (including live births) after *testicular tissue / spermatogonial stem cell cryopreservation and spermatogonial stem cell transplantation*	No studies
Unknown pregnancy outcomes (including live births) after *hormonal gonadoprotection*	No studies
Quality and yield of sperm and timing in male cancer patients diagnosed before age 25 years	**Quality of evidence**
Sufficient sperm quality and yield for successful cryopreservation in male patients who produced s*emen sampling via masturbation* before cancer treatment	⊕⊕⊕⊖ MODERATE[22,24-27]
Sperm motility decreases after *sperm freezing and thawing* for cryopreservation in patients who had semen sampling collected before cancer treatment	⊕⊕⊕⊖ MODERATE[22,25]
Diminished sperm count and motility for cryopreservation in male patients who produced *semen sampling via electro-ejaculation* before cancer treatment	⊕⊖⊖⊖ VERY LOW[24,26-28]
Unknown quality and yield of sperm after *testicular sperm extraction*	No studies
Mature sperm, spermatogonia and spermatogonial germ cells found *in testicular tissue dissection* before cryopreservation before and after cancer treatment	⊕⊕⊖⊖ LOW[29-32]
Unknown quality and yield of sperm after *hormonal suppression*	No studies
Pregnancy outcomes and live births in partners of male cancer patients *(evidence cited in high-quality existing evidence-based guidelines)*	**Guideline**
Clinical pregnancies and live births were achieved using *cryopreserved semen* after thawing	NICE[33]
20%-72% pregnancy success among use of *banked sperm*	ASCO,[34,35] COG[36]
Successful pregnancies with *sperm stored* for up to 28 years	COSA[37]

Testicular tissue or spermatogonial stem cell cryopreservation and transplantation or testis xenografting are still experimental and have not yet been successfully tested in humans	ASCO,[34.35] NCCN,[38] SIGN[39]
Quality and yield of sperm in male cancer patients *(evidence cited in high-quality existing evidence-based guidelines)*	**Guideline**
Sperm cryopreservation is an effective method of fertility preservation in males treated for cancer	ASCO,[34,35] NCCN,[38] SIGN[39]
Post-pubertal males can effectively collect and freeze *sperm via masturbation* prior to start cancer treatment; 65%-98% produced a semen sample; mean sperm count = 40-56 mil/mL; median motility = 38%-50%	COG[36]
Case reports and small case series show successful collection of sperm from a *post-masturbation urine sample, rectal electroejaculation under anesthesia, and testicular sperm aspiration*, but these remain uncommon and/or investigational; If sperm is obtained, success rates are similar to standard sperm banking	ASCO,[34.35] COSA[37]
Sperm retrieved in 37% of patients after *testicular sperm extraction* with higher success rates in testicular cancer patients and lower success rates in patients exposed to alkylating agents	ASCO,[34.35]
Testicular tissue biopsy samples from prepubertal boys have been cryopreserved in the expectation of successful future transplantation of spermatogonial stem cells	COSA[37]
No significant effect of *hormonal gonadoprotection* in reducing the risk of male infertility during chemotherapy.	ASCO,[34.35] NCCN,[38] ESMO[40]
Complications after reproductive (preservation) methods in male cancer patients diagnosed before age 25 years	**Quality of evidence**
Unknown complications after *sperm cryopreservation via masturbation*	No studies
No reported complications after *sperm cryopreservation via electro-ejaculation*	⊕⊖⊖⊖ VERY LOW[28]
No reported complications after *sperm cryopreservation via testicular sperm extraction*	⊕⊖⊖⊖ VERY LOW[23]
Three male patients with wound infection, 1 with post-operative bleeding, 1 with ipsilateral epididymo-orchitis, 1 with ipsilateral torsed appendix testis, 1 with scrotal cellulitis after *testicular tissue cryopreservation*	⊕⊕⊖⊖ LOW[29,30,32,41]
Unknown complications after *hormonal suppression*	No studies
Unknown complications among *offspring* after reproductive (preservation) methods	No studies
Complications after reproductive (preservation) methods in male cancer patients *(evidence cited in high-quality existing evidence-based guidelines)*	**Guideline**
No reported complications related to *testicular tissue cryopreservation*	COG[36]
Risk of reseeding malignant cells if malignant tissue is reimplanted	COG[36]
Quality of sperm and length of storage in male cancer patients diagnosed before age 25 years	**Quality of evidence**
Unknown association between length of sperm storage and possibility to use the stored material and risk of chromosomal abnormalities	No studies
Unknown association between length of storage of testicular extracted sperm and possibility to use the stored material and risk of chromosomal abnormalities	No studies
Unknown association between length of storage of spermatogonial stem cells and possibility to use the stored material and risk of chromosomal abnormalities	No studies

* These studies assessed the risk of lower, but not necessarily abnormal, testosterone levels.

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