Summary of the evidence from the supplemental literature search and expert opinion for impaired spermatogenesis, testosterone deficiency and physical sexual dysfunction after cancer treatment

Impaired spermatogenesis

Busulfan and cyclophosphamide for haematopoietic stem cell transplant (HSCT)

- Two studies in adult males measuring sperm counts found that the risk of impaired spermatogenesis was increased after treatment with busulfan and cyclophosphamide for HSCT conditioning in univariable analyses.[37,38]
- One study in pubertal and post-pubertal males measuring FSH found that the risk of impaired spermatogenesis was increased after treatment with busulfan and cyclophosphamide for HSCT conditioning in a univariable analysis.[39]

Fludarabine and melphalan for HSCT

- One study in pubertal and post-pubertal males measuring FSH found that the risk of impaired spermatogenesis was increased after treatment with fludarabine and melphalan for HSCT conditioning in a univariable analysis.[39]

Ifosfamide

- One small study in male childhood cancer survivors measuring sperm counts found that the risk of impaired spermatogenesis was increased after ifosfamide at doses of >60 g/m^2 in a univariate analysis.[40]

Cisplatin

- A very small study in male childhood cancer survivors and four large studies in adult cancer survivors measuring sperm counts found that the risk of impaired spermatogenesis was increased after treatment with cisplatin in univariable analyses.[56-59,73]
- In contrast, two large studies in male childhood cancer survivors measuring inhibin B and FSH did not find that the risk of impaired spermatogenesis was increased after treatment with cisplatin in multivariable analyses.[47,60]
- Two studies in male adult cancer survivors measuring sperm counts found that spermatogenesis recovered 1 to 7 years after treatment with bleomycin, etoposide, and cisplatin (BEP), with slower recovery in those receiving more BEP courses in univariable and multivariable analyses.[55,61]

Radiotherapy potentially exposing the testes

- Five studies in male childhood and adult cancer survivors measuring either sperm counts or FSH found that the risk of impaired spermatogenesis was increased after treatment with radiotherapy exposing the testes at doses of 10-25 Gy in univariable and multivariable analyses.[41-44,47]
- Three studies in male childhood cancer survivors measuring either sperm counts or inhibin B and FSH found that the risk of impaired spermatogenesis was increased after treatment with total body irradiation (TBI) in univariable and multivariable analyses[36,47,48] although a multivariable analysis in one of these studies did not demonstrate that TBI was independently associated with azoospermia.[36]
- Two small studies in male adult cancer patients measuring either sperm counts or FSH found persistent azoospermia for several years after treatment with radiotherapy exposing the testes at doses as low as 2-3 Gy in univariable analyses.[45,46]
- In contrast, four studies in adults measuring sperm counts did not find that the risk of impaired spermatogenesis was increased after treatment with radiotherapy to the testes at doses of <6 Gy.[50-53]

Unilateral orchiectomy

- One study in male adult cancer survivors measuring sperm counts did not find that the risk of impaired spermatogenesis was increased after treatment with unilateral orchiectomy in a univariable analysis.[54]

Testosterone deficiency

Cyclophosphamide

- One case-control study in male childhood cancer survivors found that cyclophosphamide was associated with lower but not necessarily abnormal testosterone levels.[44]
- In contrast, three studies in male childhood cancer survivors measuring either testosterone or LH did not find that the risk of testosterone deficiency was increased after treatment with cyclophosphamide in univariable and multivariable analyses.[63,69,70]

Busulfan and cyclophosphamide for HSCT

- One study in adult males measuring testosterone found that the risk of testosterone deficiency was increased after treatment with busulfan and cyclophosphamide for HSCT conditioning in a univariable analysis.[38]
- One study in adult males measuring testosterone or LH did not find that the risk of testosterone deficiency was increased after treatment with busulfan and cyclophosphamide for HSCT conditioning in a univariable analysis.[37]
- One study in pubertal and post-pubertal males measuring testosterone and LH did not find that the risk of testosterone deficiency was increased after treatment with busulfan and cyclophosphamide for HSCT conditioning in a univariable analysis.[39]

Fludarabine and melphalan for HSCT

- One study in pubertal and post-pubertal males measuring testosterone and LH did not find that the risk of testosterone deficiency was increased after treatment with fludarabine and melphalan for HSCT conditioning in a univariable analysis.[39]

Procarbazine and mechlorethamine

- Two studies in male childhood and adult cancer survivors measuring either testosterone or LH did not find that the risk of testosterone deficiency was increased after treatment with procarbazine and mechlorethamine given as MVPP or MOPP in univariable analyses.[48,71]

Ifosfamide

- One study in male childhood cancer survivors measuring testosterone did not find that the risk of testosterone deficiency was increased after treatment with ifosfamide in a univariable analysis.[40]

Cisplatin

- Three studies in male adult cancer survivors measuring testosterone found that the risk of testosterone deficiency was increased after treatment with cisplatin in univariable analyses.[56,58,72]
- Three studies in male childhood and adult cancer survivors measuring testosterone did not find that the risk of testosterone deficiency was increased after treatment with cisplatin in univariable analyses.[57,59,73]

Radiotherapy potentially exposing the testes

- Five studies in male childhood cancer survivors measuring testosterone found that the risk of testosterone deficiency was increased after treatment with radiotherapy exposing the testes at median doses of 21 Gy and 24 Gy in univariable analyses.[10,41,42,44,66]
- Two studies in adult cancer survivors measuring testosterone found that the risk of testosterone deficiency was increased after treatment with radiotherapy exposing the testes at doses of 14-20 Gy in multivariable and univariable analyses.[65,67]
- Four studies in childhood and adult cancer survivors measuring testosterone did not find that the risk of testosterone deficiency was increased after treatment with radiotherapy exposing the testes at doses up to 15 Gy in univariable analyses. However, nearly all of these patients were of adult age at treatment and received much lower doses (≤6 Gy).[42,50,52,53]

- Four studies in male childhood cancer survivors measuring either testosterone or use of testosterone replacement therapy found that the risk of testosterone deficiency was increased after treatment with TBI at doses of 7.5-15 Gy in multivariable and univariable analyses.[36,47,48,68]

Physical sexual dysfunction

Surgery to the spinal cord, sympathetic nerves or pelvis

- One study in childhood cancer survivors found that the risk of erectile dysfunction was increased after surgery to the spinal cord, sympathetic nerves or prostate gland (unclear if univariable or multivariable analysis).[80]
- Three studies in adults with testicular cancer undergoing retroperitoneal lymph node dissection, and in men suffering from pelvic plexus denervation following ileal pouch and anastomosis surgery for colorectal disease or spinal cord injury found that the risk of erectile and/or ejaculatory dysfunction was increased after surgery or injury to the pelvis, spinal cord or sympathetic nerves in univariable analyses.[77-79]

Radiotherapy potentially exposing the testes or pelvis

- One study in male childhood cancer survivors found that the risk of erectile dysfunction was increased after treatment with radiotherapy exposing the testes to >4 Gy (unclear if univariable or multivariable analysis).[80]
- One review in prostate cancer patients found that the risk of erectile dysfunction was increased after treatment with radiotherapy to the prostate in univariable analyses.[81]

Hypogonadism

- One systematic review including ten studies and two other studies in adult lymphoma and testicular cancer survivors found that the risk of impaired erectile and ejaculatory function was increased in patients with low serum testosterone concentrations in univariable analyses.[74-76]