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White paper: Onco-fertility in pediatric patients with Wilms tumor

Short title: White paper: Onco-fertility after Wilms tumor

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Novelty and Impact statement:

This unique global collaboration between Children's Oncology Group (COG) and Societe Internationale D'oncologie Pediatrique (SIOP) provides the first comprehensive overview of the available evidence on the risk of gonadal damage after Wilms tumor treatment, including the patient perspective, the options for fertility preservation, ethical and genetic considerations and recommendations concerning fertility preservation in patients with Wilms tumors. This may guide personalized risk prediction and selection of patients at risk of chemotherapy or radiotherapy-induced gonadal impairment.

Keywords: Wilms tumor, pediatric cancer, gonadal damage, fertility preservation

Abbreviations:

AAD: alkylating agent dose

AMH: Anti-Müllerian hormone

AYA: adolescent and young adult

CCS: childhood cancer survivors

CCSS: Childhood Cancer Survivor Study

CED: cyclophosphamide equivalent dose

CI: confidence interval

COG: Children's Oncology Group

CR: complete remission

CYP: cytochrome

DA: diffuse anaplastic

DOR: diminished ovarian reserve

EFS: event free survival

FHWT: favorable histology Wilms tumor

FP: fertility preservation

GWAS: genome wide association study

HARMONICA: HARMONIsation and CollAboration

HR: high risk

IGHG: International Guideline Harmonization Group

IR: intermediate risk

LOH: loss of heterozygosity

NWTSG: National Wilms Tumor Study Group

OC: Oocyte cryopreservation

OP: Oophoropexy

OR: odds ratio

OS: overall survival

OTC: ovarian tissue cryopreservation

P: p-value

PESA: percutaneous epididymal sperm aspiration

POI: premature ovarian insufficiency

RR: relative risk

RT: radiotherapy

RTSG: SIOP-Renal Tumor Study Group

SIOP: Societe Internationale D'oncologie Pediatrique

SNPs: single nucleotide polymorphisms

TESE: testicular sperm extraction

US: United States of America

VMAT: Volumetric-Modulated Arc Therapy

WART: whole abdominal radiation therapy

WT: Wilms tumor

Abstract

The survival of childhood Wilms tumor is currently around 90%, with many survivors reaching reproductive age. Chemotherapy and radiotherapy are established risk factors for gonadal damage and are used in both COG and SIOP Wilms tumor treatment protocols. The risk of infertility in Wilms tumor patients is low but increases with intensification of treatment including the use of alkylating agents, whole abdominal radiation or radiotherapy to the pelvis. Both COG and SIOP protocols aim to limit the use of gonadotoxic treatment, but unfortunately this cannot be avoided in all patients. Infertility is considered one of the most important late effects of childhood cancer treatment by patients and their families. Thus, timely discussion of gonadal damage risk and fertility preservation options is important. Additionally, irrespective of the choice for preservation, consultation with a fertility preservation (FP) team is associated with decreased patient and family regret and better quality of life. Current guidelines recommend early discussion of the impact of therapy on potential fertility. Since most patients with Wilms tumors are pre-pubertal, potential FP methods for this group are still considered experimental. There are no proven methods for FP for pre-pubertal males (testicular biopsy for cryopreservation is experimental), and there is just a single option for pre-pubertal females (ovarian tissue cryopreservation), posing both technical and ethical challenges. Identification of genetic markers of susceptibility to gonadotoxic therapy may help to stratify patient risk of gonadal damage and identify patients most likely to benefit from FP methods.

Introduction

The survival rate of childhood cancer has increased tremendously over the past decades. Since the overall survival of patients with Wilms tumor (WT) is currently around 90%, nearly all patients treated for WT reach reproductive age and thus the impact of therapy on future fertility must be considered (1-5). Chemotherapy and radiotherapy are established risk factors for gonadal damage (6, 7) and both may be part of WT treatment (8, 9). Globally, most patients have been treated according to protocols from either the National Wilms Tumor Study Group (NWTSG)/Children's Oncology Group (COG) or Societe Internationale D'oncologie Pediatrique (SIOP) (10-13). Although most patients diagnosed with WT are pre-pubertal, fertility preservation (FP) options have recently become available for young patients. However, since some of these FP methods are still experimental, they have been largely reserved for patients at high risk of gonadal damage (14-19). This manuscript aims to provide an overview of the available evidence on the risk of gonadal damage after WT treatment, including the patient perspective, the options for fertility preservation, ethical and genetic considerations and recommendations concerning FP in patients with WT.

Overview of the issue of *fertility importance* to cancer patients

When considering FP for pediatric cancer patients, it is vital to understand the patient and family vantage point (Suppl. Table S1). While future fertility is generally important to most patients and caregivers, FP is not universally discussed nor undertaken prior to initiation of oncologic therapy, as the immediate focus is on achieving cure. Unfortunately, if FP is not discussed prior to treatment, this may negatively impact the utilization and success rate of FP techniques.

Several surveys have identified attitudes of parents of children with cancer as well as the adolescent and young adult (AYA) patient population toward FP in the setting of a cancer diagnosis (20-22). These surveys uncovered that nearly all AYA patients and parents are aware of a significant risk of infertility related to cancer therapy, and that FP is important to most of this population. However, only about 20% were willing to take actions toward preserving fertility (21). This finding is known as the intention-behavior gap. Nearly half of AYA patients reported limited access, such as being unaware of the options and/or cost concerns, as the reason for not making FP arrangements despite financial support by philanthropic organizations, or public or private health plans being regionally variably available. Insurance coverage of FP costs is usually limited to the procedure and not the storage of gametes, and some insurance plans may not cover all of the procedure costs. Health-related concerns are prevalent and impair access to FP, noted by about one third of male AYA patients, and over half of female AYAs. These concerns include personally not wanting to delay treatment, physician advising against treatment delay, and concerns about the effect of cancer therapy on future offspring. Personal reasons such as not wanting children or feeling too young to consider such a decision were also noted in about a third of patients (22). Research studying shared decision making in adolescents and parents of young patients with WT is lacking.

In addition, it is well-established that many patients regret deciding not to pursue FP (20, 23, 24). The level of regret tends to be higher among those who believe that the opportunity for FP was not discussed or was discussed at a time when it was too late to effectively act on it (20). Over half of surveyed patients reported feeling a moderate to high amount of concern that infertility has negatively affected their emotions, relationships, and feeling of self-worth. Additionally, patients who identified themselves as having higher concerns about fertility were more likely to suffer from depression and lower-quality of life (25). It has been reported that most male cancer patients/survivors do not feel sufficiently informed and post-pubertal boys strongly desire information on FP options (26, 27). Similarly, female cancer patients feel it is important to discuss fertility, preferably shortly after diagnosis (28-32). A recently published guideline by the International Guideline Harmonization Group (IGHG) states that current standard care should include informing all pediatric cancer patients and their families on their relative risk of gonadal damage, including the low-risk group (33-35). As such, counseling is paramount and clear discussion of the experimental nature of any intervention must be emphasized.

Taken together, these findings underscore that FP is important to pediatric cancer patients and survivors, and should be discussed early-on, when options for FP are greatest. The intention-behavior gap highlights the importance of providing adequate counseling, to support the desire for FP, and help develop that into a behavior that accomplishes that goal when feasible. While not all children and their parents will elect to proceed with FP, there is strong evidence that future regret is greatly reduced when families feel that they have made an informed decision (25, 36).

Overview of WT therapy and oncologic outcomes

Although most patients with WT are cured with surgery and two-drug chemotherapy with very low gonadotoxic potential (9), almost all patients with relapse will be exposed to intensive therapy, typically including alkylating agents. Notably these patients require counseling again at the time of relapse, providing an opportune time to discuss FP options (17). Four-year event free survival (EFS) for stages II to IV anaplastic WT with current COG/SIOP treatment regimens is 68% (37), and long-term survival for higher risk (HR) relapsed favorable histology Wilms tumor (FHWT) who were previously treated with the combination of vincristine, dactinomycin and doxorubicin is around 50% (38). The evolution of risk stratification has outlined subgroups of WT patients for whom reduction of therapy decreases long-term treatment-related morbidity exemplified by patients with very low risk favorable histology Wilms tumor (FHWT, age < 2years and tumor weight < 550 grams) who achieved excellent outcomes with surgery alone (39). On the other hand, both COG and SIOP treatment regimens for patients identified as having HR disease can increase the possibility of infertility, with exposure to alkylators, carboplatin and radiation therapy. COG protocols showed that augmentation of therapy leads to improved outcomes among patients with stage III and IV FHWT whose tumors harbor combined loss of heterozygosity (LOH) for 1p and 16q, with the use of regimen M (five-drug chemotherapy with vincristine, dactinomycin, doxorubicin, etoposide and cyclophosphamide) (40). SIOP protocols use high-dose doxorubicin, cyclophosphamide, carboplatin and etoposide for HR patients with identified risk factors of post-chemotherapy HR histology, incomplete lung metastasis response, and blastemal-predominant histology with high blastemal volume. These therapy regimens have reduced the risk of relapse for these patient groups, avoiding the use of marked intensification of therapy at relapse, but increasing the exposure to gonadotoxic agents during initial therapy. (10, 41). Tables 1 and 2 summarize the most recent published outcomes and current treatment protocols from cooperative trials (COG and SIOP) for WT patients.

<u>General impact of Wilms Tumor Chemotherapy on Fertility</u>

The COG treatment approach to WT comprises up-front tumor resection whenever feasible, usually followed by risk-adapted chemotherapy and, in certain circumstances, radiation treatment. In comparison, apart from specific clinical-radiological features, the SIOP-Renal Tumor Study Group (RTSG) advocates pre-operative chemotherapy followed by risk-adapted treatment after surgery. The differences in the COG and SIOP treatment approaches may present different logistic (timing) opportunities for FP. SIOP usually starts pre-operative chemotherapy immediately after radiological or histological confirmation. This regimen does not contain gonadotoxic agents so FP is not likely to be needed at that time. Postoperative RT and chemotherapy can usually be well anticipated, allowing a window in time to achieve FP, possibly combined with the tumor nephrectomy. Notably, COG protocols currently mandate initiating chemotherapy within 14 days after surgery/biopsy, and the stage and histology results may only be available after 10-12 days. This may leave only a short window for decision-making and FP prior to the start of chemotherapy, even in willing patients and parents. However, prior chemotherapy is not an absolute contra-indication for ovarian tissue cryopreservation and testicular biopsy. The impact of chemotherapy on future fertility is determined by the cumulative doses of chemotherapy agents utilized. Table 3 summarizes the chemotherapy regimens and cumulative doses used by the most recently completed and published COG studies and the current SIOP-RTSG UMBRELLA protocols. The potential effects of chemotherapy on future fertility differ based on gender; hence, fertility risks are discussed separately for female and male survivors. Overall, fertility impact of chemotherapy for WT patients is largely related to the cumulative doses of cyclophosphamide received (Tables 3 and 5). Of note, patients with relapsed WT usually receive doses of cyclophosphamide, ifosfamide, doxorubicin, and radiation therapy, sometimes including a high dose chemotherapy regimen or a stem cell transplant, that places them at high risk of infertility regardless of the specific chemotherapy regimen utilized (42). Tables 3 and 4 combine the fertility risk associated with both chemotherapy and radiation modalities.

Fertility Risks for Female WT Survivors

In relation to the age of exposure to gonadotoxic agents, ovarian damage from chemotherapeutic agents can result in delayed/absent/arrested puberty in pre- or peripubertal patients and diminished ovarian reserve (DOR) or premature ovarian insufficiency (POI), and infertility in post-pubertal individuals (43). The evidence describing effects on reproductive outcomes is mostly based on retrospective data, which makes it difficult to determine the exact effects of individual chemotherapy agents (44). However, alkylating agents, such as cyclophosphamide and ifosfamide, have a clear impact on female reproductive health in a dose-related manner when given either alone or in combination (45). The most important predictors of risk are the cumulative dose of radiotherapy and alkylating agents, and the patient's age at the time of therapeutic exposure (46). If doxorubicin was included in the treatment, survivors are additionally at risk of developing cardiomyopathy during pregnancy (47).

DOR is characterized by sustained menses and normal gonadotropins, but reduced indexes of ovarian reserve for age and is important in the counselling of childhood cancer survivors (CCS), as it may represent a window for performing post-treatment fertility preservation (48). POI is defined by persistent amenorrhea combined with a follicle-stimulating level > 30 IU/L before the age of 40 years. In the St. Jude Lifetime Cohort study of 921 female cancer survivors, POI is associated with administration of high-dose cyclophosphamide (49). The cyclophosphamide equivalent dose (CED) and alkylating agent dose score (AAD) are two methods used to calculate the cumulative dose of alkylating agents (Supplemental text S1) (50, 51). Multivariable analysis showed independent associations between POI and CED ≥ 8,000 mg/m^2 [8,000 to 11,999 mg/m^2 (HR= 2.77; 95% CI, 1.18 to 6.51), and 12,000 to 19,999 mg/m^2 (HR= 3.90; 95% CI, 1.80 to 8.43)] (49).

The Childhood Cancer Survivor Study (CCSS) evaluated fertility outcomes in 20,720 previously untreated patients age < 21 years at diagnosis, who survived for at least 5 years, and who were diagnosed with an eligible cancer at 27 participating institutions between 1970 and 1986 (51). Four-hundred and ninety-eight patients with WT were included in the analysis. For all patients, when controlled for education level, marital status, age at diagnosis, ethnicity, and smoking status, multivariate models demonstrated lower chance of pregnancy for those treated with cyclophosphamide (RR= 0.8; 95% CI, 0.68 to 0.93; *P*=0.005) (51). The impact was dose related, with fertility decreasing with increased dose. When CED was categorized by quartile, female survivors diagnosed between 1970 and 1999 who were exposed to the upper quartile (≥ 11,295 mg/m^2) had a lower likelihood of pregnancy than those not exposed (HR= 0.85; 95% CI, 0.74 to 0.98; *P*=0.023) (52). Notably, the evidence regarding the threshold for ovarian damage is scarce, and ranges from 6000mg/m2 to 12,000mg/m2 (11). Currently a CED score of > 6000mg/m^2 is classified as high risk (10, 11, 17).

<u>Fertility Risks for Male WT Survivors</u>

In general, Leydig cell function is preserved, but germ cell failure is very common in men treated with high cumulative doses of cyclophosphamide (≥ 7,500 mg/m^2) (53). To date in the SIOP-RTSG, no retrospective analyses have been done to correlate childhood WT treatment with gonadal function in adulthood. However, within the CCSS, 1,622 survivors completed the Male Health Questionnaire, with a self-reported prevalence of infertility of 46% (defined as taking > 1 year to get a female pregnant) (54). Forty-nine male patients with kidney tumors were included in this analysis. In addition, a report from the St. Jude Lifetime Cohort Study found laboratory-evaluated impaired gonadal function in 55.6% of 304 male survivors of childhood cancer (55). In the CCSS multivariable analysis, an AAD of ≥ 3 (RR= 2.13; 95% CI, 1.69 to 2.68) was associated with a high risk for infertility versus an AAD < 3 (54). Male survivors who received cumulative cyclophosphamide doses of ≥ 7,412 mg/m^2 reported a significantly decreased likelihood of fathering a child compared with those not exposed (52). Notably, although irreversible gonadal impairment may occur, in some patients with azoospermia before or after treatment, recovery is seen over time in sperm production (56, 57).

<u>Impact on fertility after radiotherapy for Wilms tumor (WT)</u>

Radiotherapy (RT) is an established, efficacious modality for treating select WT patients. NWTS-3 demonstrated that EFS of patients with stage III FHWT treated with 1000cGy of abdominal radiation was not significantly different from that of patients who received 2000cGy (58). Standard of care RT in the COG and SIOP protocols is described in Table 4. AREN0321 established 1980cGy flank RT is beneficial in cases of diffuse anaplastic (DA) WT stage III tumors (59, 60). Whole lung RT is standard of care for treating pulmonary metastases in the COG protocol, excepting cases of favorable histology with lung-only metastases who have complete response to chemotherapy by week 6. (Table 4) While the impact of whole lung RT on gonadal damage is expected to be minimal since ovaries and testes are not located in the radiation field, increased risk of complications during pregnancy and labor may occur due to radiation and anthracycline induced cardiotoxicity (61). In SIOP-RTSG, approximately 25% of patients receive abdominal RT (62). In most patients the pelvic area is not included in the radiation field but 20% of irradiated patients (5% of the total number of patients with WT) are also treated on a HR protocol which includes cyclophosphamide. A radiation boost is delivered to any micro- or macroscopic residual abdominal disease (63). In SIOP, no radiation is needed in local stage I with anaplasia (62, 64). Whole lung RT is given for intermediate risk (IR) tumors with no complete remission (CR) after preoperative chemotherapy and/or metastasectomy and to all HR tumors. (Table 4)

These established regimens result in variable gonadal exposure in male and female patients. Patients with early-stage local disease and lung metastases may require lung-only RT and have very low dose gonadal exposure from indirect internal and external scatter. Those requiring flank RT may have little to no direct exposure in males and variable exposure in females depending upon lesion size at diagnosis and age of the patient, which influences the location of the ovaries (65). In cases with a large primary tumor or those requiring whole abdominal radiation therapy (WART), gonadal tissue may receive full prescription dose (see supplemental Figures S1-S4 for illustrations of flank and WART dose distributions for female and male pediatric WT patients). New approaches to reducing target volumes for flank radiation by combining highly conformal target volumes with Volumetric-Modulated Arc Therapy (VMAT) will likely have a clinical benefit by dose reduction to organs of risk (66). In the first single center study of VMAT, excellent locoregional control could be achieved by this technique (67). Unfortunately, gonadal toxicity was not formally assessed in these two papers, but this risk is predicted to be reduced.

There are limited published reports detailing the impact of RT on fertility in WT survivors, and most of these include small patient numbers. In a study of 23 pre-pubertal children aged 6 months to >4 years following therapy for WT, 1500-3000cGy hemiabdominal RT or WART resulted in serum hormone levels which indicate gonadal damage in both males and females compared with normal controls and those receiving chemotherapy only (68).

An analysis of testicular function of 10 young adult WT survivors who received 268-983cGy to the testes from WART without chemotherapy revealed all of these men to have decreased testicular volume compared to “normal males of the same age” and eight of the nine with evaluable sperm counts had oligo- or azoospermia (69).

The impact of RT prior to puberty on ovarian size, based on ultrasound analysis, was conducted on 18 female WT survivors, 14 of whom were evaluated post-puberty (70). Of 10 post-pubescent females treated with 400-4096 cGy flank RT, five had a small or not visible ipsilateral ovary; the ovaries of all three treated with 2100-3000cGy WART were small or not seen. Of note, the uterine length was also decreased in the post-pubertal females treated with WART. In general, cases with major tumor rupture that require WART are most at risk (10, 11, 17).

In a more recent questionnaire-based analysis of male fertility in a large retrospective cohort of 6,224 childhood cancer survivors participating in the CCSS, 429 of whom had WT, testicular RT dose >750cGy was significantly associated with decreased likelihood of being able to establish paternity compared with those not receiving RT (57). This study identified the subgroup with younger age at diagnosis (0-4 years), in which most WT subjects fall, to be associated with higher likelihood of being able to sire a child. This analysis, however, did not separate survivors by cancer type and is confounded by variable chemotherapy exposure.

In addition to potential impact on gonadal function, late effects of RT to the abdominopelvic region in young children may impair normal growth and development of the irradiated pelvic bones, vasculature and organs including the uterus, which are critical to successful gestation. There have been several studies of pregnancy outcomes of WT survivors, including those receiving RT either to flank only or to upper abdomen/WART on NWTS 1-4. Review of 309 medical records of at least 20-week gestation pregnancies showed female WT survivors receiving >2500cGy flank RT to have increased risk for preterm labor (OR=2.36), fetal malposition (OR=6.26), and birth before 36 weeks gestation (OR=4.07) compared with non-irradiated female survivors, whereas there was no difference noted in those receiving chemotherapy only or in pregnancies conceived with male survivors treated in NWTS 1-4 (71). While radiation may result in decreased distensibility of the uterus during pregnancy, leading to pre-term delivery, no correlation between birth weight in offspring and radiation dose has been found (46, 72, 73). RT dose to ipsilateral and contralateral ovary as well as to the uterus from flank RT was estimated to range from 2-7% of the prescription dose (71).

Regarding radiation-dose correlations, as little as 5 Gy cumulative exposure to reproductive organs augments the risk of infertility by a factor of 1.6 (46). Of female WT survivors from NWTS 1-4 cohort who received RT beyond the flank, only seven (5.5%) of 126 with known RT fields had at least one pregnancy. Nine of 10 babies were live born from five female survivors receiving upper abdominal RT only, whereas only one of four pregnancies resulted in a viable child from two female survivors who received WART. Notably, the WART dose was 1050cGy for the live birth and 2100cGy for the three non-viable pregnancies (74). These findings support earlier retrospective analyses of pregnancy outcomes of WT survivors, including one study by Li et al. (1987) of 114 pregnancies in 99 WT survivors (65 female, 34 male), which showed a 30% incidence of adverse outcomes including perinatal death and low birthweight in females receiving 2000-3500cGy flank RT compared with 3% in non-irradiated female survivors or wives of irradiated male survivors (75). The relative risk (RR) of perinatal mortality (RR 7.9; $P<0.0001$) and low birthweight (RR 4.0; $P<0.0001$) was significantly higher in the mothers irradiated for WT than expected for pregnancy outcomes for white women in the United States (US) at that time (75). In another study of 47 WT survivors, 43 of whom received abdominal RT(76), female WT survivors had a more than 4-fold increased risk of adverse birth outcomes, including preterm birth and birth defects, compared with sibling controls and wives of male WT survivors. The addition of chemotherapy did not modify this risk. Adverse pregnancy outcomes following RT for WT in the above studies have been attributed to uterine fibrosis, impaired placentation, vascular insufficiency, altered bone growth, scarring/adhesions, and/or genitourinary malfunction (46, 74-76). The most important factor for a successful pregnancy after pelvic radiotherapy is the cumulative dose to the ovaries and uterus and the age of the patient at the time of radiation (72). Pre-pubertal age at time of antineoplastic therapy exposure has been associated with a lower risk of ovarian failure, with mathematical models suggesting this finding may be due to increased follicular reserve in these very young patients (51, 77). While younger age is considered protective for gonadal damage, the growth and function of the uterus may be impaired due to the radiation. Radiation to a pre-pubertal uterus may lead to incomplete pubertal growth and development. This may pose difficulties regarding embryo implantation or fetal growth (to term).

Continued efforts to limit RT dose to the adjacent organs-at-risk, including but not limited to the gonads, is essential to improve reproductive success in this patient population. Advances in molecular biology and imaging as well as increased international collaboration between COG and SIOP will be very beneficial in this respect (78). An example of this partnership is the monthly HARMONIsation and CollAboration (HARMONICA) meetings in which SIOP and COG collaborate on numerous projects including plans for a unified approach to FP in children with renal tumors. Refining flank field and dose exposures in a manner that optimizes cancer control while concurrently limiting gonadal toxicity is also a topic amenable to international discussion. In addition, education and counseling of the parents of these young patients about the risk-benefit ratio of tumor control and late fertility risks, as well as early involvement of endocrinology/fertility experts, is critical to optimize outcomes and expectations (79).

Options for fertility preservation

As early as 2005, multiple international organizations, including the National Comprehensive Cancer Network, American Society of Clinical Oncology, European Society for Medical Oncology, American Academy of Pediatrics, Children's Oncology Group, and the American Society of Reproductive Medicine created strong guidelines around FP (80). For post-pubertal patients, there are clear data to guide counseling and intervention. Challenges to FP efforts include patient and provider knowledge of options, as well as logistical considerations. For example, FP measures should generally precede administration of any chemotherapy or radiation treatment. If possible, the FP surgery will be combined with another surgical procedure (line placement, nephrectomy) to limit the number of times a child has to undergo anesthesia and surgery. This poses an additional logistic challenge. This time pressure often factors into decisions made by patients and families. Furthermore, not all pediatric oncology treatment centers offer all FP options, which may further delay FP and initiation of definitive oncologic therapy (17, 81-85).

Females with preoperative tumor rupture and most relapsed Wilms tumor patients are at especially high risk of gonadal damage due to radiation and chemotherapy intensification. In these cases, fertility counseling is mandatory and FP procedures may be considered. Fertility risk is generally triaged early after initial diagnosis, however, sometimes the definitive treatment plan and subsequent gonadal damage risk is determined after the assessment of the initial treatment period. The response determines the treatment intensity and potential impact on fertility. Furthermore, treatment intensification may need to occur at any time depending on disease response or other factors. Thus FP discussion and plan for FP intervention is needed when intensification is suggested (17).

Currently, FP for patients with WT is largely experimental. Most patients are pre-pubertal, there are no established methods considered clinically standard for FP for pre-pubertal males, and just a single option for pre-pubertal females. As previously noted, patients report a desire to learn more about FP and regret that they were not more comprehensively counseled; as such, clinicians should proactively initiate conversations around standard and experimental options for FP. Figures 1 and 2 summarize FP options for patients, and Supplemental Table S2 provides more details about each option (86-89). Other options that exist for both genders include adoption, surrogacy, and the use of donor sperm/eggs or embryos.

Boys: Post-pubertal boys are defined as Tanner stage ≥3 (34), corresponding to a testicular volume of ≥6cc (90). Therapy-related impaired spermatogenesis, testosterone deficiency, hypogonadotropic and hypergonadotropic hypogonadism may all lead to infertility. In pre-pubertal boys, options for FP are testicular biopsy, testicular sperm extraction (TESE) and percutaneous epididymal sperm aspiration (PESA) (14, 16, 91-93). However, these procedures are not standard of care in all countries for young children. In post-pubertal boys, freezing of ejaculated sperm is offered also in case of a low risk of gonadal damage. For boys who are Tanner ≥3 with unsuccessful attempts at masturbation, electroejaculation can be considered. However, due to the invasive nature of the procedure, this should be considered primarily as an option for patients with high estimated risk of gonadal damage (94).

Girls: Cryopreservation of ovarian tissue (OTC) is now offered around Europe and at selected centers in the US to pre-pubertal and post-pubertal girls with cancer who are at high risk of infertility (15, 17). An ovary can be completely or partially removed and harvested tissue frozen. Oocyte cryopreservation (OC) is another FP option available in some jurisdictions for post-pubertal girls in which postponement of cancer treatment for at least 2 weeks is feasible. Due to the intensive hormone therapy required and the psychological impact, this is offered to physically and emotionally mature post-menarcheal girls, usually aged 16 years and older (11). As most WT patients are pre-pubertal, this is a very rare occurrence. Nevertheless (young) adult WT patients are registered (95). Oophoropexy (OP), in which the ovary is surgically secured in a location outside of the planned radiation field, is rarely used in WT patients, when flank radiation reaches into the pelvis. For WART only heterotopic OP would be applicable and this has multiple limitations (96).

Currently, future success of pregnancy after auto-transplantation of pre-pubertally harvested ovarian tissue is under extensive investigation (97-99). As the effect of OTC on the future ovarian function is still unknown, OTC is limited to patients with a high risk of infertility (100). Additionally, dormant malignant cells may be present in the harvested ovarian tissue sample, which complicates auto-transplantation (11). However, promising preclinical research is being conducted to ensure ovarian tissue can be used safely (101, 102). GnRH antagonists use to preserve ovarian function is highly debated and currently is not considered a reliable/effective option for children and AYAs for fertility preservation according to international consensus (11).

In the US and many other countries, FP services (including both procedural costs and storage of the procured tissue) are not universally covered by insurance programs, although some need-based financial assistance programs are available (103, 104). There is a general shift towards covering these services and procedures in some states, but it is far from a universally available service. In most European countries, FP for oncologic reasons is covered by insurance programs. Notably, while FP options are available in high income nations, access to these options in middle- and low-income countries is more limited (105). Therefore, finding strategies for less gonadotoxic therapy remains important.

Ethics of Fertility Preservation in patients with WT

An overview of ethical considerations concerning FP has recently been published by the PanCareLIFE consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) (33). It is important to consider ethical, cultural, and religious issues since available FP options for pre-pubertal boys and girls involve invasive procedures, the harvested tissue contains gametes, and not all FP technologies are standard of care for all patients. Most WT patients are minors, and there is no universal consensus at what age a child is competent to make medical decisions (106). Issues such as the use of stored gametes after reaching adulthood as well as handling the material after the death of a child with cancer pose ethical dilemmas. Finally, the risk of not being able to guarantee the efficacy of auto-transplanted tissue in future settings raises additional ethical challenges (33, 107-113).

Since most patients diagnosed with WT are under the age of 10 years (median: 3.4 years) (113), parents are typically the medical decision-makers. Yet internationally the importance of respecting the autonomy of children is reflected in the need for assent or consent for research or treatment, though these ages vary by country (106, 114, 115). While the parents are the primary decision-makers, the patient's perspective should be incorporated, and clinicians should ensure that information is provided to the child in an age-appropriate manner. It is important to primarily keep the interest of the child in mind, as the decision made by parents may be influenced by their own interests (116). The possibility may arise that the view of a maturing child may differ from the view of his or her parents. Especially in the case of OTC, the fact that 50% of the ovarian reserve is removed and stored, automatically reducing that child's ovarian reserve by 50%, and that future efficacy of use of the material is uncertain need to be considered and weighed (117).

The impact of genetic susceptibility on FP

The most important known risk factors for treatment-related gonadal damage in WT are use of alkylating agents (boys and girls) and full abdominal radiotherapy (girls). However, previously published work shows that female patients with similar oncologic treatment at the same age can have variable gonadal damage (79, 118). This inter-individual variability suggests that genetic factors modify gonadotoxicity of the treatment (79, 118, 119).

So far, large-scale genome wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs), such as rs11668344 (*BRSK1*), rs365132 (*UIMC1*) and rs16991615 (*MCM8*), relevant for age at natural menopause or POI in the general population (119-125). In contrast, only two GWAS studies have been performed to explore genetic susceptibility of cancer treatment-related gonadal damage in girls (126-128). Brooke et al identified and replicated a common haplotype associated with increased prevalence of premature menopause among childhood cancer survivors exposed to ovarian RT (126). Results of a European GWAS study are currently pending. *BRSK1* (rs11668344) appears to be a relevant SNP in childhood cancer survivors treated with 8000mg/m^2 cyclophosphamide or more (118, 119). It is hypothesized that the presence of the BRSK1 SNP leads to a less efficient DNA damage response system and this may result in more damage caused by the alkylating agents in healthy cells, including the gonadal cells (119). In addition, SNPs in cytochrome (CYP) 450 genes have been shown to be associated with cyclophosphamide metabolism and ovarian function, and recently also with Anti-Müllerian hormone (AMH) levels in CCSS (129-131). The field of genetic susceptibility as it relates to oncofertility is new and should be further explored.

The role of genetic variation in male infertility in the general population is still unclear and has not been studied extensively in male childhood cancer patients (132). Although evidence is limited, it should be mentioned during counseling that genetic susceptibility may contribute to the risk of future infertility in childhood cancer when discussing fertility in newly diagnosed and especially relapsed WT patients.

Conclusions

Fertility concerns in WT survivors may be related to treatment (surgical intervention, chemotherapy, and/or radiotherapy) or underlying patient-specific risk factors (including syndromes associated with WT development). Fortunately, the reproductive organs are rarely directly affected by surgical intervention for primary WT. Unfortunately, the young age of most children diagnosed with WT makes fertility preservation prior to treatment difficult, although both testicular and ovarian tissue harvest have been described. The absence of effective and widely available methods to preserve fertility in very young patients undergoing cancer treatment may place an emotional burden on families. It should not be assumed that parents will initiate a discussion about fertility preservation and thus, initiation of this discussion by the treating team together with an offer of a consult from an onco-fertility team, where available, should be a standard of care for all patients with WT.

In summary, with improved survival for children treated for WT there is an associated risk of late effects including fertility impairment. Refinements in oncologic treatments and an understanding of late effects help to limit morbidity. However, patient, family, and clinician education on fertility preservation in this population is necessary to provide the best and most holistic care possible. Our goal is that this review serves as a statement that we must turn our focus to this area as stated by G.J. D'Angio, "cure is not enough(133)."

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References

1. de Kraker J, Graf N, van Tinteren H, Pein F, Sandstedt B, Godzinski J, et al. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. Lancet. 2004;364(9441):1229-35.
2. Graf N, van Tinteren H, Bergeron C, Pein F, van den Heuvel-Eibrink MM, Sandstedt B, et al. Characteristics and outcome of stage II and III non-anaplastic Wilms' tumour treated according to the SIOP trial and study 93-01. Eur J Cancer. 2012;48(17):3240-8.
3. Green DM, Breslow NE, D'Angio GJ, Malogolowkin MH, Ritchey ML, Evans AE, et al. Outcome of patients with Stage II/favorable histology Wilms tumor with and without local tumor spill: a report from the National Wilms Tumor Study Group. Pediatr Blood Cancer. 2014;61(1):134-9.
4. Pritchard-Jones K, Moroz V, Vujanic G, Powis M, Walker J, Messahel B, et al. Treatment and outcome of Wilms' tumour patients: an analysis of all cases registered in the UKW3 trial. Ann Oncol. 2012;23(9):2457-63.
5. Weirich A, Ludwig R, Graf N, Abel U, Leuschner I, Vujanic GM, et al. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. Ann Oncol. 2004;15(5):808-20.
6. Armstrong GT, Sklar CA, Hudson MM, Robison LL. Long-term health status among survivors of childhood cancer: does sex matter? J Clin Oncol. 2007;25(28):4477-89.
7. van den Berg MH, Overbeek A, Lambalk CB, Kaspers GJL, Bresters D, van den Heuvel-Eibrink MM, et al. Long-term effects of childhood cancer treatment on hormonal and ultrasound markers of ovarian reserve. Hum Reprod. 2018;33(8):1474-88.
8. Brok J, Treger TD, Gooskens SL, van den Heuvel-Eibrink MM, Pritchard-Jones K. Biology and treatment of renal tumours in childhood. Eur J Cancer. 2016;68:179-95.
9. Dome JS, Graf N, Geller JI, Fernandez CV, Mullen EA, Spreafico F, et al. Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration. J Clin Oncol. 2015;33(27):2999-3007.
10. Mulder RL, Font-Gonzalez A, Green DM, Loeffen EAH, Hudson MM, Loonen J, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2021;22(2):e57-e67.
11. Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2021;22(2):e45-e56.
12. Vujanic GM, Gessler M, Ooms A, Collini P, Coulomb-l'Hermine A, D'Hooghe E, et al. The UMBRELLA SIOP-RTSG 2016 Wilms tumour pathology and molecular biology protocol. Nat Rev Urol. 2018;15(11):693-701.
13. Janssens GO, Melchior P, Mul J, Saunders D, Bolle S, Cameron AL, et al. The SIOP-Renal Tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy. Lancet Child Adolesc Health. 2020;4(11):846-52.
14. Portela JMD, de Winter-Korver CM, van Daalen SKM, Meissner A, de Melker AA, Repping S, et al. Assessment of fresh and cryopreserved testicular tissues from (pre)pubertal boys during organ culture as a strategy for in vitro spermatogenesis. Hum Reprod. 2019;34(12):2443-55.
15. Practice Committee of the American Society for Reproductive Medicine. Electronic address aao. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019;112(6):1022-33.
16. Uijldert M, Meissner A, de Melker AA, van Pelt AMM, van de Wetering MD, van Rijn RR, et al. Development of the testis in pre-pubertal boys with cancer after biopsy for fertility preservation. Hum Reprod. 2017;32(12):2366-72.
17. van der Perk MEM, van der Kooi ALF, van de Wetering MD, IM IJ, van Dulmen-den Broeder E, Broer SL, et al. Oncofertility care for newly diagnosed girls with cancer in a national pediatric

oncology setting, the first full year experience from the Princess Maxima Center, the PEARL study. PLoS One. 2021;16(3):e0246344.
18. van der Kooi ALF, Mulder RL, Hudson MM, Kremer LCM, Skinner R, Constine LS, et al. Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Am J Obstet Gynecol. 2021;224(1):3-15.
19. van Dorp W, Mulder RL, Kremer LC, Hudson MM, van den Heuvel-Eibrink MM, van den Berg MH, et al. Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium. J Clin Oncol. 2016;34(28):3440-50.
20. Jayasuriya S, Peate M, Allingham C, Li N, Gillam L, Zacharin M, et al. Satisfaction, disappointment and regret surrounding fertility preservation decisions in the paediatric and adolescent cancer population. J Assist Reprod Genet. 2019;36(9):1805-22.
21. Panagiotopoulou N, van Delft FW, Stewart JA. Fertility preservation knowledge, attitudes and intentions among children by proxy and adolescents with cancer. Reprod Biomed Online. 2019;39(5):802-8.
22. Shnorhavorian M, Harlan LC, Smith AW, Keegan TH, Lynch CF, Prasad PK, et al. Fertility preservation knowledge, counseling, and actions among adolescent and young adult patients with cancer: A population-based study. Cancer. 2015;121(19):3499-506.
23. Armuand GM, Wettergren L, Rodriguez-Wallberg KA, Lampic C. Desire for children, difficulties achieving a pregnancy, and infertility distress 3 to 7 years after cancer diagnosis. Support Care Cancer. 2014;22(10):2805-12.
24. Benedict C, Thom B, Kelvin JF. Young Adult Female Cancer Survivors' Decision Regret About Fertility Preservation. J Adolesc Young Adult Oncol. 2015;4(4):213-8.
25. Su HI, Lee YT, Barr R. Oncofertility: Meeting the fertility goals of adolescents and young adults with cancer. Cancer J. 2018;24(6):328-35.
26. Wyns C, Collienne C, Shenfield F, Robert A, Laurent P, Roegiers L, et al. Fertility preservation in the male pediatric population: factors influencing the decision of parents and children. Hum Reprod. 2015;30(9):2022-30.
27. Gupta AA, Edelstein K, Albert-Green A, D'Agostino N. Assessing information and service needs of young adults with cancer at a single institution: the importance of information on cancer diagnosis, fertility preservation, diet, and exercise. Support Care Cancer. 2013;21(9):2477-84.
28. Deshpande NA, Braun IM, Meyer FL. Impact of fertility preservation counseling and treatment on psychological outcomes among women with cancer: A systematic review. Cancer. 2015;121(22):3938-47.
29. Jardim FA, Lopes-Junior LC, Nascimento LC, Neves ET, Lima RAG. Fertility-Related Concerns and Uncertainties in Adolescent and Young Adult Childhood Cancer Survivors. J Adolesc Young Adult Oncol. 2020:doi: 10.1089/jayao.2020.0058. Online ahead of print.
30. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118(6):1710-7.
31. Newton K, Howard AF, Thorne S, Kelly MT, Goddard K. Facing the unknown: uncertain fertility in young adult survivors of childhood cancer. J Cancer Surviv. 2020:doi: 10.1007/s11764-020-00910-x. Online ahead of print.
32. Skaczkowski G, White V, Thompson K, Bibby H, Coory M, Orme LM, et al. Factors influencing the provision of fertility counseling and impact on quality of life in adolescents and young adults with cancer. J Psychosoc Oncol. 2018;36(4):484-502.
33. Font-Gonzalez A, Mulder RL, van Dulmen - den Broeder E, Quinn GP, Ginsberg JP, Loeffen EAH, et al. Recommendations for communication and ethical considerations related to fertility preservation in children, adolescents and young adult cancer patients: a report from the PanCareLIFE

consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group The Lancet Oncology. 2020:Forthcoming.
34. Mulder RL, Font-Gonzalez A, Green DM, Loeffen EAH, Hudson MM, Loonen J, et al. Recommendations for fertility preservation for male childhood, adolescent and young adult cancer patients: a report from the PanCareLIFE consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2020:Forthcoming.
35. Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, et al. Recommendations for fertility preservation for female childhood, adolescent and young adult cancer patients: a report from the PanCareLIFE consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2020:Forthcoming.
36. Flink DM, Sheeder J, Kondapalli LA. A Review of the Oncology Patient's Challenges for Utilizing Fertility Preservation Services. J Adolesc Young Adult Oncol. 2017;6(1):31-44.
37. Daw NC, Anderson J, Kalapurakal JA, Hoffer FA. Treatment of stage II-IV diffuse anaplastic wilms tumor: results from the children's oncology group AREN0321 study. Pediatric Blood & Cancer. 2014;61:S113-S.
38. Malogolowkin M, Cotton CA, Green DM, Breslow NE, Perlman E, Miser J, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer. 2008;50(2):236-41.
39. Fernandez CV, Perlman EJ, Mullen EA, Chi YY, Hamilton TE, Gow KW, et al. Clinical Outcome and Biological Predictors of Relapse After Nephrectomy Only for Very Low-risk Wilms Tumor: A Report From Children's Oncology Group AREN0532. Ann Surg. 2017;265(4):835-40.
40. Dix DB, Fernandez CV, Chi YY, Mullen EA, Geller JI, Gratias EJ, et al. Augmentation of Therapy for Combined Loss of Heterozygosity 1p and 16q in Favorable Histology Wilms Tumor: A Children's Oncology Group AREN0532 and AREN0533 Study Report. J Clin Oncol. 2019;37(30):2769-77.
41. Dix DB, Seibel NL, Chi YY, Khanna G, Gratias E, Anderson JR, et al. Treatment of Stage IV Favorable Histology Wilms Tumor With Lung Metastases: A Report From the Children's Oncology Group AREN0533 Study. J Clin Oncol. 2018;36(16):1564-70.
42. Ha TC, Spreafico F, Graf N, Dallorso S, Dome JS, Malogolowkin M, et al. An international strategy to determine the role of high dose therapy in recurrent Wilms' tumour. Eur J Cancer. 2013;49(1):194-210.
43. Anderson RA, Mitchell RT, Kelsey TW, Spears N, Telfer EE, Wallace WH. Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. The lancet Diabetes & endocrinology. 2015;3(7):556-67.
44. van Dorp W, Haupt R, Anderson RA, Mulder RL, van den Heuvel-Eibrink MM, van Dulmen-den Broeder E, et al. Reproductive Function and Outcomes in Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Review. J Clin Oncol. 2018;36(21):2169-80.
45. Overbeek A, van den Berg MH, van Leeuwen FE, Kaspers GJ, Lambalk CB, van Dulmen-den Broeder E. Chemotherapy-related late adverse effects on ovarian function in female survivors of childhood and young adult cancer: A systematic review. Cancer treatment reviews. 2017;53:10-24.
46. Sudour H, Chastagner P, Claude L, Desandes E, Klein M, Carrie C, et al. Fertility and pregnancy outcome after abdominal irradiation that included or excluded the pelvis in childhood tumor survivors. Int J Radiat Oncol Biol Phys. 2010;76(3):867-73.
47. Thompson KA. Pregnancy and Cardiomyopathy After Anthracyclines in Childhood. Front Cardiovasc Med. 2018;5:14.
48. Practice Committee of the American Society for Reproductive M. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2012;98(6):1407-15.
49. Chemaitilly W, Li Z, Krasin MJ, Brooke RJ, Wilson CL, Green DM, et al. Premature Ovarian Insufficiency in Childhood Cancer Survivors: A Report From the St. Jude Lifetime Cohort. The Journal of clinical endocrinology and metabolism. 2017;102(7):2242-50.

50. Green DM, Nolan VG, Goodman PJ, Whitton JA, Srivastava D, Leisenring WM, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2014;61(1):53-67.
51. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2009;27(16):2677-85.
52. Chow EJ, Stratton KL, Leisenring WM, Oeffinger KC, Sklar CA, Donaldson SS, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. The Lancet Oncology. 2016;17(5):567-76.
53. Kenney LB, Laufer MR, Grant FD, Grier H, Diller L. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer. 2001;91(3):613-21.
54. Wasilewski-Masker K, Seidel KD, Leisenring W, Mertens AC, Shnorhavorian M, Ritenour CW, et al. Male infertility in long-term survivors of pediatric cancer: a report from the childhood cancer survivor study. Journal of cancer survivorship : research and practice. 2014;8(3):437-47.
55. Lehmann V, Chemaitilly W, Lu L, Green DM, Kutteh WH, Brinkman TM, et al. Gonadal Functioning and Perceptions of Infertility Risk Among Adult Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(11):893-902.
56. Meistrich ML. Effects of chemotherapy and radiotherapy on spermatogenesis in humans. Fertil Steril. 2013;100(5):1180-6.
57. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(2):332-9.
58. Thomas PR, Tefft M, Compaan PJ, Norkool P, Breslow NE, D'Angio GJ. Results of two radiation therapy randomizations in the third National Wilms' Tumor Study. Cancer. 1991;68(8):1703-7.
59. Daw NC, Chi YY, Kalapurakal JA, Kim Y, Hoffer FA, Geller JI, et al. Activity of Vincristine and Irinotecan in Diffuse Anaplastic Wilms Tumor and Therapy Outcomes of Stage II to IV Disease: Results of the Children's Oncology Group AREN0321 Study. J Clin Oncol. 2020;38(14):1558-68.
60. Dome JS, Cotton CA, Perlman EJ, Breslow NE, Kalapurakal JA, Ritchey ML, et al. Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. J Clin Oncol. 2006;24(15):2352-8.
61. van der Kooi ALF, Mulder RL, Hudson MM, Kremer LCM, Skinner R, Constine LS, et al. Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Am J Obstet Gynecol. 2021;224(1):3-15.
62. van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, van Tinteren H, Furtwangler R, Verschuur AC, et al. Position paper: Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol. 2017;14(12):743-52.
63. Davila Fajardo R, Oldenburger E, Rube C, Lopez-Yurda M, Pritchard-Jones K, Bergeron C, et al. Evaluation of boost irradiation in patients with intermediate-risk stage III Wilms tumour with positive lymph nodes only: Results from the SIOP-WT-2001 Registry. Pediatr Blood Cancer. 2018;65(8):e27085.
64. Fajardo RD, van den Heuvel-Eibrink MM, van Tinteren H, Spreafico F, Acha T, Bergeron C, et al. Is radiotherapy required in first-line treatment of stage I diffuse anaplastic Wilms tumor? A report of SIOP-RTSG, AIEOP, JWiTS, and UKCCSG. Pediatr Blood Cancer. 2020;67(2):e28039.
65. Bardo DM, Black M, Schenk K, Zaritzky MF. Location of the ovaries in girls from newborn to 18 years of age: reconsidering ovarian shielding. Pediatr Radiol. 2009;39(3):253-9.
66. Mul J, Seravalli E, Bosman ME, van de Ven CP, Littooij AS, van Grotel M, et al. Estimated clinical benefit of combining highly conformal target volumes with Volumetric-Modulated Arc

Therapy (VMAT) versus conventional flank irradiation in pediatric renal tumors. Clin Transl Radiat Oncol. 2021;29:20-6.
67. Mul J, van Grotel M, Seravalli E, Bosman ME, van Tinteren H, Roy P, et al. Locoregional control using highly conformal flank target volumes and volumetric-modulated arc therapy in pediatric renal tumors: Results from the Dutch national cohort. Radiother Oncol. 2021;159:249-54.
68. Perrone L, Sinisi AA, Sicuranza R, Di Tullio MT, Indolfi P, Giuliano MG, et al. Prepubertal endocrine follow-up in subjects with Wilms' tumor. Med Pediatr Oncol. 1988;16(4):255-8.
69. Shalet SM, Beardwell CG, Jacobs HS, Pearson D. Testicular function following irradiation of the human prepubertal testis. Clin Endocrinol (Oxf). 1978;9(6):483-90.
70. Nussbaum Blask AR, Nicholson HS, Markle BM, Wechsler-Jentzch K, O'Donnell R, Byrne J. Sonographic detection of uterine and ovarian abnormalities in female survivors of Wilms' tumor treated with radiotherapy. AJR Am J Roentgenol. 1999;172(3):759-63.
71. Green DM, Peabody EM, Nan B, Peterson S, Kalapurakal JA, Breslow NE. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2002;20(10):2506-13.
72. Denzer C. Disorders of Gonadal and Reproductive Function in Survivors of Childhood and Adolescent Cancer. In: Beck JD, Bokemeyer C, Langer T (eds) Late Treatment Effects and Cancer Survivor Care in the Young Springer, Cham 2021. p. 87-95.
73. Green DM, Lange JM, Peabody EM, Grigorieva NN, Peterson SM, Kalapurakal JA, et al. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. J Clin Oncol. 2010;28(17):2824-30.
74. Kalapurakal JA, Peterson S, Peabody EM, Thomas PR, Green DM, D'Angio G J, et al. Pregnancy outcomes after abdominal irradiation that included or excluded the pelvis in childhood Wilms tumor survivors: a report from the National Wilms Tumor Study. Int J Radiat Oncol Biol Phys. 2004;58(5):1364-8.
75. Li FP, Gimbrere K, Gelber RD, Sallan SE, Flamant F, Green DM, et al. Outcome of pregnancy in survivors of Wilms' tumor. JAMA. 1987;257(2):216-9.
76. Byrne J, Mulvihill JJ, Connelly RR, Austin DA, Holmes GE, Holmes FF, et al. Reproductive problems and birth defects in survivors of Wilms' tumor and their relatives. Med Pediatr Oncol. 1988;16(4):233-40.
77. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005;62(3):738-44.
78. Pater L, Melchior P, Rube C, Cooper BT, McAleer MF, Kalapurakal JA, et al. Wilms tumor. Pediatr Blood Cancer. 2021;68 Suppl 2:e28257.
79. van Santen HM, van de Wetering MD, Bos AME, Vd Heuvel-Eibrink MM, van der Pal HJ, Wallace WH. Reproductive Complications in Childhood Cancer Survivors. Pediatr Clin North Am. 2020;67(6):1187-202.
80. ESHRE Guideline Group on Female Fertility Preservation, Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open. 2020;2020(4):hoaa052.
81. Klipstein S, Fallat ME, Savelli S, Committee On B, Section On HO, Section On S. Fertility preservation for pediatric and adolescent patients with cancer: Medical and ethical considerations. Pediatrics. 2020;145(3).
82. Fuchs A, Kashanian JA, Clayman ML, Gosiengfiao Y, Lockart B, Woodruff TK, et al. Pediatric Oncology Providers' Attitudes and Practice Patterns Regarding Fertility Preservation in Adolescent Male Cancer Patients. J Pediatr Hematol Oncol. 2016;38(2):118-22.
83. Goodwin T, Elizabeth Oosterhuis B, Kiernan M, Hudson MM, Dahl GV. Attitudes and practices of pediatric oncology providers regarding fertility issues. Pediatr Blood Cancer. 2007;48(1):80-5.
84. Adams E, Hill E, Watson E. Fertility preservation in cancer survivors: a national survey of oncologists' current knowledge, practice and attitudes. Br J Cancer. 2013;108(8):1602-15.

85. Louwe LA, ter Kuile MM, Hilders CG, Jenninga E, Tiemessen SM, Peters AA, et al. Oncologists' practice and attitudes regarding fertility preservation in female cancer patients: a pilot study in the Netherlands. J Psychosom Obstet Gynaecol. 2013;34(3):129-32.
86. Dolmans MM, Taylor HS, Rodriguez-Wallberg KA, Blumenfeld Z, Lambertini M, von Wolff M, et al. Utility of gonadotropin-releasing hormone agonists for fertility preservation in women receiving chemotherapy: pros and cons. Fertil Steril. 2020;114(4):725-38.
87. Halpern JA, Das A, Faw CA, Brannigan RE. Oncofertility in adult and pediatric populations: options and barriers. Transl Androl Urol. 2020;9(Suppl 2):S227-S38.
88. Lambertini M, Peccatori FA, Demeestere I, Amant F, Wyns C, Stukenborg JB, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines(dagger). Ann Oncol. 2020;31(12):1664-78.
89. Moravek MB, Appiah LC, Anazodo A, Burns KC, Gomez-Lobo V, Hoefgen HR, et al. Development of a Pediatric Fertility Preservation Program: A Report From the Pediatric Initiative Network of the Oncofertility Consortium. J Adolesc Health. 2019;64(5):563-73.
90. Tanner JM. Growth at adolescence. 2nd. Oxford, England: Blackwell Scientific Publications; 1962.
91. Shah R. Surgical sperm retrieval: Techniques and their indications. Indian J Urol. 2011;27(1):102-9.
92. Franik S, Hoeijmakers Y, D'Hauwers K, Braat DD, Nelen WL, Smeets D, et al. Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. Hum Reprod. 2016;31(9):1952-9.
93. Lopategui DM, Yechieli R, Ramasamy R. Oncofertility in sarcoma patients. Transl Androl Urol. 2017;6(5):951-8.
94. Adank MC, van Dorp W, Smit M, van Casteren NJ, Laven JS, Pieters R, et al. Electroejaculation as a method of fertility preservation in boys diagnosed with cancer: a single-center experience and review of the literature. Fertil Steril. 2014;102(1):199-205 e1.
95. Segers H, van den Heuvel-Eibrink MM, Pritchard-Jones K, Coppes MJ, Aitchison M, Bergeron C, et al. Management of adults with Wilms' tumor: recommendations based on international consensus. Expert Rev Anticancer Ther. 2011;11(7):1105-13.
96. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol. 2003;188(2):367-70.
97. Anderson RA, Baird DT. The development of ovarian tissue cryopreservation in Edinburgh: Translation from a rodent model through validation in a large mammal and then into clinical practice. Acta Obstet Gynecol Scand. 2019;98(5):545-9.
98. Dolmans MM, Donnez J. Fertility preservation in women for medical and social reasons: Oocytes vs ovarian tissue. Best Pract Res Clin Obstet Gynaecol. 2021;70:63-80.
99. Bertoldo MJ, Smitz J, Wu LE, Lee HC, Woodruff TK, Gilchrist RB. Prospects of Rescuing Young Eggs for Oncofertility. Trends Endocrinol Metab. 2020;31(10):708-11.
100. Donnez J, Dolmans MM. Fertility Preservation in Women. N Engl J Med. 2017;377(17):1657-65.
101. Telfer EE. Future developments: In vitro growth (IVG) of human ovarian follicles. Acta Obstet Gynecol Scand. 2019;98(5):653-8.
102. Telfer EE, Andersen CY. In vitro growth and maturation of primordial follicles and immature oocytes. Fertil Steril. 2021;115(5):1116-25.
103. Benoit M, Chiles K, Hsieh M. The Landscape of Coverage for Fertility Preservation in Male Pediatric Patients. Urol Pract. 2018;5(3):198-204.
104. Dupree JM, Dickey RM, Lipshultz LI. Inequity between male and female coverage in state infertility laws. Fertil Steril. 2016;105(6):1519-22.
105. Salama M, Ataman-Millhouse L, Sobral F, Terrado G, Scarella A, Bourlon MT, et al. Barriers and Opportunities of Oncofertility Practice in Nine Developing Countries and the Emerging Oncofertility Professional Engagement Network. JCO Glob Oncol. 2020;6.

106. Grootens-Wiegers P, Hein IM, van den Broek JM, de Vries MC. Medical decision-making in children and adolescents: developmental and neuroscientific aspects. BMC Pediatr. 2017;17(1):120.
107. Van Den Broecke R, Pennings G, Van Der Elst J, Liu J, Dhont M. Ovarian tissue cryopreservation: therapeutic prospects and ethical reflections. Reprod Biomed Online. 2001;3(3):179-84.
108. Deepinder F, Agarwal A. Approach to Fertility Preservation in Adult and Pre-pubertal Males (Chapter 27). In: Seli E, Agarwal A, editors. Fertility Preservation Emerging Technologies an Clinical Applications. New York: Springer; 2012.
109. Patrizio P. Ethical Discussions in Approaching Fertility Preservation (Chapter 2). In: Seli E, Agarwal A, editors. In Fertility Preservation Emerging Technologies an Clinical Applications. New York: Springer; 2012.
110. Multidisciplinary Working Group convened by the British Fertility S. A strategy for fertility services for survivors of childhood cancer. Hum Fertil (Camb). 2003;6(2):A1-A39.
111. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;6(4):209-18.
112. Pastore G, Znaor A, Spreafico F, Graf N, Pritchard-Jones K, Steliarova-Foucher E. Malignant renal tumours incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006;42(13):2103-14.
113. Hol JA, Lopez-Yurda MI, Van Tinteren H, Van Grotel M, Godzinski J, Vujanic G, et al. Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001. PLoS One. 2019;14(8):e0221373.
114. Health NIo. Children's assent to clinical trial participation 2005 [Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials/patient-safety/childrens-assent.
115. Mayer R, Moreno R. Nine ways to reduce cognitive load in multimedia learning. Educ Psychol. 2003;38:43-52.
116. Elster N. Legal aspects of fertility preservation (Chapter 42). In: Donnez J, Kim S, editors. Principles and practice of fertility preservation. Cambridge: Cambridge University Press; 2011.
117. Corkum KS, Rhee DS, Wafford QE, Demeestere I, Dasgupta R, Baertschiger R, et al. Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: A systematic review. J Pediatr Surg. 2019;54(11):2200-9.
118. van Dorp W, van den Heuvel-Eibrink MM, Stolk L, Pieters R, Uitterlinden AG, Visser JA, et al. Genetic variation may modify ovarian reserve in female childhood cancer survivors. Hum Reprod. 2013;28(4):1069-76.
119. van der Kooi ALF, van Dijk M, Broer L, van den Berg MH, Laven JSE, van Leeuwen FE, et al. Possible modification of BRSK1 on the risk of alkylating chemotherapy-related reduced ovarian function. Hum Reprod. 2021;36(4):1120-33.
120. Day FR, Ruth KS, Thompson DJ, Lunetta KL, Pervjakova N, Chasman DI, et al. Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. Nat Genet. 2015;47(11):1294-303.
121. Day FR, Thompson DJ, Helgason H, Chasman DI, Finucane H, Sulem P, et al. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. Nat Genet. 2017;49(6):834-41.
122. He C, Kraft P, Chasman DI, Buring JE, Chen C, Hankinson SE, et al. A large-scale candidate gene association study of age at menarche and age at natural menopause. Hum Genet. 2010;128(5):515-27.
123. Perry JR, Corre T, Esko T, Chasman DI, Fischer K, Franceschini N, et al. A genome-wide association study of early menopause and the combined impact of identified variants. Hum Mol Genet. 2013;22(7):1465-72.
124. Perry JR, Stolk L, Franceschini N, Lunetta KL, Zhai G, McArdle PF, et al. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. Nat Genet. 2009;41(6):648-50.

125. Stolk L, Zhai G, van Meurs JB, Verbiest MM, Visser JA, Estrada K, et al. Loci at chromosomes 13, 19 and 20 influence age at natural menopause. Nat Genet. 2009;41(6):645-7.
126. Brooke RJ, Im C, Wilson CL, Krasin MJ, Liu Q, Li Z, et al. A High-risk Haplotype for Premature Menopause in Childhood Cancer Survivors Exposed to Gonadotoxic Therapy. J Natl Cancer Inst. 2018;110(8):895-904.
127. Byrne J, Grabow D, Campbell H, O'Brien K, Bielack S, Am Zehnhoff-Dinnesen A, et al. PanCareLIFE: The scientific basis for a European project to improve long-term care regarding fertility, ototoxicity and health-related quality of life after cancer occurring among children and adolescents. Eur J Cancer. 2018;103:227-37.
128. van der Kooi ALF, Clemens E, Broer L, Zolk O, Byrne J, Campbell H, et al. Genetic variation in gonadal impairment in female survivors of childhood cancer: a PanCareLIFE study protocol. BMC Cancer. 2018;18(1):930.
129. Shu W, Guan S, Yang X, Liang L, Li J, Chen Z, et al. Genetic markers in CYP2C19 and CYP2B6 for prediction of cyclophosphamide's 4-hydroxylation, efficacy and side effects in Chinese patients with systemic lupus erythematosus. Br J Clin Pharmacol. 2016;81(2):327-40.
130. Su HI, Sammel MD, Velders L, Horn M, Stankiewicz C, Matro J, et al. Association of cyclophosphamide drug-metabolizing enzyme polymorphisms and chemotherapy-related ovarian failure in breast cancer survivors. Fertil Steril. 2010;94(2):645-54.
131. van der Perk MEM, Broer L, Yasui Y, Robison LL, Hudson MM, Laven JSE, et al. Effect of Genetic Variation in CYP450 on Gonadal Impairment in a European Cohort of Female Childhood Cancer Survivors, Based on a Candidate Gene Approach: Results from the PanCareLIFE Study. Cancers. 2021;13(4598).
132. Greither T, Schumacher J, Dejung M, Behre HM, Zischler H, Butter F, et al. Fertility Relevance Probability Analysis Shortlists Genetic Markers for Male Fertility Impairment. Cytogenet Genome Res. 2020;160(9):506-22.
133. D'Angio GJ. Pediatric cancer in perspective: cure is not enough. Cancer. 1975;35(3 suppl):866-70.
134. Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey ML, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2005;23(29):7312-21.
135. Daw NC, Chi YY, Kim Y, Mullen EA, Kalapurakal JA, Tian J, et al. Treatment of stage I anaplastic Wilms' tumour: a report from the Children's Oncology Group AREN0321 study. Eur J Cancer. 2019;118:58-66.
136. Fernandez CV, Mullen EA, Chi YY, Ehrlich PF, Perlman EJ, Kalapurakal JA, et al. Outcome and Prognostic Factors in Stage III Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group Study AREN0532. J Clin Oncol. 2018;36(3):254-61.
137. van den Heuvel-Eibrink MM, van Tinteren H, Bergeron C, Coulomb-L'Hermine A, de Camargo B, Leuschner I, et al. Outcome of localised blastemal-type Wilms tumour patients treated according to intensified treatment in the SIOP WT 2001 protocol, a report of the SIOP Renal Tumour Study Group (SIOP-RTSG). Eur J Cancer. 2015;51(4):498-506.
138. Pritchard-Jones K, Bergeron C, de Camargo B, van den Heuvel-Eibrink MM, Acha T, Godzinski J, et al. Omission of doxorubicin from the treatment of stage II-III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial. Lancet. 2015;386(9999):1156-64.
139. Daw NC, Chi YY, Kalapurakal JA, Kim Y, Hoffer FA, Geller JI, et al. Activity of Vincristine and Irinotecan in Diffuse Anaplastic Wilms Tumor and Therapy Outcomes of Stage II to IV Disease: Results of the Children's Oncology Group AREN0321 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(14):1558-68.
140. Klipstein S, Fallat ME, Savelli S. Fertility Preservation for Pediatric and Adolescent Patients With Cancer: Medical and Ethical Considerations. Pediatrics. 2020;145(3).

Figure legends

Figure 1. Male fertility preservation options

Figure 2. Female fertility preservation options

† Only in selected cases receiving abdominal radiotherapy (RT) with an ovary in the RT field

* In rare cases, older patients with a partner may want to opt for embryo cryopreservation. However, for most Wilms tumor patients this will not be an option.

^ Currently, no strong evidence exists that hormonal suppression has a protective effect on gonadal damage in children. However, it can be used in addition to other fertility preservation methods.

Tables

Table 1. Current treatment protocols and published outcomes according to COG (9)

Stage	Histology	Risk stratification	Chemotherapy	Radiation	Outcomes 4-year EFS / OS (%)	Gonadotoxicity potential / risk to fertility
I	Favorable	Very low risk	None	None	89.7 / 100 (39)	None
		Standard	EE4A (VA) 19 weeks	None	94 / 98 (134)	Very low
	Focal/Diffuse Anaplastic		DD4A (VAD) 25 weeks	10.8 Gy (flank)	100 / 100 (135)	Very low
II	Favorable	Standard	EE4A (VA) 19 weeks	None	86 / 98 (134)	Very low
	Focal anaplasia		DD4A (VAD) 25 weeks	None	n/a	Very low
	Diffuse anaplasia		Revised UH-1 (VCDBE) 30 weeks	10.8 Gy (flank)	86.7 / 86.2 (59)	Yes
I/II	Favorable	High risk (LOH 1p and 16q)	DD4A (VAD) 25 weeks	None	87.3 / 100 (40)	Very low
III	Favorable	Standard	DD4A (VAD) 25 weeks	10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease	87.1 / 94.4 (136)	Possible depending on radiation field
	Focal anaplasia		DD4A (VAD) 25 weeks	10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease	n/a	Possible depending on radiation field
	Diffuse anaplasia		Revised UH-1 (VCDBE) 30 weeks	10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease	80.9 / 88.6 (59)	Yes

III/IV	Favorable	High risk -LOH 1p and 16q (40) OR no CR lung nodule(s) at week 6 for stage IV (41)	Regimen M (VADCE) 31 weeks	10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease 12 Gy lungs if lung metastasis	90.2 / 96.1 (40) 88.5 / 99.8 (41)	Yes
IV	Favorable	Standard AND CR lung nodule(s) at week 6	DD4A (VAD) 25 weeks	No lung rads	79.5 / 96.1 (41)	Very low
	Focal anaplasia		Revised UH-1 (VCDBE) 30 weeks	12 Gy lungs if lung metastasis	n/a	Yes
	Diffuse anaplasia		Revised UH-2 (VCDBEI) 36 weeks	12 Gy lungs if lung metastasis	41.7 / 49.2 (59)	Yes

EFS – event-free-survival; OS – overall survival; CR – complete response; LOH – loss of heterozygosity; VA – vincristine, dactinomycin; VAD – vincristine, dactinomycin, doxorubicin; VADCE – vincristine, dactinomycin, doxorubicin, cyclophosphamide and etoposide; VCDBE – vincristine, carboplatin, doxorubicin, cyclophosphamide and etoposide; VCDBEI – vincristine, carboplatin, doxorubicin, cyclophosphamide, etoposide and irinotecan; Gy - Gray.

Table 2. Current treatment protocols and published outcomes according to SIOP (9)

Stage	Preoperative chemotherapy	Risk stratification	Postoperative chemotherapy	Radiotherapy	Outcomes 5-year EFS/OS % SIOP-2001	Gonadotoxicity potential / risk to fertility
I	AV 4 weeks	Low		None	n/a	Very low
		Intermediate^	AV1 4 weeks	None	n/a	Very low
		High	AVD 27 weeks	None	96/100 (137)	Very low
II	AV 4 weeks	Low	AV2 27 weeks	None	n/a	Very low
		Intermediate*^	AV2 / AVD^ 27 weeks	None	84.8 / 95.5 91.6 / 97.6 (138)	Very low
III	AV 4 weeks	Low	AV2 27 weeks	None	n/a	Very low
		Intermediate*^	AV2 / AVD^ 27 weeks	14.4 Gy to flank + 10.8 Gy boost (only in case of) gross disease or positive nodes	85.1 / 96.0 90.5 / 93.8 (138)	Possible depending on radiation fields.
II and III	AV 4 weeks	High	HR-1 (DCBE) 34 weeks	25.2 Gy to flank + 10.8 Gy boost (only in case of) gross disease or positive nodes	77 / 82 (137)	Yes
IV	AVD 6 weeks	Low: Lung CR No lung CR	AVD150/250 27 weeks HR-2 (DCBE) 34 weeks	No lung RT 15Gy lung	n/a n/a	Very low Yes
	AVD 6 weeks	Intermediate: Lung CR No lung CR	AVD150/250 27 weeks HR-2 34 weeks	No lung RT 15Gy lung + abdominal RT (see local stage I-III)	n/a n/a	Very low Yes
	AVD 6 weeks	High: Lung CR No lung CR	HR-2 34 weeks	No lung RT 15Gy lung + abdominal RT(see stage I-III)	n/a	Yes Yes

* non-epithelial and non-stromal post-chemotherapy nephrectomy histology; ^ with tumor volume > 500ml at diagnosis

EFS – event-free-survival; OS – overall survival; CR – complete response; AV1/AV2 – vincristine, dactinomycin; AVD – vincristine, dactinomycin, doxorubicin; AVD150/250 – vincristine, dactinomycin, doxorubicin (dose 150/250mg/m^2) HR-1/HR-2 (DCBE) – doxorubicin, cyclophosphamide, carboplatin, etoposide; Gy – Gray; RT - Radiotherapy.

Table 3. Cumulative Chemotherapy Doses per Treatment Regimen used by COG and the SIOP Renal Tumour study Group (SIOP-RTSG)

COG	**Cumulative Dose (mg/m^2 unless otherwise specified)**						
Chemotherapy Agent	**EE4A**	**DD4A**	**VAD†**	**Regimen M**	**Regimen I**	**Revised UH-1**	**Revised UH-2**
Vincristine	21	25	18	25	23	22.5	34.5*
Dactinomycin	0.315 mg/kg	0.225 mg/kg	0.18 mg/kg	0.145 mg/kg	0	0	0
Doxorubicin	0	150	140	195	225	225	225
Cyclophosphamide	0	0	0	8,800	15,400	14,800	14,800
Carboplatin	0	0	0	0	0	2,800	2,800
Etoposide	0	0	0	2,000	2,000	2,000	2,000
Irinotecan	0	0	0	0	0	0	800*
SIOP-RTSG							
	Pre-operative		***Post-operative***				
Chemotherapy Agent	**AV**	**AVD**	**AV-1**	**AV-2**	**AVD**	**HR**	
Vincristine	6	9	6	30	30	0	
Dactinomycin	0.09 mg/kg	0.135 mg/kg	0.045 mg/kg	0.405 mg/kg	0.405 mg/kg	0	
Doxorubicin	0	100	0	0	250^	250^	
Cyclophosphamide	0	0	0	0	0	8,100	
Carboplatin	0	0	0	0	0	3,600	
Etoposide	0	0	0	0	0	2,700	

*Including 2 cycles of vincristine and irinotecan given during the upfront window on the COG AREN0321 clinical trial.(139)
^Cumulative doxorubicin dose for both pre- and post-operative chemotherapy. † VAD is a preoperative regimen for bilateral Wilms tumor.
In Table 2 it is specified to which risk groups the regimens AV, AVD, AV-1, AV-2 and HR are given.

Table 4. Cumulative Radiotherapy Doses used by COG and SIOP RTSG

	Local Stage II	Local Stage III	Intra-abdominal dissemination	Macroscopic residual tumor	Lung metastasis
COG					
	DA: 1080cGy flank RT (6 fractions)	1080cGy flank RT (6 fractions) DA: 1980cGy flank RT	1050cGy WART		>12 mo: 1200cGy (8 fractions)^ <12 mo: 1050cGy (7 fractions)^
SIOP					
IR		14.4 Gy flank RT (8 fractions)	WART: 15 Gy (10 fractions)	Boost 10.8 Gy	12 Gy *
HR	DA: 25.2 Gy flank RT (14 fractions)	25.2 Gy flank RT (14 fractions)	WART: 19.5 Gy (13 fractions)	Boost 10.8 Gy	15 Gy

DA = Diffuse anaplastic type; RT = radiotherapy; WART = whole abdomen RT; IR = intermediate risk; HR = high risk; Gy = Gray; CR = complete response.

^ Exception: favorable histology + lung-only metastases (CR at week 6)

* IR (no CR after preoperative chemotherapy and/or metastasectomy)

Table 5. Infertility Risk per Treatment Regimen

Treatment Regimen	Female	Male	CED score (mg/m2)
COG Treatment Regimens			
Surgery only / Observation	Low Risk	Low Risk	0
EE4A	Low Risk	Low Risk	0
DD4A	Low Risk	Low Risk	0
Regimen M	High Risk	High Risk	8800
Regimen I ^	High Risk	High Risk	15400
Regimen Revised UH-1	High Risk	High Risk	14800
Regimen Revised UH-2	High Risk	High Risk	14800
SIOP-RTSG Treatment Regimens			
AV, AV-1, AV-2	Low Risk	Low Risk	0
AVD	Low Risk	Low Risk	0
HR	High Risk	High Risk	8100

^ currently only used for bilateral patients and for CCSK patients

CED = cyclophosphamide equivalent dose; EE4A: Regimen containing vincristine, dactinomycin; DD4A: Regimen containing vincristine, dactinomycin, doxorubicin; Regimen M: Regimen containing vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide; Regimen I: Regimen containing vincristine, doxorubicin, cyclophosphamide, etoposide; Regimen Revised UH-1: Regimen containing vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide; Regimen Revised UH-2: Regimen containing vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide, Irinotecan; AV, AV-1, AV2: Regimen containing vincristine, dactinomycin; AVD: Regimen containing vincristine, dactinomycin, doxorubicin; HR: high risk regimen.

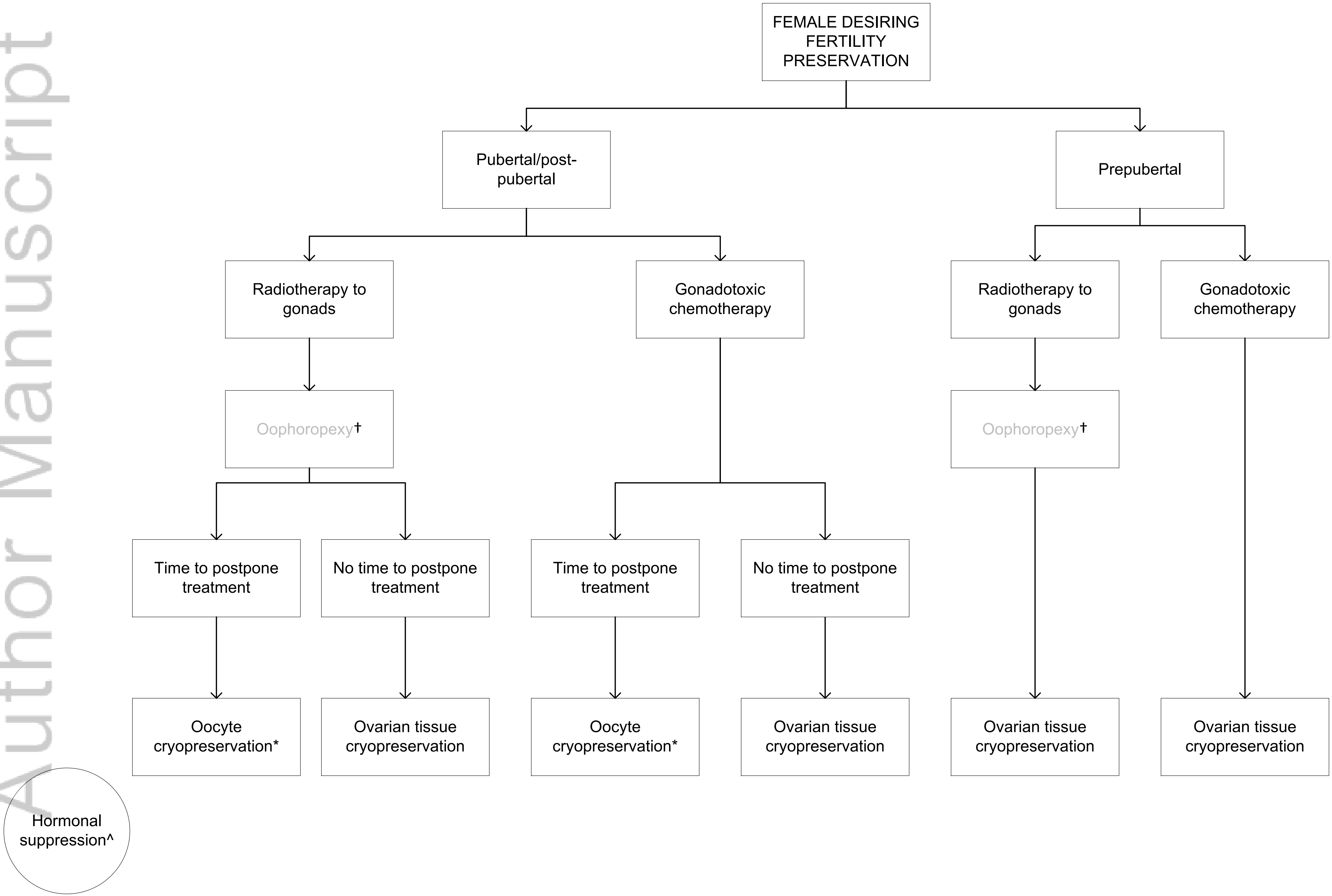
Table 6. Risk of Compromised Fertility Associated with Treatment Modality for Wilms Tumor, according to gender (adapted from Klipstein) (140)

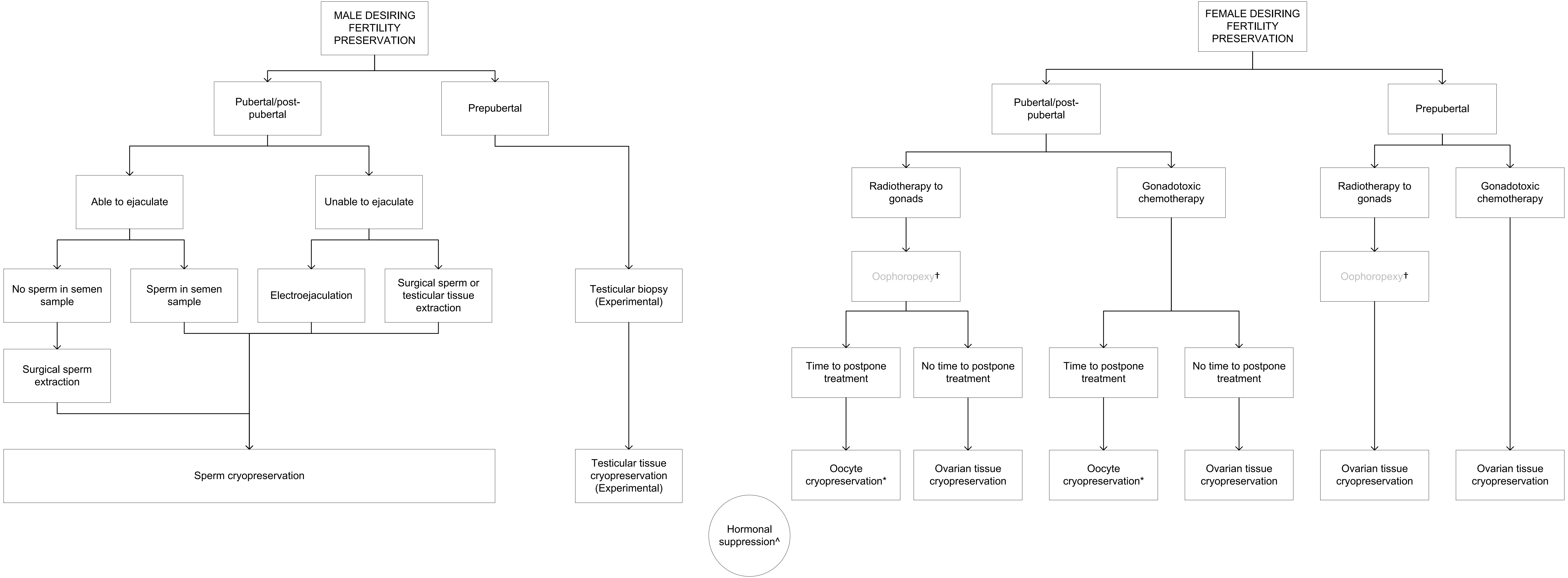
	Risk	Treatment predisposing to compromised fertility	Effect on reproduction

Female	High	• Alkylating-agent chemotherapy (Cyclophosphamide equivalent dose 6 g/m^2 in women and girls <20 year, Ifosfamide, Melphalan)(11)
		• Radiation affecting the female reproductive system (whole abdomen, pelvis, lumbosacral spine, total body)
		  • > 10 Gy in post-pubertal girls
		  • > 15 Gy in pre-pubertal girls
		• Oophorectomy
			Acute ovarian failure (ovarian failure within 5 years of diagnosis), premature menopause (cessation of menses before age 40 years)

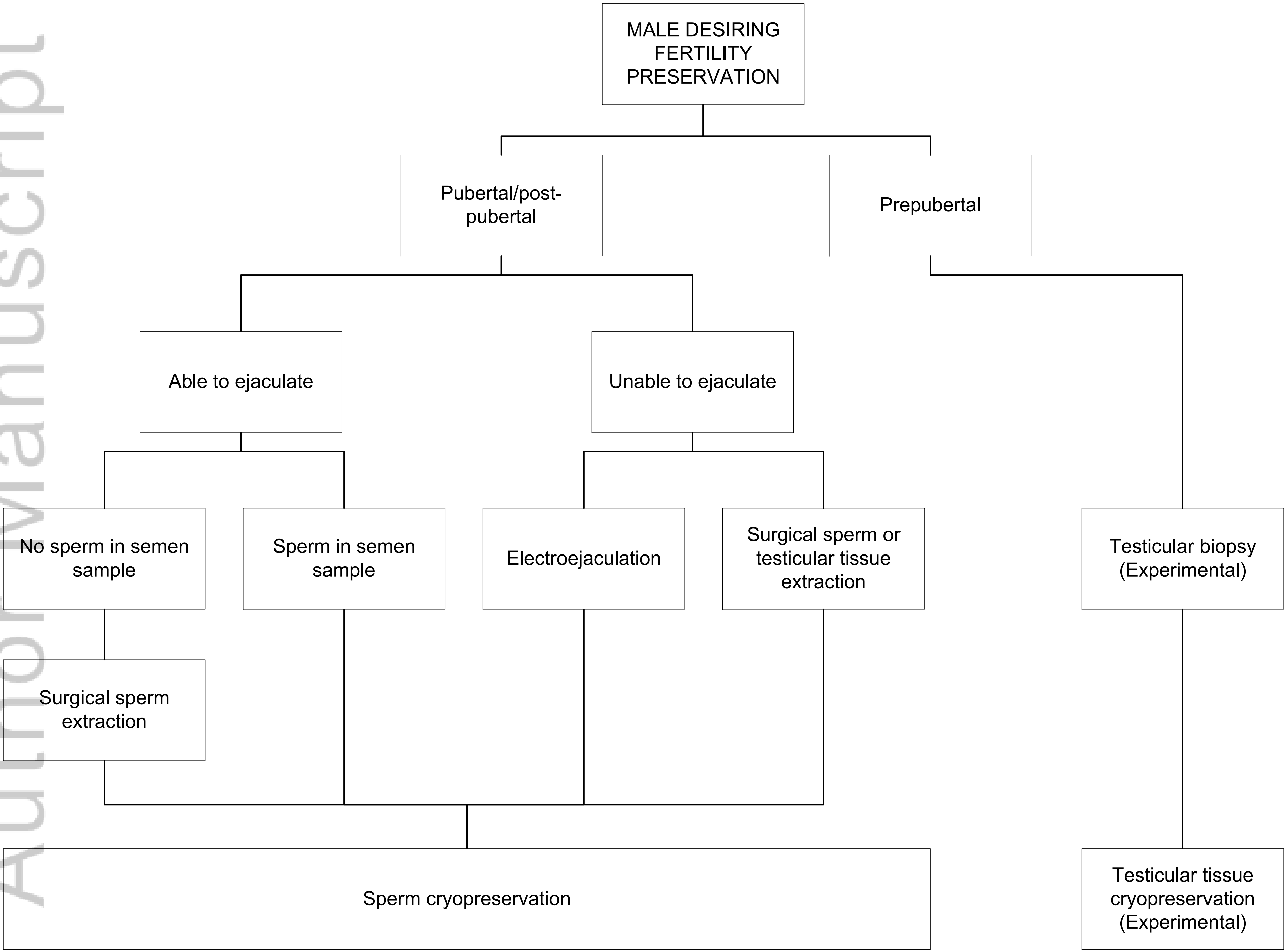
	Intermediate	Radiation affecting the uterus (whole abdomen, pelvis, lumbosacral spine, total body)	Uterine vascular insufficiency, uterine growth impairment. Spontaneous abortion, neonatal death, premature labor, neonate with low birth weight, fetal malposition
Male	High	• Alkylating-agent chemotherapy (Cyclophosphamide equivalent dose 4 g/m^2, Ifosfamide, Melphalan)(10) • Pelvic radiation affecting the male reproductive system (1-6 Gy scatter to testes)	Azoospermia, oligospermia
	Intermediate	• Pelvic surgery (retroperitoneal node or tumor dissection, cystectomy) • Radiation to pelvis, bladder, or spine (1-6 Gy scatter to testes) • Chemotherapy with heavy metals: carboplatin >2 g/m^2	Retrograde ejaculation, anejaculation Erectile dysfunction Azoospermia, oligospermia

Wilms tumor (WT), a childhood kidney cancer, has a survival rate of around 90%. Because most patients survive to reproductive age, treatment decisions must take into account the risk of gonadal damage. Here, the authors present an overview of the evidence regarding the future fertility after WT treatment, collected through a global collaboration between Children's Oncology Group (COG) and Societe Internationale D'oncologie Pediatrique (SIOP). They describe options for fertility preservation as well as ethical and genetic considerations. Consultation with a fertility preservation team, they found, was associated with decreased patient and family regret and better quality of life.


FEMALE DESIRING FERTILITY PRESERVATION
Pubertal/post-pubertal
Prepubertal
Radiotherapy to gonads
Gonadotoxic chemotherapy
Radiotherapy to gonads
Gonadotoxic chemotherapy
Oophoropexy†
Oophoropexy†
Time to postpone treatment
No time to postpone treatment
Time to postpone treatment
No time to postpone treatment
Oocyte cryopreservation*
Ovarian tissue cryopreservation
Oocyte cryopreservation*
Ovarian tissue cryopreservation
Ovarian tissue cryopreservation
Ovarian tissue cryopreservation
Hormonal suppression^



† Only in selected cases receiving abdominal radiotherapy (RT) with an ovary in the RT field
* In rare cases, older patients with a partner may want to opt for embryo cryopreservation. However, for most Wilms tumor patients this will not be an option.
^ Currently, no strong evidence exists that hormonal suppression has a protective effect on gonadal damage in children. However, it can be used in addition to other fertility preservation methods.


MALE DESIRING FERTILITY PRESERVATION
Pubertal/post-pubertal
Prepubertal
Able to ejaculate
Unable to ejaculate
No sperm in semen sample
Sperm in semen sample
Electroejaculation
Surgical sperm or testicular tissue extraction
Testicular biopsy (Experimental)
Surgical sperm extraction
Sperm cryopreservation
Testicular tissue cryopreservation (Experimental)