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Fertility Preservation in Pediatric Solid Tumors: A Report from the Children's Oncology Group

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Abstract

Treatment for childhood solid tumors may lead to an increased risk for gonadal dysfunction/infertility. Discussion of risk should occur at diagnosis, any changes in therapy, and during survivorship. Gonadotoxic therapies were abstracted from 32 Children's Oncology Group (COG) phase III, frontline solid tumor protocols, in use from 2000-2022. Risk for gonadal dysfunction/infertility was assessed based on gonadotoxic therapies, sex, and pubertal status and assigned as *minimal*, *significant*, and *high* following the Oncofertility Consortium Pediatric Initiative Network (PIN) risk stratification. Most protocols (65.6%, 21/32) contained at least one therapeutic arm with a *high* level of increased risk. Solid tumor therapies present challenges in risk stratification due to response-adjusted therapy and the need to account for radiation field in the risk assessment. This guide hopes to serve as a tool to assist in standardizing gonadotoxic risk assessments across disciplines and improve referral for fertility services and reproductive health counseling for patients receiving COG based solid tumor therapy. Internationally, many solid tumor therapies follow similar paradigms to COG studies, and risk stratifications may be generalizable to similar styles of therapy. In addition, this model may be applied to other international groups with the goal of standardizing fertility assessments.

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Keywords

Oncofertility; fertility preservation; solid tumors

Introduction

Cancer directed therapy may have adverse long-term effects on the health of patients diagnosed with malignancies as children, adolescents, and young adults, including gonadotoxicity and infertility^{1,2}. Gonadal late effects occur through multiple mechanisms secondary to various treatment exposures with chemotherapy, radiation, and surgery. Chemotherapy exposure to alkylating agents and heavy metals are known to damage gonads through a dose dependent relationship, in which they impair DNA synthesis, causing cell death³⁻⁶. Radiation therapy to either the gonads^{1,7} (ovarian tissue in females and testicular tissue in males) or the hypothalamus⁸ can lead to direct damage to gonadal tissue or disruption of hormonal signaling, respectively, impairing normal physiologic functions.

Due to the gonadotoxic risks of therapy, multiple national and international cancer organizations, including the American Society of Clinical Oncology (ASCO), American Society of Reproductive Medicine (ASRM), European Society for Medical Oncology (ESMO), European Society for Paediatric Oncology (SIOPE), American Academy of Pediatrics (AAP), and the National Comprehensive Cancer Network (NCCN), suggest that fertility risk counseling should occur for all patients at the time of diagnosis and continue through survivorship, and that those interested should be referred for fertility preservation⁹⁻¹⁴, including ovarian stimulation and oocyte retrieval, ovarian tissue cryopreservation (OTC), testicular tissue cryopreservation (TTC), currently an experimental technology^{15,16}, and sperm cryopreservation. We have previously summarized gonadotoxic risk for leukemia and lymphoma protocols from the COG¹⁷. Due to the complexity of treatment for many solid tumors, such as exposure to more than one gonadotoxic chemotherapy agent or multiple treatment modalities, risk assessments for gonadotoxicity can be challenging and we present a summary of those protocols in this manuscript. Some treatment protocols may be modified based on treatment response, resulting in an inability to fully characterize risk for gonadal damage at the time of diagnosis. This requires expertise to understand an individual patient's treatment-related risk for gonadotoxicity, a necessity if one is to counsel patients and families regarding fertility preservation options. Fertility preservation programs vary between institutions and may have team members from multiple disciplines, including oncology, endocrinology, obstetrics and gynecology, reproductive endocrinology, and psychology. Historically, due to the wide variability in expertise, as well as a lack of a common language for the assessment of risk, there has been difficulty in comparing patient outcomes and practices across programs. In 2020, the Pediatric Initiative Network (PIN) of the Oncofertility Consortium brought together 27 clinicians and researchers from 15 institutions to create a consensus regarding the levels of treatment related gonadotoxic risk to aid in the standardization of risk level and allow for research¹⁸. Treatment exposures included in this risk schema were selected from the literature¹⁹⁻²¹, and include alkylator and heavy metal therapy, radiation to the hypothalamus and ovarian or testicular tissue, hematopoietic stem cell transplant and some forms of

genitourinary surgery. Risk levels were defined as *minimally increased risk*, *significantly increased risk*, and a *high level of increased risk*, with specific cut points based on sex and pubertal status (Figure 1).

The Children's Oncology Group (COG) is an international network of over 200 children's hospitals and cancer centers across North America, Australia, and New Zealand. COG institutions treat approximately 90% of pediatric patients diagnosed with cancer in the United States and most of these patients in the United States will be treated as part of an open COG clinical trial, or as per a closed COG protocol²². Given that the expertise of providers who counsel patients about future infertility may not be specifically in oncology, there may be challenges in interpreting COG roadmaps. Additionally, some providers are not familiar with the risk stratification system, making the level of risk for various COG protocols difficult to discern across team members and institutions. For this reason, we reviewed frontline Phase III COG Solid Tumor protocols instituted between 2000 and 2022 to assess gonadotoxic risk from planned therapy on each treatment arm. We aim to provide a comprehensive guide in gonadotoxic risk categorization for pediatric and adolescent patients diagnosed with solid tumors to be used to aid in the counseling of patients regarding gonadotoxicity of therapy and fertility preservation.

MATERIALS AND METHODS

Data abstraction

Phase III, new diagnosis solid tumor treatment protocols from 2000-2022 were identified using the COG members' website. Protocols were divided into bone tumors (Ewing sarcoma and osteosarcoma), hepatic and renal tumors, soft tissue sarcomas, neuroblastoma, germ cell tumors, rare tumors, and retinoblastoma. Protocols were evaluated for gonadotoxic therapies (alkylating agents, heavy metals, hematopoietic stem cell transplant (HSCT) or hypothalamic or gonadal radiation) and cumulative alkylating agent dose was calculated based on the planned alkylator therapy and converted to cyclophosphamide equivalent dosing (CED)²¹. Dosing in mg/m² was utilized for risk stratification, and any dosing in mg/kg was converted to mg/m² using the 30-rule²³. Relapsed trials, pilot studies, ancillary studies not containing chemotherapy, and phase I-II studies were excluded¹⁷. Two phase III therapeutic trials for melanoma were also excluded, as they were coordinated by study groups other than the COG. All data was reviewed and abstracted by two authors, while a third author was utilized to evaluate and resolve any discrepancies. Individual treatment arms listed in the protocols along with specific permutations in therapy are outlined in Tables 1-5.

Risk assignment

Similar to prior published reports¹⁷, risk levels (*minimal*, *significant* or *high*) were assigned by two separate authors based on the previously published PIN Risk Stratification System (Figure 1) for prepubertal females, pubertal females, and males¹⁸. Any discrepancies in risk assignment were resolved through team consensus. High risk therapy includes treatment that exceeds a CED of 4 g/m² in males, 8 g/m² in pubertal females, 12 g/m² in prepubertal females or any hematopoietic stem cell transplant (myeloablative or reduced intensity)

containing at least one alkylating agent or total body irradiation (TBI). High risk therapy also includes gonadal radiation exposure (direct or indirect) ≥ 15 Gy in prepubertal females, ≥ 10 Gy in pubertal females and ≥ 4 Gy in males or hypothalamic radiation of ≥ 40 Gy in both males and females. Surgery to remove a single gonad was not included as a gonadotoxic risk factor in the risk schema, however, it may impact a patient/family's desire for fertility preservation or for preservation modality, particularly if in combination with other gonadotoxic therapies. Additionally, the level of risk is based on chemotherapy alone, however, additional additive risk from radiation exposure may be conferred depending on radiation field, dose and modality. Patient regimens without one of the gonadotoxic exposures listed in the PIN Risk Stratification System were considered unlikely to place patients at risk for gonadal dysfunction/infertility²⁴.

RESULTS

In total, data from 32 protocols with 107 treatment arms were reviewed. Overall, 65.6% (21/32) of solid tumor protocols had at least one patient group in a treatment arm that potentially placed patients at *high* risk. Males were most commonly at *high* risk, with at least one *high* risk treatment arm in 21/32 protocols (65.6%), followed by pubertal females with at least one *high* risk treatment arm in 19/32 protocols (59.4%) and prepubertal females with at least one *high* risk treatment arm in 17/32 protocols (53.1%) (Supplemental Figure 1).

Bone Tumors

Altogether, four Ewing sarcoma and one osteosarcoma protocol, with 13 arms, were reviewed (Table 1). All bone tumor protocols (5/5) included at least one *high* risk arm for both males and females. In one osteosarcoma protocol (AOST0331), two of the three arms (66.7%) conferred a *minimal* level of risk to all three patient and gender/puberty groups while the other arm was *high* risk for all three groups. The CED range for bone tumor protocols was 0 g/m² – 28.4 g/m². In addition, all Ewing sarcoma protocols carry the additional possibility of radiation therapy. This could confer an additional risk factor for future infertility/gonadal dysfunction depending on whether the gonad or hypothalamus were in the treatment field.

Hepatic and Renal Tumors

We reviewed two hepatic tumor and three renal tumor protocols with a total of 28 treatment arms (18 hepatic, 10 renal; Table 2). There were no hepatic tumor protocol arms containing alkylating agents, however, 7/18 (38.9%) contained heavy metals at doses reaching a potentially significant impact among male patients. Most arms conferred *minimal* risk to females and radiation is not expected to be a modifier in hepatic tumor protocols.

Unlike hepatic tumor treatment protocols which did not use radiation, all three renal protocols recommend radiation treatment for certain subsets of patients, which may modify risk. Only 3/10 arms (30%) contained alkylating agents, all at doses that put both males and pubertal females at *high* risk. For the remaining arms, most patients were unlikely to be at risk unless modified by radiation dose and field.

Soft Tissue Sarcomas

We reviewed 7 soft tissue sarcoma protocols subdivided into 21 arms (Table 3). All protocols have at least one arm conferring *high* risk for males. Most protocols have at least one arm that met the threshold for *high* risk for prepubertal females (5/7; 71.4%) and pubertal females (6/7; 85.7%). The CED range among protocols was 0g/m² – 21.8g/m². Two protocols, ARST0332 and ARST0431, have a range of alkylating agent dose for patients less than 1 year of age due to variability in number of cycles and total dose secondary to chemotherapy tolerability. All arms in all protocols have potential for radiation therapy for local control which could modify risk, depending on dose delivered and radiation field.

Neuroblastoma

Neuroblastoma patients were treated on 6 protocols with 21 treatment arms. Of the 6 protocols, all (100%) have at least one treatment arm that may put male patients at *high* risk. Five protocols (83.3%) have at least one arm that puts both prepubertal and pubertal females at *high* risk. ANBL0032 and ANBL0931 are both protocols that contained additional therapy to follow up-front high-risk neuroblastoma therapy. While they themselves, do not contain alkylating agent therapy or direct radiation, patients enrolled on these studies must have received prior upfront therapy that conferred *high* risk status across males and females. Furthermore, ANBL0531 and ANBL1232 have treatment arms that deliver a range of alkylating agent dose depending on treatment response, conferring risk to patients (male, pubertal and prepubertal females) ranging from *minimal* to *high*. The CED range across protocols is 0 g/m² – 66.2 g/m², with two protocols (ANBL0532, ANBL1531) which also include radiation, potentially contributing further gonadotoxic risk.

Germ Cell Tumors, Rare Tumors and Retinoblastoma

Three germ cell tumor protocols and two rare tumor protocols were reviewed (Table 5). Among germ cell studies, no arms met the threshold for *high* level of risk for males or females. Only one arm of one protocol (AGCT0132) included chemotherapy that was higher than *minimal* risk, with a range of cisplatin dosing (300-600 mg/m²) that could confer a *significant* risk to males, depending on the total number of cycles. Only one protocol, AGCT1532, employs the use of alkylating agents, however, the dose does not rise above *minimal* risk for males or females (Table 5). Unique to germ cell tumor treatment, all studies may include the surgical removal of one or both gonads, which was not directly calculated in gonadotoxic risk¹⁸.

Rare tumors, including nasopharyngeal carcinomas and adrenocortical tumors, were represented with two protocols. Only one of two protocols contained a single arm with therapy that could reach *significant* risk for males (ARAR0332). No alkylating agents are planned in protocol therapy, and any increase in risk from chemotherapy is due to cisplatin use. Of note, ARAR0331 is the only protocol that includes radiation that may increase risk secondary to hypothalamic exposure (Table 5).

We reviewed four retinoblastoma protocols with 8 arms. One out of the 4 protocols (25%) have at least one arm that puts prepubertal females, pubertal females, and male patients

at *high* risk (ARET0321). All protocols use heavy metals with carboplatin, but only one, ARET0321, uses alkylating agents or cisplatin. The CED range is 0 g/m² – 60.6 g/m².

DISCUSSION

While we found that based on the PIN risk stratification system from the Oncofertility Consortium that there was a range of risk levels across COG protocols, a significant proportion of studies contained at least one arm conferring a high level of risk to female patients (17/32 or 53.1% prepubertal and 19/32 or 59.4% of pubertal) and male patients (21/32 or 65.6%). Compared to our prior report on leukemia/lymphoma protocols¹⁷, solid tumor protocols were more likely to deliver therapy in the *high* gonadotoxic risk category to all sex/pubertal groups, and the total dose of alkylating agents was substantially higher across solid tumor protocols. If considering the highest possible CED among protocol arms containing alkylating agents, the average CED dose among solid tumor protocols is 20.9 g/m², with a maximum of 70.6 g/m², compared to 4 g/m², with a maximum of 13.2 g/m² among leukemia/lymphoma protocols. Unlike differences in the number of *high* gonadotoxic risk protocols between sex and pubertal groups in leukemia/lymphoma, there was less variation among sex/pubertal groups, mostly secondary to the very high alkylating doses that conferred *high* levels of risk to all groups.

This information may assist individual programs to prioritize fertility consults among diagnostic groups. Among solid tumor diagnoses, protocols for patients with sarcomas, including both those of bone and soft tissues, are the most likely to receive therapy with a *high* gonadotoxic risk. In addition, over half (18/32 or 56.2%) of all solid tumor protocols may involve radiation therapy as part of treatment. These characteristics make patients with solid tumors an important group of patients to offer risk counseling and options for fertility preservation, when available. This counseling should occur at multiple time points from diagnosis to survivorship, as many solid tumor protocols involve risk-adapted or response-based therapy. Thus, the total CED and/or radiation fields may not be available at the time of initial consult as protocol-driven treatment will change based on tumor response. This is further illustrated in the example below.

Solid tumor therapies have several particularities that can make accurate gonadotoxic risk prediction challenging. Some characteristics that necessitate consideration are response-based treatments, particularly those seen in some neuroblastoma protocols. Take for example in ANBL0531²⁵, a protocol for intermediate risk neuroblastoma, there is a range of cumulative alkylator dose patients may receive (Table 4). A patient stratified into group 2 based on age and biologic features may receive a cumulative alkylator dose between 1-12.55 mg/m² CED, dependent upon the total number of cycles of chemotherapy required. The decision to give additional chemotherapy cycles is dependent on the individual patient response to therapy and is difficult to predict at diagnosis. This requires both that the original discussion regarding gonadotoxicity encompass all possible risk levels to allow for an informed decision regarding fertility preservation, and that repeated conversations occur with the patient/family as the addition of chemotherapy cycles modify that risk. Not only is this important for patient/family knowledge, but changes in the cumulative dose of therapy delivered may alter decisions regarding fertility preservation. Both OTC and TTC can be

performed after patients have received some therapy and could be offered if a patient's risk level increases due to the response-based treatment plan. Outcomes of ovarian tissue collected after exposure to chemotherapy is limited, however promising²⁶. Centers may vary regarding how much previous exposure they deem acceptable prior to OTC. All TTC procedures should be performed under an IRB approved protocol, and will include guidance regarding when, and to whom, a procedure can be performed.

There may be additional considerations for patients treated off study when patients are taken off study due to toxicities requiring alterations in the proposed therapy that may change risk prediction, or to allow for the addition of other chemotherapeutic agents. For example, the addition of vinorelbine/cyclophosphamide maintenance has become more commonly used in patients undergoing therapy for rhabdomyosarcoma but is not included in the original protocol²⁷.

Unique to the treatment of solid tumor diagnoses is the need for abdominopelvic surgery in some settings, including unilateral gonadectomy, as well as retroperitoneal lymph node dissection (RPLND). Unilateral oophorectomy alone has not been shown to significantly contribute to premature ovarian insufficiency or menopause prior to the age of 40 years^{28,29}. In a cohort of men with a single testis, there were not significant differences in sperm parameters³⁰, and similarly, in young men with testicular germ cell tumors, there was not a significant difference in semen parameters pre- and post-orchietomy³¹. In addition, there have been other reports showing abnormal semen parameter prior to orchietomy for testicular germ cell tumor³² and improvement of semen parameters after the orchietomy³³. Other surgical interventions include RPLND, which may not interfere with male fertility by inhibiting spermatogenesis, but can lead to retrograde ejaculation, even with modern nerve-sparing techniques^{34,35}. Due to uncertainties in the clinical course for these patients, we recommend sperm banking ahead of any treatment for all males who are interested and able to do so. For those pubertal males whose testes are mature enough to produce sperm but are unable to produce an adequate semen sample for banking secondary to ejaculatory or other disorders, consideration should be made for other ways of collecting a sample, pre or post therapy. This includes urine collection in retrograde ejaculation³⁶, or other techniques including testicular sperm aspiration (TESA) or testicular sperm extraction (TESE) with or without microdissection³⁷.

Consideration must be given to radiation therapy, as the field and dose may alter the risk estimate and is additive to chemotherapy exposures. Knowledge of how radiation therapy may affect gonadal tissue is vital to offering appropriate fertility preservation options. For example, consider a female patient with an abdominopelvic Ewing sarcoma treated per AEWS0331 regimen B, who is ill and not able to delay therapy to undergo ovarian stimulation and oocyte retrieval, yet is facing a high risk of gonadal dysfunction/infertility secondary to high doses of alkylating agents, and in addition will also receive radiation that is proposed to affect ovarian tissue on only one side. As radiation therapy results in more immediate gonadal failure, a possible recommendation for fertility preservation may be OTC with single oophorectomy on the side of radiation, prior to the start of radiation therapy and incurring radiation tissue damage. When considering the gonadotoxic effects of proton vs photon therapy the field of exposure is most important. Proton therapy is not less

toxic to the gonadal tissue than photon therapy. Rather, the radiation field is more focused resulting in less “scatter”/off target gonadal exposure. For any radiation therapy focused on or near gonadal tissue it is important to discuss with radiation oncology. They will be able to calculate the radiation exposure specific to the gonadal tissue and may recommend gonadal shielding, transposition of the ovary or orchiopexy to limit gonadal exposure. This dose (regardless of photon vs proton) can then be factored into gonadotoxic risk calculation.

Importantly, discussions regarding gonadotoxic risk need to continue into and throughout survivorship as survivors age and developmentally mature such that they can understand the information more completely³⁸⁻⁴¹. Given that over 50% of protocols will put females at a significant or high risk for future gonadal dysfunction or infertility, on-going conversations are imperative as there may be a window of time for the ability to intervene post-therapy. Take, for example, a 20-year-old female survivor treated with ARST0531 therapy at 5 years of age. She received therapy that placed her at *high* risk of gonadal dysfunction/infertility and did not undergo any fertility preservation prior to chemotherapy. She is now thinking of starting a family in the future and interested in learning more about fertility preservation options. There may be the opportunity to freeze oocytes now, prior to the onset of premature ovarian insufficiency. For this patient who is a survivor of childhood cancer, there may be the opportunity to undergo ovarian stimulation and oocyte cryopreservation at age 20, prior to her ovarian reserve being completely diminished. This requires an organized approach by oncology, gynecology, reproductive endocrinology, and survivorship teams as to not miss these patients who may still have a window to undergo fertility preservation post-therapy. Equally important to all groups of patients, is counseling regarding contraception use to prevent an unwanted pregnancy as the risk of gonadal dysfunction and future risk of premature ovarian insufficiency may be confused with current infertility.

Solid tumor treatment has been evolving to include newer, more targeted agents, including monoclonal antibodies, tyrosine kinase or multi-kinase inhibitors, and others, which may have off-target effects including gonadotoxicity. While these therapies may improve therapeutic outcomes and lead to less acute toxicity, there is a paucity of data regarding long-term outcomes in pediatric patients, including infertility and gonadotoxicity. There is opportunity here to include gonadotoxic outcomes in future COG protocols to specifically address these questions moving forward. Currently, therapies that includes newer, immune-based, or targeted agents carry unknown risks of gonadotoxicity.

CONCLUSIONS

We hope this article can serve as a reference to standardize risk counseling in patients who are undergoing COG-based therapy for solid tumors and can be used across the continuum of care, from diagnosis to survivorship. We recommend that all patients are offered fertility risk counseling prior to the initiation of therapy, and that it encompasses the potential range of gonadotoxicity based on proposed treatment. When this is not feasible and consults must be triaged, we recommend prioritizing those who are at significant or high risk. Males, especially those at high risk, should be counseled regarding options for sperm cryopreservation or TTC. Females who are at significant or high risk should be counseled regarding their options for oocyte/embryo cryopreservation both before and after

therapy. They should also be counseled regarding OTC. Although certainly not guaranteed, survivors may have opportunities for fertility preservation post-therapy, which underscores the importance of on-going conversations post therapy and into survivorship. COG Phase III leukemia and lymphoma protocols have been published¹⁷ and we are currently working on similarly stratifying the COG Phase III neuro-oncology protocols. It is our hope that in the future, these risk stratifications will be imbedded into research protocols further reducing the barriers to fertility preservation and that a similar model can be employed throughout other international cooperative groups to allow for more uniform risk stratification and risk counseling globally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

COG	Children's Oncology Group
PIN	Pediatric Initiative Network
ASCO	American Society of Clinical Oncology
ASRM	American Society of Reproductive Medicine
ESMO	European Society for Medical Oncology
SIOPE	European Society for Paediatric Oncology
AAP	American Academy of Pediatrics
NCCN	National Comprehensive Cancer Network
OTC	Ovarian tissue cryopreservation
TTC	Testicular tissue cryopreservation
TBI	Total body irradiation
CED	cyclophosphamide equivalent dosing
HSCT	hematopoietic stem cell transplant
TBI	Total body irradiation
RPLND	Retroperitoneal lymph node dissection
TESA	Testicular sperm aspiration

TESE	Testicular sperm extraction
IRB	Institutional Review Board

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(A)

Female Risk Chart			Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED gm/m ²	Prepubertal		CED < 8	CED 8-12	CED > 12
	Pubertal		CED < 4	CED 4-8	CED > 8
Heavy Metal mg/m ²			Cisplatin Carboplatin		
Hematopoietic Stem Cell Transplant					Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Radiation Exposure	Ovary	Prepubertal		< 15 Gy	≥ 15 Gy
		Pubertal		< 10 Gy	≥ 10 Gy
	Hypothalamus		22-29.9 Gy	30-39.9 Gy	≥ 40 Gy

(B)

Male Risk Chart			Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED gm/m ²			CED < 4		CED ≥ 4
Hematopoietic Stem Cell Transplant					Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Heavy Metal mg/m ²			Cisplatin Carboplatin	Cisplatin > 500	
Radiation Exposure	Testicular		0.2-0.6 Gy	0.7-3.9 Gy	≥ 4 Gy
	Hypothalamic		26-29.9 Gy	30-39.9 Gy	≥ 40 Gy
	Surgery			RPLND	

Figure 1. Level of risk for gonadal failure/infertility above that of the general population: (A) female risk level; (B) male risk level. Reprinted with permission. CED: Cyclophosphamide equivalent dosing; RPLND: Retroperitoneal lymph node dissection

Table 1.

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Bone Tumors: Ewing Sarcoma and Osteosarcoma

Protocol and Therapy Arms	Gonadotoxic Therapy			Level of Risk for Future Infertility/Gonadal Dysfunction [^]		
	Alkylator (CED g/m ²)	Cisplatin (mg/m ²)	Rads	Prepubertal Females	Pubertal Females	Males
AEWS0031						
Regimen A Radiation OR surgery	23.8	0	*	high **	high **	high **
Regimen A Radiation + surgery	23.8	0	*	high **	high **	high **
Regimen B Radiation OR surgery	23.8	0	*	high **	high **	high **
Regimen B Radiation + surgery	23.8	0	*	high **	high **	high **
AEWS0331						
VAI	24.9	0	*	high **	high **	high **
Busulfan-Melphalan	25.5	0	*	high **	high **	high **
AEWS1031						
Regimen A	28.4	0	*	high **	high **	high **
Regimen B	27.6	0	*	high **	high **	high **
AEWS1221						
Regimen A	23.8	0	*	high **	high **	high **
Regimen B	23.8	0	*	high **	high **	high **
AOST0331						
MAP	0	480		minimal	minimal	minimal
MAPIE	14.6	480		high	high	high
MAPIfn	0	480		minimal	minimal	minimal

CED – cyclophosphamide equivalent dose; VAI – vincristine, actinomycin D, ifosfamide; MAP – methotrexate, adriamycin, cisplatin; MAPIE – methotrexate, Adriamycin, cisplatin, ifosfamide, etoposide; MAPIfn – methotrexate, adriamycin, cisplatin, interferon alpha

[^] Level of Risk is defined as minimal, significant, high level of increased risk (see Figure 1) or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines

* Radiation dose varies based on tumor site, plan. If radiation field includes gonadal tissue or hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1)

** Patients are considered high risk based on chemotherapy alone, however, additional additive risk may be conferred by radiation depending on radiation field, dose, and modality of radiation

Table 2.

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Hepatic and Renal Tumors

Protocol and Therapy Arms	Gonadotoxic Therapy			Rads	Level of Risk for Future Infertility/Gonadal Dysfunction [^]		
	Alkylator (CED g/m ²)	Cisplatin (mg/m ²)	Carbo~ (Yes)		Prepubertal Females	Pubertal Females	Males
AHEP0731							
VLR-Stratum 1	0	0			unlikely	unlikely	unlikely
LR-Stratum 2	0	200			minimal	minimal	minimal
IR-Stratum 3	0	600			minimal	minimal	significant
HR-Stratum 4	0	600			minimal	minimal	significant
AHEP1531							
Group A1	0	0			unlikely	unlikely	unlikely
Group A2	0	200			minimal	minimal	minimal
Group B1 Arm4	0	320			minimal	minimal	minimal
Group B1 Arm6	0	480			minimal	minimal	minimal
Group B2	0	480			minimal	minimal	minimal
Group C Arm CDDP	0	600			minimal	minimal	significant
Group C Arm C5VD	0	600			minimal	minimal	significant
Group D1	0	630	Yes		minimal	minimal	significant
Group D Arm CE	0	630	Yes		minimal	minimal	significant
Group D Arm VI	0	630	Yes		minimal	minimal	significant
Group E1	0	0			unlikely	unlikely	unlikely
Group E2	0	320			minimal	minimal	minimal
Group F Arm PLADO	0	240-480 [†]			minimal	minimal	minimal
Group F Arm GemOx	0	320			minimal	minimal	minimal
AREN0532							
VLR	0	0		*	unlikely [‡]	unlikely [‡]	unlikely [‡]
SR	0	0			unlikely	unlikely	unlikely
SR+radiation	0	0		*	unlikely [‡]	unlikely [‡]	unlikely [‡]
AREN0533							
Regimen DD-4A	0	0			unlikely	unlikely	unlikely
Regimen M	8.8	0		*	significant [‡]	high ^{**}	high ^{**}
AREN0534							
Regimen EE-4A	0	0			unlikely	unlikely	unlikely
Regimen DD-4A	0	0		*	unlikely [‡]	unlikely [‡]	unlikely [‡]
Regimen VAD	0	0		*	unlikely [‡]	unlikely [‡]	unlikely [‡]
Regimen I	11.9	0		*	significant [‡]	high ^{**}	high ^{**}
Regimen UH-1	14.8	0	Yes	*	high ^{**}	high ^{**}	high ^{**}

CED – cyclophosphamide equivalent dosing; Carbo – carboplatin (risk is not stratified by dose); Rads – radiation therapy; VLR – very low risk; LR – low risk; IR – intermediate risk; HR – high risk; CDDP – cisplatin; C5VD – cisplatin, doxorubicin, 5-fluorouracil, vincristine; CE –

carboplatin, etoposide; VI – vincristine, irinotecan; PLADO – cisplatin, doxorubicin; GemOx – gemcitabine/oxaliplatin; DD-4A – vincristine, doxorubicin, dactinomycin; M – vincristine, doxorubicin, dactinomycin, cyclophosphamide, etoposide; EE-4A – vincristine, dactinomycin; VAD – vincristine, doxorubicin; I – vincristine, doxorubicin, cyclophosphamide, etoposide, UH-1 – vincristine, doxorubicin, carboplatin, cyclophosphamide, etoposide

[^] Level of Risk is defined as minimal, significant, high level of increased risk (see Figure 1) or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines

[~] Carboplatin is not risk stratified by dose

^{*} Radiation dose varies based on tumor site, plan. If radiation field includes gonadal tissue or hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

^{**} Patients are considered high risk based on chemotherapy alone, however, additional additive risk may be conferred depending on radiation field, dose, and modality of radiation

[†] Final cumulative dose varies based on total number of cycles and/or dose modifications due to tolerability

[‡] Level of risk not high based on cumulative chemotherapy but risk may be increased due to radiation depending on radiation site, plan (see Figure 1).

Table 3.

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Soft Tissue Sarcomas

Protocol and Therapy Arm	Gonadotoxic Therapy			Level of Risk for Future Infertility/Gonadal Dysfunction [^]		
	Alkylator (CED g/m ²)	Cisplatin (mg/m ²)	Rads	Prepubertal Females	Pubertal Females	Males
ARST0331						
Regimen A	4.8	0	*	minimal [†]	significant [†]	high ^{**}
Regimen B	4.8	0	*	minimal [†]	significant [†]	high ^{**}
ARST0332						
Arm A	0	0		unlikely	unlikely	unlikely
Arm B	0	0	*	unlikely [†]	unlikely [†]	unlikely [†]
Arm C						
Age <1 year	6.6-11.5 [†]	0	*	min-sig [†]	--	high ^{**}
Age ≥/ = 1 year	13.2	0	*	high ^{**}	high ^{**}	high ^{**}
Arm D						
Age <1 year	6.6-11.5 [†]	0	*	min-sig [†]	--	high ^{**}
Age ≥/ = 1 year	13.2	0	*	high ^{**}	high ^{**}	high ^{**}
ARST0431						
HR						
Age <1 year	16.3-21.8 [†]	0	*	high ^{**}	--	high ^{**}
Age ≥/ = 1 year	21.8	0	*	high ^{**}	high ^{**}	high ^{**}
ARST0531						
Regimen A	16.8	0	*	high ^{**}	high ^{**}	high ^{**}
Regimen B	8.4	0	*	significant [†]	high ^{**}	high ^{**}
ARST1321						
Regimen A	10.98	0	*	significant [†]	high ^{**}	high ^{**}
Regimen B	10.98	0	*	significant [†]	high ^{**}	high ^{**}
Regimen C	0	0	*	unlikely [†]	unlikely [†]	unlikely [†]
Regimen D	0	0	*	unlikely [†]	unlikely [†]	unlikely [†]
ARST1431						
Regimen A	12.6	0	*	high ^{**}	high ^{**}	high ^{**}
Regimen B	12.6	0	*	high ^{**}	high ^{**}	high ^{**}
Regimen C	4.8	0	*	minimal [†]	significant [†]	high ^{**}
ARST2031						
Regimen A	21	0	*	high ^{**}	high ^{**}	high ^{**}
Regimen B	21	0	*	high ^{**}	high ^{**}	high ^{**}

CED – cyclophosphamide equivalent dose; Rads – radiation therapy

[^] Level of Risk is defined as minimal, significant, high level of increased risk (see Figure 1) or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines

* Radiation dose varies based on tumor site, plan. If radiation field includes gonadal tissue or hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

** Patients are considered high risk based on chemotherapy alone, however, additional additive risk may be conferred depending on radiation field, dose, and modality of radiation

[†] Final cumulative dose varies based on total number of cycles and/or dose modifications due to tolerability

[‡] Level of risk not high based on cumulative chemotherapy but risk may be increased due to radiation depending on radiation site, plan (see Figure 1).

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Table 4.

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Neuroblastoma

Protocol and Therapy Arms	Gonadotoxic Therapy			Rads	Level of Risk for Future Infertility/Gonadal Dysfunction [^]		
	Alkylator (CED g/m ²)	Cisplatin (mg/m ²)	Carbo~ (Yes)		Prepubertal Females	Pubertal Females	Males
ANBL0032							
Regimen A	0	0			high [§]	high [§]	high [§]
Regimen B	0	0			high [§]	high [§]	high [§]
ANBL0531							
Group 2	1-5 [†]	0	Yes		minimal	min-sig	min-high
Group 2 + cyclo/topo	3.5-12.5 [†]	0	Yes		min-high	min-high	min-high
Group 3	2-5 [†]	0	Yes		minimal	min-sig	min-high
Group 3 + cyclo/topo	4.5-12.5 [†]	0	Yes		min-high	sig-high	high
Group 4	5 [†]	0	Yes		minimal	significant	high
Group 4 + cyclo/topo	7.5-12.5 [†]	0	Yes		min-high	sig-high	high
ANBL0532							
Regimen A	20.8	400	Yes	*	high ^{**}	high ^{**}	high ^{**}
Regimen B	70.6	400	Yes	*	high ^{**}	high ^{**}	high ^{**}
ANBL0931							
HR post-consolidation	0	0			high [§]	high [§]	high [§]
ANBL1232							
Group A	0	0			unlikely	unlikely	unlikely
Group B PR or better	1	0	Yes		minimal	minimal	minimal
Group B no PR	2-5 [†]	0	Yes		minimal	min-sig	min-high
Group C observation	0	0			unlikely	unlikely	unlikely
Group C response-based	1-5 [†]	0	Yes		minimal	min-sig	min-high
ANBL1531							
Arm A	66.2	360	Yes	*	high ^{**}	high ^{**}	high ^{**}
Arm B	66.2	360	Yes	*	high ^{**}	high ^{**}	high ^{**}
Arm C	14.5-27.7 [†]	360		*	high ^{**}	high ^{**}	high ^{**}
Arm D	66.2	360	Yes	*	high ^{**}	high ^{**}	high ^{**}
Arm E	66.2	360	Yes	*	high ^{**}	high ^{**}	high ^{**}

CED – cyclophosphamide equivalent dose; Carbo – carboplatin; Rads – radiation therapy; Cyclo/topo – cyclophosphamide, topotecan; HR – high risk; PR – partial response

[^] Level of Risk is defined as minimal, significant, high level of increased risk (see Figure 1) or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines

~ Carboplatin is not risk stratified by dose

* Radiation dose varies based on tumor site, plan. If radiation field includes gonadal tissue or hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

** Patients are considered high risk based on chemotherapy alone, however, additional additive risk may be conferred depending on radiation field, dose, and modality of radiation

† Final cumulative dose varies based on total number of cycles and/or dose modifications due to tolerability

§ No additional gonadotoxic risk conferred in this protocol, however, patients in this protocol will have had prior high-risk therapy and thus remain high risk

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Table 5.

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Germ Cell Tumors, Rare Tumors and Retinoblastoma

Protocol and Therapy Arm	Gonadotoxic Therapy				Level of Risk for Future Infertility/Gonadal Dysfunction [^]		
	Alkylator (CED g/m ²)	Cisplatin (mg/m ²)	Carbo~ (Yes)	Rads	Prepubertal Females	Postpubertal Females	Males
AGCT0132							
LR	0	0			unlikely [†]	unlikely [†]	unlikely [†]
IR	0	300-600 [‡]			minimal [†]	minimal [†]	min-sig [†]
AGCT1531							
LR	0	0			unlikely [†]	unlikely [†]	unlikely [†]
SR1 Arm CEb	0	0	Yes		minimal [†]	minimal [†]	minimal [†]
SR1 Arm PEB	0	400			minimal [†]	minimal [†]	minimal [†]
SR1 Arm BEC	0	0	Yes		minimal [†]	minimal [†]	minimal [†]
SR2 Arm PEB	0	300			minimal [†]	minimal [†]	minimal [†]
AGCT1532							
Arm A	0	400			minimal [†]	minimal [†]	minimal [†]
Arm B	0	400			minimal [†]	minimal [†]	minimal [†]
Arm B/VIP x2 cycles	2.93	400			minimal [†]	minimal [†]	minimal [†]
Arm B/VIP x1 cycle	1.46	400			minimal [†]	minimal [†]	minimal [†]
ARAR0331							
Stratum A	0	0			unlikely	unlikely	unlikely
Stratum B	0	440		*	minimal [‡]	minimal [‡]	minimal [‡]
ARAR0332							
Stratum 1	0	0			unlikely	unlikely	unlikely
Stratum 2	0	0			unlikely	unlikely	unlikely
Stratum 3	0	200-800 [‡]			minimal	minimal	min-sig
ARET0231							
	0	0	Yes		minimal	minimal	minimal
ARET0321							
Stage 2/3	15.6	420		*	high ^{**}	high ^{**}	high ^{**}
Stage 2/3 alt induction	7.8	0	Yes	*	minimal [‡]	significant [‡]	high [‡]
Stage 4a/4b	60.6	420		*	high ^{**}	high ^{**}	high ^{**}
Stage 4a/4b alt induction	52.8	0	Yes	*	high ^{**}	high ^{**}	high ^{**}
ARET0331							
	0	0	Yes		minimal	minimal	minimal
ARET0332							
HR	0	0	Yes		minimal	minimal	minimal
Not HR	0	0			unlikely	unlikely	unlikely

CED – cyclophosphamide equivalent dose; Carbo – carboplatin; Rads – radiation therapy; LR – low risk; IR – intermediate risk; SR – standard risk; CEB – carboplatin, etoposide, bleomycin; PEb – cisplatin, etoposide, bleomycin; BEC – bleomycin, etoposide, carboplatin; PEB – cisplatin, etoposide, bleomycin; bleo – bleomycin; VIP – ifosfamide, etoposide, cisplatin; alt – alternate; HR – high risk

[^] Level of Risk is defined as minimal, significant, high level of increased risk (see Figure 1) or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines

[~] Carboplatin is not risk stratified by dose

^{*} Radiation dose varies based on tumor site, plan. If radiation field includes gonadal tissue or hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

[†] Final cumulative dose varies based on total number of cycles and/or dose modifications due to tolerability

[‡] Level of risk not high based on cumulative chemotherapy but risk may be increased due to radiation depending on radiation site, plan (see Figure 1).

[¶] Treatment may include surgical removal of one or both gonads. This has not been factored into gonadotoxic risk calculation

^{**} Patients are considered high risk based on chemotherapy alone, however, additional additive risk may be conferred depending on radiation field, dose, and modality of radiation