Supplementary material

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

M.E. Madeleine van der Perk and Nicholas G. Cost, Annelies M.E. Bos, Robert Brannigan, Tanzina Chowdhury, Andrew M. Davidoff, Najat C. Daw, Jeffrey S. Dome, Peter Ehrlich, Norbert Graf, James Geller, John Kalapurakal, Kathleen Kieran, Marcus Malek, Mary F. McAleer, Elizabeth Mullen, Luke Pater, Angela Polanco, Rodrigo Romao, Amanda F. Saltzman, Amy L. Walz, Andrew D. Woods, Marry M. van den Heuvel-Eibrink and Conrad V. Fernandez.

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Supplemental Text S1. Calculations for cyclophosphamide equivalent dose and alkylating agent dose (1, 2)

Cyclophosphamide equivalent dose (CED):

CED (mg/m^2) =
1.0 (cumulative cyclophosphamide dose (mg/m^2)) +
0.244 (cumulative ifosfamide dose (mg/m^2)) +
0.857 (cumulative procarbazine dose (mg/m^2)) +
14.286 (cumulative chlorambucil dose (mg/m^2)) +
15.0 (cumulative BCNU dose (mg/m^2)) +
16.0 (cumulative CCNU dose (mg/m^2)) +
40 (cumulative melphalan dose (mg/m^2)) +
50 (cumulative Thio-TEPA dose (mg/m^2)) +
100 (cumulative nitrogen mustard dose (mg/m^2)) +
8.823 (cumulative busulfan dose (mg/m^2))

Alkylating agent dose (AAD): (3)

Alkylating agent cumulative dose: Tertile distribution

Alkylating agent (parenteral) (mg/m2)	First tertile	Second tertile	Third tertile
Cyclophosphamide	< 3,705	3,705 - 9,201	≥ 9,201
Ifosfamide	< 16,772	16,772 - 55,759	≥ 55,759
Procarbazine	< 4,201	4,201 - 7,001	≥ 7,001
Chlorambucil	< 166	166 - 635	≥ 635
Carmustine (BCNU)	< 301	301 - 530	≥ 530
Lomustine (CCNU)	< 362	362 - 611	≥ 611
Melphalan	< 40	40 - 138	≥ 138
Thiotepa	< 78	78 - 221	≥ 221
Nitrogen mustard	< 45	45 - 65	≥ 65
Busulfan	< 318	318 - 510	≥ 510

AAD = Sum of scores for all alkylating agents.

Dose (mg/m2)	AAD score
0	0
First tertile	1
Second tertile	2
Third tertile	3

Supplemental Table S1. Patient and family perspectives

Perspective of a US patient:	"I am a survivor of stage IV anaplastic Wilms tumor, I went through a lot!!! Now I am currently 8 years cancer free!! Because of my treatments I may not have the chance to have kids of my own when I am older. I think that all kids with cancer should have the chance to have children." -Wilms tumor survivor, age 13
Perspective of a US Parent:	"When our oldest daughter was diagnosed with an aggressive form of kidney cancer at 4 years of age, the last thing on our minds was fertility preservation. At the time, we were much more concerned with the possibility of losing our daughter and the immediate efforts needed to hopefully save her life. Fortunately, for our family, Stella survived her cancer and is now a thriving teenager. As she has matured into adolescence, the side effects from her treatments have become more apparent, not the least of which has been hormonal imbalances and the strong likelihood that she will be infertile and unable to have children in adulthood. Our family remains eternally grateful for the therapies which Stella received, yet in hindsight we share a certain sense of regret that fertility preservation was not considered at the time of initial diagnosis."
Perspective of a UK Parent:	"I lost my daughter to stage III favourable Wilms tumour that sadly relapsed twice in 2012. Fertility preservation at that time was unheard of, however I distinctly remember this being one of my main concerns when she relapsed, and we realized that the treatment would make her infertile. I wondered how I would tell her this as a teenager, the impact it would have on her life and when trying to fit in with her friends, it broke my heart. I have been doing research in the oncofertility area in the United Kingdom and we are very fortunate to have a funded fertility preservation programme through the National Health Service (NHS), with two specialist centres of excellence. Fertility preservation options are now routinely discussed at diagnosis and although there is still work to improve on the options given and communications with families following remission, we have come a long way since 2012. Fertility may not seem like an important factor when faced with a life-threatening disease, but what I have found is that it is important, cure is something that families need to assume WILL happen and issues such as planning for a family in the future are key to keeping this hope alive."

Supplemental Table S2. Fertility Preservation (FP) options presently available (4-7)

	What is this?	Delay of therapy	Pros	Cons	Success
Female					
Oocyte cryopreservation ^	The ovary is stimulated with hormones to induce multiple mature oocytes, these are then removed and frozen for use in the future *	Long; 2-4 weeks depending on ovarian stimulation schedule	• Good for those without partner	• Hormonal injections and procedure to harvest oocytes • Experimental in pre-pubertal females • Follicles are more susceptible to damage during thawing than embryos • IVF needed post-thaw • Side effects of ovarian stimulation	• Age-dependent • Live birth rate 20% lower than for embryo cryopreservation • Pregnancy rate 38-55% in general population
Ovarian tissue cryopreservation	The ovary is biopsied or completely removed and frozen for reimplantation into the patient in the future to allow pregnancy to be achieved via regular intercourse. *	Short; days depending on availability of operating room for procedure	• Short delay • No need for hormone stimulation • Can be combined with another surgery • Can be used for pre-pubertal girls	• Invasive procedure • Cannot be used with certain cancers (leukemias), history of gonadotoxic therapy exposure • Best for those <36y old • Best avoided in those with low ovarian reserve • Risk of transmission of cancer during transplantation • Not widely available	• >180 live births worldwide • Live birth rate >35% • Hormonal restoration >65% • Success rates reported for general population
Hormonal suppression	Gonadotropin releasing hormone agonists are given	No	• No delay • Non-invasive	• Experimental in all females • Data limited to breast cancer and	• Reduces premature ovarian failure by 15%

	(ex. Luprolide 75mg q3mos)		• May be combined with other FP methods	lymphoma patients • Limited data that this protects ovarian reserve, improves pregnancy rates/outcomes • Symptoms of menopause	• Conflicting results on achieving pregnancy and delivery • Reduces time to resumption of regular cycles
Ovarian transposition	This surgically moves the ovaries out of the radiation field	Short; days depending on availability of operating room for procedures	• Can be combined with another surgical procedure • Protects against radiation effects	• Does not protect against chemotherapy toxicities • Invasive procedure	
Male					
Sperm cryopreservation	Semen is collected, processed and sperm is frozen for use in the future	Short; days to collect samples	• Standard of care • Quick and easy	• Must be pubertal/post-pubertal • May need multiple collections • Some specific conditions are ideal (abstinence before, transport time and temperature, etc.)	• 50% in patients with cancer • Success greatly influenced by female component
Testis biopsy and cryopreservation	The testis is biopsied and seminiferous tubules removed. Sperm are extracted and then frozen or future use.	Short; days depending on availability of operating room for procedures	• Can be done for pre-pubertal patients • Can be combined with another surgical procedure	• Experimental in all males • No human pregnancies reported using this yet	• No human success yet
Electroejaculation	A machine is used to induce ejaculation on those who	Short; days depending on	• Allows for mature sperm collection	• Requires special equipment • Requires anesthesia	

	cannot collect a semen sample by conventional methods	availability of operating room for procedures	• Can be combined with another surgical procedure	• Pubertal and post-pubertal patients	
Sperm extraction	Sperm are extracted surgically from testis or epididymis and frozen	Short; days depending on availability of operating room for procedures	• Reserved for those who do not have sperm in semen sample collected by conventional methods	• Invasive procedure • Requires embryologist on site	

^ Embryo cryopreservation is only an option for older adolescents and adults with a partner.

* Future development of direct in vitro maturation without hormonal stimulation followed by future *in vitro* fertilization is currently underway.

<u>Illustrations of radiation field and dose to the abdomen using COG dosing.</u>

Figure S1. Female right flank radiation (COG dosage: 1080cGy)

Calculated dose to the left ovary: Max 7cGy Mean 3cGy. Right ovary had been cryopreserved

Uterus dose: Max 11cGy Mean 2cGy

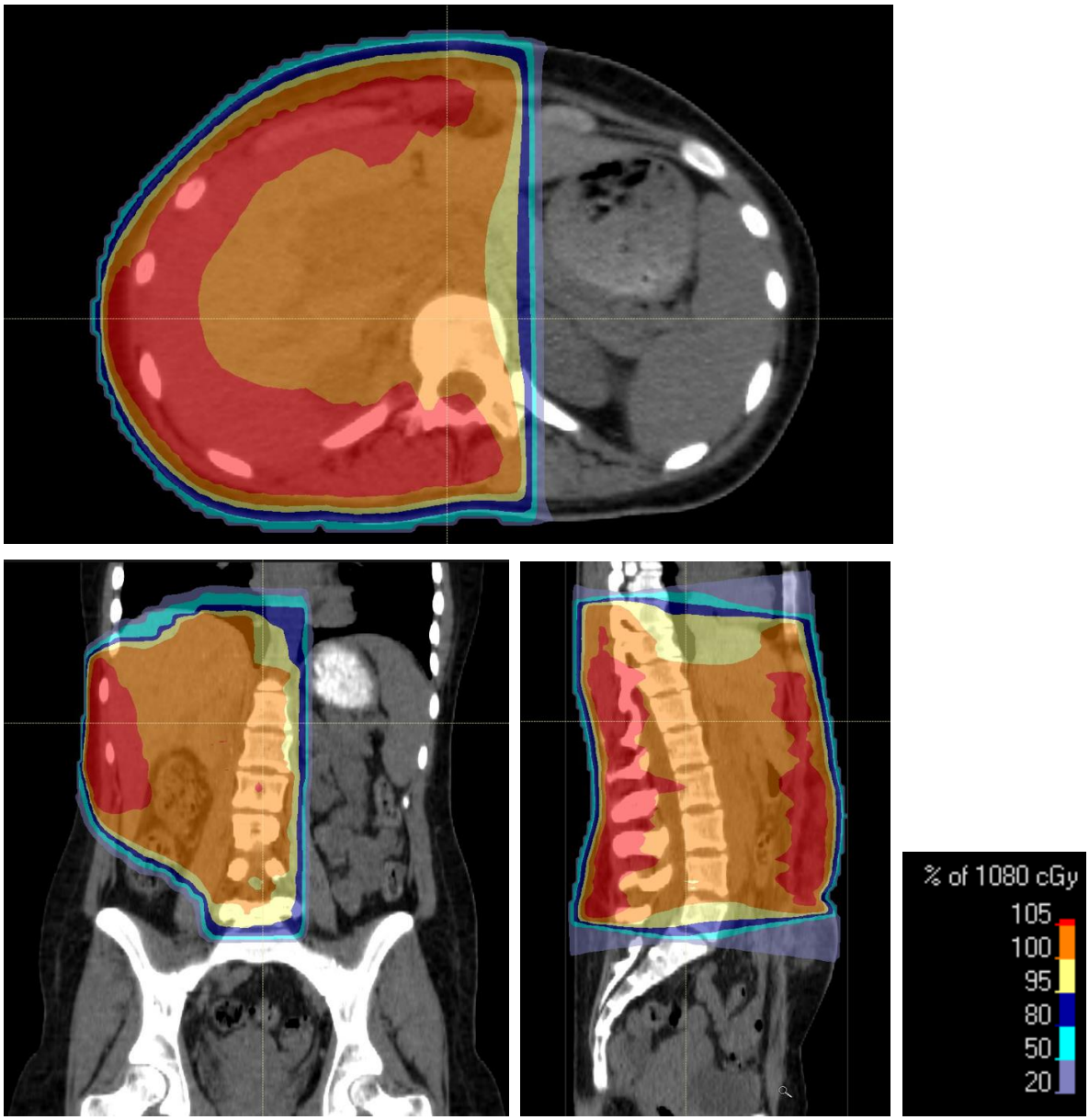


Figure S2. Female whole abdomen radiation (COG dosage: 1050cGy)

Calculated dose to the right ovary: Max 1077cGy Mean 1054cGy. Left ovary had been cryopreserved.

Uterus dose: Max 1069cGy Mean 1056cGy

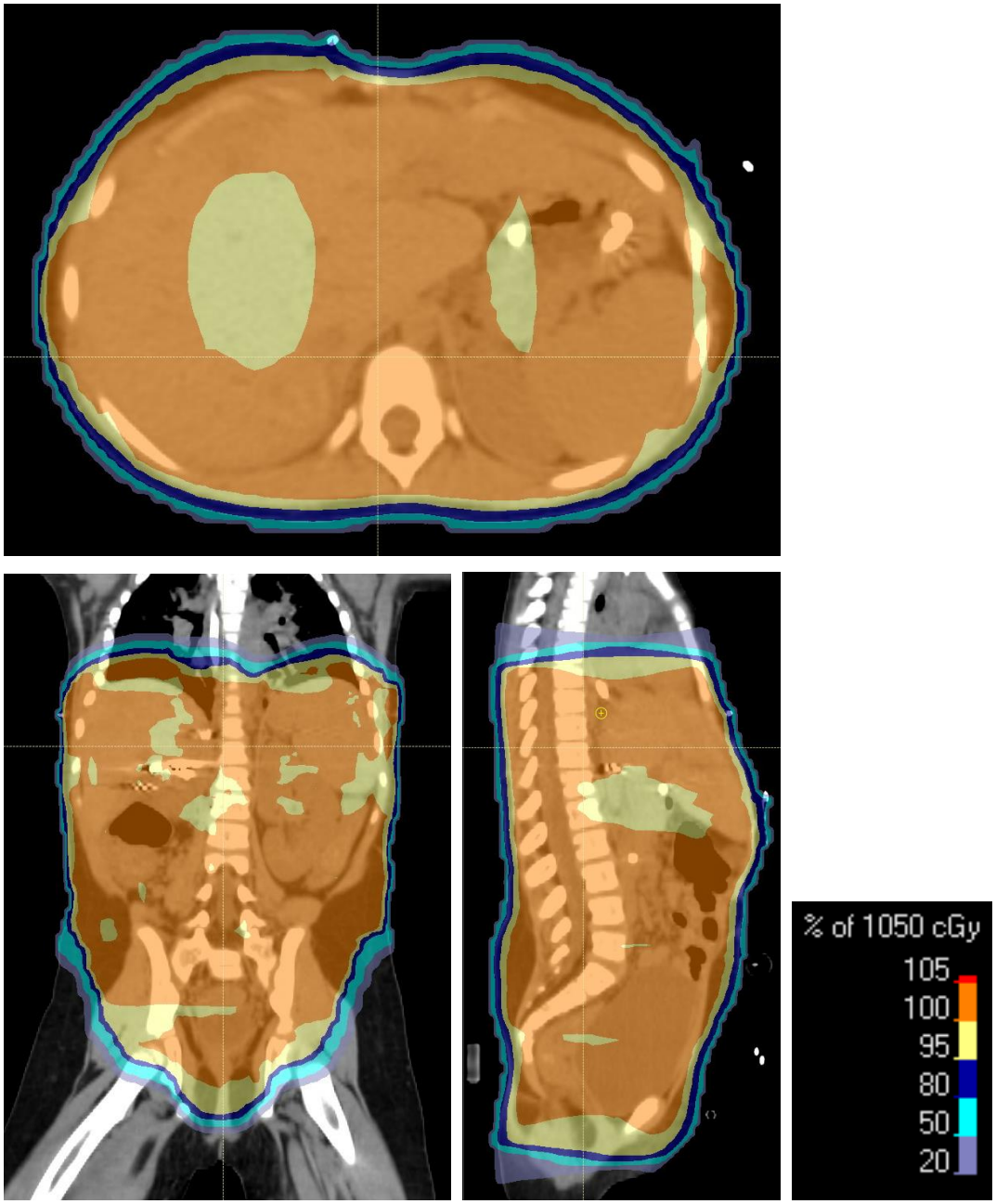


Figure S3. Male right flank radiation (COG dosage: 1080cGy)

No calculable exposure to testes

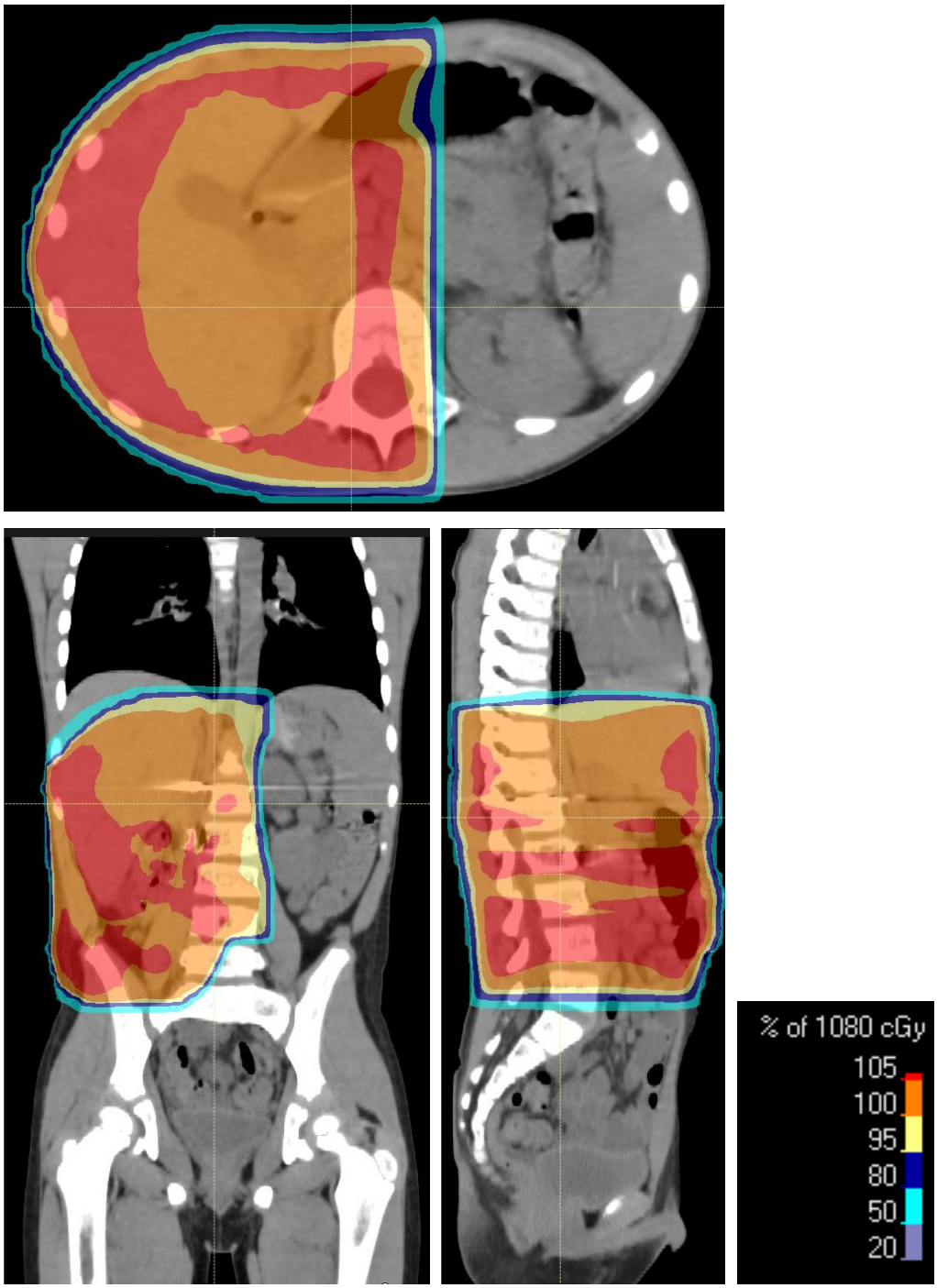
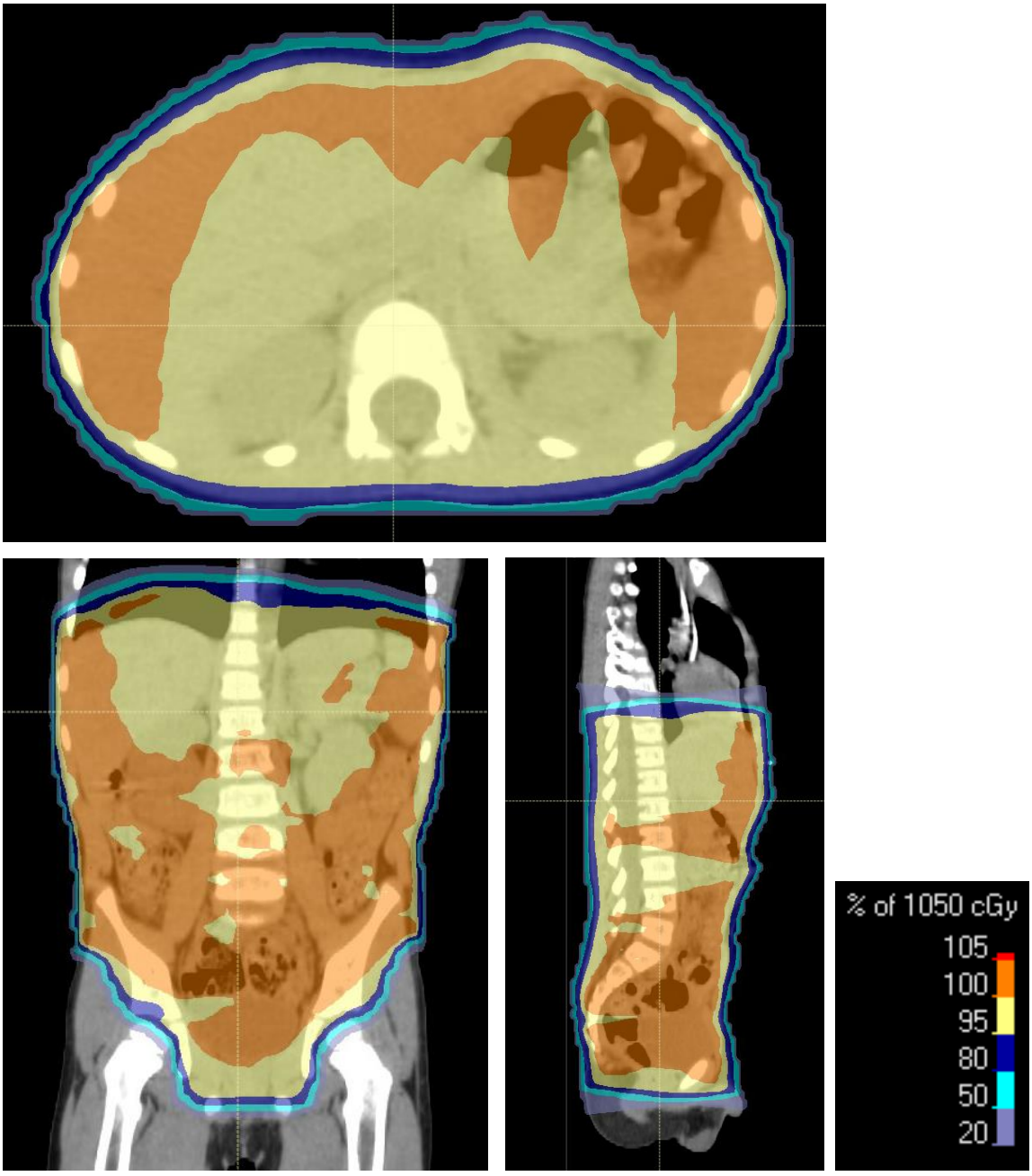


Figure S4. Male whole abdomen radiation (COG dosage: 1050cGy)

Calculated dose to the left testicle: Max 78cGy Mean 51cGy

Calculated dose to the right testicle: Max 91cGy Mean 54cGy



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