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Evidence to Incorporate Inclusive Reproductive Health Measures in Guidelines for Childhood and Adolescent Cancer Survivors

Sana. M. Salih, M.D., M.M.S.^{1,*}, Sarah Z. Elsarrag, B.A.¹, Elizabeth Prange, M.D.², Karli Contreras, B.A.¹, Radya G Osman, M.D.¹, Jens Eikoff, Ph.D.³, and Diane Puccetti, M.D.²

¹Department of Obstetrics and Gynecology, University of Wisconsin, Madison, WI, USA

²Department of Pediatrics, University of Wisconsin, Madison, WI, USA

³Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA

Abstract

Objective—Female childhood cancer survivors are at an increased risk of reproductive health impairment. We compared reproductive health outcomes with the recommended standard in a cohort of childhood cancer survivors.

Study Design and Participants—A retrospective chart review of 222 female childhood cancer survivors aged 21 years or younger that presented to a tertiary referral center between 1997–2008 was initiated. The main outcome measures were the abidance with the American Society of Clinical Oncology (ASCO) guidelines for childhood cancer survivor management of reproductive health. In particular, we evaluated menstrual cycle regularity, fertility preservation counseling, and endocrine profile, as defined by FSH and AMH levels as surrogate markers for ovarian reserve. Secondary outcomes were to study the contribution of survivor clinics in enforcing these guidelines.

Results—Of 136 patients older than 13 years at their last visit, 58 patients (43%) had FSH data available and none had AMH data. Patients were stratified into three groups according to FSH levels. 40 of 58 patients (69%) have normal ovarian reserve (FSH level <10), 10 of 58 patients (17%) have decreased ovarian reserve (FSH levels 10 – 40), and 8 of 58 patients (14%) have premature menopause, defined as FSH>40. Most patients with amenorrhea have elevated FSH levels indicating primary ovarian insufficiency, while 3 patients (2.2%) have low FSH levels consistent with hypothalamic amenorrhea. None of the patients were counseled on fertility preservation.

Conclusions—Reproductive health follow-up in children with cancer, including FSH and AMH measurement when indicated, should be established and strictly adhered.

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*Address all correspondence and requests for reprints to: Sana M. Salih, MD., MMS., Department of Obstetrics and Gynecology, 600 Highland Avenue, Clinical Science Center, H4/626, University of Wisconsin, Madison, WI 53791, Phone: 608 262 2122, Fax number: 608 265 6572, salih@wisc.edu.

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Keywords

childhood cancer; fertility preservation; reproductive health; ovarian reserve; survivor clinics

Introduction

The advent of cancer treatment in the past 25 years has led to a huge success in increasing survival of cancer patients today to over 83%, as compared to 45% in the early 1970s¹. As a consequence, successfully treated children are expected to survive longer. This miraculous improvement of cancer treatment came with a high price - evidence has shown that cancer treatment, in particular chemotherapy and pelvic radiotherapy, has detrimental effects on reproductive function in both male and female childhood cancer survivors^{2; 3}. Alkylating agents and procarbazine have been found to be highly gonadotoxic^{4; 5} and direct dose and scattered doses of radiotherapy and bone marrow radiation carry high risks of ovarian damage⁶. While guidelines for fertility preservation and assessment of reproductive health in childhood cancer survivors have been emphasized by multiple national and international organizations, including American Society of Clinical Oncology (ASCO) and American Society of Reproductive Medicine (ASRM), the adherence to these guidelines in oncology clinics is not well documented⁷.

One of the grave consequences of cancer treatment is ovarian hormone deficiency. It is predicted that 1 in 800 young women will be childhood cancer survivors by 2020⁴. Roughly 6.3% of childhood cancer survivors suffer from acute ovarian failure as compared to 0.8% of their siblings⁸. 22.6% of childhood cancer survivors suffer from imminent ovarian failure and this is strongly related to the age when the diagnosis is made⁹. Primary ovarian insufficiency (POI) causes estrogen deficiency, which leads to failure of pubertal development in prepubescent girls and increases the risk of long-term health complications, including osteoporosis, mental health disorders, cardiovascular disease, and urogenital dysfunctions in older women^{10; 11}. A small longitudinal and cross-sectional study of young cancer patients demonstrates that gonadotoxic chemotherapy impacts serum hormones, with anti-Mullerian hormone (AMH), follicle stimulating hormone (FSH), and antral follicle count (AFC) levels being the most affected⁵. Cancer survivors continue to have significantly impaired FSH, AMH, AFC and ovarian volume when measurements are adjusted for age, BMI, and race¹². In addition, survivors who experienced spontaneous menstrual cycles were found to have a smaller ovarian volume than controls (4.8 and 6.8 cm medium, respectively) and less antral follicles in each ovary as compared to controls (7.5 and 11 median, respectively)¹³. Survivors who experienced radiation in the abdomen/pelvis region are more apt to having a premature, low-birth weight infant or neonatal death, but were not at increased risk of malformations or deaths compared to those who underwent surgery¹⁴.

Female cancer survivors have an increased risk of infertility, as defined as >1 year of attempts at conception without success. Clinical infertility was most pronounced at early reproductive ages, with a relative risk of 2.92 in participants <24 years, a relative risk of 1.61 in those aged 25-29 years, and a relative risk of 1.37 in those aged 30-40 years old, as compared to normal individuals¹³. Although female cancer survivors are equally likely to

seek treatment for infertility as compared to the control group, they are less likely to be prescribed drugs for treatment of infertility than other patients with no history of cancer¹³.

The field of oncofertility was founded to find solutions regarding the reproductive future of cancer survivors¹⁵. Embryo and oocyte cryopreservation is approved for female fertility preservation; however, these fertility preservation options are not yet viable for prepubescent or adolescent girls and do not preserve endogenous estrogen^{16; 17; 18; 19; 20}. While ovarian tissue cryopreservation is available for children, it is still considered experimental²¹. Research has shown that ovarian tissue cryopreservation is largely safe for childhood cancer survivors to reproduce. Only one known reported case of auto transplantation of cancer in a patient with breast cancer and another with cervical cancer²². Currently, GnRH agonists are used to preserve ovarian reserve. While GnRH agonists are effective in preventing uncontrolled menstrual bleeding during chemotherapy, their efficacy for preventing POI has given mixed results. New ovoprotection drugs are currently being investigated. Some of these drugs, such as SIF, prevent ovarian cell death and apoptosis^{23; 24}, while other drugs, such as Dexrazoxane and Bortezomib, inhibit the toxic effects of chemotherapy earlier at the level of drug transport and DNA intercalation prior to DNA damage in the ovary²⁵.

Until the present time, there is no standard of care regarding counseling and offering fertility preservation options for every age group prior to commencing with cancer therapy, resulting in a wide variation of utilization of available services. 23% of oncologists usually never discuss any fertility preservation guidelines with their patients²⁶. In a survey of oncologists from the United Kingdom, only 38% admitted to giving written information on fertility preservation to their patients and 66% consulted a fertility specialist^{27; 28}. Furthermore, only one third of women with hematological cancer pursue fertility preservation and half of those patients have already been exposed to chemotherapy²⁹. The reasons for not having a discussion about fertility preservation are lack of time, lack of knowledge, perceived poor success rates of fertility preservation, poor patient prognosis, patient already had children, was single, or could not afford fertility preservation costs²⁸.

Considering the overreaching and devastating effects of cancer and cancer treatment on reproductive health in children and adolescents, we initiated this cohort study to assess the current compliance with available reproductive health national guidelines in cancer patients and investigate additional measurements to include in these guidelines.

Materials and Methods

Study Design and Protocol

A retrospective cohort study of all patients who presented to the pediatric oncology clinic in a tertiary referral center (diagnosed between 1997-2008) was initiated. The electronic medical records of 222 female patients were reviewed. Information regarding initial diagnosis, management, and follow-up was gathered. General demographic data as well as tumor type, treatment, reproductive health (fertility preservation counseling, menstrual history, and hormonal contraception) was collected. The study was approved by the Institutional Review Board of the University of Wisconsin # M-2009-1006.

Outcome Measures

The main outcome measures were 1) compliance with ASCO guidelines for reproductive health preservation and assessment in childhood cancer survivors. In particular we investigated ovarian reserve. Secondary outcome measure was the contribution of survivor clinics in enforcing these guidelines. We evaluated the effect of participation in the multidisciplinary survivor clinic. To evaluate ovarian reserve, the surrogate markers of menstrual cycle regularity, amenorrhea following chemotherapy, and FSH levels (the highest value for a patient if more than one value exists) were used. None of the patients had AMH measured and hence this was not included in the analysis. Pubertal and reproductive information was also recorded, including: age of menarche, most recent menstrual history including history of irregular cycles, oligomenorrhea, amenorrhea, and pregnancy outcomes following chemotherapy. History of premature ovarian insufficiency hormone therapy, including hormonal contraception and hormone replacement therapy, were recorded. Finally, written evidence of conversations between clinician and patients regarding reproductive health counseling was also recorded. This includes counseling regarding fertility preservation, contraception and hormone therapy, referral to reproductive endocrinologist when desired, and embryo, oocyte, and ovarian tissue cryopreservation when appropriate. The standard chemotherapy and radiation consent forms include all risks, including potential effects on ovarian reserve and ovarian failure. This site uses these forms and therefore each patient was given written information about reproductive risks of chemotherapy. Recording data about additional counseling allows evaluation of conversations outside of this setting.

Statistical Analyses

Categorical variables were summarized in tabular format using frequencies and percentages. Variables on a continuous scale were summarized in terms of medians and ranges. The comparisons of categorical variables between groups e.g., FSH ≤ 10 versus >10 , survivor clinic attendance versus no attendance, etc, were conducted using chi-square analysis with continuity correction, Fisher's exact test, or multivariable logistics regression analysis. Analogously, the comparison of continuous variables between groups was performed using the nonparametric Wilcoxon Rank Sum test. All p-values were 2-sided and were considered significant at <0.05 . Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Demographics and treatment of children diagnosed with cancer in a comprehensive cancer center

The initial data set includes all surviving female patients diagnosed at this cancer center from 1997 through 2008. The charts of 222 patients were reviewed. The median age of the childhood cancer survivor at the time of diagnosis was 7.0 years (range 0 – 20). On average, these patients were followed for 5 years (range 0 – 30). Patients with any oncologic diagnosis were included in this study and represent over 23 different diseases. Of those, the most common diagnosis was acute lymphoblastic leukemia (ALL), followed by Hodgkin's Lymphoma, astrocytoma, and soft tissue/bone tumors (Table 1). All modalities of cancer

treatment were represented in the cohort. Seventy-four percent of the patients were treated with chemotherapy, radiation therapy, bone marrow transplant, or combination treatments (Table 2). 165 (74%) of the patients received chemotherapy. The most common class of chemotherapy received in this cohort of patients was anthracycline antibiotics (n=103, 46%), followed by alkylating agents (n= 96, 46%). Most patients (n=75, 34%) received a combination of these two classes of chemotherapy agents. Bone marrow transplant was administered in 16 patients (7%), while radiation therapy in 50 (23%).

Reproductive health outcomes

To evaluate ovarian reserve, clinical evidence of amenorrhea and/or elevated day 3 FSH level was recorded for patients older than 13 years of age at their last visit. Only 58 (52%) of eligible patients had FSH data available. Of patients with FSH data available, they were stratified into three groups, according to FSH levels: 40 of 58 patients (69%) have normal ovarian reserve (FSH level <10), 10 of 58 patients (17%) have decreased ovarian reserve (FSH levels 10 – 40), and 8 of 58 patients (14%) have premature ovarian failure defined as FSH>40 (Table 1).

Cycle irregularity (e.g. amenorrhea) was also evaluated in patients 13 years of age or older in order to determine ovarian reserve. Of those patients, 25 (11%) were pre-menarcheal at last follow-up as opposed to 59 (26%) who were pre-menarcheal before the diagnosis, consistent with the expected natural transition through puberty.. 197 patients were older than 13 years of age at their last visit. Of those 197 patients, 34 (17%) patients were taking hormone therapy (OCP, Nuva Ring, and Depo Provera) and 106 (54%) patients were not on hormonal therapy and had updated data recorded about the regularity of their menstrual cycle. 76 (72%) of the 106 not on hormonal therapy had normal periods, while 27 (25%) had irregular periods without any other information recorded, and 15 (14%) had reported amenorrhea for longer than 12 months after chemotherapy ended (Table 1). 8 patients had known pregnancies after treatment, one had multiple pregnancies, and 6 resulted in live births. 33 patients had reproductive counseling prior to treatment, 2 had counseling during or after treatment. Very few patients were referred to REI or an endocrine specialist for further discussions. One patient had oocyte cryopreservation performed prior to initiation of chemotherapy.

Correlation of demographics and menstrual history with elevated FSH levels

Elevated levels of FSH were statistically correlated with the incidence of amenorrhea> 12 months post treatment. Children who have elevated FSH levels >10 (n=18, 31%) were generally older at the time of diagnosis (median 15 years versus 9.5 years, p=0.006), more likely to have gone through menarche prior to diagnosis (75% versus 39%, p=0.0301), received radiation therapy (78% versus 35%, p=0.0026), and received anthracycline chemotherapy (72% versus 53%, p=0.2615) (Table 3A). ALL is significantly more prevalent in patients with FSH<10 than ≥10 while Hodgkin's lymphoma is more prevalent in patients with FSH≥10 (Table 3A). None of the patients had risk factors for ovarian insufficiency prior to cancer diagnosis. Six patients, however, underwent unilateral oophorectomy for ovarian tumors, and one patient required an interval removal of the second ovary. Two patients developed reduced ovarian reserve following surgery (Table 3B).

Association between survivor clinic attendance or survivor clinic assistance and reproductive/follow-up outcomes

Subjects with at least 5-year post-treatment follow-up qualified to attend the pediatric survivor clinic. To assess the utilization and relationship between survivor clinic attendance/survivor clinic assistance and therapy and reproductive outcomes, patients were classified according to their post-therapy follow-up and reproductive outcomes. 47 patients (21%) included in the study attended the multidisciplinary survivor clinic. 94 patients (42%) were seen by an oncology sub-specialty group. 76 (34%) patients who are eligible to attend the survivor clinic and who were still following up with their primary treating physician also received the caring for life summaries prepared by the survivor clinic (Table 4). Some patients are not associated in any way with the survivor clinic. These included 41 (18%) patients followed by a primary care physician, 14 patients (6%) lost to follow-up, and 2 patients (1%) where follow-up was deemed unnecessary. Overall, 148 (76%) of survivors did not attend survivor clinic, while 47 (24%) did attend survivor clinic.

Patients who attended the survivor clinics were younger (median age 4.5 vs. 9.0 years, $P=0.0124$). The proportions of patients who received chemotherapy among patients who attended survivor clinics was significantly higher than in patients who did not attend survivor clinics (98% vs. 72%, $p<0.001$, Table 5). Both alkylating agents and anthracyclines were statistically significantly associated with survivor clinic attendance ($p=0.004$ and $p<0.001$, respectively). Similarly, patients who received survivor clinic assistance were more likely to receive chemotherapy than patients who did not receive survivor clinic assistance (99% vs. 63%, $p<0.001$, Table 6). Analogously, the proportion of patients undergoing radiation therapy was significantly higher in patients receiving survivor clinics assistance (34% versus 18%, $p=0.0178$, Table 6).

The impact of survivor clinic and follow up of reproductive health outcomes was analyzed (Tables 5 and 6). Of the patients with decreased ovarian reserve (as measured by having an elevated FSH and amenorrhea), 4/18 (22%) were seen in the survivor clinic (Table 5) while 9/18 (50%) were seen by their own physicians in the cancer center but were also cared for by the survivor clinic nurse (Survivor Clinic Assistance, Table 6). There was no association between survivor clinic attendance and reproductive health outcome as manifested by menarche before diagnosis, irregular periods, or amenorrhea >12 months post treatment at last follow-up; neither was there an association to the distance of hometown to Madison, WI.

Discussion

According to ASCO Survivorship Guidelines, all health care providers “should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists”³⁰. Our data draws attention to the lack of adherence to current cancer survivorship guidelines and calls for closer collaboration between reproductive health specialists and medical oncologists before and after cancer treatment to optimize the health of these patients. This lack of compliance is most likely due to the lack of precise language characterizing the guidelines. We recommend that FSH and AMH be checked in all

prepubescent children from the age of 13 and closely followed up afterward. The age 13 is recommended because it is the median age of menarche where ovarian insufficiency could be consistently predicted by elevated FSH data for younger patients³¹. Currently, ASCO guidelines do not specify the need to measure FSH and AMH by a certain age.

Many of our patients received anthracycline, alkylating agents, or a combination of both agents and few patients received a bone marrow transplant. Many of our colleagues described the negative effect of these chemotherapeutic agents on ovarian function including both alkylating and non-alkylating agents^{4; 22; 32}. Despite a wealth of evidence regarding the risk of POI in these children, the data about reproductive health outcomes such as FSH levels and menstrual cycle details, and use of hormone therapy was sparse, further solidifying confusion about ASCO guidelines.

Chemotherapy induced menopause risk was found to range between 22% and 61% in women below 40 years of age³³. Out of 222 subjects in our study however, only 58 (52%) had FSH data available. The data found that 10 of 58 patients (17%) have decreased ovarian reserve (FSH levels 10 – 40) and 8 of 58 patients (14%) have premature ovarian failure. Based on FSH levels, our data indicates a lower number (14%) with premature ovarian failure than the minimum of the range found previously (22%); this indicates that the amount of FSH data collected was too low. The lack of these data in our childhood cancer survivors shows the variable interpretation of providers to the current guidelines for reproductive health. Furthermore, none of the existing guidelines recommends measurement of FSH in all childhood survivors at 13 years of age. We recommend that guidelines include measurement of FSH and AMH in children age 13 or older. In addition, we recommend assessment of prolactin in patients who continue to have amenorrhea, especially in children who receive hypothalamus or pituitary irradiation or surgery, since up to half of those patients will have hyperprolactinemia³⁴.

In follow-up with cancer survivors, anti-müllerian hormone (AMH) levels can be used to measure ovarian function following cancer treatment³⁵. In a follow-up study measuring AMH levels on young women with lymphoma prior and after chemotherapy, it was found that AMH levels significantly dropped to barely detectable levels after chemotherapy³⁶. In another cohort study, lower AMH levels were found in childhood cancer survivors as compared to the control, where the lowest level was marked in patients receiving bone marrow transplant or diagnosed with Hodgkin's lymphoma³⁷. Essentially, these data signify the importance of measuring AMH levels after treatment as part of attentiveness to reproductive health. Measurement of AMH is currently not included in either ASCO or ASRM guidelines. Further studies of utility of AMH in childhood cancer survivors may lead to the incorporation of AMH levels for assessing ovarian reserve in childhood cancer survivors.

Despite efforts to establish effective protocols to improve fertility preservation and standardize reproductive health follow-up of ovarian reserve in children and adolescents with cancer³⁰, there are wide variations in the accepted standard of care for management of childhood and adolescent cancer survivors. According to one study, there are disagreements between the primary care provider and the medical oncologist with regards to the patient's

primary cancer follow-up in survivor clinics, with a total 97% disagreement³⁸. Due to such confusion in survivorship care, the recommending bodies, such as the National Cancer Institute (NCI) and ASCO, should create detailed guidelines detailing follow-up care, including mandatory and recommended labs. This will serve to enrich current guidelines³⁹, which are currently not comprehensive and do not cater to the special needs of this population.

The role of survivor clinics and multispecialty clinics may also play an active role in reformatting current follow-up guidelines following cancer treatment as highlighted by the children's oncology group⁴⁰. Overall, in our study, 148 (76%) of survivors did not attend survivor clinic, while only 47 (24%) did attend survivor clinic. Currently, the National Cancer Institute (NCI) recommends regular medical follow-up for cancer patients to check for recurrence or metastasis of the cancer. NCI however does not have guidelines for follow-up care for adult and pediatric cancer survivors⁴¹. Although follow-up care is encouraged, it is unclear how it should be carried out. Survivor clinics would be the ideal place for follow up and lab testing. The NCI highly encourages attendance at survivor clinics, although it is not mandatory. Primary care physicians and medical oncologists should be vigilant in referring patients to child or adult survivor clinics, as patients may be reluctant to request it. Furthermore, reproductive health counseling should be mandatory both prior to treatment, at follow-up, and throughout puberty, when indicated.

We believe that survivor clinics can greatly assist with following up the patient's reproductive health outcomes and should follow a shared care model with collaboration between primary care doctor, medical oncologist, and/or reproductive specialist. In general, the current survivor clinic model consists of a clinic at a major academic center. It can be difficult for patients that live far away to commute long distances for short clinic appointments. It may also be disruptive to the patient's work and/or academic responsibilities. According to a recent study, fertility preservation consultation for women with cancer was greatly influential in the patients' final decision and indecisiveness about fertility preservation was lower post consultation with a specialist⁴². However, as noted, the referral rate from oncologists to reproductive specialists is low⁴². Thus, we recommend that collaboration and a shared care model is implemented between specialist and primary care provider and that follow-up is carried out by the patient's main treating doctor, whether that is primary care, medical oncologist, or reproductive specialist, in order to ease as much burden as possible from the patient. In this new model of survivor clinic assisted care, the patients will be followed by their own oncologists or primary care physicians, but have their long-term survivorship care reviewed and monitored by a nearby survivor clinic to ensure compliance with national guidelines.

In conclusion, we strongly suggest that measures of reproductive health should be performed at the beginning and conclusion of cancer therapy, in addition to fertility preservation counseling with a specialist. Guidelines should include measuring the FSH and AMH level pre and post cancer treatment in all children older than 13 years of age, gathering and documenting a menstrual history, as well as measuring prolactin in those patients who underwent hypothalamus pituitary radiotherapy. Further studies should investigate the effect of survivor clinics on enhancing adherence to guidelines, whether survivor clinics lead to

better reproductive outcomes, and to design effective and comprehensive protocols of reproductive health follow up in children with cancer.

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Table 1
Patients' characteristics

	MEDIAN	RANGE
Age at Diagnosis (yrs)	7.0	0 – 20
Age at last follow-up (yrs)	14.0	2 – 34
Years since first diagnosis (yrs)	5.0	0 – 30
BMI at Diagnosis	18.0	12.2 – 33.5
BMI at Follow-up	22.5	13.7 – 45.4
	N	%
Diagnosis		
ALL	56	25
AML	7	3
Medulloblastoma/PNET	5	2
Astrocytoma	18	8
Other CNS	16	7
Hodgkin's Lymphoma	20	9
NHL	6	3
Wilms tumor	13	6
Neuroblastoma	12	5
Soft Tissue/Bone	17	8
Histiocytosis	9	4
Other Leukemia	3	1
Retinoblastoma	7	3
Other [†]	33	15
Menarche before Diagnosis	59	26
Pre-menarche at last follow-up	25	11
Total patients in whom period regularity was reported (N=106)		
Regular periods at the last visit	76	72
Irregular Periods at last follow-up	27	25
Amenorrhea > 12 months post treatment	15	14
FSH (N=58 total)		
FSH 10	40	69
FSH 10-40	10	17
FSH >40	8	14

[†] include melanoma, teratoma, hepatoblastoma, cystic hygroma, yolk sac tumor, mucinous ovarian carcinoma, carcinoid tumor of appendix, nasopharyngeal carcinoma, thyroid, hemangioepithelial blastoma

Table 2**Summary of treatments**

	N	%
Chemotherapy	165	74
Radiation Therapy	50	23
Bone Marrow Transplant	16	7
Chemotherapy & Radiation Therapy	44	20
Chemotherapy & Bone Marrow Transplant	16	7
Radiation Therapy & Bone Marrow Transplant	11	5
Anthracycline Antibiotics	103	46
Alkylating Agents	96	43
Anthracycline Antibiotics & Alkylating Agents	75	34

Table 3A

Comparison FSH 10 versus >10

	FSH 10 (N=40)			FSH> 10 (N=18)		
	Median	Range		Median	Range	p-value
Age at Diagnosis (yrs)	9.5	0-18		15.0	6-20	0.0062
	N	%		N	%	
Irregular Periods At last follow-up	12	40		6	67	0.2552
Menarche before Diagnosis	14	39		9	75	0.0301
Amenorrhea> 12 months post treatment	2	9		11	79	<0.001
Received Radiation	14	35		14	78	0.0026
Anthracycline chemotherapy	21	53		13	72	0.2615
Diagnosis						
ALL	13	33		1	6	0.0438
Hodgkins	7	18		8	44	0.0502
Soft Tissue/Bone	0	0		1	6	0.3103
Astrocytoma	6	15		1	6	0.4171

Table 3B
Patients who underwent oophorectomy prior to chemotherapy and/or radiation

	AGE	OVARIAN SURGERY	TYPE OF TUMOR	FSH LEVEL
Subject # 4	15	Right salpingo-oophorectomy	Immature teratoma	Not done
Subject # 5	18	Left salpingo-oophorectomy	Germ cell tumor	Not done
Subject # 3	19	Interval bilateral salpingo-oophorectomy, hysterectomy	Mucinous cystadenocarcinoma	Not done
Subject # 2	20	Left salpingo-oophorectomy	Immature teratoma	Not available
Subject # 6	21	Right salpingo-oophorectomy	Sertoli-Leydig cell tumor	1.7
Subject # 1	25	Right salpingo-oophorectomy	Germ cell tumor	44.4

Table 4
Summary of follow-up outcomes

	N	%
Loss of Follow-up	94	42
Remission	153	69
Relapse	32	14
Time to relapse	Median 2 yrs	Range 0-8 yrs
Survivor Clinic		
Yes	47	21
No – followed by primary care physician	41	18
No – but seen regularly by oncology sub specialty group	94	42
No – due to loss to follow-up	14	6
No – as follow-up deemed necessary	2	1

Table 5
Comparison between subjects who attended the survivor clinic versus subjects who did not attend the clinic (in subjects with at least 5-year post-treatment follow-up)

	SURVIVOR CLINIC ATTENDANCE (N=47)		NO SURVIVOR ATTENDANCE CLINIC (N=148)		p-value
	Median	Range	Median	Range	
Age at Diagnosis (yrs)	4.5	0.5-19.0	9.0	0-20.0	0.0124
	N	%	N	%	p-value
Irregular Periods at last follow-up	4	9	10	25	0.7733
Menarche before Diagnosis	9	19	46	43	0.033
Amenorrhea >12 months post treatment	4	9	10	20	0.7275
FSH level >10 (more than 10)	4	9	13	9	0.9999
Radiation Therapy	13	28	35	24	0.611
Chemotherapy	46	98	104	72	<0.001
Bone Marrow Transplant	5	11	10	7	0.3622
Alkylating Agent	31	66	60	42	0.004
Anthracycline Agent	39	83	61	42	<0.001

Comparison between subjects who received survivor clinic assistance versus subjects who did not receive assistance (in subjects with at least 5-year post-treatment follow-up)

Table 6

	ASSISTANCE (N=76)		NO ASSISTANCE (N=119)		p-value
	Median	Range	Median	Range	
Age at Diagnosis (yrs)	6.0	0.5-19.5	9.0	0-20.0	0.2688
	N	%	N	%	p-value
Irregular Periods at last follow-up	13	17	10	8	0.1428
Menarche before Diagnosis	17	22	38	32	0.0609
Amenorrhea >12 months post trt	9	12	5	4	0.0715
FSH level 10 (more than 10)	8	11	9	8	0.6490
Radiation Therapy	26	34	22	18	0.0178
Chemotherapy	75	99	75	63	<0.001
Bone Marrow Transplant	9	12	6	5	0.0822
Alkylating Agent	54	71	37	31	<0.001
Anthracycline Agent	67	88	33	28	<0.001