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CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS PROPOSAL

TITLE: Fertility Rates in Long-Term Survivors of Childhood Cancer

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BACKGROUND AND RATIONALE:

The treatment of children and adolescents with cancer has become increasingly successful. Approximately 70% of all patients diagnosed prior to 15 years of age will survive for five years. The majority is expected to survive for many years after diagnosis (1).

The treatment these patients receive may adversely affect their reproductive function. Germ cell survival may be adversely affected by radiation therapy and chemotherapy. Ovarian damage results in both sterilization and loss of hormone production because ovarian hormonal production is closely related to the presence of ova and maturation of the primary follicle. These functions are not as intimately related in the testis. As a result, men may have normal androgen production in the presence of azoospermia.

Ovary

All women who receive total body irradiation prior to bone marrow transplantation develop amenorrhea. Recovery of normal ovarian function occurred in only nine of 144 patients in one series, and was highly correlated with age at irradiation of less than 25 years (2). In a series restricted to patients who were prepubertal at the time of bone marrow transplantation, 44% (7/16) had clinical and biochemical evidence of ovarian failure (3).

The frequency of ovarian failure following abdominal radiation therapy is related both the age of the woman at the time of irradiation and the radiation therapy dose received by the ovaries. Whole abdomen irradiation produces severe ovarian damage. Seventy-one percent of women in one series failed to enter puberty, and 26% had premature menopause following whole abdominal radiation therapy doses of 2000 to 3000 cGy (4). Others reported similar results in women treated with whole abdomen irradiation (5) or craniospinal irradiation (6,7) during childhood.

The frequency of ovarian failure is correlated with the treatment volume. Ovarian failure occurred in none of 34 women who received abdominal irradiation to a volume which did not include both ovaries, 14% of 35 whose ovaries were at the edge of the abdominal treatment volume, and 68% of 25 whose ovaries were entirely within the treatment volume (8). These reports corroborated a study of ovarian histology that identified severe ovarian damage in children who had received abdominal irradiation, with or without chemotherapy (9).

Ovarian function may be impaired following treatment with combination chemotherapy (Table 1) (10,11,12, 13,14,15,16,17).

Table 1

FREQUENCY OF AMENORRHEA FOLLOWING
TREATMENT WITH COMBINATION CHEMOTHERAPY

PATIENT AGE	REGIMEN	FREQUENCY OFAMENORRHEA
All ages	MVPP	63% (20/32)
All ages	MOPP	39% (17/44)
2 – 15 years	MOPP	11% (2/18)
All ages	ChlVPP	19% (6/32)
9.0 – 15.2 years	ChlVPP	31% (10/32)
All ages	ChlVPP/EVA	80% (16/20)
6.1 – 20.0 years	MDP	13% (3/23)
4 – 20 years	COP/ABVD	0% (0/17)

These studies, performed following treatment with the combination of nitrogen mustard, vincristine, procarbazine and prednisone (MOPP), the combination of nitrogen mustard, vinblastine, procarbazine and prednisone (MVPP) or the combination of chlorambucil, vinblastine, procarbazine and prednisone (ChlVPP), doxorubicin, prednisone,procarbazine, vincristine and cyclophosphamide (MDP) or cyclophosphamide,vincristine, procarbazine (COP/ABVD) demonstrated the sensitivity of the older patient to the gonadal toxicity of such therapy (14,15,16, 17,18,19,20,21), whether three or six cycles were administered (Table 2) (22). Younger women had a lower frequency of amenorrhea following treatment with one of these combinations.

Table 2

RELATIONSHIP AMONG AGE AT TREATMENT, NUMBER OF CYCLES AND
FREQUENCY OF AMENORRHEA FOLLOWING TREATMENT
WITH COMBINATION CHEMOTHERAPY

PATIENT AGE	NUMBER OF CYCLES	REGIMEN	FREQUENCY OF AMENORRHEA
16 - 30 years	3	MOPP	3% (1/31)
	6		9% (1/11)
31 - 45 years	3		61% (11/18)
	6		62% (5/8)

Ovarian function was evaluated in women treated with drug combinations that did not include procarbazine. Ovarian function was normal in all of six women treated for non-Hodgkin's lymphoma with a cyclophosphamide containing drug combination (23). Others reported that pubertal progression was adversely affected in 5.8% of 17 patients treated before puberty, compared to 33.3% of 18 patients treated during puberty or after menarche. However, the administration of cyclophosphamide did not correlate with the abnormal pubertal progression observed in these patients (24). Cis-platinum administration resulted in amenorrhea in 14% of seven patients (25).

Women who received high dose (50 mg/kg/day x 4 days) cyclophosphamide prior to bone marrow transplantation for aplastic anemia all developed amenorrhea following transplantation. In one series, 36 of 43 had recovery of normal ovarian function 3 – 42 months after transplantation (2).

The presence of apparently normal ovarian function at the completion of chemotherapy should not be interpreted as evidence that no ovarian injury has occurred. Premature menopause is well documented in childhood cancer survivors, especially those women treated with both an alkylating agent and abdominal irradiation (26). When the pelvis is excluded from the treatment volume, and treatment does not include combination chemotherapy, premature menopause is infrequent (27).

Testis

Surgery, irradiation and/or chemotherapy may damage testicular function. Retrograde ejaculation is a frequent complication of bilateral retroperitoneal lymph node dissection performed on males with testicular neoplasms (28,29), and impotence may occur following extensive pelvic dissections as may be performed to remove a rhabdomyosarcoma of the prostate (30).

Men treated with whole abdomen irradiation may develop gonadal dysfunction. Five of ten men were azoospermic, and two were severely oligospermic when evaluated at ages 17 - 36 years following treatment with whole abdomen irradiation for Wilms tumor at ages 1 - 11 years, with the penis and scrotum either excluded from the treatment volume, or shielded with 3 mm of lead. The testicular radiation doses varied from 796 - 983 cGy (31). Others reported azoospermia in 100% of 10 men 2 - 40 months after radiation therapy doses of 140 - 300 cGy to both testes (32). Similarly azoospermia was demonstrated in 100% of ten men following testicular radiation therapy doses of 118 - 228 cGy. Recovery of spermatogenesis occurred after 44 - 77 weeks in 50% of the men, although three of the five with recovery had sperm counts below 20 x 106/ml (33). Oligo- or azoospermia was reported in 33% of 18 men evaluated 6 - 70 months after receiving testicular radiation doses of 28 - 135 cGy (34). In another report, none of five men who received testicular radiation doses of less than 20 cGy became azoospermic. By contrast, two who received testicular radiation doses of 55 - 70 cGy developed temporary oligospermia, with recovery to sperm counts greater than 20 x 106/ml 18 - 24 months after treatment (35).

Administration of higher doses, such as 2400 cGy which is used for the treatment of testicular relapse of acute lymphoblastic leukemia, results in both sterilization and Leydig cell dysfunction (36). Craniospinal irradiation produced primary germ cell damage in 17% of 23 children with acute lymphoblastic leukemia (37), but in none of four children with medulloblastoma (38). With adequate shielding, gonadal failure following radiation therapy to a volume that does not include the testis is infrequent (39).

Combination chemotherapy that includes an alkylating agent and procarbazine causes severe damage to the testicular germinal epithelium (11,12,13,40,41,42,43,44,45,46,47,48,49). Azoospermia was present in all men by the start of the third cycle of MVPP chemotherapy (45), and less than 20% of men had recovery of spermatogenesis when evaluated 37-48 months after treatment, suggesting that recovery of spermatogenesis in this population of patients was infrequent (44). Azoospermia occurred less frequently following treatment with two, rather than six, cycles of MOPP (50), and elevation of the basal FSH level, reflecting impaired spermatogenesis, was less frequent among patients receiving two courses of OPPA (vincristine, procarbazine, prednisone, Adriamycin), than among those who received two courses of OPPA in combination with two or more courses of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) (51).

Most studies suggest that procarbazine contributes significantly to the testicular toxicity of combination chemotherapy regimens. The combination of doxorubicin, bleomycin, vinblastine and DTIC produced oligo- or azoospermia frequently during the course of treatment. However recovery of spermatogenesis occurred after treatment was completed, in contrast to the experience reported following treatment with MOPP (46).

An early report suggested that the prepubertal testis was less sensitive than the postpubertal testis to damage by MOPP chemotherapy (43). Several groups of investigators reported that damage to the prepubertal testis could not be identified until the patient entered puberty, if the frequency of testicular damage was estimated by the presence of an elevated serum FSH level (40, 52,53,54,55). None of these studies reported that prepubertal males were at lower risk for chemotherapy induced testicular damage than were postpubertal patients.

Testicular function was evaluated in patients following treatment with combination chemotherapy for acute lymphoblastic leukemia during childhood. Basal serum FSH and LH levels were normal in 32 prepubertal boys evaluated, whereas 37.5% of eight early pubertal, and 50% of four late pubertal subjects had raised basal serum FSH levels (56). The factors that influenced the severity of testicular damage were the total dose of cyclophosphamide, administration of a cumulative dose of cytosine arabinoside

that exceeded 1 gm/M2, and the length of time between the cessation of treatment and testicular biopsy (57). Blatt et al. reported normal testicular function in 14 boys treated for ALL with therapy which did not include either cyclophosphamide or intravenous cytosine arabinoside, emphasizing the importance of the agents employed in determining the gonadal toxicity of a combination chemotherapy program (58).

Male survivors of non-Hodgkin lymphoma who received pelvic radiation therapy and cumulative cyclophosphamide dose greater than 9.5 gm/M2 were at increased risk for failure to recover spermatogenesis (59); and in survivors of Ewing and soft tissue sarcoma, in whom treatment with a cumulative cyclophosphamide dose greater than 7.5 gm/M2 was correlated with persistent oligo- or azoospermia (60).

FERTILITY

The fertility of survivors of childhood cancer, when evaluated in aggregate is impaired. The adjusted relative fertility of survivors, compared to that of their siblings was 0.85 (95% confidence interval (CI) - 0.78 - 0.92). The adjusted relative fertility of male survivors (0.76, 95% CI - 0.68 - 0.86) was slightly lower than that of female survivors (0.93, 95% CI - 0.83 - 1.04). The most significant differences in the relative fertility rates were demonstrated in male survivors who had been treated with alkylating agents, with or without infradiaphragmatic irradiation (61). This study included five-year survivors who had attained the age of 21 years, and excluded patients who had never married or who became pregnant prior to their first marriage. Women who had never menstruated and those who had undergone sterilizing surgery were excluded from the analysis. Thus the absence of a significant difference in the relative fertility for female survivors rate may be partly explained by the exclusion criteria employed.

Fertility may be impaired by factors other that the absence of sperm and ova. Conception requires delivery of sperm to the uterine cervix and patency of the Fallopian tubes for fertilization to occur and appropriate conditions in the uterus for implantation.

Retrograde ejaculation occurs with a significant frequency in men who undergo bilateral retroperitoneal lymph node dissection. Uterine structure may be affected by abdominal irradiation. A recent study demonstrated that uterine length was significantly less in ten women with ovarian failure who had been treated with whole abdomen irradiation. Endometrial thickness did not increase in response to hormone replacement therapy in three women who underwent weekly ultrasound examination. No flow was detectable with Doppler ultrasound through either uterine artery of five women, and through one uterine artery in three additional women (62).

SPECIFIC AIMS

Define fertility.

1. Compare the fertility of CCSS members to that of their sex-matched siblings by age at diagnosis, age at start of first pregnancy, diagnosis, treatment (surgery only, radiation therapy only, chemotherapy only, surgery + radiation therapy, surgery + chemotherapy, surgery + radiation therapy + chemotherapy), sterilizing surgery (yes/no – include hysterectomy, bilateral salpingo-oophorectomy). Amenorrhea (yes/no – include never had their first spontaneous menstrual period and those who never had recovery of spontaneous menstrual periods after completion of cancer therapy)
2. Compare the fertility of CCSS members by pituitary irradiation (No RT, 1 - 1800 cGy, 1801 – 2399 cGy, 2400 – 4000 cGy, > 4000 cGy, Unknown) , ovarian (testicular) irradiation (No RT, 1 – 500 cGy, 501 – 1000 cGy, 1001 - 2000 cGy, > 2000 cGy, Unknown), uterine irradiation (No RT, 1 – 500 cGy, 501 – 1000 cGy, 1001 - 2000 cGy, 2001 - 4000 cGy, > 4000 cGy, Unknown), drug administration (yes/no; drug tertiles), tobacco use (yes/no), alcohol use (yes/no)
3. Develop multivariate models for fertility using the results of the univariate analyses performed above.

HYPOTHESES

1. The fertility of CCSS members will be decreased compared to their sex-matched siblings.
2. The fertility of CCSS female members who received uterine irradiation will be decreased compared to those who did not receive such irradiation.

3. The fertility of female CCSS members who received ovarian irradiation will be decreased compared to those who did not. The relative fertility following ovarian irradiation will show a dose-response relationship, with decreasing fertility after increasing doses of ovarian irradiation.
4. The fertility of male CCSS members who received testicular irradiation will be decreased compared to those who did not. The relative fertility following testicular irradiation will show a dose-response relationship, with decreasing fertility after increasing doses of testicular irradiation.
5. The fertility of CCSS members who received pituitary irradiation will be decreased compared to those who did not. The relative fertility following pituitary irradiation will show a dose-response relationship, with decreasing fertility after increasing doses of pituitary irradiation.
6. The fertility of female and male CCSS members who received nitrogen mustard, cyclophosphamide, busulfan, chlorambucil, ifosfamide, melphalan, thiotepa, cis-platinum, cytosine arabinoside or procarbazine will be decreased compared to those CCSS members who did not receive the agent. Relative fertility following treatment with each of these agents will demonstrate a dose-response relationship, with decreasing fertility with increasing tertile of cumulative drug dose.

ANALYSIS FRAMEWORK:

These analyses will include all CCSS members who reported that they were sexually active. Comparisons will be made internally, when examining specific treatment effects, and to the sibling controls when evaluating diagnostic categories, broad treatment groups, age at diagnosis, attained age at the time of first pregnancy. The number of person-years until time of first pregnancy will be determined: those who have not become pregnant will be treated as censored data, with date of questionnaire completion (or death) as the end-point. Poisson regression models will be used for the comparisons listed in aims 1 and 2 above, using multiple regression to determine end-points for those cases whose date of first pregnancy is unknown. A multivariate model will be constructed after review of the univariate results.

TABLE I

RELATIVE FERTILITY OF FEMALES (MALES) BY AGE AT START OF PREGNANCY

AGE AT START OF FIRST PREGNANCY	CASES	SIBS	RELATIVE FERTILITY (95% CI)
< 15			
15-20			
21-25			
26-30			
31-35			
> 35			
UNKNOWN			
TOTAL			
CASES			
SIBS			

* - 95% CI – 95% Confidence Interval

TABLE II

RELATIVE FERTILITY OF FEMALES (MALES) BY DIAGNOSIS

DIAGNOSIS	N	RELATIVE FERTILITY (95% CI)
LEUKEMIA		
CNS		
HODGKIN'S		
NHL		
KIDNEY (WILMS)		
NEUROBLASTOMA		
STS		
BONE CANCER		
SIBLING CONTROL		

CNS – Central Nervous System, NHL – Non-Hodgkin's Lymphoma, STS – Soft Tissue Sarcoma
N – Number, 95% CI - 95% Confidence Interval

TABLE III

RELATIVE FERTILITY OF FEMALES (MALES) BY TREATMENT

TREATMENT	N	RELATIVE FERTILITY (95% CI)
CHEMO ONLY		
SURG ONLY		
RT ONLY		
CHEMO+SURG		
CHEMO+RT		
SURG+RT		
CHEMO+SURG+RT		
UNKNOWN		
SIBLING CONTROL		

CHEMO – Chemotherapy, SURG – Surgery, RT – Radiation therapy, N – Number, 95% CI – 95% Confidence Interval

TABLE IV

RELATIVE FERTILITY AMONG FEMALES (MALES)
BY PITUITARY IRRADIATION DOSE

	N	RELATIVE FERTILITY (95% CI)*
NO RT		
PITUITARY RT DOSE 1 - 1800 cGy		
PITUITARY RT DOSE 1801 – 2399 cGy		
PITUITARY RT DOSE 2400 – 4000 cGy		
PITUITARY RT DOSE > 4000 cGy		
PITUITARY RT UNKNOWN		

N – Number, * - 95% CI – 95% Confidence Interval

TABLE V
RELATIVE FERTILITY OF FEMALES (MALES) BY OVARIAN (TESTICULAR) IRRADIATION DOSE

TREATMENT	N	RELATIVE FERTILITY (95% CI)
NO RT		
OVARIAN (TESTICULAR) RT DOSE 1 – 500 cGy		
OVARIAN (TESTICULAR) RT DOSE 501 – 1000 cGy		
OVARIAN (TESTICULAR) RT DOSE 1001 - 2000 cGy		
OVARIAN (TESTICULAR) RT DOSE > 2000 cGy		
OVARIAN (TESTICULAR) RT UNKNOWN		

N – Number, 95% CI – 95% Confidence Interval, RT – Radiation Therapy

TABLE VI

RELATIVE FERTILITY AMONG FEMALES BY UTERINE IRRADIATION DOSE

	N	RELATIVE FERTILITY (95% CI)*
NO RT		
UTERINE RT DOSE 1 - 1800 cGy		
UTERINE RT DOSE 1801 – 2400 cGy		
UTERINE RT DOSE 2401 – 4000 cGy		
UTERINE RT DOSE > 4000 cGy		
UTERINE RT UNKNOWN		

N – Number, * - 95% CI – 95% Confidence Interval

TABLE VII
RELATIVE FERTILITY OF FEMALES (MALES) BY CHEMOTHERAPY DRUG

CHEMOTHERAPY DRUG	N	RELATIVE FERTILITY (95% CI)
ACTINOMYCIN-D		
BCNU (CARMUSTINE		
CCNU (LOMUSTINE)		
CIS-PLATINUM		
CYCLOPHOSPHAMIDE (CYTOXAN)		
DAUNORUBICIN (DAUNOMYCIN)		
DOXORUBICIN (ADRIAMYCIN)		
DTIC		
NITROGEN MUSTARD		
PROCARBAZINE		
VINBLASTINE (VELBAN)		
VINCRISTINE		
VM-26 (TENIPOSIDE)		
VP-16 (ETOPOSIDE)		

N – Number, 95% CI – 95% Confidence Interval

TABLE VIII

RELATIVE FERTILITY OF FEMALES BY CHEMOTHERAPY DRUG TERTILE

	ROUTE	DOSE	N	RELATIVE FERTILITY (95% CI)
ACTINOMYCIN-D	IV			
		LOW		
		MEDIUM		
		HIGH		
BCNU (CARMUSTINE)	IV			
		LOW		
		MEDIUM		
		HIGH		
CCNU (LOMUSTINE)	PO			
		LOW		
		MEDIUM		
		HIGH		
CIS-PLATINUM	IV			
		LOW		
		MEDIUM		
		HIGH		
CYCLOPHOSPHAMIDE	IV			
		LOW		
		MEDIUM		
		HIGH		
	PO			
		LOW		
		MEDIUM		
		HIGH		
DAUNORUBICIN	IV			
		LOW		
		MEDIUM		
		HIGH		
DOXORUBICIN	IV			
		LOW		
		MEDIUM		
		HIGH		
NITROGEN MUSTARD	IV			
		LOW		
		MEDIUM		
		HIGH		
PROCARBAZINE	PO			
		LOW		
		MEDIUM		
		HIGH		
VM-26 (TENIPOSIDE)	IV			
		LOW		
		MEDIUM		
		HIGH		
VP-16 (ETOPOSIDE)	IV			
		LOW		
		MEDIUM		

HIGH

N – Number, 95% CI – 95% Confidence Interval

REFERENCES

1. Gloeckler Ries LA, Smith MA, Gurney JG, Linet M, Tamra T, Young JL Jr, et al (editors). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975 – 1995. National Cancer Institute. SEER Program. NIH. Publication Number 99-4649. Bethesda MD. 1999.
2. Sanders JE, Buckner CD, Amos D, Levy W, Appelbaum FR, Doney K, Storb R, Sullivan KM, Witherspoon RP, Thomas Ed. Ovarian function following marrow transplantation for aplastic anemia or leukemia. Blood 1988;6:813-818.
3. Sarafoglou K, Boulad F, Gillio A,Sklar C. Gonadal function after bone marrow transplantation for acute leukemia during childhood. J Pediatr 1997;130:210-216.
4. Wallace WHB, Shalet SM, Crowne EC, Morris-Jones PH, Gattamaneni HR. Ovarian failure following abdominal irradiation in childhood: Natural history and prognosis. Clin Oncol 1989;1:75-79.
5. Scott JES. Pubertal development in children treated for nephroblastoma. J Pediatr Surg 1981;16:122-125.
6. Hamre MR, Robison LL, Nesbit ME, et al. Effects of radiation on ovarian function in long-term survivors of childhood acute lymphoblastic leukemia: A report from the Children's Cancer Study Group. J Clin Oncol 1987;5:1759-1765.
7. Wallace WHB, Shalet SM, Tetlow LJ, et al. Ovarian function following the treatment of childhood acute lymphoblastic leukemia. Med Pediatr Oncol 1993;21:333-339.
8. Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, Jaffe N and Li FP. Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol 1981;139:62-66.
9. Himelstein-Braw R, Peters H, Faber M. Influence of irradiation and chemotherapy on the ovaries of children with abdominal tumours. Br J Cancer 1977;36:269-275.
10. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effect of combination chemotherapy on ovarian function in women treated for Hodgkin's disease. Cancer 1983;52:988-993.
11. King DJ, Ratcliffe MA, Dawson AA, Bennett F, MacGregor JE, Klopper AI. Fertility in young men and women after treatment for lymphoma: A study of a population. J Clin Pathol 1985;38:1247-1251.
12. Mackie EJ, Radford M, Shalet SM. Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 1996;27:74-78.
13. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Gonadal function following chemotherapy for Hodgkin's disease: A comparative study of MVPP and a seven-drug hybrid regimen. J Clin Oncol 1995;13:134-139.
14. Hudson MM, Greenwald C, Thompson, E, Wilimas J, Marina N, Fairclough D, Kaufffman W, Bozeman P, Mackert PW, Abromowitch M, Jenkins J, Boulden T, Kun L. Efficacy and toxicity of multiagent chemotherapy and low-dose involved-field radiotherapy in children and adolescents with Hodgkin's disease. J Clin Oncol 1993;11:100-108.
15. Papadakis V, Vlachopapadopoulou E, Van Cyckle K, Granshaw L, Kalmanti M, Tan C, Sklar C. Gonadal function in young patients successfully treated for Hodgkin disease. Med Pediatr Oncol 1999;32:366-372.
16. Mackie EJ, Radford M, Shalet SS. Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 1996;27:74-78.
17. Sy Ortin TT, Shostak CA, Donaldson SS. Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: the Stanford experience. Int J Rad Oncol Biol Phys 1990;19:873-880.
18. Chapman RM, Sutcliffe SB, Malpas JS. Cytotoxic-induced ovarian failure in women with Hodgkin's disease. I. Hormone function. JAMA 1979;242:1877-1881.
19. Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT. Long-term follow-up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 1981;71:552-556.
20. Waxman JHX, Terry YA, Wrigley PFM, Malpas JS, Rees LH, Besser GM, Lister TA. Gonadal function in Hodgkin's disease:long-term follow-up of chemotherapy. Br Med J 1982;285:1612-1613.
21. Santoro A, Bonadonna G, Valagussa P, Zucali R, Viviani S, Villani F, Pagnani AM, Bonfante V, Musumeci R, Crippa F, Tess JDT, Banfi A. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease:Superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 1987;5:27-37.
22. Andrieu JM, Ochoa-Molina ME. Menstrual cycle, pregnancies and offspring before and after MOPP therapy for Hodgkin's disease. Cancer 1983;52:435-438.

23. Green DM, Yakar D, Brecher ML, Lindsay AN, Voorhess ML, MacGillivray MH. Ovarian function in adolescent women following successful treatment for non-Hodgkin's lymphoma. Am J Pediatr Hematol/Oncol 1983;5:27-31.
24. Siris ES, Leventhal BG, Vaitukaitis JL. Effects of childhood leukemia and chemotherapy on puberty and reproductive function in girls. N Engl J Med 1976;294:1143-1146.
25. Wallace WHB, Shalet SM, Crowne EC, Morris-Jones PH, Gattamaneni HR, Price DA. Gonadal dysfunction due to cis-platinum. Med Pediatr Oncol 1989;17:409-413.
26. Byrne J, Fears TR, Gail MH, Pee D, Connelly RR, Austin DF, Holmes GF, Holmes FF, Latourette HB, Meigs JW, Strong LC, Myers MH, Mulvihill JJ. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 1992;166:788-793.
27. Madsen BL, Giudice L, Donaldson SS. Radiation-induced premature menopause: A misconception. Int J Rad Oncol Biol Phys 1995;32:1461-1464.
28. Narayan P, Lange PH, Fraley EE. Ejaculation and fertility after extended retroperitoneal lymph node dissection for testicular cancer. J Urol 1982;127:685-688.
29. Nijman JM, Jager S, Boer PW, Kremer J, Oldoff J, Schraffordt-Koops H. The reatment of ejaculation disorders after retroperitoneal lymph node dissection. Cancer 1982;50:2967-2971.
30. Schlegel PN, Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol 1987;138:1402-1406.
31. Shalet SM, Beardwell CG, Jacobs HS, et al. Testicular function following irradiation of the human prepubertal testis. Clin Endocrinol 1978;9:483-490.
32. Speiser B, Rubin P, Casarett G. Aspermia following lower truncal iradiation in hodgkin's disease. Cancer 1973;32:692-698.
33. Hahn EW, Feingold SM, Nisce L. Aspermia and recovery of spermatogenesis in cancer patients following incidental gonadal irradiation during treatment: A progress report. Radiology 1976;119:223-225.
34. Pedrick TJ, Hoppe RT. Recovery of spermatogenesis following pelvic irradiation for Hodgkin's disease. Int J Rad Oncol Biol Phys 1986;12:117-121.
35. Kinsella TJ, Trivette G, Rowland J, et al. Long-term follow-up of testicular function following radiation therapy for early-stage Hodgkin's disease. J Clin Oncol 1989;7:718-724.
36. Blatt J, Sherins RJ, Niebrugge D, Bleyer WA, Poplack DG. Leydig cell function in boys following tratment for testicular relapse of acute lymphoblastic leukemia. J Clin Oncol 1985;3:1227-1231.
37. Sklar CA, Robison LL, Nesbit ME, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: A report from the Childrens Cancer Study Group. J Clin Oncol 1990;8:1981-1987.
38. Ahmed SR, Shalet SM, Campbell RHA, et al. Primary gonadal damage following treatment of brain tumors in childhood. J Pediatr 1983;103:562-565.
39. Fraass BA, Kinsella TJ, Harrington FS, et al. Peripheral dose to the testes: The design and clinical use of a practical and effective gonadal shield. Int J Rad Oncol Biol Phys 1985;11:609-615.
40. Shafford EA, Kingston JE, Malpas JS, Plowman PN, Pritchard J, Savage MO, Eden OB. Testicular function following the treatment of Hodgkin's disease in childhood. Br J Cancer 1993;68:1199-1204.
41. DeVita VT, Arseneau JC, Sherins RJ, Canellos GP, Young RC. Intensive chemotherapy for Hodgkin's disease:Long-term complications. Nat Cancer Inst Monogr 1973;36:447-454.
42. Asbjornsen G, Molne K, Klepp O, Aakvaag A. Testicular function after combination chemotherapy for Hodgkin's disease. Scand J Haematol 1976;16:66-69.
43. Sherins RJ, Olweny CLM, Ziegler JL. Gynecomastia and gonadal dysfunction in adolescent boys treated with combination chemotherapy for Hodgkin's disease. N Engl J Med 1978;299:12-16.
44. Chapman RM, Rees LH, Sutcliffe SB, Edwards CRW, Malpas JS. Cyclical combination chemotherapy and gonadal function. Lancet 1979;1:285-289.
45. Chapman RM, Sutcliffe SB, Malpas JS. Male gonadal dysfunction in Hodgkin's disease. JAMA 1981;245:1323-1328.
46. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol 1985;21:601-605.
47. Charak BS, Gupta R, Mandrekar P, Sheth NA, Banavali SD, Saikia TK, Gopal R, Dinshaw KA, Advani SH. Testicular dysfunction after cyclophosphamide-vincristine-procarbazine-prednisolone

chemotherapy for advanced Hodgkin's disease. A long-term follow-up study. Cancer 1990;65:1903-1906.
48. Dhabhar BN, Malhotra H, Joseph R, Garde S, Bhasin S, Sheth A, Advani SH. Gonadal function in prepubertal boys following treatment for Hodgkin's disease. Am J Pediatr Hematol/Oncol 1993;15:306-310.
49. Heikens J, Behrendt H, Adriaansse R, Berghout A. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. Cancer 1996;78:2020-2024.
50. da Cunha MF, Meistrich ML, Fuller LM, Cundiff JH, Hagemeister FB, Velasquez WS, McLaughlin P, Riggs SA, Cabanillas FF, Salvador PG. Recovery of spermatogenesis after treatment for Hodgkin's disease:Limiting dose of MOPP chemotherapy. J Clin Oncol 1984;2:571-577.
51. Braumswig JH, Heimes U, Heiermann E, Schletel W, Nieschlag E, Schellong G. The effects of different cumulative doses of chemotherapy on testicular function. Results in 75 patients treated for Hodgkin's disease during childhood or adolescence. Cancer 1990;65:1298-1302.
52. Green DM, Brecher ML, Lindsay AN, Yakar D, Voorhess ML, MacGilivray MH, Freeman AI. Gonadal function in pediatric patients following treatment for Hodgkin's disease. Med Pediatr Oncol 1981;9:235-244.
53. Whitehead E, Shalet SM, Morris-Jones PH, Beardwell CG, Deakin DP. Gonadal function after combination chemotherapy for Hodgkin's disease in childhood. Arch Dis Child 1982;47:287-291.
54. Aubier F, Flamant F, Brauner R, Caillaud JM, Chaussin JM, Lemerle J. Male gonadal function after chemotherapy for solid tumors in childhood. J Clin Oncol 1989;7:304-309.
55. Jaffe N, Sullivan MP, Ried H, Boen H, Marshall R, Meistrich M, Maor M, da Cunha M. Male reproductive function in long-term survivors of childhood cancer. Med Pediatr Oncol 1988;16:241-247.
56. Shalet SM, Hann IM, Lendon M, Morris-Jones PH, Beardwell CG. Testicular function after combination chemotherapy for acute lymphoblastic leukemia. Arch Dis Child 1981;56:275-278.
57. Lendon M, Palmer MK, Morris-Jones PH, Hann IM, Shalet SM. Testicular histology after combination chemotherapy in childhood for acute lymphoblastic leukaemia. Lancet 1978;2:439-441.
58. Blatt J, Poplack DG, Sherins RJ. Testicular function in boys after chemotherapy for acute lymphoblastic leukemia. N Engl J Med 1981;304:1121-1124.
59. Pryzant RM, Meistrich ML, Wilson G, et al. Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphoma. J Clin Oncol 1993;11:239-247.
60. Meistrich ML, Wilson G, Brown BW, et al. Impact of cyclophosphamide and long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer 1992;70:2703-2712.
61. Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K, Holmes GF, Holmes FF, Latourette HB, Weyer PJ, Meigs JW, Teta MJ, Cook JW, Strong LC. Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 1987;317:1315-1321.
62. Critchley HOD, Wallace WHB, Shalet SM, Mamtora H, Higginson J, Anderson DC. Abdominal irradiation in childhood:the potential for pregnancy. Br J Obstet Gynecol 1992;99:392-394.