

**JOVENS  
NA ONCOLOGIA**

SIMPÓSIO NACIONAL

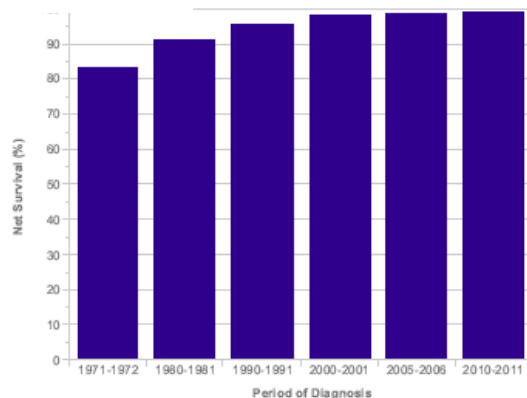


# PRESERVAÇÃO FERTILIDADE HOMEM

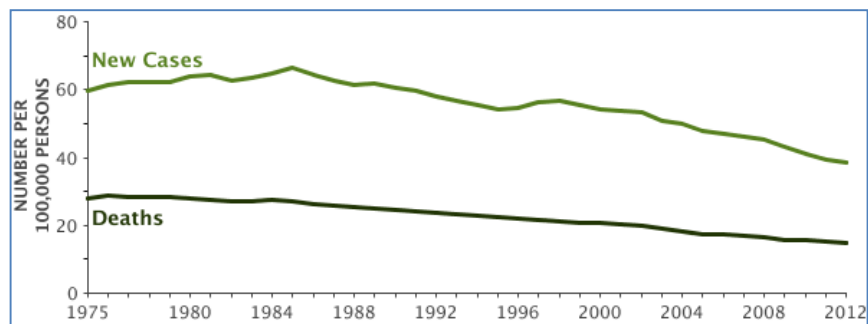
## Recomendações

Alexandra Teixeira

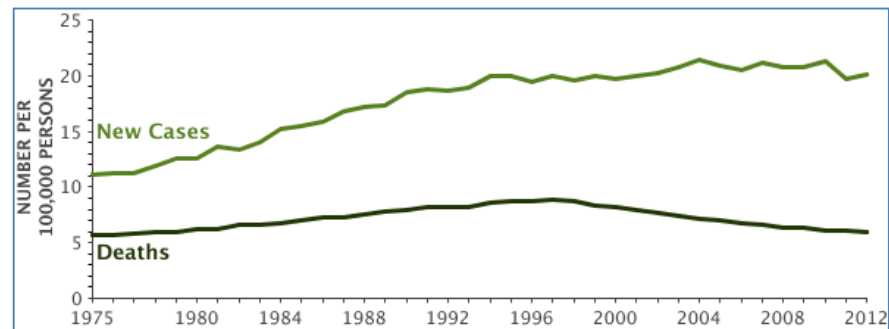
O número de adultos jovens "long survivors" tem crescido e a preocupação com os efeitos tardios relacionados com os tratamentos tem emergido, dentro deles o comprometimento com fertilidade futura.



**Testicular Cancer (C62): 1971-2011**  
Age-Standardised One-Year Net Survival, England and Wales



SEER Stat Fact Sheets: Colon and Rectum Cancer



SEER Stat Fact Sheets: Non-Hodgkin Lymphoma

## Fertility of Male Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Ann C. Mertens, Sarah S. Donaldson, Julianne Byrne, and Leslie L. Robison

### ABSTRACT

#### Purpose

This study was undertaken to determine the effect of treatment for childhood cancer on male fertility.

#### Patients and Methods

We reviewed the fertility of male Childhood Cancer Survivor Study survivor and sibling cohorts who completed a questionnaire. We abstracted the chemotherapeutic agents administered, the cumulative dose of drug administered for selected drugs, and the doses and volumes of all radiation therapy from medical records. Risk factors for siring a pregnancy were evaluated using Cox proportional hazards models.

#### Results

The 6,224 survivors age 15 to 44 years who were not surgically sterile were less likely to sire a pregnancy than siblings (hazard ratio [HR], 0.56; 95% CI, -0.49 to 0.63). Among survivors, the HR of siring a pregnancy was decreased by radiation therapy of more than 7.5 Gy to the testes (HR, 0.12; 95% CI, -0.02 to 0.64), higher cumulative alkylating agent dose (AAD) score or treatment with cyclophosphamide (third tertile HR, 0.42; 95% CI, -0.31 to 0.57) or procarbazine (second tertile HR, 0.48; 95% CI, -0.26 to 0.87; third tertile HR, 0.17; 95% CI, -0.07 to 0.41). Compared with siblings, the HR for ever siring a pregnancy for survivors who had an AAD score = 0, a hypothalamic/pituitary radiation dose = 0 Gy, and a testes radiation dose = 0 Gy was 0.91 (95% CI, 0.73 to 1.14;  $P = .41$ ).

#### Conclusion

This large study identified risk factors for decreased fertility that may be used for counseling male cancer patients.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

- **Risco de infertilidade** dependente da idade do doente, do tipo de tumor e do tratamento a realizar: Elevado (probabilidade superior a 80%), Intermédio (probabilidade 20-80%), Baixo (probabilidade inferior a 20%)
- **Mecanismos:**
  - Gonadotoxicidade directa, qdo lesão direta do epitélio seminífero no testículo
  - Gonadotoxicidade indirecta, qdo alterações a nível do funcionamento do eixo hipotálamo- hipófise-gónadas
  - Alts a nível das funções erétil ou ejaculatória

## CIRURGIA:

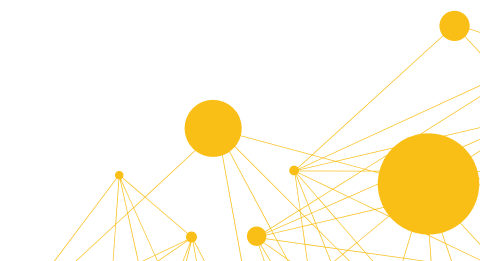
- Local da cirurgia fator mais relevante
- Impacto direto na função reprodutora, com possibilidade de infertilidade permanente.

CIRURGIA CONSERVADORA/ PRESERVADORA DE FERTILIDADE deve ser oferecida sempre que possível, aos doentes em idade fértil e que manifestem desejo de vir a ter filhos.

## **QUIMIOTERAPIA:**

- Lesão no epitélio seminífero, com alts consequentes da espermatogénese
- Dano nas células de Leydig, responsáveis pela produção de testosterona.
- Potencialmente causador de mutações nas células germinativas

Jensen J. et al. Fertility preservation. Mayo Clin Proc. 2011; 86: 45-49  
Meistrich M. Pediatr Blood Cancer. 2009; 53(2): 261-266



**Table 1: The impact of common chemotherapeutics on male fertility**

Agent	Mechanism of action	Example (s)	Some diseases utilizing drugs	Effect on spermatogenesis
Platinum based agents	Cross-linking DNA, impair DNA synthesis/transcription and function	Cisplatin, carboplatin	Bladder cancer, germ cell tumor, HL, NHL	Spermatogenesis affected, possible chromosomal aberrations <sup>[19]</sup> Less impact with carboplatin <sup>[20]</sup>
Antimetabolites	Interferes with DNA transcription	Fluorouracil, 6-mercaptopurine, methotrexate, gemcitabine	Colorectal cancer, HL, NHL, bladder cancer, leukemia	Spermatogenesis affected, <sup>[21]</sup> possible chromosomal aberrations <sup>[22]</sup>
Vinca alkyloids	Inhibit microtubule polymerization	Vincristine, vinblastine	HL, NHL, leukemia	Arrest in spermatogenesis and affects spermatozoa motility <sup>[23]</sup> Vinblastine is cytotoxic to primary spermatocytes <sup>[24]</sup>
Alkylating agents	DNA base pair alkylation, formation of abnormal DNA cross-bridges, and mis-pairing of nucleotides	Busulfan, cyclophosphamide, chlorambucil, procarbazine, ifosfamide	Germ cell tumors, sarcomas, HL, NHL	Most toxic class; Induces azoospermia within 90 days <sup>[25]</sup> Irreversible effect <sup>[7,26]</sup> mutagenic in all stages of spermatogenesis; but does not cause aneuploidy <sup>[27]</sup>
Topoisomerase Inhibitors	prevents DNA supercoiling and interfere with DNA transcription/replication,	Etoposide, doxorubicin	Sarcomas, germ cell tumors, HL, NHL,	Cytotoxic with possible chromosomal anomalies <sup>[28]</sup>

HL: Hodgkin's lymphoma, NHL: NonHodgkin's lymphoma, DNA: Deoxyribonucleic acid

## **TERAPÊUTICAS BIOLÓGICAS:**

- Pouca informação sobre impacto destas na fertilidade

## **IMUNOTERAPIA:**

- Impacto na fertilidade pouco conhecido (ipilimumab com interferência na fertilidade por via de endocrinopatia imune)

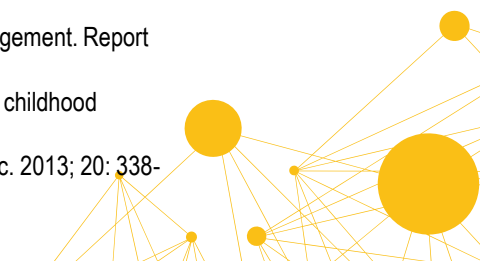
## **IDO RADIOACTIVO:**

- Não causador de infertilidade

## **RADIOTERAPIA:**

- Gónadas muito sensíveis à radiação
- Efeito dependente: dose, esquema de fracionamento, campo de irradiação
- Espermatozoides extremamente sensíveis à radiação independentemente da idade; as células de Leydig são altamente sensíveis à radiação antes da puberdade e mais resistentes em idade adulta.

"The Effects of cancer treatment on reproductive functions". Guidance of Management. Report of a working group. Nov 2007  
Green D. et al. Fertility of male survivors of childhood cancer: a report from the childhood cancer survivor study. JCO. 2010; 28: 332-8  
Roon R. et al. Oncofertility in Canada: the impact of cancer on fertility. Curr Onc. 2013; 20: 338-344



### **Table 3** Radiation therapy protocols with high or intermediate impact on ovarian and testicular function

#### **Prolonged azoospermia in males or amenorrhea in females**

##### **High risk**

Total body irradiation for bone marrow transplant/stem cell transplant

Testicular radiation dose  $>2.5$  Gy in adult men

Testicular radiation dose  $\geq 6$  Gy in prepubertal boys

Pelvic or whole abdominal radiation dose  $\geq 6$  Gy in adult women

Pelvic or whole abdominal radiation dose  $\geq 10$  Gy in postpubertal girls

Pelvic or whole abdominal radiation dose  $\geq 15$  Gy in prepubertal girls

##### **Intermediate risk**

Testicular radiation dose 1–6 Gy from scattered pelvic or abdominal radiation

Pelvic or whole abdominal radiation dose 5–10 Gy in postpubertal girls

Pelvic or whole abdominal radiation dose 10–15 Gy in prepubertal girls

Craniospinal radiotherapy dose  $\geq 25$  Gy

**Note:** Reprinted with permission from Rodriguez-Wallberg KA, Oktay K. Fertility preservation medicine: options for young adults and children with cancer. *J Pediatr Hematol Oncol.* 32(5):390–396.<sup>48</sup>



# TÉCNICAS PRESERVAÇÃO FERTILIDADE:

- Criopreservação de espermatozoides
- Criopreservação de tecido testicular



## **CRIOPRESERVAÇÃO ESPERMATOZOIDES:**

- Procedimento bem estabelecido e simples
- Recomendadas 3 colheitas pela Sociedade Americana de Reprodução, com período de abstinência de 48 horas.
- Qdo colheita não possível por masturbação, colheita de esperma por meio de outros procedimentos: electroejaculação, estimulação por vibrador ou biópsia testicular

"The Effects of cancer treatment on reproductive functions". Guidance of Management. Report of a working group. Nov 2007

Osterberg C. et al. Current practices in fertility preservation in male cancer patients. Urology Annals. 2014; 6: 13-6

Rodriguez et al. Fertility preservation during cancer treatment: clinical guidelines. Cancer management and research 2014




TABLE 1

Overview of recent studies describing use rate of cryopreserved semen and outcome.

	Total no. of patients who banked semen	Discontinuation	Disease group	Duration of the program	No. of patients who used their banked semen (%)	IUI cycles (pregnancies)	IVF cycles (pregnancies)	ICSI cycles (pregnancies)	Frozen ETs (pregnancies)	No. of pregnancies with ART	Couples achieving parenthood (%)	Live births
(20)	—	—	Diverse	1–18 years + IVF treatment in 1999–2002	21	—	—	62	18	26	12/21 (57.0)	23 (5 twins)
(21)	164 92 prior to therapy	37	Diverse	10 years, 1993–2003	6/164 (3.7)	10 (0); 3 intracervical inseminations	5 (1)	3 (1)	—	2	2/6 (33.3)	2
(22)	422	—	Testicular germ cell tumors	1983–2002	29/422 (6.9)	—	—	—	—	16	14/29 (48.3)	15; 1 twice pregnant; 1 triple pregnancy
(23)	686	124	Diverse	1986–2001	36/686 (5.2)	40 (3)	6 (0)	42 (11)	—	14	12/28 (43); 8 lost to follow-up	12; 2 ongoing
(24)	184	16	Diverse	1991–2004	30/184 (16.3)	5 (1)	—	25 (14)	5 (1)	16	12/30 (40.0)	12; 3 ongoing
(25)	316	—	Diverse	1982–2001	29/316 (9.2)	42 (3)	26 (6)	19 (7)	—	15	11/29 (37.9)	19; 3 twins; 2 triplets
(26)	833	191	Diverse	1980–2002	64/833 (7.7)	35 (11)	22 (6)	22 (12)	—	20	29 (45.3)	39
(27)	306	?	Diverse	11 years	11/306 (3.6)	12 (3)	14 (2)	6 (4)	7 (0)	9	8/11 (72.3)	9; 1 twin
Our results	557	120	Diverse	1983–2004	42/557 (7.5)	7 (1)	32 (8)	53 (16)	9 (2)	27	18/37 (46.8)	25; 3 twins; 2 ongoing

van Casteren. Use rate and ART outcome of banked semen. Fertil Steril 2008

## **CRIOPRESERVAÇÃO TECIDO TESTICULAR:**

- Em doentes que não conseguem obter uma amostra de esperma adequada ou a rapazes pré-puberes (nesta idade considerada experimental)
- Objectivo: utilização de espermatozoides isolados do tecido biopsado em técnicas de PMA ou transplantação deste tecido de volta para o doente após a cura (no caso de crianças) com a possibilidade de restaurar a espermatogénese a partir das espermatogónias criopreservadas.
- Ainda não possível demonstrar eficácia

# TÉCNICAS PROTEÇÃO FERTILIDADE:

- Cirurgia Conservadora: Cancro do testículo, se massa de tumoral pequenas dimensões e se a orquiectomia radical resultar em anorquia. Devem ser avaliados benefícios vs risco de recidiva tumoral.
- Análogos LHRH: sem eficácia na preservação de fertilidade ou na obtenção de retorno mais rápido da espermatogénese após quimioterapia.
- Proteção gonadal: com material blindado, quando RT local para reduzir exposição à radiação dos órgãos reprodutores e proteger função reprodutora.

"The Effects of cancer treatment on reproductive functions". Guidance of Management. Report of a working group.  
Nov 2007

Rodriguez et al. Fertility preservation during cancer treatment: clinical guidelines. Cancer management and research  
2014

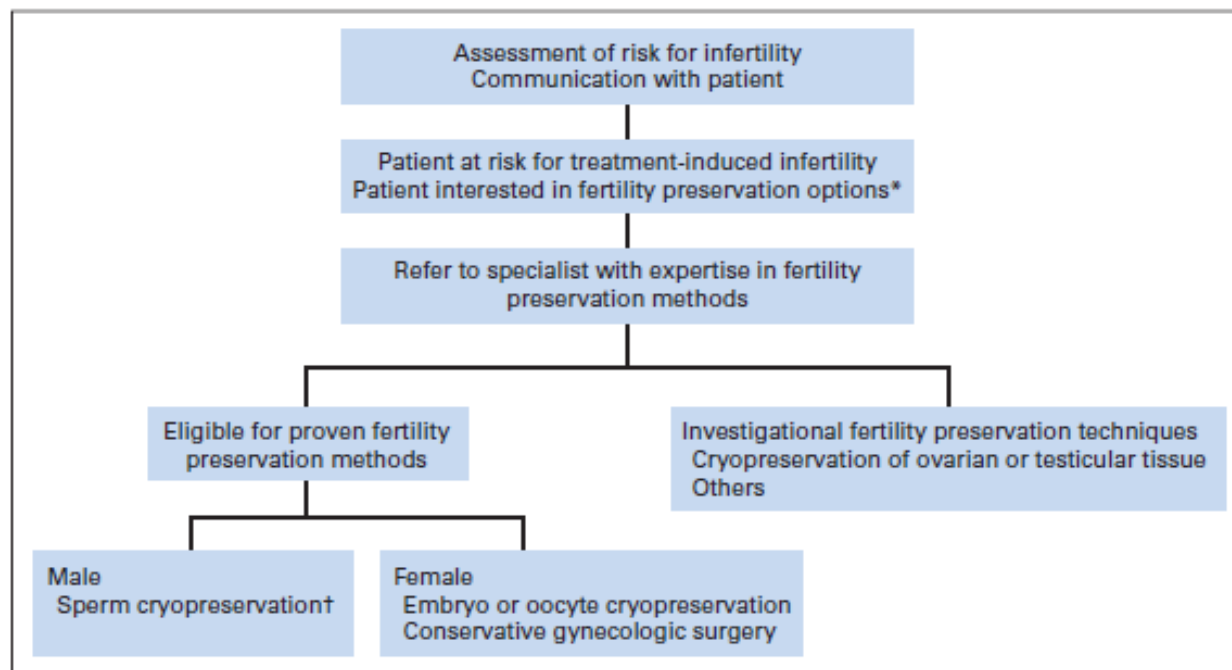
Loren et al. Fertility Preservation for Patients with Cancer: ASCO Clinical Practice Guideline Update. JCO 2013; 31:  
2500

### ***Key Recommendations***

- Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy
- Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists
- Address fertility preservation as early as possible, before treatment starts
- Document fertility preservation discussions in the medical record
- Answer basic questions about whether fertility preservation may have an impact on successful cancer treatment
- Refer patients to psychosocial providers if they experience distress about potential infertility
- Encourage patients to participate in registries and clinical studies

### ***Adult Males***

- Present sperm cryopreservation (sperm banking) as the only established fertility preservation method
- Do not recommend hormonal therapy in men; it is not successful in preserving fertility
- Inform patients that other methods (eg, testicular tissue cryopreservation, which does not require sexual maturity, for the purpose of future reimplantation or grafting of human testicular tissue) are experimental
- Advise men of a potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy



**Fig 1.** Fertility preservation assessment and discussion algorithm for patients with cancer. (\*) Patients should be encouraged to contact their insurance company to ascertain out-of-pocket costs. (†) Some patients may proceed with this without the prior step of seeing a reproductive specialist. However, consultation with a reproductive specialist is recommended.

