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IRCBG_20085
"La preservazione della fertilità in oncoematologia "

Neoplasie in età pediatrica e rischi per la fertilità

Trieste, 15 dicembre 2020

Dott. Marco Rabusin

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DIAGNOSI	Tasso/1.000.000
totali	**146.7**
LLA	40
LMA	8.2
T SnC	33.4
Hodgkin	7.2
LnH	6.8
Neuroblastoma	10.4
Sarcomi parti molli	8.5
Tumori ossei	8.3

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DIAGNOSI	Tasso /1.000.000
Totali	**204.0**
Hodgkin	34.4
Tumori a cell. germinali	26.0
T SNC	20
LLA/LMA	20
Ca tiroide	16.8
Melanoma	15.5
Tumori ossei	14.9

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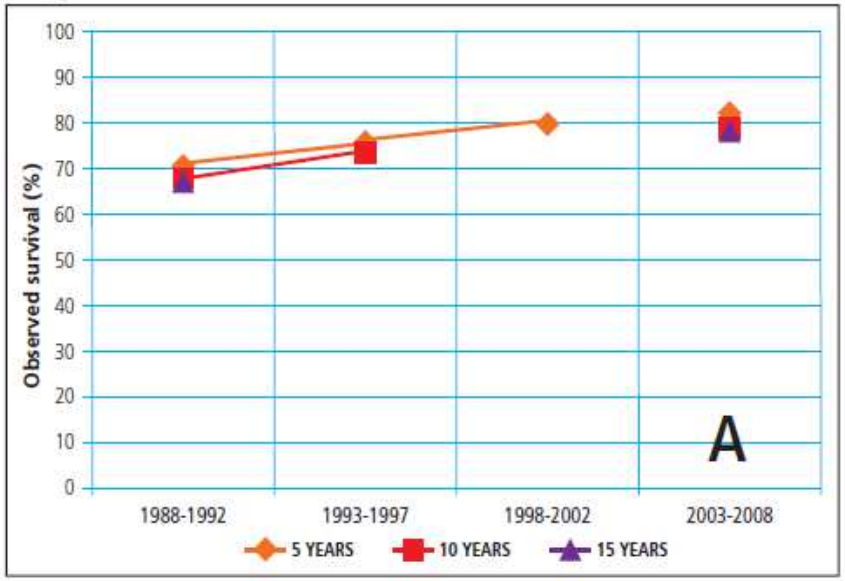
ALL MALIGNANT TUMOURS

AIRTUM

CUMULATIVE SURVIVAL BY PERIOD
POOL 1988-2008

0-14
YEARS

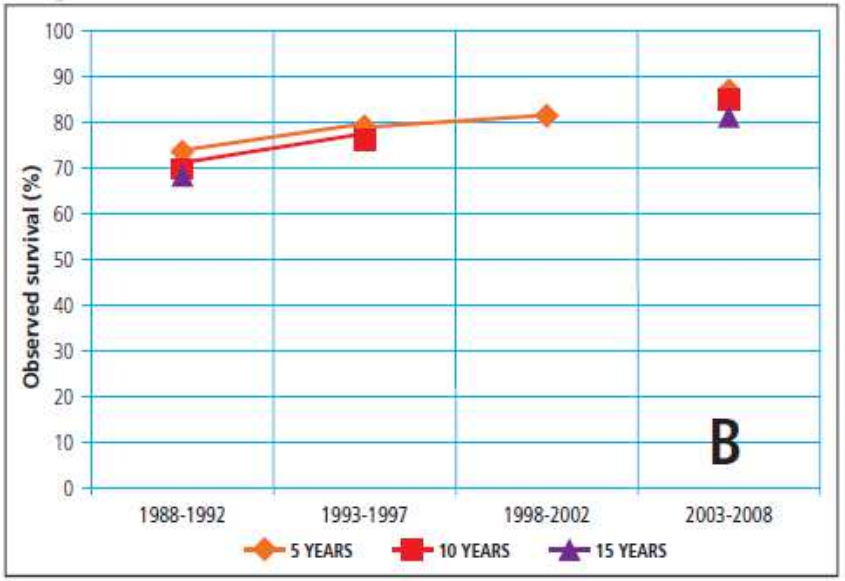


ALL MALIGNANT TUMOURS

AIRTUM

CUMULATIVE SURVIVAL BY PERIOD
POOL 1988-2008

15-19
YEARS



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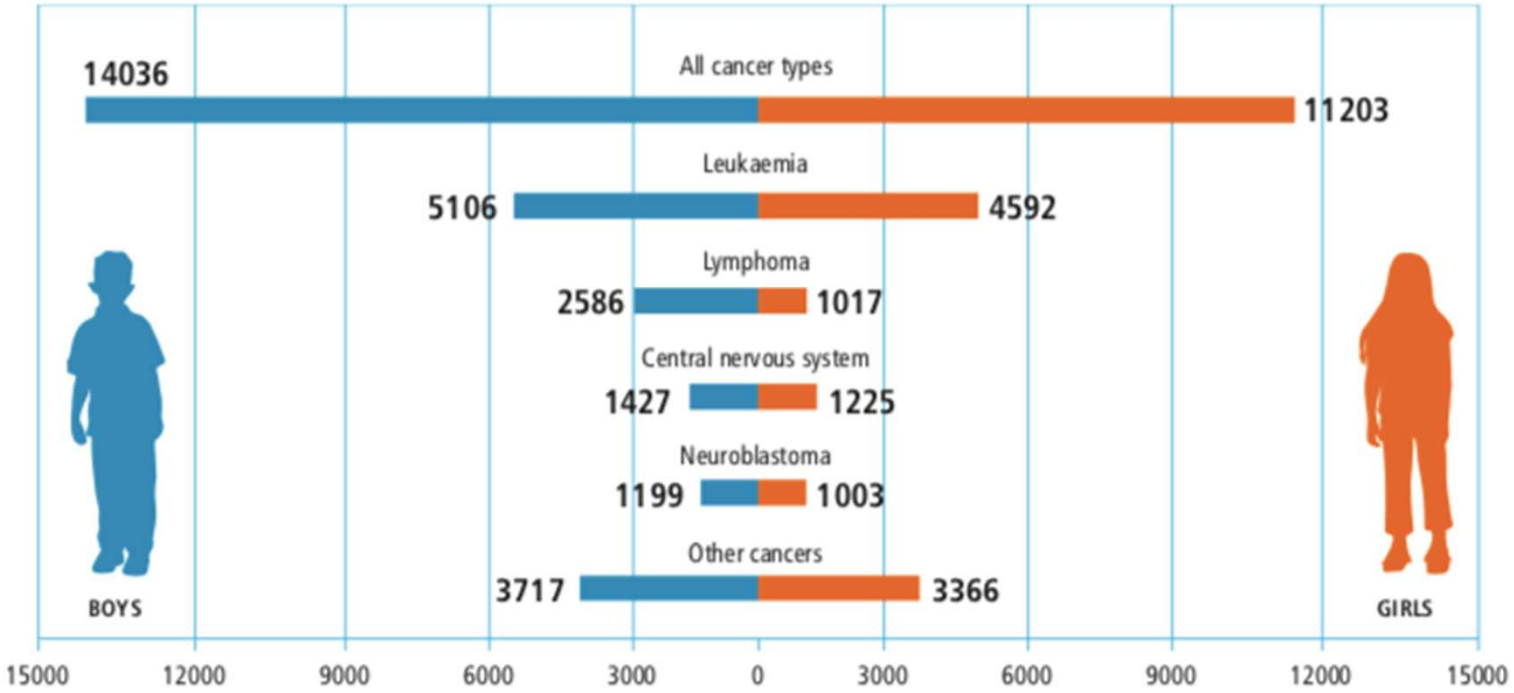

Figura 1. Numero stimato di persone di età 0-33 anni in vita dopo una diagnosi di tumore all'età di 0-14 anni, per sesso per una scelta di sede o tipologia, secondo la classificazione ICCC.[3] Italia – 1 gennaio 2009.

Figure 1. Estimated number of peolpe aged 0-33 years living after a cancer diagnosis at ages 0-14 years, by sex for selected cancer sites or types, according to the International Classification of Childhood Cancer (ICCC).[3] Italy – January 1, 2009.

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- Tra gli adulti guariti da tumore in età pediatrica il 60 % presenta una o più malattie croniche
- Gruppi a maggiore rischio guariti da tumore SNC o dopo trapianto CSE
- Età alla diagnosi, dosaggio cumulativo di chemioterapia e radioterapia fattori di rischio
- Rischio di mortalità triplo rispetto alla popolazione generale con neoplasie secondarie, patologie cardiocircolatorie e polmonari come cause principali

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Complicanze endocrinologiche

- Frequenti, dal 20 al 50 % dei pazienti guariti
- Difetto dell'ormone della crescita, dopo trattamento con RTC
- Insufficienza ovarica secondaria a radioterapia addominale e trattamento con agenti alchilanti, minor rischio in età precoce
- Danno testicolare con maggiore sensibilità delle cellule di Sertoli, età indifferente
- Ipotiroidismo clinico o subclinico

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Insufficienza ovarica precoce non chirugica

- Causa di infertilità e di numerose sequele legate alla ridotta produzione di estrogeni
- Agenti alchilanti : busulfano, ciclofosfamide, ifosfamide, melfalan, tiotepa, carmustina,lomustina
- Procarbazina, temozolamide, carbo+cisplatino
- RT ovarica
- Ovariectomia
- Rischio di danno aumenta con l'età

- Agenti alchilanti a dosaggio elevato (TCSE)
- Agenti alchilanti in combinazione
- Dosaggio di radioterapia con coinvolgimento ovarico nel paziente pre-pubere >10-15 Gy o > 5-10 Gy in età puberale
- Agenti alchilanti in associazione a RT

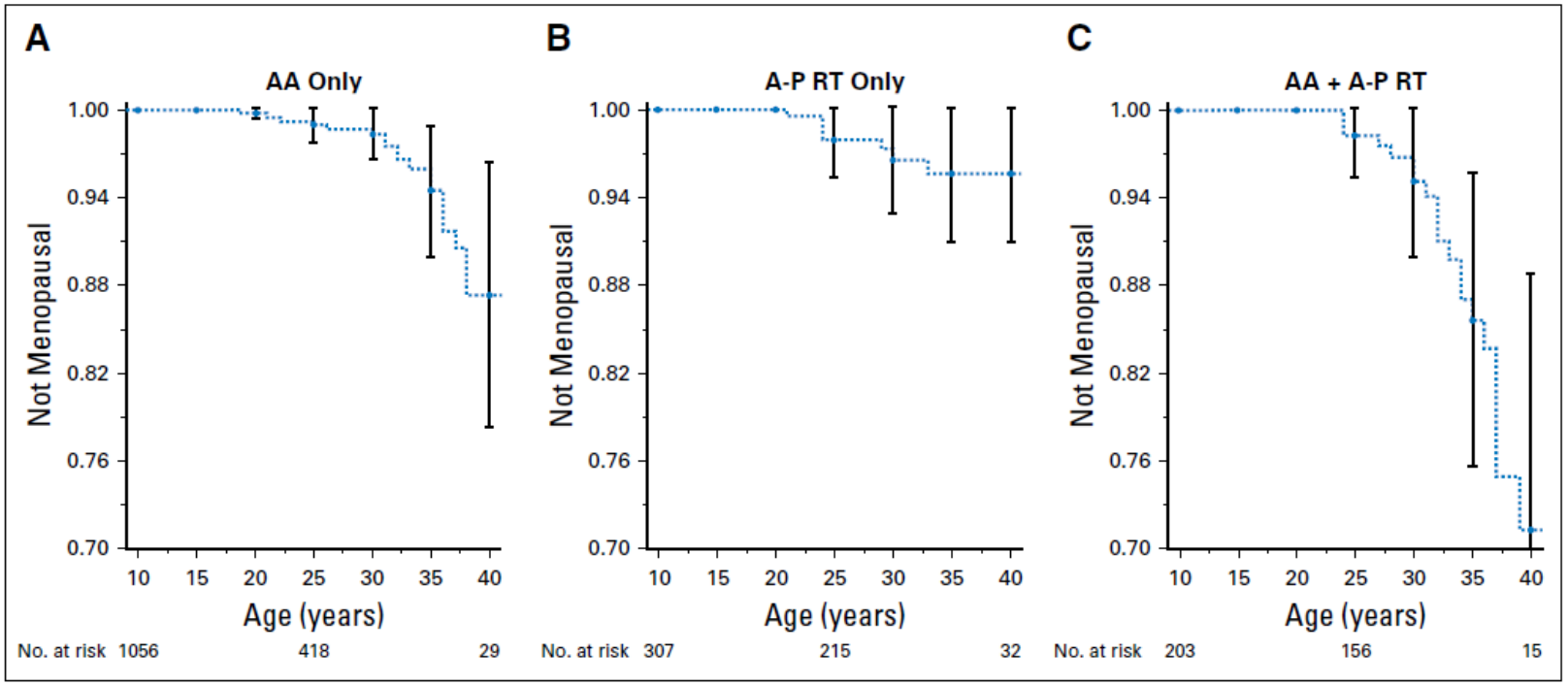

Fig 3. The cumulative incidence of nonsurgical menopause in female survivors of childhood cancer demonstrating increasing incidence of menopause with advancing age and relationship to gonadotoxic cancer therapy. (A) Treatment with alkylating agents (AA); (B) treatment with abdominal-pelvic radiotherapy (A-P RT) only; and (C) treatment with AA plus A-P RT, which was associated with the highest incidence. NOTE. Study cohort does not include females who developed ovarian failure within the first 5 years. Reprinted with permission from Sklar et al.[9]

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Danno gonadico nel maschio : età al trattamento indifferente

- **Alterata spermatogenesi** con azospermia o oligospermia
- Agenti alchilanti, procarbazina,temozolamide, carboplatino/cisplatino
- RT testicolare: 1-3 Gy azospermia potenzialmente reversibile, > 6 Gy azospermia permanente
- Orchiectomia unilaterale

- **Difetto di testosterone**
- Classi di chemioterapici analoghe
- Cellule di Leydig più resistenti al danno da RT che si instaura a dosaggi > a 20 Gy in fase pre-puberale o 30 Gy in età post-pubere
- **Disfunzione erettile o eiaculatoria**
- Associata con chirurgia spinale,pelvica e vescicale o RT

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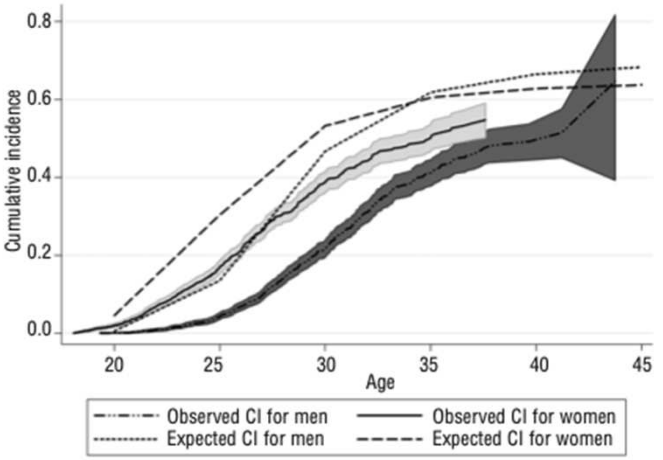
haematologica | 2011; 96(5)

Original Articles

Marriage and parenthood among childhood cancer survivors: a report from the Italian AIEOP Off-Therapy Registry



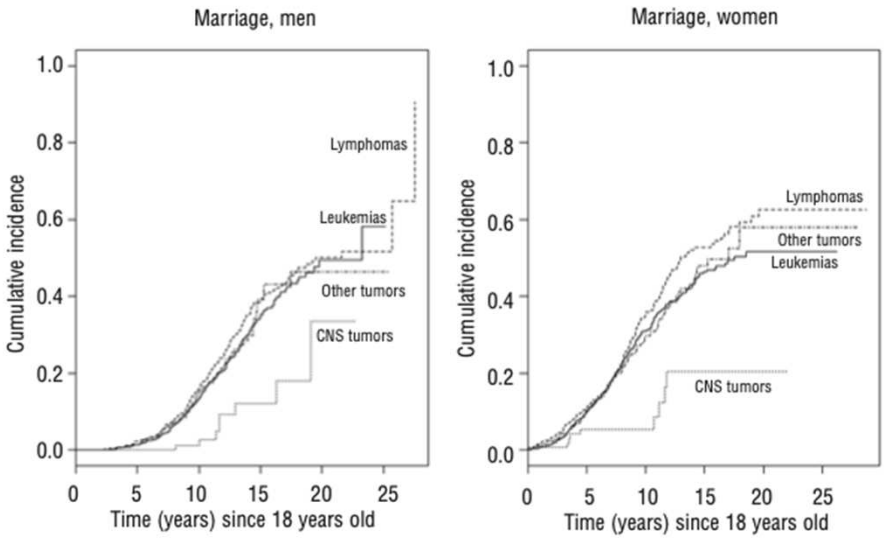


Figure 3. Off-Therapy Registry 1960-1998. Cumulative incidence (CI) of marriage in childhood cancer survivors (observed) and in the general population (expected) by gender in 1980-2004, with 95% confidence limits.

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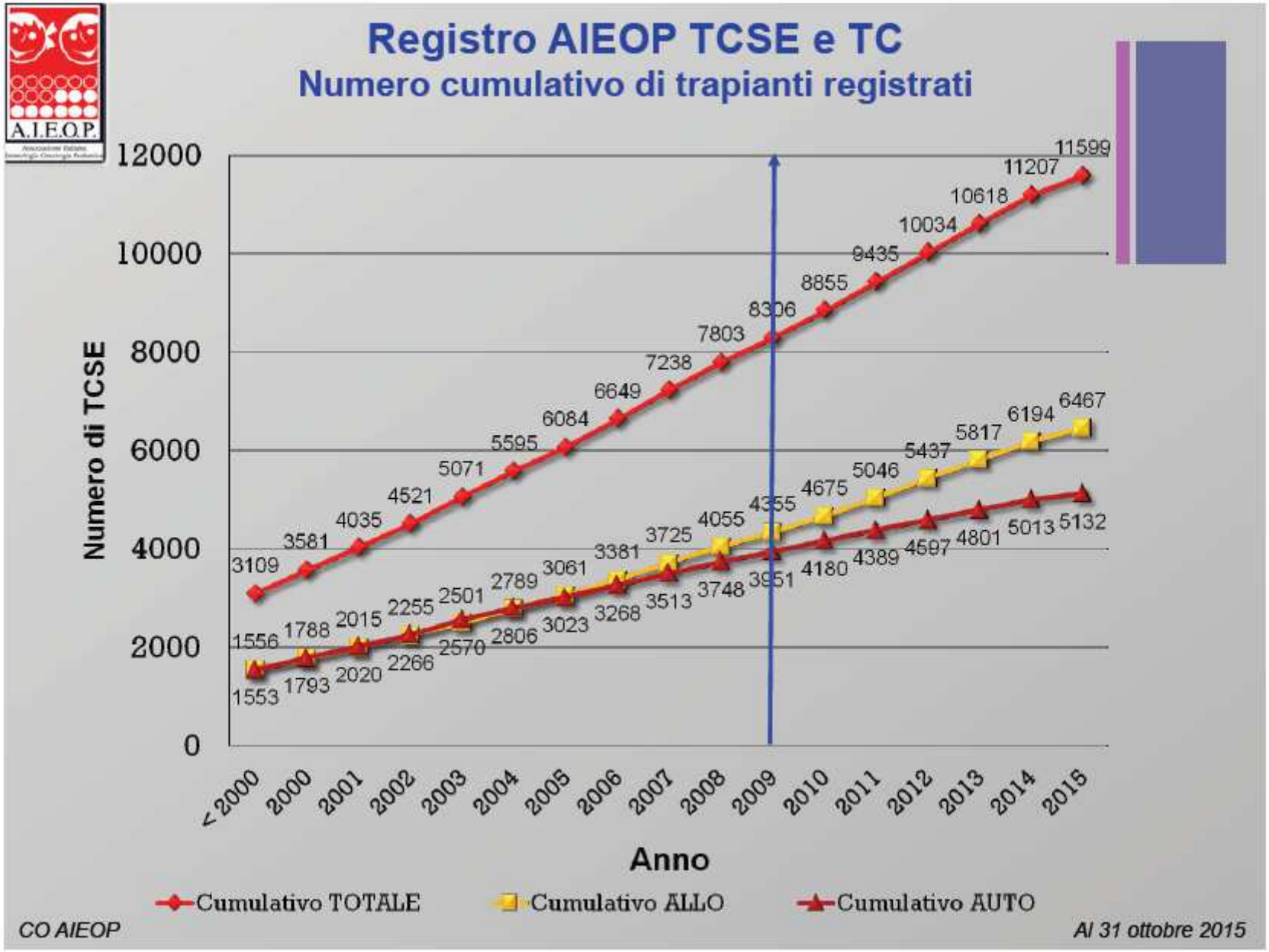
Table 3. Off-Therapy Registry 1960-1998. Ratio of observed (O) to expected (E) number of liveborn children for selected tumor types in 1979-2004 and corresponding 95% Confidence Interval (CI) by age and period of diagnosis among women. Analyses include (a) all women of the cohort of survivors; (b) only married or cohabitant women of the cohort of survivors.

	All tumor types		Acute lymphoblastic leukemia		Acute non-lymphobastic leukemia		Hodgkin's disease		Non-Hodgkin's lymphoma		Central Nervous System tumors		Other tumor types	
(a) ALL	n=2589		n=1248		n=103		n=271		n=170		n=123		n=674	
WOMEN	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI
Age at diagnosis														
0-4	0.57	0.49-0.65	0.56	0.46-0.67	0.59	0.12-1.74	0.57	0.23-1.18	0.56	0.07-2.01	0.35	0.07-1.02	0.59	0.46-0.75
5-9	0.60	0.52-0.68	0.55	0.46-0.65	0.57	0.26-1.09	0.74	0.50-1.07	0.78	0.48-1.19	0.15	0.00-0.86	0.67	0.46-0.93
10-14	0.56	0.48-0.64	0.76	0.62-0.93	0.46	0.18-0.94	0.45	0.34-0.59	0.51	0.30-0.81	0.16	0.03-0.47	0.42	0.22-0.72
Period of diagnosis														
1960-1969	0.59	0.40-0.85	0.87	0.46-1.48	-	-	0.25	0.05-0.73	-	-	1.14	0.14-4.12	0.55	0.28-0.96
1970-1979	0.59	0.53-0.66	0.59	0.51-0.68	0.61	0.24-1.25	0.63	0.48-0.83	0.54	0.31-0.87	0.32	0.09-0.83	0.60	0.46-0.76
1980-1989	0.54	0.47-0.62	0.57	0.46-0.69	0.58	0.30-1.01	0.45	0.30-0.64	0.70	0.42-1.09	0.06	0.00-0.35	0.60	0.42-0.83
1990-1998	0.57	0.39-0.80	0.97	0.53-1.62	0.00	0.00-0.96	0.44	0.14-1.04	0.70	0.26-1.52	0.00	0.00-1.01	0.49	0.20-1.01
Test for trend	P=0.410		P=0.969		P=0.276		P=0.595		P=0.469		P=0.006		P=0.871	
Total	**0.57**	**0.53-0.62**	**0.60**	**0.54-0.67**	**0.53**	**0.32-0.82**	**0.53**	**0.42-0.64**	**0.62**	**0.45-0.85**	**0.21**	**0.08-0.43**	**0.59**	**0.49-0.70**


Registro AIEOP TCSE e TC
Numero cumulativo di trapianti registrati
A.I.E.O.P.
Numero di TCSE
12000
10000
8000
6000
4000
2000
0
3109
3581
4035
4521
5071
5595
6084
6649
7238
7803
8306
8855
9435
10034
10618
11207
11599
1556
1788
2015
2255
2501
2789
3061
3381
3725
4055
4355
4675
5046
5437
5817
6194
6467
1553
1793
2020
2266
2570
2806
3023
3268
3513
3748
3951
4180
4389
4597
4801
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5132
< 2000
2000
2001
2002
2003
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Anno
Cumulativo TOTALE
Cumulativo ALLO
Cumulativo AUTO
CO AIEOP
Al 31 ottobre 2015

Pregnancy and paternity after HSCT

	Female patients		Male patients	
	patients	pregnancies Number (%)	patients	paternitiy Anzahl (%)
All	7'615	113 (1.5%)	10'467	119 (1.1)
Allogeneic HSCT	3'695	74 (2%)	5'124	93 (1.8%)
Autologous HSCT	3'920	39 (1%)	5'343	26 (0.5%)
Leukemia	3713	32 (0.9%)	5152	59 (1.4%)
Aplastic anemia	385	47 (12.2%)	605	32 (5.3%)
Myeloma	323	1 (0.3%)	485	2 (0.4%)

Low risk <20%	Medium risk (20-80%)	High risk (>80%)
– Acute lymphoblastic leukemia – Wilm's tumour – Soft-tissue sarcoma (stage I) – Germ-cell tumours – Retinoblastoma – Brain tumour: surgery only	– Acute myeloblastic leukemia – Hepatoblastoma – Osteosarcoma – Ewing's sarcoma – Soft-tissue sarcoma (stage II or III) – Neuroblastoma – Non-Hodgkin lymphoma – Hodgkin's disease alternative treatment – Brain tumour: craniospinal radiotherapy	– Whole-body irradiation – Pelvic radiotherapy – Chemotherapy conditioning for bone-marrow transplantation – Treatment with alkylating drugs for Hodgkin's disease – Soft-tissue sarcoma (stage IV) – Metastatic Ewing's sarcoma

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VOLUME 34 · NUMBER 28 · OCTOBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium

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General recommendation
Survivors treated with one or more potentially gonadotoxic treatments*, and their providers, should be aware of the risk of premature ovarian insufficiency and its implications for future fertility (level A and level C evidence).
Who needs surveillance?
Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility *is recommended* for survivors treated with: • Alkylating agents in general (level A evidence) • Cyclophosphamide and procarbazine (level C evidence) • Radiotherapy potentially exposing the ovaries (level A evidence)
What surveillance modality should be used for pre- and peri-pubertal survivors?
Monitoring of growth (height) and pubertal development and progression (Tanner stage) *is recommended* for pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion/no literature search).*† FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who fail to initiate or progress through puberty (expert opinion/no literature search).‡§

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What surveillance modality should be used for post-pubertal survivors?

A detailed history and physical examination with specific attention for premature ovarian insufficiency symptoms, e.g. amenorrhoea and irregular cycles *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion/no literature search).*

FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility. Hormone replacement therapy should be discontinued prior to laboratory evaluation when applicable (expert opinion/no studies).§‖

AMH *is not recommended* as the *primary surveillance modality* for evaluation of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who desire assessment about potential future fertility (expert opinion/no studies).

AMH *may be reasonable* in conjunction with FSH and oestradiol for identification of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* aged ≥25 years who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility (expert opinion/no studies).

When should pre- and peri-pubertal survivors be referred?

Referral to paediatric endocrinology / gynaecology *is recommended* for any survivor who has

- No signs of puberty by 13 years of age.
- Primary amenorrhoea by 16 years of age.
- Failure of pubertal progression.[1]

(expert opinion/no literature search)

When should post-pubertal survivors be referred?

Referral to gynaecology / reproductive medicine / endocrinology (according to local referral pathways) *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency (expert opinion/ no literature search).

What should be done when abnormalities are identified in pre-, peri- and post-pubertal survivors?

Consideration of sex steroid replacement therapy *is recommended* for pre-, peri- and post-pubertal survivors diagnosed with premature ovarian insufficiency *by referral to gynaecology/ endocrinology* (expert opinion/no literature search).

What should be done when potential for future fertility is questioned?

Referral to gynaecology / reproductive medicine / endocrinology (according to local referral pathways) *is recommended* for post-pubertal females treated with potentially gonadotoxic chemotherapy and/or ovarian irradiation* without signs and symptoms of premature ovarian insufficiency who desire assessment about potential for future fertility (expert opinion/no literature search).

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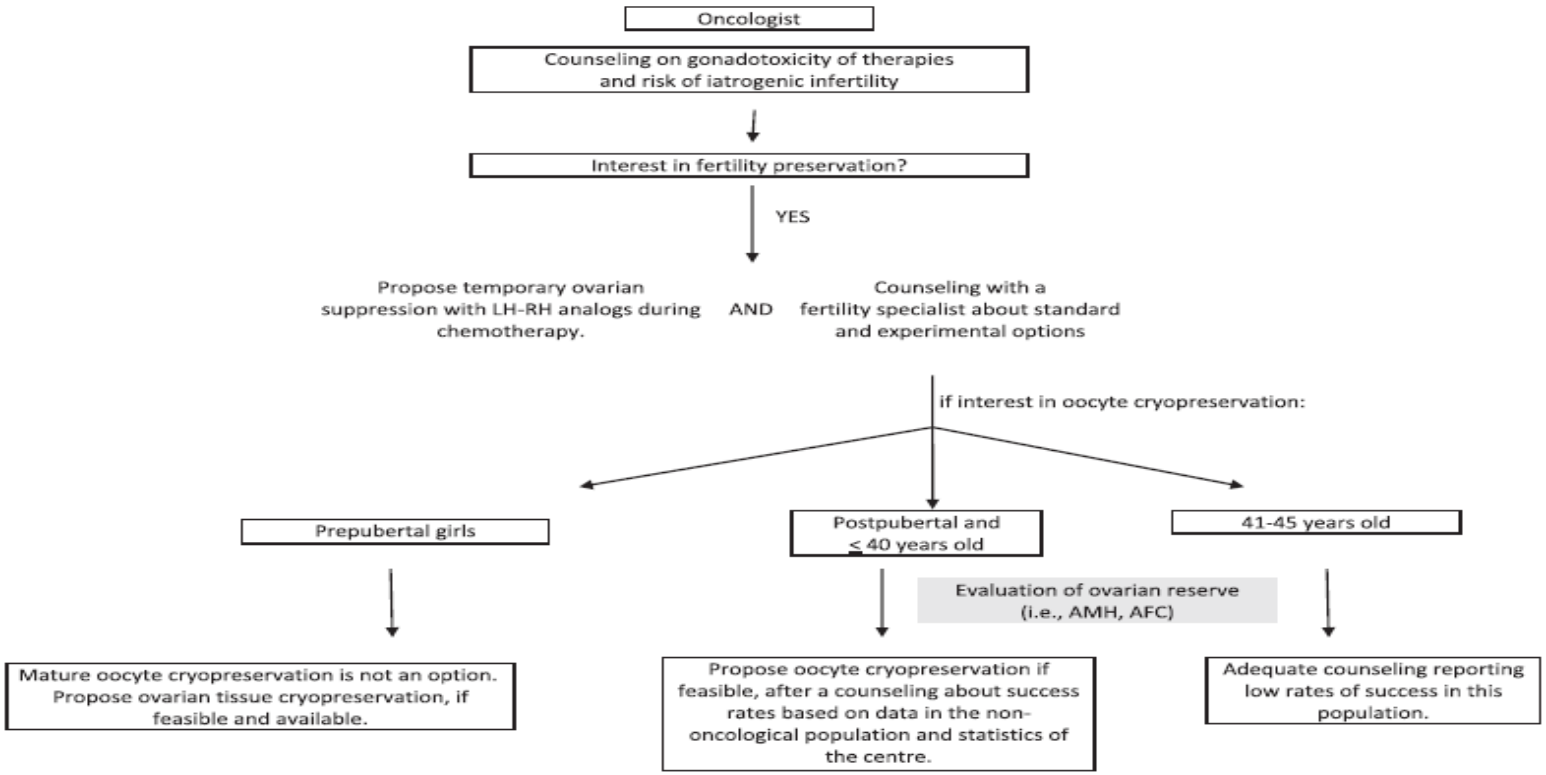
State of the art on oocyte cryopreservation in female cancer patients: A critical review of the literature

Claudia Massarotti [a,*], Paola Scaruffi [b], Matteo Lambertini [c,d], Valentino Remorgida [a], Lucia Del Mastro [e], Paola Anserini [a,b]

Cancer Treatment Reviews 57 (2017) 50–57



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Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium

Roderick Skinner, Renee L Mulder, Leontien C Kremer, Melissa M Hudson, Louis S Constine, Edit Bardi, Annelies Boekhout, Anja Borgmann-Staudt, Morven C Brown, Richard Cohn, Uta Dirksen, Alexsander Giwercman, Hiroyuki Ishiguro, Kirsi Jahnukainen, Lisa B Kenney, Jacqueline J Loonen, Lilian Meacham, Sebastian Neggers, Stephen Nussey, Cecilia Petersen, Margarett Shnorhavorian, Marry M van den Heuvel-Eibrink, Hanneke M van Santen, William H B Wallace, Daniel M Green

Lancet Oncol 2017; 18: e75–90

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Impaired spermatogenesis

General recommendation	Survivors treated with one or more potentially gonadotoxic agents, and their health-care providers, should be aware of the risk of impaired spermatogenesis and its implications for future fertility (level C evidence and supplemental literature search and expert opinion)
Who needs surveillance?	Counselling regarding the risk of impaired spermatogenesis and its implications for future fertility is recommended for survivors treated with: • Cyclophosphamide, chlormethine, procarbazine (level C evidence), busulfan and cyclophosphamide or fludarabine and melphalan for haematopoietic stem-cell transplant, ifosfamide (supplemental literature search and expert opinion) • Radiotherapy potentially exposing testes (supplemental literature search and expert opinion)
Which surveillance modality should be used?	In survivors who desire assessment about possible future fertility after treatment with potentially gonadotoxic chemotherapy or radiotherapy potentially exposing the testes, † semen analysis is recommended as the gold standard primary surveillance modality for evaluation of spermatogenesis (expert opinion)
	Clinical measurement of testicular volume and of follicle-stimulating hormone and inhibin B might be reasonable for the identification of impaired spermatogenesis in survivors treated with potentially gonadotoxic chemotherapy or radiotherapy potentially exposing the testes* in whom semen analysis has been declined or is not possible and who desire assessment about possible future fertility. Be aware of the diagnostic limitations of these tests that may result in false positives or false negatives (level B evidence)
At what frequency and for how long should surveillance be performed?	Surveillance for impaired spermatogenesis should be performed only at the request of the survivor after informed discussion or when paternity is desired in the foreseeable future (expert opinion)
When should survivors with impaired spermatogenesis be referred?	Referral to a male reproductive health specialist should be offered to survivors with severely impaired spermatogenesis, defined as severe oligospermia (sperm counts ≤5 × 10⁶/mL), or to those who are seeking paternity after potentially gonadotoxic chemotherapy or radiotherapy potentially exposing the testes, and to those whose attempts to conceive have been unsuccessful for 6 months or more, regardless of sperm count, for detailed specialist counselling or consideration of sperm cryopreservation if not already performed (expert opinion)

Testosterone deficiency

General recommendation	Survivors treated with a potentially gonadotoxic agent, and their health-care providers, should be aware of the risk of testosterone deficiency and its implications for future health and fertility (supplemental literature search and expert opinion)
Who needs surveillance?	Counselling regarding the risk of testosterone deficiency and its implications for future health and fertility is recommended for survivors treated with radiotherapy potentially exposing the testes to 12 Gy or more or with total body irradiation (supplemental literature search and expert opinion)
Which surveillance modality should be used for prepubertal and peripubertal survivors? At what frequency and for how long?	Monitoring of growth (height) and pubertal development and progression (Tanner stage including testicular volume)†‡§ is recommended for prepubertal and peripubertal survivors treated with radiotherapy potentially exposing the testes to 12 Gy or more or with total body irradiation (expert opinion)
Which surveillance modality should be used for postpubertal survivors? At what frequency and for how long?	Measurement of testosterone concentration in an early morning blood sample at clinically appropriate intervals is reasonable in postpubertal survivors treated with radiotherapy potentially exposing the testes to 12 Gy or more or with TBI (expert opinion). In the presence of clinical signs of hypogonadism, or of previous low-normal or borderline testosterone concentrations, or if it is not possible to obtain an early morning blood sample, it is reasonable to measure luteinising hormone concentration in addition to testosterone (expert opinion)
When should survivors with abnormalities of pubertal development be referred?	Referral to a paediatric endocrinologist is recommended for any survivor who has no signs of puberty by 14 years of age or failure of pubertal progression¶ (expert opinion)
When should postpubertal survivors with suspected testosterone deficiency be referred??	Referral to a specialist in male reproductive health, andrology, endocrinology or urology (according to local referral pathways) is recommended for postpubertal survivors treated with radiotherapy potentially exposing the testes to 12 Gy or more or with TBI, and in whom laboratory results suggest testosterone deficiency (expert opinion)

VOLUME 35 · NUMBER 34 · DECEMBER 1, 2017
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Prevalence and Predictors of Sperm Banking in Adolescents Newly Diagnosed With Cancer: Examination of Adolescent, Parent, and Provider Factors Influencing Fertility Preservation Outcomes

Table 2. Logistic Regression Predicting CA Among at-Risk Adolescent Males Newly Diagnosed With Cancer (n = 146)

Variable	β	SE	*P*	OR	95% CL
Adolescent report					
Fertility risk communication from provider	1.34	1.17	.251	3.82	0.39 to 37.71
Parent(s) recommended SB	2.51	0.93	.007	12.30	2.01 to 75.94
Medical team recommended SB	1.28	0.89	.148	3.60	0.63 to 20.49
Met with fertility specialist	3.40	1.27	.007	29.96	2.48 to 361.41
Health belief: benefits of banking	0.19	0.11	.085	1.21	0.97 to 1.51
Tanner stage	1.69	0.58	.003	5.42	1.75 to 16.78
Parent report					
Communication with friends or family about son's fertility risk	0.92	1.16	.430	2.51	0.26 to 24.29

Abbreviations: CA, collection attempt; CL, confidence limit; OR, odds ratio; SB, sperm banking.

SUMMARY OF CANCER TREATMENT

This Survivorship Passport is a short summary extracted from the information reported in the medical record. It describes the disease and its clinical course as well the treatments you received.This document does not replace the medical record that is always available at our center.

*****

Passport Number: IT12509**85**

PERSONAL DATA

Date of birth	**/**/2002	**Sex**	Female

FIRST TUMOR

DIAGNOSIS

Date of diagnosis	20/09/2005
Institution	Istituto "Giannina Gaslini", Genova
Diagnosis	Nephroblastoma, NOS
Diagnosis description	Wilms' Tumor
Site	Kidney, NOS
Laterality	Left
Metastatic	No

OTHER DISEASES

Hereditary Cancer Predisposition Syndrome or medical condition cancer associated	No
Other medical conditions, not cancer associated	No

FRONT LINE TREATMENT

The treatment has been executed following	Trial/Protocol: AIEOP TW 2003	
Group/Arm/Randomization	1A	
Summary of major treatments	Chemotherapy	Yes
	Stem Cell transplantation	No
	Radiotherapy	No
	Major Surgery	Yes
Progression/relapse during frontline treatment	No	
Date of first elective end of treatment	04/11/2005	

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT

N. 1

Type of event	Relapse	
Date	08/02/2006	
Type	Local	
The salvage treatment has been executed following	Trial/Protocol: AIEOP TW 2003	
Summary of major treatments	Chemotherapy	Yes
	Stem Cell transplantation	Yes
	Radiotherapy	Yes
	Major Surgery	No
Date of end of treatment	13/06/2006	

CHEMOTHERAPY

CLINICAL COURSE

Start date	20/09/2005	**End date**	04/11/2005

CLASSIC/TRADITIONAL ANTINEOPLASTIC AGENTS

Drug name	**Total cumulative dose**	**Measure unit**
Vincristine	8.64 (Dose given)	mg/m2
Dactinomycin	3.9 (Dose given)	mg/m2
Intrathecal injections	No	

OTHER ANTINEOPLASTIC AGENTS

Hormones	No
Immunotherapy	No

OTHER TREATMENTS

Other treatments	No

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

Start date	08/02/2006	**End date**	13/06/2006

CLASSIC/TRADITIONAL ANTINEOPLASTIC AGENTS

Drug name	**Total cumulative dose**	**Measure unit**
Etoposide	1161.29 (Dose given)	mg/m2

STEM CELL TRANSPLANTATION

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

Date of transplant	27/04/2006
Type of donor	Autologous

RADIATION THERAPY EPISODE

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

Type of radiotherapy		External beam: Linac (Linear Accelerator) electrons			
Start date	29/05/2006	**End date**	13/06/2006		
Site (1)		Flank / hemiabdomen (top of diaphragm to iliac crest) (left)		**Dose**	20 Gy

MAJOR SURGERY

CLINICAL COURSE

N. 1

Date of surgery	20/09/2005
Surgery description	Left Nephrectomy

OTHER INFORMATION AND RELEVANT CLINICAL EVENTS DURING TREATMENT

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

CVC positioning	Yes
If yes, specify the site	Right jugular vein
Last transfusion date	05/05/2006

RECOMMENDATIONS FOR FOLLOW-UP

Because of the treatment you have had we have listed the tests recommended for you. This advice is because a few people who had the same treatment as you have developed problems which we hope can be picked up at an early and treatable stage.

Cardiomyopathy Screening

We think that you need regular checks on how your heart is working.

Premature Ovarian Insufficiency Surveillance

We think that you need regular checks to monitor your ovarian function.

Although the risk is greater with higher doses of treatment, it is still possible for lower doses to cause premature ovarian insufficiency in a few females.