12th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice and Post-MASCC

Fertility, Sexuality and Cancer (in Young Adult Women)

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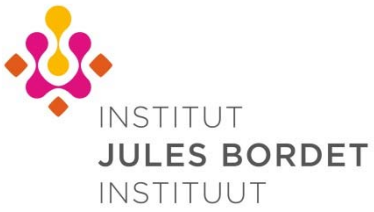

Disclosure Information

Relationship Relevant to this Session

Lambertini, Matteo:

- **Consultant or advisor:** Teva
- **Honoraria:** Theramex

Outline

- Introduction
- Fertility in cancer patients:
  - Embryo/oocyte cryopreservation
  - Cryopreservation of ovarian tissue
  - Temporary ovarian suppression with GnRHa during chemotherapy
- Sexuality in cancer patients
- Conclusions

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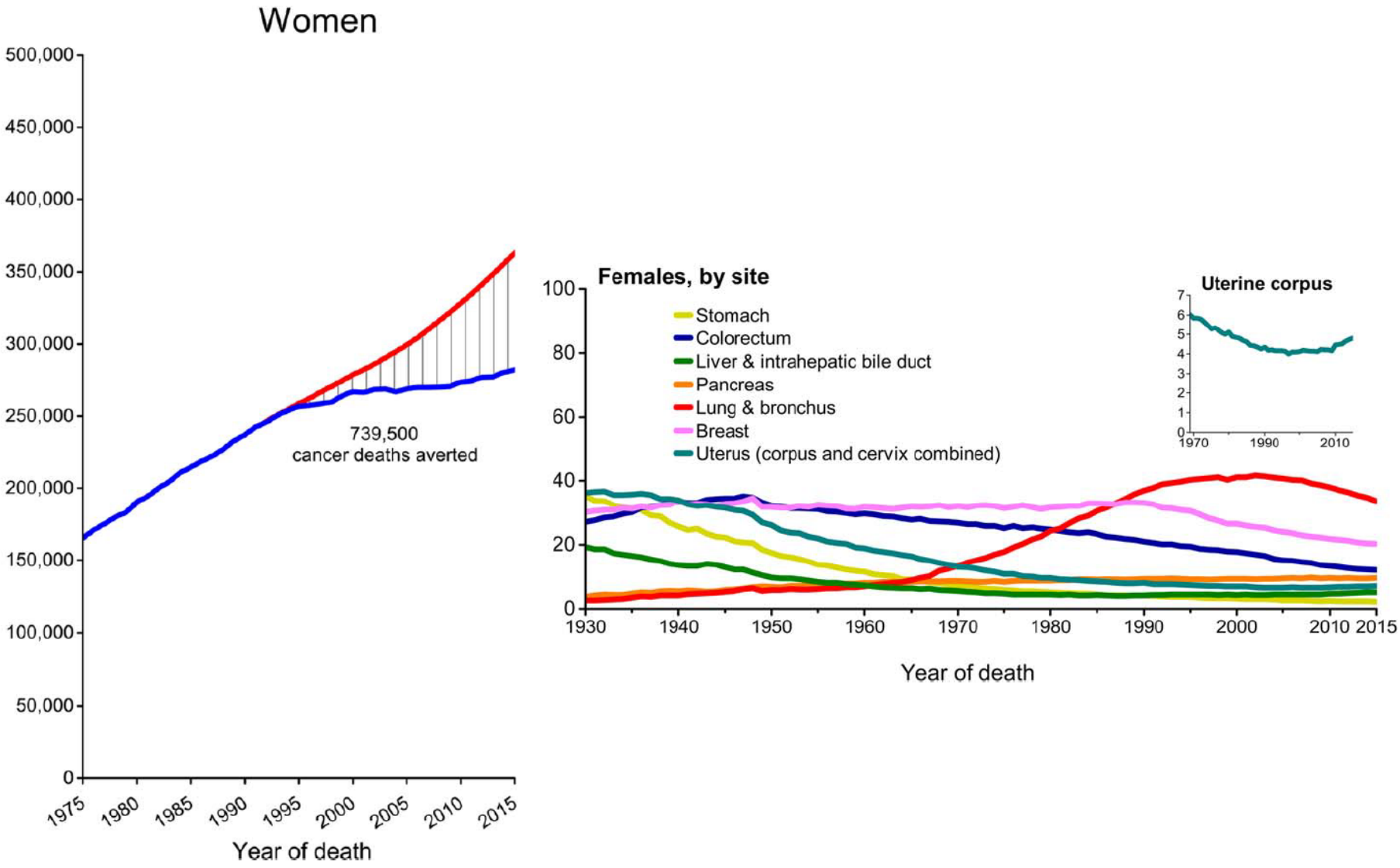
Cancer Burden: Survivorship Issues



Siegel RL et al, CA Cancer J Clin 2018;68(1):7-30

Cancer Burden in Young Adult Women

	Both sexes			Men			Women		
	New cases	%	ASR	New cases	%	ASR	New cases	%	ASR
All cancers except non-melanoma skin cancer	975 396	100·0%	43·3	342 721	100·0%	30·1	632 675	100·0%	57·0
Breast	191 105	19·6%	8·4	..	..	..	191 105	30·2%	17·0
Cervix uteri	110 749	11·4%	4·9	..	..	..	110 749	17·5%	9·9
Thyroid	78 568	8·1%	3·5	15 681	4·6%	1·4	62 887	9·9%	5·7
Leukaemia	49 293	5·1%	2·2	28 020	8·2%	2·5	21 273	3·4%	2·0
Colorectal	41 117	4·2%	1·8	21 055	6·1%	1·8	20 062	3·2%	1·8
Liver	40 720	4·2%	1·8	31 767	9·3%	2·8	8953	1·4%	0·8
Brain and CNS	40 363	4·1%	1·8	22 822	6·7%	2·0	17 541	2·8%	1·6
Non-Hodgkin lymphoma	40 212	4·1%	1·8	23 746	6·9%	2·1	16 466	2·6%	1·5
Testis	30 580	3·1%	1·4	30 580	8·9%	2·7	..	..	..
Ovary	29 262	3·0%	1·3	..	..	..	29 262	4·6%	2·6
Stomach	25 768	2·6%	1·1	13 276	3·9%	1·2	12 492	2·0%	1·1
Melanoma of skin	25 248	2·6%	1·1	9553	2·8%	0·8	15 695	2·5%	1·4
Lip or oral cavity	23 041	2·4%	1·0	14 634	4·3%	1·3	8407	1·3%	0·8
Hodgkin's lymphoma	22 973	2·4%	1·1	12 426	3·6%	1·1	10 547	1·7%	1·0
Lung	22 512	2·3%	1·0	13 080	3·8%	1·1	9432	1·5%	0·9
Kaposi's sarcoma	20 153	2·1%	0·9	12 741	3·7%	1·1	7412	1·2%	0·7
Corpus uteri	15 391	1·6%	0·7	..	..	..	15 391	2·4%	1·4

Fidler MM et al, Lancet Oncol 2017;18(12):1579-89

Gonadotoxicity of Anticancer Treatments in Young Adult Women

High risk (>80 % risk of permanent amenorrhea in women;	-HSC transplantation with cyclophosphamide/ TBI or cyclophosphamide/busulfan -External beam radiation to a field that includes the ovaries -CMF, CEF, CAF, TAC x 6 cycles in women ≥ 40 years
Intermediate risk (40 % - 60 % risk of permanent amenorrhea in women;	-BEACOPP -CMF, CEF, CAF, TAC x 6 cycles in women age 30–39 -AC x 4 cycles in women ≥ 40 years -AC or EC x 4 → Taxanes
Low risk (<20 % risk of permanent amenorrhea in women;	-ABVD in women ≥ 32 years -CHOP x 4–6 cycles -CVP -AML therapy (anthracycline/cytarabine) -ALL therapy (multi-agent) -CMF, CEF, CAF, TAC x 6 cycles in women ≤ 30 years -AC x 4 cycles in women ≤ 40 years
Very low or no risk (risk of permanent amenorrhea in women;	-ABVD in women < 32 years -Methotrexate -Fluorouracil -Vincristine -Tamoxifen

Lambertini M et al, BMC Med 2016;14:1

Fertility and Pregnancy Concerns

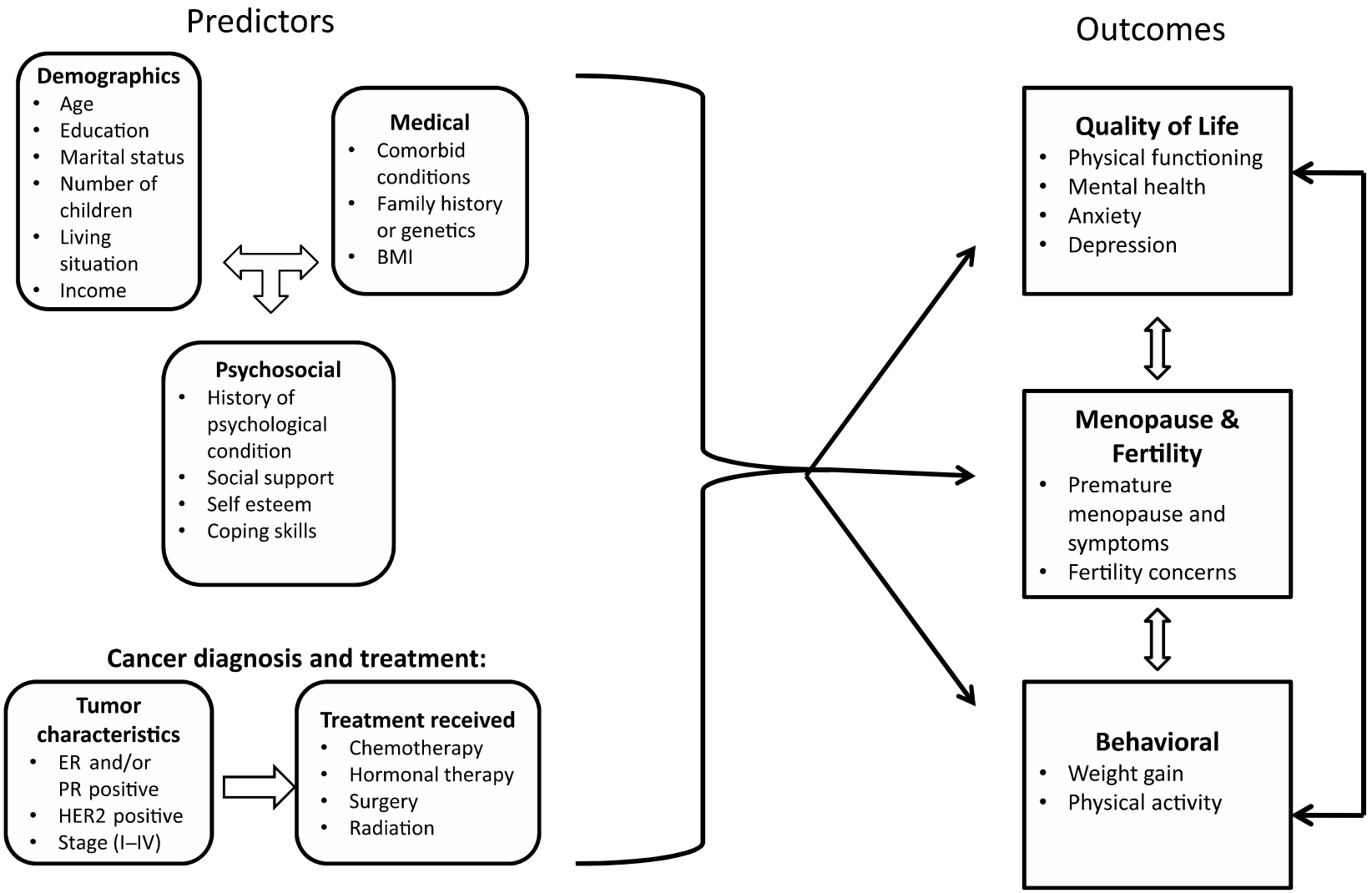
At time of decision making about treatment, concerned about fertility		
Not at all	301	49
A little	83	13
Somewhat	88	14
Very	148	24

→ ≈ 50%

Characteristic	Total Sample, n=918	Type of Cancer				
		Leukemia, n=121	Hodgkin Disease, n=286[a]	Non-Hodgkin Lymphoma, n=169[a]	Breast Cancer, n=223	Gastrointestinal Cancer, n=108
Age at diagnosis, y, mean (SD)	31.5 (6.7)	28.3 (7.2)	27.9 (6.2)	31.6 (6.0)	36.3 (4.0)	34.9 (4.6)
Age at survey, y, mean (SD)	40.9 (8.4)	37.0 (8.3)	36.5 (8.0)	40.5 (7.1)	47.1 (5.9)	44.6 (6.2)
Years since diagnosis, mean (SD)	9.6 (4.4)	8.7 (4.3)	8.6 (4.4)	8.9 (3.9)	10.8 (4.5)	9.7 (4.0)
Children before treatment, No. (%)	476 (52%)	46 (38%)	105 (37%)	88 (52%)	163 (73%)	76 (70%)
Desiring children after treatment, No. (%)	504 (54%)	71 (59%)	181 (63%)	82 (49%)	104 (47%)	61 (56%)

Ruddy KJ et al, J Clin Oncol 2014;32:1151-1156. Letourneau JM et al, Cancer 2012;118:1710-7

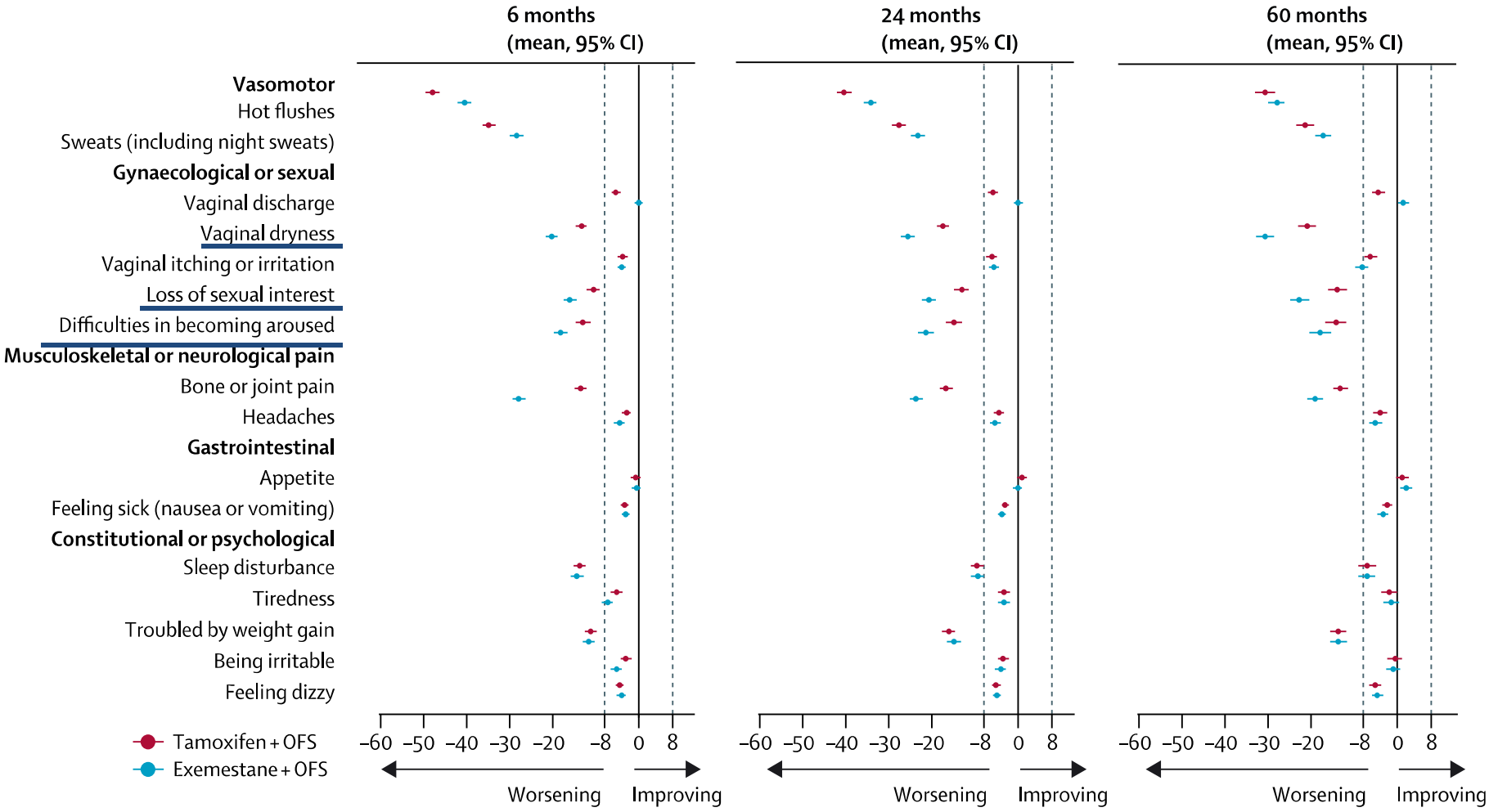
Not only Fertility and Pregnancy Concerns !



Howard-Anderson J et al, J Natl Cancer Inst 2012;104:386-405

Not only Fertility and Pregnancy Concerns !

Patient-Reported Outcomes SOFT&TEXT Trials



Bernhard J et al, Lancet Oncol 2015;16:848-58

Failure to Address these Concerns may Negatively Impact on Patients' Outcomes

Available at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: www.ejconline.com

Early discontinuation of tamoxifen intake in younger women with breast cancer: Is it time to rethink the way it is prescribed?

Laetitia Huiart [a,b,c,*], Anne-Déborah Bouhnik [b,c], Dominique Rey [b,c,d], Carole Tarpin [e], Camille Cluze [b,c,d], Marc Karim Bendiane [b,c,d], Patrice Viens [e,f], Roch Giorgi [g,h]

MUNICH 2018 ESMO congress

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

SERUM ASSESSMENT OF NON-ADHERENCE TO ADJUVANT ENDOCRINE THERAPY (ET) AMONG PREMENOPAUSAL PATIENTS IN THE PROSPECTIVE MULTICENTER CANTO COHORT

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3. Oncostat team-INSERM U1018, Department of Biostatistics and Epidemiology Methodology-Gustave Roussy, Villejuif, FR;
4. Breast Cancer Survivorship Clinical and Research Program-Gustave Roussy, Villejuif, FR; 5.Department of Oncology Institut Curie, Paris,FR;
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10.Department of Medical Oncology- Centre Oscar Lambret, Lille, FR; 11. Depatment of Medical Oncology-Institut Jean Godinot, Reims, FR;
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UNICANCER canto

JNCI J Natl Cancer Inst (2015) 107(10): djv202

doi:10.1093/jnci/djv202
First published online August 25, 2015
Article

ARTICLE

Impact of Fertility Concerns on Tamoxifen Initiation and Persistence

Natalia C. Llarena, Samantha L. Estevez, Susan L. Tucker, Jacqueline S. Jeruss

Breast Cancer Res Treat (2011) 126:529–537
DOI 10.1007/s10549-010-1132-4

EPIDEMIOLOGY

Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer

Dawn L. Hershman · Theresa Shao · Lawrence H. Kushi · Donna Buono · Wei Yann Tsai · Louis Fehrenbacher · Marilyn Kwan · Scarlett Lin Gomez · Alfred I. Neugut

Huiart L et al, Eur J Cancer 2012;48:1939-46. Pistilli B et al, ESMO 2018
Llarena NC et al, J Natl Cancer Inst 2015;107(10):djv202. Hershman DL et al, Breast Cancer Res Treat 2011;126:529-37

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Oncofertility Counseling is Mandatory As soon as Possible after Diagnosis

ESMO GUIDELINES 2013

Young women desiring future fertility should be counselled on available fertility preserving options before starting anticancer treatments. Counselling should be implemented soon after diagnosis, to allow prompt referral to fertility specialists [IV, B].

ASCO GUIDELINES 2018

Recommendation 1.1. People with cancer are interested in discussing fertility preservation. Health care providers caring for adult and pediatric patients with cancer (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons, and others) should address the possibility of infertility as early as possible before treatment starts.

Peccatori F et al, Ann Oncol 2013;24:vi160-70. Oktay K et al, J Clin Oncol 2018;36(19):1994-2001

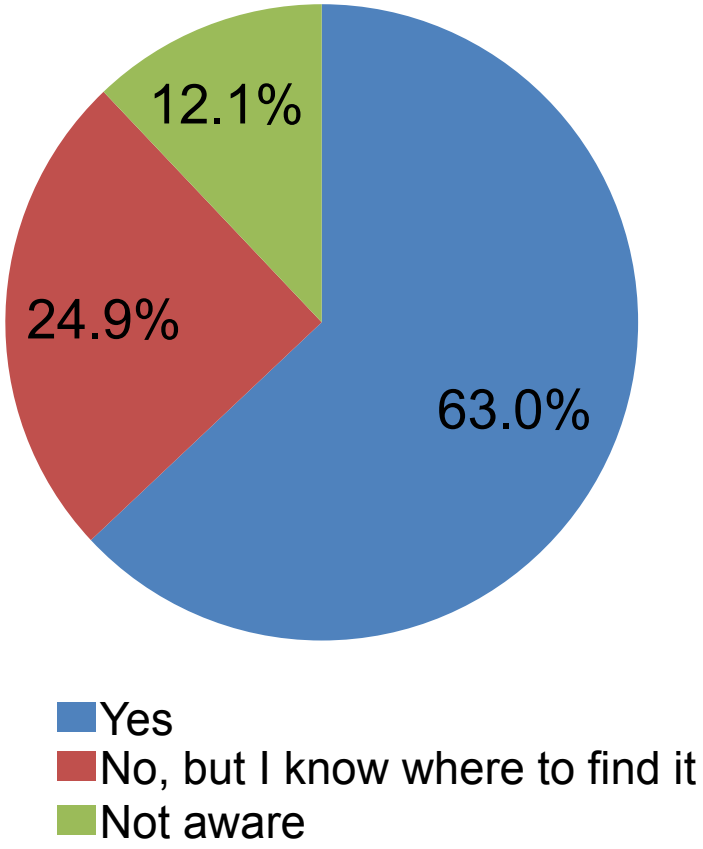
Oncofertility Counseling is Mandatory As soon as Possible after Diagnosis Including in Patients with Advanced Disease

Guideline statement	LoE/GoR	Consensus
Fertility preservation: the impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).	Expert opinion/ B	100%

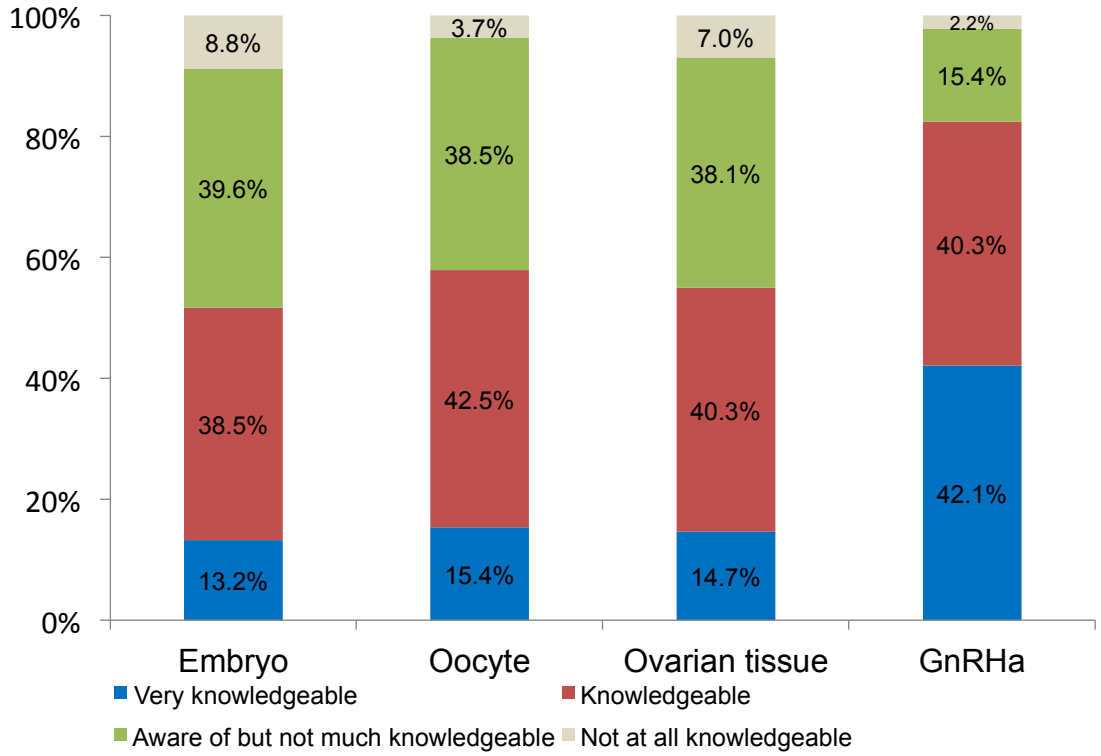
Cardoso F et al, Ann Oncol 2018;29(8):1634-57

Physicians' Knowledge and Attitudes Towards Fertility Preservation

Fertility Guidelines



Fertility Preservation Strategies



Lambertini M et al, Breast 2018;42:41-9

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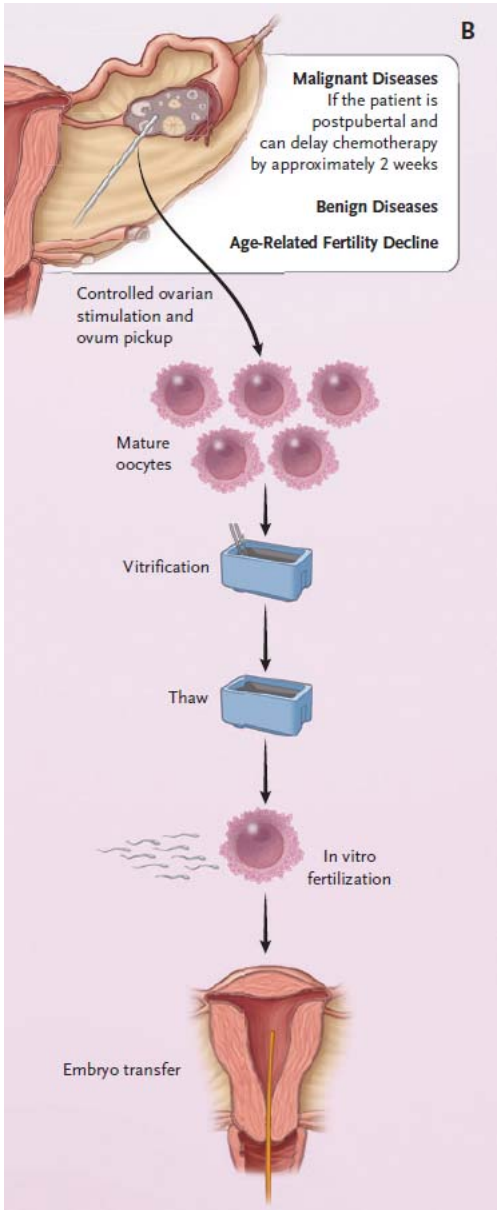
Embryo/Oocyte Cryopreservation: Available Guidelines

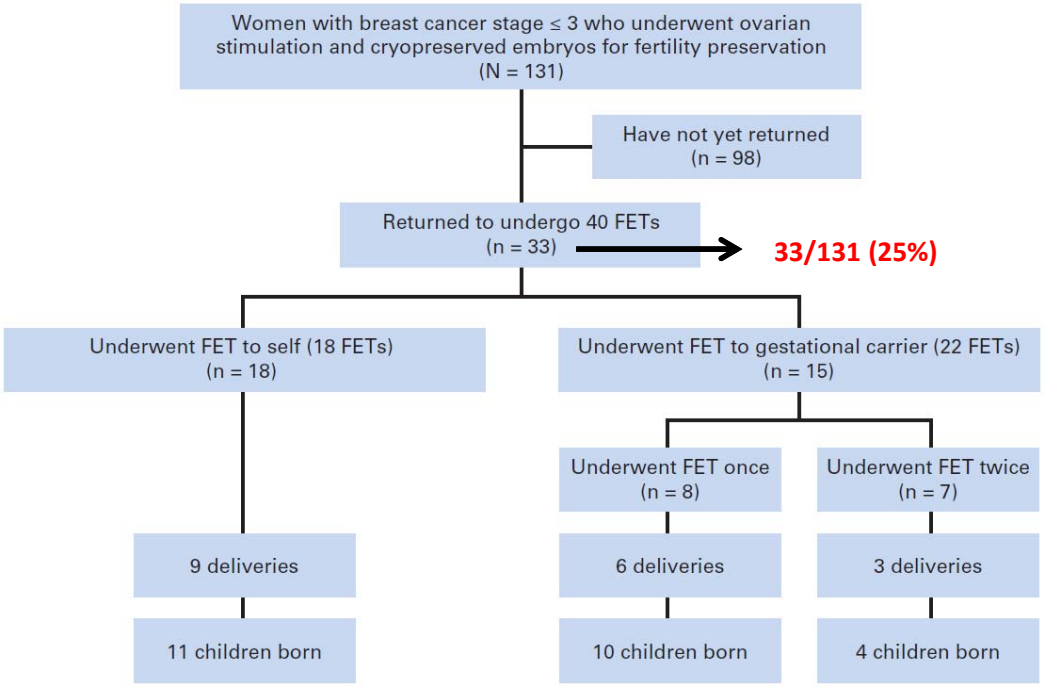


Guidelines	Year	Recommendations
ESMO	2013	**Embryo or oocyte cryopreservation** is the main method to preserve female fertility. Ovarian stimulation should be carried out before commencing chemotherapy.
ASCO	2018	**Embryo cryopreservation** is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization. **Cryopreservation of unfertilized oocytes** is an option, and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing.

Donnez J & Dolmans MM, N Engl J Med 2017;377(17):1657-65
Peccatori F et al, Ann Oncol 2013;24:vi160-70. Oktay K et al, J Clin Oncol 2018;36(19):1994-2001

Embryo/Oocyte Cryopreservation: Efficacy Data

Embryo cryopreservation
Prospective single-center cohort study



Pregnancy rate = 20/33 (61%)

Ooctye cryopreservation
Prospective multicenter cohort study

Variable	OV (n = 49)
Status of patient at reimplantation	
Amenorrhea >1 y	9 (18.4)
POI without amenorrhea	34 (69.4)
Regular menstruations	6 (12.3)
Age at retrieval, y	35.2 (3.1)
Age at reimplantation, y	39.0 (3.8)
AMH before reimplantation, pM	0 [0–1.29]
No. of pregnant patients	20 (40.8)
No. of patients with live births	16 (32.6)

49/1024 (5%)

Pregnancy rate = 20/49 (41%)

Oktay K et al, J Clin Oncol 2015;33(22):2424-9. Diaz-Garcia C et al, Fertil Steril 2018;109(3):478-85

Embryo/Oocyte Cryopreservation: Efficacy Data

Comparison of efficacy data between healthy women and cancer patients patients

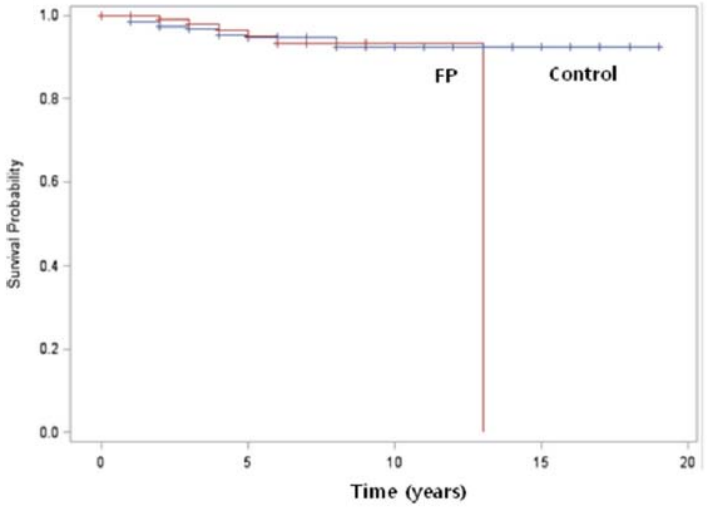
	'Fresh' embryo transfers		
	Elective fertility preservation	**ONCO-fertility preservation**	***P* Value**
Patients returning (%)	641 /5289 (12.1)	80/1073 (7.4)	<0.0001
Mean age at vitrification	37.6 ± 3.5	34.8 ± 2.1	<0.0001
Mean age at return	39.9 ± 0.7	38.8 ± 3.5	0.004
Mean storage time (years)	2.1 ± 1.6	4.1 ± 0.9	<0.0001
Warming cycles/patient	680/641 (1.1 ± 0.5)	81/80 (1.01 ± 0.7)	0.123
Warmed oocytes/patient	5830/641 (9.1 ± 3.8)	605/80 (7.5 ± 2.8)	0.025
Survival rate (%)	4891/5830 (83.9)	495/605 (81.8)	0.188
Patients with surplus embryos vitrified (%)	325/641 (50.7)	37/80 (46.2)	0.509
Surplus embryos vitrified/patient	833/325 (2.7 ± 0.7)	90/37 (2.4 ± 1.2)	0.325
Transfers/warming cycle (%)	341/680 (50.2)	58/80 (72.5)	0.0002
Embryos transferred/cycle	469/341 (1.1 ± 0.8)	83/58(1.4 ± 0.1)	<0.0001
Implantation rate (%)	42.6	32.5	0.014
Clinical pregnancies/transfer (%)	173/341 (50.7)	24/58 (41.4)	0.237
Ongoing pregnancies/transfer (%)	134/341 (39.2)	18/58 (31.0)	0.128
Live births	115	18	

Cobo A et al, Hum Reprod 2018; [Epub ahead of print]

Embryo/Oocyte Cryopreservation: Safety Data

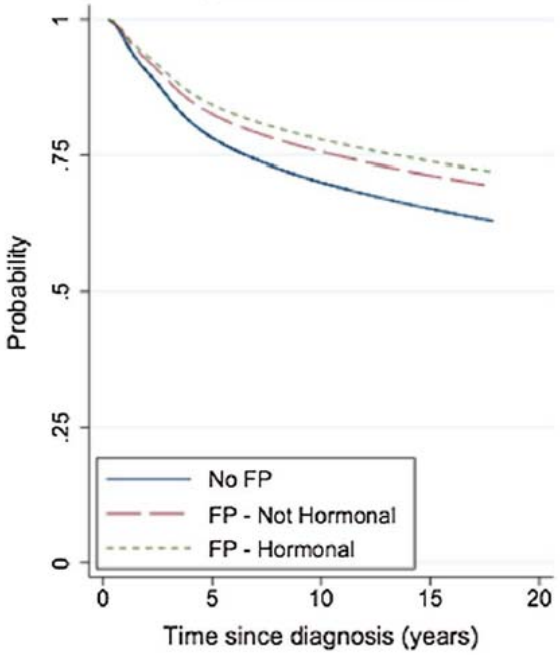
Prospective single-center cohort study
n=120 FP & n=217 no FP

Relapse-free survival

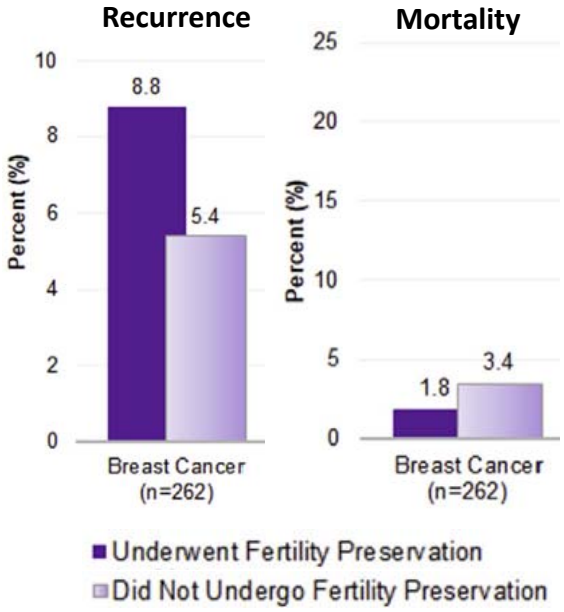


Retrospective cohort study (Swedish registry)
n=188 FP & n=378 no FP

Relapse-free survival



Retrospective single-center cohort study
n=114 FP & n=148 no FP

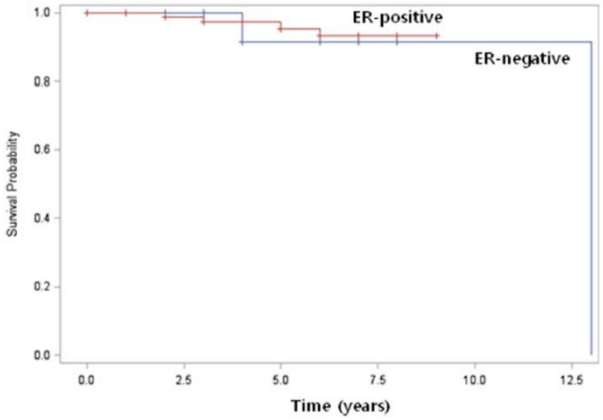


Kim J et al, J Clin Endocrinol Metab 2016;101(4):1364-71

Rodriguez-Wallberg KA et al, Breast Cancer Res Treat 2018;167(3):761-9. Moravek MB et al, Fertil Steril 2018;109(2):349-55

Embryo/Oocyte Cryopreservation: Safety Data

Hormone-receptor status



Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies

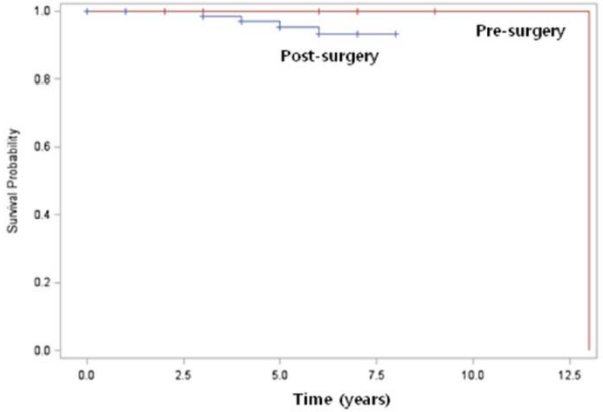
Dror Meirow, M.D.,[a] Hila Raanani, M.D.,[a] Ettie Maman, M.D.,[a] Shani Paluch-Shimon, M.B., B.S., M.Sc.,[b] Moran Shapira, B.Sc.,[a] Yoram Cohen, M.D.,[a] Irena Kuchuk, M.D.,[b] Ariel Hourvitz, M.D.,[a] Jacob Levron, M.D.,[a] Michal Mozer-Mendel, M.D.,[b] Masha Brengauz, Ph.D.,[a] Hana Biderman, B.Sc.,[a] Daphna Manela, R.N.B.A.,[a] Rephael Catane, M.D.,[b] Jehoshua Dor, M.D.,[a] Raoul Orvieto, M.D.,[a] and Bella Kaufman, M.D.[b]

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer

Kutluk Oktay, Volkan Turan, Giuliano Bedoschi, Fernanda S. Pacheco, and Fred Moy

Timing of chemotherapy administration



human reproduction | ORIGINAL ARTICLE *Reproductive endocrinology*

Random start ovarian stimulation for fertility preservation appears unlikely to delay initiation of neoadjuvant chemotherapy for breast cancer

Joseph M. Letourneau[1,*], Nikita Sinha[1], Kaitlyn Wald[1,2], Eve Harris[1], Molly Quinn[1], Tal Imbar[4], Evelyn Mok-Lin[1], A. Jo Chien[3], and Mitchell Rosen[1]

EPIDEMIOLOGY

Fertility preservation with ovarian stimulation and time to treatment in women with stage II–III breast cancer receiving neoadjuvant therapy

A. Jo Chien[1] · Julia Chambers[2] · Fiona Meauley[1] · Tessa Kaplan[3] · Joseph Letourneau[4] · Jimmy Hwang[1] · Mi-Ok Kim[1] · Michelle E. Melisko[1] · Hope S. Rugo[1] · Laura J. Esserman[1] · Mitchell P. Rosen[4]

Kim J et al, J Clin Endocrinol Metab 2016;101(4):1364-71. Meirow D et al, Fertil Steril 2014;102(2):488-95. Oktay K et al, J Clin Oncol 2015;33(22):2424-9. Letourneau JM et al, Hum Reprod 2017;32(10):2123-9. Chien AJ et al, BCRT 2017;165(1):151-9

Embryo/Oocyte Cryopreservation: Who Are the Best Candidates ?

- Patients interested in fertility preservation with:

1. Age < 38 – 40 years

1. Good ovarian reserve

1. The possibility to delay the start of chemotherapy (2 weeks or more)

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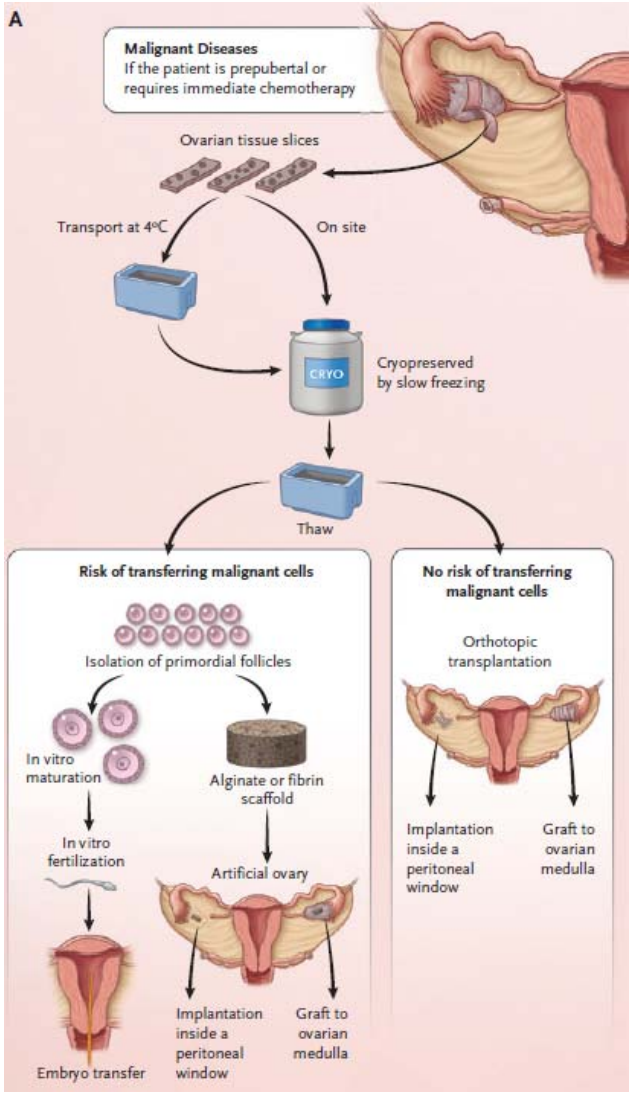
Ovarian Tissue Cryopreservation: Updated Guidelines

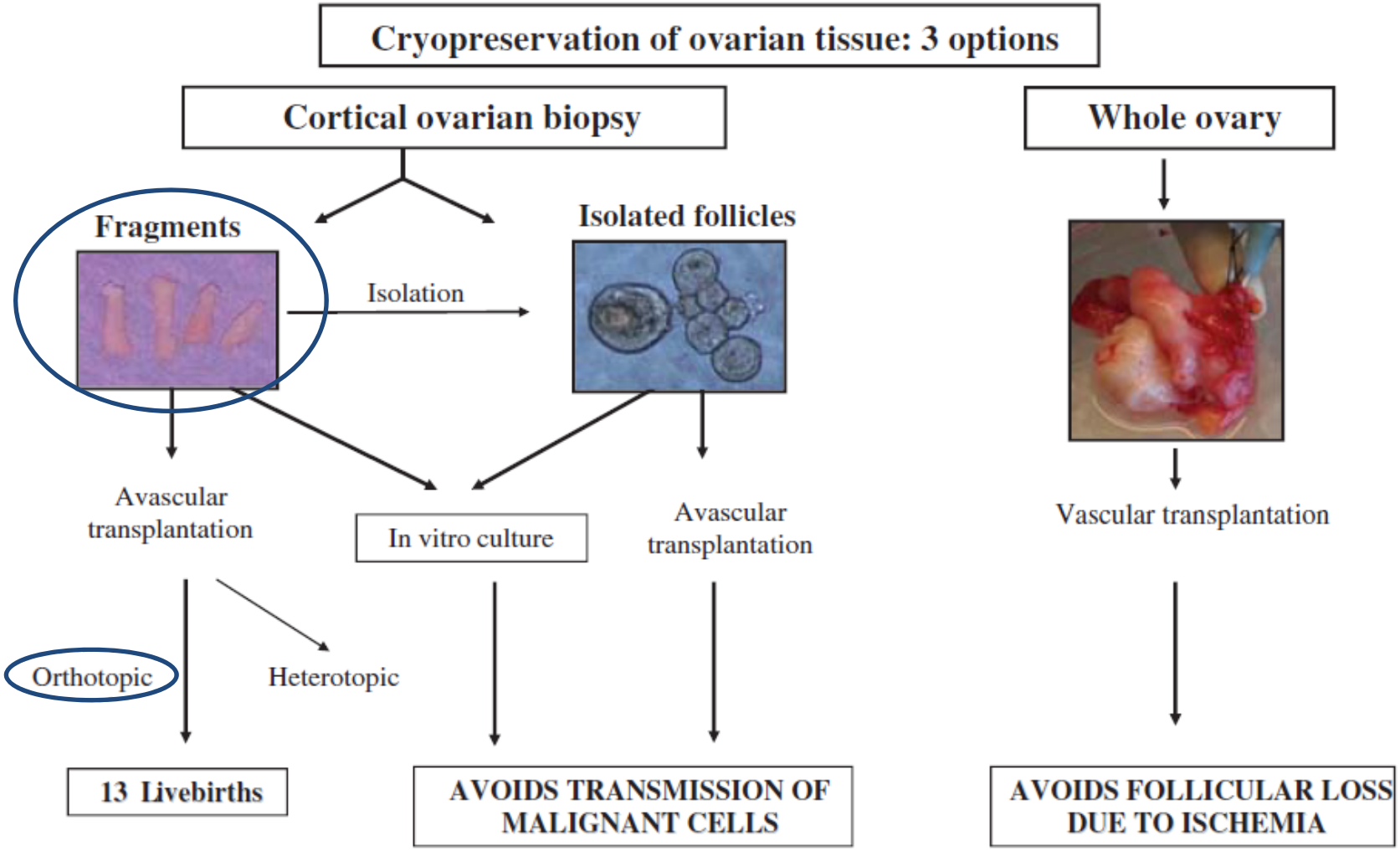


Guidelines	Year	Recommendations
ESMO	2013	Ovarian tissue cryopreservation is still considered **experimental**, but remains a unique option for young girls with cancer
ASCO	2018	Ovarian tissue cryopreservation remains **experimental**. However, emerging data may prompt reconsideration of this designation in the future (this technique is already considered non-experimental in some countries, and its experimental status is undergoing evaluation in the United States)

Donnez J & Dolmans MM, N Engl J Med 2017;377(17):1657-65

Peccatori F et al, Ann Oncol 2013;24:vi160-70. Oktay K et al, J Clin Oncol 2018;36(19):1994-2001

Ovarian Tissue Cryopreservation: The Technique



Donnez J et al, Ann Med 2011; 43(6):437-50

Ovarian Tissue Cryopreservation: Efficacy Data

Variable	OV (n = 49)	OCT (n = 44)	*P*
Status of patient at reimplantation			.04
Amenorrhea >1 y	9 (18.4)	20 (45.4)	
POI without amenorrhea	34 (69.4)	21 (47.8)	
Regular menstruations	6 (12.3)	3 (6.8)	
Age at retrieval, y	35.2 (3.1)	34.3 (7.2)	NS
Age at reimplantation, y	39.0 (3.8)	38.9 (4.1)	NS
AMH before reimplantation, pM	0 [0–1.29]	0 [0–0.30]	NS
No. of pregnant patients	20 (40.8)	12 (27.3)	NS
No. of patients with live births	16 (32.6)	8 (18.2)	NS

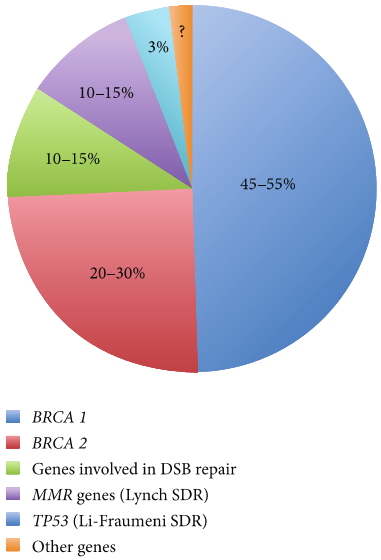
Diaz-Garcia C et al, Fertil Steril 2018;109(3):478-85

Ovarian Tissue Cryopreservation: Safety Data

Risk of malignant contamination by type of cancer

Low risk	Medium risk	High risk
Breast cancer stage I–II and infiltrating ductal subtype	Breast cancer stage IV and infiltrating lobular subtype	Leukaemia
Squamous cell carcinoma of the cervix	Colon cancer	Neuroblastoma
Hodgkin's lymphoma	Adeno carcinoma of the cervix	Burkitt lymphoma
Osteogenic carcinoma	Non-Hodgkin's lymphoma	Ovarian carcinoma
Wilms tumour	Ewing sarcoma	
Non-genital rhabdomyosarcoma		

Risk of ovarian cancer in hereditary syndrome



To be considered only in patients diagnosed at a very young age who cannot perform embryo/oocyte cryopreservation

von Wolff M et al, Arch Gynecol Obstet 2018;297(1):257-67

Toss A et al, Biomed Res Int 2015;2015:341723. Lambertini M et al, Cancer Treat Rev 2017;59:61-70

Ovarian Tissue Cryopreservation: Who Are the Best Candidates ?

- Patients interested in fertility preservation with high risk of premature ovarian insufficiency:

  1. Prepubertal girls
  2. Who cannot delay treatment initiation
  3. With contraindication to controlled ovarian stimulation

Outline

- Introduction
- **Fertility in cancer patients:**
  - Embryo/oocyte cryopreservation
  - Cryopreservation of ovarian tissue
  - **Temporary ovarian suppression with GnRHa during chemotherapy**
- Sexuality in cancer patients
- Conclusions

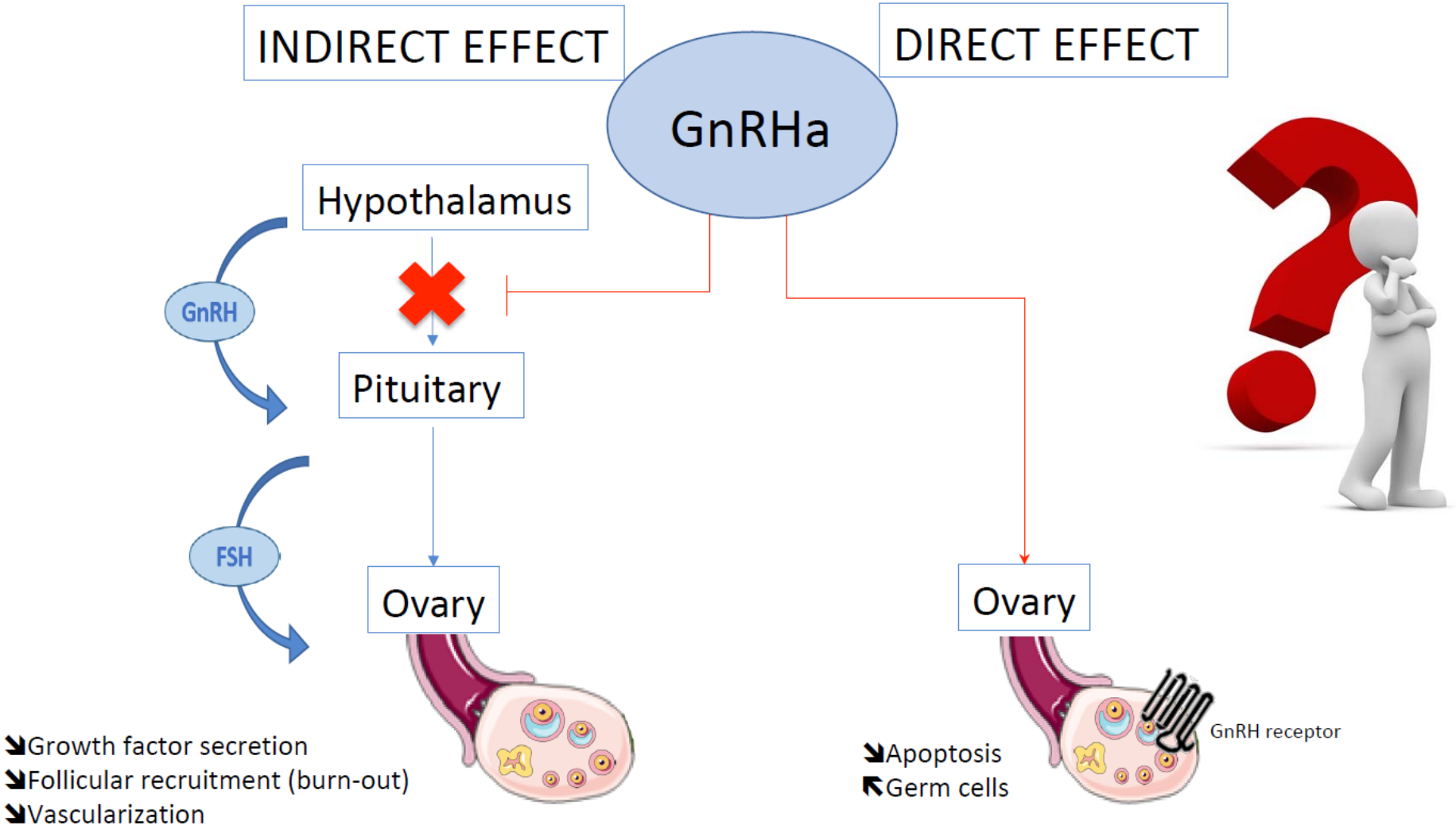
Ovarian Suppression with GnRHa during CT: Updated Guidelines

Guidelines	Year	Recommendations
ESO-ESMO BCY3	2017	GnRHa **should be discussed** as an option with all breast cancer patients interested in potentially preserving fertility and/or ovarian function who are candidates for chemotherapy, irrespective of tumor subtype
AIOM	2017	GnRHa during chemotherapy **should be recommended** to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation
ASCO	2018	When proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa **may be offered** to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. GnRHa **should not** be used in place of proven fertility preservation methods.

Updated ESMO and ESHRE guidelines are upcoming

Paluch-Shimon S et al, Breast 2017;35:203-17. Lambertini M et al, Eur J Cancer 2017;71:25-33
Oktay K et al, J Clin Oncol 2018;36(19):1994-2001

Ovarian Suppression with GnRHa during CT: Mechanism of Action



Lambertini M et al, submitted

Hematological Malignancies (HL&NHL): RCTs

Authors	Type of disease	POI definition (timing of its evaluation)	Timing POI evaluation (months)	No. patients	Main results (GnRHa vs. control)	Overall results
Waxman JH et al. 1987	HL	Amenorrhea	Up to 36	18	• POI rate: 50% vs. 33.3% • Pregnancies: 0 vs. 1	No protection
Loverro G et al. 2007*	HL	Amenorrhea	NR	29	• POI rate: 0% vs. 46% • Pregnancies: 0 vs. 2	No protection
Behringer K et al. 2010	HL	AMH levels below normal range	12	23	• POI rate (AMH): 100% vs. 100% • Amenorrhea rate: 30.0% vs. 33.3% • Pregnancies: 0 vs. 0	No protection
Demeestere I et al. 2013 Demeestere I et al. 2016	HL and NHL	Postmenopausal levels of FSH	12	84	• 1-y POI rate: 20% vs. 19% (p=1.00) • 1-y AMH at ≥ 1 ng/mL: 50.0% vs. 13.3% (p=0.023) • Long-term POI rate: 19.4% vs. 25.0% (p=0.763) • Pregnancies: 17 vs. 15 (p=0.467)	No protection

Waxman JH et al, Cancer Chemother Pharmacol 1987;19:159-62. Giuseppe L et al, Hematol 2007;12:141-7.
Behringer K et al, Ann Oncol 2010;21:2052-60. Demeestere I et al, J Clin Oncol 2013;31:903-9 & 2016;34:2568-74

Breast Cancer: IPD Metanalysis

Study Characteristics

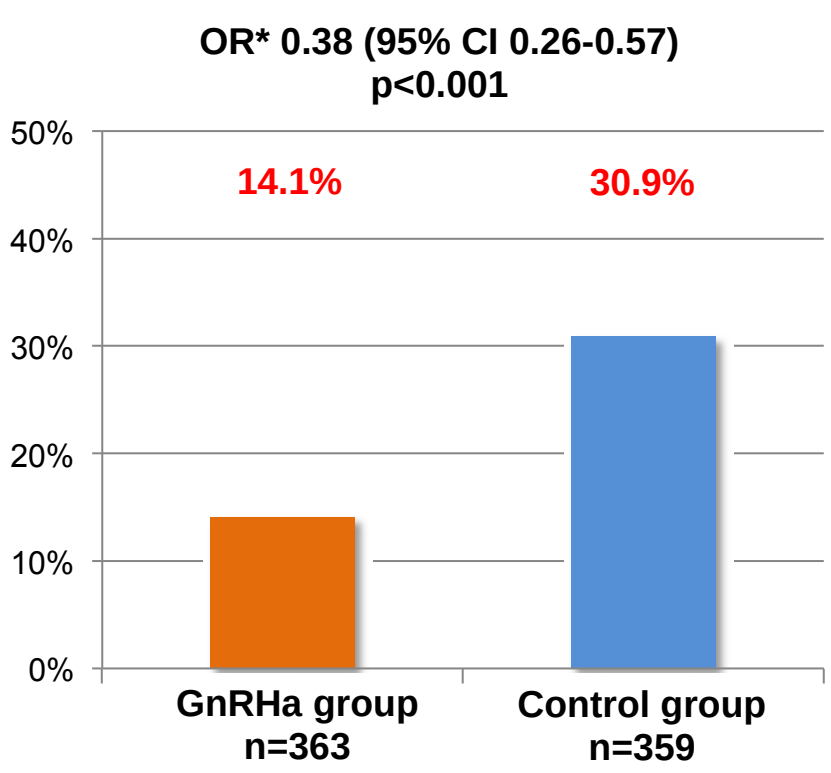
	PROMISE-GIM6[1,2]	POEMS/SWOG S0230[3]	Moffitt-led trial[4]	GBG-37 ZORO[5]	Anglo Celtic Group OPTION[6]
Definition of POI	No resumption of menstrual activity and postmenopausal levels of FSH and E2	Amenorrhea for the prior 6 months and postmenopausal levels of FSH	No maintenance of menses and no resumption of menses	No re-appearance of two consecutive menstrual periods within 21 to 35 days	Amenorrhea with elevated FSH
Timing of POI after chemotherapy	12 months	24 months	24 months	6 months	Between 12 and 24 months
Sample size	281	257	48	60	227
ER status for eligibility	ER-positive and ER-negative	ER-negative only	ER-positive and ER-negative	ER-negative only	ER-positive and ER-negative
Upper age limit for eligibility	≤ 45 years	≤ 49 years	≤ 44 years	≤ 45 years	None
Type of GnRHa	Triptorelin	Goserelin	Triptorelin	Goserelin	Goserelin

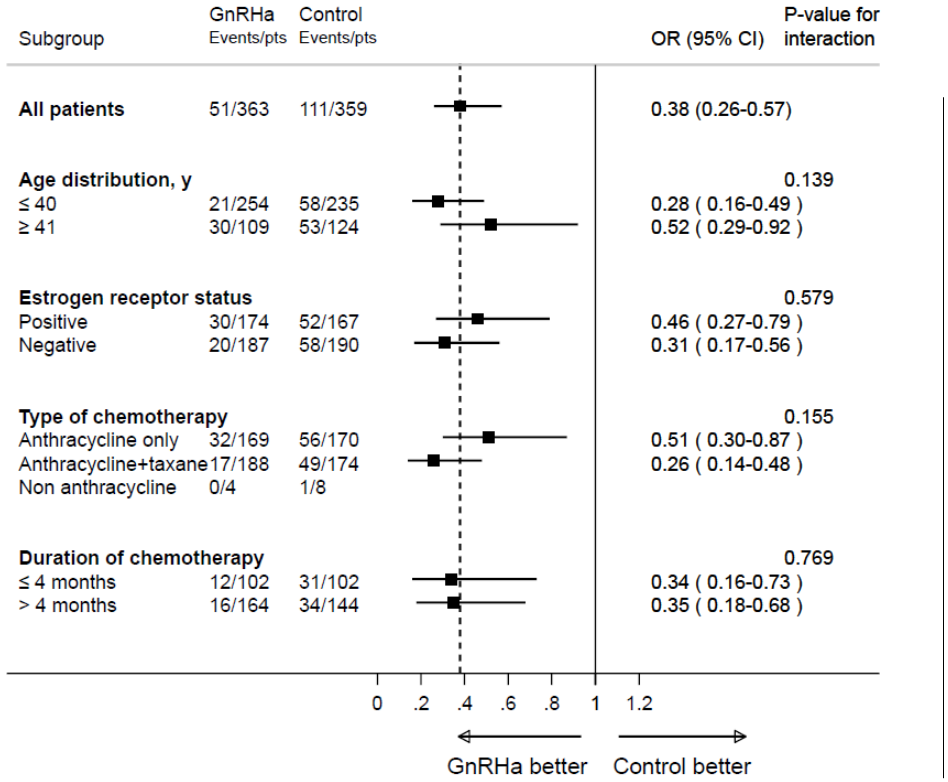
1. Del Mastro L et al, *JAMA* 2011;306:269-76. 2. Lambertini M et al, *JAMA* 2015;314:2632-40. 3. Moore HCF et al, *N Engl J Med* 2015;372:923-32.
4. Munster P et al, *J Clin Oncol* 2012;30:533-38. 5. Gerber B et al, *J Clin Oncol* 2011;29:2334-41. 6. Leonard RCF et al, *Ann Oncol* 2017;28:1811-16.

Lambertini M et al, J Clin Oncol 2018;36(19):1981-90

Breast Cancer: IPD Metanalysis
Efficacy Data

Premature-Ovarian Insufficiency Rate





*Odds ratio (OR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered

Lambertini M et al, J Clin Oncol 2018;36(19):1981-90

Breast Cancer: IPD Metanalysis
Efficacy Data

Post-Treatment Pregnancy Rate

GnRHa Group: 37/359 (10.3%)
vs.
Control Group: 20/367 (5.5%)

IRR* 1.83 (95% CI 1.06-3.15)
p=0.030

	GnRHa group (n = 37) No. (%)	Control group (n = 20) No. (%)
Age distribution, years		
≤ 40	37 (100)	20 (100)
≥ 41	0 (0.0)	0 (0.0)
Estrogen receptor status		
Positive	6 (16.2)	2 (10.0)
Negative	31 (83.8)	18 (90.0)

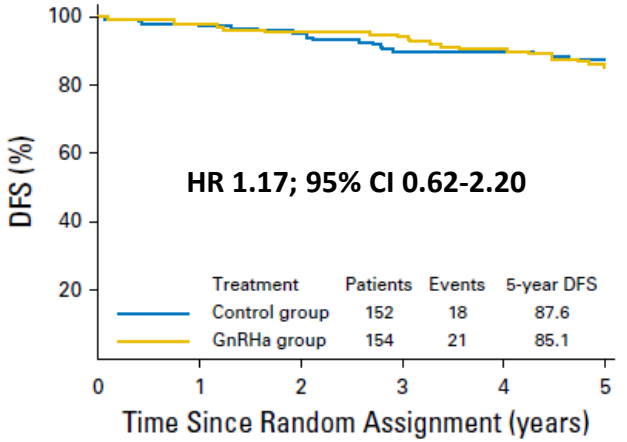
*Incidence rate ratio (IRR)

Lambertini M et al, J Clin Oncol 2018;36(19):1981-90

Breast Cancer: IPD Metanalysis
Safety Data

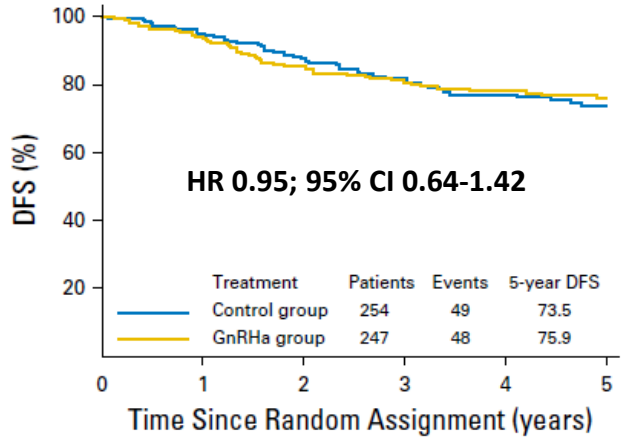
Disease-Free Survival

ER+



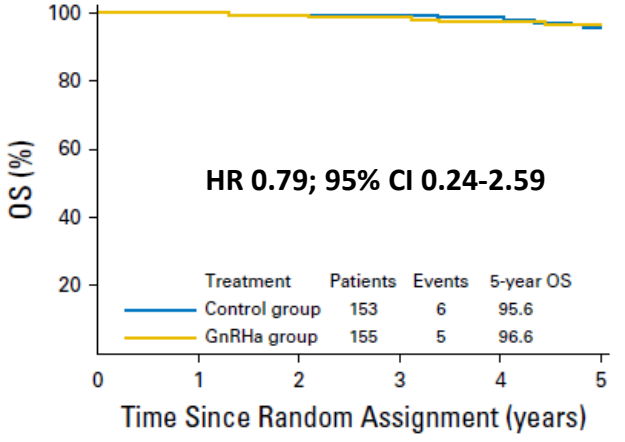
No. at risk						
Control group	152	145	140	129	124	110
GnRHa group	154	151	144	137	123	102

ER-

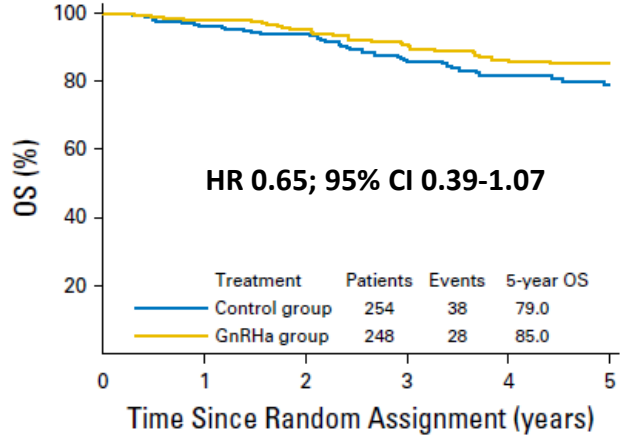


No. at risk						
Control group	254	206	181	138	108	62
GnRHa group	247	204	178	148	116	71

Overall Survival



No. at risk						
Control group	153	150	146	141	136	119
GnRHa group	155	155	151	146	135	118



No. at risk						
Control group	254	211	195	149	118	69
GnRHa group	248	214	198	166	129	80

Lambertini M et al, J Clin Oncol 2018;36(19):1981-90

Potential Explanations on the Differences Breast Cancer vs. HL&NHL

Breast Cancer

- 14 RCTs including 1,647 patients
- 4 RCTs including > 200 patients
- Older age at diagnosis (≈40 years)
- Treatment with chemotherapy regimens having moderate risk of gonadotoxicity (cyclophosphamide-based regimens)

HL&NHL

- 4 RCTs including 154 patients
- The largest RCT included 84 patients
- Younger age at diagnosis (≈25 years)
- Treatment with chemotherapy regimens having high (conditioning regimens for HSCT) or low (ABVD) risk of gonadotoxicity

Lambertini M et al, submitted

Ovarian Suppression with GnRHa during CT: Who Are the Best Candidates ?

- Patients interested in ovarian function preservation (premenopausal women)
- Patients interested in fertility preservation (age < 38 – 40 years):
  1. Following embryo/oocyte cryopreservation
  2. With no access to embryo/oocyte cryopreservation

Outline

- Introduction
- Fertility in cancer patients:
  - Embryo/oocyte cryopreservation
  - Cryopreservation of ovarian tissue
  - Temporary ovarian suppression with GnRHa during chemotherapy
- **Sexuality in cancer patients**
- Conclusions

Sexual Side Effects of Anticancer Treatments in Young Adult Women

Cancer Diagnosis	Most Common Sexual Problems	Prevalence
Women		
Breast	Overall	30%–100%
	Desire	23%–64%
	Arousal or lubrication	20%–48%
	Orgasm	16%–36%
	Pain/dyspareunia	35%–38%
	Body image concerns	30%–67%
	Poor nipple sensation	> 90%
Gynecologic (ovarian and cervical only)	Overall	≤ 80%

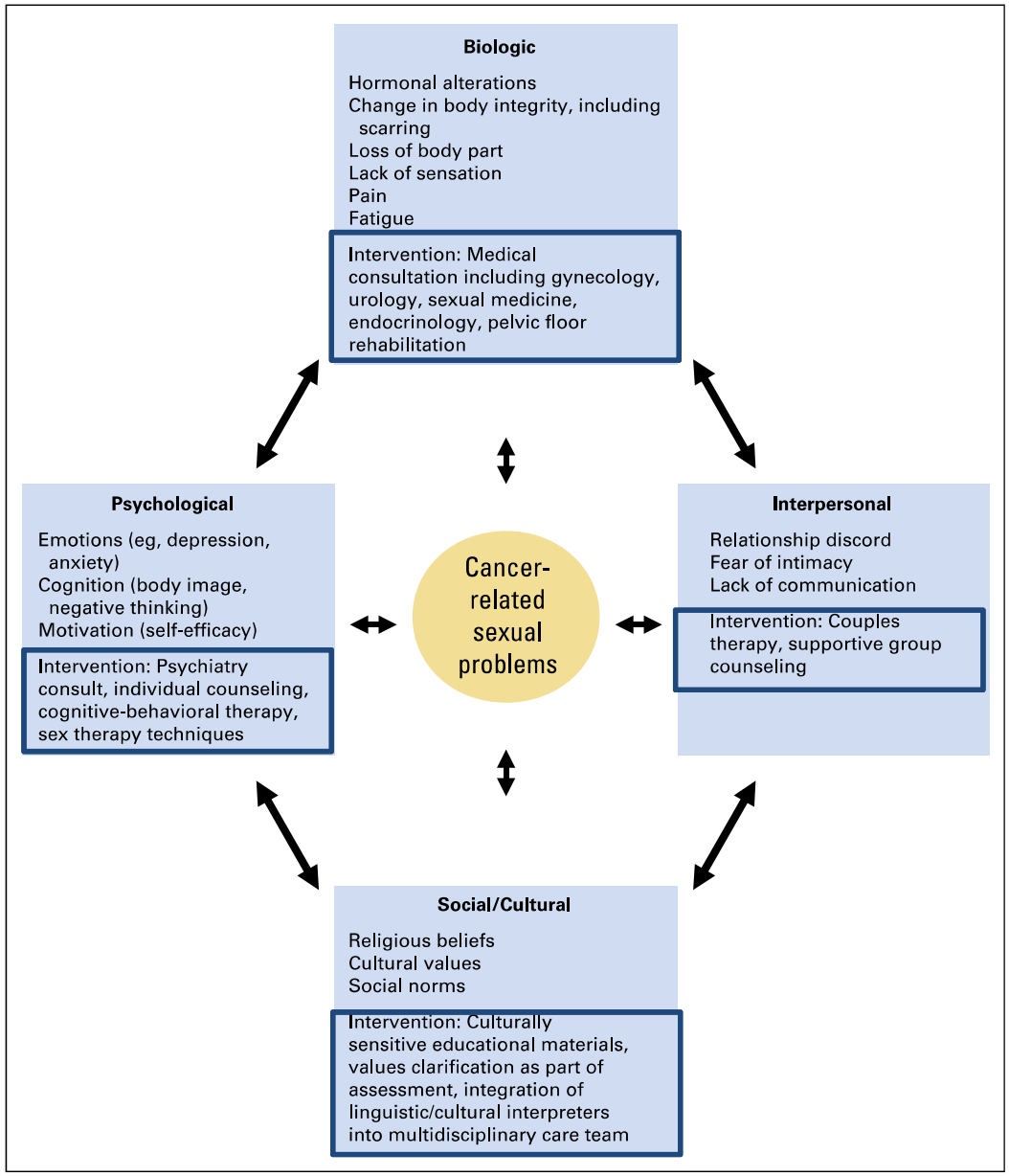
Bober S et al, J Clin Oncol 2012;30:3712-9

Sexual Side Effects of Anticancer Treatments in Young Adult Women

- Unlike other side effects, sexual symptoms do not self-resolve
- Untreated sexual dysfunction tends to worsen over time
- Sexual Dysfunction is associated with
    1. Anxiety
    2. Depression
    3. Loss of perceived self-efficacy

Brotto LA et al, J Cancer Surviv 2010;4:346-60
Gilbert E et al, Maturitas 2010:66:397-407. Leung MW et al, Curr Oncol Rep 2016;18:11

Integrative Model for Intervention



Bober S et al, J Clin Oncol 2012;30:3712-9

Non-Pharmacological Interventions

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Efficacy of Internet-Based Cognitive Behavioral Therapy in Improving Sexual Functioning of Breast Cancer Survivors: Results of a Randomized Controlled Trial

Susanna B. Hummel, Jacques J.D.M. van Lankveld, Hester S.A. Oldenburg, Daniela E.E. Hahn, Jacobien M. Kieffer, Miranda A. Gerritsma, Marianne A. Kuenen, Nina Bijker, Paul J. Borgstein, Gijsbert Heuff, Alexander M.F. Lopes Cardozo, Peter W. Plaisier, Herman Rijna, Suzan van der Meij, Eric J. van Dulken, Bart C. Vrouenraets, Eva Broomans, and Neil K. Aaronson

- Breast cancer survivors (n=169) randomized to internet-based cognitive behavioral therapy (CBT) or waiting-list control group

- Internet-based CBT showed to significantly improve:
  - Overall sexual functioning (sexual desire, sexual arousal, sexual pleasure)
  - Vaginal lubrification
  - Body image
  - Menopausal symptoms

Hummel SB et al, J Clin Oncol 2017;35:1328-40

Non-Pharmacological Interventions

Over-the-Counter Products	
Water-based lubricants	• Aid in vaginal insertion and manual stimulation by decreasing dryness and friction • Safe to use with latex condoms • Apply to both partners during sexual activity • Break down easily after washing with warm water • Examples: KY Jelly, Astroglide, Eros for Women and Liquid Silk
Silicone-based lubricants	• Increase comfort with sexual activity • Longer lasting than water-based lubricants • Apply to both partners during sexual activity • Safe to use with latex condoms • Cannot be used with silicone sex toys • Examples: KY Intrigue, Eros Body Glide, Wet Platinum Silver, Pink, Pjur Eros
Vaginal moisturizers	• Hydrate vulvo-vaginal tissue • Improve dryness, pruritus, elasticity, and irritation • Used 3 to 5 times per week • Take 2 months to realize full benefit • May cause watery discharge • Examples: Replens, hyaluronic acid,

Therapeutic Approach	
Dilator therapy	• Mechanically stretches vaginal tissue • Use to decrease pain with intercourse or gynecologic exams • Use to prevent or treat vaginal stenosis/ adhesions • Dilators usually come in a set of increasing size • Help to reduce anxiety about pain, and increases confidence • Use for 5 to 10 minutes several times per week
Pelvic floor exercises	• Stretch and relax pelvic floor muscles • Improve control and strength of pelvic muscles • Use to decrease pain with intercourse or gynecologic exams • May promote circulation and pelvic blood flow • Daily use recommended
Increase blood flow to pelvic floor	• May promote circulation and arousal response • May have rehabilitative effects by drawing oxygenated blood • Methods include pelvic floor exercises, vibrators, and self-stimulation

Goldfarb S et al, Semin Oncol 2013;40(6):726-44

Pharmacological Interventions

Treatment for VVA	Specific Therapy/Use
Vaginal Estrogen	Local (not systemic) therapy Tablet/ring/cream
Vaginal DHEA	Intravaginal ovules (prasterone)
Lidocaine	For insertional pain. Topical application to vestiblule (4% aqueous lidocaine) before sexual activity
Off-label vaginal testosterone	Controversial
Off-label fractional CO_2 laser	No evidence-base for use

Treatment for Low Desire	Mechanism of Action
Flibanserin (daily use at bedtime)	5-HT1A serotonin receptor agonist and 5-HT2A receptor antagonist
Bremalanotide (on-demand use)	Melanocortin 1 & 4 receptor agonist

Courtesy of Sharon Bober, PhD

Outline

- Introduction
- Fertility in cancer patients:
  - Embryo/oocyte cryopreservation
  - Cryopreservation of ovarian tissue
  - Temporary ovarian suppression with GnRHa during chemotherapy
- Sexuality in cancer patients
- **Conclusions**

Conclusions

- **Fertility preservation and sexuality are priority areas of concern for young adult cancer patients**
- **As early as possible after diagnosis, a proper oncofertility counseling is mandatory to inform all women irrespectively of the stage of their disease**
- **Embryo/oocyte cryopreservation are standard options for fertility preservation**
- **Ovarian tissue cryopreservation remains experimental in most of the countries but may be discussed in specific circumstances**
- **Temporary ovarian suppression with GnRHa during chemotherapy should now be considered an available option to preserve ovarian function and potential fertility in young breast cancer patients (but not an alternative to cryopreservation techniques)**
- **More attention should be paid to sexuality in cancer survivors; integrative treatment model suggested for addressing sexual dysfunction**

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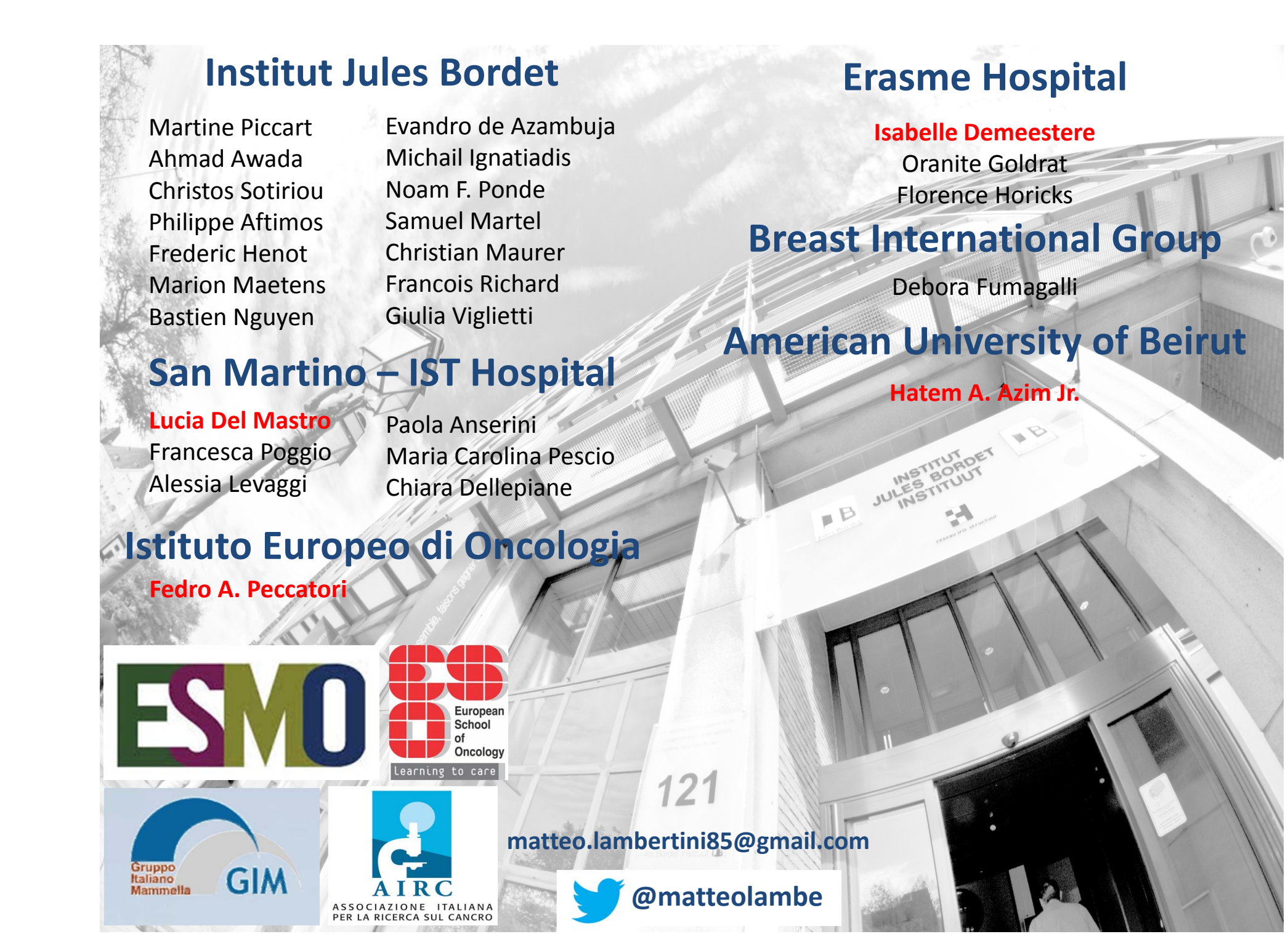

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