La preservazione della fertilità in oncoematologia

Tumori ematologici nell'adulto: epidemiologia e problematiche riproduttive

15/12/2020

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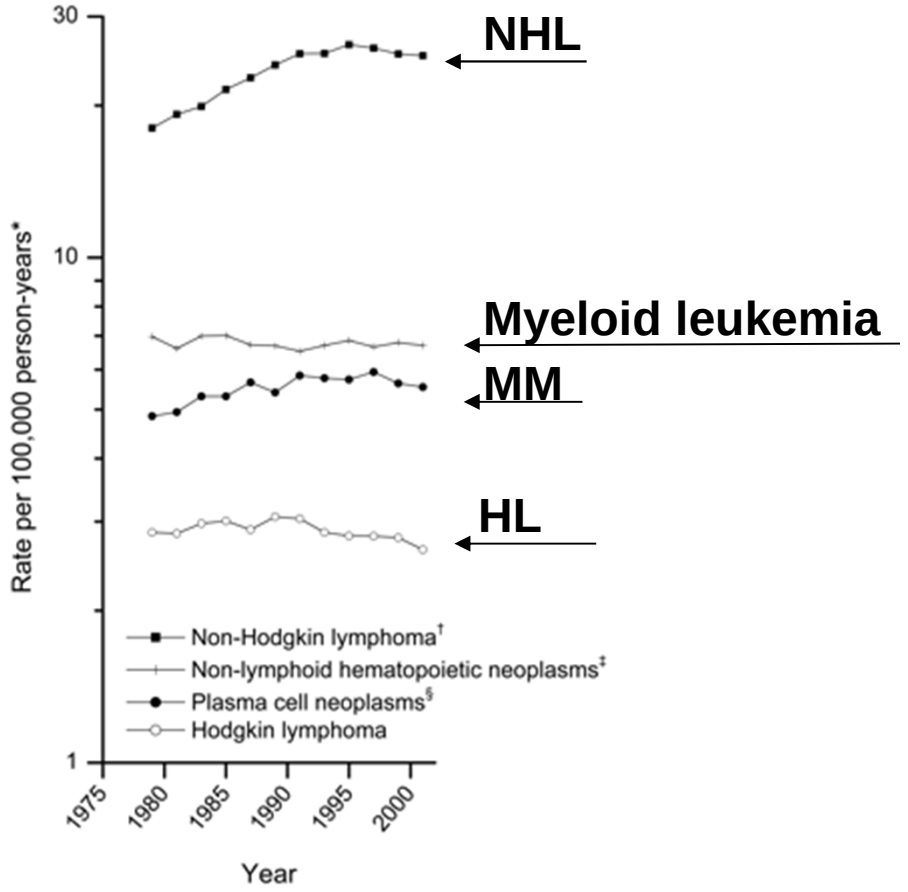
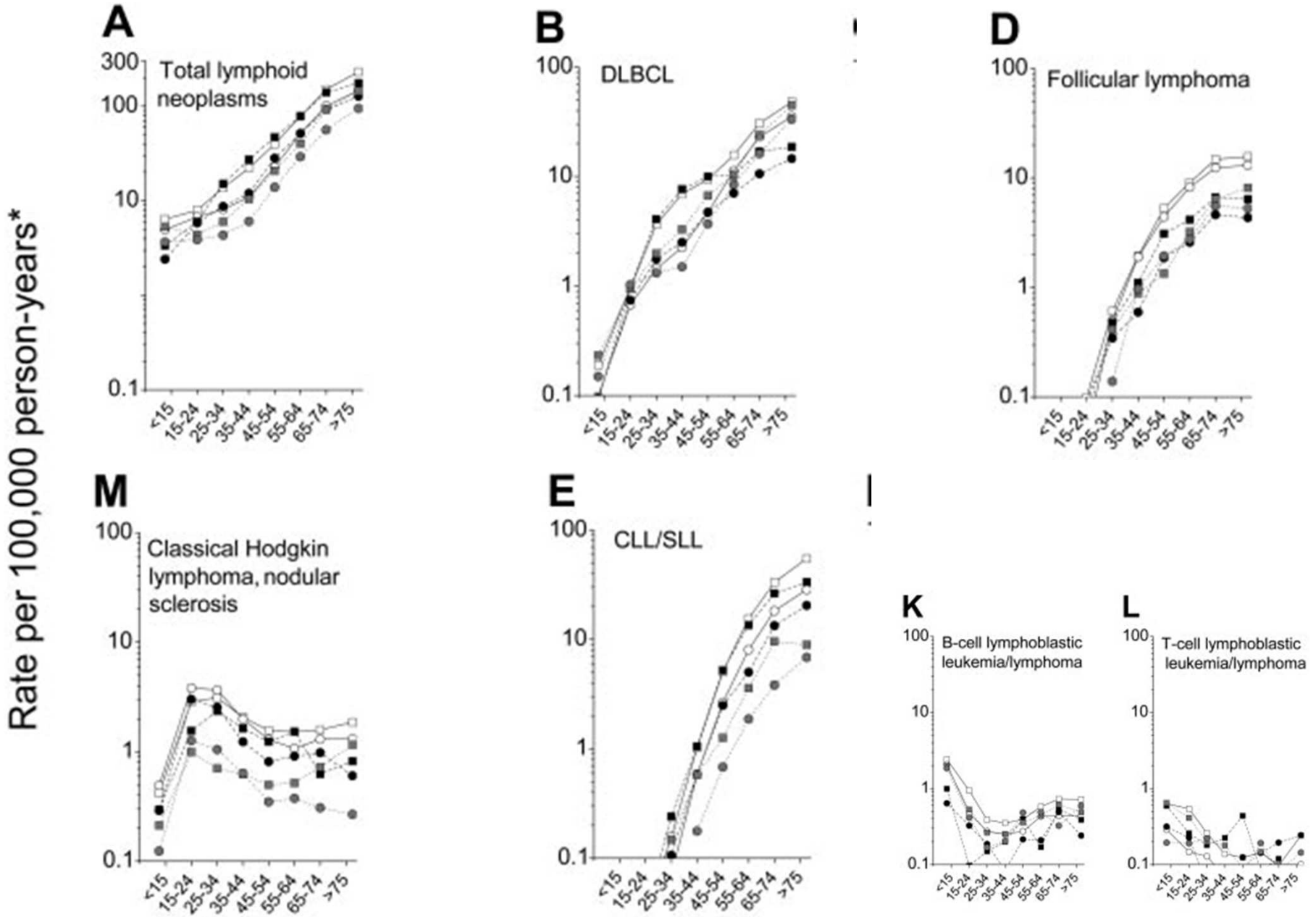


Trends in incidence of hematopoietic neoplasms, 9 SEER registries, 1978-1979 to 2000-2001.
*All incidence rates are age adjusted to the 2000 USA population and presented for 12 fixed 2-year time periods (1978-1979 to 2000-2001).

Morton et al Blood 2006

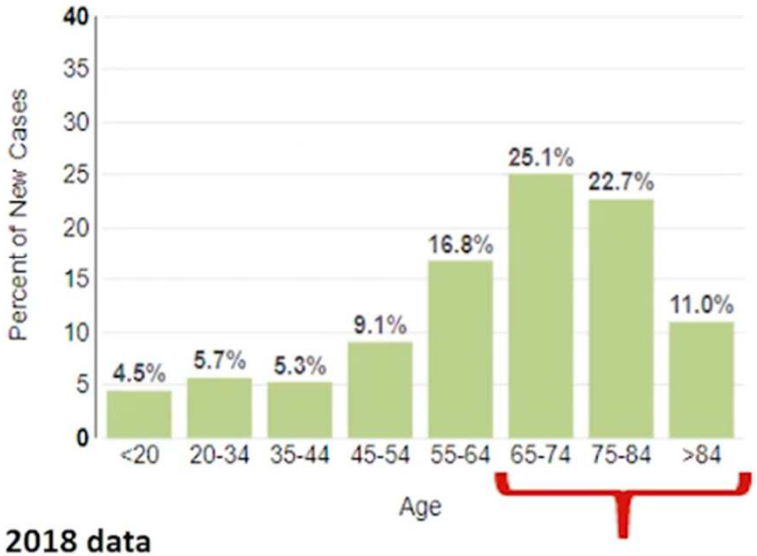


Morton et al Blood 2006

Median age at diagnosis:
68-70+ years

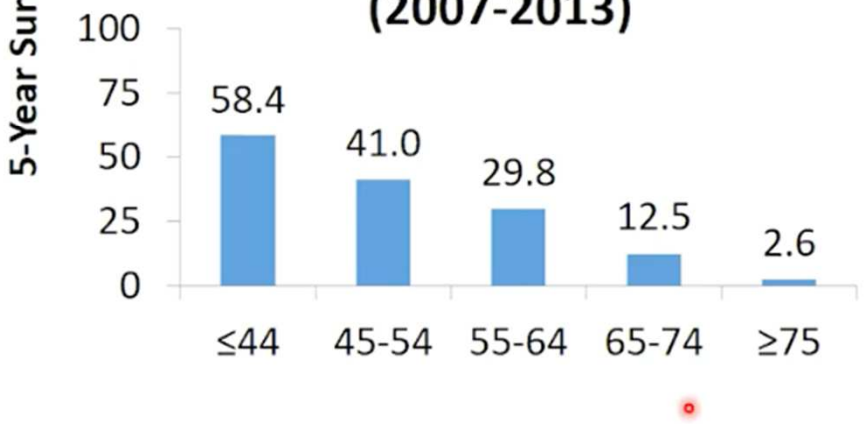
5-yr survival is 28.3%

Incidence of AML by Age Group

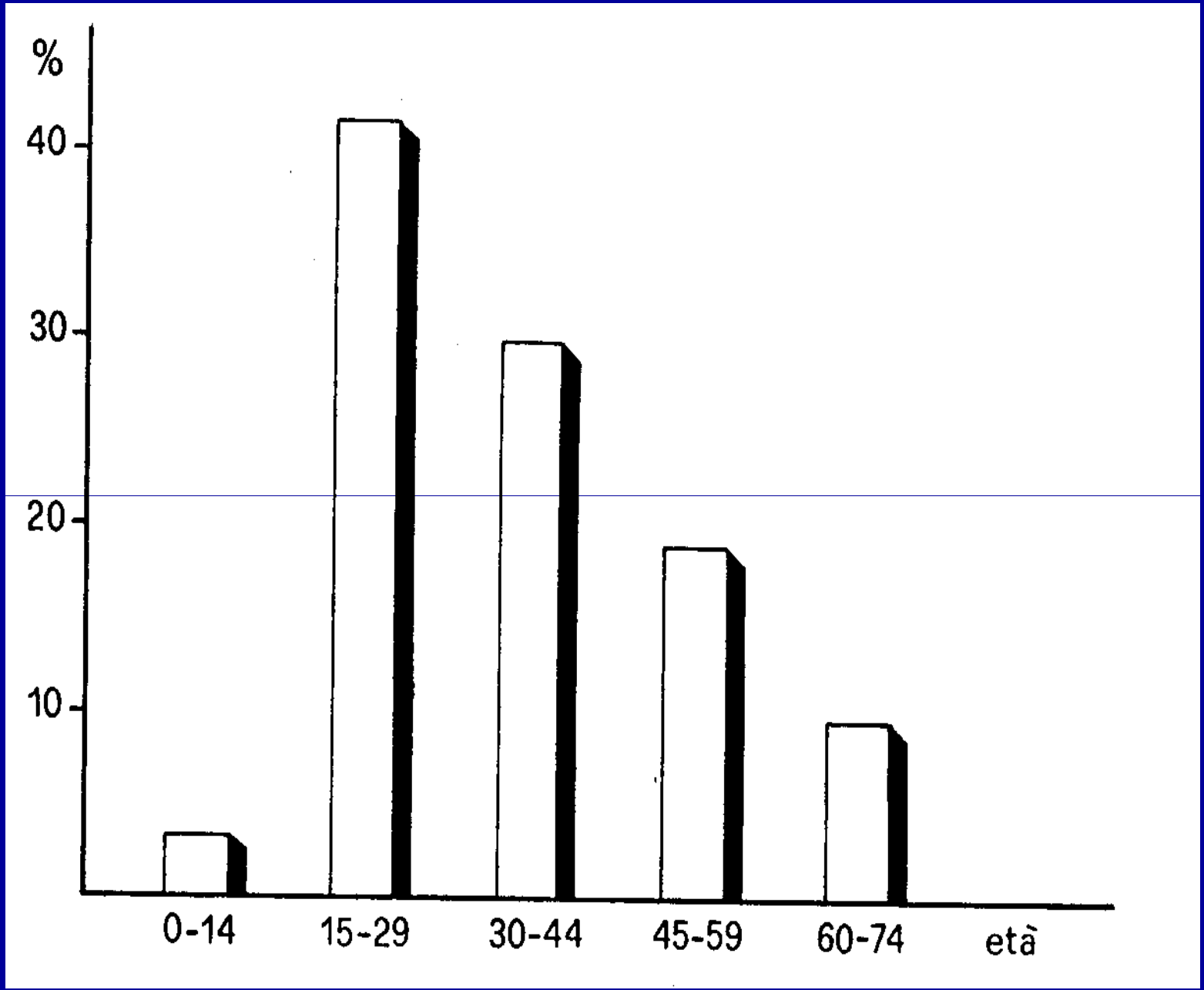


SEER 2018 data
https://seer.cancer.gov/statfacts/html

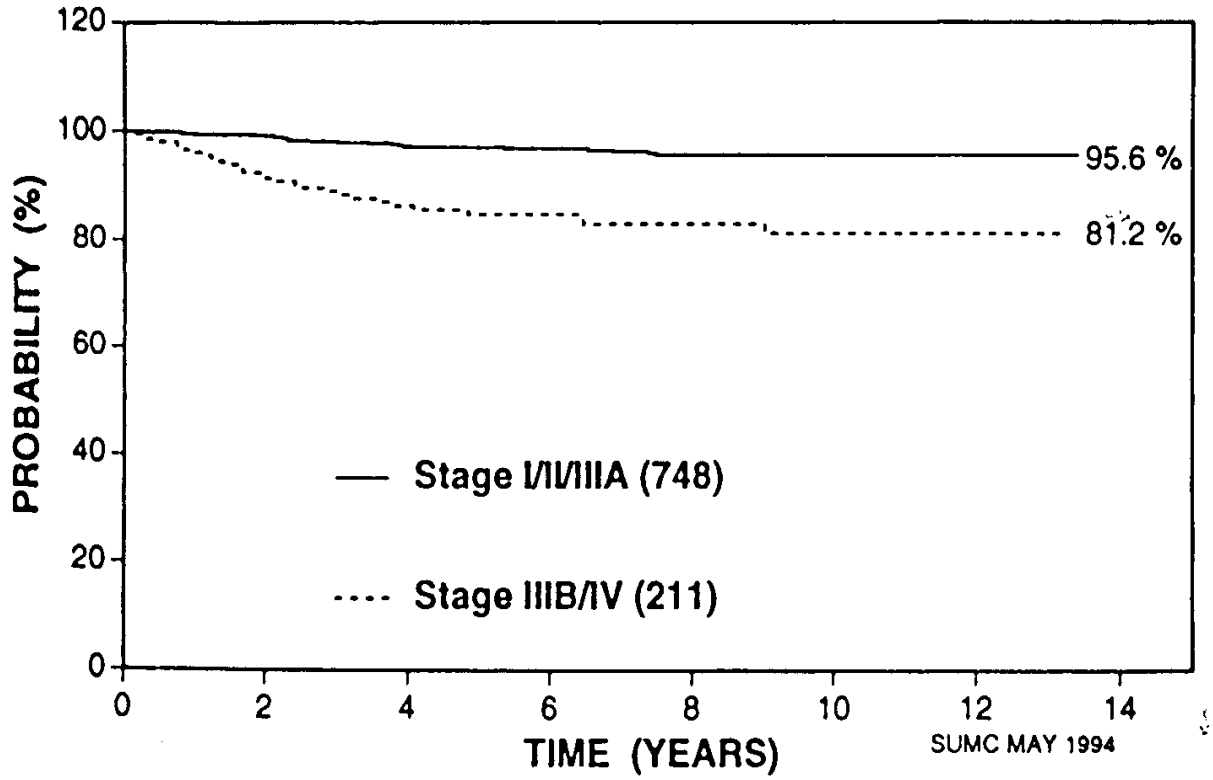
5-Year Survival of Newly Dx AML, Stratified by Age at Diagnosis (2007-2013)



LINFOMA DI HODGKIN – DISTRIBUZIONE PER ETA'



LINFOMA DI HODGKIN



OS

	Sopravvivenza a 10 aa
Linfoma Hodgkin	80-90%
LNH alto grado	60%
LNH basso grado	80%
Mieloma Multiplo	50-60%
Leucemia acuta mieloide	30%
Leucemia acuta linfoide	30%
Leucemia linfatica cronica	60%
Trombocitemia Essenziale	85%
Pollicitemia Vera	65%
Mielofibrosi primitiva	30%
Leucemia Mieloide Cronica	90%

Risks of gonadotoxicity in female patients with hematological malignancies

- Type and dosage of CHT
- Alkylating CHT and TBI
- Type and stage of the disease
- The age of the patient at the beginning of treatment.

Risk category	Risk of permanent amenorrhoea	Agent/regime
High risk	80%	HSC-TX with cyclophosphamide/TBI or cyclophosphamide/busulfan
		External beam radiotherapy including the ovaries
		BEACOPP escalated (≥ 30 years)
		6× CMF, CEF, CAF, TAC (≥ 40 years)
		Procarbazine
		Chlorambucil
Intermediate risk	40–60%	BEACOPP escalated (< 30 years)
		6× CMF, CEF, CAF, TAC (30–39 years)
		4× AC (≥ 40 years)
		4× AC or EC → Taxanes
	30%	Monoclonal antibody: bevacizumab
	12–54%	MTX (cumulative risk increased in repeated treatment of autoimmune disorders)
Low risk	< 20%	ABVD (≥ 32 years)
		4–6× CHOP
		CVP
		AML therapy (anthracycline/cytarabine)
		ALL therapy (multi-agent)
		6× CMF, CEF, CAF, TAC (≤ 30 years)
		4× AC (≤ 40 years)
Very low or no risk	–	ABVD (< 32 years)
		Methotrexate
		Fluorouracil
		Vincristine
		Tamoxifen
Unknown risk	–	Monoclonal antibodies: trastuzumab, cetuximab
		Tyrosine kinase inhibitors: erlotinib, imatinib

Schuring et al 2018

STUDIO RETROSPETTIVO, MULTICENTRICO OSSERVAZIONALE DELLA FONDAZIONE ITALIANA LINFOMI

Periodo di osservazione: 1/10/2010-31/05/2018

Criteri di Inclusione: donne con età compresa tra 18-40 aa trattate con Immuno-CHT e/o RT per LH e LNH in RC da 2 aa

Obiettivi dello studio

Primario:

- Raccogliere informazioni sui metodi utilizzati per la conservazione della fertilità prima della terapia nei diversi centri partecipanti

Secondari:

- Determinare il tasso di amenorrea post trattamento ed i possibili fattori di rischio (età al trattamento, regime chemioterapico, protezione con OC o analoghi del GnRH)
- Tasso di gravidanze post CHT

Courtesy of Annibali O. on behalf of the Master Lymphoma Group

POPOLAZIONE		
Pazienti: 414	Mediana ± SD, range	
Età alla diagnosi	28.0 ± 6.0 (18,0-40,0)	
TIPO DI LINFOMA	N	%
LH	308	74
PMBL	56	13
DLBCL	43	10
MCL/LNH-T/Follicolari	7	3
STADIO ANN ARBOR		
I-II	250	60
III-IV	164	40

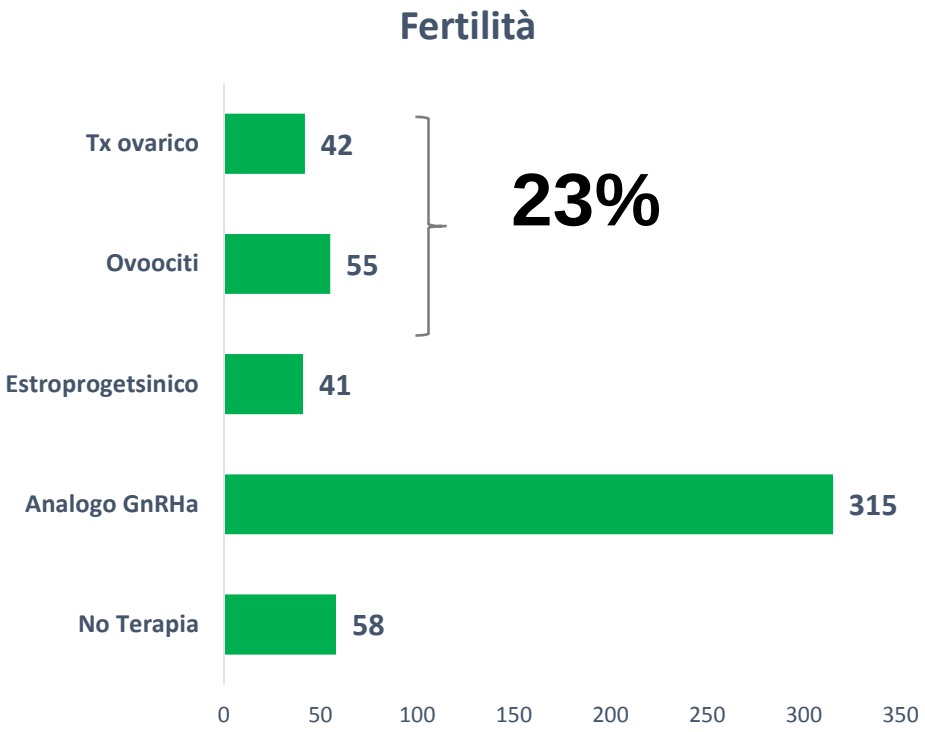
Courtesy of Annibali O. on behalf of the Master Lymphoma Group

TRATTAMENTO		
Prima Linea	n	%
ABVD	295	71
R-CHOP/CHOEP/MACOP-B/DA-EPOCH	102	25
BEACOPP /BEACOPP esc/CHT + ASCT	17	4
RT di consolidamento	203	49
Recidiva/Progressione	48	11
ASCT	25	52
CHT	23	48

Courtesy of Annibali O. on behalf of the Master Lymphoma Group

PRE-TERAPIA	
	# (%)
Regolarità ciclo mestruale (Y/N)	217/52 (80/20)
Gravidanza (Y/N)	106/308 (26/74)
Aborto (Y/N)	36/365 (9/91)

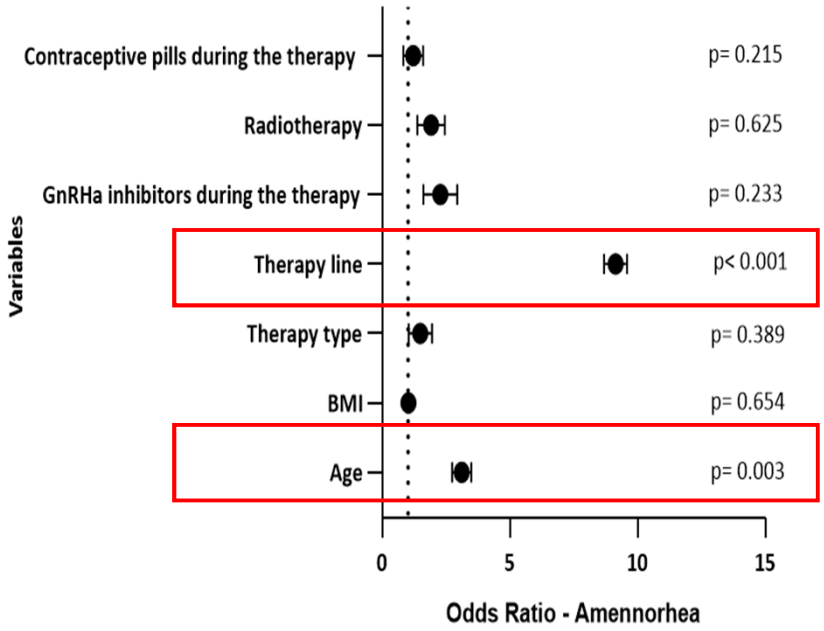
POST- TERAPIA	
	# (%)
Amenorrea transitoria (Y/N)	216/74 (75/25)
Gravidanza	43 (10)
Ciclo mestruale regolare(Y/N)	293/32 (90/10)
Aborto (Y/N)	17/293 (4/96)
Amenorrea definitiva (Y/N)	33/342 (9/91)
Menopausa (aa, mediana ± SD, range)	34.5 ± 7.8 (19.0-47.0)

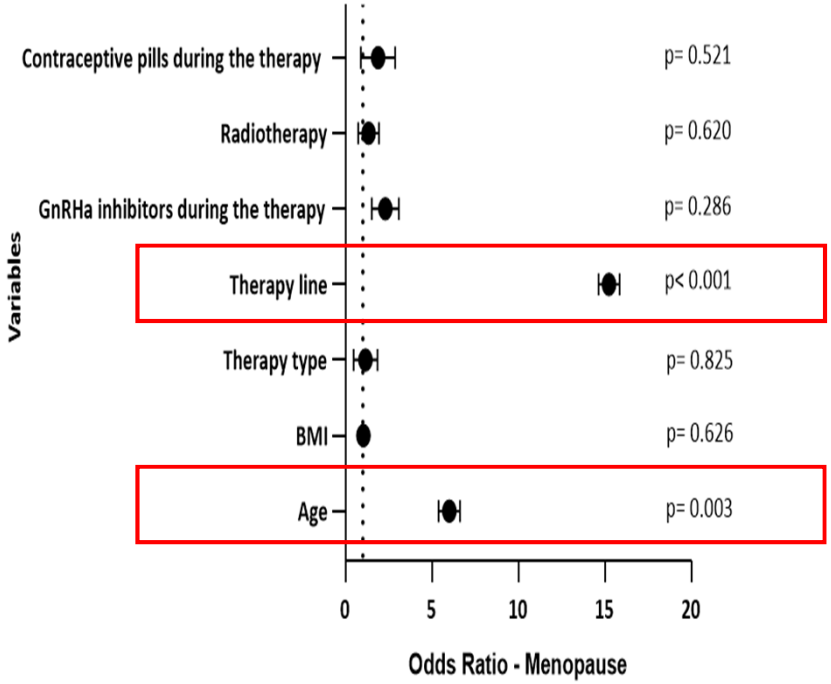


7/414 non criopreservate per urgenza terapeutica

Courtesy of Annibali O. on behalf of the Master Lymphoma Group

TIPO DI TERAPIA ED ETA' CORRELANO CON RISCHIO DI AMENORREA E MENOPAUSA





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CONCLUSIONI DELLO STUDIO

- 23% Criopresevazione (Tx ovarivo/ovoociti)
- Nessun utilizzo
- Metodi in uso per conservazione della fertilità
  - ✓ 76% protezione famacologica con GnRHa
  - ✓ 10% terapia con EP
  - ✓ 14% nulla
- 75% di tasso di amenorrea transitoria post terapia
- 9% di menopausa
- Tasso di gravidanze del 10% della popolazione generale
- Non effetto protettivo sulla fertilità dell'analogo del GnRHa
- Impatto dell'età, numero di linee terapeutiche sulla Amenorrea e Menopausa

Courtesy of Annibali O. on behalf of the Master Lymphoma Group

VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren

General reccommendations:

1. **Are patients with cancer interested in interventions to preserve fertility ?**

   People with cancer are interested in discussing fertility preservation.

2. **What is the role of the oncologist in advising patients about fertility preservation options**

   Oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons should address the possibility of infertility and refer patients to reproductive specialists as early as possible before treatment starts.

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Adult men:

- **sperm cryopreservation** is effective
- hormonal gonadoprotection: hormonal therapy in men is **not successful** in preserving fertility. It is not recommended
- potentially higher risk of genetic damage in sperm collected **after initiation of therapy**
- it is strongly recommended that sperm be collected **before initiation** of treatment because the quality of the sample and sperm DNA integrity may be compromised after a single treatment
- sperm counts and quality of sperm **may be diminished even before** initiation of therapy
- these concerns **should not dissuade** patients from banking sperm
- **intracytoplasmic sperm injection** allows the future use of a very limited amount of sperm; thus, even in these compromised scenarios, fertility may still be preserved

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Adult women:

1. Embryo cryopreservation
2. Cryopreservation of unfertilized oocytes
3. Ovarian transposition can be offered when pelvic irradiation is performed as cancer treatment (not always successful)
4. Ovarian suppression (GnRHa) (conflicting evidence)
5. Ovarian tissue cryopreservation and transplantation (remain experimetal)

No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group

K. Behringer[1]*, L. Wildt[2], H. Mueller[1], V. Mattle[2], P. Ganitis[1], B. van den Hoonaard[1], H. W. Ott[3], S. Hofer[3], A. Pluetschow[1], V. Diehl[1], A. Engert[1]& P. Borchmann[1] on behalf of the German Hodgkin Study Group

[1]German Hodgkin Study Group, First Department of Internal Medicine, University Hospital Cologne, Cologne, Germany; [2]University Hospital for Gynecology and Reproduction Medicine; [3]Institute of Medical and Chemical Laboratory Diagnostics (ZIMCL), University Hospital Innsbruck, Innsbruck, Austria

Received 18 December 2009; accepted 4 February 2010

Patients and methods: Women (18–40 years) were randomly assigned either to receive daily OC or monthly GnRH-a during escalated combination therapy with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc). Hormonal levels were determined at baseline, during therapy, and at follow-up.

Results: The study was closed prematurely after an interim analysis of 12 patients in arm A (OC) and 11 in arm B (GnRH-a), 9 and 10 are assessable for the primary end point. Women's median age was 25 years in both arms. The anti-Mullerian hormone level after at least 12 months was reduced in all patients. For the entire study cohort, the respective ovarian follicle preservation rate was 0% (95% confidence interval 0% to 12%).

Conclusion: We observed no protection of the ovarian reserve with hormonal co-treatment during BEACOPPesc. This result supports efforts of ongoing trials to reduce chemotherapy intensity and toxicity. Alternative strategies for the protection of fertility must be offered to young female HL patients before the start of BEACOPPesc therapy.

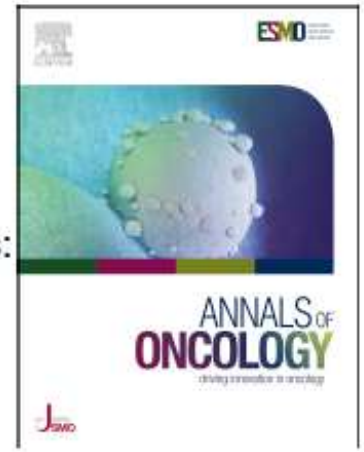
No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial

Isabelle Demeestere, Pauline Brice, Fedro A. Peccatori, Alain Kentos, Jehan Dupuis, Pierre Zachee, Olivier Casasnovas, Eric Van Den Neste, Julie Dechene, Viviane De Maertelaer, Dominique Bron, and Yvon Englert

- Multivariate analysis showed significantly increased risk of POI in patients according to:
  - age (P = .047)
  - conditioning regimen for hematopoietic stem cell transplant (P = .002)
  - cumulative dose of cyclophosphamide > 5 g/m2 (P = .019)
  - but not to the coadministration of GnRHa (odds ratio, 0.702; P = .651)
- The ovarian reserve, evaluated using anti-Mullerian hormone and FSH hormone levels, was similar in both groups
- 53% and 43% achieved pregnancy in the GnRHa and control groups (P = .467)

J Clin Oncol 34:2568-2574.

Journal Pre-proof



Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines†

M. Lambertini, F.A. Peccatori, I. Demeestere, F. Amant, C. Wyns, J.-B. Stukenborg, S. Paluch-Shimon, M.J. Halaska, C. Uzan, J. Meissner, M. von Wolff, R.A. Anderson, K. Jordan, on behalf of the ESMO Guidelines Committee

Male patients

- A potential negative impact of cancer on semen parameters has been described for patients with testicular tumours and Hodgkin lymphoma.

Female patients

- Cancer and anticancer treatments may affect post-treatment ovarian function by a reduction in ovarian reserve, a disturbed hormonal balance, or by anatomical or functional changes to the ovaries, uterus, cervix or vagina.
- Reduced ovarian function may result in infertility and POI
- In cancer patients, menstrual function can resume many months after completion of treatment; in addition, infertility and POI may occur despite temporary resumption of menses

Journal Pre-proof

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General reccommendations:

- Cancer patients of reproductive age should receive complete oncofertility counselling **as early as possible** in the treatment planning process
- Oncofertility counselling should be **individualised** based on patient/couple- and disease/treatment-related factors, with patient interest and age as well as type of treatment being the most important
- As there is no absolute threshold of exposure to anticancer therapies that determines gonadal failure and infertility, every patient should be considered as being at potential risk of developing treatment-related gonadotoxicity

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Male patients:

- Sperm cryopreservation
- Intracytoplasmic sperm injection
- Sperm cryopreservation should be offered **before** treatment initiation because of potential genetic abnormalities in sperm after exposure to CHT or RT
- Gonadal shielding during RT
- Hormone suppression treatments such as a gonadotropin-releasing hormone agonist (GnRHa), with or without androgens, antiandrogens or progestins, **are not protective**

Journal Pre-proof

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Female patients

1. Oocyte and embryo cryopreservation

- Approximately two weeks of ovarian stimulation with gonadotropins is required, followed by follicle aspiration. Ovarian stimulation can be started at any time of the menstrual cycle (random start stimulation)
- Indicated for women preferably ≤40 years
- Ovarian stimulation can lead to side-effects caused by the medication as well as complications during the oocyte pick-up, including bleeding from the ovary and pelvic infection

2. Ovarian tissue cryopreservation

- Still regarded as experimental in some countries
- Laparoscopy under general anaesthesia
- No pre-treatment is required

3. Ovarian transposition and gonadal shielding during RT

4. Medical gonadoprotection

Journal Pre-proof

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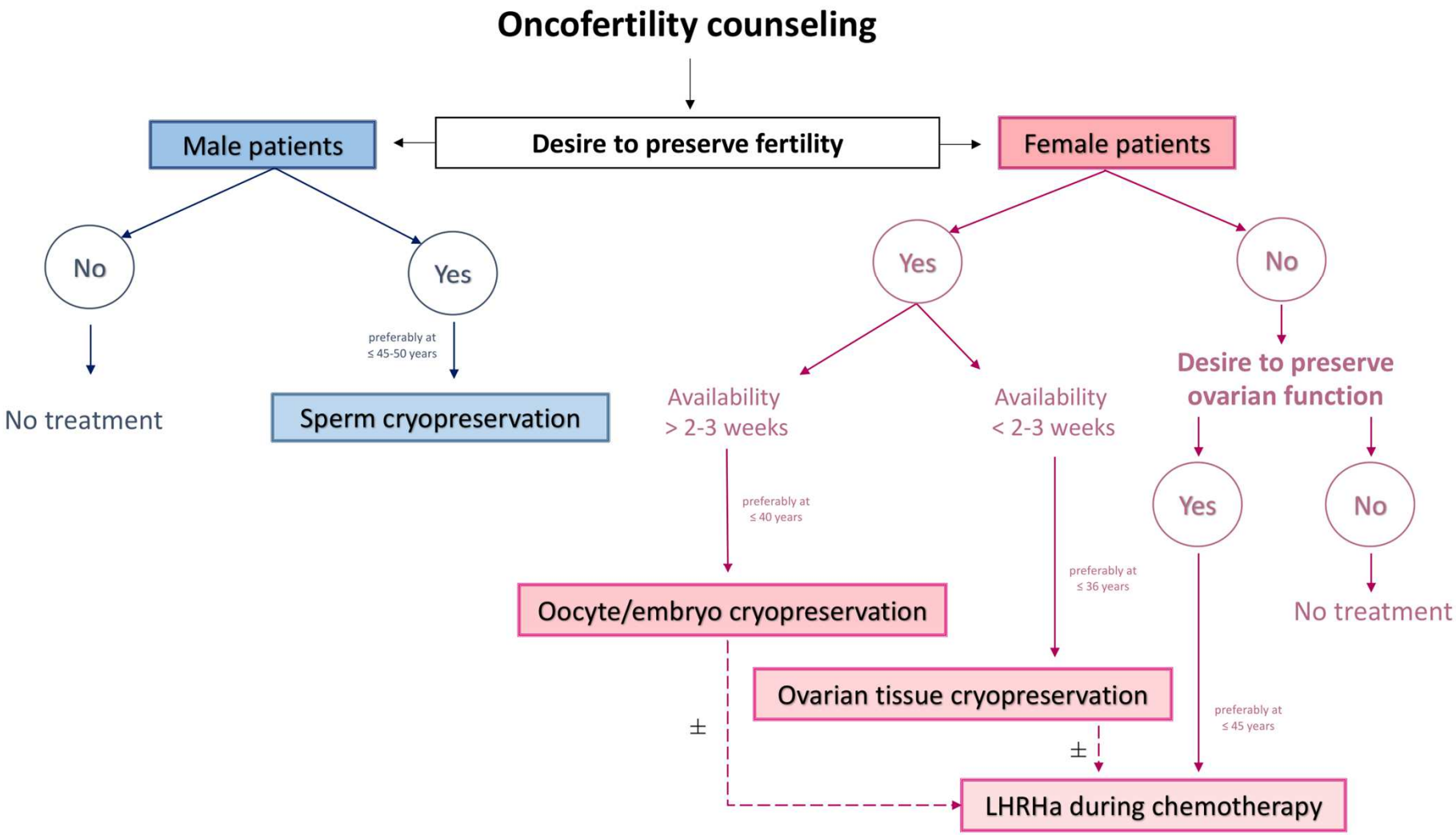
POST-TREATMENT PREGNANCIES IN CANCER SURVIVORS

Female partners of male cancer survivors	Female cancer survivors
• No increase	• Increased risk of developing obstetric and birth complications*

*: risk of prematurity, low birth weight, elective and emergency caesarean section, assisted vaginal delivery and post-partum haemorrhage; the risk of these complications appears to be higher when the interval between the end of treatment and conception is **short** (12 months); pregnancies should be monitored more closely.


Oncofertility counseling
Desire to preserve fertility
Male patients
Female patients
No
Yes
No treatment
preferably at
≤ 45-50 years
Sperm cryopreservation
Yes
No
Availability
> 2-3 weeks
Availability
< 2-3 weeks
Desire to preserve
ovarian function
preferably at
≤ 40 years
Yes
No
No treatment
Oocyte/embryo cryopreservation
preferably at
≤ 36 years
Ovarian tissue cryopreservation
±
±
preferably at
≤ 45 years
LHRHa during chemotherapy

Sicurezza per la paziente onco-ematologica: possibili problematiche

1. Ritardo nell'inizio della terapia
2. Rischio anestesiologico
3. Rischio trombotico
4. Rischio di re-inoculazione di cellule tumorali dopo autotrapianto di tessuto ovarico

1. Ritardo nell'inizio della terapia

Tempi per esecuzione criopreservazione:

- Stimolazione e raccolta ovociti: 10-15 giorni
- Criopresevazione tessuto ovarico: 7 giorni

Purtroppo diverse variabili provocano un allungamento dei tempi

Cause del ritardo:

- Logistiche (pazienti o HCP)
- Spesso la paziente riferisce allo specialista con diagnosi già fatta
- Tempi refertazione patologica a volte (troppo !) lunghi
- Stadiazione più o meno completa

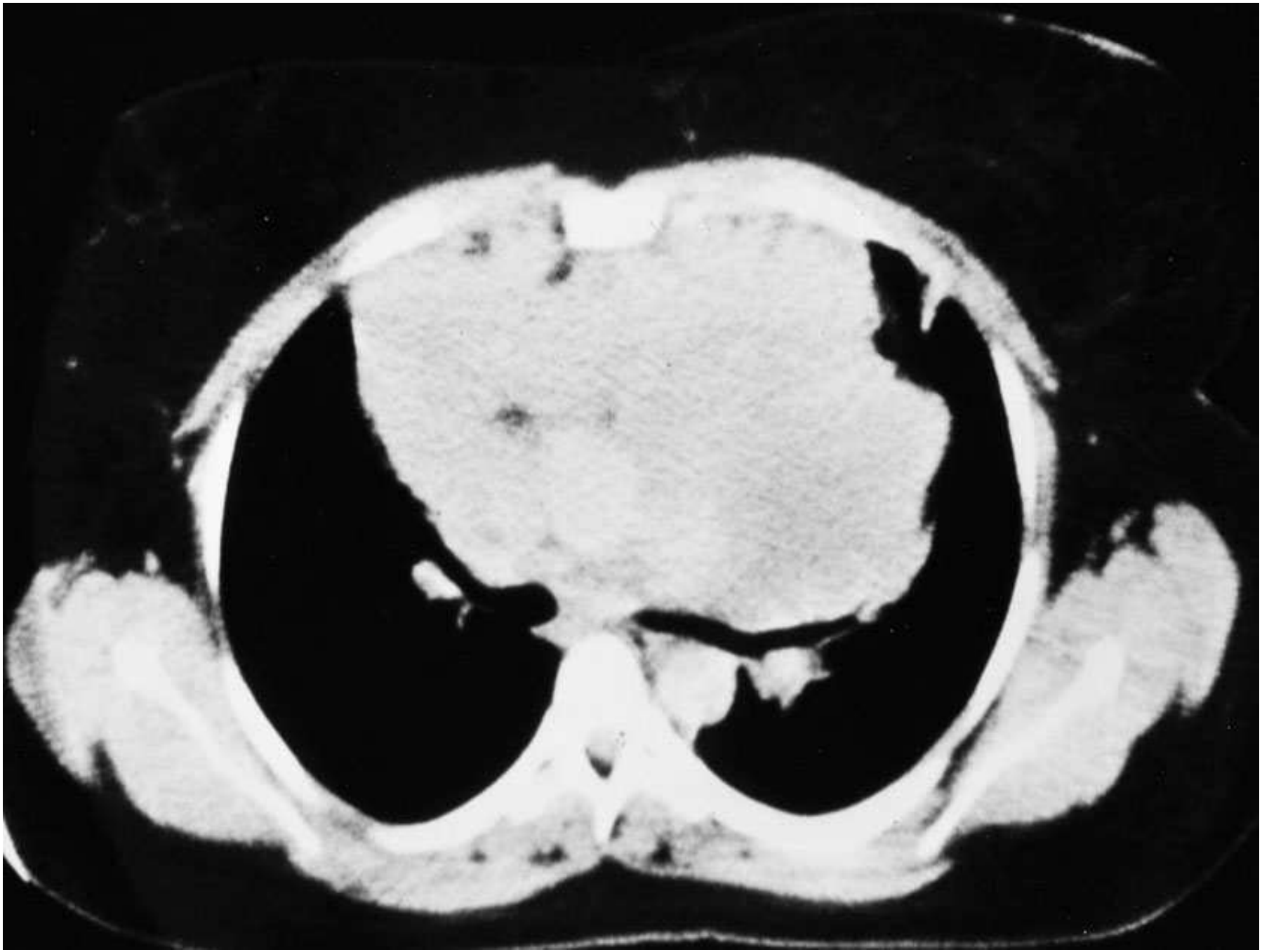
Per alcune neoplasie 2 settimane di attesa possono non essere possibili:

- Leucemie acute
- Linfomi o altri tumori aggressivi

2. Rischio anestesiologico

Linfomi o altre neoplasia con importante interessamento mediastinico

Criopreservazine ovarica	Aspirazione transvaginale di ovociti
L'intubazione può risultare a rischio	10-15 giorni di attesa possono non essere possibili



3. Rischio trombotico in corso di stimolazione ormonale

Aumentato rischio trombotico	Ridotto rischio trombotico
• l'incidenza di VTE nei pazienti con cancro **è fino 10-volte** più rispetto alla popolazione generale • cambiamenti **pro-coagulanti** in corso di stimolazione ovarica • eventi trombotici arteriosi e venosi dopo stimolazione ovarica • sindrome da iperstimolazione ovarica (**OHSS**)	• le pazienti che si sottopongono a stimolazione ovarica per la preservazione della fertilità sono in genere a ridotto rischio trombotico se confrontate con la popolazione generale affetta da cancro (più **giovani**; **stadio precoce** di malattia)

Somigliana et al 2014

Table IV Main findings of the observational controlled studies on the relationship between ovarian stimulation and thrombosis (see also Table III).

Authors, year	Outcome	Subgroup	Incidence in treated women	OR, HR or IRR (95% CI)
Jacobsen et al. (2008a)	VTE	Pregnancy	n.a.	OR = 4.4 (2.6–7.5)*
	VTE	Puerperium	n.a.	OR = 2.2 (1.1–4.3)*
Jacobsen et al. (2008b)	VTE	Pregnancy	n.a.	OR = 4.3 (2.0–9.4)*
	VTE	Puerperium	n.a.	OR = 2.6 (0.8–8.5)
Rova et al. (2012)	VTE	Pregnancy (all trimesters)	2.7‰	OR = 2.7 (2.1–3.6)*
	VTE	First trimester	1.7‰	OR = 9.8 (6.7–14.3)*
	VTE	Second trimester	0.3‰	OR = 1.5 (0.6–3.6)
	VTE	Third trimester	0.7‰	OR = 1.1 (0.7–2.0)
	VTE	Puerperium	0.6‰	OR = 1.2 (0.6–2.0)
	VTE	non-OHSS	0.8‰	OR = 4.8 (2.7–8.7)*
	VTE	OHSS	16.8‰	OR = 99.7 (61.8–161.1)*
	VTE	Frozen embryos	0.3‰	OR = 1.7 (0.2–11.8)
Hansen et al. (2012)	VTE	Non-pregnant at 6 months	0.3‰	IRR = 1.0 (0.4–2.0)
	VTE	Non-pregnant at 12 months	0.4‰	IRR = 1.3 (0.7–2.1)
	ATE	Non-pregnant at 6 months	0.1‰	IRR = 0.4 (0.04–1.3)
	ATE	Non-pregnant at 12 months	0.2‰	IRR = 0.7 (0.3–1.6)
Henriksson et al. (2013)	VTE	Pregnancy (all trimesters)	4.2‰	HR = 1.8 (1.4–2.2)*
	VTE	First trimester	1.5‰	HR = 4.6 (3.0–7.2)*
	VTE	Second trimester	1.0‰	HR = 1.0 (0.5–2.0)
	VTE	Third trimester	1.4‰	HR = 1.0 (0.6–1.7)
	VTE	Puerperium	1.0‰	HR = 1.3 (0.8–2.0)
	PE	Pregnancy (all trimesters)	0.8‰	HR = 1.4 (0.9–2.4)
	PE	First trimester	0.3‰	HR = 7.0 (2.2–22.0)*
	PE	Second trimester	0.2‰	HR = 0.4 (0.1–3.2)
	PE	Third trimester	0.3‰	HR = 0.4 (0.1–1.7)
	PE	Puerperium	0.1‰	HR = 0.6 (0.2–2.0)
Hansen et al. (2014)	VTE	Pregnancy (all trimesters)	2.9‰	IRR = 3.0 (2.1–4.3)*
	VTE	First trimester[a]	n.r.	IRR = 5.9 (2.7–13.0)*
	VTE	Second trimester[a]	n.r.	IRR = 2.4 (0.9–6.6)
	VTE	Third trimester[a]	n.r.	IRR = 2.3 (1.4–3.8)*
	VTE	Puerperium	2.8‰	IRR = 1.7 (0.9–3.0)

Data in parentheses are 95% CI. Only adjusted measurements of associations are reported.
VTE, venous thromboembolism; PE, pulmonary embolism; ATE, arterial thrombotic events; OR, odds ratio; HR, hazard ratio; IRR, incidence rate ratio.
[a]Only singleton pregnancies included in the subgroup analyses.
*Statistically significant.

Somigliana et al 2014

Risk of thrombosis due to ovarian stimulation

- The available evidence suggests that the risk of **thrombosis may not be of major concern** in women undergoing ovarian stimulation for fertility preservation
- Systematic **antithrombotic prophylaxis** during fertility preservation for cancer patients is **not justified**
- Prophylaxis reserved in **high risk groups** (OHSS, most thrombogenic malignancies, personal history of thrombosis)
- Women should therefore be **informed** about the risk of thrombosis but concomitantly **reassured** regarding the magnitude of this risk
- Finally, there is also no indication (and time) for **testing thrombophilia** since the available evidence showed that it may play only a secondary role in the context of ovarian stimulation-related thrombosis

Somigliana et al 2014

4. Rischio di re-inoculazione di cellule tumorali dopo autotrapianto di tessuto ovarico

Autotransplantation of cryopreserved ovarian tissue in cancer survivors and the risk of reintroducing malignancy: a systematic review

Human Reproduction Update, Vol.19, No.5 pp. 483–506, 2013

- Ovarian grafts from oncological patients may harbour cancer cells and autotransplantation of such grafts could theoretically lead to recurrence of oncological disease
- The magnitude of the risk of reintroduction of a malignancy in specific situations is currently unknown, although it has been hypothesized to be influenced by cancer type and stage, the mass of malignant cells transferred, and the time of ovarian tissue harvesting in relation to oncological treatment

Basting et al. 2013

Ovarian involvement and the risk of reintroducing malignancy: hematological malignancies

Disease	Risk of ovarian involvement
Hodgkin lymphoma	Rare
Non-Hodgkin Lymphoma	High in Burkitt's lymphoma. Moderate in other high grade NHL. Rare in other NHL but should be evaluated. Primary ovarian lesions are rare (0.5%)
Acute myeloid leukemia	14-41%
Acute lymphoid leukemia	15-58%
Chronic myeloid leukemia	33-100%

Basting et al. 2013

Take home messages (1)

- In linea generale una gravidanza nelle pazienti in remissione dopo trattamento per una neoplasia maligna deve essere considerata possibile, sicura e non deve essere scoraggiata
- La procedura di preservazione della fertilità deve essere considerata prima di iniziare il trattamento nelle donne < 40 aa e discussa con le pazienti
- Approccio multidisciplinare
- L'approccio alla problematica della preservazione della funzione ovarica deve essere tempestivo
- Selezione delle pazienti/malattie/procedure

Take home messages (2)

- Criopreservazione di ovociti o di tessuto ovarico rappresentano il gold standard
  - Bilancio rischio beneficio
  - Ritardo inizio terapia
  - Possibili effetti collaterali
  - Rischio di re-impianto di tessuto metastatico
- **Migliori candidate per la criopreservazione di ovociti:**
  - Pazienti con controindicazioni alla manovra di intubazione
  - Altre controindicazioni chirurgiche
  - Non urgenza terapeutica
- **Migliori candidate per la criopreservazione di tessuto ovarico:**
  - Bambine pre-puberi
  - Pazienti da sottoporre a trattamenti ad alto rischio di POI
  - Pazienti che non possono ritardare l'inizio del trattamento
  - Pazienti con controindicazioni alla stimolazione ovarica