VIII SIMPOSIUM
ICAPEM
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PRESENCIAL
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Long-Term Survival: Sex/Gender Perspectives

Lorenza Landi, Regina Elena National Cancer Institute, Rome, Italy

Disclosures

- Dr Landi discloses the following conflicts of interest:

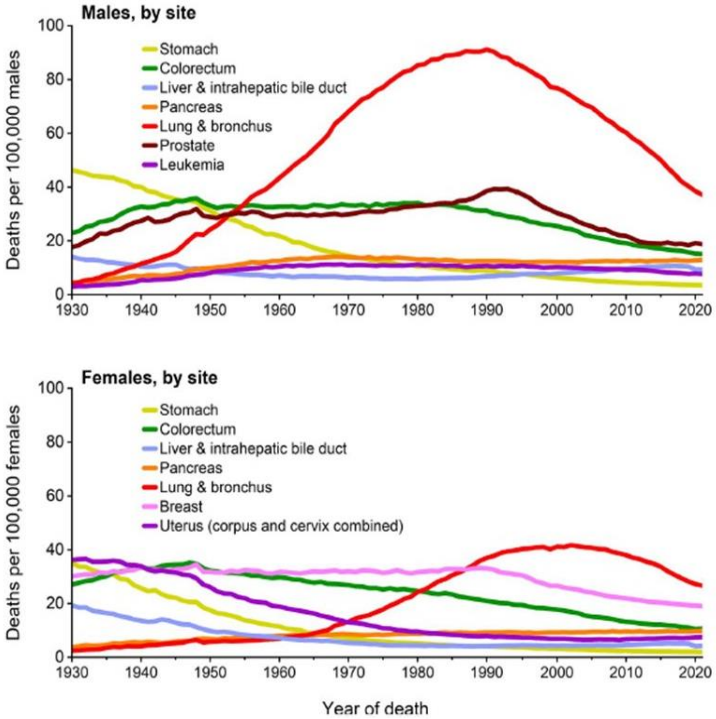
- Fees for membership of an advisory board or lectures from Pfizer, Novartis, AstraZeneca, Roche, BMS, MSD, Lilly, Amgen, Sanofi, AbbVie and J&J

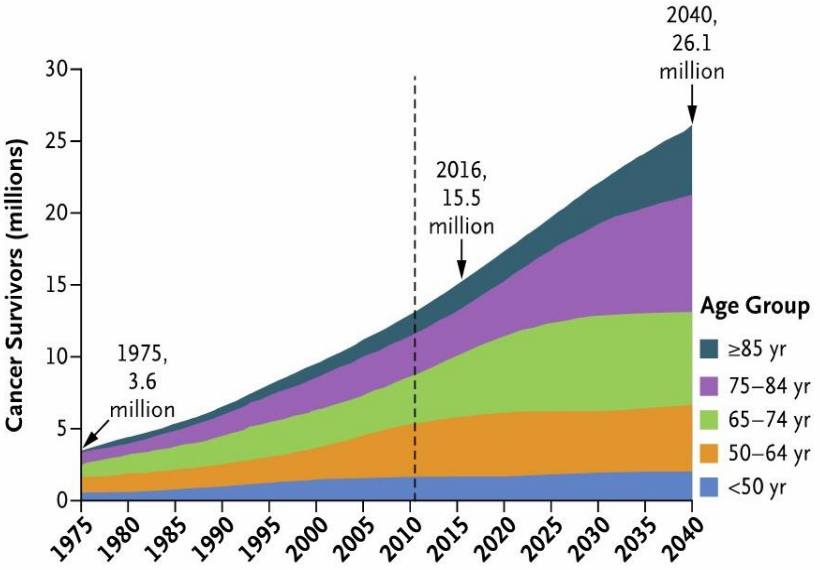
Outline

- Introduction
- How sex/gender affects:
  - Outcome and safety to treatment strategies
  - Sexual health
  - Fertility preservation
  - Smoking cessation
  - Psychological health
  - End of life (EOL) issues
- Conclusion

Prognosis of lung cancer improved over time

[People living with cancer are growing]



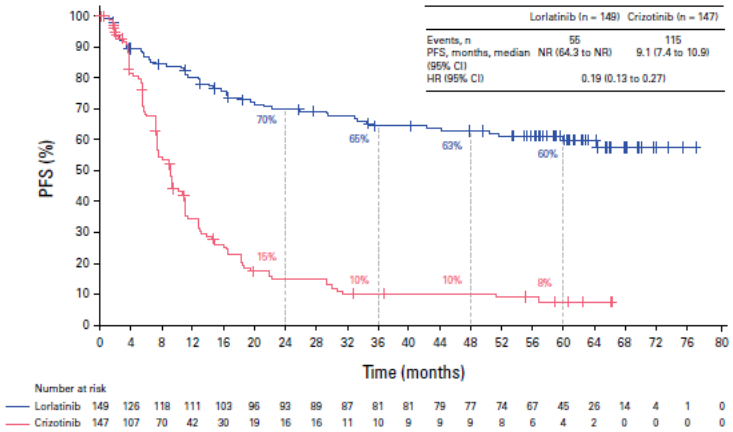


Siegel RL, et al. CA Cancer J Clin 2024; Shapiro CL, et al. NEJM 2018

Long survival and Survivorship

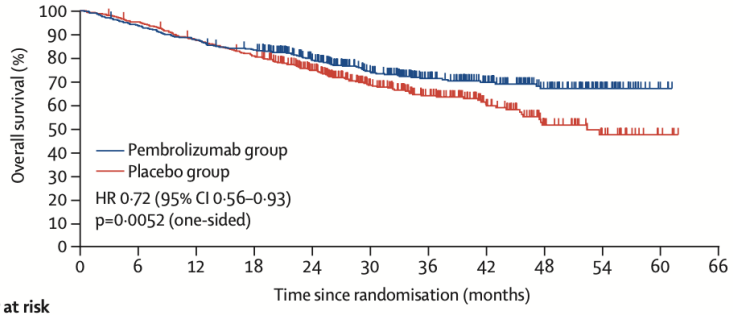
[Patients living with cancer and patients free of cancer]

CROWN , Ph. III, ALK + **metastatic** NSCLC



Solomon B, et al. JCO 2024

KEYNOTE 671, Ph. III, **resectable**, non-oncogene driven NSCLC



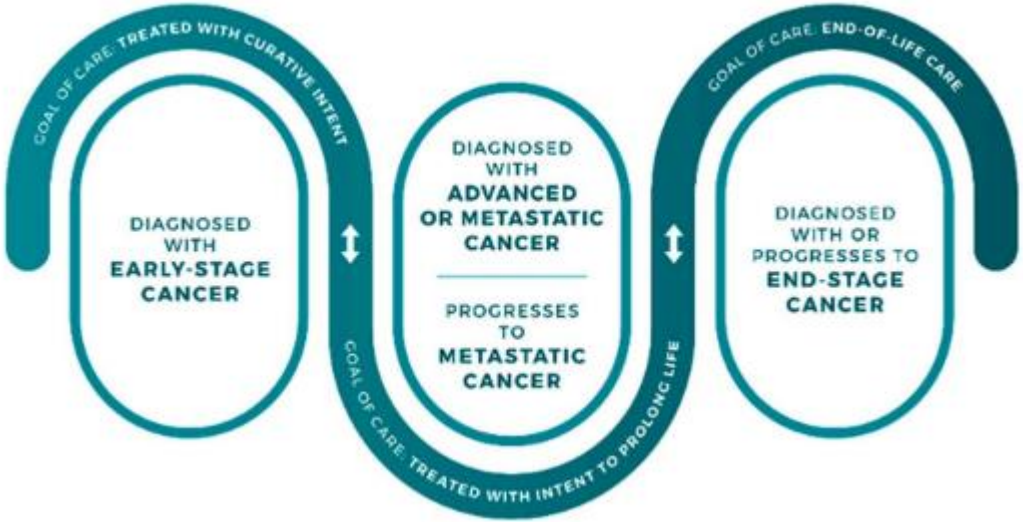
Number at risk (number censored)												
Pembrolizumab group	397 (0)	371 (1)	347 (1)	327 (4)	277 (38)	205 (95)	148 (145)	108 (182)	69 (218)	32 (255)	4 (283)	0 (287)
Placebo group	400 (0)	379 (2)	347 (4)	319 (5)	256 (45)	176 (106)	125 (147)	77 (190)	39 (219)	20 (236)	4 (252)	0 (256)

Spicer JD et al Lancet 2024

Phase of cancer survivorship care: different settings, different needs

Pts treated with curative intent

- Health promotion
- Comorbidities management
- Second/other primary prevention
- Fertility and sexual health preservation



Pts in their EOL

- AD* discussion
- Reduction in ICU** admissions
- Psychological care promotion

Pts treated with palliative intent

- Symptoms management
- QoL preservation
- Social role preservation
- Sexual health preservation

Presley CJ, et al. ASCO Ed. Book 2024

* AD, advanced directives ; ICU, intensive care unit

Women have better lung cancer outcomes

Table 1. Demographics, Risk Factors, and Cancer Characteristics by Sex for Patients With Lung Cancer From Our Institution (UH) (2005-2020) and SEER (2005-2018) Databases

	UH			SEER		
Feature	Male 4366 (49%)	Female 4543 (51%)	*p* Value	Male 378,452 (52.2%)	Female 346,566 (47.8%)	*p* Value
Age at diagnosis, n (%)[a]						
<65 y	1543 (35.5)	1604 (35.4)	0.94	118,047 (31.2)	103,886 (30)	<0.001
≥65 y	2804 (64.5)	2926 (64.5)		260,405 (68.8)	242,680 (70)	
Unknown	19	13		–	–	
Race, n (%)[a]						
White	2798 (81.8)	2913 (79.4)	0.008	307,077 (81.7)	289,058 (84)	<0.001
Black	603 (17.6)	745 (20.3)		44,419 (11.8)	35,630 (10.4)	
Asian	18 (0.5)	12 (0.3)		24,255 (6.5)	19,289 (5.6)	
Other or unknown	947	873		2701	2589	
Ethnicity, n (%)[a]						
Hispanic	22 (0.5)	26 (0.6)	0.77	22,018 (5.8)	19,741 (5.7)	0.02
Non-Hispanic	4023 (99.5)	4203 (99.4)		356,434 (94.2)	326,825 (94.3)	
Unknown	321	314		–	–	–
Primary payer, n (%)[a]						
Insured	864 (28.5)	941 (28.9)	0.52	–	–	–
Medicare	1789 (59)	1889 (58)		–	–	–
Medicaid	262 (8.6)	311 (9.5)		–	–	–
Not insured	119 (3.9)	117 (3.6)		–	–	–
Other or unknown	1332	1285		–	–	–
Median income, n (%)[a]						
≤$50,648	1888 (51.6)	1855 (48.6)	0.01			
>$50,648	1770 (48.4)	1960 (51.4)		–	–	–
Unknown	708	728				

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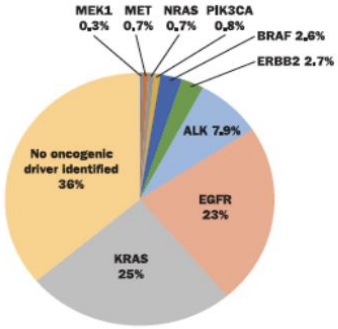
	UH			SEER		
Feature	Male 4366 (49%)	Female 4543 (51%)	*p* Value	Male 378,452 (52.2%)	Female 346,566 (47.8%)	*p* Value
Educational level						
% Population with only high school diploma, mean, SD[b]	32.3, 9	31.3, 8.9	<0.001	–	–	–
% Population with less than high school diploma, mean, SD[b]	10.2, 6.3	10, 6.3	0.02	–	–	–
Employment						
% Population unemployed, mean, SD[b]	4.3, 2.8	4.3, 2.8	0.80	–	–	–
Histology, n (%)[a]						
NSCLC	2732 (88.2)	2805 (86.7)	0.07	231,893 (83.8)	203,630 (80.4)	<0.001
SCLC	364 (11.8)	429 (13.3)		44,753 (16.2)	49,532 (19.6)	
Other or unknown	1270	1309		101,806	93,404	
Histology subtype, n (%)[a]						
Adenocarcinoma	1150 (62.4)	1399 (74.2)	<0.001	–	–	–
Squamous cell carcinoma	692 (37.6)	486 (25.8)		–	–	
Clinical staging, *n* (%)[a]						
0-II	646 (26.1)	736 (28.9)	0.02	61,712 (20.3)	69,596 (25.4)	<0.001
III-IV	1832 (73.9)	1807 (71.1)		242,304 (79.7)	203,956 (74.6)	
Unknown	1888	2000		74,436	73,014	
Smoker, n (%)[a]						
Yes	543 (26.8)	492 (23.1)	<0.001	–	–	–
No	180 (8.9)	326 (15.3)		–	–	
Former	1300 (64.3)	1309 (61.5)		–	–	
Unknown	2343	2416				
Charlson score, n (%)[a]						
1-2	2486 (56.9)	2686 (59.1)	0.001	–	–	–
3-4	1147 (26.3)	1221 (26.9)		–	–	
≥5	733 (16.8)	636 (14)		–	–	

[a]Compared with Pearson's chi-square test.
[b]Compared with Kruskal-Wallis test.
SEER, Surveillance, Epidemiology, and End Results; UH, University Hospital.

Relation with prognostic factors

Stabellini N, et al. JTO CRR 2022

Distribution of driver mutations in adenocarcinoma differ by sex



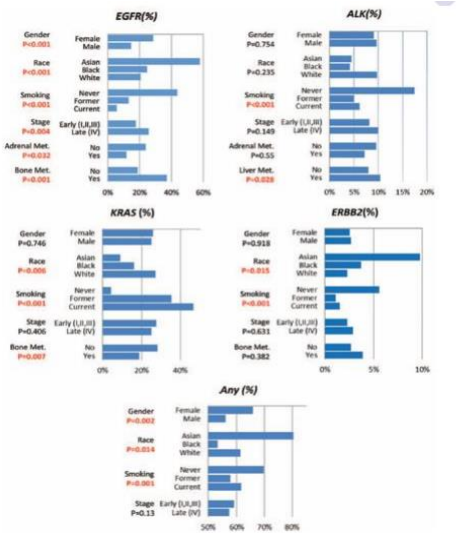
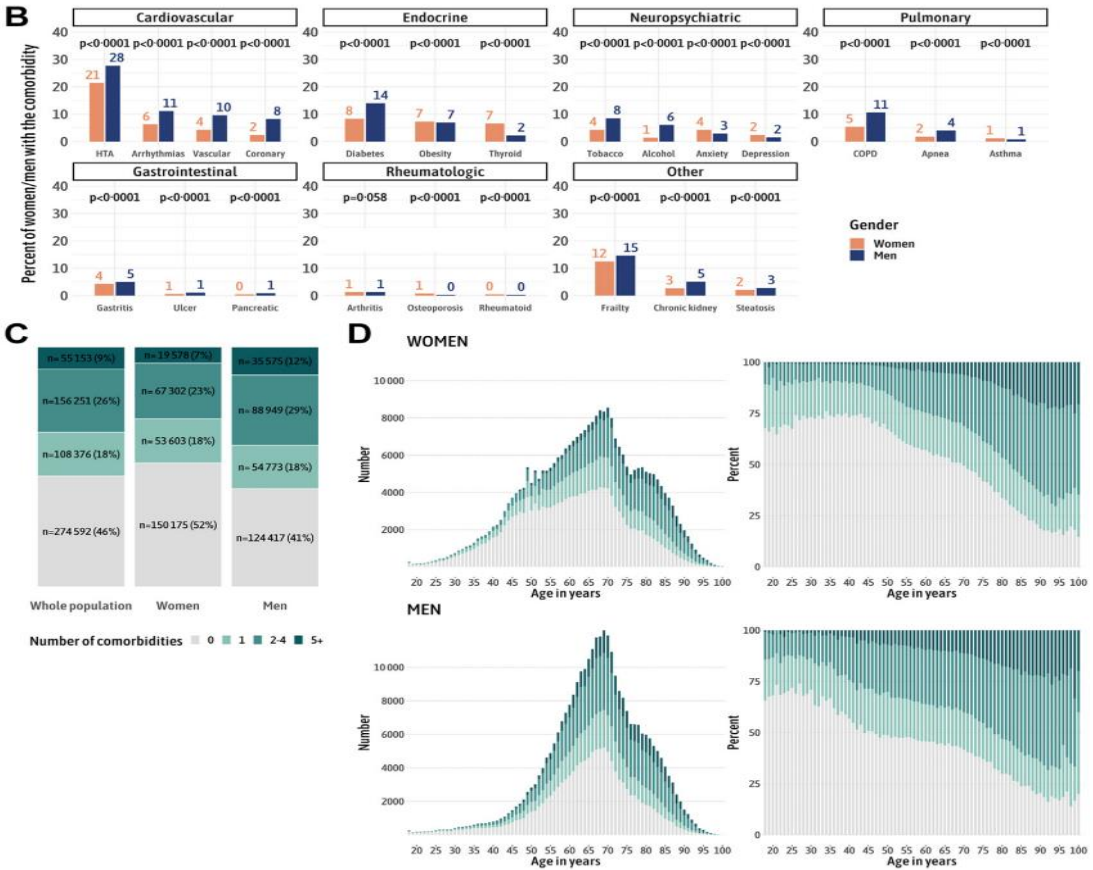


Table 1 Most Common Molecular Driver Alterations Among Women; Created Using cBioPortal on 9.8.23 9:03 AM EST, an Open-Access, Open-Source Resource for Interactive Exploration of Multidimensional Cancer Genomics Data Sets, on August 9, 23

Genes	Female Frequency (%)	Male Frequency (%)	*p*-value
EGFR	27.45	16.62%	<10e-10
KRAS	29.08	22.51	1.89e-9
BRAF	5.61	6.16	.366
ALK	5.38	6.04	.263
ERBB2 (HER2)	5.19	4.74	.450
ROS1	4.89	5.25	.504
MET	5.36	5.86	.387
RET	3.79	4.31	.311
NTRK1	4.33	6.31	5.689e-4

Sholl LM, et al. J Thorac Oncol 2015; Florez N, et al. Clin Lung Cancer 2024

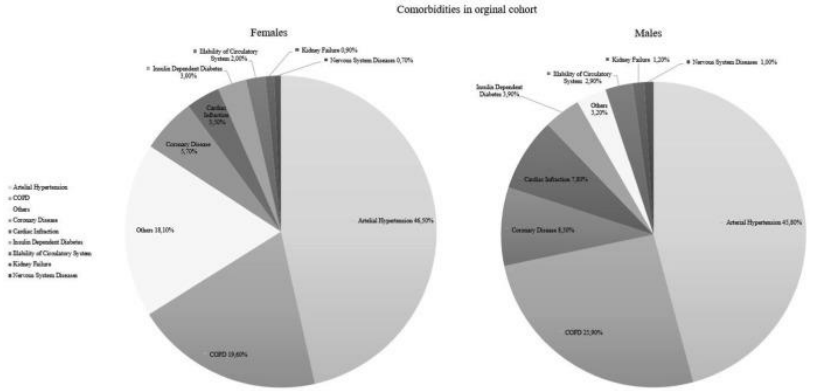
Comorbidity patterns by sex in patients with cancer



Jochum F, et al. Lancet 2023

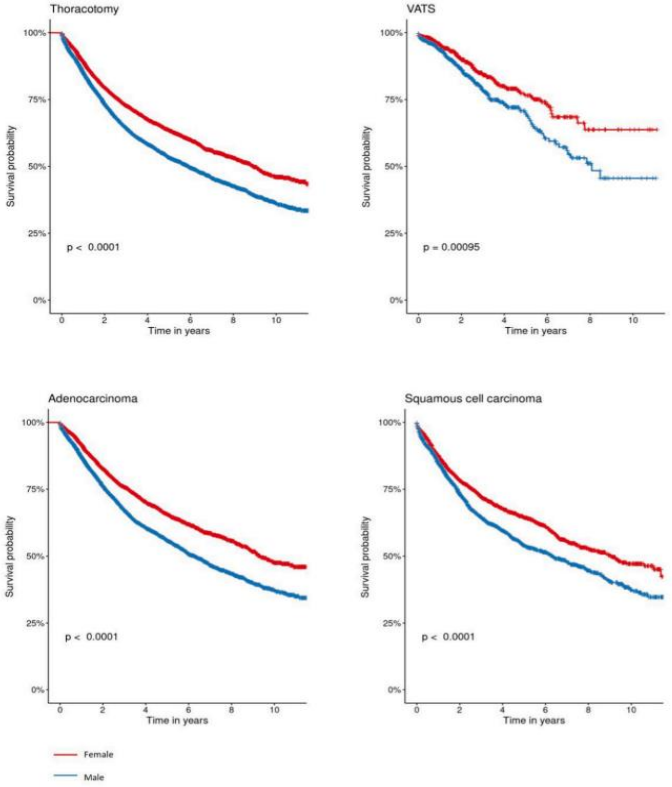
Sex differences in clinico-pathologic characteristics and long-term survival In surgically resected NSCLC

Comorbidities in women vs men



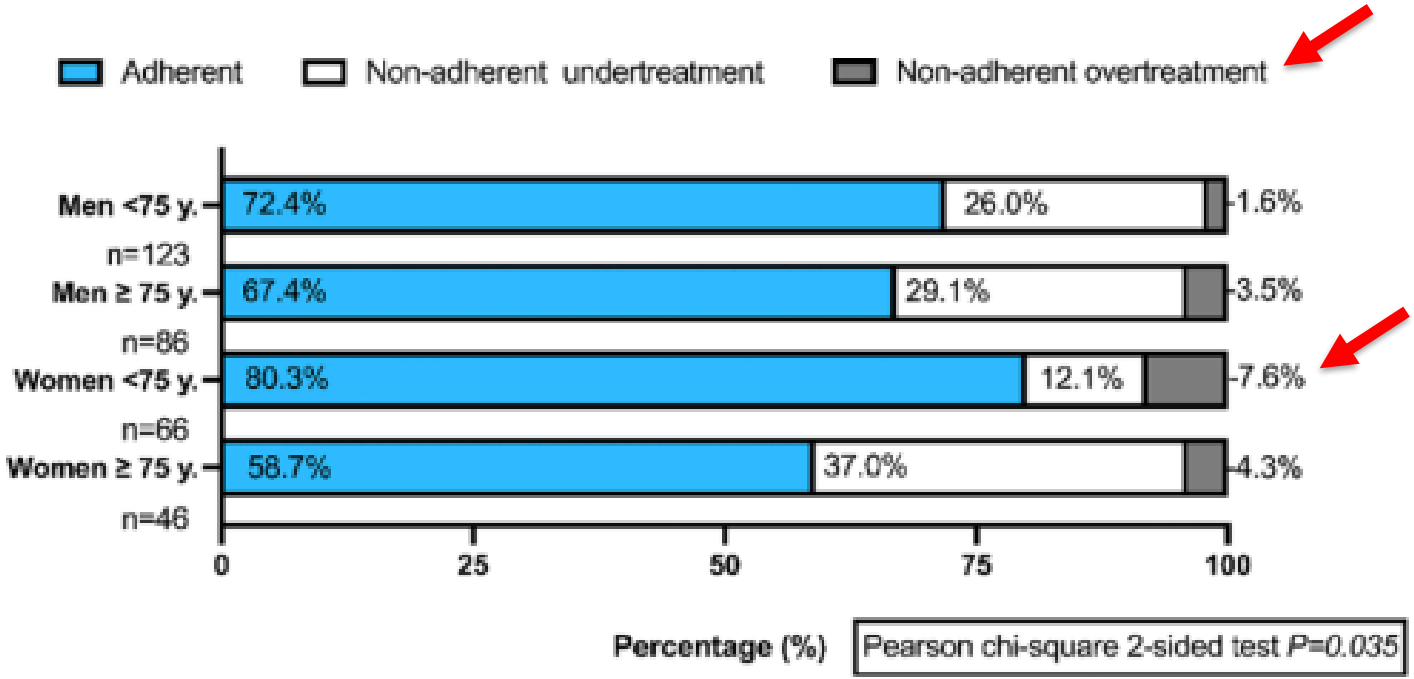
Trojnar A, et al. Surgical Oncology 2022

Better survival in women*



* Irrespective of type of surgery, histology or stage

Sex differences in adherence to treatment guidelines



Paakkola N-M, et al. Cancer Treatment and Research Communications 2023

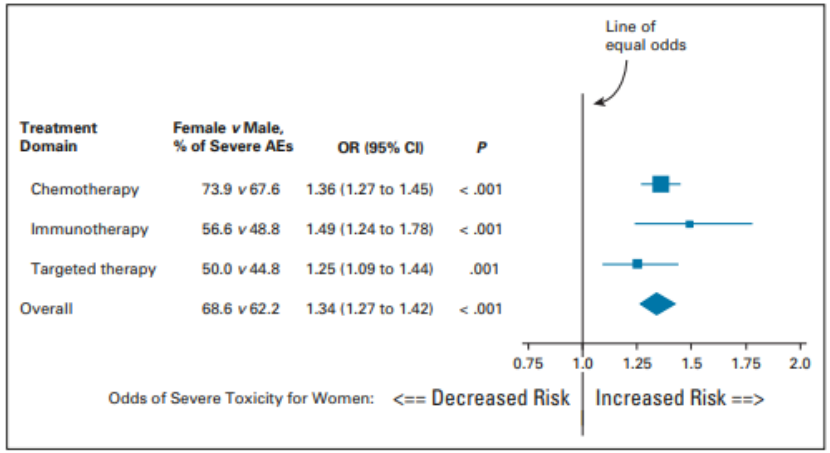
Lower benefit with single-agent immune checkpoint in women versus men

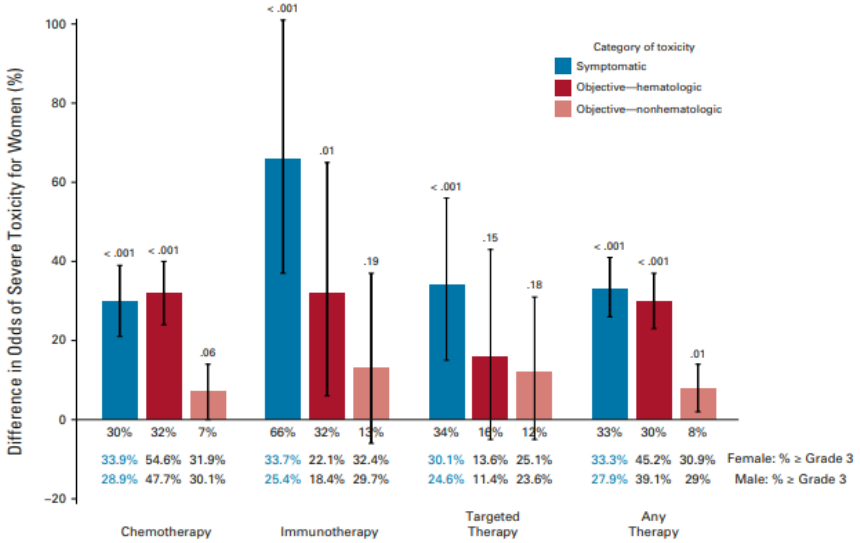
Table 2 Hazard Ratios for Death Across Cancer Lines, by Patients' Sex in Patients With NSCLC Receiving Immunotherapy[a]

Clinical Trial	Therapy Evaluated	HR for Death (Women)	HR for Death (Men)	Overall HR *p*-value
Borghaei et al, 2015	Nivolumab vs. docetaxel	0.78	0.73	.002
Brahmer et al, 2015	Nivolumab vs. docetaxel	0.67	0.57	<.001
Herbst et al, 2016	Pembrolizumab vs. docetaxel	0.69	0.65	<.001
Reck et al, 2016	Pembrolizumab vs. investigator's choice chemotherapy	0.96	0.54	.005
Carbone et al, 2017	Nivolumab vs. platinum-based chemotherapy	1.15	0.97	N/A
Govindan et al, 2017	Ipilimumab or placebo plus paclitaxel and carboplatin	1.33	0.85	.25

Florez N, et al. Clin Lung Cancer 2024

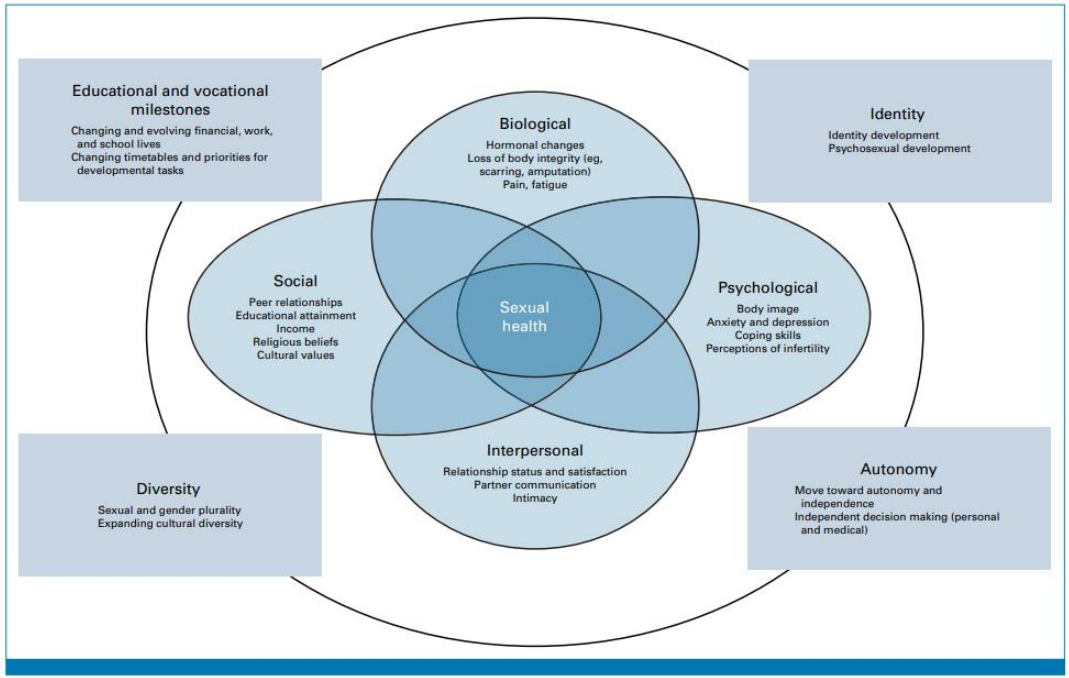
Female sex is associated with higher risk of toxicity from anticancer therapies





Unger JU, et al. JCO 2022

Sexual dysfunction in patients with lung cancer



Self reported sexual concerns in up to 95% of patients with lung cancer (both sexes)

Causes

- **Cancer related symptoms**
- **Psycological concerns: anxiety, depression, fear,**
- **Adverse events**

Cherven B, et al. JCO 2023

Sexual Dysfunction in Patients with Lung Cancer

Narjust Florez
Principal Investigator
Dana-Farber Cancer Institute

Sexual Health Assessment in Women with Lung Cancer

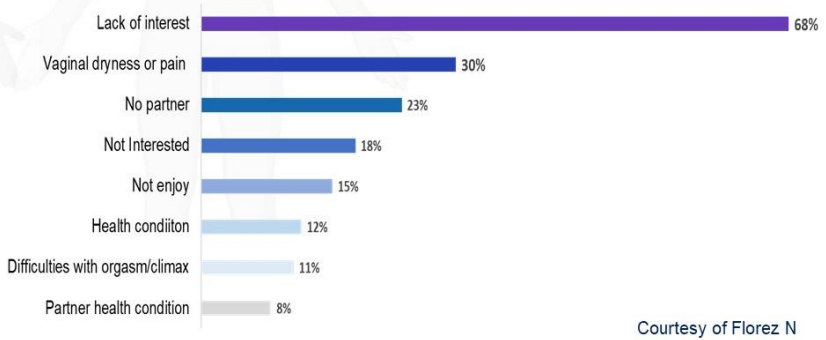
Observational, cross-sectional, international study

PROMIS® questions

- Participants: 249
- Average age: 61 years
- Non-hispanic white 88%
- NSCLC-adenocarcinoma: 84%
- Stage IV: 67%
- In targeted therapy: 47%

77% of patients reported moderate to severe sexual dysfunction

- **Determinants** of sexual dissatisfaction **in women** with lung cancer younger than 50y included **fatigue (56%), sadness and unhappiness (42%), issue with the partner (26%) and shortness of breath (9%)**



Courtesy of Florez N

Florez N et al, Cancer 2024;130(3):375-84 (presented at WCLC 2022)

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@matteolambe
matteo.lambertini@unige.it

Oncofertility counseling mandatory before starting therapy

SPECIAL ARTICLE

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

M. Lambertini[1,2], F. A. Peccatori[3], I. Demeestere[4], F. Amant[5,6], C. Wyns[7], J.-B. Stukenborg[8], S. Paluch-Shimon[9], M. J. Halaska[10], C. Uzan[11], J. Meissner[12], M. von Wolff[13], R. A. Anderson[14] & K. Jordan[12], on behalf of the ESMO Guidelines Committee*

Recommendations

- All cancer patients of reproductive age should receive complete oncofertility counselling as early as possible in the treatment planning process, irrespective of the type and stage of disease [III, A].
- 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 [V, A].

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

Recommendations

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.

Recommendation 1.3. To preserve the full range of options, fertility preservation approaches should be discussed as early as possible, before treatment starts. The discussion can ultimately reduce distress and improve quality of life. Another discussion and/or referral may be necessary when the patient returns for follow up after completion of therapy and/or if pregnancy is being considered. The discussions should be documented in the medical record.

Lambertini M, ASCO 2024

Risk of treatment-induced gonadotoxicity

Risk of azoospermia and infertility in man

Degree of risk	Treatment type/regimen
High risk	**RADIOTHERAPY (RT)** **Total body RT** **Testicular RT:** germ cells >20 Gy somatic cells >30 Gy **CHEMOTHERAPY (ChT)** **Alkylating agents** (cyclophosphamide, ifosfamide, procarbazine, **cisplatin**, chlorambucil, carmustine, lomustine, melphalan, thiotepa, busulfan, mechlorethamine) with CED >5 g/m2 for germ cells and 20 g/m2 for somatic cells **Conditioning ChT for bone marrow transplantation** (busulfan and cyclophosphamide, fludarabine and melphalan)
Intermediate risk	**Alkylating agents** (thiotepa, **cisplatin** <0.6 g/m2, oxaliplatin, **carboplatin**, dacarbazine) **Anthracyclines** (doxorubicin, idarubicin, daunorubicin) **Mitoxantrone** **Antimetabolites** (cytarabine, **gemcitabine**)
Low risk	**Antimetabolites** (mercaptopurine, methotrexate, fludarabine) **Tubulin-binding agents/vinca alkaloids** (vincristine, vinblastine) **Topoisomerase inhibitors** (**etoposide**) **Antitumour antibiotics** (bleomycin, dactinomycin, mitomycin C)
Unknown risk	**Antimetabolites** (fluorouracil, thioguanine) **Taxanes** (**paclitaxel**, **docetaxel**) **Topoisomerase inhibitors** (irinotecan, **topotecan**, teniposide) **Immunotherapy** **Targeted therapies** (including monoclonal antibodies and small molecules)

Risk of premature-ovarian insufficiency in women

Degree of risk	Treatment type/regimen
High risk (>80%)	Haematopoietic stem cell transplantation (especially alkylating agent-based myeloablative conditioning with cyclophosphamide, busulfan, melphalan or total body RT) External beam RT >6 Gy to a field including the ovaries 6–8 cycles of CMF, CEF, CAF or TAC in women of ≥40 years 6–8 cycles of escalated BEACOPP in women of ≥30 years
Intermediate risk (20%–80%)	6 cycles of CMF, CEF, CAF or TAC in women of 30–39 years) 4 cycles of AC in women of ≥40 years 4 cycles of AC/EC → taxane 4 cycles of dd (F)EC → dd taxane 6–8 cycles of escalated BEACOPP in women of <30 years 6 cycles of CHOP in women of ≥35 years 6 cycles of DA-EPOCH in women of ≥35 years
Low risk (<20%)	6 cycles of CMF, CEF, CAF or TAC in women of <30 years 4 cycles of AC in women of <40 years 2 cycles of escalated BEACOPP, ABVD 6 cycles of CHOP in women of <35 years 6 cycles of DA-EPOCH in women of <35 years AML therapy (anthracycline/cytarabine), ALL therapy (multi-agent) Multi-agent ChT for osteosarcoma (doxorubicin, cisplatin, methotrexate, ifosfamide) in women of <35 years Multi-agent ChT for Ewing's sarcoma (doxorubicin, vincristine, dactinomycin, cyclophosphamide, ifosfamide, etoposide) in women of <35 years FOLFOX in women of ≤40 years **Antimetabolites** and vinca alkaloids BEP or EP in women of <30 years Radioactive iodine (I-131) **Bevacizumab**
Unknown risk	**Platinum- and taxane-based ChT** Most **targeted therapies** (including monoclonal antibodies and small molecules)

Chemotherapy

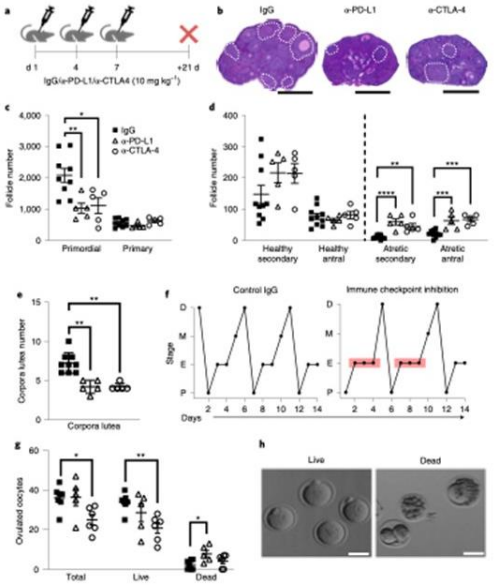
Targeted agents

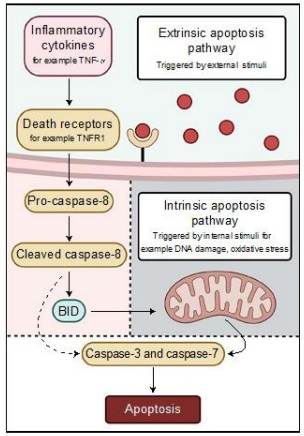
Clinical data are needed !

Treatment type/regimen	Treatment-induced azoospermia ♂	Treatment-induced amenorrhea ♀
EGFR TKI	Afatinib, gefitinib, osimertinib: may decrease ovarian corpora lutea	Osimertinib: possible testicular damage, inconclusive data
ALK, ROS1, KRAS TKI, MET TKI	No specific animal data Tepotinib: No relevant effect on fertility in animals	No specific animal data Tepotinib: No relevant effect on fertility in animals
BRAF/MEK TKI	May decrease ovarian corpora lutea	No specific animal data
RET TKI	May compromise fertility	May compromise fertility
NTRK TKI	No relevant effect on fertility in animals	No relevant effect on fertility in animals

Lambertini M, ASCO 2024

Risk of treatment-induced gonadotoxicity
Immunotherapy





Risk of primary and/or seconday hypogonadism

PMID	Adverse effect	Evidence	Drug	Sample size
28039179	Primary hypogonadism	Bilateral orchitis	Anti-PD1 + anti-CTLA4	1
30936376	Primary hypogonadism	Epididymo-orchitis + encephalitis	Anti-PD1	1
32556068	Primary hypogonadism	Altered spermatogenesis	Anti-PD1 + anti-CTLA4	7
33613847	Primary hypogonadism	Testosterone deficiency	Anti-PD1 and/or anti-CTLA4	49
33299797	Primary hypogonadism	Azoospermia	Anti-PD1 + anti-CTLA4	1
31235040	Primary hypogonadism	Azoospermia	Anti-PD1 and/or anti-CTLA4	22
30861560	Secondary hypogonadism	Metanalysis of endocrine irAEs	Anti-PD1 and/or anti-CTLA4	19922
31021376	Secondary hypogonadism	Metanalysis of irAEs	Anti-PD1 or anti-PDL1	20128
32507965	Secondary hypogonadism	Endocrine irAEs	Anti-PD1 and/or anti-CTLA4	6089
24610577	Secondary hypogonadism	Endocrine irAEs	Anti-CTLA4	256
31235040	Secondary hypogonadism	Isolated hypogonadotropic hypogonadism	Anti-PDL1	1
33646368	Secondary hypogonadism	Increased LH-to-FSH ratio and estradiol	Anti-PD1	22
31235040	Sexuality	No sexual alterations during or after ICIs	Anti-PD1 and/or anti-CTLA4	25
31672171	Sexuality	Autoimmune vulvitis	Anti-PD1	1

Adverse event	Clinical approaches	Unsolved questions
Primary hypogonadism	• Discuss the possibility of infertility linked with the treatment and the strategies of fertility preservation (e.g. cryopreservation)	• Frequency • Duration after discontinuation of immunotherapy • Alteration of sex hormones levels (e.g. testosterone, estradiol) • Impact on fertility, pregnancy, and complicated pregnancy • Impact on libido and sexual life
Secondary hypogonadism	• Discuss the possibility of hypopituitarism-induced infertility linked with the treatment and the strategies of fertility restoration (e.g. hormonal therapy if clinically safe)	• Frequency of secondary hypogonadism • Frequency of isolated secondary hypogonadism • Impact on fertility, pregnancy, and complicated pregnancy • Impact on libido and sexual life

Winship A et al, Nat Cancer 2022;3(8):1-13. Duma N et al, The Oncologist 2020;25(4):277-8. Garutti M et al, ESMO Open 2021;6(5):100276

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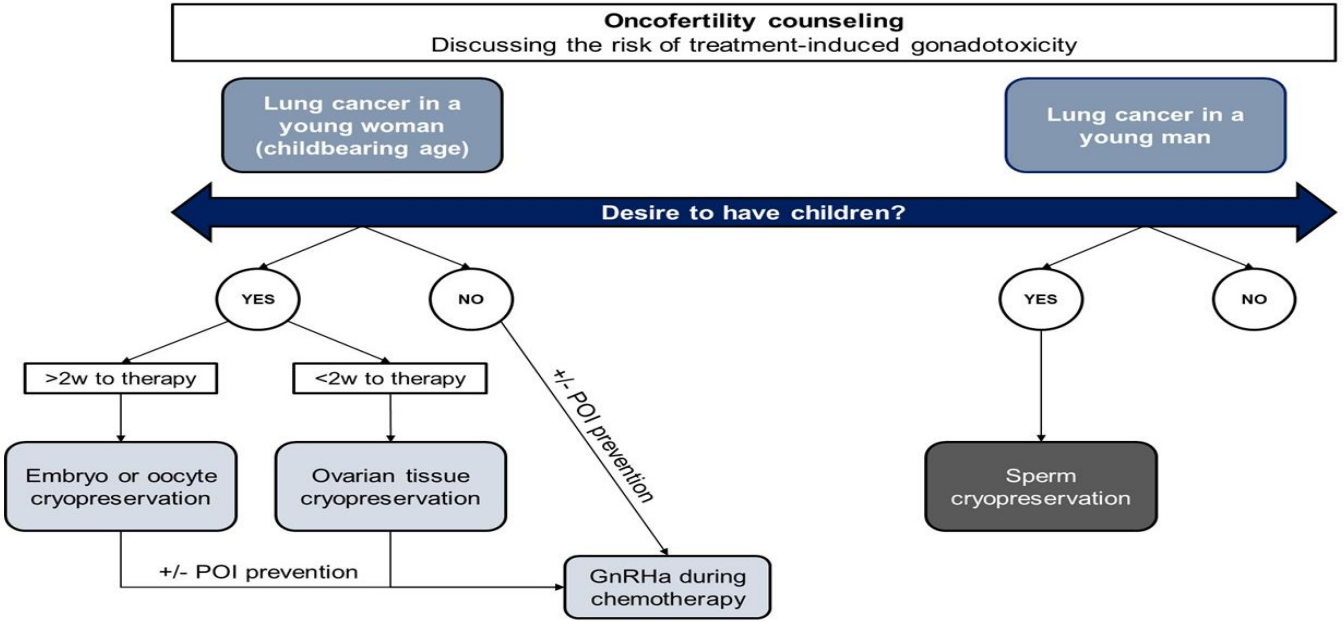
@matteolambe
matteo.lambertini@unige.it

How to perform an oncofertility counseling



Laguna JC et al, Am Soc Clin Oncol Educ Book 2024;44:e432488

However, while men were often encouraged to preserve sperm, women described **negative feelings** about fertility conservation due to poor presentation of their options

Peddie V, et al. *BJOG* 2012

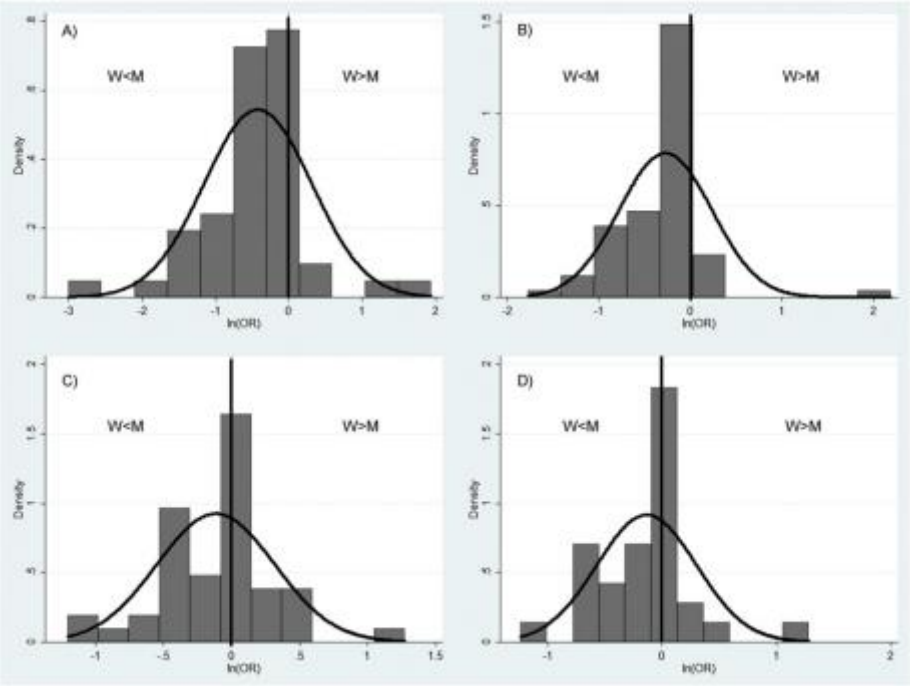
Sex/gender differences in smoking cessation

Number of studies finding sex/gender differences in the likelihood of smoking cessation, by study type.

	W < M *n*	W > M *n*	p-Value[a]	W = M *n*	*k*(*n*)[b]
Efficacy intervention	25	1	<0.001	21	37(47)
Effectiveness intervention	34	1	<0.001	44	77(79)
Community-based intervention	2	0	NA	2	4(4)
Prospective observational	10	5	0.007	31	40(46)
Cross-sectional observational	11	9	0.369	18	32(38)
Total	82	16		116	190(214)

Women were less likely to quit smoking and more likely to re-start after a period of smoking abstinence

Effect size distributions, by study type



Smith P, et al. Prev Med 2016

Women have significantly higher rates of psychological disorders

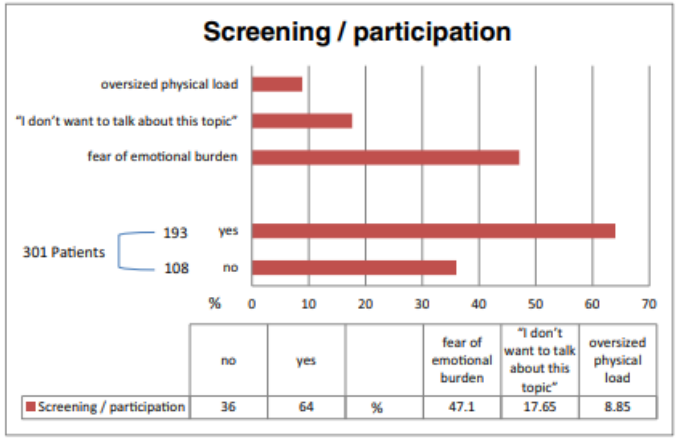
Table 4. Complications After Any Treatment, Chemotherapy, and Surgery by Sex for Patients With Lung Cancer From UH (2005-2020) Database

	UH		
Feature General treatment	Male 2716 (48.5%)	Female 2887 (51.5%)	*p* Value
Cognitive decline or dementia, n (%)[a]			
Yes	24 (0.9)	29 (1)	0.74
Psychological disorders, n (%)[a]			
Yes	104 (3.8)	219 (7.6)	<0.001
Subtypes of psychological disorders, n (%)[a]			
Depression	73 (2.7)	123 (4.3)	0.001
Anxiety	55 (2)	143 (5)	<0.001
Bipolar disorder	8 (0.3)	11 (0.4)	0.74
O_2 dependence after treatment, n (%)[a]			
Yes	30 (1.1)	44 (1.5)	0.20

Stabellini N, et al. JTO CRR 2022

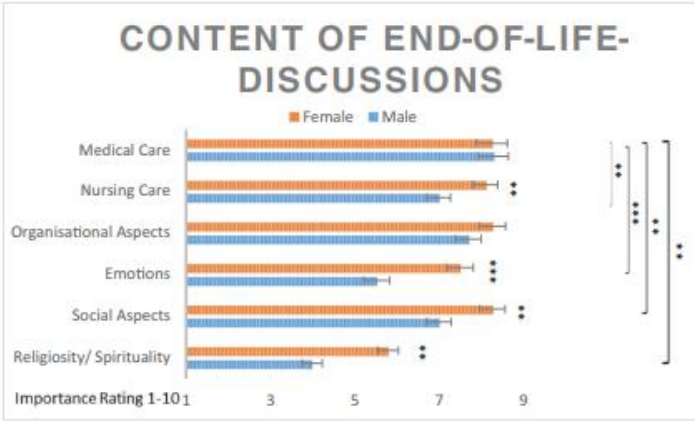
End of Life (EOL): does sex/gender matter?

Refusal rates and reasons



	no	yes		fear of emotional burden	"I don't want to talk about this topic"	oversized physical load
Screening / participation	36	64	%	47.1	17.65	8.85

Importance ratings for the content of EOL discussions



- Females were less likely to avoid talking about issues of death and dying during their illness
- Females rated nursing care and "soft" topics, such as emotional, social, and religious aspects,
- Females talked more frequently about organizational aspects and nursing care
- Females had an easier approach to EOL conversations
- Males having not discussed EOL care were significantly more likely to receive ICU care in their last week of life

Seifart C, et al. Supportive Care in Cancer 2020

Top takeaways

- Lung cancer is a prime example of sex-related differences in tumor biology

- Sex/gender deeply affects
- (long term) Treatment outcome
- Safety
- Psychological consequences of lung cancer diagnosis

- Fertility and sexual health are critical aspects of survivorship care

- Further research is needed to develop and investigate gender-sensitive approaches to treat lung cancer in all phases of the disease including EOL