

XXXIII CONGRESSO NAZIONALE AIRO

# AIRO2023

BOLOGNA,  
27-29 OTTOBRE 2023

PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

**La medicina di genere in Radioterapia**

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Università degli studi di Torino

## Dichiarazione conflitti

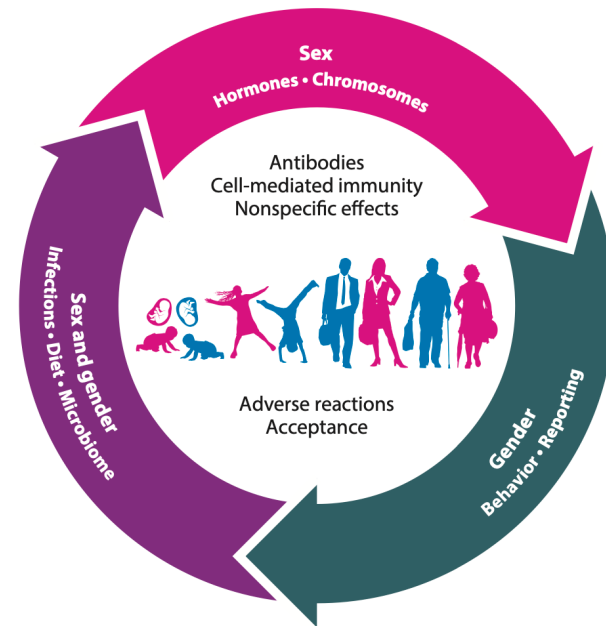
Relatore: CRISTIANO GROSSI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Consulenza ad aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Partecipazione ad Advisory Board (**NIENTE DA DICHIARARE**)
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Altro

# Introduction

- Sex refers to biological and genetic characteristics and influences sex steroid hormones.
- Gender, in contrast to sex, refers to a chosen sexual identity.
- Together, these factors affect metabolism, immunity and inflammation.
- To accurately understand how human defences against cancer erode, it is crucial to establish the influence of sex.



**(Flanagan et al., 2017)**

## Sex differences

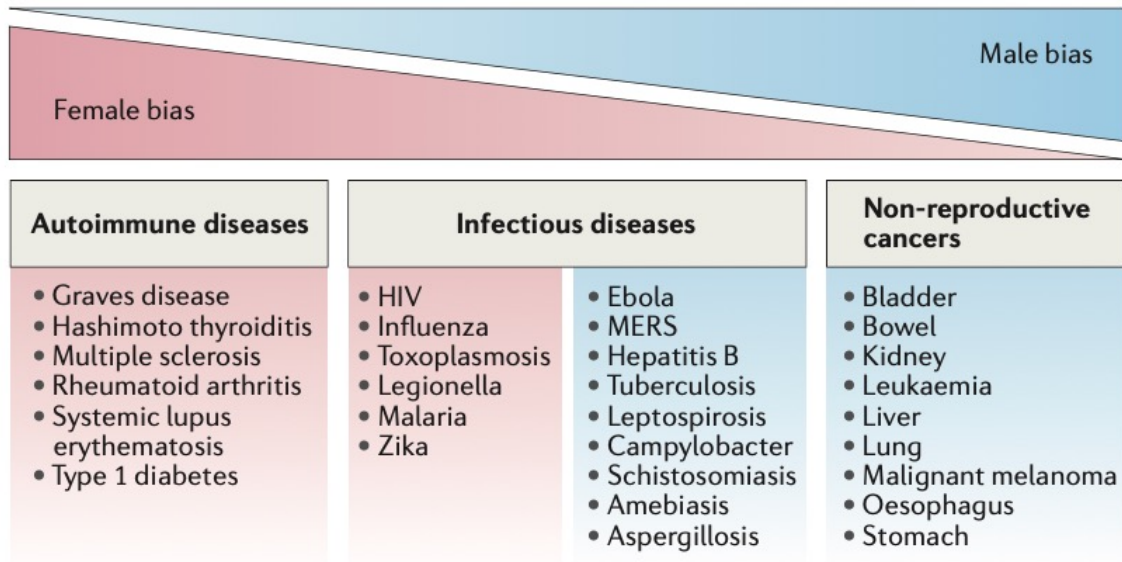
- the balance of Th2 vs Th1-type cytokines in inflammation (Fairweather et al., 2008),
- recruitment of x-chromosome tumour suppressor genes which escape inactivation (Dunford et al., 2017),
- the modulation of inflammatory response by sex hormones (Klein, 2000),
- the protective properties of oestrogen and its receptors (Iorga et al., 2017; Zarate et al., 2017),
- differing anatomy and body habitus/lipid distribution.

## Gender differences

- WHO estimated that 40% of men smoked worldwide, as opposed to only 9% of women.
- Men tend to consume more alcohol, drink more frequently, and are more likely to become hazardous drinkers than women (Erol and Karpyak, 2015),
- Females outperform men in exercise, particularly in light and moderate activity

## Different disease

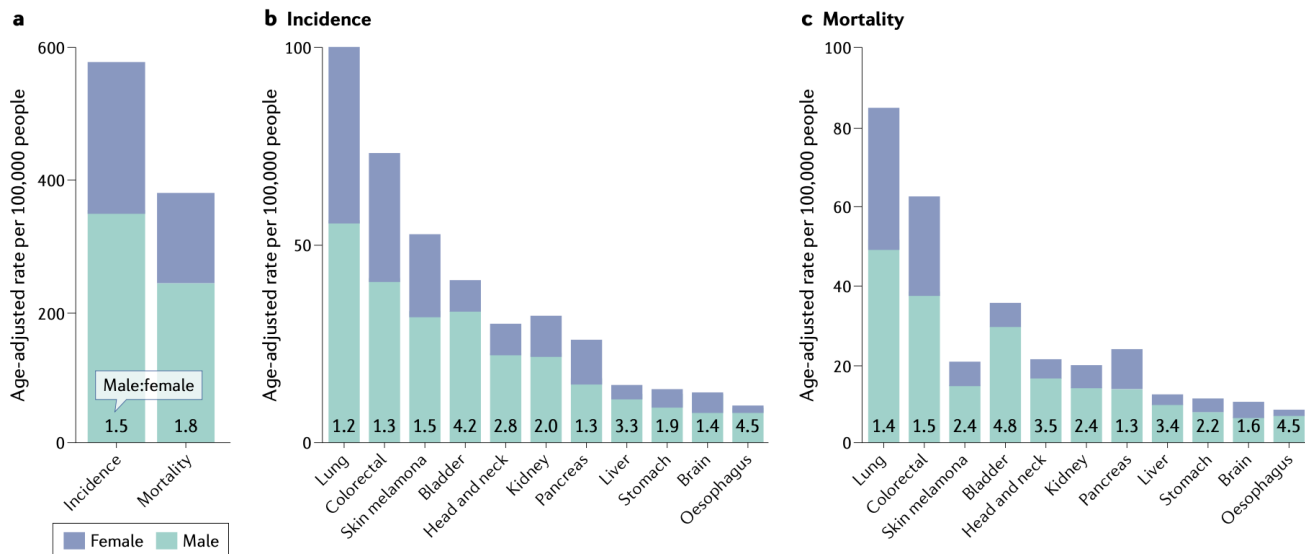
- 80% of auto
- men show a
- generally, a



es.

(Klein et al., 2016)

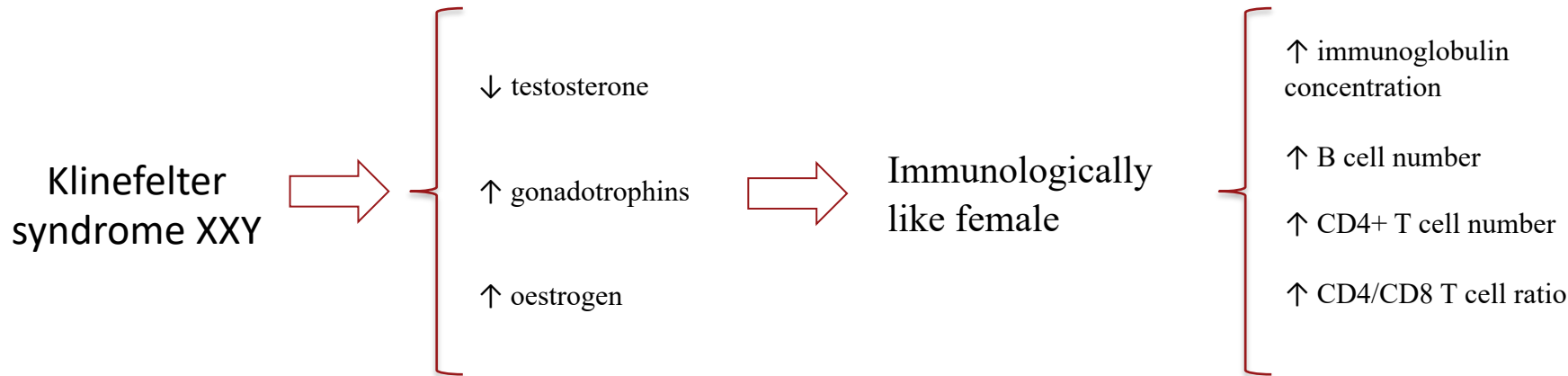
Cancers of non-reproductive tissues occur in males at an overall higher frequency and lead to nearly twice the mortality rate compared with these cancers in females



Haupt et al., 2021

## Genetic mediators

**Many genes on the X chromosome regulate immune function**



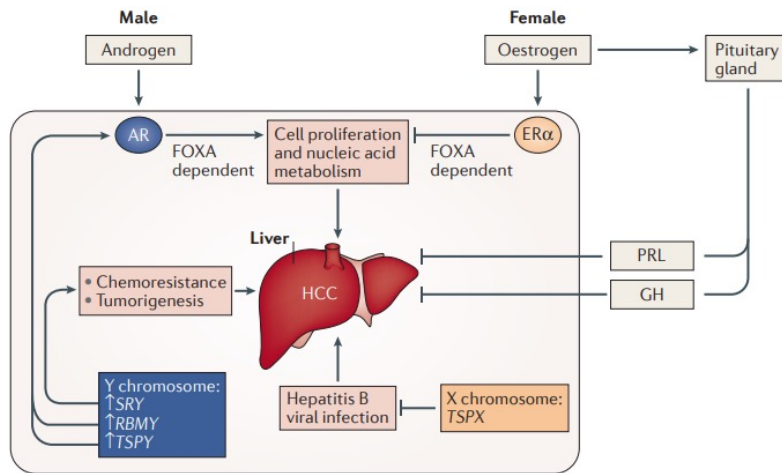
**Kocar et al. 2000**



## Hormonal mediators

- Oestradiol  $\uparrow$  IFN $\alpha$  and proinflammatory cytokines and greater internalization and presentation of antigen to naive T cells (Seillet et al., 2012)
- Progesterone has broad anti-inflammatory effects (Klein et al., 2016)
- Testosterone increases anti-inflammatory response (D'Agostino et al., 1999; Liva et al., 2001)

## Sex steroid hormones and metabolic differences



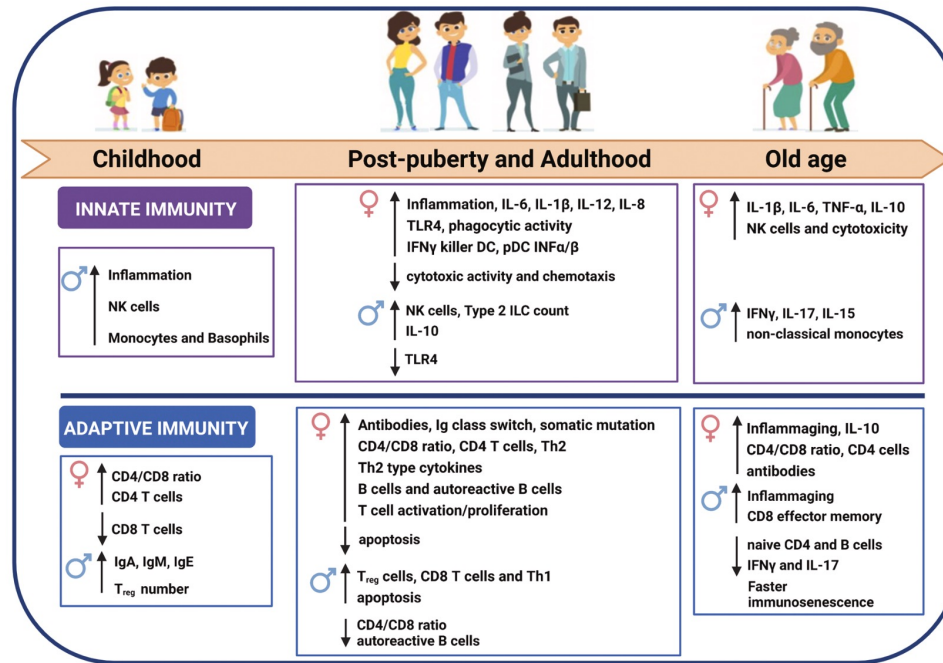
**Men**  
↑ chronic hepatitis (B and C) and hepatocellular carcinoma.

**Women**  
↑ drug-induced injury, autoimmune and vascular disease

Possible mechanisms contributing to gender dimorphism in hepatocellular carcinoma

Clocchiatti et al., 2016

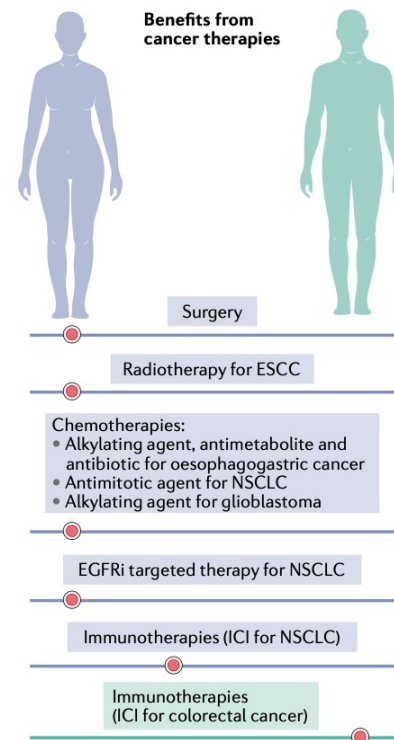
## Differences in immune response



Santoro et al., 2021

## Sex considerations in therapy

- Females ↑ OS from surgery for lung cancer and **less sepsis than males**. (*Wisnivesky et al., 2007*)
- RT offers survival advantage to females at the expense of toxicity in patients with **oesophageal squamous cell carcinoma (ESCC)**. (*Snyder et al., 2012*)
- CT ↑ female survival in responses to:
  - combined treatment with **platinum agent**, pyrimidine and anthracycline in oesophagogastric cancer;
  - **paclitaxel in NSCLC** (*Wheatley-Price et al., 2010*)
  - **temozolomide in glioblastoma** (with surgery and radiotherapy). (*Yang et al., 2019*)
- **Targeted therapies show greater efficacy in females for an epidermal growth factor receptor inhibitor (EGFRi) in NSCLC**. (*Pinto et al. 2018*)
- Immune checkpoint inhibitors (ICIs; anti- PD1 or anti- PDL1) trend to greater individual female survival benefit in NSCLC, **whereas male outcomes are better for colorectal cancer**. (*Ye et al. Nat. Commun. 2020*)



Haupt et al., 2021

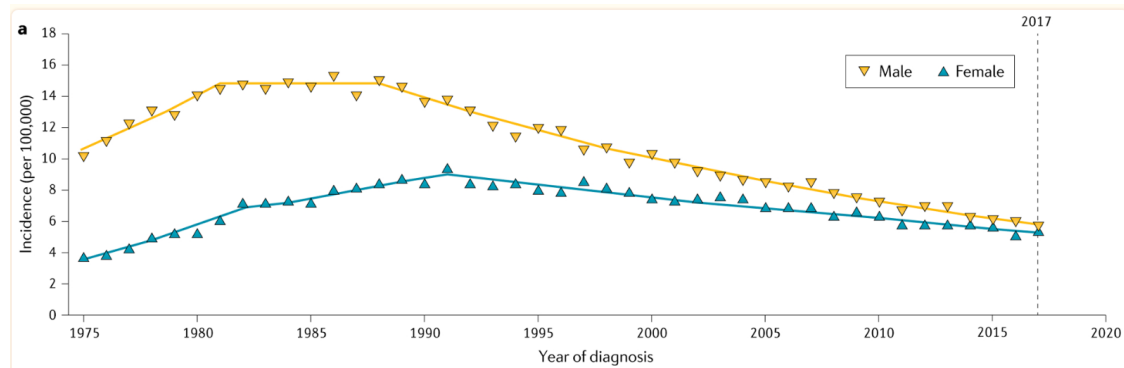
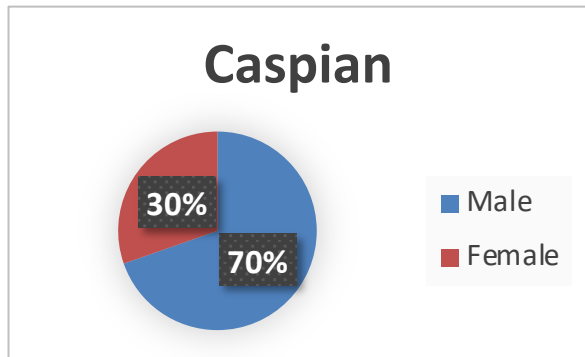
## Sex considerations in studies

### Under-representation of females:

1. fewer females with non-reproductive cancers in the general population
2. females tend to be less likely to enroll in clinical trials older age of females, on average, at cancer diagnosis (exemplified in colorectal cancer)
3. toxicities associated with exposure to numerous standard chemotherapies
4. greater risk of autoimmune responses triggered by overreaction to immunotherapies.

## CASPIAN Study

Sex				
Men	123/190	131/184		0.76 (0.59-0.97)
Women	32/78	50/85		0.63 (0.40-0.98)



**Rudin et al., 2021**

## Sex disparities matter in cancer development and therapy

Recognition of cancer sex disparity is relatively recent.

It was only in 2016 that the US National Institutes of Health (NIH) introduced policy changes requiring that investigator-initiated grants make reasonable effort to consider sex as a biological variable for medical research.



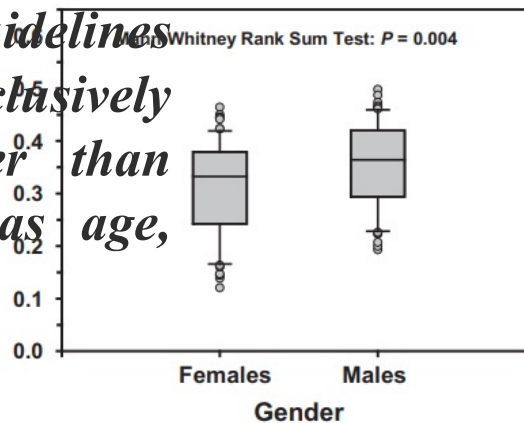
## NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

## Gender Radiosensitivity

*“Most radiotherapy guidelines recommendations are based exclusively on population averages rather than demographic subgroups such as age, race and sex.”*

Gender related variation in radiosensitivity. While women are slightly but significantly more radiosensitive than men.



Alsbeih et al., 2016

In young children receiving cranial radiotherapy, IQ damage was greater in girls than boys. (Christie et al., 1995)



## Consequences of RT responses in females and males

1 Gy of  
ionising  
radiation  
absorbed dose,  
generates  
approximately  
40 DSBs

acute or  
chronic toxic  
effects

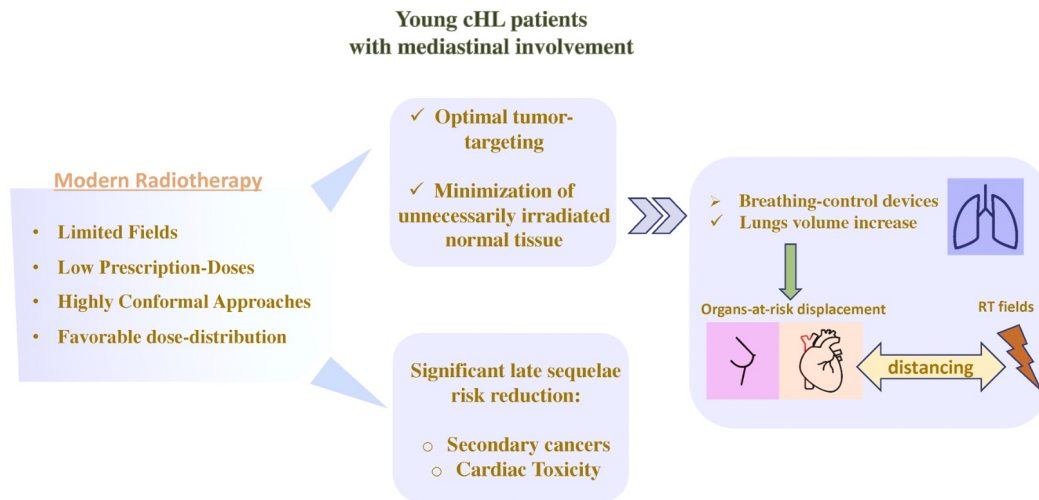
incidence is  
influenced by  
the radio-  
sensitivity of  
the tissue

Recent radiogenomic research has proven that individual polymorphisms can correlate with treatment response most likely due to variation in the ability to recognise and repair DNA double-strand breaks (DSB), with significant differences shown between genders.

Alsbeih et al., 2016

# Second Malignant Neoplasm

Risk factors associated with solid tumor SMNs were female sex and thoracic exposure to RT. (Bluhm et al., 2008)



Iorio et al., 2021

# Gender Radiosensitivity

Compilation of studies reporting on gender-specific differences in response to radiotherapy.

Study [ref]	Malignancy Studied / time frame	Metric(s) studied	Sample size/patient cohort	Dose delivered	Irradiated male outcome	Irradiated female outcome	Cohort without radiotherapy
Sex-specific olfactory memory impairment in a rodent model of paediatric RT. <i>Pre-clinical mice study</i> [Perez et al, 2018]	No malignancy involved Cognitive impairment measured at 1 week and again at 3 months	Cognitive Impairment (via novel odour recognition (NOdorR))	60 mice (24 male and 36 female)	5 Gy at a rate of 110 cGy/min	Irradiated males had impaired odour recognition memory in adulthood, compared to non-irradiated males	Irradiated females showed cognitive impairment only during certain stages of oestrus.	Males show no cognitive impairment, while females show similar oestrus-dependent fluctuations.
Gender differences on radiation-induced acute lung toxicity <i>Pre-clinical mouse study</i> [Bilal et al, 2014]	No initial malignancy 6 weeks post-RT	RT-related pneumonitis and vasculitis	40 rats (20 male and 20 female)	10 Gy in a single fraction	60% males developed RT-related pneumonitis after RT, 80% developed vasculitis	50% females developed RT-related pneumonitis after RT, 70% developed vasculitis	0% non-irradiated males and females developed pneumonitis
Gender-differences of colonic motility after chemo- RT in humans. <i>In-vitro study</i> [Maselli et al, 2018]	Rectal cancer October 2015 - August 2017	Motor response of colonic samples in response to carbachol, histamine or electric field stimulation	29 patients- 15 without (8 male and 7 female) in control group,	50.4 Gy over 28 fractions	Higher sensitivity and greater response to both carbachol and histamine in the study group compared to control group	No significant difference in sensitivity or response to carbachol or histamine in the study group compared to control group	EC50 of maximal response to carbachol and histamine dropped significantly in males. In females, EC50 dropped, but not as significantly. The same applied to EFS, with an even greater gap between the sexes. N/A
Gender differences in NTCP model for heart toxicity during RT for esophageal cancer <i>Retrospective cohort study</i> [Snyder et al., 2012]	Oesophageal Cancer June 2002 - April 2011	Toxicity using LKB model of Normal Tissue Complication Probability	127 patients with EC	Varied dosages	Td50 of 55.3 Gy	Td50 of 36.6 Gy	

De Courcy et al., 2020

# Gender Radiosensitivity

Impact of sex on prognosis of esophageal squamous cell cancer after RT <i>Retrospective cohort study</i> [Luo et al. 2019]	Oesophageal squamous-cell carcinoma January 2009-December 2015	Progression-free survival (PFS) and Overall survival (OS)	683 (497 male and 186 female) ESCC patients with definitive radiotherapy	Average of 64 Gy (50-78)	Whole cohort- Median PFS of 10.6 months, OS of 15.9 months. Matched cohort- Median PFS of 11.6 months, OS of 16.1 months	Whole cohort- Median PFS of 14 months, OS of 20.8 months. Matched cohort- Median PFS of 13.5 months, OS of 19.6 months	Sex not an independent prognostic factor (Zhang 2013)
Gender differences in RT for Head and Neck Cancer <i>Prospective cohort study</i> [Page et al, 2018]	Oral cavity, oropharynx, larynx, nasopharynx/sinonasal, and upper digestive tract cancer 2010- 2017	Clinical measures (e.g dermatitis, CTCAE grading) and patient-reported outcomes (e.g FACT score)	363 patients (277 male and 86 female)	Not specified	Men reported higher FACT scores both pre-treatment and 1 year after treatment, with the exception of Social Well-being. There was no difference in clinically assessed adverse effects	No difference with clinical	N/A
Gender-related prognostic significance of tumour features in rectal cancer after preoperative RT. <i>Retrospective cohort study</i> [Gasinska et al, 2017, 2011]	Rectal cancer November 2004-January 2006	Oncogene expression, recurrence, metastasis and overall survival	126 patients (84 men and 42 women)	5 Gy delivered over 5 days	Patients treated with shorter break (< 17 days) survived better than the longer break, which was particularly important for the males	Patients treated with shorter break (< 17 days) survived better than the longer break. This was not significant in the female group. In terms of OS, low expression of KU70 was the only significant parameter for females.	N/A

De Courcy et al., 2020

## Gender Radiotherapy

REVIEW

### Radiogenomics helps to achieve personalized therapy by evaluating patient responses to radiation treatment

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*“As healthcare marches progressively towards a system more tailored to the individual, gender is a factor that may not only have a profound effect, but can be implemented with relative ease. Moving forward, gender may be included as a matched variable in cohort studies and randomised control trials. There is also already great opportunity to exploit the vast quantities of data available to look at male versus female outcomes post RT.”*

## Conclusion

- ✓ Better understand the different biomolecular mechanisms of immunotherapy and radiotherapy
- ✓ look for any gender constraints
- ✓ Reduce side effects
- ✓ Improve outcomes

## Take home message

*The one-size-fits-all  
approach does not work!  
We need to move forward  
towards a Gender  
Radiotherapy.....*

## Take home message

*We will ultimately treat  
males and females  
differently in an effort to  
protect them equally*

**Grazie per l'attenzione!**