



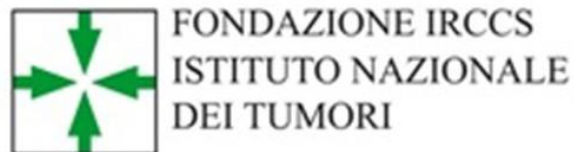
Risk assessment *Tools* for severe side *Effects* after *breasT* Radiotherapy:
radiation safety through biological extended models and *digital twinS*

Male Breast Cancer: what is different?

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**Fondazione IRCCS Istituto Nazionale Tumori
di Milano**



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DECLARATION OF INTERESTS

Personal financial interests

Consulting fees: Novartis, Pfizer, Gilead

Institutional financial interests

Research grants: Collaborator of AIRC IG24864, AIRC IG21479 and PNNR-POC-2023 12378113;
Clinical Coordinator HORIZON-EURATOM 101166699

Non-financial interests

Member of the AIRO BREAST, ESTRO, COBCG

Principal Investigator of many academic research (EUROPA trial, Taormina Trial, etc)





«We have no evidence»



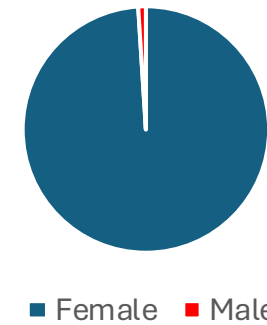
OUTLINE

- 1. Epidemiology and Biological Differences**
 2. Diagnostic Work-up and Staging
 3. Treatment of Early Male Breast Cancer
 4. Treatment of Metastatic Male Breast Cancer
 5. Conclusions
-

EPIDEMIOLOGY

1. 1% of all male tumours
2. 1% of all breast cancer
3. Increasing incidence in recent decades
4. Population heavily underrepresented in clinical trials on breast cancer
5. Therapeutic guidelines extrapolated from female breast cancer

Breast Cancer



Yousef AJ. Male breast cancer: epidemiology and risk factors. Semin Oncol. 2017

Miglietta et al. Gender minorities in breast cancer – clinical trials enrollment disparities: focus on male, transgender and gender diverse patients. Breast. 2024

POV: You took "matching
outfits" too literally

MATCHING OUTFITS



1. Anatomical Reasons

Zheng G - J Oncol. 2022

1. Anatomical Reasons

2. Surgical Reasons

Zheng G - J Oncol. 2022

1. Anatomical Reasons

2. Surgical Reasons

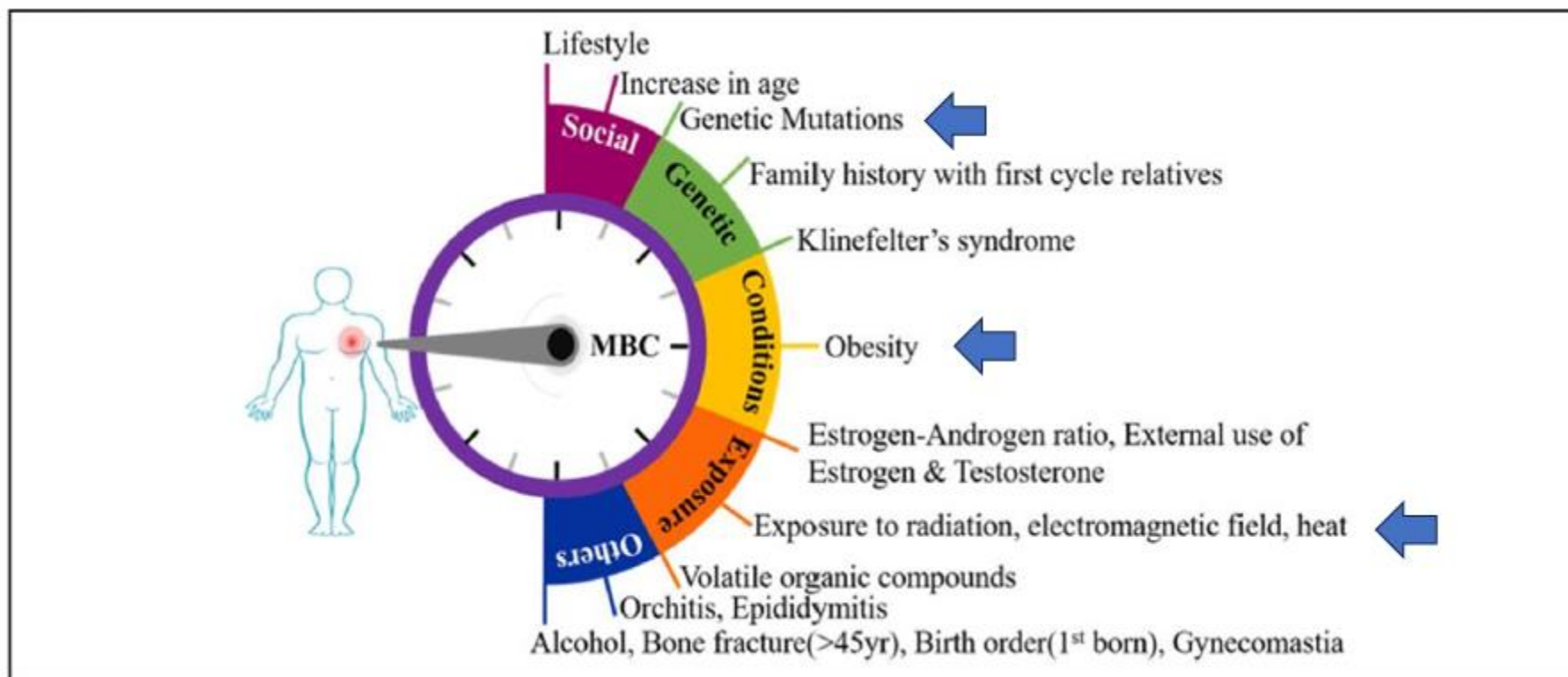
3. Hormonal Reasons

Zheng G - J Oncol. 2022

1. Anatomical Reasons
2. Surgical Reasons
3. Hormonal Reasons
4. Genetic Reasons

Zheng G - J Oncol. 2022

RISK FACTORS



HidambaramA et al. Male breast cancer: current scenario and future perspectives. Technol Cancer Res Treat. 2024

BIOLOGICAL DIFFERENCES

1. Histological differences: NST prevalent histology (absence of terminal lobules in males)
2. Low incidence of DCIS
3. Molecular differences: 99% of male breast cancers are HR+
4. IMBCP data:
42% luminal A-like,
49% luminal B-like HER2-
9% HER2+
<1% TNBC

	Men	Women
HR-positive, HER2-negative	90	71
HR-positive, HER2-positive	9	12
HR-negative, HER2-positive	<1	5
HR-negative, HER2-negative	<1	12

Cardoso F et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/ NABCG International Male Breast Cancer Program. Ann Oncol 2018
Giordano SH. Breast cancer in men. N Engl J Med. 2018

MOLECULAR AND GENOMIC DIFFERENCES

1. Less frequent 16q loss, PIK3CA mutation, TP53 mutation
2. More frequently, the presence of DNA-repair gene alterations (30% versus ~15%)
3. gBRCA2mut 10–15%, gBRCA1mut 2–3%
4. BRCA2 lifetime breast cancer risk 5%-10% (inferior for BRCA1 carriers)
5. BRCA2-related tumors have a more aggressive profile (younger age, bilateral tumors, higher grade, lymph node involvement)

Chatterji S et al. Defining genomic, transcriptomic, proteomic, epigenetic, and phenotypic biomarkers with prognostic capability in male breast cancer: a systematic review. *Lancet Oncol.* 2023

Silvestri V et al. Male breast cancer in BRCA1 and BRCA2 mutation carriers: pathology data from the Consortium of Investigators of Modifiers of BRCA1/2. *Breast Cancer Res.* 2016

MOLECULAR AND GENOMIC DIFFERENCES



Storia personale di:
1. Carcinoma mammario maschile



Recommendation 10.

Male patients with breast cancer should be offered genetic counseling and genetic testing for germline mutations (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).



1. Multigene panel for assessing high-penetrance genes: BRCA1, BRCA2, PALB2
2. Multigene panel for the evaluation of moderate-penetrance genes: CHEK2, ATM

Prophylactic surgery to discuss together with the patient in the absence of solid survival data

OUTLINE

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-

CLINICAL ASPECTS

1. Hard and fixed retroareolar nodule
2. Nipple retraction with or without discharge (often bloody)
3. Early ulceration

Compared to the female population:

- Men are diagnosed at an older age (67 vs 62 years)
- May present more often with locally advanced disease (lymph node/chest wall involvement)

LOCAL STAGING

Variant: 5 Male of any age with physical examination suspicious for breast cancer (suspicious palpable breast mass, axillary adenopathy, nipple discharge, or nipple retraction). Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	⊕⊕
Mammography diagnostic	Usually Appropriate	⊕⊕
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○

Diagnostic core biopsy ultrasound-guided, primitive lesion +/- possible suspicious lymph nodes

SYSTEMIC STAGING

- Chest X-ray/abdominal ultrasound
 - TB CT with contrast
 - Bone scan
 - PET-FDG
 - Multidimensional evaluation (cardiology, geriatric, psychological assessment)
 - Discussion in a multidisciplinary team
-

OUTLINE

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SURGERY

- In localized disease, surgery is the treatment of choice, with mastectomy being the most commonly performed procedure.
- Breast-conserving surgery (BCS) can be considered in selected cases with outcomes similar to those of the female population (rarely used in clinical practice)
- Axillary surgery follows the same indications as for the female population

Leone JP et al. Locoregional treatment and overall survival of men with T1a,b,cN0M0 breast cancer: a population-based study. EurJ Cancer. 2017

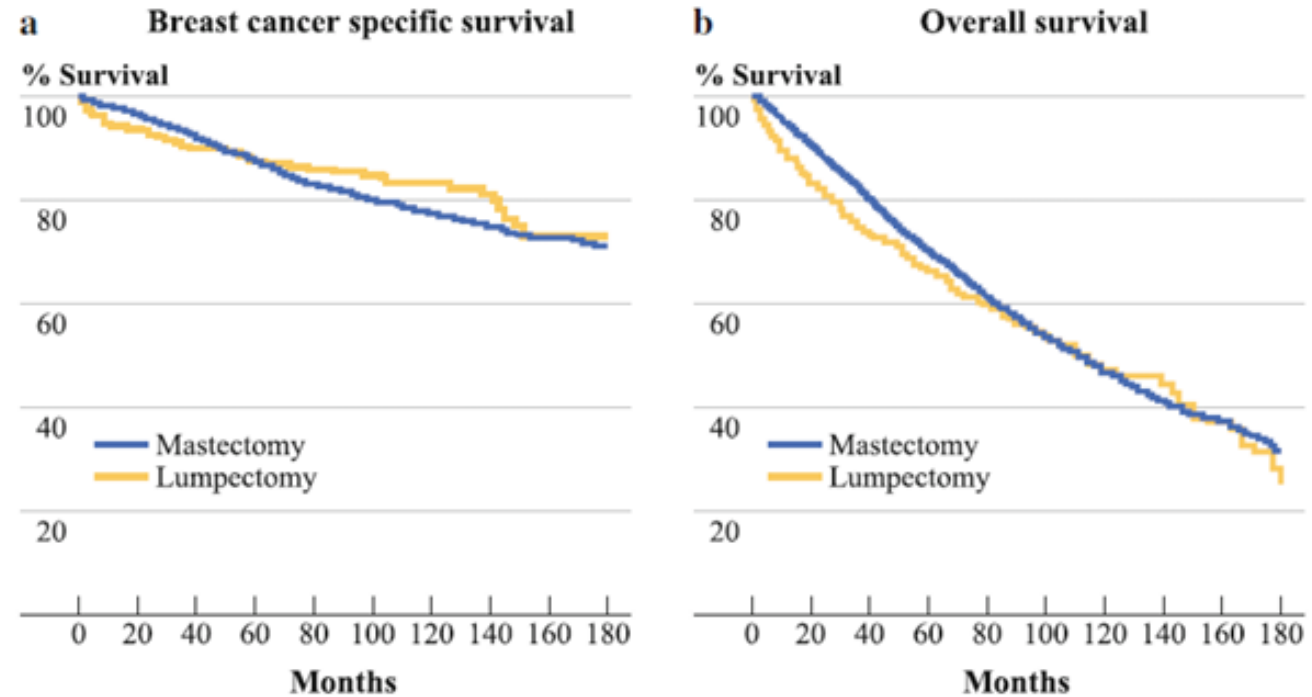
Cloyd JM et al. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983–2009. Ann Surg Oncol. 2013

ZaengerD, Rabatic BM, Dasher B, Mourad WF. Is breast conserving therapy a safe modality for early-stage male breast cancer? Clin Breast Cancer. 2016

SURGERY

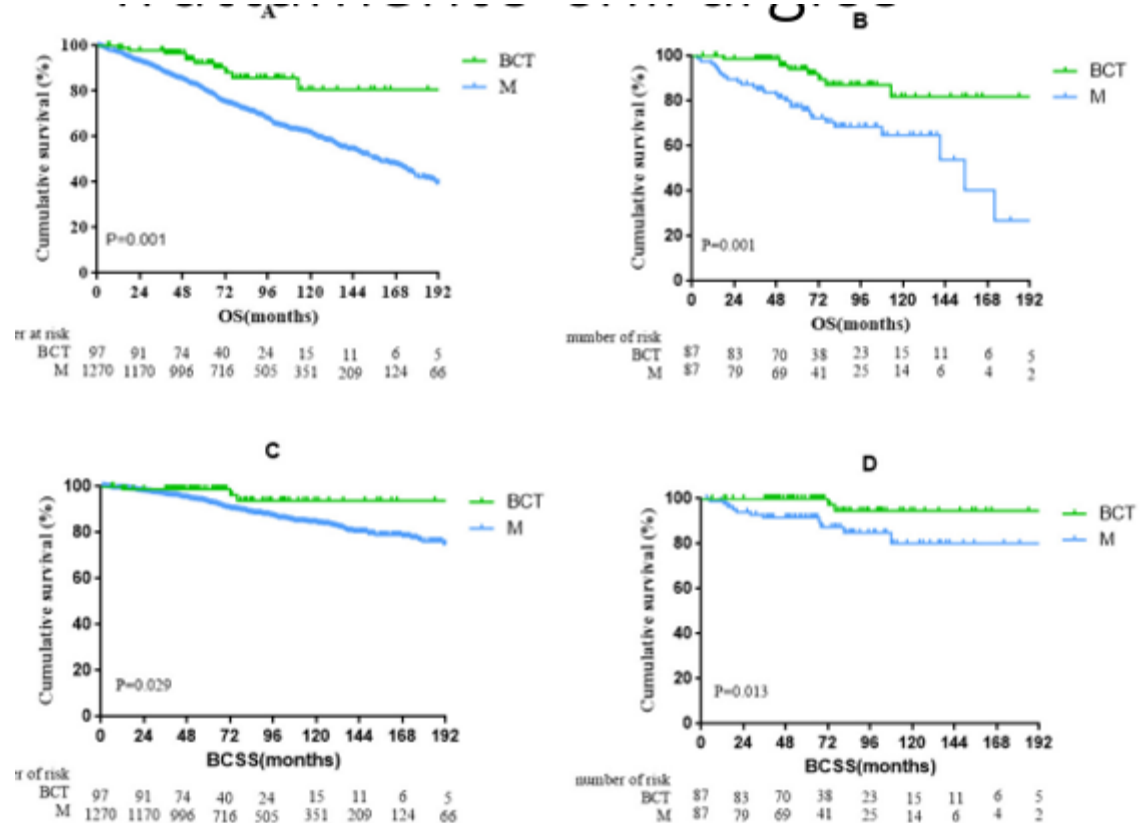
FIG. 2 Kaplan–Meier analysis of
a breast cancer-specific survival and
b overall survival of MBC patients
undergoing mastectomy vs.
lumpectomy

Studio retrospettivo
population-based (SEER)
1983-2009
4707 Pazienti



Cloyd JM et al. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983–2009. Ann Surg Oncol. 2013.

SURGERY



Retrospective population-based study (SEER)

2000-2018: 1369 patients

Stages I-II (T1-2 N0-1 M0)

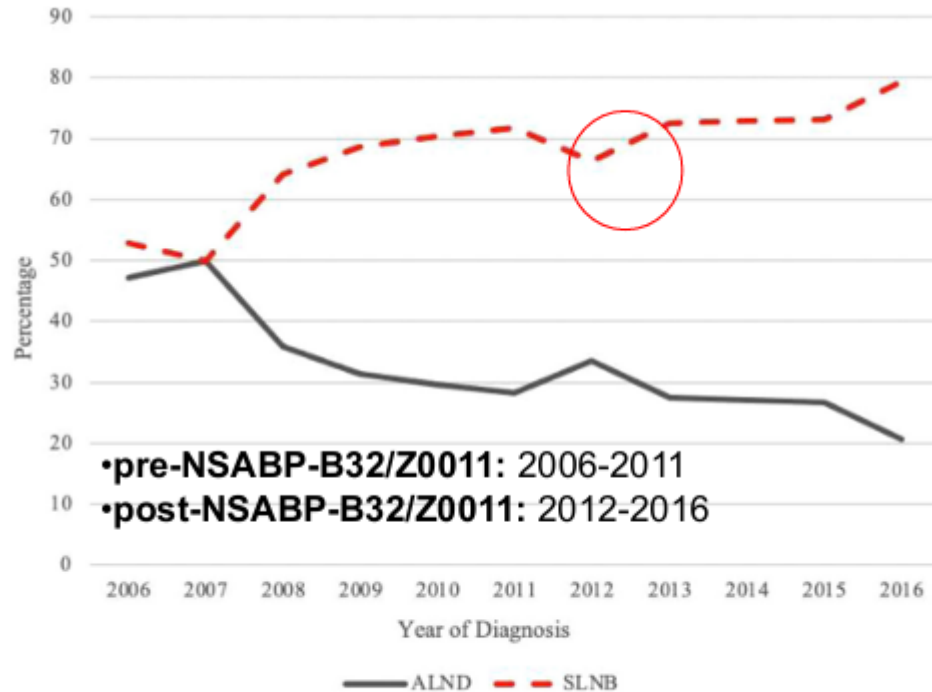
- BCS 7%
- Mastectomy 93%

A OS before PSM **B** after PSM

C BCSS before PSM, **D** after PSM

He Y et al. –Effect of Breast Conservation Therapy vs Mastectomy on Overall Survival and Breast Cancer-Specific Survival Among Men With Stage I-II Breast Cancer (SEER 2000-2018) Clinical Breast Cancer, 2022

SURGERY



Retrospective study population-based

2646 patients

cT1-4cN0

Anno	BLS
2006	52.8%
2011	71.7%
2016	79.3%

Fig. 1 – Trends in Use of Sentinel Lymph Node Biopsy and Axillary Lymph Node Dissection for cT1-4 and cN0 Male Breast Cancer based on NCDB data from 2006-2016.

Carter M et al. Trends and outcomes associated with axillary management of males with clinical N0 breast cancer – an NCDB analysis. J Surg Res. 2021

Giuliano AE et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569-575.



SYSTEMIC THERAPY

- Genomic tests and chemotherapy
- Hormone therapy
- PARP inhibitors
- CDK4/6 therapy

GENOMIC TESTS AND CHEMOTHERAPY

oncotype dx®
Breast Recurrence Score

- Increasing use of genomic tests (e.g., OncotypeDX) in male breast cancer
- Data extrapolated from the female population

Differences compared to the female population:

- Male patients more often have $RS \geq 31$ or < 11
- For the same high-risk score (defined as ≥ 26), male patients have a worse prognosis

CHEMOTHERAPY

- Indications similar to those for female patients (high clinical risk N2-3 or genomic tests)
- Chemotherapy regimens based on anthracyclines and taxanes, using anti-HER2 if the disease is HER2+ or immunotherapy in case of TNBC
- Overall assessment is key (cardiovascular risk, older age, comorbidities)

HORMONOTHERAPY

- Key point for HR+/HER2 breast cancer
- Tamoxifen is the first choice
- Aromatase inhibitors only if there are absolute contraindications to tamoxifen therapy (like thromboembolic risk) and always together with LHRHa (testicular hormone production and hypothalamic-pituitary loop)

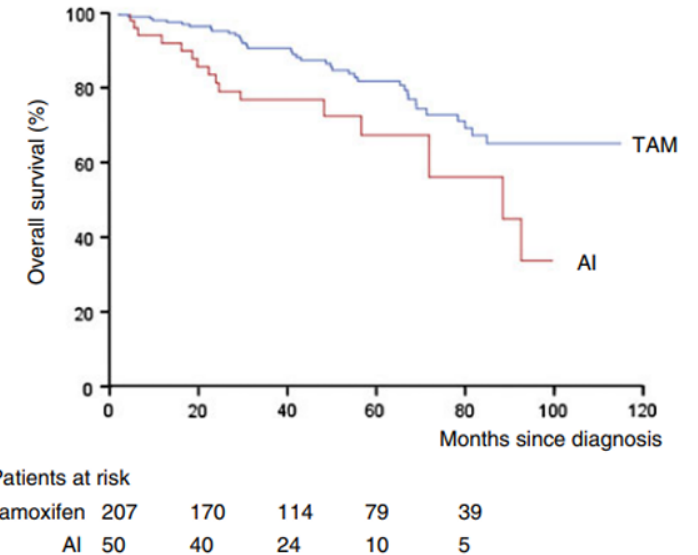


Fig. 1 Overall survival estimated by Kaplan–Meier method

PARPi

PARP inhibition → accumulation of DNA damage → selective death of HRD cells.

1) Clinical evidence: OlympiA study Phase III, HER2–, gBRCA1/2, high risk.

Olaparib 1 year vs placebo after local therapy ± chemotherapy. Significant benefit on:

- iDFS
- DDFS
- Overall Survival (follow-up update)

2) Specific data in male patients

- Registration trials include very few men (in OlympiA: 6 male patients).
- No published analysis stratified by sex in the adjuvant setting.
- Clinical application based on:
overlapping biological rationale
sex-agnostic indication

Particularly relevant in BRCA2-mutated men (more frequent than BRCA1)

CD4/6i

- Men have been included in adjuvant trials with CDK4/6 (MonarchE and NATALEE), but they represent <1% and there's no statistical power for dedicated conclusions
- To date, biological treatment should be considered in patients who meet the inclusion criteria
- Frevert et al. estimate that 1 of 5 male patients meets MonarchE criteria and almost 1 of 2 meets NATALEE criteria

Frevert ML et al. Feasibility of targeted therapies in the adjuvant setting of early breast cancer in men: real-world data from a population-based registry. Arch Gynecol Obstet. 2024-
Johnston SRD, et al. Abemaciclib combined with endocrine therapy for high-risk early breast cancer (monarchE). N Engl J Med. 2020.
Slamon DJ, et al. Ribociclib plus endocrine therapy in early breast cancer (NATALEE). N Engl J Med. 202

RADIOTHERAPY



Radiotherapy must be done

RADIOTHERAPY



Radiotherapy must be done

Radiotherapy must be done!

RADIOTHERAPY

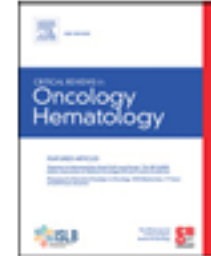
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The role of radiation therapy in the multidisciplinary management of male breast cancer: A systematic review and meta-analysis on behalf of the Clinical Oncology Breast Cancer Group (COBCG)

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RADIOTHERAPY

Table 1

Search strategy and results.

N°	Search query	Pubmed	Embase	Cochrane
#1	Cancer* OR tumor* OR tumour* OR carcinoma* OR neoplasm* OR malignancy*	5.366.728	7.561.422	1.231.567
#2	Breast OR mammary	644.223	845.231	458.654
#3	Male OR man OR men	9.659.247	11.567.983	3.679.874
#4	Radiation OR radiotherapy OR X- ray OR irradiation OR RT	3.463.124	4.567.843	1.234.618
#5	#1 AND #2 AND #3 AND #4	3.154	5.569	1.537

Legend: RT: radiation therapy.



RADIOTHERAPY

We included studies with

1. More than **20 male** invasive breast cancer patients
 2. that reported HR comparing the impact of **RT versus no RT** on **OS**,
 3. were published in **English**
 4. between January 1, **2000**, and December 31, **2022**.
 5. Articles non reporting on radiation therapy or OS analysis were also excluded.
- 

RADIOTHERAPY

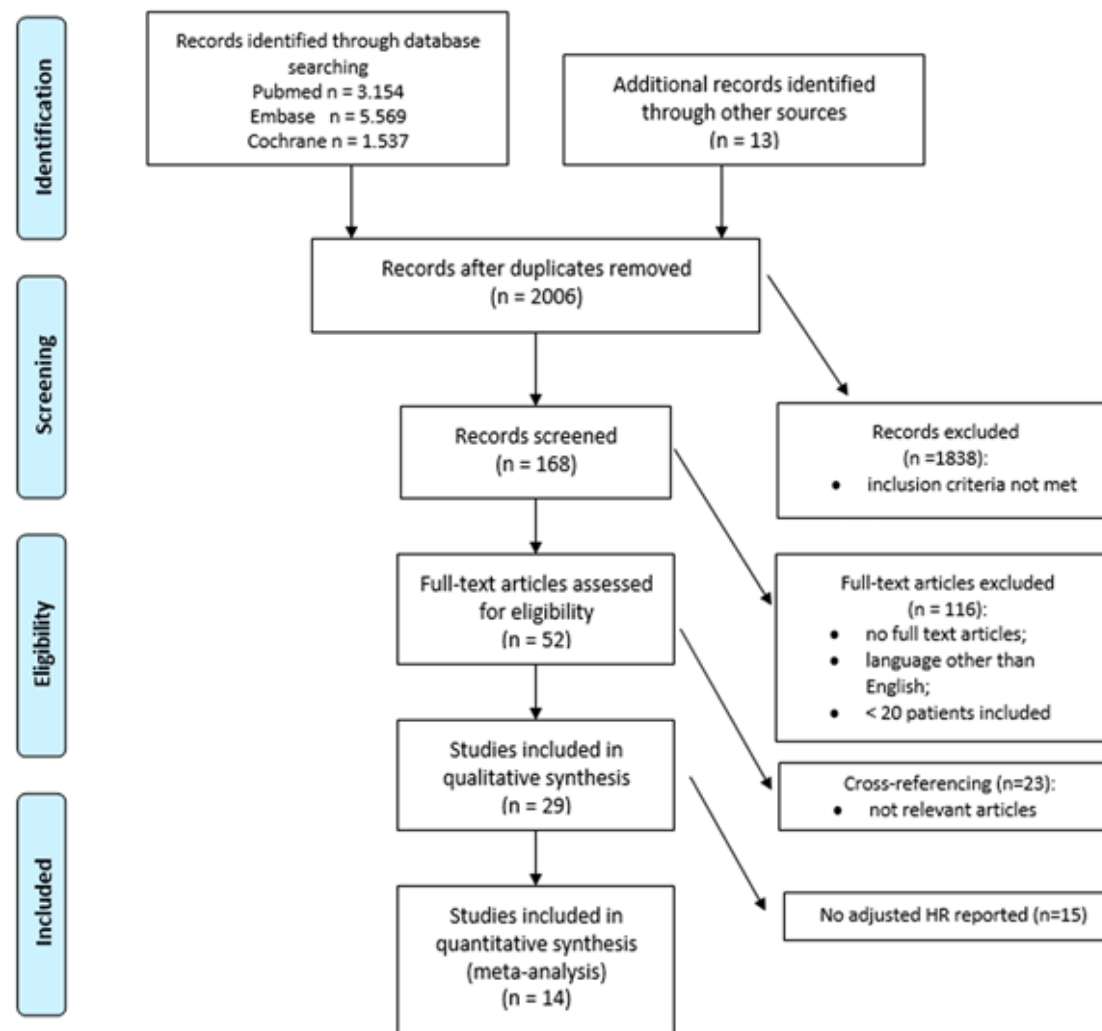


Fig. 1. Flowchart summarizing search results and study selection.

RADIOTHERAPY

N° of patients	Age	Follow-Up	Loco-regional advanced disease	T4
80'219	61 – 79	31 – 314	0 – 82%	0 – 62.5%

- The included studies are heterogeneous.
- The number of patients varies widely, as do age, follow-up and the proportions of locally advanced or T4 disease.

RADIOTHERAPY

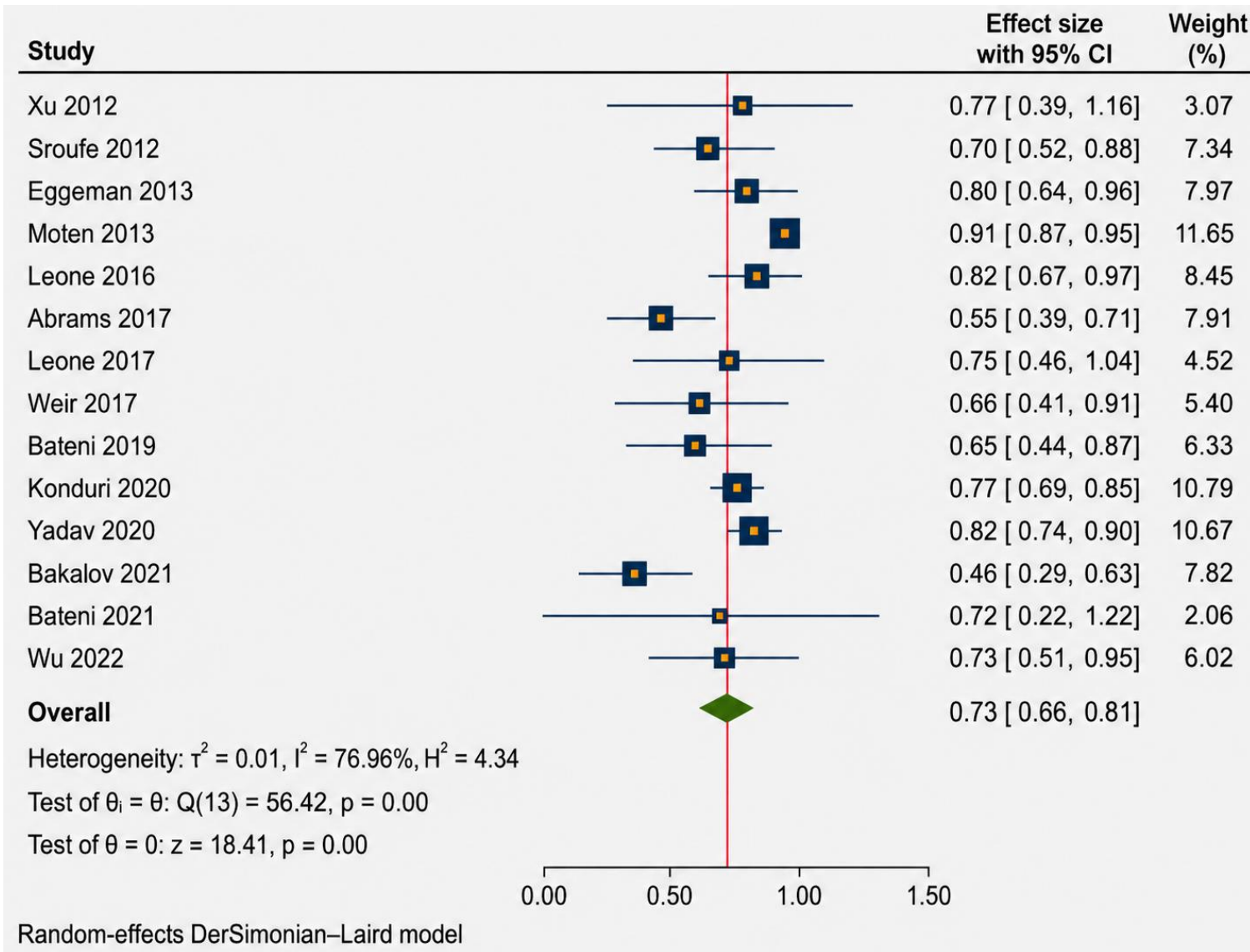
Table 3

Crude survival outcome for patients receiving or not post-operative radiation therapy.

Study, year	Surgery	5-year OS		10-year OS	
		<i>RT</i>	<i>No RT</i>	<i>RT</i>	<i>No RT</i>
Sroufe 2012	Mastectomy	72.4 %	74.7 %	46.3 %	50.8 %
Eggeman 2016	Mastectomy	NA	NA	35.1 %	34.2 %
Abrams 2017	Mastectomy	83 %	54 %	NA	NA
Weir 2018	BCS	NA	NA	74 %	60 %
	Mastectomy	NA	NA	44 %	41 %
Bateni 2019	BCS	86.8 %	84.9 %	73.8 %	56.3 %
	Mastectomy	81.9 %	80.6 %	56.3 %	58 %
Bakalov 2021	BCS	75 %	52 %	NA	NA
	Mastectomy	56 %	50 %	NA	NA
Median		78.4 %	64.3 %	54.3 %	54.1 %
Weighted mean		75.8 %	62.2 %	52.3 %	50.1 %

Legend: RT: radiation therapy; OS: overall survival; BCS: breast-conserving surgery; NA: not available.

RADIOTHERAPY



RADIOTHERAPY

Breast Cancer Research and Treatment (2024) 208:29–40

<https://doi.org/10.1007/s10549-024-07380-0>

RESEARCH



Male breast cancer: a multicenter study to provide a guide for proper management

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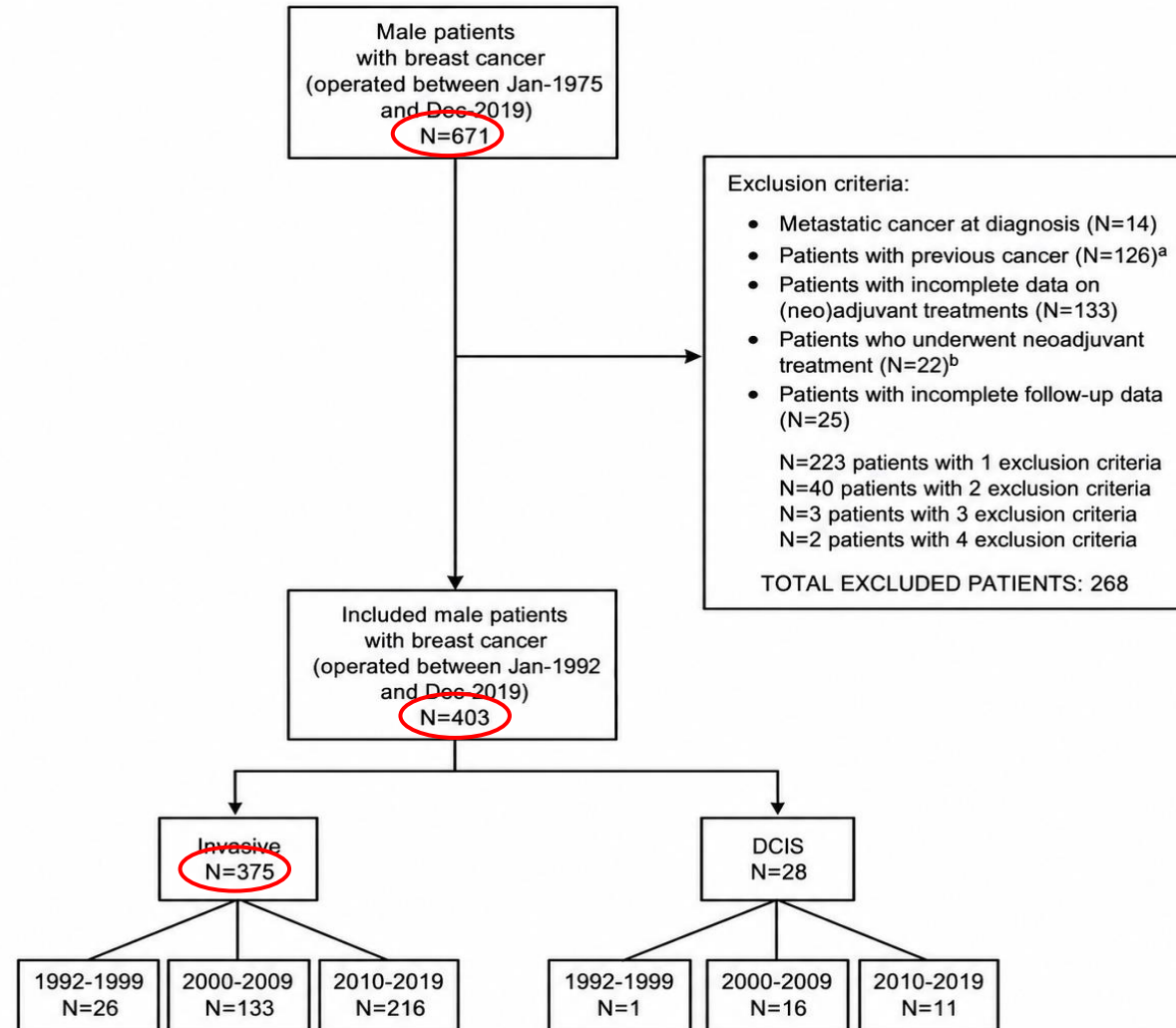
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RADIODTHERAPY

1. **Multicenter retrospective** observational cohort study
2. **12** Italian breast units
3. Male patients, 18 years of age or older, **diagnosed with breast cancer** (invasive or in situ)
4. Between **1992 and 2019**
5. Endpoints evaluated were **DFS and OS**

RADIOTHERAPY



RADIOTHERAPY

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
Grade						
G1	26	6.9	8	28.6	34	8.4
G2	196	52.3	11	39.3	207	51.4
G3	139	37.1	0	—	139	34.5
Unknown	14	3.7	9	32.1	23	5.7
pT						
pT1	224	59.7	12	42.9	236	58.6
pT2	123	32.8	7	25.0	130	32.3
pT3	3	0.8	1	3.6	4	1.0
pT4	14	3.7	0	—	14	3.5
Unknown	11	2.9	8	28.6	19	4.7
pN						
pN0	174	46.4	21	75.0	195	48.4
pN1	111	29.6	0	—	111	27.5
pN2	30	8.0	0	—	30	7.4
pN3	42	11.2	0	—	42	10.4
pNx	18	4.8	7	25.0	25	6.2
SLNB						
Missing	2	0.5	1	3.6	3	0.7
No	168	44.8	11	39.3	179	44.4
Yes	205	54.7	16	57.1	221	54.8
Number of sentinel lymph nodes removed						
Unknown	3	1.5	0	—	3	1.4
1	113	55.1	8	50.0	121	54.8
> 1	89	43.4	8	50.0	97	43.9
Number of sentinel lymph nodes positive						
Unknown	3	1.4	0	—	3	1.4
0	130	63.4	16	100	146	66.1
1	66	32.2	0	—	66	29.9
> 1	6	2.9	0	—	6	2.7
Axillary dissection						
No	153	40.8	26	92.9	179	44.4
Yes	206	54.9	1	3.6	207	51.4
Unknown	16	4.3	1	3.6	17	4.2

DCIS ductal carcinoma in situ, SLNB sentinel lymph node biopsy

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
ER/PR						
Not expressed (Both 0)	6	1.6	0	—	6	1.5
Incompletely expressed (ER < 50 or PR < 50)	119	31.7	7	25.0	126	31.3
Highly expressed (ER ≥ 50 & PR ≥ 50)	244	65.1	13	46.4	257	63.8
Unknown	6	1.6	8	28.6	14	3.5
Ki67 (%)						
< 20%	120	32.0	13	46.4	133	33.0
≥ 20%	244	65.1	3	10.7	247	61.3
Unknown	11	2.9	12	42.9	23	5.7
HER2						
Negative	309	82.4	15	53.6	324	80.4
Positive	50	13.3	0	—	50	12.4
Unknown	16	4.3	13	46.4	29	7.2
Subtype						
Luminal A	99	26.4	12	42.9	111	27.5
Luminal B (Ki67 ≥ 20%)	203	54.1	3	10.7	206	51.1
Luminal B (HER2 positive)	46	12.3	0	—	46	11.4
HER2 positive	3	0.8	0	—	3	0.7
Triple negative	3	0.8	0	—	3	0.7
Unknown	21	5.6	13	46.4	34	8.4
Histotype						
Ductal	326	86.9	28	100.0	354	87.8
Lobular	6	1.6	0	—	6	1.5
Papillary	27	7.2	0	—	27	6.7
Other	8	2.1	0	—	8	2.0
Unknown	8	2.1	0	—	8	2.0
Systemic adjuvant treatment						
No adjuvant treatment	27	7.2	24	85.7	51	12.7
Only CT	13	3.5	0	—	13	3.2
Only HT	207	55.2	4	14.3	211	52.4
CT + HT	128	34.1	0	—	128	31.8
Radiotherapy						
No	202	53.9	27	96.4	229	56.8
Yes	173	46.1	1	3.6	174	43.2

CT chemotherapy, DCIS ductal carcinoma in situ, ER estrogen receptor, HER2 human epidermal growth factor receptor 2, HT hormone therapy, PR progesterone receptor

RADIOTHERAPY

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
Median follow-up, yrs (IQR)	7.5 (3.9–12.3)		8.9 (3.3–12.3)		7.5 (3.9–12.3)	
Overall survival (OS)						
Observed deaths	82	21.9	3	10.7	85	21.1
5-yr OS (95% CI)	88.6 (84.4–91.7)		95.0 (69.5–99.3)		89.0 (85.0–92.0)	
10-yr OS (95% CI)	73.6 (67.0–79.1)		90.0 (65.6–97.4)		74.9 (68.7–80.1)	
Disease-free survival (DFS)						
Observed events, N (%)	123	32.8	6	21.4	129	32.0
Death from breast cancer	5	4.1	0	–	5	3.9
Death from non-breast cancer cause	13	10.6	2	33.3	15	11.6
Death from unknown cause	21	17.1	1	16.7	22	17.1
Distant recurrence	46	37.4	0	–	46	35.7
Invasive contralateral breast cancer	9	7.3	0	–	9	7.0
Invasive ipsilateral breast tumor recurrence	1	0.8	0	–	1	0.8
Local/regional invasive recurrence	11	8.9	2	33.3	13	10.1
Second primary invasive cancer (non-breast)	17	13.8	1	16.7	18	14.0
5-yr DFS (95% CI)	78.0 (73.0–82.2)		90.0 (65.6–97.4)		78.8 (74.0–82.8)	
10-yr DFS (95% CI)	59.9 (53.0–66.0)		75.6 (44.8–90.7)		61.1 (54.5–67.0)	

DCIS ductal carcinoma in situ, IQR interquartile range

RADIOTHERAPY

	Number of patients	Number of events	Univariable		Multivariable	
			OS-HR (95% CI)	<i>p</i> -value	OS-HR (95% CI)	<i>p</i> -value
Grade						
G1	26	4	1.00	–	1.00	–
G2	196	45	2.19 (0.79–6.11)	0.134	1.49 (0.43–5.21)	0.529
G3	139	32	3.10 (1.09–8.82)	0.034	1.34 (0.35–5.05)	0.667
pT						
pT1	224	31	1.00	–	1.00	–
pT2/3/4	140	47	3.81 (2.37–6.12)	<.001	3.14 (1.83–5.39)	<.001
pN						
pN0	174	28	1.00	–	1.00	–
pN1	111	19	1.24 (0.69–2.23)	0.478	0.79 (0.42–1.49)	0.469
pN2/3	72	27	2.86 (1.67–4.88)	<.001	1.50 (0.80–2.80)	0.207
Subtype						
Luminal A	99	18	1.00	–	1.00	–
Luminal B (Ki67 ≥ 20%)	203	48	1.77 (1.03–3.06)	0.039	1.37 (0.75–2.48)	0.303
Luminal B (HER2 positive)	46	8	1.13 (0.49–2.59)	0.779	0.78 (0.32–1.91)	0.586
HER2 positive/triple negative	6	3	2.57 (0.76–8.77)	0.130	4.76 (1.26–18.1)	0.022
Systemic adjuvant treatment						
No adjuvant treatment	27	7	1.00	–	1.00	–
Only CT	13	7	2.09 (0.73–5.98)	0.167	–	–
Only HT	207	36	0.52 (0.23–1.18)	0.117	–	–
CT + HT	128	32	0.91 (0.40–2.06)	0.819	–	–
Radiotherapy						
No	202	34	1.00	–	–	–
Yes	173	48	1.63 (1.05–2.54)	0.031	–	–
Year of surgery						
1992–1999	26	11	1.00	–	–	–
2000–2009	133	46	1.13 (0.56–2.30)	0.726	–	–
2010–2019	216	25	1.23 (0.55–2.75)	0.607	–	–

CT chemotherapy, DCIS ductal carcinoma in situ, HER2 human epidermal growth factor receptor 2, HT hormone therapy

RADIOTHERAPY

	Number of patients	Number of events	Univariable		Multivariable	
			OS-HR (95% CI)	<i>p</i> -value	OS-HR (95% CI)	<i>p</i> -value
Grade						
G1	26	4	1.00	–	1.00	–
G2	196	45	2.19 (0.79–6.11)	0.134	1.49 (0.43–5.21)	0.529
G3	139	32	3.10 (1.09–8.82)	0.034	1.34 (0.35–5.05)	0.667
pT						
pT1	224	31	1.00	–	1.00	–
pT2/3/4	140	47	3.81 (2.37–6.12)	<.001	3.14 (1.83–5.39)	<.001
pN						
pN0	174	28	1.00	–	1.00	–
pN1	111	19	1.24 (0.69–2.23)	0.478	0.79 (0.42–1.49)	0.469
pN2/3	72	27	2.86 (1.67–4.88)	<.001	1.50 (0.80–2.80)	0.207
Subtype						
Luminal A	99	18	1.00	–	1.00	–
Luminal B (Ki67 ≥ 20%)	203	48	1.77 (1.03–3.06)	0.039	1.37 (0.75–2.48)	0.303
Luminal B (HER2 positive)	46	8	1.13 (0.49–2.59)	0.779	0.78 (0.32–1.91)	0.586
HER2 positive/triple negative	6	3	2.57 (0.76–8.77)	0.130	4.76 (1.26–18.1)	0.022
Systemic adjuvant treatment						
No adjuvant treatment	27	7	1.00	–	1.00	–
Only CT	13	7	2.09 (0.73–5.98)	0.167	–	–
Only HT	207	36	0.52 (0.23–1.18)	0.117	–	–
CT + HT	128	32	0.91 (0.40–2.06)	0.819	–	–
Radiotherapy						
No	202	34	1.00	–	–	–
Yes	173	48	1.63 (1.05–2.54)	0.031	–	–
Year of surgery						
1992–1999	26	11	1.00	–	–	–
2000–2009	133	46	1.13 (0.56–2.30)	0.726	–	–
2010–2019	216	25	1.23 (0.55–2.75)	0.607	–	–

CT chemotherapy, DCIS ductal carcinoma in situ, HER2 human epidermal growth factor receptor 2, HT hormone therapy

La radiologia medica

<https://doi.org/10.1007/s11547-026-02276-z>

RADIOTHERAPY



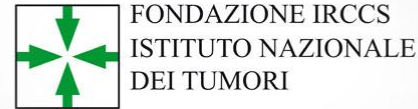
Radiation therapy and overall survival in male breast cancer: a multicenter analysis of 302 patients

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Radiation Therapy Improves Overall Survival in Male Breast Cancer: A Multicenter Analysis of 302 Patients

Clinical Oncology Breast Cancer Group



RADIOTHERAPY

1. **Multicenter retrospective** observational cohort study
2. **302 patients** with a median age of 69 years
3. **74.5%** had stage I to IIIa disease, while **15.2%** had stage IIIb to IV disease, with stage unknown in **10.3%**.
4. 95.7% underwent total mastectomy

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RADIO THERAPY

Table 1 Patients' and tumor characteristics for male breast cancer diagnosed during 2005–2023 and clinically followed up to 2024 in 10 Italian centers

	All patients	
	No	% or IQR
Total patients	302	100.0
<i>Age at diagnosis</i>		
Median (IQR)	299	69 (61–76)
Unknown	3	0.0
<i>Body mass index</i>		
Median	194	26 (24–29)
Normal weight	68	22.5
Overweight	90	29.8
Obese	36	11.9
Unknown	108	35.8
<i>Alcohol consumption</i>		
No	230	76.2
Yes	44	14.6
Unknown	28	9.3
<i>Smoking history</i>		
Never smoker	185	61.3
Current/former	89	29.5
Unknown	28	9.3
<i>Packs of cigarettes per year*</i>		
Median	53	20 (10–40)
Unknown	36	40.5
<i>Diabetes</i>		
No	236	78.1
Yes	42	13.9
Unknown	24	7.9

Table 1 (continued)

	All patients	
	No	% or IQR
pT2	111	36.8
pT3	7	2.3
pT4	32	10.6
Unknown	7	2.3
<i>Tumor size (in mm)</i>		
Median (IQR)	236	20 (14–25.5)
Unknown	66	0.2
<i>Pathological N stage</i>		
pN0	133	44.0
pN1	94	31.1
pN2	36	11.9
pN3	20	6.6
Unknown	19	6.3
<i>Number of removed lymph nodes</i>		
Median (IQR)	261	8 (2–19)
Unknown	41	0.1
<i>Number of positive lymph nodes</i>		
Median (IQR)	253	1 (0–3)
Unknown	49	0.2
<i>Lymph nodal ratio[§]</i>		
Median (IQR)	248	0.04 (0–0.23)
Unknown	54	0.2
<i>Clinical M stage</i>		
cM0	259	85.8
cM1	7	2.3
Unknown	36	11.9

Hypertension

No	143	47.4
Yes	126	41.7
Unknown	33	10.9

Use of anticoagulants

No	231	76.5
Yes	44	14.6
Unknown	27	8.9

Presence of lymph vascular invasion

No	180	59.6
Yes	102	33.8
Unknown	20	6.6

Presence of peri-neural invasion

No	228	75.5
Yes	54	17.9
Unknown	20	6.6

BRCA 1/2 mutation

No	162	53.6
Yes	41	13.6
Unknown	99	32.8

Pathological T stage

pT1	145	48.0
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Grouped stage

I–IIIa	225	74.5
IIIb–IIIc, IV	46	15.2
Unknown	31	10.3

Histology

Ductal	265	87.7
Other**	33	10.9
Unknown	4	1.3

Tumor grade

I	16	5.3
II	159	52.6
III	122	40.4
Unknown	5	1.7

Molecular subtype

Luminal A	107	35.4
Luminal B	160	53.0
HER2-positive	22	7.3
Triple-negative	1	0.3
Unknown	12	4.0

*Evaluated on current/former smokers only; Number of positive over removed lymph nodes; IQR, interquartile range; ** Tubular, cribriform, papillary and other

Table 2 Distribution (No, %) of male breast cancer patients by treatment

	All patients	
	No	%
Total patients	302	100.0
<i>Axillary management</i>		
Not done	20	6.6
Axillary lymph node dissection	127	42.1
Sentinel lymph node biopsy	136	45.0
Sampling	15	5.0
Unknown	4	1.3
<i>Type of surgical treatment</i>		
Total mastectomy	289	95.7
Quadrantectomy	7	2.3
Other not specified	4	1.3
Unknown	2	0.7
<i>Margins of resection</i>		
Negative	271	89.7
Close	14	4.6
Positive	3	1.0
Unknown	14	4.6
<i>Neo-adjuvant chemotherapy</i>		
No	286	94.7
Yes	13	4.3
Unknown	3	1.0
<i>Adjuvant chemotherapy</i>		
No	194	64.2
Yes	94	31.1
Unknown	14	4.6

Chemotherapy

No	182	60.3
Yes	106	35.1
Unknown	14	4.6

Endocrine therapy

Not done	33	10.9
Aromatase inhibitors	22	7.3
Tamoxifene	209	69.2
LHRH analogues	18	6.0

Unknown type	1	0.3
Unknown	19	6.3

Targeted therapy

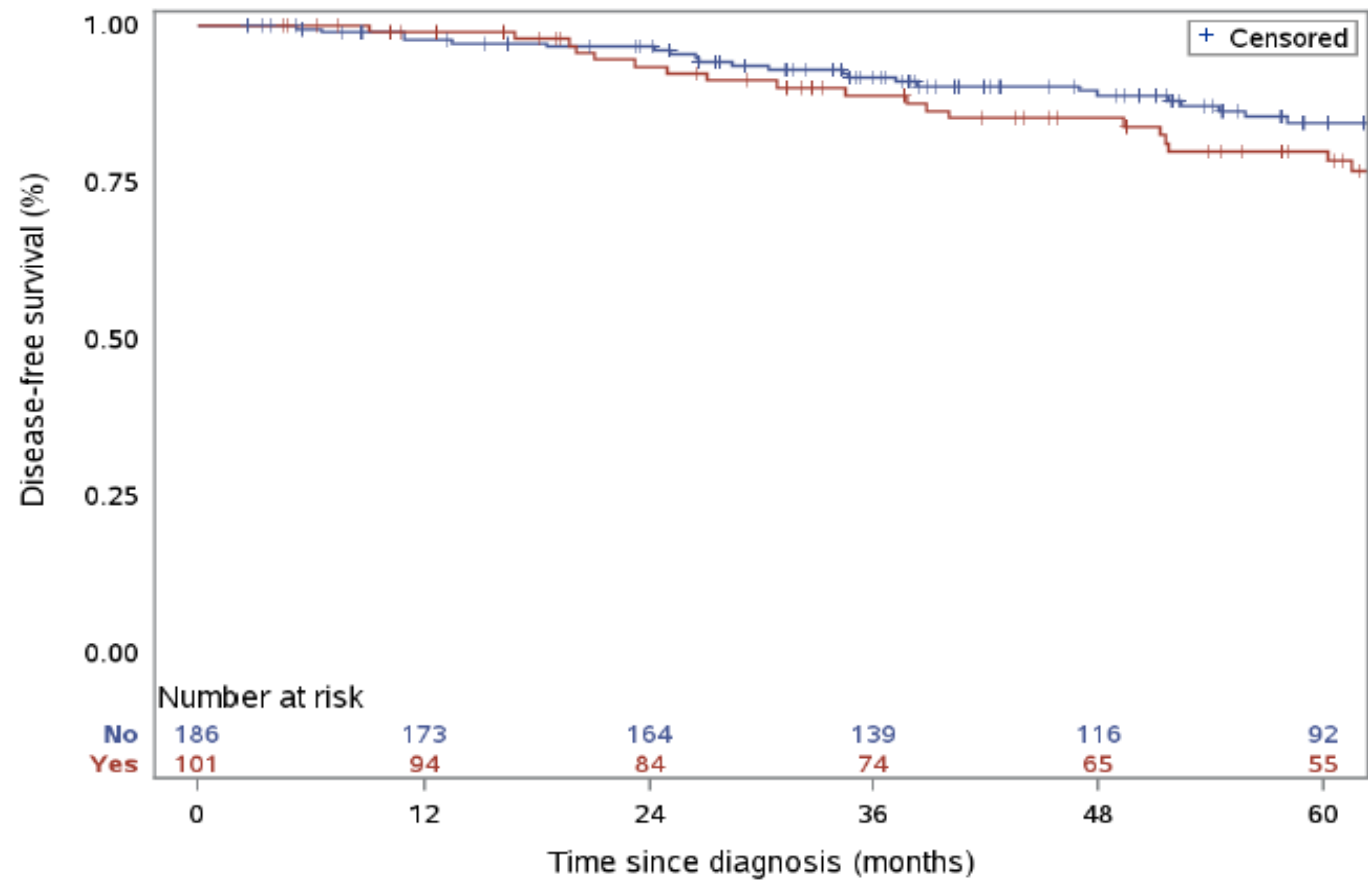
No	262	86.8
Yes	21	7.0
Unknown	19	6.3

Radiation therapy (RT)

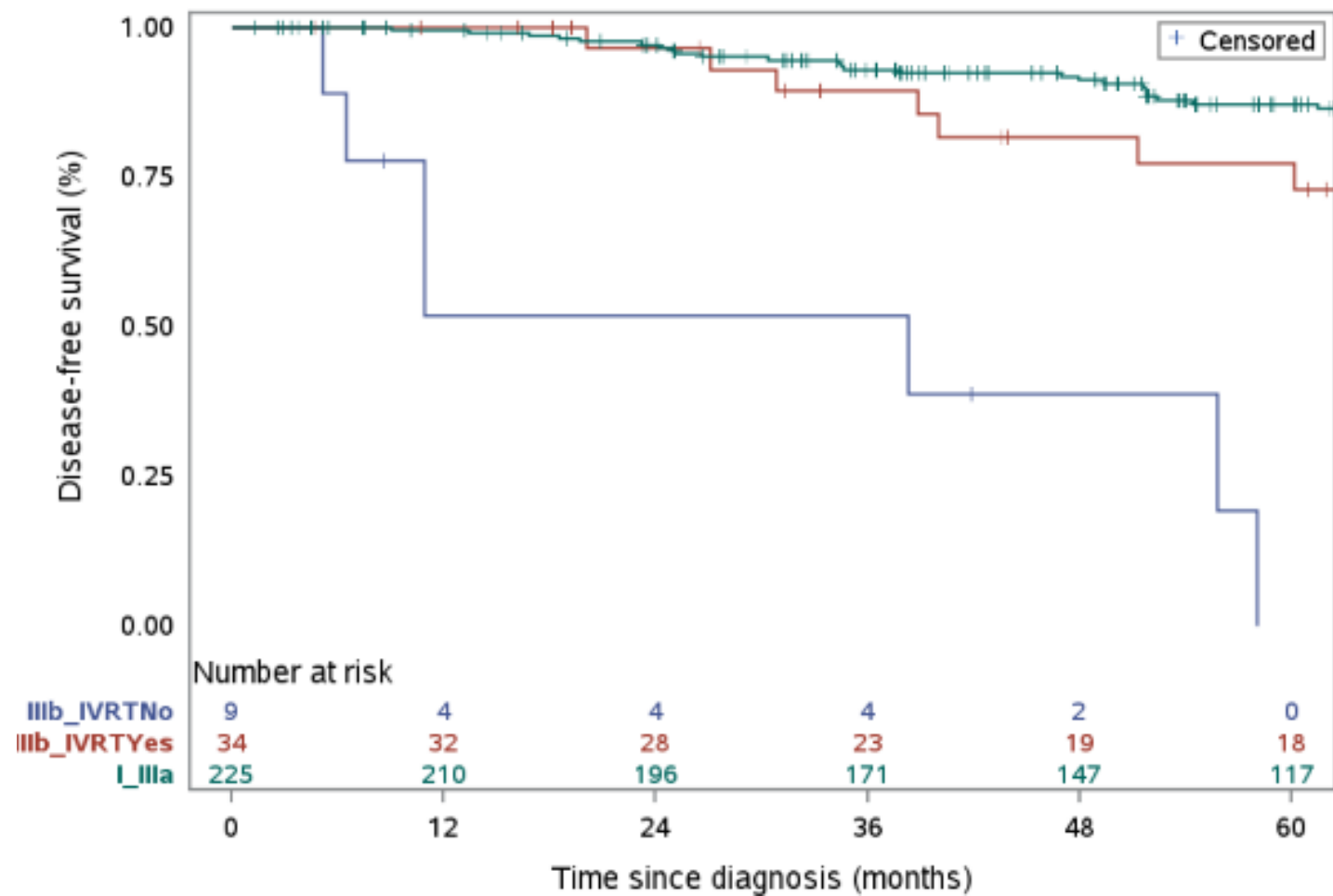
No	188	62.3
Yes	101	33.4
Unknown	13	4.3

Radiation therapy and grouped stage

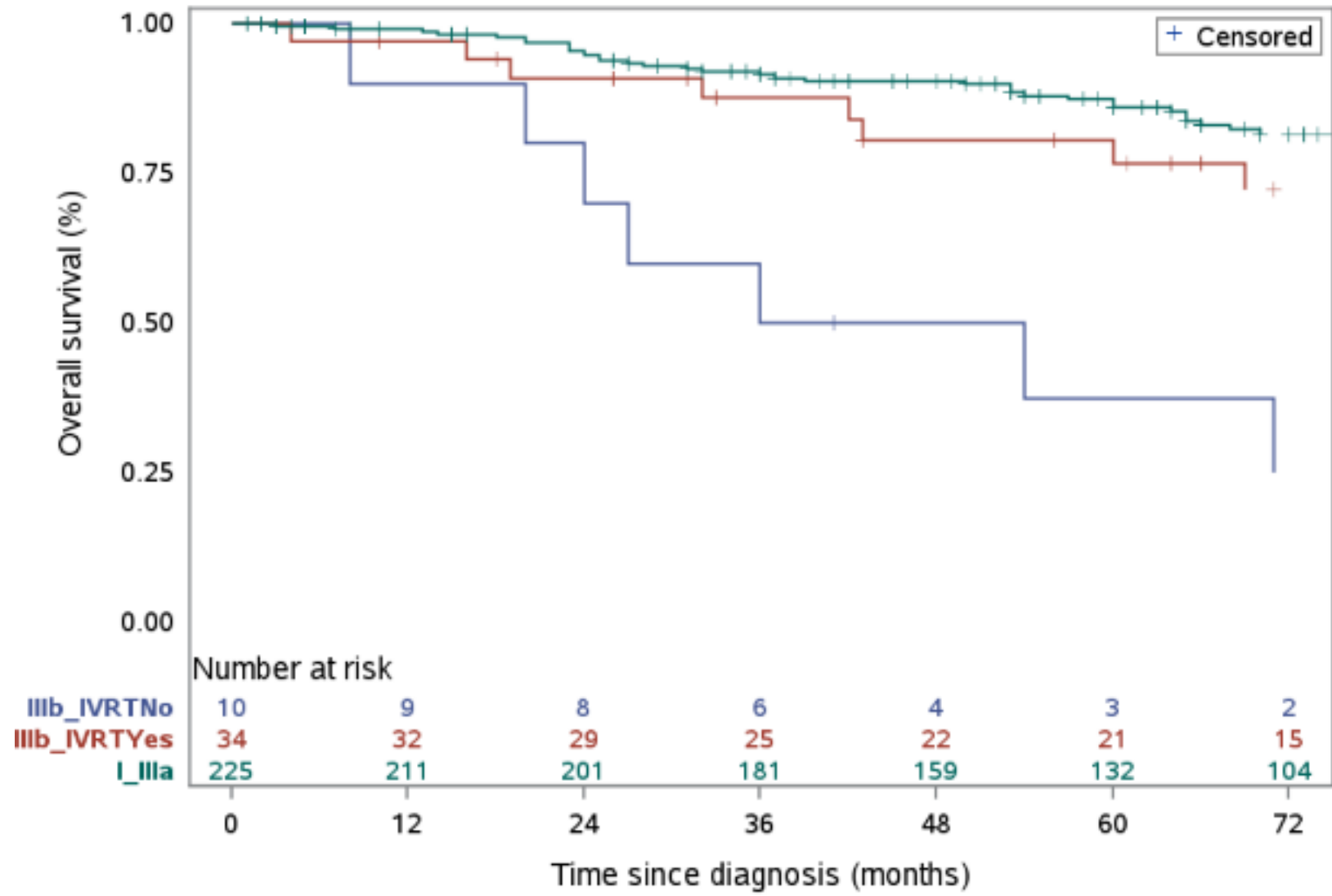
I–IIIa	225	74.5
IIIb–IIIc and IV, RT Yes	34	11.3
IIIb–IIIc and IV, RT No	10	3.3



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Table 3 Significance evaluation of analyzed variables in either disease-free or overall survival context

	Any recurrences			Death for any causes						
	HR	95% CI	p-value	p-value*	p-value**	HR	95% CI	p-value	p-value*	p-value**
<i>Age at diagnosis</i>										
per unit-increase	0.98	0.96–1.01	0.2051			1.06	1.03–1.08	<0.0001	Na	
<i>Alcohol consumption</i>										
Yes vs No	0.77	0.31–1.92	0.5814			0.85	0.39–1.88	0.6949		
<i>Smoking history</i>										
Current/former smoker vs Never-smoker	0.93	0.46–1.88	0.8421		0.0123	1.07	0.59–1.93	0.8281		
<i>Diabetes</i>										
Yes vs No	1.72	0.85–3.51	0.1340			1.89	1.05–3.41	0.0351	0.0247	0.0965
<i>Hypertension</i>										
Yes vs No	1.04	0.57–1.88	0.9005			1.75	1.06–2.9	0.0284	0.0380	
<i>Use of anticoagulants</i>										
Yes vs No	0.71	0.3–1.7	0.4476			1.37	0.71–2.66	0.3477		
<i>Presence of lymph vascular invasion</i>										
Yes vs No	2.5	1.39–4.48	0.0021	0.0003		1.36	0.83–2.23	0.2158		
<i>Presence of peri-neural invasion</i>										
Yes vs No	1.09	0.51–2.32	0.8300			1.8	1.01–3.2	0.0463	0.2221	
<i>Lymph nodal ratio (asin transformation)</i>										
per unit-increase	2.64	1.29–5.37	0.0076	na	0.0054	1.35	0.7–2.59	0.3738	Na	
<i>Grouped stage</i>										
IIIb-IV vs I-IIIa	2.46	1.21–5.02	0.0134	0.0007	<0.0001	1.77	1.01–3.11	0.0460	0.0018	0.0014
<i>Histology</i>										
Other vs Ductal	0.35	0.08–1.48	0.1538			0.91	0.38–2.17	0.8345		
<i>Tumour grade</i>										
II vs I	1.79	0.41–7.77	0.4363			5.14	0.7–37.71	0.1076		
III vs I	2.3	0.53–9.93	0.2663			5.87	0.8–43.15	0.0821		
<i>Molecular subtype</i>				0.0080					0.0139	
Luminal B vs Luminal A	2.07	1.04–4.14	0.0393			1.56	0.89–2.74	0.1192		
HER2-positive or triple-negative vs Luminal A	3.25	1.03–10.27	0.0447			3.12	1.25–7.77	0.0148		0.0968
<i>Axillary management</i>									0.0448	
Axillary lymph node dissection vs Sentinel lymph node biopsy/Sampling	1.66	0.9–3.05	0.1058			1.7	1.04–2.76	0.0333		
Not done vs Sentinel lymph node biopsy/Sampling	0.99	0.27–3.57	0.9840			2.04	0.85–4.92	0.1128		
<i>Chemotherapy</i>										
Yes vs No	2.9	1.63–5.15	0.0003	0.0009	0.0826	0.74	0.45–1.22	0.2349		
<i>Endocrine therapy</i>										

Colciagio RR

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Table 3 (continued)

	Any recurrences					Death for any causes				
	HR	95% CI	p-value	p-value*	p-value**	HR	95% CI	p-value	p-value*	p-value**
Yes vs No	0.5	0.21–1.18	0.1132			0.26	0.14–0.47	<0.0001	<0.0001	
<i>Targeted therapy</i>										
Yes vs No	1.16	0.41–3.3	0.7852		0.0458	0.81	0.28–2.32	0.6905		0.0778
<i>Radiotherapy</i>										
Yes vs No	1.38	0.74–2.57	0.3128		–	1.11	0.66–1.87	0.6998	0.2737	–
<i>Radiotherapy and grouped stage</i>				<0.0001	–				<0.0001	–
IIIb-IV, RT Yes vs I-IIIa	0.97	0.37–2.53	0.9439			1.12	0.56–2.25	0.7492		
IIIb-IV, RT No vs I-IIIa	18.8	7.09–49.63	0.0000			6.45	2.66–15.62	<0.0001		

Hazard ratios (HRs) estimated by center-adjusted univariate Cox proportional hazard models;

*Results from log-rank test, where applicable;

**Referring to the first-order interaction term from multivariate Cox proportional hazard models including radiation therapy, the variable of interest and the first-order interaction term between the two covariates

OUTLINE

1. Epidemiology and Biological Differences
 2. Diagnostic Work-up and Staging
 3. Treatment of Early Male Breast Cancer
 - 4. Treatment of Metastatic Male Breast Cancer**
 5. Conclusions
-

Systemic treatment of the metastatic disease HR+/HER2-

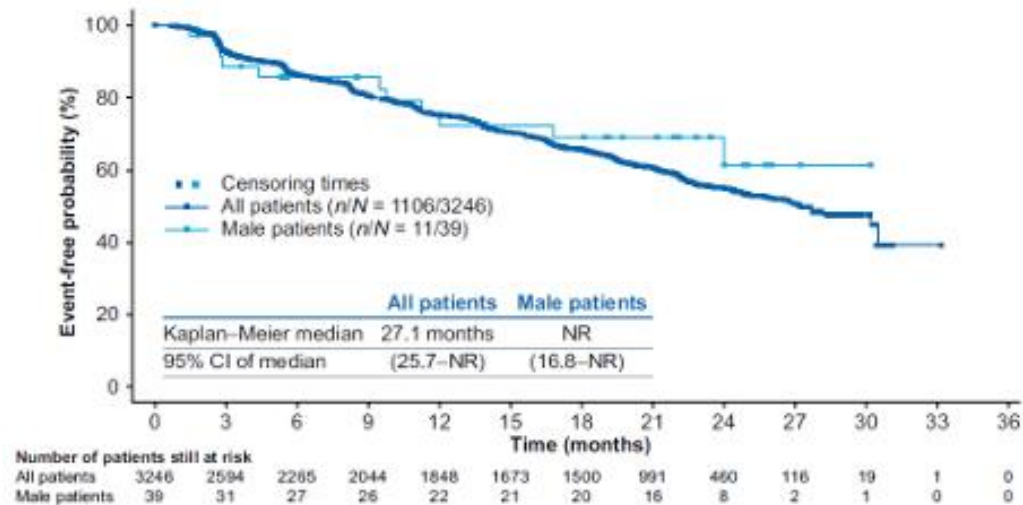
- Majority of metastatic breast cancers in men
- Treatment with endocrine therapy alone (Tamoxifen) was historically the gold standard
- The novel combination therapy with CDK4/6 inhibitors has helped change the paradigm
- Data extrapolated from the female population (virtually no enrollment in RCTs)
- Mostly real-world data

REAL WORLD DATA

- Campone, M et al. (2022). Ribociclib plus letrozole in male patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: subgroup analysis of the phase IIIb ComPLEEment-1 trial. Breast cancer research and treatment
- Yıldırım, HÇ et al (2024). The efficacy of palbociclib and ribociclib in the first-line treatment of metastatic hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer in male patients: a Turkish oncology group (TOG) study. International journal of clinical oncology (retrospective)
- Blum, JL et al (2024). Outcomes of male patients with HR+/HER2- advanced breast cancer receiving palbociclib in the real-world POLARIS study. Breast cancer research and treatment (prospective)

REAL WORLD DATA

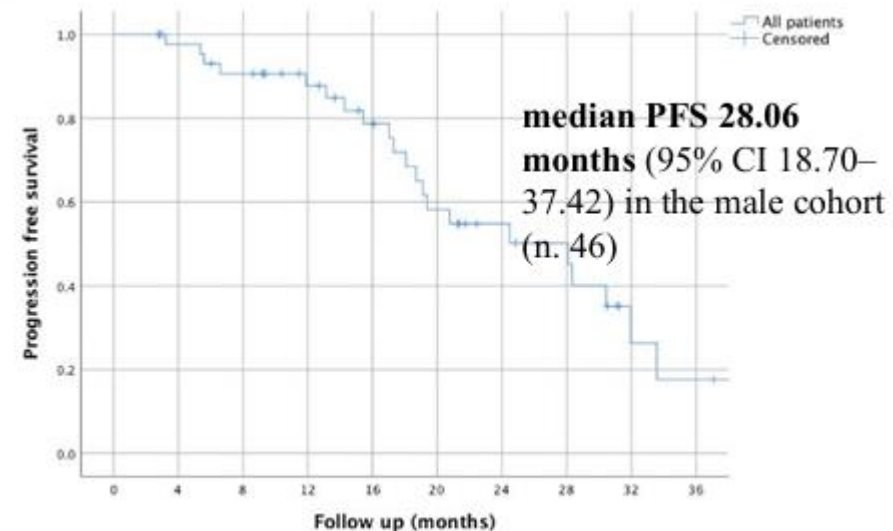
Complement study: 39 MBC patients treated with ribociclib + ET



Turkish Oncology Group (TOG) study: 46 patients MBC

25 treated with palbociclib

21 treated with ribociclib.



Campone M, et al. Ribociclib plus letrozole in men with HR+/HER2- advanced breast cancer (ComPLEEment-1). Breast Cancer Res Treat. 2022
Yıldırım HÇ, et al. Palbociclib and ribociclib in first-line treatment of HR+/HER2- metastatic breast cancer in men. Int J Clin Oncol. 2024

OUTLINE

1. Epidemiology and Biological Differences
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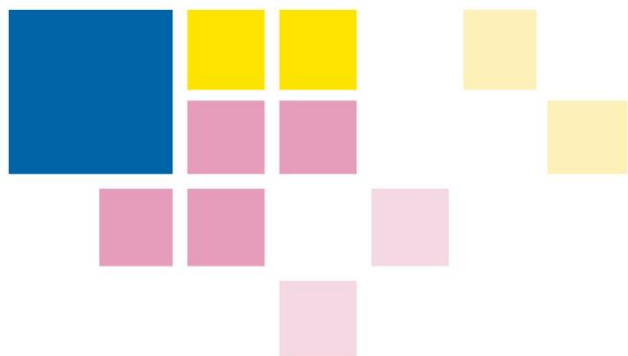


CONCLUSIONS(1)

- Male breast cancer is rare, but it has specific anatomical, biological and genetic features.
- Most tumours are hormone receptor positive, making endocrine therapy the gold standard, with tamoxifen as the preferred option.
- Genetic testing has a pivotal role, especially because of the frequency of BRCA2 alterations.
- Modern systemic therapies, including PARP and CDK4/6 inhibitors, can be considered in men when indicated, but male-specific evidence remains limited.

CONCLUSIONS(2)

- Radiotherapy is an important component of locoregional management; observational studies and meta-analyses show an association with better outcomes, particularly in more advanced disease.
- The major limitation of the literature remains the scarcity of male-specific randomized trials.
- Optimal management requires a dedicated multidisciplinary approach and greater inclusion of men in clinical research.
- **Studies like TETRIS will be the challenge!!!!!!!**



THANK YOU

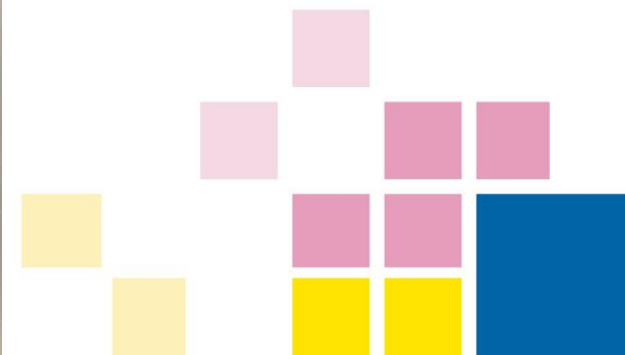
TETRIS - Risk assessment *Tools* for severe side *Effects* after *breasT* Radiotherapy:
radiation safety through biological extended models and *digital twinS*

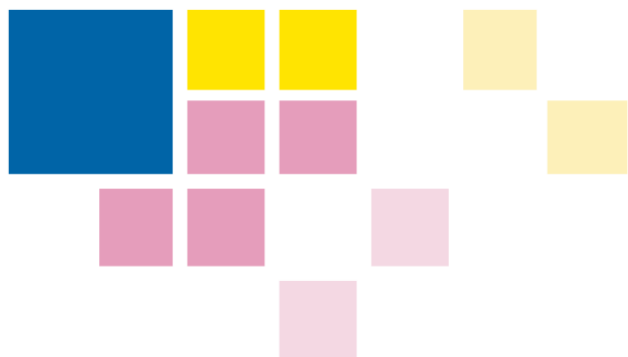


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