Omissione della radioterapia dopo chirurgia conservativa mammaria Quando è possibile?

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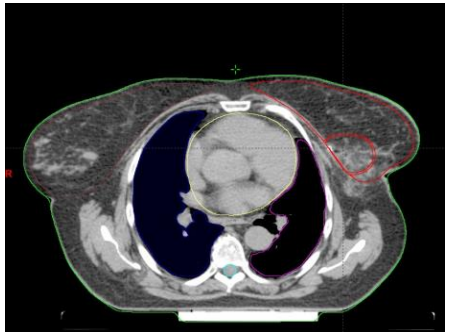
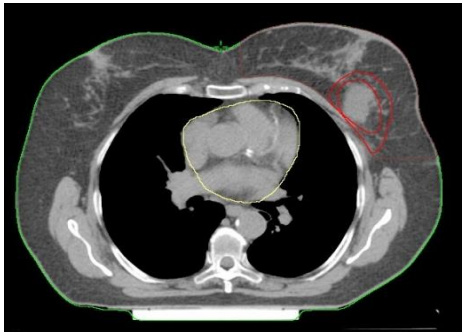
Background

"…**Radiation** treatments are well tolerated and, when delivered using modern technologies, carry a low risk of serious morbidity…"

Smith B. D., et al. J Clin Oncol 2013
Williams L. J., et al. Health technology assessment 2011



Hypofractionated Radiotherapy
15/20 fractions in 3/4 weeks
Ultra-hypofractionated Radiotherapy
5 fractions/one week

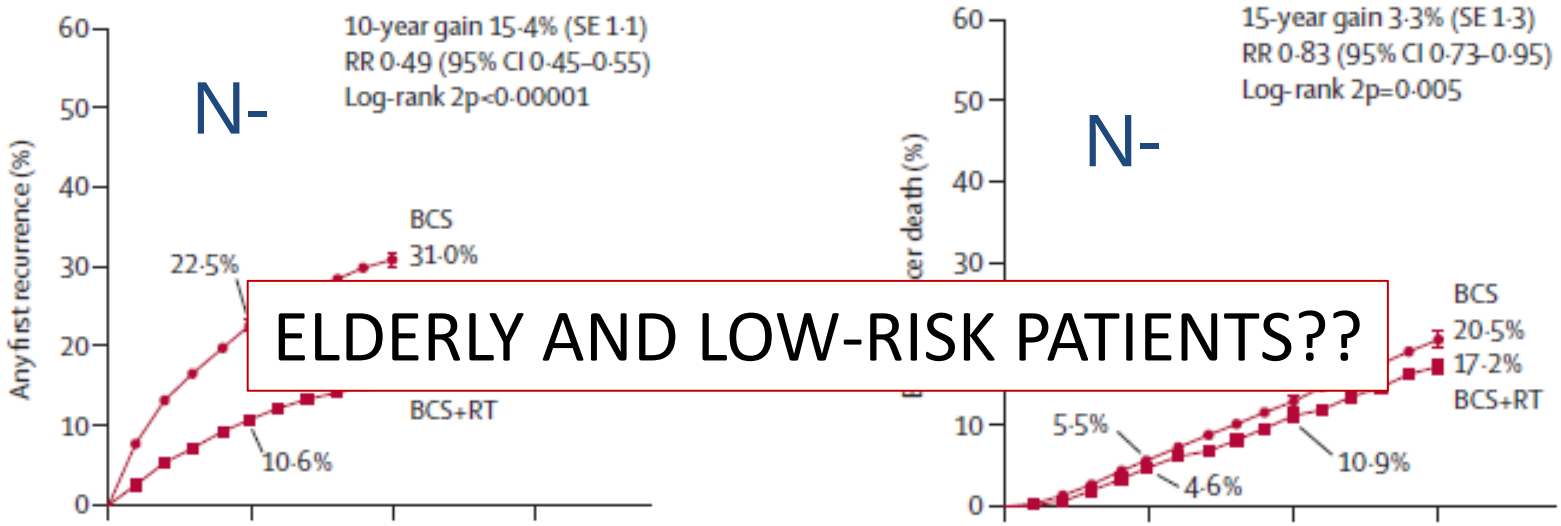


Partial Irradiation
5/10 fractions in 1/2 weeks

"…The 1-week ultra-hypofractionated schedule of 26 Gy, as well as partial breast irradiation, represent excellent treatment options for the majority of low-risk early breast cancer patients. **These options have demonstrated high efficacy while significantly reducing treatment-related burdens, minimizing toxicity, and even lowering costs** when compared to endocrine therapy."

Meattini I al. Radiotherapy and Oncology 2024

Background



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ELDERLY AND LOW-RISK PATIENTS??

RT halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth

Early Breast Cancer Trialists' Collaborative Group, Lancet 2011

Outline

- Literature data
- Current recommendations
- Future perspectives

Literature data

Clinical and Translational Radiation Oncology 21 (2020) 112–119

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Review Article

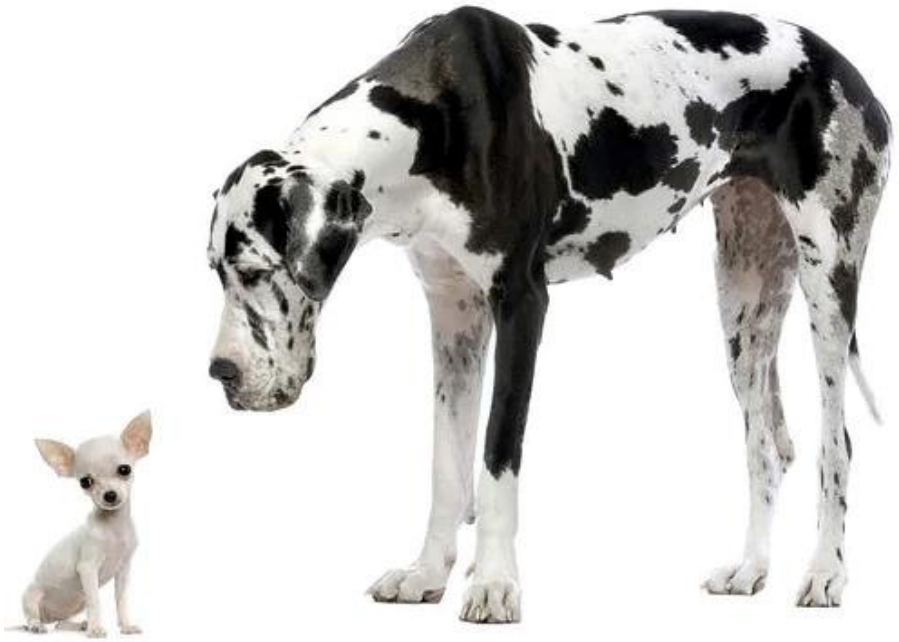
Omission of postoperative radiation after breast conserving surgery: A progressive paradigm shift towards precision medicine

Pierfrancesco Franco [a,b,*], Fiorenza De Rose [c], Maria Carmen De Santis [d], Nadia Pasinetti [e], Valentina Lancellotta [f], Bruno Meduri [g], Icro Meattini [h,i], Clinical Oncology Breast Cancer Group (COBCG) Investigators

First generation trials exploring radiotherapy omission after breast conservation in unselected breast cancer patients.

Author	Years	Pts	Age (yrs)	Surgery	pT stage	pN stage	Size	Adjuv treat	Random	IBTR rate	OS	Median FU (mos)	Factors predicting IBTR
Clark et al *OCOG trial*	1984-1989	837	All	Lump + AD	T1-T2	N0	≤ 4 cm	No	RT vs no RT	11% vs 35%	79% vs 76%	91	Age (< 50 yrs), size (>2cm) poor tumor grade
Veronesi et al *Milan III trial*	1987-1989	567	≤ 70	Quad + AD	T1-T2	N0	< 2.5 cm	Tam or CT	RT vs no RT	5.8% vs 23.5%	82.4% vs 76.9%	120	Age
Liljegren et al *Uppsala-Orebro trial*	1981-1988	381	< 80	Sector res + AD	T1-T2	N0	≤ 2 cm	No	RT vs no RT	8.5% vs 24%	77.5% vs 78%	120	Age (< 60 yrs), comedo or lobular histology
Fisher B et al *NSABP-B21 trial*	1989-1998	1009	All	Lump + AD	T1a-T1b	N0	≤ 1 cm	Tam on radom	RT + Tam vs RT vs Tam	2.8% vs 9.3% vs 16.5%	3% vs 94% vs 93%	96	DCis compontent, poor tumor grade
Forrest et al *Scottish trial*	1985-1991	585	≤ 70	Lump + AD or AS	T1-T2	N0	≤ 4 cm	Tam or CT	RT vs no RT	5.8% vs 24.5%	No diff (HR:0.98)	68	None
Killander et al *SweBCG 91 RT trial*	1991-1997	1187	< 76	Sector res + AD	T1-T2	N0	< 5 cm	Tam or CT	RT vs no RT	11.5% vs 23.9%	71.1% vs 68.4%	180	None
Holli et al *Finnish trial*	1990-1995	152	> 40	Lump + AD	T1	N0	< 2 cm	No	RT vs no RT	7.5% vs 18.1%	97.1% vs 98.6% CSS	80	None

Literature data



Can Less Be More? Evolving Strategies for Therapy De-escalation in Early-Stage Breast Cancer

Corey Speers, MD, PhD,* and Bethany Anderson, MD†

*Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH; and †Department of Radiation Oncology, University of Wisconsin Carbone Cancer Center, Madison, WI

2024

ONCOLOGY SCAN

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RADIATION ONCOLOGY • BIOLOGY • PHYSICS

Literature data

	CALBG 9343 *(JCO 2013)*	**PRIME II** *(N Engl J Med 2023)*	**LUMINA** *(N Engl J Med 2023)*	**IDEA** *(J Clin Oncol 2024)*
N° pts	636	1326	500	200
Age	>/= 70y	>/= 65y	>/= 55y	50-69y (postmenopausal)
Inclusion criteria	pT1-2 (<2 cm) cN0 ER+	pT1-2 (<3 cm) pN0 HR+ LVI or G3 allowed (but not both) >/= 1mm margins	pT1pN0 – non lobular G1-2, ER>1%, PgR>20% Her2-, Ki67</= 13.25%	pT1pN0 ER-PgR+; >/= 2 mm margins Oncotype DX </= 18
Treatment type	RT+HT vs HT	RT+HT vs HT	HT alone (single arm)	HT alone (single arm)
HT adherence (5y)	--	60-70%	82.7%	84.5%
Primary endpoint	Local recurrence	Local recurrence	Local recurrence	Local recurrence
Results	98% vs 90% (**10y free from LLR**)	0.9% vs 9.5% (**10y LR**) ER-low pts: 0% vs 19.1% (10y LR)	2.3% (**5y LR**)	50-59: 5% (**5y LR**) 60-69: 3.6% (**5y LR**)

Literature data

Trial ClinicalTrials.gov Identifier, Trial Status	Design, Target Accrual	Demographics	Pathologic	Hormone Receptors (all require HER2- tumors)	Additional RT Omission Criteria	Primary Outcome	Other
PRECISION[28] NCT02653755, Closed to accrual	Prospective Phase II cohort 345 patients in investigational cohort	Female Age 50-75	Unicentric pT1 pN0-pN0(i+) No tumor on ink Grade 1-2 (cN0 allowed if ≥70)	ER ≥10% or PgR+	Prosigna PAM50 low Risk Of Recurrence score (ie, luminal A subtype)	5-year LRR	Optional survey component on decision comfort/regret
PRIMETIME[29] ISRCTN: 41579286, Open to accrual	Prospective cohort 1550 patients in RT omission cohort	Female Age ≥60	Unifocal pT1 pN0-pN0(i+) Margins ≥1 mm Grade 1-2	ER+ (PgR incorporated into IHC4+C score)	Central Ki-67 staining IHC4+C risk category very low (<5% distant recurrence rate at 10 years)	5-year IBR	Postmenopausal women <60 with comorbidities placing at significant risk of RT toxicity allowed
EXPERT[30] NCT02889874, Open to accrual	Randomized, non-inferiority, Phase III 1170 patients randomized	Female Age ≥50	Unifocal pT1 pN0-pN0(i+) No tumor on ink Grade 1-2	ER ≥10% and PgR ≥10%	Prosigna PAM50 Risk Of Recurrence ≤60 and luminal A subtype	Non-inferiority of RT omission to adjuvant RT, followed up to 10 years	PRO, QALY, fear of recurrence assessment
DEBRA[31] NCT04852887, Open to accrual	Randomized, non-inferiority, Phase III 1670 patients randomized	Female or male Age 50-69	Unicentric pT1 pN0 (i+ not allowed) No tumor on ink No grade requirement	ER ≥1% or PgR ≥1%	Oncotype DX Recurrence Score ≤18	Non-inferiority of RT omission to adjuvant RT, followed up to 10 years	PRO, QoL, distress of recurrence assessment

Allen SG et al. Semin Radiat Oncol 2022

Literature data

European Journal of Surgical Oncology 50 (2024) 108058

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Omission of radiation therapy after breast conserving surgery for older women at low-risk of local recurrence: One option among many

Icro Meattini [a,b,*], Ian H. Kunkler [c]

Radiotherapy and Oncology 190 (2024) 110045

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Perspective

Omission of radiation therapy after breast-conserving surgery for biologically favourable tumours in younger patients: The wrong answer to the right question

"… two research approaches should be favoured:

a) **to assess/validate predictive tests**, not only prognostic, **for response to adjuvant therapies**, including but not exclusive to RT, and
b) **to promote the design of clinical studies** that are not "one-way," involving the optimisation of treatment **through omission or de-escalation testing of all possible therapeutic options**."

Meattini I and Kunkler IH. EJSO 2024
Meattini I et al Radiotherapy and Oncology 2024

Literature data

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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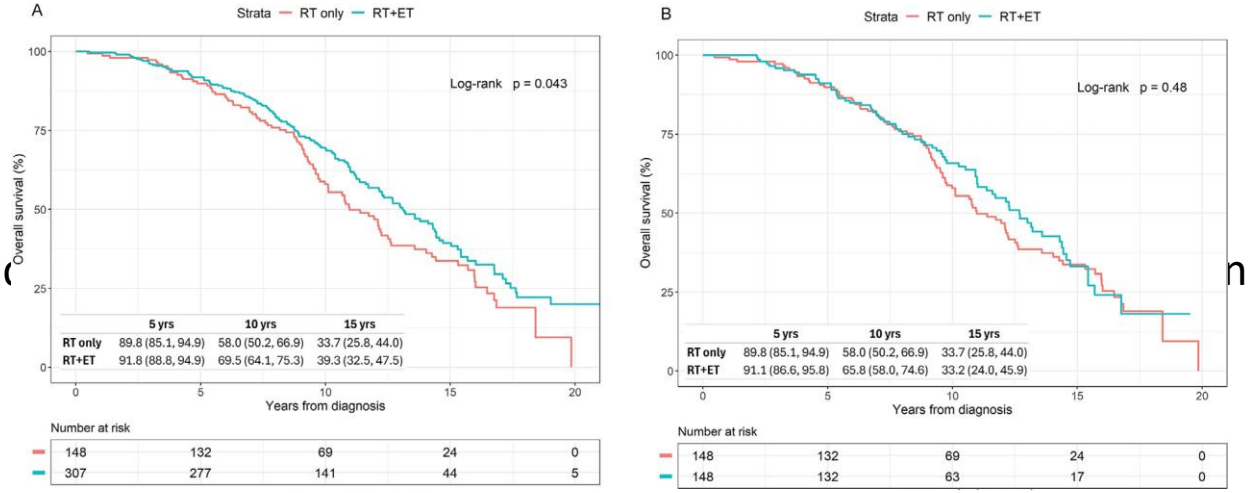
CLINICAL INVESTIGATION

Long-Term Outcomes of Radiation Monotherapy Versus Combined Radiation Monotherapy + Hormone Therapy in Low-Risk Early-Stage Breast Cancer Patients 70 Years or Older After Breast-Conserving Surgery

Patients treated from 2000 to 2015

No d ncers



Morris AD et al. IJRBP 2024

Literature data

Single-modality endocrine therapy versus radiotherapy after breast-conserving surgery in women aged 70 years and older with luminal A-like early breast cancer (EUROPA): a preplanned interim analysis of a phase 3, non-inferiority, randomised trial

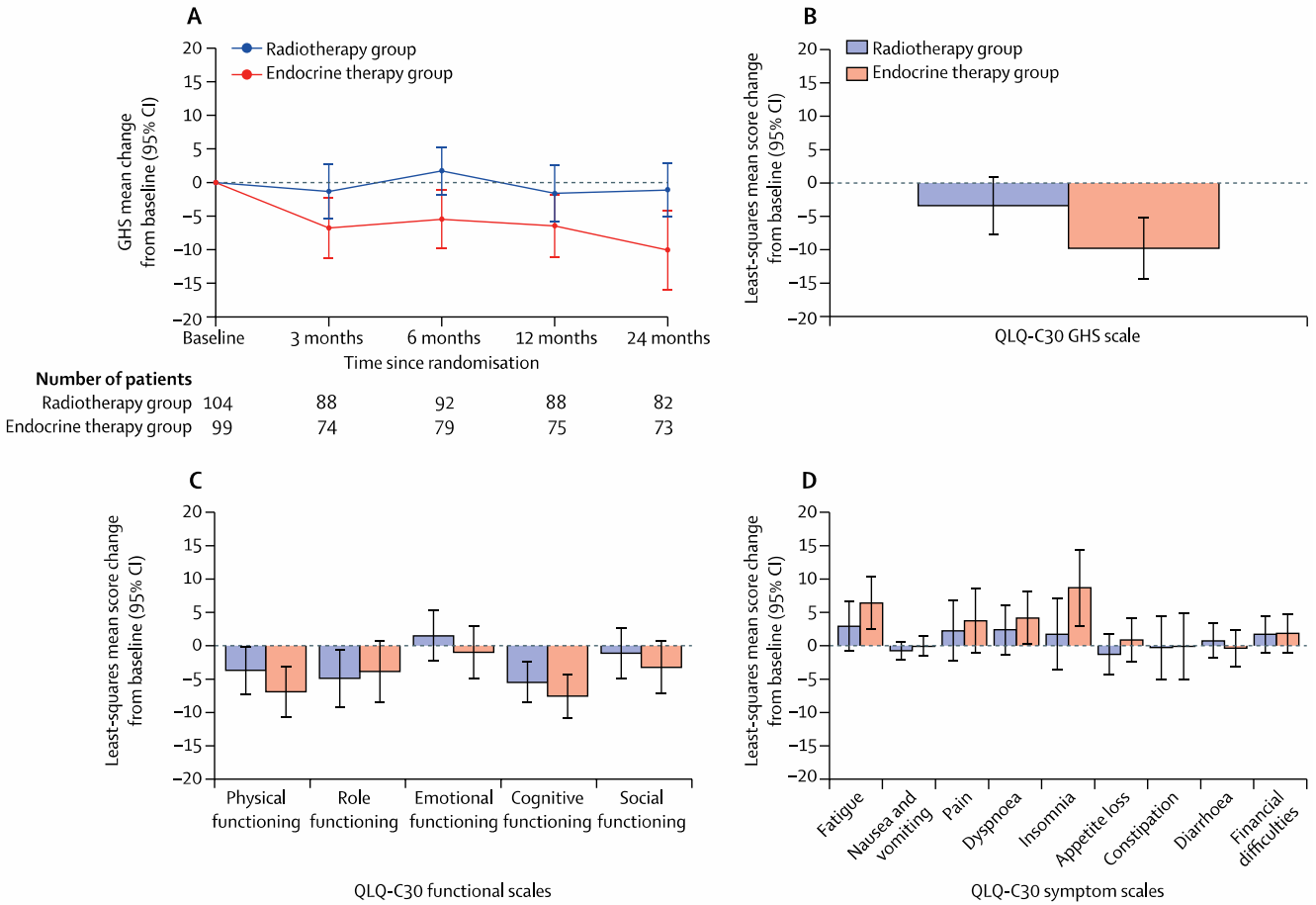
Icro Meattini, Maria Carmen De Santis, Luca Visani, Marta Scorsetti, Alessandra Fozza, Bruno Meduri, Fiorenza De Rose, Elisabetta Bonzano, Agnese Prisco, Valeria Masiello, Eliana La Rocca, Ruggero Spoto, Carlotta Becherini, Gladys Blandino, Luca Moscetti, Riccardo Ray Colciago, Riccardo A Audisio, Etienne Brain, Saverio Caini, Marije Hamaker, Orit Kaidar-Person, Matteo Lambertini, Livia Marrazzo, Calogero Saieva, Tanja Spanic, Vratislav Strnad, Sally Wheelwright, Philip M P Poortmans, Lorenzo Livi*, on behalf of the EUROPA Trial Investigators†*

Non-inferiority, phase 3, randomised study
18 Centres (17 Italy, 1 Slovenia)
Women aged 70 years or older, ECOG 0-1
Stage I, luminal A-like
Randomisation stratified by health status according to the Geriatric 8 (G8) screening tool and by age
Co-primary endpoints: Local recurrence (5-y) and QoL (24 months)

Preplanned interim analysis
207 patients completed the 24-month GHS HRQOL assessment

Meattini I et al. Lancet Oncol 2025

Literature data



«These results suggest that radiotherapy allows better maintenance of GHS compared with endocrine therapy, which was associated with a more pronounced deterioration in HRQOL

…several functional scales, including cognitive function and future perspective, favoured the radiotherapy group for long-term HRQOL compared with endocrine therapy.»

Meattini I et al. Lancet Oncol 2025

Outline

- Literature data
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Current recommendations

Linee guida NEOPLASIE DELLA MAMMELLA Edizione 2021. 2021 AIOM - AIRO

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
ALTA	In pazienti di età ≥ 70 anni, che sono state sottoposte a chirurgia conservativa sulla mammella (BCS) per un carcinoma mammario invasivo a basso rischio e che ricevono endocrinoterapia adiuvante, l'omissione della radioterapia può rappresentare un'alternativa alla radioterapia su tutto il corpo mammario (WBI)[2,4]	**Condizionata a sfavore**
NOTA: La scelta in merito all'omissione della WBI va attentamente discussa con la paziente, in relazione agli obiettivi ed alle aspettative. In particolare, la paziente deve essere informata del possibile maggior rischio di recidive locali (studio PRIME II). Inoltre, la possibilità di "de-escalare" il trattamento radioterapico attraverso la PBI e l'ipofrazionamento appare una possibile alternativa alla omissione della radioterapia (vedi Capitolo "Trattamento del Carcinoma mammario invasivo –Trattamenti locoregionali").		

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

Omission of RT after BCS remains investigational. However, women at advanced age and/or with comorbidities, who intend to take >/=5 years of adjuvant endocrine therapy (ET), may forego RT if they accept an **increased risk for local recurrences** especially at long term as well as the possible side-effects of the ET.

Loibl SI al. Annals of Oncology 2024

Outline

- Literature data
- Current recommendations
- Future perspectives

Future perspectives: preoperative radiotherapy

Escalation and Descalation in breast RT are extensively adapted to clinicopathologic features

- **GARD**: The genomic-adjusted radiation dose - *Lancet Oncol 2015 -2021*
- **ARTIC**: The Adjuvant Radiotherapy Intensification Classifier (27 Genes signature) - *JCO 2019*
- **POLAR**: The Profile for the Omission of Local Adjuvant Radiotherapy (16 Genes signature) - *JCO 2023*

… «the emergence of **molecular signatures** like OncotypeDx, MammaPrint, and Prosigna have been transformative in shaping **personalized treatment recommendations for adjuvant chemotherapy** in early-stage breast cancer based on molecular risk. **Similarly, the development of prognostic and predictive biomarkers for determining the necessity and effectiveness of RT in patients** with breast cancer **is poised to make an equally significant effect**»…

Speers C et al. Semin Radiat Oncol 2022

Conclusions

… «**the ultimate goal of therapy de-escalation is to identify a patient population that is at low risk of disease recurrence in the absence of RT and does not derive additional risk reduction from RT**.

This is particularly true in the modern area, in which **options such as 5-fraction partial and whole breast RT have significantly reduced the toxicity and inconvenience of treatment**»…

Speers C et al. Semin Radiat Oncol 2022

BREAST UNIT TRENTO

GRAZIE PER L'ATTENZIONE