Policy Review

International multidisciplinary consensus on the integration of radiotherapy with new systemic treatments for breast cancer: European Society for Radiotherapy and Oncology (ESTRO)-endorsed recommendations

Integrating Radiotherapy with Novel Systemic Treatments in Breast Cancer – ESTRO Consensus

Background

- Rapid advancements in systemic therapies (e.g., targeted drugs, immunotherapies) are revolutionising breast cancer management
- Combining these therapies with radiotherapy presents challenges in safety, efficacy, and clinical trial design
- ESTRO-endorsed consensus provides multidisciplinary recommendations for optimal integration

Methods

- Objective: Develop consensus statements on combining radiotherapy with novel systemic therapies in curative and metastatic breast cancer settings
- Process:
  - Systematic literature review of preclinical and clinical evidence
  - Modified Delphi process with multidisciplinary experts and patient advocates
  - Consensus achieved through iterative voting on key topics
  - Focus Areas: Radiotherapy parameters, safety profiles, and best practices for drug-radiotherapy combinations

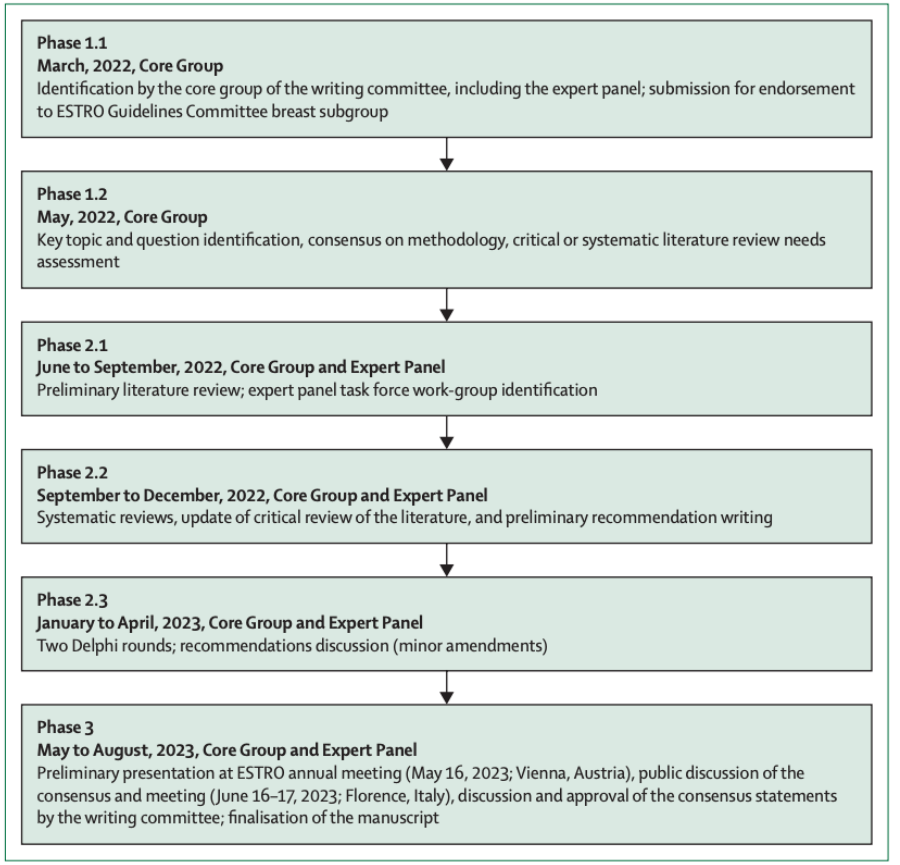

Figure: **Consensus-based guidance workflow based on the modified Delphi process**
The writing committee included Core Group and Expert Panel members. ESTRO=European Society for Radiotherapy and Oncology

Meattini, et al. Lancet Oncol. 2024 Feb;25(2):e73-e83. doi: 10.1016/S1470-2045(23)00534-X

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Findings

Key Recommendations:

- Radiotherapy Reporting:
  - Mandatory to report parameters and toxicity in clinical trials
  - Long-term safety data critical for new drug–radiotherapy combinations
- Targeted Drugs:
  - Safe Combinations: Trastuzumab, pertuzumab, and immunotherapies with radiotherapy
  - Caution Advised: PARP inhibitors, CDK4/6 inhibitors, and antibody-drug conjugates
  - Not Recommended: PI3K and mTOR inhibitors with radiotherapy

Panel 1: **Final consensus statements on key question 1—minimum requirements of reporting radiotherapy parameters in clinical trials assessing new systemic treatments for breast cancer**

1a) Long-term safety data are needed for combining new biological drugs with radiotherapy for patients with early breast cancer [V, A]
- Strong consensus (95%)

1b) When combining new systemic treatments and radiotherapy, reporting of radiotherapy parameters and toxicity is mandatory when reporting safety data in both early and advanced disease settings [V, A]
- Unanimous consensus (100%)

1c) There are few or no high-quality clinical data concerning the combination of radiotherapy and new systemic treatments for breast cancer: prospective research studies are strongly recommended to strengthen the available evidence [V, A]
- Unanimous consensus (100%)

1d) The potential risks, benefits, and uncertainties regarding the combination of radiotherapy and new systemic treatments for breast cancer should be fully discussed with the patient [V, A]
- Unanimous consensus (100%)

Levels of evidence (I–V) and grades of recommendation (A–E) have been applied using the system shown in the appendix (p 10).

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Challenges:

- Heterogeneity in trial designs and radiotherapy dosimetry
- Lack of robust data for many novel therapies

Conclusions

- Establishing rigorous standards for integrating systemic therapies with radiotherapy is essential
- Further research needed to optimise safety and efficacy of combinations
- Patient-centred discussions about risks and benefits are critical for shared decision-making

Panel 2: **Final consensus statements on key question 2—current evidence regarding the safety profile of a specific new systemic treatment when used in combination with ablative or palliative radiotherapy for intracranial or extracranial sites of disease in the metastatic and locoregional settings**

1) CDK4 or CDK6 inhibitors

1a) CDK4 or CDK6 inhibitors and concomitant radiotherapy during adjuvant locoregional radiotherapy for breast cancer should be investigated in the context of clinical trials or prospective registration cohorts [V, A]*
- Unanimous consensus (100%)

1b) CDK4 or CDK6 inhibitors and concomitant radiotherapy during whole-brain radiotherapy or intracranial stereotactic radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [IV, A]
- Strong consensus (92·5%)

1c) CDK4 or CDK6 inhibitors and concomitant radiotherapy could be offered during palliative and ablative extracranial radiotherapy [IV, B]
- Strong consensus (90%)

2) PIK3 inhibitors

2a) PIK3 inhibitors and concomitant radiotherapy should not be offered [V, D]†
- Strong consensus (90%)

3) mTOR inhibitors

3a) mTOR inhibitors and concomitant radiotherapy should not be offered [V, C]†
- Strong consensus (95%)

4) Anti-HER-2 drugs (non-antibody–drug conjugates)

4a) Trastuzumab or pertuzumab and concomitant radiotherapy could be offered during locoregional radiotherapy for breast cancer [I, A]
- Unanimous consensus (100%)

4b) Trastuzumab or pertuzumab and concomitant radiotherapy could be offered during whole brain and ablative intracranial stereotactic radiotherapy [IV, B]
- Strong consensus (97·5%)

4c) Lapatinib and concomitant radiotherapy during locoregional radiotherapy for breast cancer is safe [II, B]‡
- Consensus (85%)

4d) Lapatinib and concomitant radiotherapy could be offered during whole brain and ablative intracranial stereotactic radiotherapy [II, B]
- Consensus (87·5%)

4e) Newer tyrosine kinase inhibitors (ie, neratinib, tucatinib) and concomitant radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [V, C]†
- Strong consensus (97·5%)

5) Antibody–drug conjugates

5a) Trastuzumab emtansine (T-DM1) and concomitant radiotherapy might be considered during adjuvant locoregional radiotherapy for breast cancer [II, B]
- Strong consensus (92·5%)

5b) T-DM1 and concomitant radiotherapy should not be offered for whole-brain and ablative intracranial stereotactic radiotherapy [IV, D]
- Strong consensus (90%)

5c) Newer antibody–drug-conjugates (ie, trastuzumab deruxtecan) and concomitant radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [V, C]†
- Unanimous consensus (100%)

6) PARP inhibitors

6a) PARP inhibitors and concomitant radiotherapy for primary, adjuvant, and metastatic breast cancer settings should be investigated in the context of clinical trials or prospective registration cohorts [II, A]
- Strong consensus (97·5%)

6b) PARP inhibitors and concomitant radiotherapy should not be offered for advanced breast cancer outside clinical trials [II, D]§
- Consensus (80%)

7) Immunotherapy

7a) Immunotherapy and concomitant radiotherapy could be considered during locoregional radiotherapy for breast cancer [II, B]
- Strong consensus (95%)

7b) Immunotherapy and concomitant radiotherapy including ultra hypofractionated regimens used for stereotactic radiotherapy could be offered for advanced breast cancer [II, B]¶
- Strong consensus (92·5%)

Levels of evidence (I–V) and grades of recommendation (A–E) have been applied using the system shown in the appendix (p 10). *No safety report for concomitant CDK4 or CDK6 inhibitors with postoperative locoregional radiotherapy for breast cancer; data derived from metastatic setting. †Currently, there is no clear evidence on the safety of combined treatment with these inhibitors in both metastatic and non-metastatic settings. ‡Lapatinib is not approved in the early breast cancer setting. §Safety data for PARP inhibitors and concomitant radiotherapy are scarce; few data are available in the metastatic setting. ¶Data derived from other solid organ tumours.

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The *Lancet* Breast Cancer Commission

Charlotte E Coles, Helena Earl, Benjamin O Anderson, Carlos H Barrios, Maya Bienz, Judith M Bliss, David A Cameron, Fatima Cardoso, Wanda Cui, Prudence A Francis, Reshma Jagsi, Felicia Marie Knaul, Stuart A McIntosh, Kelly-Anne Phillips, Lukas Radbruch, Mareike K Thompson, Fabrice André, Jean E Abraham, Indrani S Bhattacharya, Maria Alice Franzoi, Lynsey Drewett, Alexander Fulton, Farasat Kazmi, Dharmesha Inbah Rajah, Miriam Mutebi, Dianna Ng, Szeyi Ng, Olufunmilayo I Olopade, William E Rosa, Jeffrey Rubasingham, Dingle Spence, Hilary Stobart, Valentina Vargas Enciso, Ines Vaz-Luis, Cynthia Villarreal-Garza on behalf of the Lancet Breast Cancer Commission*

The Lancet Breast Cancer Commission Addressing Global Inequities

Background

- Breast cancer is the most prevalent cancer worldwide, with over 2.3 million new diagnoses and 685,000 deaths in 2020
- Significant global disparities in prevention, detection, treatment, and survival exist, especially in low- and middle-income countries (LMICs)
- The Lancet Breast Cancer Commission identifies gaps and provides a roadmap to improve equity and outcomes

	Definition	Rationale	Data sources	Responsible entity	Target
Data collection	Improvements in cancer registry data collection: stage at diagnosis, including de novo metastatic disease and breast cancer relapse data	Knowing the number of people living with metastatic breast cancer would allow a better allocation of resources	Cancer registries	Ministry of Health	Minimum of 70% of global cancer registries registering people with metastatic breast cancer, aiming at 100%.
Multidisciplinary meeting review	Patients with metastatic breast cancer discussed at a multidisciplinary meeting	Improve outcomes: survival and quality of life	Facility records; national and international certification procedures for breast units	Ministry of Health	Minimum of 50%, aiming at 95% of patients with metastatic breast cancer discussed at multidisciplinary meetings
Metastatic breast cancer outcomes	Improvements in median overall survival	Improve outcomes	Cancer registries; facility records; national and international certification procedures for breast units	Facility; Ministry of Health	Record the number of people with metastatic breast cancer and double the median overall survival in a decade
End-of-life care	Number of patients with breast cancer dying in pain: morphine use as an indicator of suffering.	Improved quality of life and reduced suffering	Pharmacy registries	Ministry of Health	Aiming for less than 5% of patients at end of life without access to morphine
Essential medicines for metastatic breast cancer are affordable globally	Updates and uptake in WHO essential medicines to promote equal access	Improve outcomes	WHO essential medicines list updates; national regulators data	Ministry of Health	All patients with metastatic breast cancer have access to life-saving cancer medicines

Table 3: **Optimal inclusive management of metastatic breast cancer proposed measurable indicators of change**

Coles CE, et al. Lancet. 2024 May 11;403(10439):1895-1950. doi: 10.1016/S0140-6736(24)00747-5

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The Lancet Breast Cancer Commission Addressing Global Inequities

Key Findings

Global Inequities in Care:

- Many patients with metastatic breast cancer lack access to proper care
- Inequities persist across socioeconomic, racial, and geographical lines

Hidden Costs of Breast Cancer:

- Breast cancer imposes substantial financial, psychological, and social burdens on patients, families, and communities
- Exposing these hidden costs provides incentives for policy changes and investment in prevention and early detection

Prevention Potential:

- Up to 25% of breast cancers in high-income countries could be prevented by addressing modifiable risk factors (e.g., obesity, alcohol, physical inactivity)
- Early detection initiatives in LMICs can significantly reduce late-stage diagnoses

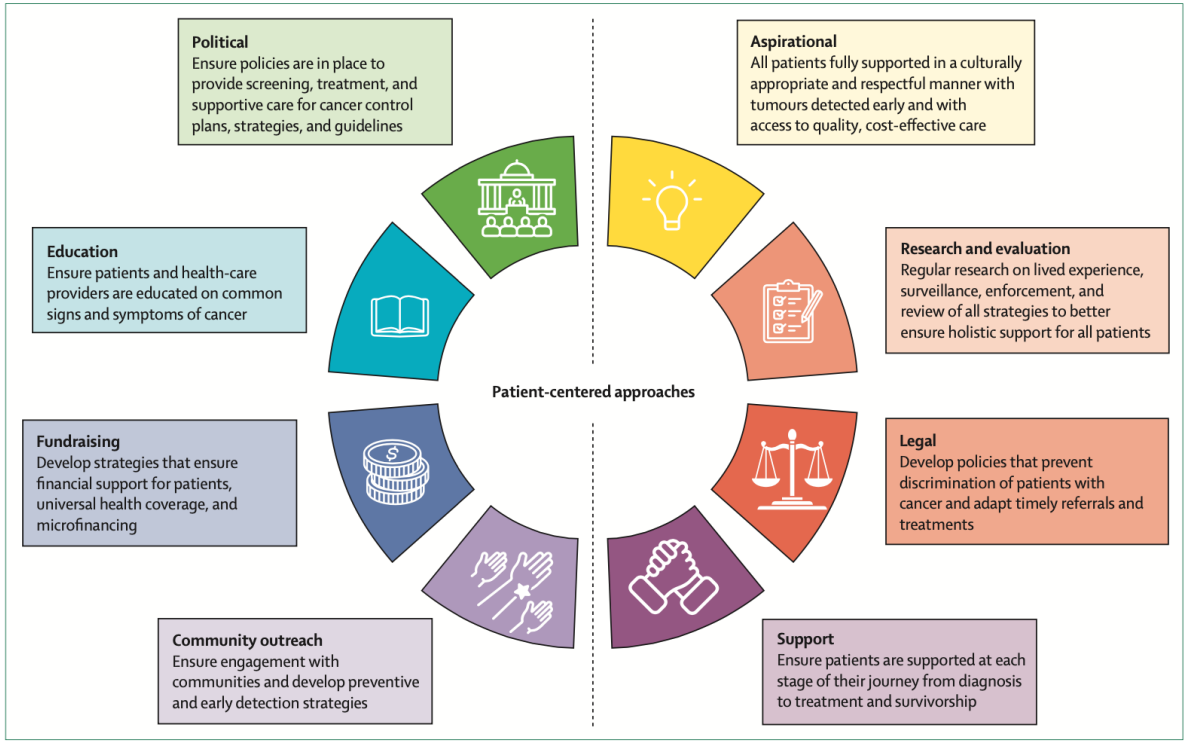

Figure 6: **Aspirational advocacy framework**
Eight patient-centred approaches in different areas that intersect to form the aspirational advocacy framework.

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The Lancet Breast Cancer Commission
Addressing Global Inequities

Roadmap for Change

Prevent: Develop global policies to reduce risk factor exposure and promote personalised prevention programmes

Personalise: Enable equitable access to appropriate treatments based on individual needs and biomarkers

Include: Integrate metastatic breast cancer patients into clinical research and optimal care frameworks

Collaborate: Strengthen international partnerships for equitable early detection, treatment, and innovative technologies

Identify Costs: Recognise and mitigate the economic and social costs of breast cancer on patients and families

Empower: Improve patient-centred communication to enhance autonomy, adherence, and outcomes

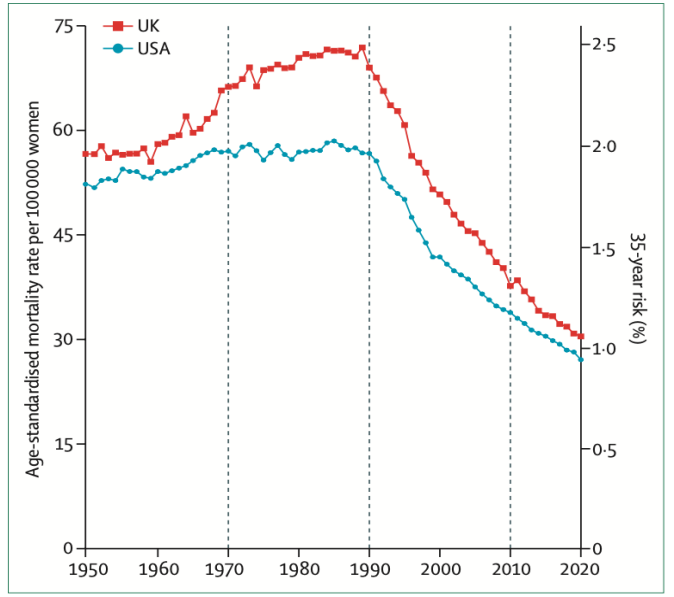

Figure 4: **Fall in breast cancer mortality rates in the UK and USA in people aged 35–69 years (1950–2020)**
The age-standardised mortality rate is a mean of annual rates in the seven component 5-year age groups (ages 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, and 65–69 years). At a death rate of 30 per 100 000 women, there was a large effect on UK and USA breast cancer mortality due to the combination of several moderate effects. At a mortality rate of 15 per 100 000 women, further moderate effects are still necessary and achievable. Data is from the WHO Mortality Database and UN World Population Prospects 2022 revision. Graph reproduced with permission from the Early Breast Cancer Trialists' Collaborative Group.

Coles CE, et al. Lancet. 2024 May 11;403(10439):1895-1950. doi: 10.1016/S0140-6736(24)00747-5

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Essential Requirements for Radiotherapy in Breast Cancer Trials – ESTRO Consensus

Background

- Radiotherapy (RT) is critical in breast cancer management, but variability in trial reporting creates inconsistencies in outcomes
- ESTRO-endorsed consensus defines essential and optimal requirements for RT reporting in clinical trials
- Goal: Enhance precision, quality assurance, and integration of RT with systemic therapies

Methods

Approach:

- Multidisciplinary expert panel using a modified Delphi process
- Focused on trials combining RT with systemic therapies in metastatic and non-metastatic breast cancer

Key Areas:

- Quality Assurance in Radiotherapy (QART)
- Reporting guidelines for RT parameters, toxicity, and treatment delivery

Table 1
Impact of QART protocol on trial outcomes in selected locoregional trials.

Trial	Trial's question	RT details	Impact
RT/QART protocol unspecified			
ACOSOG Z0011 [41,42]	cT1-2 N0, 1–2 positive nodes, SLNB or ALND	RT was defined in the trial protocol. Noncompliance with trial recommendation: 51 % "high tangents", 19 % third regional nodal irradiation field.	The impact of RT on disease outcomes is unknown.
Sinodar One [43]	cT1-2 N0, 1–2 positive nodes, SLNB or ALND	RT was not defined and not reported.	The impact of RT on disease outcomes is unknown.
Sound trial [44]	cT1N0 Omission of SLNB	RT was not defined and not reported.	The impact of RT on disease outcomes is unknown. Early publication by the trial PI suggest that incidental dose of the tangential fields are important regional control
NSABP B-40 **NSABP B-41** [30]	Stage T1c-3, and cN0, cN1, or cN2a. Sequencing of different systemic therapies and its effect on pCR	No RT protocol and quality assurance Regional node RT allowed at physician's discretion	The true impact of RT on disease outcomes is unknown. Disparity of care of Hispanic population was suggested.
RT protocol package and centralised QART			
EORTC 22922/ 10925 [8,45,46]	Stage I-III, the role of IMN-MS irradiation	RT protocol was only for IMN-MS RT, variation in RT to primary, including boost, chest wall, breast. RT was subjected to central quality assurance.	Central quality assurance for data collection and RT allowed for subsequent unplanned analysis. Unplanned analyses and limited event rates restrict in providing firm recommendations.
FAST-Forward [17]	pT1–3, pN0 [a] Two 5 fractions regimens were compared to standard of care	RT protocol and additional RT planning pack was predefined. RT was subjected to central quality assurance. Tumour bed boost was at the discretion of the treating physician, two dose/fractionation schemes were allowed.	Trial tested whole breast RT effectiveness.

Abbreviations. QART, quality assurance in radiotherapy; pCR, pathological complete response; RT, radiation therapy; IMN-MS, internal mammary nodes and medial supraclavicular nodes; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.
[a] pN1 was allowed in FAST-Forward nodal trial.

Kaidar-Person O, et al. Radiother Oncol. 2024 Jun;195:110060. doi: 10.1016/j.radonc.2023.110060

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Findings

Essential Requirements:

- Define RT indications, dose/fractionation, and planning objectives
- Standardise reporting templates for RT protocols in clinical trials
- Collect and report RT data even when RT is not the trial's primary focus

Optimal Requirements:

- Use predefined RT planning packs for target volume delineation, dosimetry, and quality control
- Employ centralised QART protocols, including audits and dummy runs

Table 2
Minimal RT details requirements for a trial case report form (CRF) for locoregional RT (adapted from [24]).

Locoregional RT		
Date of RT start	DD/MM/YYY	
Date of last RT fraction	DD/MM/YYY	
Laterality breast/chest wall RT treated		
Left	No	Yes
Right	No	Yes
Bilateral	No	Yes
Breast Reconstruction present prior to RT		
Was breast reconstruction present prior to RT?	No	Yes
if Yes, implant-based reconstruction	No	Yes
if Yes, autologous tissue reconstruction	No	Yes
if Yes, tissue expander	No	Yes
Prescribed Dose and Fractionation		
Target volume	Total prescribed dose (Gy)	Number of fractions
Breast/chest wall		
Tumour bed boost/partial breast		
Axilla level 1		
Axilla level 2		
Axilla interpectoral nodes (Rotter)		
Axilla level 3		
Axilla level 4		
Internal mammary nodes (parasternal)		
Use of bolus		
Did you use the bolus?	No	Yes
if Yes, daily	No	Yes
if Yes, alternating days	No	Yes
if Yes, until skin reaction (specify number of fractions with bolus)	No	Yes
if Yes, specify bolus thickness (mm)	No	Yes
RT course completion		
Did the patient complete RT course?	No	Yes
if no, total dose received (Gy)		
if no, specify the reason (comment):		
RT given during systemic therapy [a,b]		
Was RT given during systemic therapy?	No	Yes
if Yes, CDK4/6 inhibitors (specify)	No	Yes
if Yes, trastuzumab	No	Yes
if Yes, pertuzumab	No	Yes
if Yes, PARP inhibitors	No	Yes
if Yes, ADC TDM1	No	Yes
if Yes, other ADC (specify)	No	Yes
if Yes, capecitabine	No	Yes
if Yes, immunotherapy (specify)	No	Yes
if Yes, other (specify)	No	Yes
Timing [b]		
Systemic treatment interrupted ≤ 1 week before RT	No	Yes
Systemic treatment (re)started ≤ 1 week after last RT fraction	No	Yes
Systemic therapy interrupted 5-half lives of the drug before RT	No	Yes
Systemic therapy continued during RT	No	Yes
Toxicity		
Did any adverse events occur after the last visit	No	Yes
If yes, was the adverse event assumed to be associated with RT?	No	Yes
If yes, date of adverse event started	DD/MM/YYY	
Did the adverse event resolved?	No	Yes
If yes, date of adverse event resolved	DD/MM/YYYY	
If yes, specify type of adverse event (e.g., dermatitis, pneumonitis)		
Maximal grade of toxicity CTCAE v.05		
Has the patients had any other RT related conditions events since the last visit?	No	Yes Not assessed
if Yes, please complete the following section *		
* CTCAE v.5.0 grade		
Describe	0 1 2 3 4 5	Present, not graded
Other, specify		
Other, specify		
Other, specify		

Kaidar-Person O, et al. Radiother Oncol. 2024 Jun;195:110060. doi: 10.1016/j.radonc.2023.110060

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Challenges:

- Variability in RT techniques and adherence across centres
- Lack of robust data on RT-systemic therapy combinations

Conclusions

- Implementation of essential RT reporting standards will improve trial quality and data reliability
- Recommendations support precision RT in breast cancer trials, fostering better integration with systemic therapies
- Standardisation enhances reproducibility and informs future clinical practice

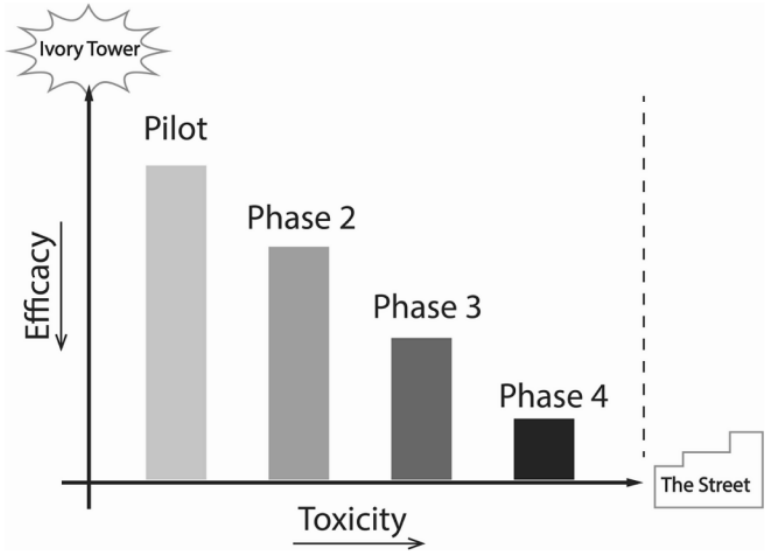


Fig. 1. This illustration depicts that early-phase trials are often not directly applicable to the general population. As a result, in routine clinical practice, efficacy may be compromised while toxicity increases. An example of this scenario is trials designed to assess a new systemic therapy for breast cancer, excluding RT in the trial design. In daily clinical practice, RT may need to be administered concurrently, but the lack of reporting on RT in the trial design can create challenges (Original illustration by Professor David Brizel, Duke, North Carolina, USA, 2016).

Kaidar-Person O, et al. Radiother Oncol. 2024 Jun;195:110060. doi: 10.1016/j.radonc.2023.110060

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

Interim Results of the EUROPA Trial Comparing Single-Modality Radiotherapy and Endocrine Therapy in Older Breast Cancer Patients

Background

- Postoperative treatment in older women with low-risk, luminal A-like breast cancer is debated
- Dual therapy (radiotherapy and endocrine therapy) may not always be necessary
- EUROPA trial compares radiotherapy (RT) and endocrine therapy (ET) as single-modality treatments focusing on HRQOL and ipsilateral breast tumour recurrence (IBTR)

Methods

Trial Design: Phase 3, non-inferiority, randomised controlled trial across 18 academic centres (Italy, Slovenia)

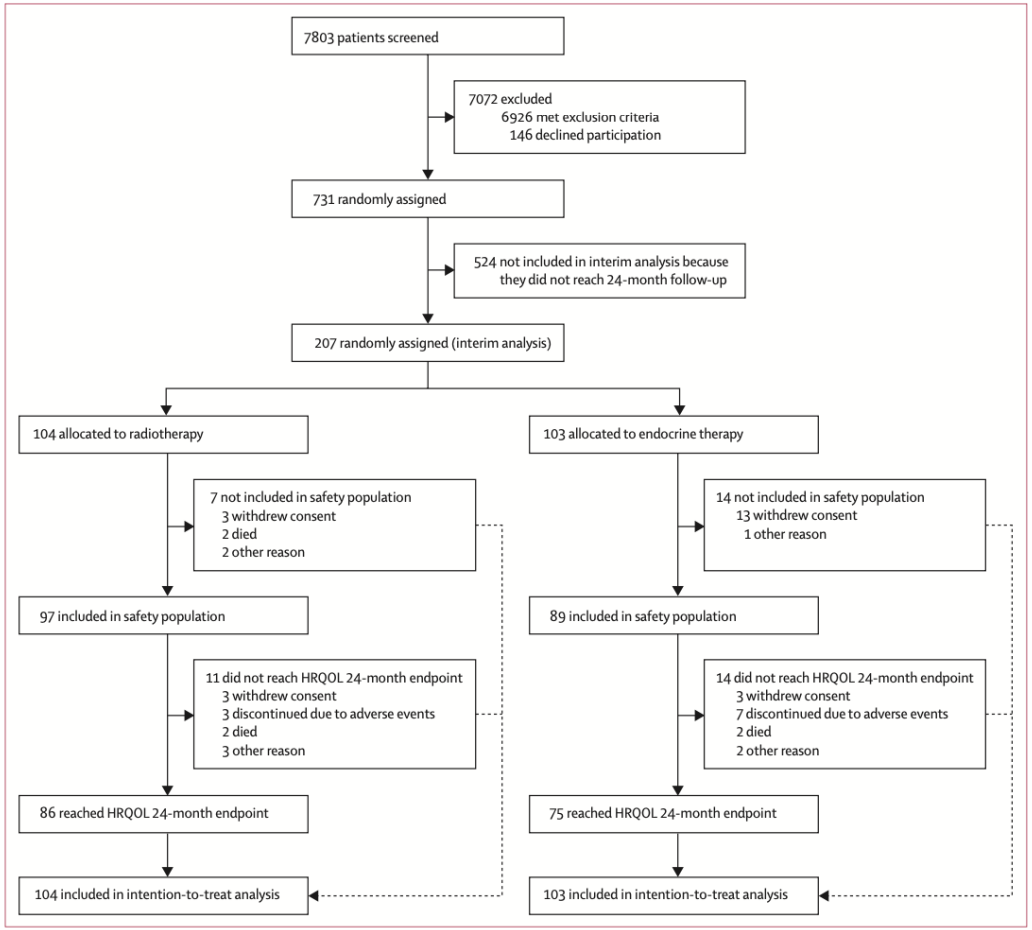
Population: 731 women aged ≥70 years with stage I, luminal A-like breast cancer after breast-conserving surgery

Intervention Groups:

- Radiotherapy (whole or partial breast irradiation)
- Endocrine therapy (aromatase inhibitors or tamoxifen for 5–10 years)

Primary Endpoints:

- Health-related quality of life (HRQOL, measured by global health status) at 24 months
- 5-year IBTR rates (not yet reported)



Meattini I, et al. Lancet Oncol. 2024 Dec 11:S1470-2045(24)00661-2. doi: 10.1016/S1470-2045(24)00661-2

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Interim Results of the EUROPA Trial Comparing Single-Modality Radiotherapy and Endocrine Therapy in Older Breast Cancer Patients

Findings (Interim Analysis)

HRQOL (GHS Scores at 24 Months):

- RT Group: Mean change –3.40 (95% CI –7.82 to 1.03; p=0.13)
- ET Group: Mean change –9.79 (95% CI –14.45 to –5.13; p<0.0001)
- Adjusted mean difference: 6.39 (95% CI 0.14 to 12.65; p=0.045), favouring RT

Adverse Events:

- RT group had fewer treatment-related adverse events (67% vs. 85%)
- Severe adverse events (e.g., arthralgia, fractures) were more common in the ET group

Clinical Outcomes (24 Months):

- No IBTR, locoregional recurrence, or distant metastases observed
- Non–breast cancer-related deaths: RT group (4%), ET group (2%)

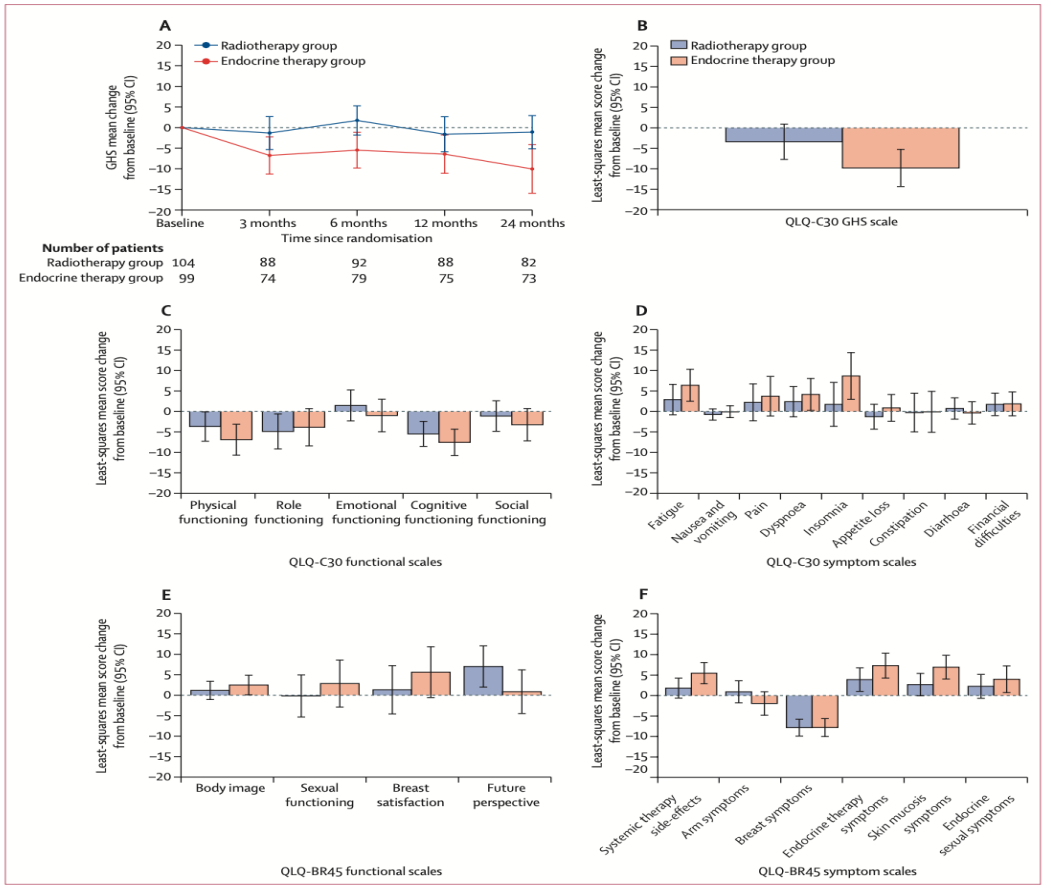

Figure 2: **Mean change from baseline to 24 months in patient-reported outcome scores for radiotherapy and endocrine therapy groups**
Empirical (A) and least-squares (B) mean change from baseline in GHS score of the QLQ-C30 questionnaire. Least-squares mean change from baseline in functional (C) and symptom (D) scales of the QLQ-C30 questionnaire, and functional (E) and symptom (F) scales of the QLQ-BR45 questionnaire. For functional scales, a change of less than 0 indicates worse scores over time, while for symptom scales, a change greater than 0 indicates worse scores over time. GHS=global health status. QLQ-C30=Quality of Life Questionnaire 30-item core module. QLQ-BR45=Quality of Life Questionnaire 45-item breast module.

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Conclusions

RT preserved HRQOL better than ET over 24 months

RT had a more favourable safety profile with fewer severe adverse events

Further data on disease control and survival are needed to confirm these findings

	Radiotherapy group	Endocrine therapy group	Difference, percentage points (95% CI)
Adverse events			
Number of patients in safety population	97	89	..
At least one pre-randomisation adverse event	2 (2%)	1 (1%)	0·9 (–4·2 to 6·2)
At least one TEAE	89 (92%)	86 (97%)	–4·9 (–12·6 to 2·3)
At least one treatment-related TEAE	65 (67%)	76 (85%)	–18·4 (–30·2 to –6·2)
At least one serious TEAE	15 (15%)	13 (15%)	0·9 (–9·8 to 11·3)
At least one serious treatment-related TEAE	0	1 (1%)	–1·1 (–6·1 to 2·7)
Fatal TEAE	2 (2%)	2 (2%)	–0·2 (–6·0 to 5·3)
Fatal treatment-related TEAE	0	0	
Clinical events			
Number of patients in intention-to-treat population	104	103	..
Ipsilateral breast tumour recurrence	0	0	..
Locoregional recurrence	0	0	..
Contralateral breast cancer	2 (2%)	1 (1%)	..
Distant metastases	0	0	..
Death	4 (4%)	2 (2%)	..
Breast cancer-related death	0	0	..

Data are n or n (%) unless otherwise indicated. Among fatal TEAEs, causes in the radiotherapy group included oesophageal neoplasia and *Listeria* meningitis, while in the endocrine therapy group, causes were pneumonia and ischaemic heart disease. Pre-randomisation adverse events refer to those that began before the date of randomisation. Percentages are calculated relative to the total number of patients in the safety population in each treatment group. Only adverse events occurring on or before 24 months from randomisation are included in this analysis. All clinical events occurring in the first 24 months after randomisation are included in this analysis. Percentages are calculated relative to the total number of patients in the intention-to-treat population in each treatment group. TEAE=treatment-emergent adverse event.

Table 3: **Summary of adverse events (safety population) and time-dependent clinical events (intention-to-treat population) during the first 24 months of the study**

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