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

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Summary

Background Optimal therapy following breast-conserving surgery in older adults with low-risk, early-stage breast cancer remains uncertain. The EUROPA trial aims to compare the effects of radiotherapy and endocrine therapy as single-modality treatments on health-related quality of life (HRQOL) and ipsilateral breast tumour recurrence (IBTR) outcomes in this population.

Methods This non-inferiority, phase 3, randomised study was conducted at 18 academic hospitals across Italy (17 centres) and Slovenia (one centre). Eligible patients were women aged 70 years or older with histologically confirmed, stage I, luminal A-like breast cancer, who had undergone breast-conserving surgery and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1) to receive single-modality endocrine therapy or radiotherapy. Endocrine therapy consisted of daily oral aromatase inhibitors or tamoxifen, for a total planned duration of 5–10 years as per clinical discretion, while radiotherapy was administered as either whole breast or partial breast irradiation, delivered in 5–15 fractions. Randomisation was stratified by health status according to the Geriatric 8 (G8) screening tool and by age, with allocation concealed and no blinding. The co-primary endpoints were the change in HRQOL, assessed by the global health status (GHS) scale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item core module at 24 months, and 5-year IBTR rates (not reported here). This preplanned interim analysis was performed once at least 152 patients completed the 24-month GHS HRQOL assessment. The safety population comprised patients who received the study intervention at least once after randomisation. The study is registered with ClinicalTrials.gov, NCT04134598, and is ongoing and actively recruiting.

Findings Between March 4, 2021, and June 14, 2024, 731 women were randomly assigned to receive radiotherapy (n=365) or endocrine therapy (n=366). This analysis included 104 patients in the radiotherapy group and 103 in the endocrine therapy group, with a median follow-up of 23·9 months (IQR 22·9–24·2). Patients were predominantly White (204 [99%] of 207) and the median age was 75·0 years (IQR 73·0–80·0) in the radiotherapy group and 74·0 years (72·0–80·0) in the endocrine therapy group. 86 patients in the radiotherapy group and 75 in the endocrine therapy group completed the 24-month HRQOL assessment. The mean baseline GHS score was 71·9 (SD 19·1) in the radiotherapy group and 75·5 (19·3) in the endocrine therapy group. At 24 months, the age-adjusted, G8 score-adjusted mean change from baseline in GHS was –3·40 (95% CI –7·82 to 1·03; p=0·13) in the radiotherapy group and –9·79 (–14·45 to –5·13; p<0·0001) in the endocrine therapy group, with an adjusted mean difference of 6·39 (0·14 to 12·65; p=0·045) favouring radiotherapy. Treatment-related adverse events were less frequent in the radiotherapy group (65 [67%] of 97 patients) compared with the endocrine therapy group (76 [85%] of 89). The most common grade 3–4 adverse events were arthralgia (six [7%] of 89 in the endocrine therapy group *vs* 0 of 97 in the radiotherapy group), pelvic organ prolapse (three [3%] *vs* 0), fatigue, hot flashes, myalgia, bone pain, and fractures (two [2%] *vs* 0 for each). Serious adverse events were reported in 15 (15%) patients in the radiotherapy group and 13 (15%) in the endocrine therapy group. There were no treatment-related deaths in either group.

Interpretation Endocrine therapy was associated with a greater reduction in HRQOL, as measured by GHS, compared with radiotherapy at 24 months. While these interim results suggest radiotherapy might better preserve HRQOL in older women with low-risk early breast cancer, further data on disease control outcomes and final patient accrual are needed to draw definitive conclusions.

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Introduction

Breast-conserving surgery followed by postoperative radiotherapy provides survival outcomes comparable to mastectomy, with less impact on body image and health-related quality of life (HRQOL).[1–3] Phase 3 trials have shown that hypofractionated whole breast irradiation (WBI), delivered in 5–15 fractions over 1–3 weeks, effectively shortens treatment time with a favourable safety profile.[4–6] ESTRO-ACROP guidelines (2022) recommend moderately hypofractionated WBI as the standard, with ultra-hypofractionated WBI suggested for select cases or within trials.[7] For suitable patients with early-stage breast cancer,[7,8] partial breast irradiation (PBI) offers similar local recurrence rates with improved safety and HRQOL benefits.[9–15]

Use of postoperative radiotherapy in older adults with low-risk breast cancer is debated due to potential side-effects and the inconvenience of extended schedules.[16] Data from the PRIME II trial, which included women aged 65 years and older with hormone receptor-positive, low-risk breast cancer, suggest that omitting radiotherapy in older women receiving endocrine therapy does not impact overall survival for up to 10 years, although it did result in a significantly higher local recurrence rate.[16] Similarly, the BASO II trial found that combined radiotherapy and endocrine therapy lowers local recurrence to a greater extent than either treatment alone in early breast cancer, although the modest benefit questions the necessity of dual therapy in all low-risk patients, supporting single-modality approaches for selected patients.[17] These studies provide a basis for examining the distinct effects of radiotherapy and endocrine therapy on disease control and HRQOL, as explored in the EUROPA trial. Although endocrine therapy significantly improves breast cancer outcomes,[18,19] its short-term and long-term side-effects can challenge long-term adherence to therapy.[20–22] Older patients with early breast cancer need both local and systemic treatments optimised to preserve HRQOL, considering their unique characteristics and comorbidities. HRQOL is a crucial aspect in treatment decisions for older adults, and might be as relevant as survival metrics,[23,24] but this population is often under-represented in trials.[25]

The aim of this study was to compare the impact of radiotherapy and endocrine therapy as single-modality treatments on HRQOL and ipsilateral breast tumour recurrence (IBTR) rates in women aged 70 years and older with stage I, luminal A-like breast cancer. Here, we present the results from a preplanned interim analysis after at least 152 patients completed the 24-month HRQOL assessment.

Methods

Study design and participants

This phase 3, non-inferiority, randomised controlled trial compares single-modality radiotherapy or endocrine

Research in context

Evidence before this study

We conducted a comprehensive search of PubMed up to June 14, 2024 to identify studies comparing radiotherapy and endocrine therapy in older adults with low-risk, early-stage breast cancer. Search terms included "radiation therapy", "endocrine therapy", "older adults", "breast cancer", "quality of life", and "adverse events", with a focus on randomised controlled trials and observational studies in English. Studies were included if they evaluated radiotherapy or endocrine therapy as single-modality treatments or in combination in women aged 65 years or older with hormone receptor-positive breast cancer. The PRIME II trial provided key evidence that omitting radiotherapy in older women on endocrine therapy did not affect overall survival, although it raised local recurrence risk. Other studies have highlighted long-term adverse effects and health-related quality of life (HRQOL) impact of endocrine therapy, alongside adherence challenges. However, data directly comparing HRQOL outcomes between radiotherapy and endocrine therapy in older patients with breast cancer remain scarce.

Added value of this study

The EUROPA trial is, to our knowledge, the first phase 3 randomised controlled trial to directly compare single-modality radiotherapy and endocrine therapy in women aged 70 years or older with luminal A-like, early-stage breast cancer. Results from this preplanned interim analysis suggest that endocrine therapy has a more pronounced negative effect on HRQOL (measured by global health status) at 2 years compared with radiotherapy. These findings highlight the need to weigh potential HRQOL impacts of endocrine therapy, especially in older patients, in whom quality of life is a priority.

Implications of all the available evidence

The interim findings support single-modality radiotherapy as a well tolerated treatment option in older adults, showing better HRQOL outcomes and fewer treatment-related adverse events than endocrine therapy. Final results from the EUROPA trial, including long-term recurrence and survival data, will further clarify the roles of radiotherapy and endocrine therapy in this population.

therapy following breast-conserving surgery in older patients with low-risk early-stage breast cancer. The trial was conducted at 18 academic hospitals across Italy (17 centres) and Slovenia (one centre; appendix p 60). Eligible participants were women aged 70 years or older with histologically confirmed, stage I luminal A-like breast cancer, who had undergone breast-conserving surgery and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were included on the basis of local pathology results of the breast-conserving surgery resection specimen with or without sentinel node biopsy, following these inclusion criteria: pathological T1 (pT1) stage; postoperative negative (no ink) final surgical margins; clinical and pathological N0 stage (isolated tumour cells allowed); any tumour grade if pT 10 mm or less, or grade 1–2 tumour if pT 11–19 mm; and luminal A-like biology (defined as oestrogen receptor and progesterone receptor positive [≥10%], HER2 negative [score 0 or 1+ and proven negative by in-situ hybridisation if score 2+], and Ki67 ≤20% by immunohistochemistry staining). Exclusion criteria were evidence of distant metastases or local recurrence at baseline; preoperative systemic treatments (ie, chemotherapy or endocrine therapy); adjuvant chemotherapy; current treatment with any hormonal agents (ie, tamoxifen, raloxifene, or other selective oestrogen receptor modulators); disorders associated with a higher risk for complications following radiotherapy (ie, collagen vascular disease, systemic lupus erythematosus, or scleroderma); any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up; any serious uncontrolled medical disorder; non-malignant systemic disease or active uncontrolled infection; any other cancers in the last 5 years, unless in clinical remission at the time of randomisation; and synchronous diagnosis of bilateral breast cancer. These criteria allow for clinical discretion, with specific exclusions aimed at ensuring patients' adherence to the protocol and follow-up (eg, patients in remote locations preferring local follow-up, anticipated low compliance due to socioeconomic or cognitive factors, and linguistic or cultural barriers affecting questionnaire completion).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written, informed consent was obtained from all participants before enrolment. A patient advocate (TS) was involved in the study conception to ensure prioritisation of patient-centred outcomes. The study was approved by the Italian Multi-Research Ethics Committee (AIFA/SC/P/100517) and local research and development offices. The protocol is available in the appendix. This study is registered with ClinicalTrials.gov, NCT04134598, and EudraCT, 2020-000428-21.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to either single-modality endocrine therapy (control) or radiotherapy (experimental). Randomisation was performed using a computer-generated sequence, with allocation concealment maintained through a centralised, web-based system. The sequence generation used block randomisation with stratification factors including health status according to the Geriatric 8 (G8) screening tool (≤14 *vs* >14) and age group (70–79 years *vs* ≥80 years) to ensure balanced allocation across crucial subgroups. Crossover between treatment groups was not allowed. Neither participants nor investigators were masked to treatment allocation due to the nature of the interventions.

Procedures

Patients in the control endocrine therapy group received adjuvant endocrine therapy for a total planned duration of 5–10 years, with the specific route and dosage regimen recommended according to standard guidelines for aromatase inhibitors or tamoxifen, as per clinician discretion. Options were: letrozole (2·5 mg daily), anastrozole (1 mg daily), tamoxifen (20 mg daily), or exemestane (25 mg daily after 2–3 years of tamoxifen), all administered orally. Temporary treatment interruptions were permitted for patients with adverse events, in accordance with protocol allowances to enhance tolerability and adherence.

Patients in the radiotherapy group received breast irradiation after adequate postoperative recovery, preferably within 12 weeks from surgery. The fractionation schedule adhered to the ESTRO-ACROP recommendations, with a preference for five-fraction schedules.[7] Techniques included external beam three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and interstitial brachytherapy. Allowed radiotherapy schedules were WBI or PBI using 40 Gy (15 fractions) or 26 Gy (five fractions); PBI using 30 Gy (five fractions); brachytherapy using high-dose rate 32 Gy (eight fractions, twice daily) or 30·3 Gy (seven fractions, twice daily); or brachytherapy using pulsed-dose rate 0·60–0·80 Gy/h (one pulse per h, 24 h/day) up to a total dose of 50 Gy. WBI was recommended over PBI for patients with final surgical margins from no ink on tumour to less than 2 mm, lobular invasive carcinoma, or tumour grade 3.[7] Quality assurance in radiotherapy reviews was centrally conducted by an expert team (LM, VS) to ensure protocol adherence. Dosimetry data were collected for subsequent toxicity and efficacy outcomes analysis.

Patients followed a structured clinical follow-up schedule with visits at 3, 6, 12, 18, and 24 months, then at 2·5, 3, 4, and 5 years. This follow-up schedule aligns with standard practices for low-risk early breast cancer, and supportive care was provided at the discretion of the treating physician.

HRQOL was assessed using validated questionnaires.[26–28] To avoid bias, baseline HRQOL questionnaires

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See **Online** for appendix

were administered before participants were informed of their randomisation assignment. The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30-item core module (QLQ-C30; version 3) has 30 questions with five functional scales (physical, role, social, emotional, and cognitive), three multi-item symptom scales (fatigue, nausea or vomiting, and pain), five single-item symptom scales (appetite loss, constipation, diarrhoea, dyspnoea, and insomnia), one financial difficulties item, and a two-item global health status (GHS)/HRQOL scale. The QLQ-C30 summary score was calculated by averaging 13 functional and symptom scales, excluding the GHS and financial impact scales. HRQOL outcomes were assessed at baseline, 3, 6, 12, and 24 months, and 5 years.

The EORTC QLQ-BR45 breast module focuses on issues specific to breast cancer, and has 45 questions with three multi-symptom functional scales (body image, sexual functioning, and breast satisfaction), two single-item functional scales (future perspective and sexual enjoyment), three multi-item symptom scales (systemic therapy side-effects, arm symptoms, and breast symptoms), one single item symptom scale (upset by hair loss), and three multi-item target therapy scales (endocrine therapy symptoms, skin mucosis symptoms, and endocrine sexual symptoms). All scores for the EORTC QLQ-C30 and QLQ-BR45 are on a scale from 0 to 100, with missing items accounted for using published scoring guidelines. Higher scores on the functional scales, QLQ-C30 summary score, and GHS/HRQOL scale represent a superior level of functioning or better HRQOL, whereas higher scores in the symptom scales represent worse symptoms.

Adverse events in all patients exposed to the interventions were evaluated using the National Cancer Institute Common Terminology Criteria For Adverse Events (version 5.0). Any adverse event occurring after consent but before randomisation or treatment allocation were reported if they caused trial exclusion or were linked to protocol-specified interventions. Radiotherapy-related toxicity was assessed using the Radiation Therapy Oncology Group and EORTC scores for acute and late radiation morbidity.[29] Both adverse events and serious adverse events were reported by participants, with investigators responsible for documenting, recording, and following up on serious adverse events related to the study intervention or leading to discontinuation. Treatment-emergent adverse events are defined as adverse events that started on or after the date of randomisation. Treatment-related, treatment-emergent adverse events are classified as having a definite, probable, or possible relationship with the study treatment. Any adverse event with a missing relationship category is considered related to the study treatment. Adverse events were monitored at regular intervals, aligned with clinical follow-up visits at 3, 6, 12, 18, and 24 months, with additional monitoring if clinically indicated. Information on sex and race was self-reported by patients at enrolment.

Outcomes

The co-primary endpoints of the study are HRQOL at 24 months, measured by change from baseline in the GHS scale of the EORTC QLQ-C30, and IBTR at 5 years. IBTR was defined as the proportion of patients experiencing any invasive or non-invasive carcinoma in any location in the ipsilateral breast parenchyma. Both co-primary outcomes must be achieved to meet the trial objectives, with a hierarchical prioritisation of the IBTR over the HRQOL outcome.

Secondary endpoints were locoregional recurrence (axillary, supraclavicular, or internal mammary regional lymph nodes), contralateral breast cancer, distant metastases, breast cancer-specific survival, overall survival, and treatment-related adverse events, all defined as the proportion of patients experiencing the respective event within 5 years. Additionally, patient-reported outcomes were assessed using the other EORTC QLQ-C30 modules and the QLQ-BR45 modules, with endpoints defined as the change from baseline to 24 months in each functional and symptom scale domain. The EORTC QLQ-ELD14, focusing on the HRQOL in older patients with cancer, was an optional module (prespecified in the protocol) and was not included in the present analysis due to limited data maturity. Data from the EORTC QLQ-ELD14 module will be reported in the final analysis, provided adequate completion rates to ensure data reliability.

Statistical analysis

The overall hypothesis of this study focused on comparing single-modality radiotherapy and endocrine therapy in terms of IBTR rates and HRQOL outcomes. The study sample size was calculated for the primary endpoint of IBTR, assuming a 4% IBTR rate at 5 years in the endocrine therapy group, with a non-inferiority margin of 3%, a one-sided $\alpha=0{\cdot}025$, and 80% power. This calculation yielded a minimum required sample size of 926 patients (463 per group). For the HRQOL co-primary endpoint, assuming a 2-year GHS standard deviation of 18, with a clinically significant margin of 5 points, $\alpha=0{\cdot}05$, and 90% power, the minimum sample size needed is 584 patients (292 per group). A 5-point difference between groups on HRQOL scales was considered clinically significant in the adjuvant setting.[26]

This preplanned interim analysis was performed once at least 152 patients had the 24-month GHS HRQOL follow-up assessment. Prespecified stopping rules included a yearly IBTR rate exceeding 2% or a distant metastasis rate exceeding 7% at any point during the trial. The primary focus of this analysis is the change from baseline to month 24 in the GHS score of the QLQ-C30 module, comparing the two treatment groups in the intention-to-treat population. Changes in GHS scores

from baseline to each timepoint were evaluated as the dependent variable, with treatment group, visit, treatment-by-visit interaction, and stratification factors (age and G8 score) as fixed effects, baseline GHS score and baseline GHS-by-visit interaction as covariates, and patient as a random effect. The analysis is based on a mixed model for repeated measures with the score change from baseline to each timepoint as the dependent variable.

All other HRQOL scores from the QLQ-C30 and QLQ-BR45 modules are secondary endpoints, included for exploratory purposes without formal adjustments for multiple comparisons. For HRQOL endpoints, no imputation was applied for missing data, and only patients with both baseline and at least one post-baseline HRQOL form were included. Intercurrent events such as death, treatment discontinuation, or relapse leading to missing data within the 2-year follow-up were not replaced, given the exploratory nature of this analysis. Study discontinuation distinguishes between withdrawal of study treatment only and withdrawal of consent, with only the latter resulting in the cessation of all follow-up activities, as per protocol guidelines.

Adverse events are reported descriptively and the 95% CIs for risk differences were calculated using the Miettinen–Nurminen method.

All patients who completed the 24-month visit or discontinued before the 24-month visit are included in this interim analysis. The intention-to-treat population includes all randomly assigned patients. The safety population includes all patients in the intention-to-treat population who received the study intervention at least once after randomisation.

The final analysis will be conducted on an intention-to-treat basis when all patients have completed the 5-year follow-up. Further details on data management and the statistical analysis plan are available in the appendix. All

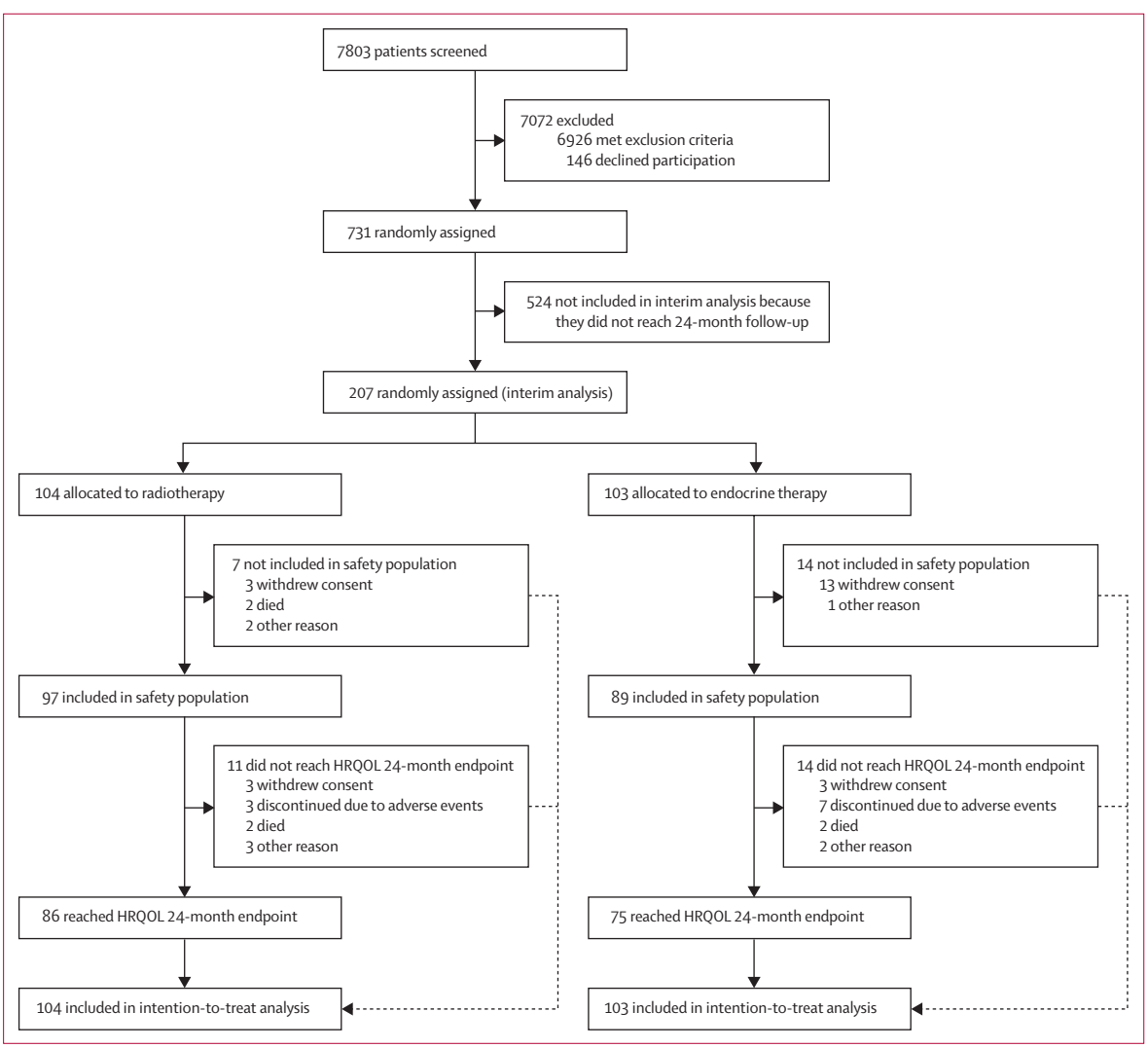

Figure 1: **Trial profile**
HRQOL=health-related quality of life.

	Radiotherapy group (n=104)	Endocrine therapy group (n=103)
Age group		
70–79 years	77 (74%)	74 (72%)
≥80 years	27 (26%)	29 (28%)
Age, years		
Mean (SD)	76·4 (4·57)	76·1 (4·90)
Median (IQR)	75·0 (73·0–80·0)	74·0 (72·0–80·0)
Range	70·0–88·0	70·0–94·0
Race		
Asian	2 (2%)	0
White	102 (98%)	102 (99%)
Other	0	1 (1%)
Weight, kg		
Mean (SD)	67·3 (12·24)	65·8 (12·01)
Median (IQR)	66·0 (58·0–75·0)	63·0 (58·0–71·0)
Range	42·0–111·0	44·5–100·0
Height, cm		
Mean (SD)	160·5 (7·06)	159·7 (6·17)
Median (IQR)	160·0 (156·0–165·0)	160·0 (155·0–165·0)
Range	139·0–178·0	142·0–173·0
BMI, kg/m²		
Mean (SD)	26·2 (4·97)	25·8 (4·80)
Median (IQR)	25·4 (22·7–29·0)	25·0 (22·6–27·8)
Range	17·5–46·7	17·6–44·4
BMI categories		
≤25 kg/m²	50 (48%)	52 (50%)
>25 kg/m²	54 (52%)	51 (50%)
ECOG performance status		
0	84 (81%)	87 (84%)
1	20 (19%)	16 (16%)
Comorbidities		
No	13 (13%)	5 (5%)
Yes	91 (88%)	98 (95%)
Concomitant medications		
No	20 (19%)	12 (12%)
Yes	84 (81%)	91 (88%)
Number of concomitant medications taken at baseline		
<3 concomitant medications	41 (39%)	38 (37%)
≥3 concomitant medications	63 (61%)	65 (63%)
Laterality		
Left	65 (63%)	54 (52%)
Right	39 (38%)	49 (48%)
Histology		
Ductal invasive	92 (88%)	80 (78%)
Lobular invasive	5 (5%)	4 (4%)
Others	7 (7%)	19 (18%)
DCIS component		
Absence	56 (54%)	52 (50%)
Presence	48 (46%)	51 (50%)

(Table 1 continues in next column)

	Radiotherapy group (n=104)	Endocrine therapy group (n=103)
(Continued from previous column)		
pT stage		
pT1a	7 (7%)	6 (5·8%)
pT1b	54 (52%)	50 (48·5%)
pT1c	42 (40%)	45 (43·7%)
pTmi	1 (1%)	2 (1·9%)
Tumour size, mm		
Mean (SD)	11·0 (8·57)	10·5 (4·52)
Median (IQR)	10·0 (7·0–13·0)	10·0 (7·0–15·0)
Range	4·0–88·0	0·6–20·0
Nodal status		
pN0	94 (90%)	93 (90%)
pN0 with isolated tumour cells (i+)	1 (1%)	2 (2%)
pNx	9 (9%)	8 (8%)
Tumour grade		
Grade 1	37 (36%)	35 (34%)
Grade 2	67 (64%)	68 (66%)
Closest final surgical margins		
≥2 mm	97 (93%)	79 (77%)
No ink to <2 mm	6 (6%)	21 (20%)
Oestrogen receptor status, %		
Mean (SD)	96·5 (4·20)	95·4 (5·20)
Median (IQR)	99·0 (95·0–100·0)	98·0 (90·0–100·0)
Range	80·0–100·0	70·0–100·0
Oestrogen receptor category		
≤50%	0	0
>50%	104 (100%)	103 (100%)
Progesterone receptor status, %		
Mean (SD)	73·2 (30·96)	72·1 (31·14)
Median (IQR)	90·0 (60·0–95·0)	90·0 (45·0–95·0)
Range	0·0–100·0	0·0–100·0
Progesterone receptor category		
≤50%	23 (22%)	26 (25%)
>50%	81 (78%)	77 (75%)
***Ki67*, %**		
Mean (SD)	11·4 (5·07)	10·8 (5·01)
Median (IQR)	10·5 (8·0–15·0)	10·0 (6·0–15·0)
Range	1·0–20·0	2·0–20·0
Ki67 index		
≤13·25%	68 (65%)	70 (68%)
>13·25%	36 (35%)	33 (32%)
HER2 status		
Score 0	47 (45%)	60 (58%)
Score 1+	46 (44%)	31 (30%)
Score 2+ not amplified in FISH or ISH	11 (11%)	12 (12%)
Lymphovascular invasion		
No	100 (96%)	89 (86%)
Yes	4 (4%)	14 (14%)

(Table 1 continues in next column)

	Radiotherapy group (n=104)	Endocrine therapy group (n=103)
(Continued from previous column)		
Surgery complications		
No	102 (98%)	97 (94%)
Yes	2 (2%)	6 (6%)
Treatment assigned		
Exclusive endocrine therapy	0	103 (100%)
Exclusive partial breast irradiation	88 (85%)	0
Exclusive whole breast irradiation	16 (15%)	0
G8 score class		
≤14	42 (40%)	41 (40%)
>14	62 (60%)	62 (60%)
Stratification group		
Age 70–79 years and G8 ≤14	24 (23%)	23 (22%)
Age 70–79 years and G8 >14	53 (51%)	51 (50%)
Age ≥80 years and G8 ≤14	19 (18%)	19 (18%)
Age ≥80 years and G8 >14	8 (8%)	10 (10%)
Completion of each study visit		
Visit 1 (baseline)	104 (100%)	103 (100%)
Visit 2 (month 3)	89 (86%)	81 (79%)
Visit 3 (month 6)	93 (89%)	83 (81%)
Visit 4 (month 12)	90 (87%)	76 (74%)
Visit 5 (month 18)	88 (85%)	73 (71%)
Visit 6 (month 24)	86 (83%)	75 (73%)
Available data rate QLQ-C30		
Baseline	104 (100%)	99 (96%)
Month 3	88 (85%)	74 (72%)
Month 6	93 (89%)	79 (77%)
Month 12	90 (87%)	75 (73%)
Month 24	82 (79%)	73 (71%)
(Table 1 continues in next column)		
(Continued from previous column)		
Completion rate QLQ-C30		
Baseline	104 (100%)	95/99 (96%)
Month 3	83/88 (94%)	64/74 (86%)
Month 6	93/93 (100%)	78/79 (99%)
Month 12	89/90 (99%)	73/75 (97%)
Month 24	79/82 (96%)	72/73 (99%)
Available data rate QLQ-BR45		
Baseline	104 (100%)	100 (97%)
Month 3	88 (85%)	75 (73%)
Month 6	93 (89%)	82 (80%)
Month 12	90 (87%)	76 (74%)
Month 24	84 (81%)	74 (72%)
Completion rate QLQ-BR45		
Baseline	104 (100%)	97/100 (97%)
Month 3	83/88 (94%)	64/75 (85%)
Month 6	93/93 (100%)	81/82 (99%)
Month 12	89/90 (99%)	71/76 (94%)
Month 24	82/84 (98%)	71/74 (96%)

Data are n (%) unless otherwise specified. Only female patients were enrolled in this study. Patient-reported outcomes completion rates and available data rates are calculated following the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium recommendations. DCIS=ductal carcinoma in situ. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in situ hybridisation. HRQOL=health-related quality of life. ISH=in situ hybridisation. G8=Geriatric 8 screening tool.

Table 1: **Baseline characteristics and HRQOL questionnaire completion rates**

statistical analyses were done at the data cutoff of June 14, 2024, and performed using SAS software (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 4, 2021, and June 14, 2024, 734 patients were enrolled, and 731 were randomly assigned to receive either single-modality radiotherapy (n=365) or endocrine therapy (n=366), representing 79% of the planned 926 patients from 21 centres; the trial is open and actively recruiting. This analysis included 104 patients in the radiotherapy group and 103 in the endocrine therapy group (figure 1), with a median follow-up of 23·9 months (IQR 22·9–24·2). Patients were predominantly White (204 [99%] of 207), and age distribution was similar across treatment groups, with 151 (73%) patients aged 70–79 years and 56 (27%) aged 80 years or older; the median age was 75·0 years (IQR 73·0–80·0) in the radiotherapy group and 74·0 years (72·0–80·0) in the endocrine therapy group (table 1). G8 scores were similar between groups, with 83 (40%) patients scoring 14 or less and 124 (60%) scoring more than 14. In the radiotherapy group, more patients received PBI (88 [85%]) than WBI (16 [15%]). Regarding radiotherapy techniques, all patients were treated using external-beam radiotherapy, and none were treated using interstitial brachytherapy. Ductal invasive carcinoma was the most common histology (92 [88%] of 104 in the radiotherapy group *vs* 80 [77%] of 103 in the endocrine therapy group). The endocrine therapy group had a slightly higher rate of baseline comorbidities (98 [95%] *vs* 91 [88%]) and concomitant medications (91 [88%] *vs* 84 [81%]) compared with the radiotherapy group. A higher proportion of patients in the endocrine therapy group did not complete the 24-month HRQOL assessment compared with the radiotherapy group (28 [27%] *vs* 18 [17%]). In the radiotherapy group, seven (7%) patients discontinued the study before receiving radiotherapy, and 11 (11%) after radiotherapy, with three discontinuations (3%) due to adverse events. Conversely, in the endocrine therapy

group, 14 (14%) patients discontinued before initiating endocrine therapy, and 14 (14%) after starting therapy, with seven discontinuations (7%) attributed to adverse events (figure 1).

The results for the GHS of the EORTC QLQ-C30 questionnaire displayed differing trajectories between the radiotherapy and endocrine therapy groups over 24 months. At baseline, the mean GHS score was slightly higher in the endocrine therapy group (75·5 [SD 19·3]) compared with the radiotherapy group (71·9 [19·1]). The endocrine therapy group showed a more pronounced decline in GHS over time; by the 24-month visit, the mean GHS score in the endocrine therapy group dropped to 67·2 (SD 23·2), representing a mean change of –10·0 (95% CI –15·92 to –4·08) from baseline, while the radiotherapy group remained relatively stable with a score of 70·7 (SD 20·4), reflecting a slight decline of –1·1 (95% CI –5·17 to 2·97; figure 2,

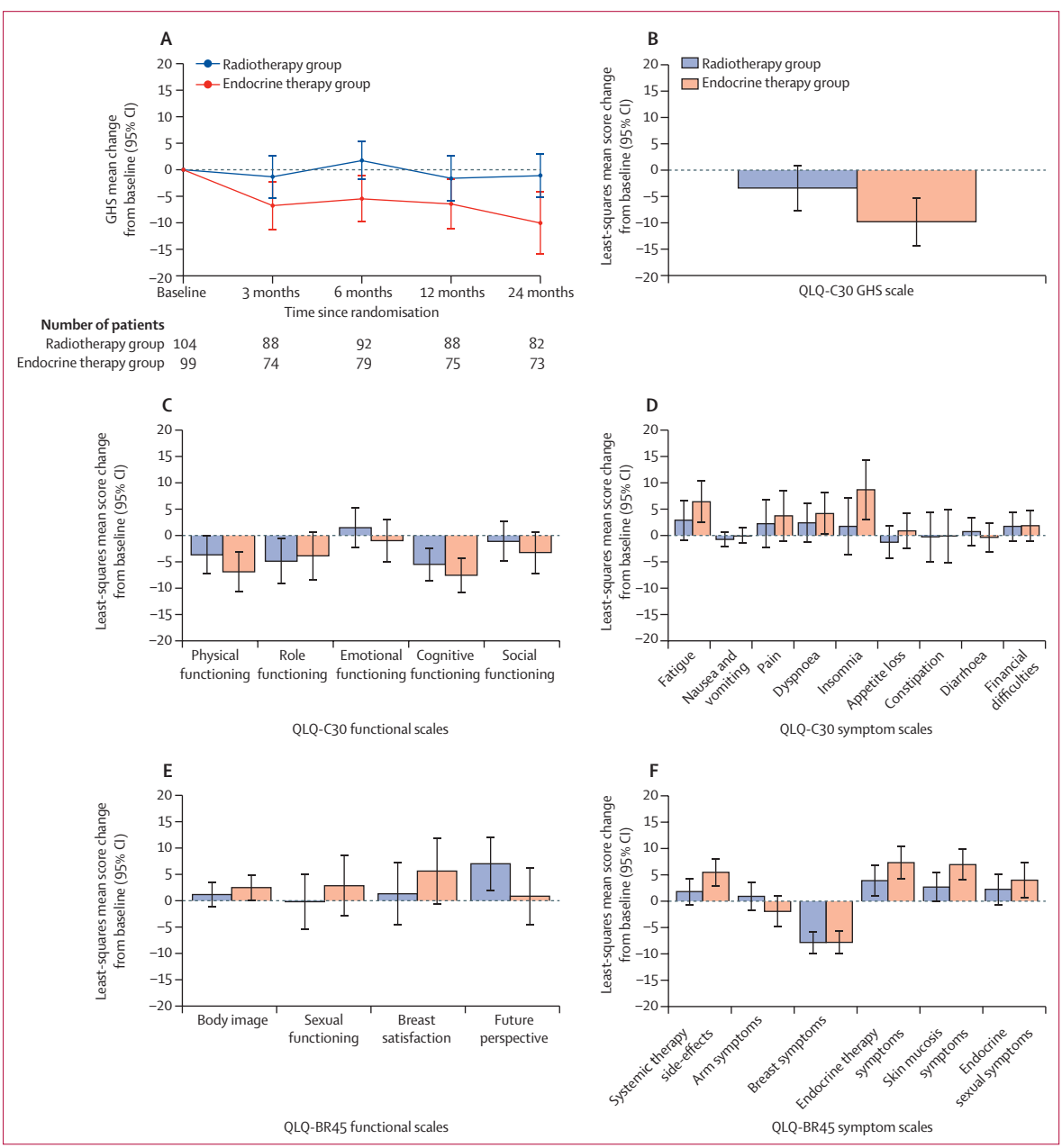

Figure 2: **Mean change from baseline to 24 months in patient-reported outcome scores for radiotherapy and endocrine therapy groups**
Empirical (A) and least-squares (B) mean change from baseline in GHS score of the QLQ-C30 questionnaire. Least-squares mean change from baseline in functional (C) and 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.

	Radiotherapy group		Endocrine therapy group		Radiotherapy *vs* endocrine therapy comparison	
	Adjusted mean (95% CI)	p value	Adjusted mean (95% CI)	p value	Adjusted mean (95% CI)	p value
QLQ-C30						
GHS	−3·40 (−7·82 to 1·03)	0·13	−9·79 (−14·45 to −5·13)	<0·0001	6·39 (0·14 to 12·65)	0·045
Functional scales						
Physical functioning	−3·68 (−7·37 to 0·02)	0·051	−6·90 (−10·80 to −3·00)	0·0006	3·22 (−2·02 to 8·46)	0·23
Role functioning	−4·88 (−9·27 to −0·49)	0·030	−3·86 (−8·52 to 0·80)	0·10	−1·02 (−7·29 to 5·25)	0·75
Emotional functioning	1·48 (−2·42 to 5·38)	0·45	−0·98 (−5·07 to 3·11)	0·64	2·46 (−3·01 to 7·93)	0·38
Cognitive functioning	−5·49 (−8·65 to −2·32)	0·0008	−7·55 (−10·88 to −4·22)	<0·0001	2·07 (−2·34 to 6·47)	0·36
Social functioning	−1·12 (−4·96 to 2·72)	0·57	−3·23 (−7·29 to 0·82)	0·12	2·11 (−3·36 to 7·59)	0·45
Symptom scales						
Fatigue	2·91 (−0·93 to 6·75)	0·14	6·40 (2·37 to 10·43)	0·0020	−3·50 (−8·89 to 1·90)	0·20
Nausea and vomiting	−0·75 (−2·24 to 0·75)	0·32	−0·04 (−1·61 to 1·52)	0·96	−0·70 (−2·77 to 1·36)	0·50
Pain	2·23 (−2·4 to 6·86)	0·34	3·73 (−1·22 to 8·68)	0·14	−1·50 (−8·11 to 5·11)	0·65
Dyspnoea	2·40 (−1·42 to 6·21)	0·22	4·16 (0·13 to 8·19)	0·043	−1·76 (−7·16 to 3·63)	0·52
Insomnia	1·73 (−3·75 to 7·22)	0·53	8·68 (2·86 to 14·5)	0·0037	−6·95 (−14·72 to 0·82)	0·079
Appetite loss	−1·28 (−4·44 to 1·87)	0·42	0·88 (−2·51 to 4·26)	0·61	−2·16 (−6·64 to 2·32)	0·34
Constipation	−0·26 (−5·10 to 4·58)	0·91	−0·09 (−5·20 to 5·03)	0·97	−0·18 (−6·97 to 6·62)	0·96
Diarrhoea	0·73 (−1·98 to 3·44)	0·59	−0·35 (−3·20 to 2·50)	0·81	1·09 (−2·73 to 4·90)	0·58
Financial difficulties	1·73 (−1·12 to 4·59)	0·23	1·86 (−1·17 to 4·89)	0·23	−0·13 (−4·20 to 3·95)	0·95
QLQ-BR45						
Functional scales						
Body image	1·17 (−1·18 to 3·52)	0·33	2·49 (−0·02 to 5·00)	0·052	−1·32 (−4·66 to 2·01)	0·43
Sexual functioning	−0·19 (−5·45 to 5·07)	0·94	2·85 (−3·01 to 8·70)	0·34	−3·03 (−10·68 to 4·61)	0·43
Breast satisfaction	1·32 (−4·70 to 7·33)	0·67	5·63 (−0·69 to 11·95)	0·081	−4·31 (−12·78 to 4·15)	0·32
Future perspective	7·02 (1·86 to 12·17)	0·0080	0·86 (−4·59 to 6·31)	0·76	6·16 (−1·03 to 13·35)	0·093
Sexual enjoyment	..	..	..	..	..	..
Symptom scales						
Systemic therapy side-effects	1·82 (−0·73 to 4·38)	0·16	5·48 (2·78 to 8·18)	<0·0001	−3·66 (−7·26 to −0·05)	0·047
Arm symptoms	0·92 (1·89 to 3·74)	0·52	−1·94 (−4·92 to 1·05)	0·20	2·86 (−1·06 to 6·78)	0·15
Upset by hair loss	..	..	..	..	..	..
Breast symptoms	−7·84 (−10·02 to −5·66)	<0·0001	−7·81 (−10·12 to −5·51)	<0·0001	−0·02 (−3·08 to 3·03)	0·99
Endocrine therapy symptoms	3·90 (0·91 to 6·89)	0·011	7·32 (4·16 to 10·48)	<0·0001	−3·42 (−7·58 to 0·75)	0·11
Skin mucosis symptoms	2·68 (−0·17 to 5·53)	0·065	6·94 (3·93 to 9·96)	<0·0001	−4·26 (−8·28 to −0·24)	0·038
Endocrine sexual symptoms	2·26 (−0·78 to 5·29)	0·14	3·99 (0·61 to 7·37)	0·021	−1·73 (−6·14 to 2·68)	0·44

Positive scores for the GHS and functional scales represent improvements from baseline, whereas positive scores for the symptom scales represent worsening of symptoms from baseline. The absence of data for the sexual enjoyment and upset by hair loss scales is due to the fact that only a small number of patients answered the questions on sexual enjoyment (which might reflect the older age of this patient cohort) and hair loss (the patients were not receiving chemotherapy causing alopecia). GHS=global health status. QLQ-C30=Quality of Life Questionnaire 30-item core module. QLQ-BR45=Quality of Life Questionnaire 45-item breast module.

Table 2: **Adjusted mean change from baseline and group comparison for QLQ-C30 GHS score and QLQ-C30 and BR45 module functional and symptoms scales**

appendix p 4). The age-adjusted, G8 score-adjusted analysis of GHS change from baseline over time maintained significant differences between the radiotherapy and endocrine therapy groups. At 24 months, the adjusted mean change from baseline in GHS for the radiotherapy group was −3·40 (95% CI −7·82 to 1·03; p=0·13), while for the endocrine therapy group, it was −9·79 (−14·45 to −5·13; p<0·0001). This resulted in a significant adjusted mean difference of 6·39 (0·14 to 12·65; p=0·045) in favour of the radiotherapy group at the 24-month timepoint, indicating better maintenance of GHS (table 2).

The actual and empirical values and changes from baseline in the functional and symptom scales of the EORTC QLQ-C30 and QLQ-BR45 are reported in the appendix (pp 5–35 and pp 36–57, respectively). Age-adjusted and G8 score-adjusted analyses of the EORTC QLQ-C30 and QLQ-BR45 scales between the radiotherapy and endocrine therapy groups over 24 months are shown in figure 2 and table 2.

Regarding the QLQ-C30 functional scales, patients treated with endocrine therapy had a significant decline from baseline in physical functioning scores (−6·90, −10·80 to −3·00; p=0·0006), although the between-group

	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**

difference was not significant (p=0·23). Role functioning scores showed a significant decline in the radiotherapy group (–4·88, –9·27 to –0·49; p=0·030) compared with the endocrine therapy group (–3·86, –8·52 to 0·80; p=0·10), but the between-group difference was not significant (p=0·75). Cognitive functioning scores declined in both groups, with a decrease of –5·49 (–8·65 to –2·32; p=0·0008) in the radiotherapy group and –7·55 (–10·88 to –4·22; p<0·0001) in the endocrine therapy group, again without significant differences (p=0·36). No changes from baseline or differences between groups were found for the remaining functioning scales (emotional and social functioning). Results for the QLQ-C30 symptom scales are shown in table 2. Although in the endocrine therapy group there was significant worsening from baseline in some symptoms (fatigue, dyspnoea, insomnia), no significant differences were found between groups.

Regarding the QLQ-BR45 functional scales, the radiotherapy group showed a significant improvement from baseline in future perspective scores (7·02, 1·86 to 12·17; p=0·0080), with no significant between-group difference (mean difference 6·16, 95% CI –1·03 to 13·35; p=0·093). For the QLQ-BR45 symptom scales, both groups exhibited similar significant improvement from baseline in breast symptom scores (p<0·0001), with no significant between-group difference (p=0·99). The endocrine therapy group had significantly worse systemic therapy side-effects compared with the radiotherapy group (mean difference –3·66, –7·26 to –0·05; p=0·047). The endocrine therapy group also reported significant worsening from baseline in skin mucosis symptoms (6·94, 3·93 to 9·96; p<0·0001), with a significant between-group difference favouring the radiotherapy group (p=0·038). Additionally, the endocrine therapy group reported significant worsening from baseline in endocrine therapy-related symptoms (7·32, 4·16 to 10·48; p<0·0001), although the difference between groups did not reach statistical significance (p=0·11). No changes from baseline or differences between groups were found for the remaining functioning scales (body image, sexual functioning, breast satisfaction) or the remaining symptom scales (arm symptoms, endocrine sexual symptoms.

In terms of clinical outcomes, no IBTR, locoregional recurrence, or distant metastases was observed in either group. Contralateral breast cancer occurred in two (2%) patients in the radiotherapy group and one (1%) patient in the endocrine therapy group. Four (4%) patients in the radiotherapy group died compared with two (2%) in the endocrine therapy group, none of which were breast cancer-related (table 3).

In the safety population (n=186), treatment-related adverse events were less frequent in the radiotherapy group (65 [67%] of 97) compared with the endocrine therapy group (76 [85%] of 89), with a difference of 18·4 percentage points (95% CI –30·2 to –6·2; table 3). The rate of serious adverse events was similar between the groups (15 [15%] in the radiotherapy group *vs* 13 [15%] in the endocrine therapy group), with no fatal treatment-related adverse events in either group (table 3). In the radiotherapy group, no treatment-emergent serious adverse events were related to treatment. In the endocrine therapy group, treatment-emergent serious adverse events included one treatment-related case of grade 4 arthralgia (1%). In the endocrine therapy group, most patients received aromatase inhibitors (79 [89%]) rather than tamoxifen (10 [11%]); 20 (22%) patients required a switch in endocrine therapy, and 11 (12%) patients permanently discontinued endocrine therapy during the study period due to adverse events. The most common grade 3–4 adverse events were arthralgia (six [7%] of 89 in endocrine therapy group *vs* 0 of 97 in radiotherapy group), pelvic organ prolapse (three [3%] *vs* 0), fatigue, hot flashes, myalgia, bone pain, and fractures (two [2%] *vs* 0 for each; table 4).

Discussion

The findings of our interim analysis suggest that patients treated with radiotherapy alone have superior 24-month GHS outcomes compared with those treated with endocrine therapy alone, supporting our initial

	Radiotherapy group (n=97)				Endocrine therapy group (n=89)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Arthralgia (joint pain)	28 (29%)	0	0	0	62 (70%)	5 (6%)	1 (1%)	0
Fatigue	32 (33%)	0	0	0	40 (45%)	2 (2%)	0	0
Breast pain	37 (38%)	0	0	0	8 (9%)	0	0	0
Hot flashes	10 (10%)	0	0	0	29 (33%)	2 (2%)	0	0
Myalgia (muscle pain)	13 (13%)	0	0	0	28 (31%)	2 (2%)	0	0
Bone pain	23 (24%)	0	0	0	25 (28%)	2 (2%)	0	0
Alopecia (hair loss)	7 (7%)	0	0	0	23 (26%)	0	0	0
Depression	15 (15%)	1 (1%)	0	0	21 (24%)	1 (1%)	0	0
Insomnia	15 (15%)	0	0	0	21 (24%)	0	0	0
Osteoporosis	3 (3%)	0	0	0	20 (22%)	0	0	0
Hypercholesterolaemia	0	0	0	0	17 (19%)	0	0	0
Vaginal dryness	7 (7%)	0	0	0	17 (19%)	0	0	0
Irritability	15 (15%)	0	0	0	12 (13%)	1 (1%)	0	0
Arthritis	15 (15%)	0	0	0	14 (16%)	0	0	0
Constipation	14 (14%)	1 (1%)	0	0	12 (13%)	1 (1%)	0	0
Dermatitis	14 (14%)	0	0	0	9 (10%)	0	0	0
Weight gain	12 (12%)	0	0	0	12 (13%)	0	0	0
Headache	9 (9%)	0	0	0	10 (11%)	0	0	0
Hypertension	9 (9%)	0	0	0	9 (10%)	0	0	0
Dizziness	7 (7%)	0	0	0	8 (9%)	1 (1%)	0	0
Fracture	3 (3%)	0	0	0	6 (7%)	2 (2%)	0	0
Weight loss	3 (3%)	1 (1%)	0	0	2 (2%)	0	0	0
Pelvic organ prolapse	0	0	0	0	0	3 (3%)	0	0
Pneumonia	2 (2%)	1 (1%)	0	0	1 (1%)	0	0	1 (1%)
Atrioventricular block	0	0	0	0	0	1 (1%)	1 (1%)	0
Pulmonary hypertension	0	0	0	0	0	1 (1%)	0	0
Cognitive disorder	0	1 (1%)	0	0	1 (1%)	0	0	0
Renal failure	0	1 (1%)	0	0	0	0	0	0
Gastritis	0	1 (1%)	0	0	0	0	0	0
Ischaemia	0	0	1 (1%)	0	0	0	0	1 (1%)
Aortic valve stenosis	0	1 (1%)	0	0	0	0	0	0
Infection	0	0	0	1 (1%)	0	0	0	0

Data are n (%). The table shows grade 1–2 adverse events occurring in at least 10% of patients in one group and all grade 3–5 adverse events.

Table 4: **Treatment-emergent adverse events by grade and treatment group**

hypothesis. We selected the 24-month timepoint as optimal for assessing medium-term toxicity after radiotherapy, as by then acute effects have subsided while the patient's experience of treatment is still relatively recent. Additionally, this timeframe allows for capturing the relevant toxicity profile of endocrine therapy, which often stabilises following the adjustment phase after initiation.[30] This approach thereby aims to balance capturing both post-acute radiotherapy effects and early-stage endocrine therapy toxicity.

In the current interim analysis of 207 patients, the baseline characteristics were well balanced between the radiotherapy and endocrine therapy groups, suggesting comparability across the two groups. Most patients in the radiotherapy group received PBI, reflecting a trend toward less extensive radiotherapy approaches in this low-risk population.[7]

It is noteworthy that a higher proportion of patients in the endocrine therapy group did not complete the 24-month HRQOL assessment compared with the radiotherapy group. This difference might indicate better tolerability of radiotherapy over endocrine therapy, related to the differing side-effect profiles. The higher rate of consent withdrawal in the endocrine therapy group further underscores this disparity, and a potential reluctance to be allocated to this group. Adverse events and overall treatment burden might have contributed to reduced patient adherence in the endocrine therapy group. Additionally, fewer patients in the endocrine therapy group completed each study visit at multiple timepoints. This lower visit adherence could lead to further underestimation of the true difference between groups in terms of GHS. Notably, the endocrine therapy group had a slightly higher percentage of baseline

comorbidities and concomitant medications, which might have influenced patient compliance independently of the study treatments.

These findings point to important considerations in the management of older patients with breast cancer. Although endocrine therapy is often seen as a less invasive option, its higher withdrawal rates and side-effect profile might affect long-term adherence and HRQOL, especially in frail patients. Conversely, short-course radiotherapy could offer a less burdensome alternative, combining similar efficacy with improved tolerability.

The findings from the GHS results highlight a notable divergence between the radiotherapy and endocrine therapy treatment groups over a period of 24 months. Although the endocrine therapy group started with a higher mean GHS score at baseline (75·5) compared with the radiotherapy group (71·9), it showed a significant decline over time, dropping to 67·2 by the 24-month visit, which is a mean change of –10·0 from baseline. In contrast, the radiotherapy group demonstrated greater stability, maintaining a mean GHS score of 70·7 with only a minor decline of –1·1. The adjusted analysis reinforced these observations, revealing a significant adjusted mean difference in favour of the radiotherapy group at 24 months (6·39, 95% CI 0·14 to 12·65; p=0·045). These results suggest that radiotherapy allows better maintenance of GHS compared with endocrine therapy, which was associated with a more pronounced deterioration in HRQOL.

Notably, several functional scales, including cognitive function and future perspective, favoured the radiotherapy group for long-term HRQOL compared with endocrine therapy. Population data show slight cognitive declines in older adults, primarily in memory, executive function, and processing speed, which might be more pronounced in cancer survivors due to treatment burden and psychological stress.[31] The endocrine therapy group also reported higher levels of endocrine-related side-effects, with significant increases in skin mucosis symptoms and systemic therapy side-effects. Fatigue, cognitive impairment, anxiety, depression, and sleep disturbances are all cancer-related behavioural symptoms that can persist for years after early-stage breast cancer, affecting HRQOL.[30]

Developing predictive models for long-term symptoms in breast cancer survivors could improve care through shared European guidelines, coordinated tools, and survivorship education. A patient-centred research agenda should focus on understanding survivors' needs and biological factors to create innovative interventions for optimal care.[32]

Several ongoing studies (EXPERT [NCT02889874], NATURAL [NCT03646955], PRIMETIME [ISRCTN41579286], DEBRA [NCT04852887], IDEA [NCT02400190], LUMINA [NCT01791829], and TOP-1 [NL58117.058.16]) are exploring the optimisation of postoperative treatment for low-risk patients. Notably, all these trials, in contrast to the EUROPA study, test the omission of radiotherapy only, without considering the non-negligible side-effects of endocrine therapy, especially in patients with comorbidities or frailty factors.[23,24] Furthermore, most of these studies select patients based on genomic tools that, although analytically validated, often lack clinical validation and utility, particularly in low-risk older patients.[33]

Concerning the safety outcomes, the radiotherapy group exhibited a notably lower rate of treatment-related adverse events compared with the endocrine therapy group (67% *vs* 85%). This difference shows that radiotherapy is better tolerated than endocrine therapy in this population. Conversely, the rate of serious adverse events was low and similar between the two groups, indicating that neither treatment carried a disproportionately high risk of severe complications. However, treatment non-compliance, particularly with endocrine therapy, has been shown to negatively affect disease control.[34] Given the observed differences in adverse events between the radiotherapy and endocrine therapy groups, our findings underscore the importance of monitoring treatment adherence to optimise patient outcomes.

Several limitations should be acknowledged. This interim analysis, based on a subset of the trial population, does not yet capture the full cohort, and therefore conclusions on long-term efficacy and safety remain preliminary. Additionally, we conducted exploratory analyses across multiple HRQOL scales without adjustments for multiple comparisons; these adjustments will be incorporated in the final analysis. The relatively short follow-up period further limits our ability to assess long-term survival outcomes. Moreover, while the study design reflects a well defined population of older adults with low-risk breast cancer, this specificity might limit the generalisability of findings to broader patient populations. However, existing studies provide context; for instance, one study found equivalent 5-year overall survival rates between older women with biologically favourable breast cancer receiving post-operative radiotherapy or endocrine therapy alone after breast-conserving surgery.[35] Additionally, models suggest that older women with low-risk breast cancer can safely choose radiotherapy alone if unwilling or unable to pursue endocrine therapy, with minimal outcome differences.[36] The current analysis does not aim to definitively demonstrate the superiority of one treatment over the other. Instead, the EUROPA trial seeks to provide clinicians and patients with robust data to discuss options for optimising treatment in low-risk cases. By combining outcomes for HRQOL and disease control, a multidisciplinary approach to early-stage breast cancer is promoted, enabling tailored therapeutic discussions after proper clinical evaluation.

The results of this preplanned interim analysis suggest that, at 24 months, endocrine therapy was associated

with a greater reduction in HRQOL (as measured by GHS) compared with radiotherapy, which exhibited a more favourable tolerability profile regarding treatment-related adverse events. While these early findings support the potential of radiotherapy to maintain HRQOL in older women with low-risk early-stage breast cancer, definitive conclusions regarding its broader clinical utility will depend on long-term disease control outcomes and the completion of patient accrual.

Contributors

IM and LL accessed and verified the data in this study. IM, PMPP, and LL contributed to the study's conceptualisation, data curation, formal analysis, and drafting of the original and revised manuscripts. IM and LL were also involved in funding acquisition. All authors contributed equally to the investigation, methodology, project administration, resources, supervision, validation, visualisation, and review and editing of the manuscript. All authors had full access to all the data in the study, take responsibility for the integrity of the data and accuracy of the analysis, and had final responsibility for the decision to submit for publication.

Declaration of interests

IM has received occasional fees for advisory board participation supported by Eli Lilly, Novartis, Pfizer, AstraZeneca, Daiichi Sankyo, Gilead, and Menarini StemLine, outside the submitted work. ML has reported advisory roles supported by Roche, Eli Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, and Menarini StemLine; speaker honoraria from Roche, Eli Lilly, Novartis, Pfizer, AstraZeneca, Takeda, Ipsen, Sandoz, Libbs, Knight, Daiichi Sankyo, Gilead, and Menarini StemLine; and travel grants from Gilead, Daiichi Sankyo, and Roche. VS has reported honoraria from Nucletron and Elekta. TS discloses unrestricted grants for programmes of Europa Donna Slovenia, as well as speaker honoraria from Pfizer, MSD, Roche, and AstraZeneca. All other authors declare no competing interests.

Data sharing

The trial's sponsor (University of Florence, Florence, Italy) is committed to sharing patient-level data and supporting clinical documents with bona fide researchers upon request to the corresponding author. Data will be made available after approval by the trial's steering committee.

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