# Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA

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## ABSTRACT

**PURPOSE** Multiple studies have shown a low risk of ipsilateral breast events (IBEs) or other recurrences for selected patients age 65-70 years or older with stage I breast cancers treated with breast-conserving surgery (BCS) and endocrine therapy (ET) without adjuvant radiotherapy. We sought to evaluate whether younger postmenopausal patients could also be successfully treated without radiation therapy, adding a genomic assay to classic selection factors.

**METHODS** Postmenopausal patients age 50-69 years with pT1N0 unifocal invasive breast cancer with margins ≥2 mm after BCS whose tumors were estrogen receptor–positive, progesterone receptor–positive, and human epidermal growth factor receptor 2–negative with Oncotype DX 21-gene recurrence score ≤18 were prospectively enrolled in a single-arm trial of radiotherapy omission if they consented to take at least 5 years of ET. The primary end point was the rate of locoregional recurrence 5 years after BCS.

**RESULTS** Between June 2015 and October 2018, 200 eligible patients were enrolled. Among the 186 patients with clinical follow-up of at least 56 months, overall and breast cancer–specific survival rates at 5 years were both 100%. The 5-year freedom from any recurrence was 99% (95% CI, 96 to 100). Crude rates of IBEs for the entire follow-up period for patients age 50-59 years and age 60-69 years were 3.3% (2/60) and 3.6% (5/140), respectively; crude rates of overall recurrence were 5.0% (3/60) and 3.6% (5/140), respectively.

**CONCLUSION** This trial achieved a very low risk of recurrence using a genomic assay in combination with classic clinical and biologic features for treatment selection, including postmenopausal patients younger than 60 years. Long-term follow-up of this trial and others will help determine whether the option of avoiding initial radiotherapy can be offered to a broader group of women than current guidelines recommend.

ACCOMPANYING CONTENT

Appendix

Protocol

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## BACKGROUND

Radiotherapy has been a key component of treatment after breast-conserving surgery (BCS) for patients with early-stage breast cancer for over three decades.[1] The landmark randomized trials in relatively unselected patients that established breast conservation as an alternative to mastectomy reduced local recurrence by approximately two-thirds proportionally, or well over 10% in absolute terms.[2] Subsequent meta-analysis suggested radiotherapy reduced the risk of overall disease recurrence by about half and resulted in a modest reduction in mortality.[3] It further demonstrated that the absolute benefits of radiotherapy varied between subgroups defined by age, hormone receptor status, and other risk factors, suggesting that omission of radiotherapy might warrant further investigation for certain subgroups.

Because radiotherapy can cause acute and long-term morbidity,[4] places cost and time burdens on patients, and is expensive, researchers have long sought to identify a low-risk population of patients in whom the risk of recurrence without adjuvant radiotherapy is sufficiently low that omission of radiotherapy after BCS is a reasonable option.

## CONTEXT

**Key Objective**

To evaluate whether adding a genomic assay to classic selection factors can identify a subset of younger postmenopausal patients with breast cancer, for whom guidelines currently recommend radiotherapy, who have low recurrence after breast-conserving surgery (BCS) and endocrine therapy (ET) alone.

**Knowledge Generated**

Among postmenopausal patients age 50-69 years with pT1N0 unifocal invasive breast cancer with margins ≥2 mm after BCS whose tumors were estrogen receptor–positive, progesterone receptor–positive, and human epidermal growth factor receptor 2–negative with Oncotype DX 21-gene recurrence score ≤18, the 5-year freedom from any recurrence was 99% (95% CI, 96 to 100). Crude rates of ipsilateral breast events for the entire follow-up period for patients age 50-59 years and age 60-69 years were 3.3% (2/60) and 3.6% (5/140), respectively.

**Relevance *(K.D. Miller)***

Local therapy decisions have historically been based on the anatomic extent of disease. The IDEA trial highlights the impact of tumor biology, providing support for the ongoing DEBRA trial and foreshadowing a future of even more individualized treatment decisions.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.



Early studies that selected patients on the basis of factors such as small primary tumor size were unsuccessful in identifying a subgroup of patients whose risk of local recurrence after BCS was acceptable without radiotherapy.[5,6] For example, in the NSABP B-21 trial, the 8-year risk of ipsilateral breast tumor recurrence was 16.5% among patients who received tamoxifen but not radiotherapy after BCS for primary tumors ≤1 cm in size.[7]

However, two trials that selected older patients on the basis of stage and hormone receptor status found lower local recurrence risks, approximately 10% at 10 years after BCS and endocrine therapy (ET) alone, an outcome that some patients consider acceptable. The Cancer and Acute Leukemia Group B (CALGB) 9343 trial randomly assigned women age 70 years and older with clinical or pathologic stage I breast cancer treated with BCS and ET to receive or omit adjuvant radiotherapy. Locoregional recurrence at 10 years was 10% among those randomly assigned to omission and 2% among those assigned to radiotherapy.[8] Similarly, the Post-Operative Radiotherapy In Minimum-Risk Elderly (PRIME) II trial randomly assigned women age 65 years and older with node-negative tumors ≤3 cm in size treated with BCS and ET to receive or omit radiotherapy. The local recurrence rate at 10 years was 10% among those randomly assigned to omission, compared with 1% among those assigned to radiotherapy.[9] Although the local control benefits of radiotherapy in these trials of older women were statistically significant, the rates of recurrence in the absence of radiotherapy were sufficiently low that some women may reasonably choose to forego radiotherapy. Thus, these trials have changed practice by providing a new option for selected older patients who wish to avoid radiotherapy.

By contrast, there has been limited information about whether select postmenopausal patients younger than 65 years could consider the option of breast conservation without radiotherapy. Local failure rates were similar between patients age 50-60 years, age 60-70 years, or older than 70 years in one retrospective study,[10] and between those age 55-64 years and age 65-75 years in a prospective randomized trial.[11] Another recent prospective study found the 5-year rate of local failure was 4% for patients younger than 65 years, compared with 2% for patients age 65 years and older ($P = .025$).[12] Still, many have been cautious about radiotherapy omission in younger postmenopausal patients, given a Canadian randomized trial in women age 50 years and older with node-negative breast cancer that revealed a risk of ipsilateral breast tumor recurrence of 15% at 8 years even among a planned subgroup analysis of patients with T1, hormone receptor–positive tumors.[13]

Advances may be possible because of the increasing appreciation that breast cancer is a heterogeneous disease for which tumor biology is likely more predictive of behavior and outcomes than classical clinical and pathologic features. For example, subsequent analyses of the Canadian randomized trial found that patients with tumors determined to be luminal A on immunohistochemistry using available tissue blocks (defined as estrogen receptor [ER]–positive, human epidermal growth factor receptor 2 [HER2]–negative, and Ki67 <14%) had a 10-year local recurrence rate of 7% without radiotherapy. Indeed, the local recurrence rate was only 1% for patients older than 60 years with grade 1 or 2 T1 lesions that were luminal A.[14] These data inspired the LUMINA prospective trial of BCS and ET without radiotherapy in Canada, which included patients age 55 years

or older with pT1N0 grade 1-2 tumors resected with margins ≥1 mm with luminal A features (ER ≥1%, progesterone receptor [PR] >20%, HER2-negative, and Ki67 as assessed in one of three laboratories ≤13.25%). The cumulative incidence of local recurrence was 2.3% (95% CI, 1.2 to 4.1) at 5 years.[15] However, the median age of patients was 67 years (IQR, 62-72), leaving a persistent gap in evidence regarding younger postmenopausal patients.

Genomic assays initially developed for determining overall prognosis and predicting the impact of systemic therapies may be useful for identifying patients at low risk for locoregional recurrence both in patients receiving radiotherapy and those treated with surgery alone. Given evidence suggesting that patients with low Oncotype DX recurrence scores have low risks of locoregional recurrence,[16] we designed a single-arm prospective trial to explore whether younger postmenopausal patients could also be successfully treated without radiotherapy using patient selection based on that commonly used genomic assay in addition to classic clinicopathologic selection factors.

## METHODS

In 2015, we initiated the IDEA (Individualized Decisions for Endocrine therapy Alone) prospective multicenter cohort trial (ClinicalTrials.gov identifier: NCT02400190), at 13 US institutions. The University of Michigan served as the coordinating site, including oversight of data safety and monitoring. Its institutional review board approved the study, as did those at each enrolling site.

Eligible patients were postmenopausal women age 50-69 years with unifocal breast cancer that was pT1 and pN0, on the basis of sentinel node evaluation or axillary dissection. Surgical margins were required to be 2 mm or wider after BCS, and the tumors were required to be ER-positive, PR-positive, and HER2-negative, with an Oncotype DX 21-gene recurrence score ≤18. Patients were required to have Zubrod performance status 0-2 and could not have received previous radiotherapy to the breast region, have bilateral disease or a previous personal history of breast cancer, have any previous malignancy other than nonmelanoma skin cancer unless no evidence of disease for over 5 years, or be a known carrier of a mutation that predisposes toward breast cancer development (including BRCA-1 and BRCA-2; see supplement for full study protocol; Appendix 1).

Patients were enrolled within 90 days of BCS and consented not to receive adjuvant radiotherapy, to take at least 5 years of ET, and to participate in surveillance on study through 10 years. The type of ET was at the treating provider's discretion but was required to conform to options in the National Comprehensive Cancer Network (NCCN) guidelines. The surveillance schedule included a history and physical examination by a surgeon, medical oncologist, or radiation oncologist (or an advanced practice provider in a specialty oncology practice) at least once every 6 months until 5 years after the date of surgery. Case report forms evaluated for vital status, evidence of recurrence, and ET compliance. Annual history and physical examinations were to continue until year 10; after year 5, these evaluations could be conducted by a specialist or by another health care professional, including a primary care provider. Imaging (mammograms or MRI) of the affected breast was to be performed at least annually after the surgical intervention.

The primary end point was the rate of locoregional recurrence at 5 years of follow-up after BCS. An interim analysis was conducted at 400 person-years to ensure the 5-year rate was not predicted to be ≥6% with high probability, given an a priori expectation of a rate of 4%.[16] A valid 5-year assessment was defined as a clinical assessment within 4 months before the 5-year anniversary or later. Follow-up time was calculated from the date of BCS until first recurrence or to last clinical follow-up. Recurrences were categorized as ipsilateral breast events (IBEs), regional nodal recurrence, or distant failure. The time-to-event end point was calculated using the product-limit method of Kaplan and Meier measured from the date of BCS. We assessed compliance with ET as receiving ET for at least 90% of the duration of clinical follow-up before 60 months; for patients with 60 or more months of clinical follow-up, compliance was defined as 54 months of ET exposure or more.

## RESULTS

Between June 2015 and October 2018, 200 eligible patients were enrolled. Patient characteristics are detailed in Table 1. The mean age was 62 years (standard deviation [SD], 4.9). The mean 21-gene recurrence score was 11.2 (SD, 4.8). Tumors were grade 1 in 85 patients, grade 2 in 109, and grade 3 in 6. Mean tumor size was 10 mm (SD, 4.6). Lymphovascular invasion was present in 16 tumors and an extensive intraductal component in 11.

Median follow-up time was 5.21 years (IQR, 5.01-5.97). Fourteen patients had <56 months of follow-up (eight of whom, or 4%, are formally lost to follow-up). Among the 186 patients with clinical follow-up of at least 56 months, overall and breast cancer–specific survival rates at 5 years were both 100%. Two deaths did occur. One death occurred in a patient who was lost to clinical follow-up approximately 14.3 months into follow-up and whose data were censored at that point. She died 59 months after BCS (site notified on the basis of death registry information); the cause of death could not be determined. The other death was in a patient who developed a stage IIIA high-grade endometrial carcinosarcoma diagnosed 3 years after her breast cancer, treated with surgery and chemotherapy, followed by recurrence, multiple medical complications, and ultimately death unrelated to breast cancer, 65 months after BCS.

The 5-year freedom from any recurrence was 99% (95% CI, 96 to 100). One of the two events occurring by 5 years was an isolated ipsilateral axillary recurrence at 21 months and the

**TABLE 1.** Characteristics of Patient Sample

| Characteristic | Statistics |
|---|---|
| Year enrolled, No. (%) | |
| 2015 | 10 (5) |
| 2016 | 58 (29) |
| 2017 | 103 (51.5) |
| 2018 | 29 (14.5) |
| Age, years | |
| Mean (SD) | 62 (4.9) |
| Median (IQR) | 63 (58-66) |
| Age group, No. (%) | |
| 50-59 | 60 (30) |
| 60-69 | 140 (70) |
| Zubrod performance status, No. (%) | |
| 0, asymptomatic | 175 (87.5) |
| 1, symptomatic, fully ambulatory | 25 (12.5) |
| MRI at the time of diagnosis, No. (%) | |
| No | 134 (67) |
| Yes | 66 (33) |
| Imaging evidence beyond primary site of tumor, No. (%) | |
| No | 188 (94) |
| Yes, biopsy-proven nonmalignant | 12 (6) |
| Nodal evaluation procedure, No. (%) | |
| SLNB only | 190 (95) |
| SLNB, ALND | 7 (3.5) |
| ALND only | 3 (1.5) |
| Histology, No. (%) | |
| Ductal | 169 (84.5) |
| Lobular | 20 (10) |
| Ductal and lobular | 4 (2) |
| Mucinous | 3 (1.5) |
| Tubular | 4 (2) |
| Oncotype DX 21-gene assay recurrence score | |
| Mean (SD) | 11.2 (4.8) |
| Median (IQR) | 12 (8-15) |
| Tumor grade, No. (%) | |
| Well differentiated | 85 (42.5) |
| Moderately differentiated | 109 (54.5) |
| Poorly differentiated | 6 (3) |
| Tumor size, mm | |
| Mean (SD) | 10 (4.6) |
| Median (IQR) | 9 (7-13) |
| Nodal status, No. (%) | |
| Node-negative without ITCs | 199 (99.5) |
| ITCs, no cluster >0.2 mm | 1 (0.5) |
| Lymphovascular invasion, No. (%) | |
| Absent | 171 (85.5) |
| Present | 16 (8) |
| Not reported/unknown | 13 (6.5) |
| Extensive intraductal component, No. (%) | |
| Absent | 90 (45) |
| Present | 11 (5.5) |
| Not reported | 99 (49.5) |

(continued in next column)

Abbreviations: ALND, axillary lymph node dissection; ITCs, isolated tumor cells; MRI, magnetic resonance imaging; SD, standard deviation; SLNB, sentinel lymph node biopsy.

other an IBE at 49 months. Six additional patients recurred later than 5 years after BCS (five IBEs and one IBE plus regional recurrence). No distant recurrences were observed. Details of the sites of recurrence, compliance with ET, and management of recurrences are listed in Table 2.

Figure 1 shows the actuarial analysis of events among patients in relation to age cohort. Crude rates of IBEs for the entire follow-up period for patients age 50-59 years and age 60-69 years were 3.3% (2/60) and 3.6% (5/140), respectively; crude rates of overall recurrence were 5.0% (3/60) and 3.6% (5/140), respectively.

Overall, 169 patients were compliant with ET. Of the 186 patients with at least 56 months of clinical follow-up, 184 were event-free at 5 years. Among these 184 were six patients who recurred after 5 years, of whom three (50%) were compliant, and 178 who have not yet recurred, of whom 154 (86.5%) were compliant. Both of the patients who recurred before 5 years were compliant with ET. Of the 14 patients with <56 months of clinical follow-up, nine were compliant with ET at the time of last data submission.

## DISCUSSION

The IDEA study was inspired by the desire to expand treatment options for de-escalation of therapy for the many thousands of patients with low-molecular-risk early-stage breast cancer on the basis of prospective clinical data. Our findings to date suggest that the risk of recurrence is very low at 5 years for postmenopausal patients with stage I cancers who were selected using a genomic assay in combination with classic clinical and biologic features, including patients younger than 60 years. Additional recurrences were observed after 5 years, and estimates of risk beyond 5 years are not currently reliable because of inadequate number of patients at risk. Longer follow-up will be important to determine if the risk of recurrence increases, particularly after discontinuation of ET.

When we initiated this trial, one other ongoing study considering tumor biology for patient selection was enrolling. The LUMINA study relied on immunohistochemical evaluation and accrued a somewhat older patient population. Given concerns about the consistency of biologic characterization using immunohistochemical techniques, we were interested in determining whether a standardized commercial genomic assay in routine clinical use

**TABLE 2.** Details of Recurrences

| Patient Age at Enrollment, Years | ET Details | Time to Recurrence (months after breast-conserving surgery) | Site of Recurrence | Recurrence Management/ Salvage Therapy |
|---|---|---|---|---|
| 58 | Compliant—tamoxifen | 21 | Regional nodal recurrence | Axillary dissection and regional nodal irradiation |
| 55 | Compliant—anastrozole and tamoxifen | 49 | Ipsilateral breast event (within 2 cm of the original tumor bed) | Local excision and ET |
| 66 | Noncompliant—40 months of ET—exemestane discontinued 9 months prior to recurrence | 64 | Ipsilateral breast event (within 2 cm of the original tumor bed) and simultaneous regional nodal recurrence | Mastectomy and postmastectomy irradiation |
| 53 | Quasi-compliant—letrozole and then changed to tamoxifen and then changed to raloxifene (nonstandard agent) on which she continued at the time of recurrence | 72 | Ipsilateral breast event (skin lesion) | Local excision, irradiation, aromatase inhibitor, and abemaciclib |
| 61 | Compliant—anastrozole, with ET continued beyond 5 years and patient on anastrozole until recurrence | 74 | Ipsilateral breast event (located more than 2 cm from original tumor bed; patient found to have a deleterious CHEK2 mutation) | Mastectomy |
| 60 | Compliant—anastrozole. Patient stopped ET at approximately 60 months, approximately 8 months before recurrence | 74 | Ipsilateral breast event (within 2 cm of the original tumor bed) | Local excision |
| 66 | Compliant—anastrozole and tamoxifen. Patient stopped ET at approximately 66 months, approximately 13 months before recurrence | 75 | Ipsilateral breast event (proximity to original tumor bed not reported) and contralateral DCIS | Local excision, irradiation, ET |
| 68 | Noncompliant—letrozole for 35 months, discontinued, approximately 48 months before recurrence | 84 | Ipsilateral breast event (within 2 cm of the original tumor bed) | Local excision |

Abbreviation: ET, endocrine therapy.

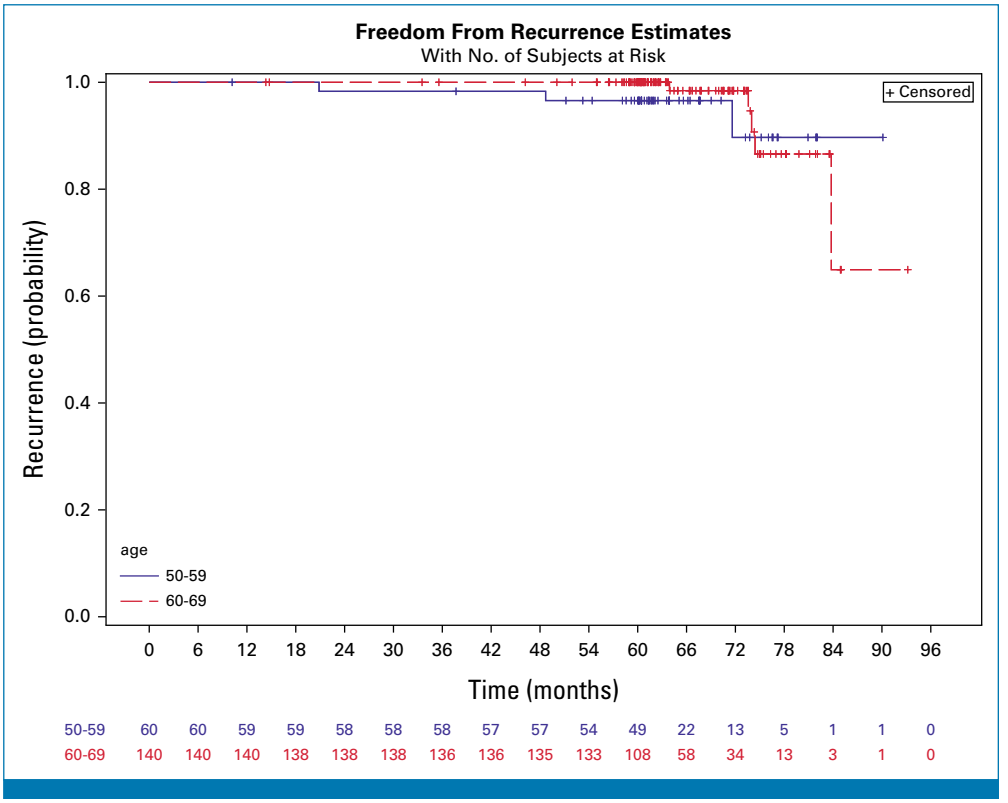


**FIG 1.** Freedom from recurrence in relation to age cohort.

would reliably identify a biologically favorable population of younger postmenopausal patients in whom radiotherapy can safely be omitted after lumpectomy. We selected the 21-gene Oncotype Dx recurrence score because it is commonly performed for adjuvant systemic therapy decision making in patients with hormone receptor–positive and HER2-negative early-stage breast cancer. The 21-gene assay was initially validated for the purposes of systemic therapy decision making. More recently, Mamounas et al[17] reported an association between the recurrence score and the risk of locoregional recurrence from the NSABP B-14 and NSABP B-20 populations. In patients treated with tamoxifen, the 10-year locoregional recurrence risk was significantly associated with recurrence score: 4.3% for low scores (≤17), 7.2% for intermediate scores (18-30), and 15.8% for high scores (≥31). Significant associations were also seen in placebo and chemotherapy-treated groups, and recurrence score was an independent predictor of locoregional recurrence along with age and treatment type in multivariable analysis. In particular, recurrence score appeared predictive in mastectomy patients who had not received radiotherapy, suggesting that it may be particularly useful in estimating locoregional recurrence risk in the absence of radiotherapy. Because all patients receiving lumpectomy for invasive cancer on these NSABP studies were required to receive adjuvant radiotherapy, we initiated the IDEA trial to evaluate whether the 21-gene recurrence score could identify a biologically favorable subgroup of patients who could be treated with lumpectomy and adjuvant ET alone with low recurrence risk. In more recent years, additional genomic assays have been developed, including ones specifically focused on local recurrences and predicting radiotherapy effect, which may offer further opportunities to refine patient selection for the option of radiotherapy omission,[18] although if a single assay could be used to support decisions about both systemic and locoregional therapy, it might be most cost-effective.

A number of complementary studies investigating radiotherapy omission have been initiated since the opening of IDEA (Table 3). After reassuring early results from a preplanned interim analysis of this trial,[16] the DEBRA trial (NRG BR007, ClinicalTrials.gov identifier: NCT04852887) opened, using similar eligibility criteria to those in IDEA. Patients are randomly allocated to receive ET with or without breast radiotherapy. This trial includes quality-of-life measures in both arms, which will further inform patient decision making.[19] Other ongoing trials include the PRIMETIME[20] cohort study in the United Kingdom, which relies on immunohistochemistry to assign biologic risk, and the PRECISION[21] and EXPERT[22] trials, which use the PAM50 assay. We eagerly anticipate the maturation of these studies, which will further extend our understanding of the options available to patients.

Limitations of this study include the modest sample size, albeit accrued exactly as predicted in the protocol, which may limit generalizability and the ability to comment on subgroups. There was modest loss to follow-up and there

**TABLE 3.** Trials Evaluating De-Escalation in Low-Risk Breast Cancer

| Characteristic | IDEA | LUMINA | PRECISION | PRIMETIME | EXPERT | Natural | EUROPA | DEBRA |
|---|---|---|---|---|---|---|---|---|
| Design | Single arm | Single arm | Single arm | Single arm | Randomized | Randomized | Randomized | Randomized |
| Years | 2015-2018 | 2013-2017 | 2016-present | 2017-2022 | 2017-present | 2018-present | 2021-present | 2021-present |
| Accrual goal | 200 | 501 | 672 | 2,400 | 1,167 | 926 | 926 | 1,670 |
| Age, years | ≥50-≤69 | ≥55 | ≥50-≤75 | ≥60 | ≥50 | ≥60 | ≥70 | ≥50-≤70 |
| T stage | pT1 | pT1 | pT1 | pT1 | pT1 | pT1 | pT1 | pT1 |
| N stage | pN0, pN0(IHC+) | pN0 | pN0, pN0(IHC+) | pN0 | pN0, pN0(IHC+) | pN0 | cN0, pN0, pN0(IHC+) | pN0 |
| Grade | Any | 1-2 | 1-2 | 1-2 | 1-2 | 1-2 | Any if ≤1 cm 1-2 if >1 cm | Any |
| Biologic criteria | Oncotype<br>Score ≤18<br>IHC<br>ER/PR+<br>HER2− | IHC<br>ER ≥1%<br>PR >20%<br>HER2−<br>Ki67 ≤13.25% | PAM-50<br>Low risk<br>IHC<br>ER/PR ≥10%<br>HER2− | IHC<br>ER/PR+<br>HER2−<br>IHC4+C<br>Very low | PAM-50<br>Luminal A<br>ROR ≤60 | IHC<br>ER ≥10%<br>HER2− | IHC<br>ER/PR ≥10%<br>HER2−<br>Ki67 ≤20% | Oncotype<br>Score ≤18<br>IHC<br>ER/PR ≥1%<br>HER2− |
| Trial arms | ET | ET | ET | ET | ET *v* ET + RT | ET *v* ET + APBI | ET *v* APBI | ET *v* ET + RT |

Abbreviations: APBI, Accelerated Partial Breast Radiation; DEBRA, De-Escalation of Breast Radiation; ET, endocrine therapy; EUROPA, Exclusive Endocrine Therapy or Radiation Therapy; EXPERT, Examining Personalized Radiation Therapy; HER2, human epidermal growth factor receptor 2; IDEA, Individualized Decisions for Endocrine Therapy Alone; LUMINA, Luminal A; Natural, RT Natural Trial; PRECISION, Profiling Early Breast Cancer for Radiotherapy Omission; PRIMETIME, Postoperative Avoidance of Radiotherapy; RT, radiation therapy.

remains a need for longer-term follow-up. Furthermore, advances in radiotherapy[17,18] have substantially reduced toxicity and short-term burden of treatment since this trial was initiated, with implications for the risk-benefit ratio of receiving radiotherapy, particularly among women with long life expectancies. The patients eligible for IDEA are now also candidates for emerging regimens treating the whole breast or partial breast in one to five fractions. Numerous prospective trials and guidelines now establish partial-breast irradiation as an acceptable standard to whole-breast radiotherapy in a selected group of low-risk patients, using a variety of delivery techniques.[23,24] For example, the 10-year safety and efficacy of 5-fraction accelerated partial-breast irradiation with an external-beam intensity-modulated technique reported equivalent disease control to whole-breast irradiation while reducing patient burden and with improved cosmetic outcomes in a trial from Florence.[25] Others have reported favorable 5-year outcomes after ultrahypofractionated 5-fraction whole-breast radiotherapy regimens in the FAST-Forward trial.[26] Regardless, some women will wish to avoid the burden and potential toxicity of radiotherapy altogether. In the absence of other evidence, the findings should not be generalized to patients who have less extensive surgery than the pathologic nodal evaluation and margin requirements of the study, and caution is necessary if compliance with ET is not expected, given that compliance was high in this sample of women who enrolled on trial.[27]

To our knowledge, the IDEA study represents the first prospective trial to incorporate a genomic assay of low molecular risk to identify optimal candidates for omission of breast radiotherapy. It demonstrates very low rates of recurrence at 5 years in a patient sample that includes women in their 50s. Specifically, the 5-year probability of recurrence in IDEA is consistent with or lower than the 4% risk estimated a priori on the basis of the 5-year results of PRIME II and CALGB 9343, although the patients accrued were younger. This study provides valuable information to support both the need for and the appropriateness of other ongoing trials evaluating radiotherapy omission in breast conservation patients. We will update our results after accumulation of follow-up data necessary to estimate risk in patients after ET is typically discontinued.

The paradigm for breast cancer treatment recommendations has recently evolved from standardized, one-size-fits-all algorithms to individualized recommendations combining clinical-pathologic, biological, and molecular predictors. Specifically, strategies to optimize radiotherapy decisions after BCS for low-risk patients include multiple short-course regimens and improved delivery techniques that reduce toxicity and burden, in addition to expansion of the criteria for safely omitting radiotherapy altogether. To our knowledge, the IDEA trial is the first to prospectively evaluate combining traditional clinical-pathologic features with a readily available genomic assay to identify a younger group of low-risk patients who might consider radiotherapy omission than currently described in guideline recommendations.

In conclusion, the IDEA trial suggests high disease control at 5 years after omission of radiotherapy in a cohort of postmenopausal patients age 50-69 years with pT1N0 unifocal invasive breast cancer favorable biologic features. These data, along with longer-term follow-up and data from ongoing trials, including larger randomized trials, inform whether the option of avoiding immediate radiotherapy after BCS can be offered to a broader group of women than current guidelines recommend. Such efforts strive to empower patients with choices and return to them a sense of agency that can be deeply meaningful in the context of a recent cancer diagnosis.



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## CLINICAL TRIAL INFORMATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

## APPENDIX 1. PROTOCOL-SPECIFIED ANALYSIS PLAN

The primary study analysis will occur when all patients enrolled at all collaborating sites have reached 5 years of follow-up. We believe that loss to follow-up and mortality will be extremely low. It is probable that we can observe the locoregional recurrence (LRR) status of each patient after 5 years of follow-up; however, product-limit methods will be used to estimate the LRR rate at 5 years in the presence of censoring. Patient will be censored on their last known clinical visit date if lost to follow-up, on the patient's death date if the patient is known to have died without LRR, and on the date of events that would preclude in-breast failure, such as elective mastectomy or prophylactic mastectomy of the breast after a new diagnosis of breast cancer in the originally unaffected breast. We will also report the proportion of individuals experiencing LRR who receive various forms of salvage therapy, including mastectomy. Cox proportional hazards regression models will be used to explore the association of endocrine therapy (ET) compliance and specific Oncotype DX RS with LRR, if sufficient LRR are observed. Compliance may be dichotomized or may be used as a time-dependent covariate in regression models. Oncotype DX RS may be used as a continuous covariate or categorized into subgroups.

The trial's results will be used to inform the design of a future cooperative group trial for the comparison with and without radiotherapy.

### Final Analysis Plan Used for Manuscript

The primary analysis was conducted when all patients had the opportunity (if not lost to follow-up) to be observed for 5 years from the date of breast-conserving surgery (BCS) for recurrence. The primary end point was the rate of breast cancer recurrence at 5 years from the date of BCS. A valid 5-year assessment was defined as a clinical assessment within 4 months before the 5-year anniversary or a finding of no recurrence after the 5-year anniversary. Follow-up time was calculated from the date of BCS until first recurrence or to last clinical follow-up. Recurrences were categorized as ipsilateral breast events, regional nodal recurrence, or distant failure. The time-to-event end point was calculated using the product-limit method of Kaplan and Meier measured from the date of BCS.

We assessed compliance with ET as a dichotomous end point defined as receiving ET for at least 90% of the duration of clinical follow-up before 60 months; for patients with 60 or more months of clinical follow-up, compliance was defined as 54 months of ET exposure or more.

Because of the paucity of recurrence events, time-to-event regression models to explain covariate associations with recurrence were not attempted.

### The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)

***Amendment Summary.*** Original Version: November 14, 2014

1. Version January 20, 2015
   - The statistical analysis section (13) of the protocol has been amended, and a detailed appendix (A) added in response to constructive comments from statistical reviewers at the Scientific Review Committees of two other participating sites. The design is unchanged, but further detail has been provided, and the stopping rule amended to appropriately balance the desire to stop the trial early if sufficient LRR events are observed to suggest that the LRR rate at 5 years is likely to be at or above 6% with the desire not to cause unnecessary distress with a false finding at a relatively early study time point if the true 5-year LRR is not above our threshold. These revisions have been discussed in detail by the Cancer Center biostatisticians, with strong support for these revisions.
2. June 12, 2025
   - Updated revision date
   - Add Alissa Stewart to cover page
   - Update typo in schedule for HER2-
   - Updated section 9.2 to clarify imaging frequency after treatment.
3. March 3, 2016
   - Changed throughout: Reduced restrictions on mammogram for eligibility. Many patients do not have mammograms in the previous time frame as part of standard-of-care treatment. Therefore, restrictions were changed to require an ipsilateral mammogram within 6 months of study entry and a mammogram of the contralateral breast within 1 year of study entry.
     a. Section 3.1.9
     b. Section 4.0
     c. Section 11.0, footnote d.
   - Section 11, footnote d: updated required frequency of follow-up diagnostic mammograms, to follow clinical guidelines.
4. April 13, 2016
   - Updated sections 3.1.9 and 4.0 to clarify frequency and timing of related breast imaging for eligibility purposes. Patients must have had breast imaging (mammogram or MRI) of the ipsilateral breast within 6 months of study entry. Patient must have had breast imaging (mammogram or MRI) of the contralateral breast within 1 year of study entry.
   - Updated section 9.2 to clarify type of imaging during patient follow-up. Patients often have MRI instead of mammograms.
   - Updated 11.0—Study Calendar—to reflect these changes. Updated footnote (d) to reflect these changes.
5. May 29, 2018
   - Section 13.1: Patients who withdraw from the trial, opting to receive radiation treatment, within 1 week of enrollment, would be replaced.
6. July 30, 2019
   - 9.2 Off Study Criteria: Patients should be followed as per the study calendar in section 11.0. Every attempt should be made to follow enrolled patients, including receiving and reviewing medical record documentation outside of the home institution. In the event that medical record information cannot be obtained for a period of 18 months, the patient will be considered lost to follow-up. The home institution study team should make three documented attempts to contact the patient to schedule a follow-up visit or obtain outside records. The attempts should include phone calls and at least one certified letter.
   - If contact is re-established after 18 months via standard clinical contact, and follow-up data can be obtained, the patient's data will be updated and the patient will no longer be considered lost to follow-up.