American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
June 13th, 2018
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Selected Common Biomarkers: Recognizing the Pattern of Malignancy

- **Elevated LDH Lactic Acid Dehydrogenase**
- **Low Serum Albumin & Albumin/Globulin Ratio**
- **Elevated Serum Ferritin**

Elevated LDH Lactic Acid Dehydrogenase

Normal: 100-333 u/l. > 245 u/L = upper quartile of normal

Elevated LDH is a sign of tumor cell proliferation.

Serum LDH is often elevated in aggressive cancers and hematological malignancies.

Elevated LDH may be a marker of early carcinogenesis, disease progression and a poor prognosis for survival.

Aberrant metabolism and inefficient fuel production is a characteristic of tumor cells dominated by aerobic glycolysis, increased lactate production and a higher uptake of glucose (the Warburg effect). Lactate dehydrogenase (LDH) catalyzes the reduction of pyruvate to form lactate**.**

LDH is elevated in melanoma, lymphoma, acute leukemia, seminoma germ cell, pancreatic, gastric, lung, renal cell, nasopharyngeal, esophageal, cervical, and prostate cancers.

Elevated LDH
>245 u/L
Independent Biomarker of:
Early Carcinogenesis
Disease Progression
Risk of Cancer-Specific Death

Poor Prognosis for Disease Free Survival & Overall Survival

Wulaningsih, W., Holmberg, L., Garmo, H., Malmstrom, H., Lambe, M., Hammar, N., ... & Van Hemelrijck, M. (2015). Serum lactate dehydrogenase and survival following cancer diagnosis. British journal of cancer, 113(9), 1389.

Zhang, J., Yao, Y. H., Li, B. G., Yang, Q., Zhang, P. Y., & Wang, H. T. (2015). Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis. Scientific reports, 5, 9800.

Low Serum Albumin (<3.5 g/dL)

Malnutrition is a significant problem in cancer patients and is a predictor of survival.

Malnutrition has been associated with deteriorated quality of life, decreased response to treatment, increased risk of chemotherapy-induced toxicity and a reduction in cancer survival.

Serum Albumin is linked to cancer survival and reflects both protein malnutrition and frailty and is often seen in patients with sarcopenia and cachexia.

Serum Albumin levels provide useful prognostic significance in cancer and can be used to better define baseline risk in cancer patients.

Serum albumin is generally used to assess the nutritional status, severity of disease, disease progression and prognosis.

In a multivariate analysis of 29 studies, Gupta and Lis concluded that “higher serum albumin levels to be associated with better survival.”

In the later stages of disease, malnutrition and inflammation suppress albumin synthesis. **The normal adult range of serum albumin is defined as 3.5-5.0 g/ dL, and a level of <3.5 g/dL is called hypoalbuminemia.**

Albumin concentration with the established cutoff point of 37.5 g/L was clearly proven as the predictive factor of both chemotoxicity and of survival (HR (95 % CI) = 0.55).

Srdic, D., Plestina, S., Sverko-Peternac, A., Nikolac, N., Simundic, A. M., & Samarzija, M. (2016). Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer—chemotherapy toxicity and prognostic value. Supportive care in cancer, 24(11), 4495-4502.

Gupta, D., & Lis, C. G. (2010). Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutrition journal, 9(1), 69.

Low Albumin-to-Globulin Ratio (<1.66)

A low albumin-to-globulin ratio is a risk factor for cancer incidence and mortality, both short- and long terms, in generally healthy screened adults**.**

Low Albumin-to-Globulin Ratio in cancer patients predicts low overall survival.

HYPOALBUMINEMIA
<3.5g/dL
Disease Progression
Increased ChemoToxicity
Poor Prognosis for Survival

There is slight or no hypoalbuminemia in the early stages of cancer.
As disease progresses, albumin levels drop significantly.

Suh, B., Park, S., Shin, D. W., Yun, J. M., Keam, B., Yang, H. K., ... & Cho, B. (2014). Low albumin-to-globulin ratio associated with cancer incidence and mortality in generally healthy adults. Annals of

oncology, 25(11), 2260-2266.

Elevated Ferritin

Ferritin, a strong **survival predictor** as well as an acute phase response protein, has been associated with the pathological processes of inflammation and infection.

Elevated serum ferritin levels have been seen in breast cancer, pancreatic cancer, non-small cell lung cancer, hepatocellular carcinoma, leukemia, colorectal cancer and lymphoma.

High ferritin levels are significantly associated with reduced survival time and increased risk of mortality in cancer patients.

*Lee, S., Song, A., & Eo, W. (2016). Serum ferritin as a prognostic biomarker for survival in relapsed or refractory metastatic colorectal cancer. Journal of Cancer, 7(8), 957.*J Cancer. 2016 May 12;7(8):957-64.

HYPERFERRITINEMIA
Serum Ferritin
> 200ng/ml (Men), >150ng/ml (Women)
indicates
Inflammation
Immunosuppression
Angiogenesis
Proliferation

Questions & Answers

Beth Meneley, L.Ac.: How do you approach women who would still like to conceive who are prescribed Tamoxifen? Insight on cancer medication and fertility.

- Ensure patient has been counseled on fertility and egg harvesting options
- Tamoxifen is a selective estrogen receptor modulator (SERM) that modulates estrogen by blocking estrogen receptors
- Commonly used for ER+ breast cancers in premenopausal women who are still producing estrogen but also used in brain, pancreatic cancers that have estrogen receptor involvement.
- Adverse side effects of Tamoxifen:
    - May cause thickening of uterine lining - monitor every 6 months with ultrasound
    - Uterine cancer
    - Greater risk of thromboembolic events - monitor D-Dimer and fibrinogen
    - High frequency of congenital abnormalities warrants reliable birth control and washout period of 2 months post treatment
- Tamoxifen is not used in post-menopausal women. Aromatase inhibitors are used instead due to lower adverse side effects.

Use of Tamoxifen Before and During Pregnancy
Geert Braems, Hannelore Denys, Olivier De Wever, Veronique Cocquyt, Rudy Van den Broecke Oncologist. 2011 Nov; 16(11): 1547–1551. Published online 2011 Oct 21. doi: 10.1634/theoncologist.2011-0121

ABSTRACT
For premenopausal patients with receptor-positive early breast cancer, administration of tamoxifen for 5

years constitutes the main adjuvant endocrine therapy. **During pregnancy, tamoxifen and its metabolites interact with rapidly growing and developing embryonic or fetal tissues.**

Information about tamoxifen and pregnancy was gathered by searching PubMed. In addition, we had access to the records of the pharmaceutical company AstraZeneca. Because these observations are retrospective and other therapies and diagnostic measures are possible confounders, a causal relationship was not established between tamoxifen treatment and pregnancy outcome.

The records from AstraZeneca documented three live births with congenital anomalies and four live births without congenital anomalies related to tamoxifen treatment before pregnancy. Tamoxifen therapy during pregnancy resulted in 16 live births with congenital malformations and a total of 122 live births without malformations. The 122 live births without malformations included 85 patients from a prevention trial that did not record a single anomaly, whereas the AstraZeneca Safety Database alone reported 11 babies with congenital malformations of 44 live
births. Additionally, there were: 12 spontaneous abortions, 17 terminations of pregnancy without known fetal defects, six terminations of pregnancy with fetal defects, one stillbirth without fetal defects, two stillbirths with fetal defects, and 57 unknown outcomes.

The relatively high frequency of severe congenital abnormalities indicates that reliable birth control during tamoxifen treatment is mandatory. After tamoxifen use, a washout period of 2 months is advisable based on the known half-life of tamoxifen. In case of an inadvertent pregnancy, risks and options should be discussed.

Impact of Fertility Concerns on Tamoxifen Initiation and Persistence
Natalia C Llarena, Samantha L Estevez, Susan L Tucker, Jacqueline S Jeruss
J Natl Cancer Inst. 2015 Oct; 107(10): djv202. Published online 2015 Aug 25.
doi: 10.1093/jnci/djv202

Safety of Tamoxifen During Pregnancy: 3 Case Reports and Review of the Literature
Emre Koca, Taha Y. Kuzan, Taner Babacan, Ibrahim H. Turkbeyler, Sarici Furkan, Kadri Altundag Breast Care (Basel) 2013 Dec; 8(6): 453–454. Published online 2013 Dec 16. doi: 10.1159/000357321

Corey Deacon: How often do biopsies need to be analyzed to adjust precise treatment? - due to cancer's adaptability?

Biopsies should only be collected conservatively as invasive procedures should be limited. Typically a course of treatment is implemented…efficacy and response are assessed over 3-6 months.

Many patients are not candidates for biopsy as there is no easily accessible tissue or the cancer is diffuse or there is not a large enough mass to yield enough tissue for analysis.

Use of genomics and proteomics is not standard of care.

Corey Deacon: How often should one run transcriptomics when looking at aggressive cancers like this?

Transcriptomics (or proteomics) is NEW. We do not know how often it changes. Probably not more than 6 months. It is costly (minimum of $5,000) and patients mostly need to pay out of pocket.

Diagnostic testing is only a piece of decision making. We do analyze and assess the tumor

microenvironment more frequently…typically every 3-6 months depending on each patient's status and progress.

Corey Deacon: You've mentioned advanced modules - are these part of this course or another course altogether?

The current course is a FOUNDATION course. I am adding to the Cancer and Diet module as it really deserves more in depth content. To be recorded this summer.

Advanced modules will likely be released one at a time to existing students and eventually these will constitute an advanced course. In process…It is very time intensive to produce each module.

Cathy Biase: Is colostrum a viable useful supplement for cancer patients and are there any contraindications with medicine or therapies?

Hao, L., Shan, Q., Wei, J., Ma, F., & Sun, P. (2018). ***Lactoferrin: major physiological functions and applications. Current protein & peptide science.***

Abstract
Lactoferrin (lactotransferrin; Lf) is an **iron-binding glycoprotein and one of the most important bioactivators in milk** and other external secretions. It has **numerous biological roles, including the regulation of iron absorption and modulation of immune responses, and has anti-microbial, anti-viral, antioxidant, anti-cancer, and anti-inflammatory activities.** Lf **regulates the quantity of iron absorbed in the intestine via its role in iron transport and can also chelate iron, directly or indirectly**. Notably, it has been used as an **adjuvant therapy for some intestinal diseases**. It is now used in nutraceutical-supplemented infant formula and other food products. This article reviews the content, distribution, physiologic functions and current applications of Lf, and aims to shed light on future prospects for additional applications of Lf.

Kruzel, M. L., Zimecki, M., & Actor, J. K. (2017). ***Lactoferrin in a Context of inflammation-induced Pathology. Frontiers in immunology****, 8, 1438.*

ABSTRACT
Much progress has been achieved to elucidate the function of **lactoferrin (LTF), an iron-binding glycoprotein**, in the milieu of immune functionality. This review represents a unique examination of LTF toward its importance in physiologic homeostasis as related to development of disease-associated pathology. The **immunomodulatory** nature of this protein derives from its unique ability to "sense" the immune activation status of an organism and act accordingly. Underlying mechanisms are proposed whereby LTF controls disease states, thereby pinpointing regions of entry for LTF in maintenance of various physiological pathways to limit the magnitude of tissue damage. LTF is examined as a first line mediator in immune defense and response to pathogenic and non-pathogenic injury, as well as a molecule **critical for control of oxidative cell function**. Mechanisms of interaction of LTF with its receptors are examined, with a focus on protective effects *via* **regulation of enzyme activities and reactive oxygen species production,** immune deviation, and prevention of cell apoptosis. Indeed, LTF serves as a critical control point in physiologic homeostasis, functioning as a sensor of immunological performance related to pathology. Specific mediation of tissue pathophysiology is described for **maintenance of intestinal integrity during endotoxemia, elicited airway inflammation due to allergens, and pulmonary damage during tuberculosis**. Finally, **the role of LTF to alter differentiation of adaptive immune function** is examined, with specific recognition of its utility as a vaccine adjuvant to control subsequent lymphocytic reactivity. Overall, it is clear that while the ability of LTF to both **sequester iron and to direct reactive oxygen intermediates is a major factor in lessening damage due to excessive inflammatory responses**,

further effects are apparent through direct control over development of higher order immune functions that regulate pathology due to insult and injury. This culminates in **attenuation of pathological damage during inflammatory injury.**

Susan Carroll: I would like to know where you/your patients obtain powdered supplements such as resveratrol, ginkgo and milk thistle?

- I ONLY RECOMMEND reliable suppliers
- Golden Lotus Herbs goldenlotusherbs.com for powdered herbs and liquid botanical extracts. They do not have EVERYTHING they carry on their website so you have to call them.
- Heron Botanicals (heronbotanicals.com) for botanical extracts

Susan Carroll: What do you think of commercial online sources such as "Bulk Herbs"?

- You have to vet EVERY manufacturer and EVERY supplier.
- I do not know if "BULK HERBS" is a reliable supplier, probably not…but the only way to know is to ask for a CERTIFICATE OF ANALYSIS for a current batch for every product in question.
- If they will not comply…then they do not analyze or assay their products for contaminants, heavy metals, authenticity, solvents.
- Do they store their product in temperature controlled warehouses?
- Do they do their own analysis of the products they sell?
- What is the concentration of the batch?

Stacy, Oncologist: Comments on how she works with repeat biopsies:

- Sends tissues to Foundation Medicine and Caris to get all mutations within tumor
- Very difficult to work with just one trait or mutation in a tumor sample
- Liquid biopsies are an alternative to tissue biopsies
- Biocept Laboratories in California for circulating tumor cells for other types of cancers

Dr. Nalini: Important to look at the whole landscape of the tumor microenvironment

Research: Chemo Not Needed for Most Early Breast Cancer: TAILORx

Roxanne Nelson, BSN, RN June 03, 2018
https://www.medscape.com/viewarticle/897537

CHICAGO — **Adjuvant chemotherapy is not necessary for a large proportion of women with early-stage breast cancer, according to new findings that experts agree are "practice changing." The results come from a federally funded study, the Trial Assigning IndividuaLized Options for TReatment (TAILORx), which involved more than 10,000 patients and tested the 21-tumor gene expression assay (*Oncotype Dx*, Genomic Health).**

"This is the largest adjuvant breast cancer trial ever performed," said lead study author Joseph A. Sparano, MD, associate director for clinical research at the Albert Einstein Cancer Center and Montefiore Health System in New York City and vice-chair of the ECOG-ACRIN Cancer Research Group.

"What we were really trying to do with this trial was 'thread the needle,'" he said.

"In terms of the big picture and the impact on care, application of this test in clinical practice in this population

will spare an estimated 70% [of patients] and limit chemotherapy to the 30% who may benefit from it," he added.

The results showed that about 70% of patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative early-stage breast cancer, who received a midrange (intermediate) score on the Oncotype Dx test, could be spared chemotherapy. The trial found no difference in the disease-free survival whether these women were treated with endocrine therapy alone or with the combination of endocrine therapy with chemotherapy.

The results were presented during the Plenary Session here at the American Society of Clinical Oncology (ASCO) 2018 and simultaneously published in the *New England Journal of Medicine*.

Undetermined Benefit

About half of all breast cancers are hormone receptor positive, HER2 negative, and axillary node negative (ie, like the trial population), but up to 30% of patients have incurable recurrences by 10 years, Sparano explained.

Adjuvant chemotherapy is typically recommended to reduce this risk for relapse, but the absolute benefit is small (3% to 5%). "This results in many women being overtreated, because endocrine therapy would be adequate," he explained.

Oncotype DX is a commercially available gene-expression assay that provides prognostic information in hormone receptor–positive breast cancer, with a recurrence score that ranges from 0 to 100.

Patients who obtain a high score (defined as 26 or higher, or sometimes as 39 or higher) are considered to be at high risk for relapse and so are considered to benefit from chemotherapy.

Patients who obtain a low score (0 to 10) are considered to have a very low rate of distant recurrence (2% at 10 years), and that recurrence is not likely to be affected with use of adjuvant chemotherapy. Thus, these women can skip it.

However, for the patients who score in the midrange between these two extremes — about two thirds who undergo testing — whether chemotherapy would reduce the risk for recurrence has been unclear.

So this is what the new trial set out to investigate.

No Benefit for Most Patients

The study enrolled 10,273 women with hormone receptor–positive, HER2-negative, axillary node–negative breast cancer, and of this group, 6711 had a midrange recurrence score of 11 to 25.

They were randomly assigned to receive endocrine therapy alone or endocrine therapy and chemotherapy. At the final analysis, with a median follow-up of 90 months, there were 836 events of invasive disease recurrence, second primary cancer, or death. This included 338 (40.4%) recurrences of breast cancer as the first event, of which 199 (23.8% of the total events) were distant recurrences.

Overall, endocrine therapy was noninferior to chemotherapy plus endocrine therapy, with a hazard ratio (HR) for invasive disease recurrence, second primary cancer, or death of 1.08 (endocrine vs combination therapy; 95% confidence interval [CI], 0.94 - 1.24; P = .26).

Similarly, endocrine therapy alone was also noninferior for other endpoints that included freedom from recurrence of breast cancer at a distant site (HR for recurrence, 1.10; P = .48), freedom from recurrence of breast cancer at a distant or local-regional site (HR for recurrence, 1.11; P = .33), and overall survival (HR

for death, 0.99; *P* = .89).

The 9-year rates were similar between both groups for disease-free survival (83.3% vs 84.3%), distant recurrence (94.5% vs 95.0%), and overall survival (93.9% vs 93.8%).

However, chemotherapy did appear to have some benefit in patients who were age 50 years or younger with a recurrence score of 16 to 25.

"A very important finding was that in an exploratory analysis in the randomized group, which we conducted to make sure that there weren't any subgroups who could derive some benefit from chemotherapy, we found an interaction between age and recurrence score," said Sparano.

Younger women (<50 years) with a recurrence score of 16 to 25 received some benefit from chemotherapy. There were 2% fewer distant recurrences for recurrence scores 16 to 20, and 7% fewer for recurrence scores of 21 to 25.

"This information can drive some women with recurrence scores in this range to accept chemotherapy," he explained.

"Definitely Practice Changing"

Approached by *Medscape Medical News* for an independent comment, Charles L. Shapiro, MD, professor of medicine and director of translational breast cancer research and cancer survivorship at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai in New York City, emphasized that "this is definitely practice changing."

"We knew about the low-risk patients and could pretty much select those out as they didn't need chemotherapy," he said. "And we knew that the high-risk patients did need chemotherapy."
Many of us were uncertain about what to do. Dr Charles Shapiro

However, the situation was quite different with intermediate-risk patients, and there was always a question as to whether they needed chemotherapy. "Many of us were uncertain about what to do," said Shapiro.

"But this answers definitively that chemotherapy doesn't benefit patients with recurrence scores of 11 to 25," he continued. "Many physicians were afraid not to give chemotherapy to patients in that group as they didn't want to take a chance of just treating with endocrine therapy alone when the benefit of chemotherapy wasn't known."

Now the situation has changed, and the results of this trial have "shut the coffin on chemotherapy."
"What this means is that 70% of patients do not need chemotherapy if they are ER [estrogen receptor] positive and node negative, and this is a definitive trial and it says no," he explained. "Many of us were torn and some of us were giving chemotherapy, but now we're not going to."

The next step is to see how well these data might extrapolate to patients with node-positive disease, he said. A prospective randomized trial has just finished enrolling for women with one to three positive nodes and a recurrence score of less than 25. He said that he believes the results will be similar to those of the TAILORx trial.

This study really gives a "plug for doing large trials, which NCI [National Cancer Institute] really doesn't do much of anymore," he commented. "The money isn't there and it cost millions to these trials and do the follow-up," he said.

"But a study this size is powered to provide definitive answers to questions."

Elias Obeid, MD, director of the Breast, Ovarian and Prostate Cancer Risk Assessment program at Fox Chase Cancer Center, Philadelphia, Pennsylvania, echoed that these data are indeed practice changing and will "save thousands of women from getting unnecessary chemotherapy."

"Up until now we have been offering women chemo because we didn't know whether there was any benefit or lack thereof in this group of patients with intermediate-risk breast cancer by the 21-gene assay," he said.

"However, now we can, with an evidence-based recommendation, de-escalate treatment, avoid chemotherapy, treat only with hormonal therapy, and still have a great survivorship rate with early-stage breast cancer.

ASCO expert Harold Burstein, MD, PhD, also weighed in on the results.

"The most challenging decision we have to make with these patients is whether to recommend adjuvant chemotherapy, with all of its side effects and its potential benefits," he said.

Burstein, who is also clinician and clinical investigator in the Breast Oncology Center at the Dana Farber Cancer Institute in Boston, Massachusetts, pointed out that if "you've ever been a clinician, or a patient in a consultation room, there's a big difference between saying, 'You may benefit a little bit or you won't benefit at all.'"

With these data, most women who have this test performed can be told that they don't need chemotherapy, and that can be said with tremendous confidence and reassurance.

However, Burstein also pointed out that because this test has already been available for 12 years, a question arises: "Why did we need this study to validate this experience?"

The study is important for several reasons, he noted. First, the original data on the Oncotype assay were based on chemotherapy regimens that are now 25 years old. "So there was the question [of whether] the results would be different with the use of modern chemotherapy agents," he said.

"Second, the endocrine therapy approaches have changed, which also could have affected these results. "Third, we now have a prospective validation of the data."

He also emphasized that this study is not really about de-escalation because its goal was not just to use less treatment. "The goal was to tailor treatment and they chose the title [TAILORx] very applicably," he added.

"This allows us to individualize treatment based on extraordinary science and validation," he added.

American Society of Clinical Oncology (ASCO) 2018. Presented June 3, 2018. Abstract LBA1: https://meetinglibrary.asco.org/record/161490/abstract

N Engl J Med. Published June 3, 2018. Abstract: https://www.nejm.org/doi/full/10.1056/NEJMoa1804710
Sparano, J. A., Gray, R. J., Makower, D. F., Pritchard, K. I., Albain, K. S., Hayes, D. F., ... & Lively, T. (2018). Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. New England Journal of Medicine.

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

ABSTRACT

BACKGROUND

The recurrence score based on the 21-gene breast cancer assay predicts chemotherapy benefit if it is high and a low risk of recurrence in the absence of chemotherapy if it is low; however, there is uncertainty about the benefit of chemotherapy for most patients, who have a midrange score.

METHODS

We performed a prospective trial involving 10,273 women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer. Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The trial was designed to show noninferiority of endocrine therapy alone for invasive disease–free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death).

RESULTS

Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease–free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local–regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease–free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.

CONCLUSIONS

Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger. (Funded by the National Cancer Institute and others; TAILORx ClinicalTrials.gov number, NCT00310180.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sparano at Montefiore Medical Center, 1695 Eastchester Rd., Bronx, NY 10461, or at jsparano@montefiore.org.

A full list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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Breast cancer is the most common cancer in women in the United States and worldwide.[1] Hormone-receptor–positive, axillary node–negative disease accounts for approximately half of all cases of breast cancer in the United States.[2] Adjuvant chemotherapy reduces the risk of recurrence,[3-5] with effects that are proportionally greater in younger women but that are little affected by nodal status, grade, or the use of adjuvant endocrine therapy.[6,7] These findings led a National Institutes of Health consensus panel to recommend adjuvant chemotherapy for most patients,[8] a practice that has contributed to declining breast cancer mortality.[9] However, the majority of patients may receive chemotherapy unnecessarily.

The 21-gene recurrence-score assay (Oncotype DX, Genomic Health) is one of several commercially available gene-expression assays that provide prognostic information in hormone-receptor–positive breast cancer.[10,11] The recurrence score based on the 21-gene assay ranges from 0 to 100 and is predictive of chemotherapy benefit when it is high, whether a high score is defined as 31 or higher[12,13] or 26 or higher[12,14]; when the recurrence score is low (0 to 10), it is prognostic for a very low rate of distant recurrence (2%) at 10 years that is not likely to be affected by adjuvant chemotherapy.[12,14] Although expert panels recommend the use of the 21-gene assay,[15,16] uncertainty remains as to whether chemotherapy is beneficial for the majority of patients, who have a mid-range recurrence score.

The Trial Assigning Individualized Options for Treatment (TAILORx) was designed to address these gaps in our knowledge by determining whether chemotherapy is beneficial for women with a mid-range recurrence score of 11 to 25. It was a prospective clinical trial, a type of trial that provides the highest level of evidence supporting the clinical usefulness of a biomarker.[17] Another objective of the trial was to prospectively confirm that a low recurrence score of 0 to 10 is associated with a low rate of distant recurrence when patients are treated with endocrine therapy alone.[18]

Methods

Trial Oversight

We conducted a prospective clinical trial sponsored by the National Cancer Institute that was coordinated by the Eastern Cooperative Oncology Group (ECOG) and subsequently by the ECOG–American College of Radiology Imaging Network (ACRIN) Cancer Research Group, with other federally funded groups participating, including the Southwest Oncology Group, Alliance for Clinical Trials in Oncology, NRG Oncology, and Canadian Cancer Trials Group. Women who participated in the trial provided written informed consent, including a statement of willingness to have treatment assigned or randomly assigned on the basis of the recurrence-score results. An Oncotype DX recurrence-score assay was performed in a central laboratory (Genomic Health) on samples obtained from every woman who participated in the trial.[10] Additional details are provided in the Supplementary Appendix and the protocol, both of which are available with the full text of this article at NEJM.org.

The authors performed the statistical analysis and wrote the first draft of the manuscript; the final submitted manuscript, which incorporated changes recommended by the coauthors and by Genomic Health, was reviewed and approved by all the authors, who vouch for the accuracy and completeness of the data and for adherence of the trial to the protocol. No one who is not an author contributed to the manuscript. Commercial support was not provided for the planning and execution of the trial but was provided by Genomic Health for the collection of follow-up information from the treating sites.

Trial Population, Treatment, and End Points

We enrolled women who were 18 to 75 years of age; had hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer; and met National Comprehensive Cancer Network guidelines for the recommendation or consideration of adjuvant chemotherapy (the full list of inclusion and exclusion criteria is provided in the Supplementary Appendix). On the basis of the 21-gene recurrence score, women were assigned to one of four treatment groups. Women with a recurrence score of 10 or lower were assigned to receive endocrine therapy only, and women with a score of 26 or higher were assigned to receive chemotherapy plus endocrine (chemoendocrine) therapy. Women with a midrange score of 11 to 25 underwent randomization and were assigned to receive either endocrine therapy alone or chemoendocrine therapy. Additional details are provided in the Supplementary Appendix.

The standardized definitions for efficacy end points (STEEP) criteria were used for end-point definitions (Section 6B in the Supplementary Appendix).[19] The primary end point was invasive disease–free survival, defined as freedom from invasive disease recurrence, second primary cancer, or death. Key secondary end points included freedom from recurrence of breast cancer at a distant site (which corresponds to the STEEP definition of distant recurrence–free interval), freedom from recurrence of breast cancer at a distant or local–regional site (which corresponds to the STEEP definition of recurrence-free interval), and overall survival. Full definitions of all the end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The overall sample size was driven by the need to include a sufficient number of patients with a recurrence score of 11 to 25 to test the noninferiority of endocrine therapy alone (the experimental group) to chemoendocrine therapy (the standard group) in this cohort of patients. Because of concern that nonadherence to the assigned treatment could make determination of an appropriate noninferiority margin problematic, the test of noninferiority used a null hypothesis of no difference, as when testing for superiority, but with a larger type I error (one-sided 10%) and smaller type II error (5%) than usual. In this approach, controlling the type II error is critical, so failure to reject equality provides evidence for a conclusion of noninferiority. A 5-year rate of invasive disease–free survival of 90% with chemoendocrine therapy and of 87% or less with endocrine therapy alone, which corresponds to a 32.2% higher risk of an invasive disease recurrence, second primary cancer, or death as a result of not administering chemotherapy (hazard ratio, 1.322), was prespecified as unacceptable.[12,14]

The primary analysis was a comparison according to the assigned treatment. Because of a rate of nonadherence (12%) that was larger than had originally been projected (5%), the sample size of the group that underwent randomization (i.e., women with a recurrence score of 11 to 25) was increased by 73% (relative to a design with 100% adherence, based on the Lachin–Foulkes correction),[20] which resulted in a target sample size of 6517 eligible patients undergoing randomization. The analysis was also performed according to the actual treatment given in order to explore the effect of nonadherence. The final analysis took place on March 2, 2018, at which time the prespecified number of events required for full information (835 events) had occurred. The analysis methods are further described in Section 6B in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 10,273 women were registered between April 7, 2006, and October 6, 2010, of whom 10,253 were eligible for participation. Among the 9719 eligible patients with follow-up information who were included in the main analysis set, 6711 (69%) had a recurrence score of 11 to 25, 1619 (17%) had a recurrence score of 10 or lower, and 1389 (14%) had a recurrence score of 26 or higher (Fig. 1). The median duration of follow-up in the cohort of patients with a recurrence score of 11 to 25 was 90 months for invasive disease–free survival and 96 months for overall survival. The characteristics of the trial population that was included in the main analysis are shown in Table 1, and in Table S1 in the Supplementary Appendix.

ADJUVANT THERAPY IN THE COHORT WITH A RECURRENCE SCORE OF 11 TO 25

The median duration of endocrine therapy was 5.4 years, with similar distributions of durations in the two randomly assigned treatment groups, including approximately 35% rates of adjuvant endocrine therapy extending beyond 5 years (Fig. S1 in the Supplementary Appendix). The most common chemotherapy regimens among the patients who were randomly assigned to and treated with chemotherapy were docetaxel–cyclophosphamide (56%) and anthracycline-containing regimens (36%). The endocrine therapy regimens among postmenopausal women most commonly included an aromatase inhibitor (91%); among premenopausal women, endocrine therapy regimens most commonly included either tamoxifen alone or tamoxifen followed by an aromatase inhibitor (78%), and suppression of ovarian function was used in 13% of premenopausal women (Table S2 in the Supplementary Appendix). The rate of nonadherence to the assigned treatment was 11.8% overall, including 5.4% among patients who were randomly assigned to receive endo-

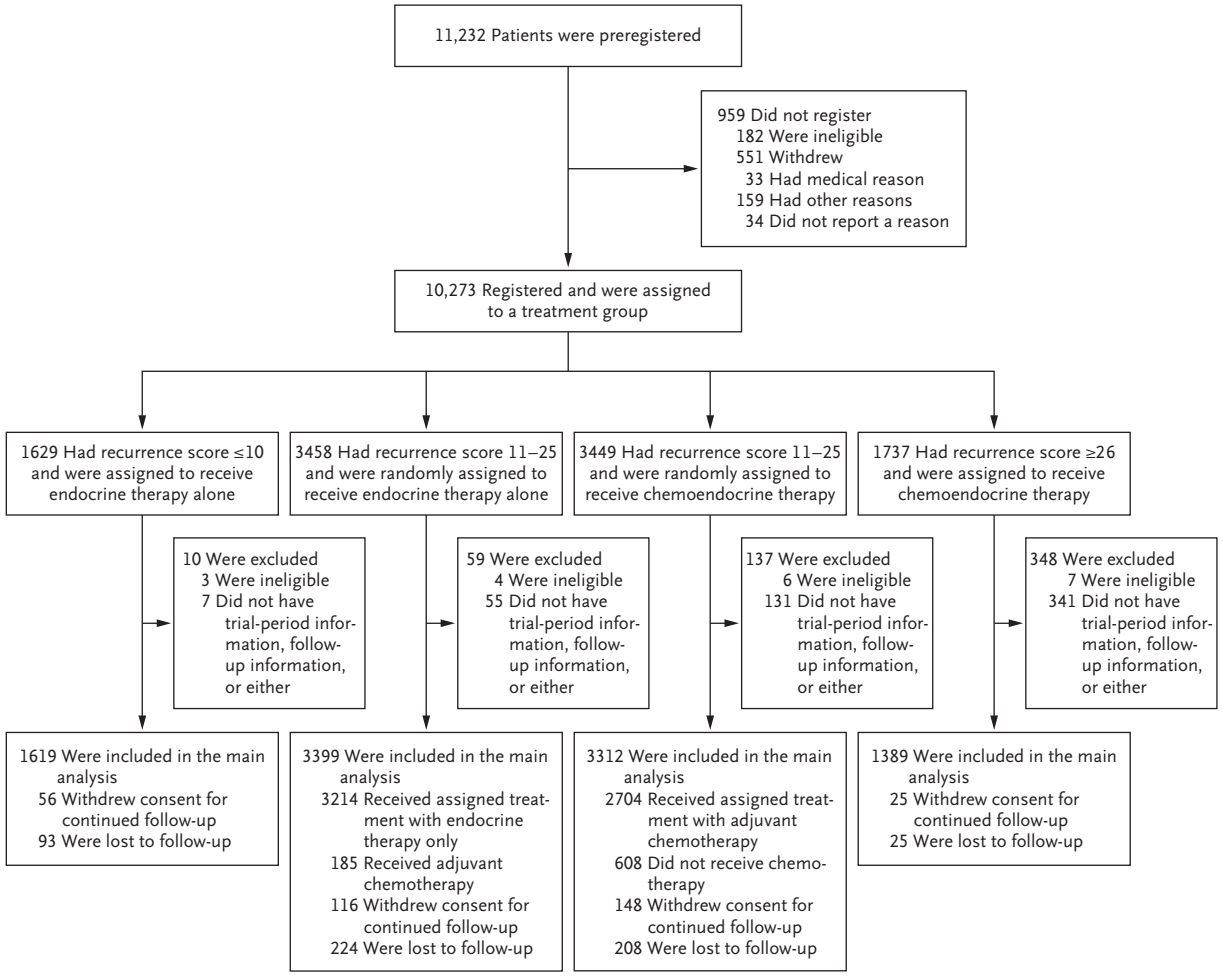

Figure 1. Registration, Randomization, and Follow-up.

All the patients who met the eligibility criteria and provided written informed consent were preregistered; a primary tumor specimen was subsequently obtained and sent to the Genomic Health laboratory for the 21-gene assay. On receipt of the assay report and recurrence-score result by the treating physician, the enrolling site then assigned patients to a treatment group. If the recurrence score was 10 or lower, the patient was assigned to receive endocrine therapy alone. If the recurrence score was 26 or higher, the patient was assigned to receive chemoendocrine therapy. If the recurrence score was 11 to 25, the patient underwent randomization and was assigned to receive either endocrine therapy or chemoendocrine therapy. The stratification factors that were used in randomization were tumor size (≤2 cm vs. >2 cm), menopausal status (pre- vs. postmenopausal), planned chemotherapy (taxane-containing vs. not), planned radiation therapy (whole breast and no boost irradiation planned vs. whole breast and boost irradiation planned vs. partial breast irradiation planned vs. no planned radiation therapy for patients who had undergone a mastectomy), and recurrence-score group (11 to 15 vs. 16 to 20 vs. 21 to 25), which was added midway through the trial.

crine therapy alone and 18.4% among those who were randomly assigned to receive chemoendocrine therapy (Table 1). In the as-treated population, some of the differences in baseline characteristics between the treatment groups were significant (Table S3 in Supplementary Appendix).

INVASIVE DISEASE–FREE SURVIVAL AND OTHER END POINTS IN THE COHORT WITH A RECURRENCE SCORE OF 11 TO 25

There had been 836 events of invasive disease recurrence, second primary cancer, or death (the components of invasive disease–free survival, the primary end point) in the two randomly as-

Table 1. Characteristics of the Patients in the Intention-to-Treat Population at Baseline.*

Characteristic	Recurrence Score of ≤10	Recurrence Score of 11–25		Recurrence Score of ≥26
	Endocrine Therapy (N=1619)	Endocrine Therapy (N=3399)	Chemoendocrine Therapy (N=3312)	Chemoendocrine Therapy (N=1389)
Median age (range) — yr	58 (25–75)	55 (23–75)	55 (25–75)	56 (23–75)
Age ≤50 yr — no. (%)	429 (26)	1139 (34)	1077 (33)	409 (29)
Menopausal status — no. (%)†				
Premenopausal	478 (30)	1212 (36)	1203 (36)	407 (29)
Postmenopausal	1141 (70)	2187 (64)	2109 (64)	982 (71)
Tumor size in the largest dimension — cm‡				
Median (IQR)	1.5 (1.2–2.0)	1.5 (1.2–2.0)	1.5 (1.2–2.0)	1.7 (1.3–2.3)
Mean	1.74±0.76	1.71±0.81	1.71±0.77	1.88±0.99
Histologic grade of tumor — no./total no. (%)				
Low	530/1572 (34)	959/3282 (29)	934/3216 (29)	89/1363 (7)
Intermediate	931/1572 (59)	1884/3282 (57)	1837/3216 (57)	590/1363 (43)
High	111/1572 (7)	439/3282 (13)	445/3216 (14)	681/1363 (50)
Estrogen-receptor expression — no. (%)				
Negative	5 (<1)	6 (<1)	3 (<1)	40 (3)
Positive	1614 (>99)	3393 (>99)	3309 (>99)	1349 (97)
Progesterone-receptor expression — no./total no. (%)				
Negative	28/1583 (2)	267/3339 (8)	251/3240 (8)	405/1353 (30)
Positive	1555/1583 (98)	3072/3339 (92)	2989/3240 (92)	948/1353 (70)
Clinical risk — no./total no. (%)§				
Low	1227/1572 (78)	2440/3282 (74)	2359/3214 (73)	589/1359 (43)
High	345/1572 (22)	842/3282 (26)	855/3214 (27)	770/1359 (57)
Primary surgery — no. (%)				
Mastectomy	516 (32)	935 (28)	917 (28)	368 (26)
Breast conservation	1103 (68)	2464 (72)	2395 (72)	1021 (74)
Adjuvant chemotherapy — no. (%)				
Yes	8 (0.5)	185 (5.4)	2704 (81.6)	1300 (93.6)
No	1611 (99.5)	3214 (94.6)	608 (18.4)	89 (6.4)

* Plus–minus values are means ±SD. The characteristics were well balanced between the two randomly assigned groups (i.e., the two groups with a recurrence score of 11 to 25) for all the factors listed. The differences between the group with a recurrence score of 10 or lower and the combined randomly assigned groups were significant for age, menopausal status, histologic grade, progesterone receptor status, and surgical procedure (P<0.001 for all comparisons). The differences between the group with a recurrence score of 26 or higher and the combined randomly assigned groups were significant for the distributions of age (P=0.003), menopausal status (P<0.001), tumor size (P<0.001), histologic grade (P<0.001), and progesterone receptor status (P<0.001).

† Among the 14 patients for whom menopausal status was not reported, those who were 50 years of age or younger were classified as premenopausal.

‡ There were 86 patients with a tumor size recorded as 0.5 cm or less and 20 patients with a tumor size greater than 5 cm. Information on tumor size was missing for 2 patients with a recurrence score of 11 to 25 in the chemoendocrine-therapy group and for 1 patient with a recurrence score of 26 or higher.

§ Clinical risk was defined as in the MINDACT (Microarray in Node Negative Disease May Avoid Chemotherapy) trial (i.e., with low risk defined as low histologic grade and tumor size ≤3 cm, intermediate histologic grade and tumor size ≤2 cm, or high histologic grade and tumor size ≤1 cm; and with high risk defined as all other cases with known values for grade and tumor size).

signed treatment groups at the time of the final analysis, including 338 (40.4%) recurrences of breast cancer as the first event, of which 199 (23.8% of the total events) were distant recurrences (Tables S4 and S5 in the Supplementary Appendix). In the intention-to-treat population, endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval [CI], 0.94 to 1.24; P=0.26) (Fig. 2A). Endocrine therapy was likewise noninferior to chemoendocrine therapy in the analyses of other end points, including freedom from recurrence of breast cancer at a distant site (hazard ratio for recurrence, 1.10; P=0.48) (Fig. 2B), freedom from recurrence of breast cancer at a distant or local–regional site (hazard ratio for recurrence, 1.11; P=0.33), and overall survival (hazard ratio for death, 0.99; P=0.89). Additional details regarding these end points are provided in Figure S2 and Section 6B in the Supplementary Appendix.

The results of the as-treated analyses were consistent with those of the intention-to-treat analyses for invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.14; 95% CI, 0.99 to 1.31; P=0.06), freedom from recurrence of breast cancer at a distant site (hazard ratio for recurrence, 1.03; P=0.81), freedom from recurrence of breast cancer at a distant or local–regional site (hazard ratio for recurrence, 1.12; P=0.28), and overall survival (hazard ratio for death, 0.97; P=0.78) (Fig. S3 in the Supplementary Appendix). The estimated 9-year rates of invasive disease–free survival in the as-treated population were 83.1% for patients who received endocrine therapy alone and 84.7% for those who received chemoendocrine therapy. The outcomes were unlikely to have been affected by incomplete follow-up information (Section 6E in the Supplementary Appendix).

SURVIVAL RATES IN ALL RECURRENCE-SCORE COHORTS AND TREATMENT GROUPS

The estimated survival rates at 5 and 9 years for all treatment groups and end points are shown in Table 2. At 9 years in the intention-to-treat population, among patients with a recurrence score of 11 to 25, the rate of invasive disease–free survival was 83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group; the corresponding rates were 94.5% and 95.0% for freedom from recurrence of breast cancer at a distant site, 92.2% and 92.9% for freedom from recurrence of breast cancer at a distant or local–regional site, and 93.9% and 93.8% for overall survival. When all recurrence-score cohorts (≤10, 11 to 25, and ≥26) and treatment-group assignments were considered, there were significant differences in the rates of invasive disease–free survival, recurrence, and death (P<0.001), driven largely by the higher likelihood of having an event in the cohort with a recurrence score of 26 or higher (Fig. S4 in the Supplementary Appendix). Distant recurrence was associated with recurrence score as a continuous variable between 11 and 25, but there was no significant interaction between chemotherapy treatment and recurrence score in this range (Figs. S5 through S10 in the Supplementary Appendix).

INTERACTIONS ACCORDING TO SUBGROUP IN THE COHORTS WITH A RECURRENCE SCORE OF 11 TO 25

We performed exploratory analyses to determine whether any subgroups might have derived some benefit from chemotherapy in the intention-to-treat population, with a focus on covariates that were prognostic or associated with greater benefit from chemotherapy, such as younger age (Section 6F and Fig. S11 in the Supplementary Appendix).[6] There were no significant interactions between chemotherapy treatment and most of the prognostic covariates examined, including recurrence-score category (either 11 to 15 vs. 16 to 20 vs. 21 to 25, or 11 to 17 vs. 18 to 25), tumor size (≤2 cm vs. >2 cm), histologic grade (low vs. intermediate vs. high), clinical risk category (high vs. low), and menopausal status (pre- vs. postmenopausal). There were significant interactions between chemotherapy treatment and age (≤50 vs. 51 to 65 vs. >65 years) for invasive disease–free survival (P=0.03) and for freedom from recurrence of breast cancer at a distant or local–regional site (P=0.02) but not at a distant site (P=0.12). The effect of treatment also varied significantly over the six combinations of menopausal status and recurrence-score category (11 to 15 vs. 15 to 20 vs. 21 to 25) (P=0.02) and over the nine combinations of age and recurrence-score category (P=0.004) for invasive disease–free survival (Figs.

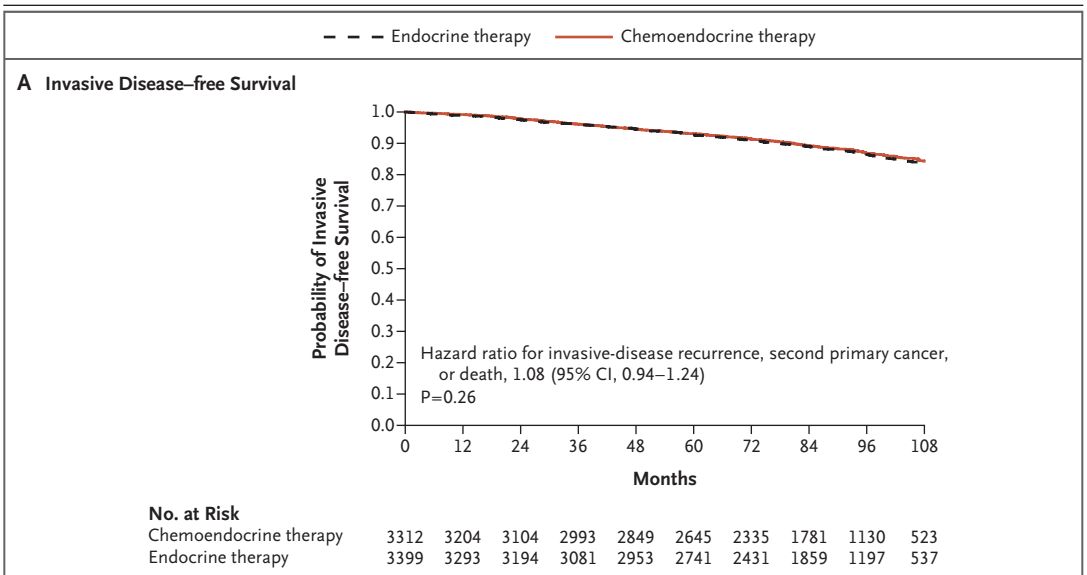

Figure 2. Clinical Outcomes among Patients with a Recurrence Score of 11 to 25.

Kaplan–Meier estimates of survival rates in the analysis according to the assigned treatment group are shown for the group that received endocrine therapy alone and the group that received chemoendocrine therapy in the intention-to-treat analysis of invasive disease–free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death) and freedom from recurrence of breast cancer at a distant site. The hazard ratios are for the endocrine-therapy group versus the chemoendocrine-therapy group.

S12 and S13 in the Supplementary Appendix) but not for freedom of recurrence of breast cancer at a distant site or distant or local–regional site. In women 50 years of age or younger, chemotherapy was associated with a lower rate of distant recurrence than endocrine therapy if the recurrence score was 16 to 20 (percentage-point difference, 0.8 at 5 years and 1.6 at 9 years) or 21 to 25 (percentage-point difference, 3.2 at 5 years and 6.5 at 9 years), although the rates of overall survival were similar (Table 3). Conversely, in the 40% of women 50 years of age or younger who had a recurrence score of 0 to 15, the rate of distant recurrence was approximately 2% at 9 years among those who had been assigned (either randomly or nonrandomly) to endocrine therapy alone.

Table 2. Estimated Survival Rates According to Recurrence Score and Assigned Treatment in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	94.0±0.6	84.0±1.3
Score of 11–25, endocrine therapy	92.8±0.5	83.3±0.9
Score of 11–25, chemoendocrine therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemoendocrine therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy	99.3±0.2	96.8±0.7
Score of 11–25, endocrine therapy	98.0±0.3	94.5±0.5
Score of 11–25, chemoendocrine therapy	98.2±0.2	95.0±0.5
Score of ≥26, chemoendocrine therapy	93.0±0.8	86.8±1.7
Freedom from recurrence of breast cancer at a distant or local–regional site		
Score of ≤10, endocrine therapy	98.8±0.3	95.0±0.8
Score of 11–25, endocrine therapy	96.9±0.3	92.2±0.6
Score of 11–25, chemoendocrine therapy	97.0±0.3	92.9±0.6
Score of ≥26, chemoendocrine therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, endocrine therapy	98.0±0.4	93.7±0.8
Score of 11–25, endocrine therapy	98.0±0.2	93.9±0.5
Score of 11–25, chemoendocrine therapy	98.1±0.2	93.8±0.5
Score of ≥26, chemoendocrine therapy	95.9±0.6	89.3±1.4

* Plus–minus values are Kaplan–Meier estimates ±SE.
† Invasive disease–free survival was defined as freedom from invasive disease recurrence, second primary cancer, or death.

DISCUSSION

In this prospective, randomized trial, we found that among 6711 women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer and a midrange recurrence score of 11 to 25 on the 21-gene assay, endocrine therapy was not inferior to chemoendocrine therapy, which provides evidence that adjuvant chemotherapy was not beneficial in these patients. This finding contrasts those of previous biomarker validation studies that were performed retrospectively with the use of archival tumor specimens, in which a substantial benefit for the prevention of distant recurrence has been found for the combination of chemotherapy and endocrine therapy in patients with a recurrence score of 26 or higher.[12,13] The 9-year rate of distant recurrence in women with a recurrence score of 11 to 25 in our trial was approximately 5%, irrespective of chemotherapy use, a finding consistent with that predicted from the original report showing a significant treatment interaction between chemotherapy benefit and a recurrence score of 26 or higher.[14] Updated results for patients with a low recurrence score of 10 or less, who were previously reported as having a 1% distant recurrence rate at 5 years in our trial,[18] now indicate a 9-year rate of distant recurrence of approximately 3%.

Population-based studies have shown a recurrence-score distribution similar to that observed in this prospective trial, along with no apparent benefit from chemotherapy in the recurrence-score range of 11 to 25 and a significant association between recurrence score and recurrence or 5-year breast cancer–specific mortality, which indicates the generalizability of our findings to clinical practice.[21,22] Although the rate of nonadherence to the assigned treatment was 12% overall, the sample size was adjusted to compensate for this, and the as-treated analysis produced results similar to those of the intention-to-treat analysis. The rate of nonadherence was similar to those in previous trials evaluating breast conservation or high-dose chemotherapy.[23,24] Only 24% of first events included in the primary end point (invasive disease recurrence, second primary cancer, or death) were distant recurrences, the type of recurrence that is most influenced by adjuvant chemotherapy,[7] which also has some effect in reducing other events, such as local–regional recurrence or contralateral breast cancer.[25,26]

A total of 40% of women who were 50 years of age or younger had a recurrence score of 15 or lower, which was associated with a low rate of recurrence with endocrine therapy alone. Exploratory analyses indicated that chemotherapy was associated with some benefit for women 50 years of age or younger who had a recurrence score of 16 to 25 (a range of scores that was found in 46% of women in this age group). A greater treatment effect from adjuvant chemotherapy has been noted in younger women,[7] which may be at least partly explained by an antiestrogenic effect associated with premature menopause induced by chemotherapy.[27] We did not collect data on chemotherapy-induced menopause. It remains unclear whether similar benefits could be achieved with ovarian suppression

plus an aromatase inhibitor instead of chemotherapy.[28,29]

The MINDACT (Microarray in Node Negative Disease May Avoid Chemotherapy) trial was also a prospective trial integrating a gene-expression assay (with 70 genes) and randomized assignment of chemotherapy.[30] The primary end point in the trial focused on 644 patients with high clinical risk (48% node-positive, 8% HER2-positive) and low genomic risk who were assigned to receive no chemotherapy, and the prespecified prognostic end point of a 5-year rate of distant metastasis–free survival of more than 92% in this group of patients was met. Evidence-based guidelines recommend that the use of the assay be considered in cases of hormone-receptor–positive, HER2-negative breast cancer and high clinical risk but not low clinical risk as defined in that trial.[31] When the same clinical risk definitions were applied in our trial, 73.9% of the patients were at low clinical risk and 26.1% were at high clinical risk in the randomized treatment groups (Table 1), and we found no evidence suggesting a chemotherapy benefit in either risk group.

On the basis of previous information regarding the clinical validity and usefulness of the 21-gene assay, the use of adjuvant chemotherapy has declined substantially in hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer.[32] The results of our trial suggest that the 21-gene assay may identify up to 85% of women with early breast cancer who can be spared adjuvant chemotherapy, especially those who are older than 50 years of age and have a recurrence score of 25 or lower, as well as women 50 years of age or younger with a recurrence score of 15 or lower. Ongoing clinical trials are obtaining additional information on the clinical usefulness of the 21-gene assay in women with hormone-receptor–positive breast cancer and positive axillary nodes[33] and evaluating the clinical usefulness of the 50-gene assay in this context.[34]

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Table 3. Estimated Survival Rates According to Recurrence Score and Assigned Treatment among Women 50 Years of Age or Younger in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	95.1±1.1	87.4±2.0
Score of 11–15, endocrine therapy	95.1±1.1	85.7±2.2
Score of 11–15, chemoendocrine therapy	94.3±1.3	89.2±1.9
Score of 16–20, endocrine therapy	92.0±1.3	80.6±2.5
Score of 16–20, chemoendocrine therapy	94.7±1.1	89.6±1.7
Score of 21–25, endocrine therapy	86.3±2.3	79.2±3.3
Score of 21–25, chemoendocrine therapy	92.1±1.8	85.5±3.0
Score of ≥26, chemoendocrine therapy	86.4±1.9	80.3±2.9
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy	99.7±0.3	98.5±0.8
Score of 11–15, endocrine therapy	98.8±0.6	97.2±1.0
Score of 11–15, chemoendocrine therapy	98.5±0.7	98.0±0.8
Score of 16–20, endocrine therapy	98.1±0.7	93.6±1.4
Score of 16–20, chemoendocrine therapy	98.9±0.5	95.2±1.3
Score of 21–25, endocrine therapy	93.2±1.7	86.9±2.9
Score of 21–25, chemoendocrine therapy	96.4±1.2	93.4±2.3
Score of ≥26, chemoendocrine therapy	91.1±1.6	88.7±2.1
Freedom from recurrence of breast cancer at a distant or local–regional site		
Score of ≤10, endocrine therapy	98.4±0.6	95.4±1.3
Score of 11–15, endocrine therapy	97.5±0.8	93.3±1.6
Score of 11–15, chemoendocrine therapy	97.2±0.9	94.4±1.5
Score of 16–20, endocrine therapy	95.7±1.0	89.6±1.9
Score of 16–20, chemoendocrine therapy	97.2±0.8	93.0±1.5
Score of 21–25, endocrine therapy	89.8±2.0	82.0±3.2
Score of 21–25, chemoendocrine therapy	94.2±1.6	90.7±2.5
Score of ≥26, chemoendocrine therapy	88.6±1.8	86.1±2.2
Overall survival		
Score of ≤10, endocrine therapy	100.0	98.6±0.9
Score of 11–15, endocrine therapy	99.3±0.4	96.8±1.0
Score of 11–15, chemoendocrine therapy	98.9±0.6	97.5±0.9
Score of 16–20, endocrine therapy	98.6±0.6	95.8±1.2
Score of 16–20, chemoendocrine therapy	99.8±0.2	96.1±1.2
Score of 21–25, endocrine therapy	98.2±0.9	92.7±2.0
Score of 21–25, chemoendocrine therapy	98.3±0.8	93.9±1.9
Score of ≥26, chemoendocrine therapy	95.6±1.1	92.4±1.9

* Plus–minus values are Kaplan–Meier estimates ±SE.
† Invasive disease–free survival was defined as freedom from invasive disease recurrence, second primary cancer, or death.

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APPENDIX

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