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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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INTERDISCIPLINARY MANAGEMENT OF BREAST CANCER

Tumor Panel Discussion Focused on Personal Cases of the Faculty

A CME Symposium Held in Conjunction with The American Society of Breast Surgeons Eighth Annual Meeting

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Breast Cancer Update for Surgeons
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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic techniques, agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing breast surgeon must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* for Surgeons utilizes one-on-one discussions with leading breast cancer investigators. By providing access to the latest research developments and expert perspectives, this CME program assists breast surgeons in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in adjuvant and neoadjuvant disease.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen.
- Develop an algorithm for ER and HER2 testing and implement a treatment plan for patients with HER2-positive breast cancer.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy.
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE* FOR SURGEONS

The purpose of Issue 2 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Silverstein, Hyams, Geyer and Rugo on the integration of emerging clinical research data into the management of breast cancer.

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Dr Silverstein — Consulting Fees: Beekley Corporation, Ethicon Endo-Surgery Inc. **Dr Hyams** — Salary: Aptium Oncology; Consulting Fees: AstraZeneca Pharmaceuticals LP, Ortho Biotech Products LP, Sanofi-Aventis; Contracted Research: AstraZeneca Pharmaceuticals LP, Ortho Biotech Products LP. **Dr Geyer** — No financial interests or affiliations to disclose. **Dr Rugo** — Fees For Non-CME Services Received Directly from Commercial Interest or Their Agents: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP; Contracted Research: Genentech BioOncology.

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UPCOMING EDUCATIONAL EVENTS

ACOSOG Annual Meeting
August 16-18, 2007
St Louis, Missouri
Website: **www.acosog.org**

American Society of Clinical Oncology 2007 Breast Cancer Symposium
September 7-8, 2007
San Francisco, California
Website: **www.asco.org**

ASTRO Annual Meeting
October 28-November 1, 2007
Los Angeles, California
Website: **www.astro.org**

San Antonio Breast Cancer Symposium
December 13-16, 2007
San Antonio, Texas
Website: **www.sabcs.org**

RTOG Fall/Winter Meeting
January 17-20, 2008
San Diego, California
Website: **www.rtog.org**

American Society of Breast Surgeons Ninth Annual Meeting
April 30-May 4, 2008
New York, New York
Website: **www.breastsurgeons.org**

INTERVIEW

Melvin J Silverstein, MD

Dr Silverstein is Professor of Surgery and Henrietta C Lee Chair in Breast Cancer Research, Chief of Breast Services at USC-Keck School of Medicine and Director of the Harold E and Henrietta C Lee Breast Center at USC/Norris Comprehensive Cancer Center and Hospital in Los Angeles, California.

CD 1, Tracks 1-16

Track 1	Historical perspective on the local treatment of breast cancer
Track 2	Methods of partial breast irradiation (PBI)
Track 3	Delivery of intraoperative radiation therapy
Track 4	Eligibility criteria for the TARGIT study of intraoperative versus conventional external beam radiation therapy
Track 5	Oncoplastic breast cancer surgery
Track 6	Thermal tumor ablation with cryosurgery or radiofrequency procedures
Track 7	Surgical margins and the necessity of radiation therapy in DCIS
Track 8	Breast cancer-specific mortality after invasive local recurrence among patients with DCIS
Track 9	Radiation therapy for small, node-negative invasive breast tumors
Track 10	Use of the Onco*type* DX™ multigene assay in clinical practice
Track 11	Comparison of the Onco*type* DX and MammaPrint® assays
Track 12	Adjuvant trastuzumab in HER2-positive early breast cancer
Track 13	Delayed and extended adjuvant hormonal therapy
Track 14	Quality of life for patients treated with an aromatase inhibitor compared to tamoxifen
Track 15	Sentinel lymph node biopsy (SLNB) for patients with DCIS
Track 16	Use of radioisotope and blue dye in SLNB

Select Excerpts from the Interview

CD 1, Track 7

DR LOVE: Has anything new emerged in the debate about ductal carcinoma in situ (DCIS) and radiation therapy?

DR SILVERSTEIN: The debate asks, does every patient with DCIS need radiation therapy? I'm on the "no" side. The proponents — the NSABP and some radiation therapists from the East Coast — believe that everybody needs radiation therapy.

Clearly American physicians and patients don't buy into that because the Surveillance, Epidemiology and End Results (SEER) data suggest that about

35 percent of patients with DCIS in this country do not undergo radiation therapy (Baxter 2004).

DR LOVE: What fraction of your patients with DCIS don't receive radiation therapy?

DR SILVERSTEIN: Probably double that. We try hard not to administer radiation therapy, but some patients do receive it. At the American Society of Breast Surgeons meeting we presented an update of our 1999 DCIS paper, in which we found that patients with 10-mm margins had an extremely low local recurrence rate — two or three percent — with or without radiation therapy (Silverstein 1999).

Now they have all been followed for a median of 123 months. The recurrence rates are only slightly higher for the excision-only patients (in the range of seven percent) versus the radiation therapy patients (about two and a half percent).

Compare that to the gold standard set by the NSABP: At 12 years they have a 16 percent recurrence rate for all their patients with DCIS who undergo excision with radiation therapy (Fisher 2001).

DR LOVE: Of course, that's an indirect comparison.

DR SILVERSTEIN: Yes, it's indirect and not a fair comparison. However, our data show exactly what the randomized trial data show: If you administer radiation therapy, you decrease the relative recurrence risk by about 50 or 60 percent.

Among the patients with 10-mm margins, that translates to an absolute benefit of only about five percent. I have to irradiate 100 patients to prevent five recurrences, of which only two will be invasive.

I can also cure at least eight out of 10 invasive recurrences because we follow them closely. This means I have to irradiate 400 patients to prevent one death.

CD 1, Track 8

DR LOVE: Can you discuss the prognosis of invasive local recurrence after DCIS?

DR SILVERSTEIN: We've evaluated the long-term prognosis of invasive recurrences. At 12 years, approximately 15 percent of those with invasive recurrence had metastatic disease and about 12 percent died (Lee 2006; [1.1]).

Among our recurrences in excision-only patients, 34 percent were invasive. Among patients who received excision and radiation therapy, 53 percent of recurrences were invasive. That's approximately a 20 percent difference, which is statistically significant.

Why is that happening? I believe it's because some patients treated with radiation therapy develop fibrosis. When that happens, their mammographic follow-up is much more difficult. People believe it's just scarring, but when the biopsy is done, it's actually a large, invasive tumor.

We can prevent recurrences with radiation therapy, but if a patient develops a recurrence, it has a higher probability of being invasive. That evens the issue out for us.

What it boils down to is how much risk a patient wants to take. In medical oncology surveys, some women have said, "For a one percent survival benefit, I'll be happy to receive the chemotherapy."

We can reduce the recurrence rate for patients with 10-mm margins from seven or eight percent to two or three percent. Only two of those recurrences are invasive. If you treat 250 patients with 10-mm margins, you will probably save one life.

But what are the costs of radiation therapy? Not every radiation therapist is a great radiation therapist. Will everybody use CT planning and protect the heart and lungs? Will you see more lung cancer, more esophageal cancer, more pulmonary disease or more heart disease?

Radiation techniques are much better today than they were in 1980, so I believe you have a good chance of preventing much of that, but you can't prevent it all. ■

1.1

Breast Cancer-Specific Mortality After Invasive Local Recurrence in Patients with Ductal Carcinoma in Situ of the Breast

"In examining the 63 patients [out of 1,236] with an invasive recurrence [after treatment of DCIS], only 10 developed evidence of both local and distant disease. The 12-year probabilities of development of distant disease and breast cancer-specific death, even after development of an invasive recurrence, were 15% and 12%, respectively...

[This is] a mortality rate similar to a patient with stage II A breast cancer. Hence, even in the small group of patients with DCIS who developed an invasive recurrence, their long-term prognosis was good."

[Text added]

SOURCE: Lee LA et al. *Am J Surg* 2006;192(4):416-9. **Abstract**

SELECT PUBLICATIONS

Baxter NN et al. **Trends in the treatment of ductal carcinoma in situ of the breast.** *J Natl Cancer Inst* 2004;96(6):443-8. **Abstract**

Clarke M et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;366(9503):2087-106. **Abstract**

Fisher B et al. **Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the National Surgical Adjuvant Breast and Bowel Project experience.** *Semin Oncol* 2001;28(4):400-18. **Abstract**

Lee LA et al. **Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in-situ of the breast.** *Am J Surg* 2006;192(4):416-9. **Abstract**

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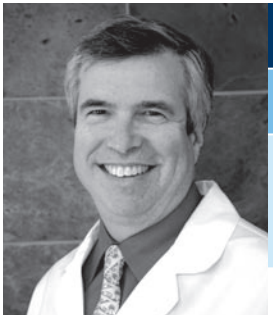


INTERVIEW

David M Hyams, MD

Dr Hyams is National Director of Clinical Research at Aptium Oncology at the Desert Regional Medical Center's Comprehensive Cancer Center in Palm Springs, California.

CD 1, Tracks 17-23 — CD 2, Tracks 1-9

CD 1

- **Track 17** Case discussion: A 61-year-old woman with a 1-cm, Grade II, strongly ER-positive and PR-positive, HER2-negative breast tumor
- **Track 18** Patient's attitude toward breast-conserving surgery and radiation therapy
- **Track 19** Oncoplastic approach to breast-conserving surgery
- **Track 20** Sentinel lymph node biopsy
- **Track 21** TAILORx: Trial Assigning Individu-aLized Options for Treatment (Rx)
- **Track 22** Patient reactions to clinical trial participation
- **Track 23** Adjuvant chemotherapy for node-negative, hormone receptor-positive tumors

CD 2

- **Track 1** Defining intermediate recurrence score in TAILORx
- **Track 2** Chemotherapy options in TAILORx
- **Track 3** Side effects and tolerability of adjuvant hormonal therapies
- **Track 4** Extended adjuvant hormonal therapy with aromatase inhibitors
- **Track 5** Long-term risk of recurrence for patients with hormone receptor-positive early breast cancer
- **Track 6** NSABP-B-39: Conventional versus partial breast irradiation
- **Track 7** Potential advantages of PBI techniques
- **Track 8** Radiation recall with external beam PBI
- **Track 9** Discussing randomized clinical trial options with patients

Select Excerpts from the Interview

CD 1, Tracks 17, 21

Case Discussion

A 61-year-old woman with a 1.5-cm, Grade II, T1b, ER-positive (100%), PR-positive (50%), HER2-negative, node-negative left breast infiltrating ductal carcinoma.

SOURCE: CD 1, Track 17.

DR LOVE: Can you discuss the conversation you had with this patient regarding the findings from her biopsy?

DR HYAMS: The final pathology demonstrated that the tumor was Grade II. Although the ER status was 100 percent, the PR status was somewhat less positive at 50 percent, which means the biological behavior of the tumor could display some variability.

According to a study of patients from the original NSABP-B-14 trial, the concordance rate among pathologists grading Stage III and IV tumors was a little less than 50 percent when available slides from all of the patients treated with tamoxifen were sent to three different breast specialty pathologists (Paik 2004).

This suggests variability in tumor grading. Two out of three pathologists have some tendency to blur the lines between the Grade I and Grade II tumors and between the Grade II and Grade III tumors.

This patient's tumor was considered a Grade II lesion, but we thought it might be useful to determine the likelihood of distant recurrence and suggested she consider participating in the TAILORx study. It would provide her with an opportunity to learn her recurrence score using the Onco*type* DX assay and participate in a trial that would help us better identify which patients benefit most from chemotherapy with hormonal therapy or from hormonal therapy alone in the intermediate-risk group.

CD 2, Track 1

DR LOVE: After this patient enrolled in TAILORx, what did her Onco*type* DX results show?

DR HYAMS: The Onco*type* DX assay returned a recurrence score of 25, which means she has approximately a 16 percent risk of developing a distant recurrence within 10 years. This score placed her in the intermediate-risk category, so she would be randomly assigned to hormone therapy alone or after chemotherapy, and she was assigned to chemotherapy followed by hormone therapy (2.1).

Her score was at the high end of the intermediate range as defined by the TAILORx criteria, but her score wasn't quite at the high end of the range specified by the commercially available Onco*type* DX assay. The scores for each are assigned a little differently.

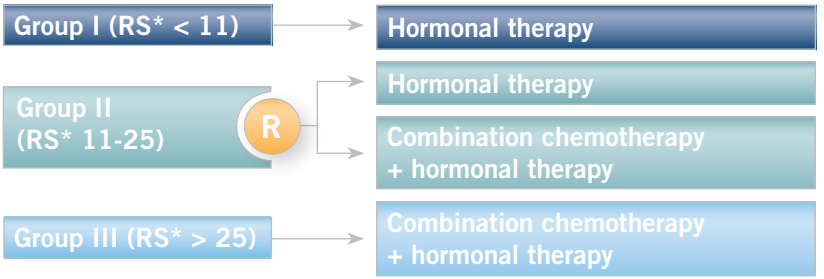
Traditional boundaries for the intermediate-risk category, as defined by the commercially available Onco*type* DX assay, are 18 and 30 — that is, low risk becomes intermediate risk when the assay score is higher than 18, and a score higher than 30 places a patient in the high-risk category.

For the TAILORx study, the recurrence score range for the intermediate-risk category was lowered to between 11 and 25. The trial designers strongly felt that if randomization methodology were to be employed and therapies prescribed or proscribed, the most conservative approach should be used to help ensure that patients who might benefit from chemotherapy would be eligible to receive it.

2.1

TAILORx: Phase III Randomized Study of Adjuvant Combination Chemotherapy and Hormonal Therapy versus Adjuvant Hormonal Therapy Alone in Women with Node-Negative Breast Cancer with Various Levels of Risk for Recurrence

Protocol IDs: ECOG-PACCT-1, TAILORx, NCT00310180
Target Accrual: 10,046 (Open)



* Onco*type* DX recurrence score

Eligibility

- Pre- or postmenopausal
- ER-positive and/or PR-positive
- HER2-negative
- Node-negative

Study Contact

Eastern Cooperative Oncology Group
Joseph Sparano, MD
Tel: 718-920-4826

SOURCE: NCI Physician Data Query, July 2007.

CD 2, Track 3

DR LOVE: Once the chemotherapy has been completed, what about hormonal therapy?

DR HYAMS: Postmenopausal women have two basic choices: Either tamoxifen or one of the aromatase inhibitors. The data have increasingly demonstrated a more favorable toxicity profile for the aromatase inhibitors, with regard to serious events, and approximately a 20 percent relative risk reduction compared to tamoxifen.

DR LOVE: What about the issue of tolerability with regard to day-to-day quality of life with tamoxifen versus the aromatase inhibitors?

DR HYAMS: That's a great question because, on paper, the aromatase inhibitors appear to have the much better toxicity profile, but in reality, that isn't true for all patients. In clinical practice, the arthralgias are bothersome enough to take a number of women off aromatase inhibitors. In my own practice, in a community of active women who play tennis and golf, the arthralgias can be extremely bothersome.

If we start them on one aromatase inhibitor and they develop arthralgias, our first move is to determine the severity of the problem. If the patient is particularly concerned, we'll try another one of the aromatase inhibitors. Often they do much better after switching, for reasons that are not clear. Some women can't tolerate any of the aromatase inhibitors. In such a circumstance we can go back to tamoxifen.

DR LOVE: Which hormonal therapy do you believe she will receive once she's finished with chemotherapy?

DR HYAMS: I believe this woman will end up on an aromatase inhibitor.

CD 2, Tracks 4-5

DR LOVE: Since the ATAC data demonstrating an advantage to anastrozole over tamoxifen came out at the end of 2001, many women are about to complete five years of an aromatase inhibitor. What are your thoughts on the treatment approach for these patients?

DR HYAMS: I believe this has to be tested. It's important to remember that after five years, a woman has a constant risk of recurrence that runs cumulatively somewhere between two and four percent per year. Taken in aggregate over 10 years, that risk is actually significantly higher than the risk for women who entered any of the prevention trials, P-1 or P-2 (Vogel 2006; Fisher 2005).

The question is being evaluated in the NSABP-B-42 trial, in which patients who have been treated for five years with an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor will be randomly assigned to either continuation with an aromatase inhibitor or placebo. That trial will provide us with valuable information.

An aromatase inhibitor is not an agent that interacts directly with the cancer cell; it blocks the availability of the agonist. Therefore, it is unlikely that continuing treatment beyond five years is going to be worse, unless there is a long-term toxicity unrelated to its effect on the cancer, of which we are unaware. If a protective effect occurs, we would expect it to continue, as would any mechanism to eliminate or absorb estrogen production. ■

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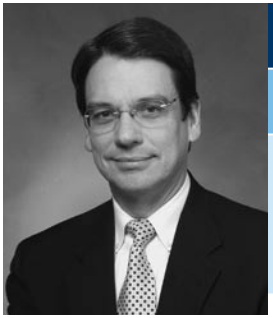
Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**



INTERVIEW

Charles E Geyer Jr, MD

Dr Geyer is Director of Medical Affairs of the National Surgical Adjuvant Breast and Bowel Project and Director of Breast Medical Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania.

CD 2, Tracks 10-25

Select Excerpts from the Interview

CD 2, Tracks 11-12

DR LOVE: What do we know about the benefits of hormonal therapy for patients with a high Onco*type* DX recurrence score?

DR GEYER: We haven't published the manuscript yet, but it appears that these patients don't receive much benefit from tamoxifen, even though they are in the subset categorized as hormone receptor-positive. We observed a clear benefit from tamoxifen for the patients in the low- and intermediate-risk categories.

I don't believe people should take that to mean that hormone therapy confers no benefit for patients characterized as being at high risk by Onco*type* DX.

It does mean that those women who don't want chemotherapy and hope to receive benefit from hormonal therapy may not be receiving as much benefit, on average, as the broader population of patients with hormone receptor-positive disease.

DR LOVE: Can you discuss the MammaPrint assay?

DR GEYER: This assay requires frozen specimens, so to use it, you have to alter your practice. It was developed to dichotomize patients into low-risk or high-risk categories, the idea being that patients at low risk would not need any therapy.

The studies were conducted with mixed populations of patients with ER-positive and ER-negative disease. The low-risk group has a rate of recurrence of approximately 10 percent, so you would certainly still administer hormonal therapy to some patients.

I don't see what MammaPrint has to offer that Onco*type* DX doesn't already provide. The Onco*type* DX assay can be performed on paraffin-embedded tissue, so you don't have to alter your practice patterns.

If you're going to use MammaPrint, you have to collect tissue from every patient, whether or not you know her nodal status, hormone receptor status and HER2 status. At least with Onco*type* DX you can wait to determine the HER2 status because with HER2 amplification, you don't need the assay.

CD 2, Tracks 13-14, 17

DR LOVE: The patient you are presenting in the American Society of Breast Surgeons meeting was perimenopausal. How are you approaching the choice of hormone therapy with postmenopausal patients?

DR GEYER: Usually, for a woman who is clearly postmenopausal, who does not have significant, chronic musculoskeletal problems and who has reasonably well-preserved bone density, I recommend an aromatase inhibitor.

I do try to help women understand that the differences between the aromatase inhibitors and tamoxifen are small — the absolute further incremental benefit is small — so what's important is that we find a hormone therapy that the patient can tolerate for five years.

All things being equal, the aromatase inhibitors do appear to be more effective, particularly when the disease is more aggressive. The more you're worried about the patient, the more you want to treat with an aromatase inhibitor.

DR LOVE: It's interesting that you raise the issue of trying to find a therapy the patient can receive for five years because I've seen a significant change in how people view the long-term history of breast cancer. I notice more sensitivity to what's happening not only later in the first five years but also in years five to 10, 10 to 15 and beyond.

DR GEYER: Without question, the MA17 data have shown us that long-term hormonal therapy does help control disease (Goss 2005a, 2005b). The trial ended early because the effects were observed quickly and the magnitude of the effects was greater than anticipated.

Another interesting observation was that patients who were on the placebo arm crossed over to letrozole and then experienced treatment benefit. Those were amazing data.

Even with the several-year break from receiving hormonal therapy, the reinstitution of therapy drove the rates of recurrence down. So the MA17 data gave oncologists a stronger sense that hormone-dependent breast cancer is the chronic disease we've talked about.

DR LOVE: How does that translate to your own clinical practice in terms of starting an aromatase inhibitor for a patient who's been off tamoxifen for a few years?

DR GEYER: Certainly, a patient who had positive nodes and was tolerating medication well but then was stopped, in a sense arbitrarily, because the available data suggested she should stop is somebody with whom you may want to revisit and share the data.

DR LOVE: That approach is exactly what I hear a lot of support for because we don't know the answer. Can you make the argument that if a surgeon is routinely following up on a patient who had an ER-positive tumor and did not receive an aromatase inhibitor, a red flag should appear on the chart?

DR GEYER: It's a reasonable question for a surgeon who continues to follow patients for years. Frequently, patients stop seeing their medical oncologist when they finish therapy, and they may not have this discussion. This is an instance in which it's useful for breast surgeons to be aware of the data and consider the issue of further therapy with their patients.

CD 2, Track 22

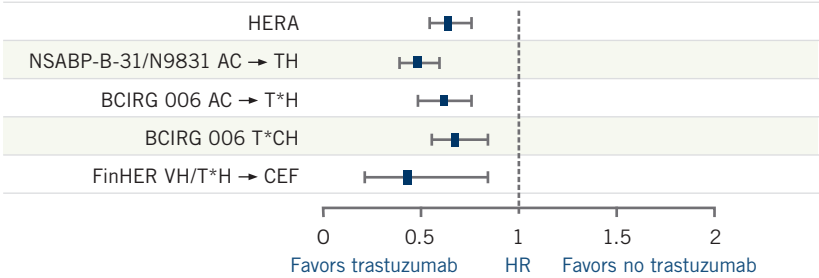
DR LOVE: Could you summarize the data with adjuvant trastuzumab for patients with HER2-positive tumors?

DR GEYER: Four large adjuvant studies were initiated to determine whether adding trastuzumab to chemotherapy could improve the outcome for women with HER2-positive breast cancer (Joensuu 2006; Perez 2007; Piccart-Gebhart 2005; Romond 2005; Slamon 2005, 2006; Smith 2007; [3.1]).

Across all trials, when trastuzumab was administered with chemotherapy, a substantial — 40 to 50 percent — reduction in risk of recurrence occurred quickly. All these trials reported early because the effects were greater than anticipated. So a striking consistency of benefit is evident when you add trastuzumab, making the nuances of chemotherapy appear less important. ■

3.1

Hazard Ratios for Disease-Free Survival with Trastuzumab



H = trastuzumab; T = paclitaxel; T* = docetaxel; V = vinorelbine

SOURCES: Smith I et al. *Lancet* 2007;369(9555):29-36. **Abstract**; Slamon D et al. *Proc SABCS* 2006;**Abstract 52**; Joensuu H et al. *N Engl J Med* 2006;354(8):809-20. **Abstract**; Perez EA et al. *Proc ASCO* 2007;**Abstract 512**.

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Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005b;97(17):1262-71. **Abstract**

Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Perez EA et al. **Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer.** *Proc ASCO* 2007;**Abstract 512**.

Piccart-Gebhart MJ et al; HERA Study Team. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

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INTERVIEW

Hope S Rugo, MD

Dr Rugo is Clinical Professor of Medicine at the Carol Franc Buck Breast Care Center and Co-director of the Breast Oncology Clinical Trials Program at the University of California San Francisco Comprehensive Cancer Center in San Francisco, California.

CD 3, Tracks 1-14

Track 1 Case discussion: A postmenopausal woman with node-positive breast cancer who received extended adjuvant hormonal therapy

Track 2 Risk of recurrence for patients with hormone receptor-positive disease after five years of treatment

Track 3 Individualizing treatment options for patients who have completed five years of adjuvant hormonal therapy

Track 4 Aging, use of aromatase inhibitors and joint pain

Track 5 Clinical disease management for premenopausal patients who have completed five years of adjuvant hormonal therapy

Track 6 Case discussion: A 60-year-old woman with hormone receptor-negative, HER2-positive breast cancer who received adjuvant chemotherapy and trastuzumab

Track 7 BCIRG 006 adjuvant trastuzumab trial: Docetaxel/carboplatin/trastuzumab (TCH)

Track 8 Risk of congestive heart failure with adjuvant trastuzumab

Track 9 Acceptance of adjuvant trastuzumab therapy by patients with HER2-positive early breast cancer

Track 10 Use of adjuvant trastuzumab without chemotherapy

Track 11 Quality of life and side effects with trastuzumab

Track 12 Importance of obtaining adequate tissue for assessment of HER2 and ER status

Track 13 Selection of patients for neoadjuvant therapy

Track 14 Treatment approach to residual disease after neoadjuvant chemotherapy

Select Excerpts from the Interview

CD 3, Tracks 1-3

Case Discussion

A 61-year-old postmenopausal woman with hormone receptor-positive, node-positive breast cancer who completed five years of adjuvant tamoxifen 18 months ago.

SOURCE: CD 3, Track 1.

DR LOVE: How did you approach the discussion of further endocrine therapy with this patient?

DR RUGO: At that point, she was six and a half years from her diagnosis of node-positive disease. Since she started therapy, the data have changed. We now understand more about the natural history of hormone receptor-positive breast cancer.

We understand that if approximately 50 percent of recurrences occur after five years, then a substantial residual risk remains. The residual risk for those patients will not be decreased much by the one or two years that she was off therapy. It's clear that hormonal therapy might provide additional benefit.

Data from MA17 demonstrated that women who allocated themselves to letrozole after unblinding did well compared to women who did not (Robert 2006; [4.1]). This suggests that if you start hormone therapy — even eight years after diagnosis — you may affect patients. For some patients who didn't receive tamoxifen early on, you can still start an aromatase inhibitor at a later time if they have higher-risk disease.

DR LOVE: Was she surprised when you broached the issue of hormone therapy, considering she had been doing so well for the last seven years?

DR RUGO: Yes. Women want to believe that five years is a magic time period. They don't want to hear that 50 percent of their recurrence risk — and, in truth, more than 50 percent of their risk of dying — lies ahead of them.

I have a patient who had a 1.9-cm, intermediate-grade, node-negative tumor. She received CMF, went into menopause in her midthirties and then received five years of tamoxifen. When she reached her five-year point, I said, "You are in menopause and could take an aromatase inhibitor." She said, "I had a

4.1

Extended Adjuvant Aromatase Inhibitor Therapy

"For patients with hormone-receptor-positive breast cancer, the risk of relapse remains significant even after successfully completing 5 years of adjuvant tamoxifen. The use of tamoxifen beyond 5 years is not recommended, but the need to protect against relapse following tamoxifen is clear. The third-generation aromatase inhibitors offer a new approach to treating postmenopausal women with receptor-positive early stage breast cancer through the potent and specific systemic inhibition of estrogen synthesis.

The updated analyses of the [MA.17] trial results (median follow-up, 2.5 years) confirm that letrozole significantly reduced the risk of recurrent breast cancer (42%) regardless of the patient's nodal status or receipt of prior chemotherapy, and significantly reduced the risk of distant metastasis (40%). Importantly, letrozole as extended adjuvant therapy achieved a significant improvement in overall survival in women with node-positive disease. Mortality was reduced by 39% among the approximately 2,500 women with node-positive disease randomized in the study. Letrozole showed minimal side effects compared with placebo; adverse effects on bone metabolism of uncertain clinical significance were the most noteworthy side effect."

SOURCE: Goss PE. *Semin Oncol* 2006;33(2 Suppl 7):8-12. **Abstract**

Stage I tumor, so I don't believe that's worthwhile." Three years later, she had metastatic disease to her bone.

Without concrete data, which we'll never have, I tailor the duration of the aromatase inhibitor therapy to the extended risk. I say, "Okay, you had node-negative disease, but an aromatase inhibitor adds to tamoxifen in every single trial that's available. Why don't we use two or three years of an aromatase inhibitor?"

If a patient has higher-risk disease, it brings up the next point: What do you do with a patient at particularly high risk who's been on five years of an aromatase inhibitor from diagnosis? Do you continue or stop?

In some ways, it's like stopping trastuzumab at one year for a patient who has inflammatory breast cancer and positive margins. At five years, I often continue the aromatase inhibitor, although it is impossible to know the optimal duration.

CD 3, Track 12

DR LOVE: Can you discuss the issue of HER2 testing?

DR RUGO: It's important to have adequate tumor tissue to make these assessments. I have had patients come in with inadequate tissue sampling — primarily women who underwent a fine-needle aspiration for diagnosis — who then received neoadjuvant therapy and underwent surgery, and nobody rechecked any of the tumor markers.

For HER2, if an immunohistochemistry (IHC) test is performed at a low-volume institution, you always want to repeat the IHC or obtain a fluorescence in situ hybridization test to pin down whether or not the patient has HER2-positive disease. It's critical to have that information as soon as possible in order to help with treatment decisions.

You don't want to be treating a woman who doesn't have HER2-positive disease with trastuzumab. However, you wouldn't want to miss administering trastuzumab to a patient who has HER2-positive disease. ■

SELECT PUBLICATIONS

Goss PE. **Preventing relapse beyond 5 years: The MA.17 extended adjuvant trial.** *Semin Oncol* 2006;33(2 Suppl 7):8-12. **Abstract**

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Ingle JN et al. **Duration of letrozole treatment and outcomes in the placebo-controlled NCIC CTG MA.17 extended adjuvant therapy trial.** *Breast Cancer Res Treat* 2006;99(3):295-300. **Abstract**

Robert NJ et al. **Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding.** *Proc ASCO* 2006;**Abstract 550**.

Charles E Geyer Jr, MD, David M Hyams, MD, Hope S Rugo, MD and Melvin J Silverstein, MD

CD 3, Tracks 15-27

Select Excerpts from the Discussion

CD 3, Tracks 15-19

Case Discussion

A 49-year-old, perimenopausal woman diagnosed with a 1-cm, Grade II, strongly ER-positive and PR-positive, HER2-negative, node-negative infiltrating ductal carcinoma. She had been amenorrheic for about 18 months (estradiol < 20 pg/mL and FSH = 43 IU/L). Her medical history was significant for fibromyalgia and a thrombotic ischemic event in 2001, for which she was taking warfarin (from the practice of Dr Charles Geyer).

SOURCE: CD 3, Track 15.

DR GEYER: Initially, I told this patient that the available data suggested that for patients with node-negative, ER-positive disease, the absolute improvement with adjuvant chemotherapy was about four percent for disease-free survival and a little less than that for overall survival, based on her profile. I entered this patient's information in Adjuvant! Online and showed her those numbers. Her attitude was, "It's got to be better than that for me to receive

chemotherapy." We discussed the Onco*type* DX assay and that the patients with a high recurrence score derive substantially larger benefits from chemotherapy — a 28 percent absolute increase in freedom from distant recurrence (Paik 2006; [5.1]).

She agreed that if that information were available, then she would reluctantly go ahead with chemotherapy. I believe that's an important element — you do need to decide before you order the test whether the results will alter how you manage the illness. Her Onco*type* DX results came back with an intermediate score of about 20. For her, that said no to chemotherapy.

DR LOVE: Hope, in your experience, when you see younger women like this with an intermediate recurrence score of 20, how do they feel about chemotherapy?

DR RUGO: I believe it's 50-50. It depends on the patients themselves. If they're absolutely sure they won't want to receive chemotherapy, you might choose hormone therapy before conducting the assay. Because those patients are randomly assigned to hormonal therapy with or without chemotherapy in TAILORx (Figure 2.1, page 8), either approach is currently acceptable.

DR LOVE: It's interesting, Chuck, that before the Onco*type* DX assay, most patients with 1-cm, ER-positive tumors were receiving chemotherapy.

DR GEYER: Yes, it was usually recommended.

DR LOVE: Hope, a study conducted in a community practice setting in Colorado showed that about one out of four times the Onco*type* DX assay was ordered, it changed what the oncologist did (Oratz 2005). What's your experience with it?

DR RUGO: It's interesting that the Colorado survey, which assessed the use of the test when it was quite new, showed that result. It's probably more like 50 percent now. I find that the test is even more useful for women who have Grade II, Stage IC tumors, for which we would have reflexively used chemotherapy. Now I avoid administering it to approximately 50 percent of those women.

5.1

Impact of Adding Chemotherapy to Tamoxifen According to Onco*type* DX Recurrence Score

	10-year distant recurrence-free survival		
Risk group	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	*p*-value
Low (RS < 18)	97%	96%	0.61
Intermediate (RS = 18-30)	91%	89%	0.39
High (RS ≥ 31)	61%	88%	<0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

DR HYAMS: I believe it's worthwhile for surgeons to consider using tests like Onco*type* DX to help prepare the patient and explain her risk. If we're concerned about the overuse of cytotoxic therapy, it helps for the patient to be brought into that loop a little sooner.

DR LOVE: We also want to talk about the issue of hormonal therapy for this patient. She was 49 years old and postmenopausal according to her estradiol and FSH levels, and she had stopped having her menstrual periods 18 months previously. How do you approach deciding whether a woman is postmenopausal or premenopausal when you factor in age and time since her last period?

DR GEYER: In a case like this, we know that aromatase inhibitors can reinduce ovarian function in some women. In this case, being amenorrheic for 18 months and having postmenopausal estradiol and FSH levels, it's likely that she is permanently postmenopausal.

Generally with these women, I transition through tamoxifen for a year or two, so I don't encounter reinduction of ovarian function. I don't believe the data indicating the aromatase inhibitors are superior to tamoxifen are so compelling that one needs to be concerned about that, particularly if you're forgoing chemotherapy because the patient has less aggressive disease and a better prognosis.

However, this patient had a history of a hypercoagulable syndrome associated with stroke. She didn't want to go near tamoxifen, so we're starting her on an aromatase inhibitor. I will watch her estradiol and FSH levels more closely than normal to see if her ovarian function starts to come back.

CD 3, Tracks 20-23

Case Discussion

An active 61-year-old woman who underwent breast-conserving surgery for a 0.8-cm, Grade II, ER-positive, PR-positive, HER2-negative, node-negative infiltrating ductal carcinoma (from the practice of Dr David Hyams).

SOURCE: CD 3, Track 20.

DR HYAMS: This patient was ambivalent about chemotherapy, and she was highly motivated to maintain her lifestyle. By the same token, she didn't want to give up an opportunity for cure. She recognized that a breast cancer recurrence would be associated with ultimate mortality, likely from breast cancer.

When we received this patient's information, it became reasonable to turn around and say, "We have a test that appears to work well. It's been reasonably well validated, but there is an area in which some questions remain. Would you have an interest in participating in a study?

If you participate in TAILORx (2.1) and you're in the low-risk category, you receive the hormonal therapy of your choice. If you are in the high-risk group, you receive hormonal therapy and chemotherapy. The intermediate-risk group

is the group for whom we're most interested in teasing out the advantages."

She was willing to participate in the trial, and she received a recurrence score of 25, which put her on the top end of the intermediate-risk category. She was randomly assigned to receive hormonal and cytotoxic therapy.

DR RUGO: Many oncologists would not generally use chemotherapy for a postmenopausal woman who has a 0.8-cm, ER-positive, PR-positive tumor. Yet we may, in that situation, be undertreating the patient. So it's important to figure that out. I applaud you for enrolling this patient in the trial.

DR LOVE: How did this woman feel about being randomly assigned to chemotherapy?

DR HYAMS: Because her recurrence score was essentially at the cutoff point for intermediate- to high-risk disease, I believe it was an easier choice for her. I have to say that even I'm uncomfortable randomly assigning a patient with a recurrence score of 12, which would be low risk, but we all agreed when we were planning this trial to be extremely conservative. That's why those cutoff points were chosen.

CD 3, Tracks 25-27

Case Discussion

A 29-year-old woman with a 6-cm, ER-positive, PR-positive, HER2-positive invasive ductal carcinoma and a 2-cm axillary node (from the practice of Dr Hope Rugo).

SOURCE: CD 3, Track 25.

DR RUGO: This patient presented a little less than a year before the first data with adjuvant trastuzumab were reported (Piccart-Gebhart 2005; Romond 2005). As we approached the reporting of the data from those trials and we couldn't accrue patients to the trials any longer, many of my colleagues and I considered the use of adjuvant trastuzumab outside of a clinical trial.

This woman presented with a large tumor and a palpable node. She was young with a nasty tumor, and I felt she deserved trastuzumab as part of her therapy. So she received an anthracycline for four cycles followed by a taxane- and trastuzumab-based regimen.

She had moderate, continued shrinkage of her tumor throughout the AC and the trastuzumab/paclitaxel. The node quickly became nonpalpable. Then she underwent a skin-sparing mastectomy and reconstruction. At the time of her surgery, she had a small amount of invasive cancer and a small amount of disease in one node.

She received radiation therapy after her surgery and did well. Then we had a discussion about her hormonal therapy options. As she had residual disease at the time of her surgery and was young with an aggressive presentation, I believed she still had substantial residual risk of recurrence and death from breast cancer.

So we thought she would potentially benefit from ovarian suppression. A lot of the data with subsets have suggested that women under age 35 might not benefit as much from hormonal therapy with tamoxifen, potentially because they have high levels of circulating estrogen. So we recommended ovarian suppression, and she is continuing to receive monthly leuprolide.

She started initially on tamoxifen, but she did not tolerate it. She experienced severe and unremitting hot flashes, despite medical therapy, and morning nausea, which is seen in approximately five percent of women receiving tamoxifen. So we switched her to anastrozole, which she tolerates well. She has a little joint stiffness, minimal hot flashes and some vaginal dryness. She is otherwise doing well approximately 3.5 years after the initial diagnosis.

We have been hesitant to use the aromatase inhibitors in very young women, even those on GnRH agonists, because you can potentiate ovarian function. Women may recover their menses, but this woman continues to show good ovarian suppression. ■

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Paik S et al. **Gene expression and benefit of chemotherapy in women with node negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

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Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

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Sparano JA. **TAILORx: Trial assigning individualized options for treatment (Rx).** *Clin Breast Cancer* 2006;7(4):347-50. No abstract available

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **SEER data suggest that approximately _____ of patients with DCIS do not receive radiation therapy.**
   a. Five percent
   b. 10 percent
   c. 35 percent
   d. 50 percent

2. **In Lee's 12-year follow-up study of patients with DCIS, the cumulative rate of recurrence for all patients was _____.**
   a. Two percent
   b. 15 percent
   c. 30 percent
   d. 50 percent

3. **Patients with hormone receptor-positive, node-negative breast cancer and a(n) _____ recurrence score on the Onco*type* DX assay have a high likelihood of benefiting from adjuvant chemotherapy.**
   a. High
   b. Intermediate
   c. Low
   d. Both a and c
   e. None of the above

4. **In the TAILORx study, intermediate risk is defined as an Onco*type* DX recurrence score from _____.**
   a. 11 to 25
   b. 18 to 30
   c. None of the above

5. **In addition to comparing five years of adjuvant tamoxifen to letrozole, BIG 1-98 will also evaluate switching from tamoxifen to letrozole or vice versa.**
   a. True
   b. False

6. **According to the MA17 study, the risk for disease recurrence was reduced by _____ among patients treated with an aromatase inhibitor following five years of adjuvant tamoxifen compared to those who received placebo following tamoxifen.**
   a. 12 percent
   b. 22 percent
   c. 42 percent

7. **Approximately 50 percent of breast cancer recurrences occur after five years of adjuvant hormonal therapy.**
   a. True
   b. False

8. **In the four adjuvant studies in HER2-positive early breast cancer, the addition of trastuzumab to chemotherapy resulted in approximately a _____ reduction in the risk of recurrence.**
   a. 10 percent
   b. 18 to 25 percent
   c. 32 to 36 percent
   d. 40 to 50 percent

9. **In the clinical trials of adjuvant chemotherapy with trastuzumab in patients with HER2-positive disease, the rate of congestive heart failure was approximately _____.**
   a. Less than one percent
   b. Two to four percent
   c. 20 to 40 percent

10. **In the TAILORx protocol, patients with a(n) _____ recurrence score on the Onco*type* DX assay will be randomly assigned to hormonal therapy with or without chemotherapy.**
    a. High
    b. Intermediate
    c. Low
    d. Both a and c
    e. None of the above

Post-test answer key: 1c, 2b, 3a, 4a, 5a, 6c, 7a, 8d, 9b, 10b

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To what extent does this issue of *BCU* for Surgeons address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in adjuvant and neoadjuvant disease. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen . . . . . 5 4 3 2 1 N/A
- Develop an algorithm for ER and HER2 testing and implement a treatment plan for patients with HER2-positive breast cancer . . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer. . . . . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Melvin J Silverstein, MD	5 4 3 2 1	5 4 3 2 1
David M Hyams, MD	5 4 3 2 1	5 4 3 2 1
Charles E Geyer Jr, MD	5 4 3 2 1	5 4 3 2 1
Hope S Rugo, MD	5 4 3 2 1	5 4 3 2 1

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
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