



COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

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Select patients carefully for **regional nodal irradiation**

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On the cover Artist's conception of cancer in the glandular tissue and lymph nodes of the right breast. Illustration: MedicalRF/Photo Researchers, Inc.

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A Better Slide

- Cancer drugs are expensive and strain patient resources.
- MD Anderson pioneered administration of patient assistance programs.
- Elderly, uninsured patients depend on assistance programs.

Using fewer words and bullet points will help make your PowerPoint slides more memorable. These and other tips for packing punch into your PowerPoint presentations are offered in this month's Technology column (see page 572).

Technology

572 Packing a punch into your PowerPoint presentations

John J. Fried

How can you make PowerPoint your friend? The answer lies in following some basic guidelines during their preparation, such as making an outline of the presentation before you start, not overloading the slides with information and dense text, and keeping it simple by following basic, audience-friendly rules of layout. If you use PowerPoint properly, it can enhance your talk, amplify your ideas, and help you deliver your message with maximum impact.

Washington Update

575 Oncology drugs hardest hit by shortages

Alicia Ault

Five therapeutic areas account for two thirds of the drug shortages in the United States, with oncology taking the hardest hit. The shortages might affect as many as a half-million cancer patients, according to a November 14 report. Dr. Chris Nunnink, of the Vermont Cancer Center in Colchester, says that shortages are not only threatening patient care but are also hastening the shift from office-based to hospital-based practices. Profit margins are slim and declining; shortages are exacerbating that and making new physicians think twice about starting their practices, he said. Patients often end up having to pay more out of pocket for the available alternatives, he continued, adding that sometimes standard chemotherapy drugs are simply not available.

LETTER FROM THE EDITOR

538 Warm reflections and a bittersweet farewell

Lee S. Schwartzberg, MD, FACP, *The West Clinic, Memphis, TN*

The Editor-in-Chief of COMMUNITY ONCOLOGY, Lee Schwartzberg, is leaving the journal he founded in May 2004 because of new responsibilities both within his practice and external to it. Dr. Schwartzberg was instrumental in launching the journal in response to the need for a platform for community-based oncologists to share their innovative approaches and solutions to the delivery of cancer care. The Medicare Modernization Act had been passed, and with it came sweeping changes in reimbursement and the challenges of navigating healthcare reform. In response to those developments, the journal often provided advice and tips that many clinics have now incorporated into their practice models.

COMMENTARY

542 Despite accommodations in the ACO final rule, oncology remains on the periphery

Matthew E. Brow, *McKesson Specialty Health, Washington, DC*

The Centers for Medicare & Medicaid Services recently released its final rule implementing the Medicare Shared Savings Program and the Advanced Payment Model through which Accountable Care Organizations would operate. The final rule contains many significant changes, but it remains clear that the agency has targeted the savings program to drive cost-effectiveness in larger, low-cost patient populations, and that specialties such as oncology that treat smaller, high-cost populations have been sidelined.

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COMMUNITY TRANSLATIONS

544 Regional nodal irradiation cuts breast cancer recurrence

Report prepared by *Patrice Wendling*

Adding regional nodal irradiation (RNI) to whole-breast irradiation (WBI) significantly improved disease-free survival in a randomized, multicenter phase III trial of 1,832 women with node-positive or high-risk node-negative disease who were treated with breast-conserving surgery and adjuvant therapy. An interim analysis found that WBI plus RNI significantly reduced the risk of locoregional recurrence from 5.5% to 3.2% and distant recurrence from 13.0% to 7.6%. Although the addition of RNI to WBI also improved overall survival, the difference did not reach statistical significance.

545 Commentary: Select patients carefully for regional nodal irradiation

Shivani Duggal, DO, and Thomas B. Julian, MD, FACS, *Allegheny General Hospital, Pittsburgh, PA*

The benefits of regional nodal irradiation (RNI) need to be carefully balanced against its risks—pain, lymphedema, pneumonitis, brachial plexus neuropathy, shoulder range of motion, malignancy, radiation dermatitis, and poor cosmetic outcome, among others. Treatment with RNI for selected patients should be based on biologic risk factors, molecular markers, and tumor genetics. This is an area that needs further study before RNI is implemented as a standard of care.

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Warm reflections and a bittersweet farewell

Lee S. Schwartzberg, MD, FACP, Editor-in-Chief

The first issue of COMMUNITY ONCOLOGY was published in May 2004 after many months of preparation. I was honored to serve the journal as founding Editor-in-Chief. At the time, community oncology practices had developed innovative approaches to delivering care to cancer patients, and state-of-the-art care was available in virtually every city and town in the country. This accomplishment represented decades of hard work and planning, yet our networking was minimal, with many practices innovating in isolation.

The birth of the journal arose out of this sense that additional communication venues were needed for us to share our solutions we had developed individually. We also sensed the beginning of what became a tsunami of change in healthcare. The Medicare Modernization Act had been passed, and reimbursement was just beginning to morph into a very different system. New cancer drugs, many of them oral, were being developed. The human genome had been sequenced. Surely, medicines based on an understanding of the biology of cancer soon would be developed.

I wrote my first Letter from the Editor excitedly as a manifesto of the challenges and successes of community-based cancer care. As I look back on that letter now, seven-and-a-half years on, it is gratifying that much of what we set out to accomplish has come to fruition. Our initially bimonthly, then monthly, print journal has become an effective tool for disseminating information to our practice-based colleagues, with hundreds of community-based practitioners contributing manuscripts on all aspects of cancer care, from original research and reviews to case reports.

Aided by two fantastic co-editors—David Henry and Linda Bosserman—we extended our print presence to new media, including monthly podcasts, a

Web-based archive, and now a Web site. We have reported on practice management and provided advice and tips that many clinics, large and small, have incorporated into their practice models. Under the able direction of our section editor and more recently, my newest co-editor, Jame Abraham, we publish the monthly Community Translations feature,

which breaks away from the purely academic approach to clinical trials by presenting data on new drugs or diagnostics with an emphasis on their use and application in the community setting and their impact on patient outcomes. Each of our journal's sections is designed to be practical and useful for those of us in the trenches who see patients on a daily basis.

In my first letter, I remarked on the work ethic of community oncologists and their desire for knowledge. That has not changed.

Earlier this month, Linda and I sat on a panel at the San Antonio Breast Cancer Symposium. The evening meeting commenced 12 hours after the start of a day that had been jam-packed with lectures and poster presentations. Yet 500 of our colleagues invested an additional 2 hours listening to a group of breast-cancer experts presenting cases and discussing their clinical management. That is remarkable dedication to acquiring knowledge to help patients. Values such as those make me proud to be a community oncologist.

Over the years, the editors have leveraged their particular talents to promote important aspects of cancer care. David Henry's interest in statistics in medical oncology and in oncologist-oriented technologies translated into two regular columns, Practical Biostatistics and Technology, which made those important topics more accessible to practicing oncologists and nurses. David's grasp of the cutting-edge issues in community practice has given rise to numerous well-received articles over the years. Linda's passion for providing and docu-



menting quality cancer care has been a touchstone for many practices around the country.

As everything in the practice of community oncology changes, so does the editorship of this fine journal. Because of new responsibilities both within my practice and external to it, it is with regret that I have decided to relinquish my position as Editor-in-Chief at COMMUNITY ONCOLOGY. I wish to thank everyone at Elsevier Oncology who has been part of a journey that began quite coincidentally with the registration of an Internet domain name in 2003. We have been blessed to have a remarkable team of editors, writers, administrators, and business staff who truly made COMMUNITY ONCOLOGY what it is today. I treasure the relationships with all involved in this journal.

I am excited to announce that the journal will remain in outstanding hands with David Henry

stepping into the Editor-in-Chief role. His humor, experience, and expertise will no doubt elevate the journal to new heights. The needs of community medical oncologists and their patients are more complex now than ever before, and the journal remains an indispensable monthly read. I leave active participation in editing COMMUNITY ONCOLOGY for now, but my heart remains with those who practice cancer care and with their patients, all of whom deserve the best.

Thank you for allowing me to play a small role in the ongoing evolution of cancer care.

A handwritten signature in black ink that reads "Lee Schwartzberg". The signature is written in a cursive, flowing style with a large, sweeping flourish at the end.

Lee S. Schwartzberg, MD, FACP

Despite accommodations in the ACO final rule, oncology remains on the periphery

Matthew E. Brow

McKesson Specialty Health, Washington, DC

The Centers for Medicare & Medicaid Services (CMS) recently released its final rule implementing the Medicare Shared Savings Program (MSSP) and the Advanced Payment Model through which Accountable Care Organizations (ACOs) would operate. The final rule contains many significant changes, made in response to the more than 1,300 comments the agency received on the proposed rule. However, it remains clear that the agency has targeted the MSSP to drive cost-effectiveness in larger, low-cost patient populations, and that specialties such as oncology that treat smaller, high-cost populations have been sidelined. The upshot is that participation in the program by community oncologists will likely not be significant, which could make management of cancer patients more difficult for primary care participants should any cancer patients be assigned to primary care ACOs. Given the projected growth rate of Medicare beneficiaries who will be fighting cancer in the coming decade, it is likely that the CMS will take a more targeted approach to driving quality-based reimbursement in oncology through cancer-specific programs, pilots, and demonstrations.

Primary care focus

The CMS has maintained its focus on primary care and the primary care physician (PCP) in the final rule. In response to comments on the proposed rule's method for assigning patients to ACOs—through a PCP only and only one who provides the largest number of primary care services—the agency has added a second level of patient assignment that would allow patients who receive no primary care services from a PCP to be assigned to the ACO of the specialist who provides most primary services. On the one hand, that could allow some oncologist-managed patients to be assigned to an ACO, but on the other hand,

it could mean that many oncologist-managed patients will not be assigned to any ACO at all or many will be assigned to ACOs of physicians who may not adequately manage their care.

Prospective vs retrospective assignment

Many parties noted their opposition to the retrospective approach to patient assignment. In response to those comments, the agency says it has taken a prospective approach to assignment in the final rule, meaning that CMS will identify patients before the performance period for assignment to an ACO rather than checking at the end of the period to determine which patients were actually managed by the ACO. However, the agency has not substantively changed the timing of patient assignment in the final rule, and it will effectively continue to be done on a retrospective basis. This is how it will work under the final rule: The agency will provide quarterly projections to the ACO as to which patients might be assigned to the ACO, but those prospective assignments will be reconciled retrospectively so that at the end of the performance period, not all patients who were prospectively identified for the ACO will be assigned to the ACO and some patients not previously identified may be assigned after all.

Outlier exclusion

In the final rule, the CMS has maintained the exclusion of patients in the 99th percentile of costs

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from the perspective of both per capita spending targets and the assessment of performance against those targets. This provision will exclude many cancer patients from ACO assignment.

Spending targets

The agency has finalized its proposal to set per capita spending targets on the basis of 3 years of historical spending on patients who would have been assigned to the ACO, weighted most heavily on the third year and adjusted upward for the 3 performance years with a minimal inflationary index. This approach has serious implications for oncologists who are considering participating in an ACO, and for ACOs that are considering inviting oncologists to participate. Given the volume of new oncologic drugs and technologies in the pipeline or under development and the likely expense of those therapies, especially those that are targeted, it will be difficult or perhaps even impossible to provide standard-of-care treatment to Medicare cancer patients at the same or lower total cost of care over any 3-year period.

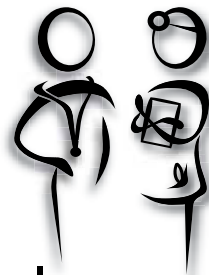
Risk approach

The CMS has made significant change in the area of risk. In the proposed rule, the agency wanted all participants to take downside risk for at least 1 year of a 3-year participation period. In the final rule, the agency has offered a true upside-only approach along with an upside-downside approach, as many health policy experts believe was required by the Affordable Care Act. In the upside-only approach, participants in the program would not be penalized for overspending on their targets but would participate in sharing the savings achieved below their targets. In

the upside-downside approach, participants would risk being penalized if they exceeded their spending targets but could still participate in a share of savings under target. This is likely to increase overall participation in the MSSP, but those who are thinking of participating in an ACO should be mindful of the anticipated expense associated with implementing their cost-effectiveness strategies before they accept that there is no downside to participation.

Conclusion

Although the agency has made significant changes to the MSSP structure, it seems to be moving ahead on the assumption that it can successfully drive cost-effectiveness in a PCP-centric model—despite its experience with the Medicare Physician Group Practice (PGP) Demonstration, which helped shape the ACO model. In the PGP project, the CMS offered incentives to large integrated primary care organizations for improving quality and reducing costs through a shared savings model similar to the MSSP but with no downside risk, a higher share of savings available to successful participants, and more flexible participation. Community oncologists should think very carefully about whether they want to align in this model, given that well-organized, well-capitalized entities within less-restrictive structures have failed to make the PGP a success. It might make more sense for oncologists to pass on the MSSP and consider participation in future oncology-focused pilots with the CMS or work with private payers to find solutions for both oncologists and their patients through the provision of quality, cost-effective care that does not weaken the community care delivery system.



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Regional nodal irradiation cuts breast cancer recurrence

Adding regional nodal irradiation to whole-breast irradiation significantly improved disease-free survival in women at high risk of recurrence following breast-conserving surgery and adjuvant therapy.

Whole-breast irradiation (WBI) plus regional nodal irradiation (RNI) significantly improved disease-free survival, but not overall survival, in a randomized, multicenter phase III trial of women with node-positive or high-risk node-negative disease who were treated with breast-conserving surgery and adjuvant therapy.

An interim analysis of 1,832 women with breast cancer found that after a median follow-up of 62 months (between March 2000 and March 2007), WBI plus RNI significantly reduced the risk of locoregional recurrence from 5.5% to 3.2% (hazard ratio [HR], 0.58; $P = 0.02$) and distant recurrence from 13.0% to 7.6% (HR, 0.64; $P = 0.002$), according to the lead investigator, Dr. Timothy Whelan, head of radiation oncology at McMaster University and the Juravinski Cancer Centre, Hamilton, Ontario, Canada.

As a result, disease-free survival rate improved from 84.0% for WBI to 89.7% for WBI plus RNI (HR, 0.67; $P = 0.003$). Overall survival in the intergroup trial was 90.7% with WBI, compared with 92.3% with the combined radiation regimen, but the difference did not reach statistical significance (HR, 0.76; $P = 0.07$).

In view of the positive findings from the National Cancer Institute of Canada Clinical Trials Group MA.20 study, the data safety monitoring committee recommended that the results be released. The data were presented by Dr. Whelan at the 2011 annual meeting of the American Society

What's new, what's important

For patients who are treated with breast-conserving surgery (BCS), the most common site of local recurrence is the ipsilateral breast itself. The risk of recurrence can be as high as 20% or more, even in node-negative women. Whole-breast irradiation (WBI) after BCS is the standard approach.

The clinical trial discussed in this report is the first study to examine the role of regional nodal radiation (RNI) in addition to WBI in patients who underwent lumpectomy. It is very interesting to see that the addition of RNI to WBI resulted in a 42% reduction in locoregional recurrence and 36% reduction in distant recurrence in this patient population. Moreover, disease-free survival at 5 years after radiation therapy increased 33% if RNI was also done ($P = 0.003$).

Patients received 50 Gy in 25 fractions with or without a 10-Gy boost or 50 Gy in 25 fractions with or without a 10-Gy boost plus RNI of 45 Gy in 25 fractions.

It is interesting to see this study, when the radiation oncology field is moving more into brachytherapy. However, WBI + RNI may be a reasonable approach for patients with early-stage disease who are at a high risk for recurrence, as defined in this study. Nonetheless, as Drs. Duggan and Julian emphasize in their commentary, it is important to consider the side effects of RNI and select patients appropriately.

—Jame Abraham, MD, *Editor*

of Clinical Oncology (ASCO).¹

ASCO and the American Society for Therapeutic Radiology and Oncology guidelines recommend locoregional irradiation after mastectomy for tumors > 5 cm or with more than three positive axillary nodes. Of the 1,832 women (mean age, 53.3 years) in the current study, 85% had one to three positive lymph nodes; 10% had high-risk, node-negative breast cancer; and 5% had more than four positive nodes. All of the women were treated with breast-conserving surgery plus adjuvant chemotherapy (91%) or endocrine therapy (71%).

The addition of RNI to WBI significantly increased the rates of grade 2 or higher dermatitis from 40% to 50% ($P < 0.001$), pneumonitis from 0.2% to 1.3% ($P = 0.01$), and lymphedema from 4% to 7% ($P = 0.004$). The lymphedema was primarily grade 2.

Adverse cosmetic outcome, a potential indicator of late-radiation morbidity, increased over time in the combination radiation and WBI treatment groups, from 29% and 26%, respectively, at 3 years ($P = 0.22$) to 36% and 29%, respectively, at 5 years, which was a statistically significant difference ($P = 0.047$). The investigators observed no increase in cardiac events or second cancers.

Radiation dosages for WBI were 50 Gy in 25 fractions plus a boost at the discretion of the cancer center of 10 Gy in 5 fractions and 45 Gy in 25 fractions for WBI plus RNI. The irradiation was applied to the internal mammary, supraclavicular, and high axillary lymph nodes. WBI and RNI were delivered concurrently, so that the added therapy would not re-

Report prepared by Patrice Wendling.

quire additional office visits for the patients.

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References

1. Whelan TJ, Olivetto I, Ackerman JW, et al. NCIC-CTG MA.20: an intergroup trial of regional nodal irradiation in early stage breast cancer. *J Clin Oncol* 2011;29(18 suppl):LBA1003.

Commentary

Select patients carefully for regional nodal irradiation

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Breast-conserving surgery (BCS) continues to be a significant option for women with early-stage breast cancer. With this, the need for regional control becomes increasingly important in high-risk patients with early-stage breast cancer. The addition of regional nodal irradiation (RNI) to whole breast irradiation (WBI) may be one means for providing further “protection” from distant and locoregional recurrence. As demonstrated by the NCIC-CTG MA.20 trial, the addition of RNI to WBI after BCS in women with node-positive or high-risk node-negative breast cancer treated with adjuvant systemic therapy improves disease-free survival (DFS) with a trend toward improvement in overall survival (OS) as well.¹ Node-negative women were considered to be at high risk if their tumor was ≥ 5 cm or if it was ≥ 2 cm and fewer than 10 axillary nodes had been removed, with either estrogen receptor negativity, nuclear grade 3, or presence of lymphovascular invasion.¹

From March 2000 to March 2007, 1,832 women were randomized to receive WBI or WBI + RNI. RNI included the internal mammary, supraclavicular, and high axillary nodes. When comparing WBI + RNI with

WBI alone, a reduction in both locoregional (96.8% vs 94.5%, respectively) and distant (92.4% vs 87%) recurrence was seen, as well as improvements in DFS (89.7% vs 90.7%) and OS (92.3% vs 90.7%).¹ Adverse outcomes included an increased risk of radiation pneumonitis and lymphedema.¹

Although the results of the MA.20 trial are significant and indicate the need to include RNI in guideline recommendations for the treatment of early-stage breast cancer, there is no true consensus among breast-care specialists in its implementation. For instance, in a study reported by Clavel et al,² 67 radiation oncologists were surveyed to document the use of RNI after BCS and to identify the factors that influenced their clinical decisions. Most of them indicated that the number of positive lymph nodes, nodal ratio, number of lymph nodes removed, and the presence of extracapsular extension were the primary factors that directed the decision to offer RNI, and few included the internal mammary chain in their treatment plan. Despite these similarities, the survey revealed a range of practices among the radiation oncologists, thus supporting the need for treatment guidelines when choosing to implement RNI.

Perhaps the variation in treatment with RNI reported by Clavel and colleagues is justified in the MA.20 trial itself. When taking cofactors into consideration, data from the trial suggest that not all patients with node-positive disease have the same risk of residual regional disease. For instance, patients with three positive lymph nodes had a locoregional recurrence (LRR) risk of 10%, compared with 2% for patients with two positive lymph nodes.¹ Similarly, extracapsular extension, lymphovascular invasion, larger primary tumor size, and larger metastatic burden were all associated with a higher risk of LRR.¹ These findings suggest that RNI should be tailored to the patient after proper assessment of tumor characteristics has taken place.

Furthermore, the LRR data reported in the MA.20 trial is somewhat predictable. Of 77 total LRRs

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reported, 48 occurred in patients in the WBI treatment arm and 29 in the WBI + RNI arm.¹ This difference translates into an absolute reduction in the rate of LRR of 2.3%, which can be reasonably expected. What is of further interest is that 67% of regional recurrences were in the axilla, supporting the need to tailor RNI not only to tumor characteristics but also to the region in which LRR is most likely.¹ In other words, perhaps RNI of the supraclavicular and internal mammary nodes should not be emphasized as highly as RNI to the high axillary nodes.

The benefits of RNI need to be carefully balanced against its risks. Those risks include (but are not limited to) pain, lymphedema, pneumonitis, brachial plexus neuropathy, shoulder range of motion, malignancy, radiation dermatitis, and poor cosmetic outcome. In a 5-year follow-up of the START trial,³ 40% of women reported at least moderate changes to the breast after WBI, and 30% reported arm and shoulder pain. Concerns for body image reduced over time.³ Women who were treated with hypofractionated radiotherapy experienced fewer adverse effects than those who received standard radiotherapy.³ The results of this survey and the frequency of adverse events following RNI in the MA.20 trial (radiation dermatitis, 50%; lymphedema, 7%) suggest that WBI + RNI may pose an even greater

How we treat breast cancer

The treatment of breast cancer at the Allegheny Cancer Center at Allegheny General Hospital centers around a multidisciplinary approach. Women undergoing breast-conserving surgery (BCS) with node-positive breast cancer, as determined from pre-operative ultrasound-guided axillary node biopsy or sentinel lymph node resection, generally undergo completion axillary lymph node dissection (ALND). Treatment with ALND, however, is based on multiple factors, including patient age and comorbidities, tumor biology, number of positive sentinel nodes, and tumor volume of the sentinel lymph node.

After undergoing ALND, patients are referred to the radiation oncology department. The implementation of regional nodal irradiation (RNI) is based on whether or not the patient has had ALND, the number of positive lymph nodes, and the nodal ratio. In the event that ALND is not performed, further treatment takes on a multidisciplinary effort that is guided by recommendations from the radiation oncologist, medical oncologist, and surgical oncologist.

The criteria used to define high-risk breast cancer at our institution are similar to those used in the MA.20 trial: tumor size > 3 cm, estrogen receptor negativity, HER2/*neu* positivity, or lymphovascular invasion. High-risk node-negative breast cancer is treated with whole-breast irradiation after BCS. Regional irradiation is generally not recommended for high-risk node-negative breast cancer at our institution.

— Shivani Duggal, DO, and Thomas B. Julian, MD, FACS

risk of adverse events than WBI alone.¹ This further supports the fact that RNI should be carefully selected for and applied in the treatment of early-stage breast cancer.

Treatment with RNI for selected patients should be based on biological risk factors, molecular markers, and tumor genetics. This is an area that needs further study. Validation of the MA.20 trial results and further research should precede the implementation of RNI as a standard-of-care guideline in the treatment of high-risk early-stage breast cancer.

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From the 2011 San Antonio Breast Cancer Symposium

New therapies, genetic assays translate into early detection of recurrence, encouraging outcomes

The following reports are based on presentations at the San Antonio Breast Cancer Symposium, held December 6–10, 2011.

Bevacizumab improves survival in HER2-positive metastatic disease

KERRI WACHTER

Bevacizumab (Avastin) improved progression-free survival (PFS) when added to standard treatment in a study of more than 400 women with human epidermal growth factor receptor 2 (HER2)-positive locally recurrent or metastatic breast cancer.

That finding, which emerged from the AVEREL trial, adds another wrinkle in the ongoing controversy regarding use of bevacizumab in breast cancer treatment.

For the primary endpoint of investigator-assessed PFS, conducted at a median follow-up of 26 months, the addition of bevacizumab resulted in a hazard ratio (HR) of 0.82 ($P = 0.0775$), compared with treatment with trastuzumab (Herceptin) and docetaxel alone. This difference was not statistically significant. Median investigator-assessed PFS was 16.5 months with bevacizumab versus 13.7 months without it.

In an assessment by an independent review committee (IRC), however, a significant improvement in PFS was seen with the addition of bevacizumab (hazard ratio, 0.72; $P = 0.0162$). Median IRC-assessed PFS

was 16.8 months with bevacizumab, compared with 13.9 months without the drug.

Lead investigator Dr. Luca Gianni reported the results at the 2011 San Antonio Breast Cancer Symposium. AVEREL is a randomized, placebo-controlled phase III trial designed to evaluate bevacizumab combined with trastuzumab and docetaxel as first-line therapy for HER2-positive, locally recurrent or metastatic breast cancer.

The findings add more data to support the effectiveness of the drug in particular subpopulations of patients with metastatic breast cancer.

In November, the US Food and Drug Administration (FDA) announced it was revoking its approval of the metastatic breast cancer indication for bevacizumab after concluding the drug had not been shown safe and effective for that use (see page 567).

Many in the breast cancer community consider the agency's decision unwarranted. "Bevacizumab improves the response rate—about doubles it—which for my symptomatic patients is a clear benefit," said press conference moderator Dr. Lisa Carey, pro-

fessor of medicine at the University of North Carolina at Chapel Hill. "It improves the progression-free survival to a greater or lesser degree in every trial in which it's ever been studied."

She conceded that the drug "doesn't do anything to overall survival." The FDA cited the lack of improvement in overall survival for metastatic breast cancer patients in its decision. Dr. Gianni noted, however, that "survival is a very important endpoint, but it's not the only endpoint in metastatic breast cancer."

Patients were eligible for the AVEREL trial if they had measurable or evaluable HER2-positive locally recurrent or metastatic breast cancer with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. They could not have received previous chemotherapy for advanced disease. Patients with central nervous system metastases were excluded.

The researchers enrolled 424 women with previously untreated disease. The women were randomized to receive either trastuzumab plus docetaxel (208 patients) or the same regimen plus bevacizumab (216

patients). Trastuzumab was given IV with an 8-mg/kg loading dose followed by 6 mg/kg given every 3 weeks. Docetaxel was given IV at a dose of 100 mg/m² every 3 weeks. Bevacizumab was given IV at a dose of 15 mg/kg every 3 weeks.

Trastuzumab and bevacizumab were given until disease progression. Docetaxel was given for a planned minimum of six cycles or until disease progression or unacceptable toxicity occurred. The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival, overall response rate, duration of response, time to treatment failure,

safety (including adverse events of special interest for bevacizumab), and quality of life. Exploratory analyses included PFS evaluated by an IRC (to comply with FDA recommendations) and biomarker assessment.

In terms of safety, “there were no new safety signals observed in this patient population with respect to what we really know from other patient populations exposed to Avastin,” said Dr. Gianni, director of medical oncology at the San Raffaele Cancer Center in Milan, Italy.

The researchers also conducted an exploratory analyses of plasma vascular endothelial growth factor- α

(VEGF-A). Their results suggest a potentially predictive effect—greater benefit with high VEGF-A levels—that is consistent with observations in HER2-negative locally recurrent or metastatic breast cancer.

The AVEREL trial was sponsored by Hoffman-La Roche. Dr. Gianni has disclosed that he is a consultant to Roche, Genentech, GlaxoSmith-Kline, Wyeth, Novartis, Eisai, Pfizer, Millennium Takeda, sanofi-aventis, Boehringer Ingelheim, Biogen Idec, AstraZeneca, Genomic Health, and Celgene. Dr. Carey reported that she has no relevant financial relationships to disclose.

Brachytherapy doubles the risk of breast loss

BRUCE JANCIN

In a large study, accelerated partial-breast brachytherapy, delivered as part of breast-conserving therapy for early-stage breast cancer, was associated with twice the mastectomy rate following standard whole-breast irradiation. Moreover, accelerated partial-breast brachytherapy entailed substantially higher rates of acute and late complications, Dr. Benjamin D. Smith said in a presentation at the symposium.

Dr. Smith and his colleagues reviewed the Medicare claims data for all 130,535 beneficiaries whose early-stage breast cancer was treated with lumpectomy followed by adjuvant irradiation during 2000–2007. The use of accelerated partial-breast brachytherapy in this population increased from less than 1% in 2000 to 13% in 2007.

The incidence of mastectomy during 5 years of follow-up was 4% in 7,291 brachytherapy recipients, compared with 2% after whole-breast irradiation ($P < 0.001$). After adjusting for the brachytherapy recipients’

older average age, more comorbid conditions, and lower rate of positive axillary lymph nodes, brachytherapy was associated with a 2.2-fold increased risk of losing the treated breast within 5 years, reported Dr. Smith, a radiation oncologist at The University of Texas MD Anderson Cancer Center, Houston. “After we had adjusted for various clinical and sociodemographic factors, we found that brachytherapy was the variable that had the strongest correlation with the risk of subsequent mastectomy,” he noted.

Partial-breast brachytherapy was also associated with significantly higher rates of postoperative wound infection and acute noninfectious complications, as well as increased 5-year rates of fat necrosis and breast pain. Fat necrosis is considered a marker of tissue injury caused by surgery and/or radiotherapy.

Within a year of breast cancer diagnosis, infectious complications involving the breast or surrounding skin or soft tissues occurred in 16% of women

treated with brachytherapy, compared with 10% of those who received standard whole-breast irradiation.

Noninfectious complications, including surgical wound breakdown, postoperative bleeding, or seroma formation, were twice as common with brachytherapy than without, 16% and 8%, respectively. The 5-year rate of fat necrosis was also higher with brachytherapy than without it (9% vs 4%, respectively) as was the rate of breast pain (15% vs 12%).

Accelerated partial-breast brachytherapy was developed to address the shortcomings of whole-breast irradiation, the historic standard of care, which entails up to 7 weeks of daily Monday-through-Friday treatment. Whole-breast irradiation is inconvenient. Indeed, it is such a hardship, especially for patients in areas distant from a radiotherapy center, that some women opt for mastectomy as a matter of convenience. Moreover, 15%–30% of women who undergo lumpectomy forgo prescribed radiation therapy, placing themselves at increased risk of local recurrence.

Accelerated partial-breast brachytherapy may improve patient compliance with radiotherapy. It shortens the treatment course to 1 week. It entails temporary placement of radioactive

beads within the breast via a catheter system. This method delivers radiation only to breast tissue immediately adjacent to the lumpectomy. This technique is but one of several forms of partial breast irradiation; however, the new findings do not apply to 3-D external-beam radiation therapy, for example.

Accelerated partial breast brachytherapy has boomed in popularity in recent years, especially in community practice. But these new data may put the brakes on that trend. “This study has changed the way I think about these two different treatment options, and it’s changed the way I practice,” Dr. Smith said in an interview.

Dr. Jennifer A. Ligibel, who chaired a press conference at which Dr. Smith

presented his findings, said the study carries an important message. “Although observational data using a claims database are no substitute for a randomized trial with long-term follow-up, what we see in this study is that this technique was not as effective, and it was also associated with a lot more complications. So if your argument in using this is that it’s sparing patients from additional problems, we’re not seeing that in this study.”

“This study really does give pause to the incorporation of accelerated partial-breast brachytherapy into routine clinical practice. These results should make people wait for the results of the ongoing randomized trials before they offer this as a standard procedure for their patients,” added

Dr. Ligibel of Dana-Farber Cancer Center, Boston.

The major randomized trial under way is the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 study. This trial has enrolled 4,000 of a planned 4,500 patients with early-stage breast cancer. The emphasis is on patients under age 50, because they have a higher local recurrence risk than older women. Participants are randomized to whole-breast irradiation or various forms of partial breast irradiation after lumpectomy. Mature results aren’t expected until mid-decade.

Dr. Smith and Dr. Ligibel reported that they had no relevant financial interests to disclose.

Gene profile identifies early recurrence in ER-positive breast cancer

KERRI WACHTER

An investigational genetic test to identify women who are likely to have early recurrence of estrogen receptor (ER)-positive breast cancer because of treatment failure could also guide physicians in deciding which patients might require agents beyond endocrine therapy to prevent the early onset of distant metastases. “We hope to exploit these molecular differences of early and later recurrences to help us guide novel drug combinations in ER-positive early-stage disease,” Dr. Minetta C. Liu said at a press briefing at the symposium.

The 91-gene classifier essentially distinguishes patients who are destined to recur early (within 3 years of diagnosis) from those who will likely recur late (beyond 10 years of diagnosis). “Our work is very much hypothesis-generating,” Dr. Lui said. “To be able to identify early and late recurrences at the time of diagnosis would

be useful, but we actually need to be able to know what to do about it once we identify it.”

Session moderator Dr. Jennifer Ligibel said that being able to do such an analysis would mean that patients who do not have tumors consistent with early relapse would not receive chemotherapy unnecessarily, and that patients whose tumors are consistent with early relapse will receive endocrine therapy beyond the initial 5 years of treatment.

Dr. Liu and his colleagues acquired snap-frozen, pretreatment tumor biopsies collected at the Edinburgh Breakthrough Breast Cancer Research Unit between 1982 and 1990. The samples were from patients with stage I, II, or III ER-positive breast cancer who were starting tamoxifen-alone adjuvant treatment. These patients had to have at least a 10-year follow-up in the absence of distant release.

The researchers performed a histologic review of the samples, and those that contained at least 50% tumor were cleared for RNA extraction for gene-expression profiling. This training dataset included 111 samples, with 57 relapses. Tumors from patients with relapse were subdivided into early recurrence (25 patients) and late recurrence (22 patients). Median follow-up was 13 years.

The researchers then selected a validation dataset from the literature that met certain criteria, such as quality of data and follow-up (*Loi S et al. BMC Genomics 2008;9:239*). This previously published data set included 255 samples from patients with stage I or II ER-positive breast cancer with tamoxifen-alone adjuvant treatment. Of those, 67 had distant relapse—25 patients had early recurrences and 7 had late recurrences. The median follow-up was 9 years. The researchers

used this training data set to develop a 91-gene classifier that separated those patients who were going to recur early from those who were going to recur late. They optimized the classifier and applied it to a validation data set.

“We had very high accuracy, sensitivity, specificity, positive predictive value, and negative predictive value, but we didn’t stop at developing a classifier. We wanted to understand what the genes were trying to tell us within the classifier...a novel compu-

tational method allowed us to look at ER network topology and to create a map basically.”

The researchers identified several genes that were overexpressed in patients with early recurrences: *CALM1*, *CALM2*, *CALM3*, *SRC*, *CDK1*, and *MAPK1*. They also identified genes that had increased expression in patients with late recurrences: *ESR1*, *ESR2*, *EGFR*, *BCL2*, and *AR*. “Clearly, there are robust molecular differences between tumors that recur

early and those that recur much later, despite adjuvant tamoxifen. Most of the genes in our classifier relate to apoptosis and proliferation,” said Dr. Liu, who is associate professor of medicine and oncology and director of translational breast cancer research at Georgetown Lombardi Comprehensive Cancer Center in Washington, DC.

Dr. Liu reported that she has no relevant financial relationships to disclose.

Zoledronic acid’s survival benefit lasts in premenopausal patients

DIANA MAHONEY

Adding zoledronic acid to adjuvant endocrine therapy significantly improves disease-free and overall survival in premenopausal women with endocrine receptor (ER)-positive early-stage breast cancer at 7 years’ follow-up, Dr. Michael Gnant reported.

Women in the Austrian Breast and Colorectal Cancer Study Group (ABCSCG)-12 trial who were randomized to receive zoledronic acid in addition to ovarian function suppression and endocrine therapy had a 28% reduction in risk of recurrence and 37% reduction in mortality risk at 84 months, compared with women randomized to adjuvant endocrine therapy alone, said Dr. Gnant, professor of surgery at the Medical University of Vienna, Austria.

The findings confirm data previously reported by the ABCSCG-12 investigators, which demonstrated disease-free and overall survival benefits associated with the treatment regimen at 48 and 62 months of follow-up (Gnant M *et al. Lancet Oncol* 2011;12:631-641). “The continued success of this treatment means we can intervene early and still observe

persistence of the benefit of treatment,” said Dr. Gnant, president of the ABCSCG.

The four-arm open-label trial randomly assigned 1,803 women to ovarian suppression and endocrine therapy with or without zoledronic acid for 3 years. Investigators used log-rank tests and Cox models to evaluate disease-free survival and overall survival, Dr. Gnant explained.

All of the patients (mean age, 44.5 years) were premenopausal and had undergone surgery for stage I or II hormone receptor-positive breast cancer. They were treated for 3 years with 3.6 mg of goserelin SC every 28 days and randomized to treatment with 20 mg/d of oral tamoxifen plus placebo, 1 mg/d of oral anastrozole plus placebo, or either of the latter with 4 mg IV zoledronic acid every 6 months.

At a median 84 months’ follow-up, the hazard ratios for breast cancer recurrence and death for women receiving adjuvant zoledronic acid were 0.72 and 0.63, respectively, Dr. Gnant reported, noting that the reductions remained significant in univariate and multivariate analyses. Further, in mul-

tivariate analysis, “there was no interaction between zoledronic acid and tumor parameters or endocrine therapy,” he said. “The hazard ratios were identical for small and large tumors, node-positive and node-negative tumors, and for patients receiving anastrozole and tamoxifen.”

There was a strong interaction between zoledronic acid and age in terms of survival benefit, however, with patients older than 40 years experiencing a 34% reduction in recurrence risk and a 44% reduction in mortality, according to Dr. Gnant. No similarly significant survival benefits were observed among patients younger than 40 years, he said.

As expected, patients receiving zoledronic acid experienced more arthralgia, Dr. Gnant stated, “but, importantly, there were no cases of osteonecrosis of the jaw and no renal failure in the treatment population.”

The findings, which are consistent with those seen in the postmenopausal cohort of the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial, “suggest that estrogen deprivation and reduction of bone turnover-derived growth factors

in the bone marrow microenvironment are needed to sufficiently suppress dormant micrometastases,” Dr. Gnant explained. Together with the known bone-protective benefits of zoledronic acid, the new data provide sufficient support for adding the bisphosphonate to adjuvant endocrine therapy in premenopausal women with early-stage ER-positive

breast cancer, he said.

Dr. James N. Ingle of the Mayo Clinic in Rochester, Minnesota, the discussant for the session, concluded that the ABCSG-12 findings provide level-one evidence for the value of adding zoledronic acid to goserelin and tamoxifen or anastrozole in this patient population. “Zoledronic acid as standard of care [in these patients]

will be more widely accepted when the results of the ongoing SOFT [Suppression of Ovarian Function trial] are reported,” which will clarify the value of tamoxifen compared with exemestane in conjunction with ovarian suppression, he said.

Dr. Gnant and Dr. Ingle reported that they had no relevant financial disclosures.

DCIS gene assay predicts recurrence risk after breast surgery

DIANA MAHONEY

A risk score based on a 12-gene assay is expected to help physicians determine whether postsurgical radiation for ductal carcinoma in situ (DCIS) would improve an individual patient’s outcome, Dr. Lawrence J. Solin reported at the symposium.

In a biomarker validation study, investigators demonstrated that a prespecified score on the *Oncotype DX* DCIS measure developed by Genomic Health can predict the risk of an ipsilateral breast event—either the development of a new invasive breast cancer or the recurrence of DCIS in the same breast—in women who have undergone breast-conservation surgery.

The 12-gene assay is a subset of the *Oncotype DX* 21-gene assay for invasive breast cancer. Dr. Solin, chair of radiation oncology at Albert Einstein Medical Center in Philadelphia, and his colleagues in the Eastern Cooperative Oncology Group (ECOG) evaluated the assay’s predictive value in 327 patients drawn from the prospective multicenter ECOG E5194 study in which the more extensive assay had been performed, he explained. All of the patients had low- or intermediate-grade DCIS, defined as ≤ 2.5 cm; or high-grade DCIS, defined as

≤ 1 cm, he said (*Hughes LL et al. J Clin Oncol 2009;27:5319–5324*).

Based on the 21-gene assay, central pathology review, and a recurrence algorithm, the investigators calculated a DCIS score from 0 to 100, with scores < 39 , 39–54, and ≥ 55 classified as low, intermediate, and high risk, respectively, for recurrence, Dr. Solin said. During nearly 9 years of follow-up, recurrent DCIS developed in 20 patients and invasive cancer in the ipsilateral breast in 26 patients, he reported. Among patients with low- or intermediate-grade DCIS and high-grade DCIS, the 10-year breast event rates were 15.4% and 15.1%, respectively, and the invasive breast event rates were 5.6% and 9.8%, he reported.

By DCIS score, “75% of the patients were in the low-risk category, compared with 14% classified as intermediate risk and 11% as high risk,” said Dr. Solin. The rates of any ipsilateral breast event and invasive breast cancer were directly related to DCIS risk score, with 12.0% of patients in the low-grade DCIS risk score group, 24.5% in the intermediate-grade group, and 27.3% in the high-grade group experiencing any ipsilateral breast event and 5.1%, 8.9%, and 19.1%, respectively, devel-

oping invasive breast cancer, he said. In multivariate analysis, DCIS score, menopausal status, and tumor size were all significantly associated with recurrence.

The DCIS score is “groundbreaking,” according to Dr. Solin, because it is the first validated molecular marker that clearly differentiates low-risk disease from high-risk disease in DCIS, Dr. Solin stressed. The tool “will help physicians understand the underlying biology of [DCIS] for the individual patient, accurately gauging the risk for that patient and helping guide treatment,” he said. Clinical and pathologic factors are not reliable enough on their own to determine whether radiation therapy following breast-conservation surgery will confer any survival benefit, he explained.

In response to questions about the price of the test and insurance coverage, Dr. Solin noted that, in aggregate, the savings associated with avoiding unnecessary additional treatment in patients with a low-risk DCIS score would more than compensate for the price of the test in individual patients.

Dr. Solin reported having no relevant financial disclosures. The study team included employees of Genomic Health.

Immediate zoledronic acid beats delayed therapy in early-stage breast cancer

DIANA MAHONEY

Immediate treatment with zoledronic acid (Zometa) in postmenopausal women with hormone receptor-positive breast cancer initiating letrozole therapy was associated with a 34% reduction in recurrence risk and 31% improvement in overall survival, compared with women of similar status who received the bisphosphonate later, according to new data from the Zometa-Femara Adjuvant Synergy Trial (ZO-FAST), which assessed the impact of zoledronic acid on aromatase inhibitor-associated bone loss after surgery for early-stage breast cancer.

Additional disease-free and overall survival benefits were observed among the subgroup of patients who had been postmenopausal for at least 5 years, according to Dr. Richard de Boer. The findings update those previously reported by Dr. de Boer of the Royal Melbourne Hospital, Australia, and his colleagues in the ZO-FAST trial, demonstrating that early treatment with zoledronic acid significantly improved bone mineral density and improved breast cancer disease-free survival.

The new, long-term data confirm the overall survival benefits, and the results of an exploratory subgroup analysis based on menopausal status indicates that the addition of zoledronic acid confers the most benefit to women who are truly menopausal at diagnosis, Dr. de Boer reported.

The study involved 1,065 postmenopausal women with hormone receptor-positive early-stage breast cancer with a bone mineral density T score of -2 . In addition to receiving adjuvant endocrine therapy with 2.5 mg of letrozole four times daily for 5 years, the women were randomized to receive

4 mg of zoledronic acid every 6 months either immediately or when their post-baseline T score dipped below -2 or they suffered a nontraumatic or asymptomatic fracture. Patients were included in the analysis if they had established menopause at the time of diagnosis or if they became menopausal as a consequence of chemotherapy or ovarian suppression, Dr. de Boer explained.

At 60 months' follow-up, the hazard ratios for recurrence and mortality in the immediate-treatment group were 0.66 and 0.69, respectively, with only the former representing a statistically significant improvement over the delayed-treatment patients, Dr. de Boer reported. Exploratory analyses of the 670 women who were postmenopausal for more than 5 years or older than 60 years at study entry showed that immediate zoledronic acid treatment significantly improved disease-free survival, with a hazard ratio of 0.63, and significantly prolonged overall survival, with a hazard ratio of 0.50, compared with the delayed treatment group.

With respect to bone mineral density in the lumbar spine, "the benefits observed in the immediate therapy group early on, when bone loss is at its greatest, continued out over 5 years, with a net difference of 10% favoring the immediate zoledronic acid [treatment] group," Dr. de Boer said, noting that similar results were observed in total hip bone mineral density, "with an overall change of close to 6% in the immediate group at the 5-year time point."

In a subset analysis comparing the immediate-treatment group with the 27% of patients who initiated zoledronic acid, "we observed a hazard

ratio 0.62 for recurrence in favor of the upfront zoledronic acid group," Dr. de Boer said. "Bone was the most common site of recurrence, and this favored the immediate-treatment group, with 14 events, compared with 24 in the delayed-treatment group."

In a comparison of patients who did and did not initiate therapy, "the hazard ratio for disease-free survival was in favor of those who did initiate treatment, suggesting a delay in bisphosphonate initiation could still have an impact on disease outcomes," Dr. de Boer said.

In terms of safety, there were three confirmed cases of osteonecrosis of the jaw in the trial, all in the immediate-treatment group. "This compares favorably with published results of studies in which zoledronic acid was administered on a 6-month schedule," said Dr. de Boer. "The AZURE study had a more intensive administration schedule, and thus had more cases of jaw osteonecrosis."

The findings of this study, together with those of other recent studies including the AZURE trial, "support the hypothesis that the anticancer benefits of zoledronic acid may best be realized in a low-estrogen environment," Dr. de Boer concluded.

The additional anticancer benefit observed in the truly postmenopausal women compared with the recently postmenopausal women in this study warrants additional investigation, according to Dr. James Ingle of the Mayo Clinic in Rochester, Minnesota, the discussant for the session. "The study met its primary analysis endpoint, which was bone mineral density improvement, but it was not powered nor designed to detect a difference in breast events. Although the findings demonstrate the value of zoledronic acid, they are based on an unplanned analysis and thus insufficient on their own to support zoledronic acid as [a] standard of care in postmenopausal women."

Dr. de Boer is on the speakers' bureau for Novartis. Dr. Ingle said he had no financial conflicts to disclose.

From the 11th annual meeting of the International Society of Geriatric Oncology

Screening and assessment are priorities for elderly cancer patients

SARA FREEMAN

The following reports are based on presentations at the 11th annual meeting of the International Society of Geriatric Oncology, November 4–5, 2011, in Paris. The International Society of Geriatric Oncology is also known as Société Internationale d'Oncologie Gériatrique, or SIOG.

Geriatric evaluation predicts overall survival in AML

Impaired physical and cognitive abilities are predictive of worse overall survival in elderly patients with acute myeloid leukemia (AML), according to findings in a prospective trial.

In a 74-patient trial, scores of less than 9 out of 12 on the Short Physical Performance Battery (SPPB) and of less than 77 out of 100 on a Modified Mini-Mental State (3MS) exam were associated with a threefold increase in risk of death, compared with scores in patients who had no physical or cognitive difficulties.

The findings could ultimately help determine which elderly patients with AML are fit enough to receive standard chemotherapy regimens for the disease and which patients might require a different therapeutic approach. However, the results should currently be viewed as a “signal” of a possible worse prognosis until further validation.

“Acute leukemia is probably one of the most dramatic examples of age-related outcome disparity in oncology,” Dr. Heidi D. Klepin, the study author, said in an interview. “Older patients consistently do much worse when diagnosed with disease than [do] young patients.”

Much research has been focused on

examining tumor biology in older and younger patients with AML, but few studies have looked at differences in the capabilities of the patients themselves, such as increasing vulnerability or frailty in the geriatric population.

“There has been so little done in geriatric assessment in the leukemia population,” Dr. Stuart M. Lichtman, of Memorial-Sloan-Kettering Cancer Center in New York, said in a separate interview. Dr. Lichtman, who was not involved in the study and served as scientific committee chair of the meeting, added the findings were important because they suggest that general and relatively simple-to-measure parameters could provide valuable information to help clinical decision-making. For example, the SPPB includes simply asking patients to perform a 4-meter timed walk, stand after being in a seated position, and show how well they balance while standing.

The objective of the study was to assess whether performing a geriatric assessment at the patient’s bedside could predict the patient’s likely overall survival. All of the patients included in the trial were about to start induction chemotherapy for AML.

The geriatric assessment consisted of multiple tests to examine cognition

(3MS), emotion (Center for Epidemiological Studies Depression Scale, Distress Thermometer), self-reported disability (Pepper Assessment Tool for Disability), objective physical function (SPPB), grip strength, and the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI).

The mean age of patients included in the study was 70 years, 56% were male, and 78% had an Eastern Cooperative Group Oncology Performance Status (ECOG PS) score of 0 or 1. Most of the patients (95%) had an intermediate or poor cytogenetic profile. The median follow-up was 7.4 months.

At baseline, 30% of patients were identified as having some form of cognitive impairment, 39% had depressive symptoms, 42% were distressed, 41% had reduced instrumental activities of daily living (IADL), 50% had reduced objective physical function, and 42% had comorbidities.

After researchers adjusted for potentially confounding factors, including age, gender, ECOG PS, and cytogenetic risk group (among others), hazard ratios for overall survival were 3.4 for an SPPB score < 9 ($P = 0.03$) and 3.0 for a 3MS score of < 77 ($P = 0.008$).

Reduced self-reported IADL was also associated with worse overall survival (hazard ratio, 2.6), but only after adjusting for confounding factors. SPPB and 3MS were also predictive on univariate analysis. These data suggest

that a better assessment of physical function could provide valuable information about a patient's likely outcome, "even in clinical practice right now," said Dr. Klepin of Wake Forest University, Winston-Salem, NC. "We can use this to improve how patients do with standard treatments by just paying attention [to baseline parameters] and changing how we manage people."

Dr. Klepin also noted that the information provided by the geriatric assessment could be used to inform and to help patients decide whether they want to be treated with standard chemotherapy or perhaps enter into an appropriate clinical trial of novel agents.

Preliminary data from the trial have been published in the *Journal of the American Geriatrics Society* (Klepin HD

et al. J Am Geriatr Soc 2011;59:1837-1846).

The study was supported by the American Society of Hematology, Atlantic Philanthropies, the John A. Hartford Association, the Association of Specialty Professors, and the Pepper Center at Wake Forest University. Dr. Klepin and Dr. Lichtman did not report any conflicts of interest.

Walking ability aids assessment of elderly breast cancer patients

Women with early-stage breast cancer who are older than 65 years of age have worse long-term survival if they report poor overall health and have significant limitations in how far they can walk, according to the results of a prospective trial.

At 10 years, 80% of women with a low self-rated health status and a walking limitation had died, compared with 50% of those with a high self-rated health status and no walking limitation ($P < 0.0001$). The probability of survival in women with low self-rated health but no walking limitation was 47% and in those with high self-rated health and a walking limitation, 44%.

"About 192,000 new cases of invasive breast cancer were diagnosed in the United States in 2009," and more than half of those cases were in women older than age 60, said study investigator Dr. Jessica A. Eng of Boston University. She added that among the many challenges in managing cancer in older adults, one of the major challenges is trying to determine optimal treatment benefits compared with the risks. Having a simple tool that could, early on, help identify patients who are likely to do worse could be of great practical benefit, she suggested at the meeting.

Dr. Eng and colleagues have pre-

viously shown that three or more deficits on a cancer-specific geriatric assessment are predictive of 5- and 10-year mortality in older women with breast cancer (Clough-Gorr KM *et al. Eur J Cancer 2011 July 7* [doi:10.1016/j.ejca.2011.06.016]).

In the current study, the researchers looked at whether self-rated health status and mobility could also be linked to mortality in the same population of 660 women who were aged 65 years or older and had stage I-III breast cancer. All of the women in the study were asked two questions at baseline: first, to rate their overall health as excellent, very good, good, or poor; and second, whether they could walk a couple of street blocks with no, a little, or a lot of limitation.

The women were followed for 10 years with annual telephone interviews, and the US National Death Index was used to determine mortality rates.

At baseline, most of the women were between 65 and 79 years old, with 18% aged 80 years or older. Most (94%) of the women were white, and 84% had 12 years or more of education. At least one comorbidity was present in 59% of participants, 51% had stage I breast cancer, and 76% had estrogen receptor-positive disease.

Dr. Eng reported that 39% of women rated their health status as low, and 28% said that their ability to

walk several street blocks was limited a little or a lot.

There was an absolute difference of 27% in the survival of women with a walking limitation plus high versus low self-rated health, and a 24% absolute difference in the survival of women with low self-rated health plus no walking limitation versus some limitation. Adjusted analysis showed that the risk of dying from any cause was doubled by being older than 80 years, with a hazard ratio (HR) of 2.11. The presence of at least one comorbidity also increased the risk of death significantly (HR, 1.37), compared with no comorbidity. The HR for low self-rated health plus a walking limitation was 1.58. Separately, low self-rated health and a walking limitation did not increase the risk of death.

"The combination of low self-rated health and limitation in walking several blocks at diagnosis is an important predictor of all-cause mortality at 10 years," concluded Dr. Eng, adding that the effect was independent of age, comorbidity, tumor characteristics, and treatment. "Using these two easily assessed questions in clinical practice may represent an effective strategy to improve treatment decision-making in older adults with cancer."

The study was supported by the National Cancer Institute. Dr. Eng had no conflicts of interest.

Cancer often goes untreated in nursing home residents

For elderly nursing home residents, a cancer diagnosis often comes at an advanced stage and fails to trigger appropriate therapy or overall general care, according to data from a study of more than 145,000 nursing home residents in the United States. Even early-stage cancers are likely to go untreated, and more than 20% of patients in pain receive no medication, regardless of the cancer site or the degree of pain.

“We saw that late and unstaged cancer was more prevalent in nursing home patients than in other elderly patients,” said Dr. Giuseppe Colloca, a geriatrician at the Università Cattolica del Sacro Cuore in Rome. “Older age was associated with late-stage diagnosis and death within a few months of diagnosis, and there was low hospice use and very little cancer-directed treatment, even among patients with early-stage cancer.”

The aim of the study was to look at patterns of cancer diagnosis, survival, treatment, and quality of care in elderly individuals who had been recently admitted to nursing homes. In the United States, an estimated 5% of elderly individuals live in nursing homes categorized as offering a high level of care, with an additional 1.5% in residential care that provides lower levels of nursing support.

Dr. Colloca and his colleagues obtained data on individuals aged 65 years or older whose records were contained within the SAGE (Systematic Assessment of Geriatric Drug Use via Epidemiology) database. This is a multilinked database of clinical care information based on a census of all nursing home residents in the United States.

The investigators evaluated data on 145,757 elderly individuals who were recently admitted to a nursing

home in five US states. Of that total number, 21,064 (14%) had a cancer diagnosis that was usually made after admission. In those residents with cancer, the most common diagnoses were prostate (10.8%) and lung (9.0%) tumors, with other known cancer types including colon (6.7%), breast (4.5%), bladder (3.1%), anal (2.9%), skin (2.2%), brain (1.6%), pancreas (1.5%), and renal (1.5%).

An analysis of sociodemographic characteristics showed that across all tumor types, the average age was between 75 and 84 years, but it varied according to the type of tumor. More than 40% of patients with prostate or colon cancer were 85 years or older, whereas only 13% of lung cancer patients were this old. Most of the elderly cancer patients were white (83.2%–91.2%), with moderate (49.7%–54.4%) or severe (34.9%–44.1%) limitations in physical function. More than half of the patients were moderately (36.4%–44.1%) or severely (7.8%–11.3%) cognitively impaired.

About a quarter of the patients experienced daily symptoms of pain, with other common symptoms including shortness of breath, constipation, unstable cognitive status, edema, and recent fall-related issues. “Control of pain symptoms has been shown to be inadequate among nursing home cancer patients,” Dr. Colloca said.

Chemotherapy and radiation treatment were “quite infrequent,” he added, noting that although 17.1% of breast cancer patients received chemotherapy, only 2.9% of those with colon cancer received such treatment. Chemotherapy rates also were low among those with lung (3%), prostate (6.3%), and other (5.4%) tumors.

Lung cancer patients were more likely to receive irradiation, with a radiotherapy rate of 10.9%. In the other

cancer patients, radiotherapy rates ranged from 0.9% for colon cancer to 4.2% for other. Only 3.8% of breast tumors and 2.9% of prostate cancers were treated with irradiation.

A terminal diagnosis of cancer was reported in 8.4% of breast, 8.9% of prostate, 10.5% of colon, 12.4% of other, and 21.5% of lung tumors. Lung cancer patients also had the highest 1-year mortality rate: 91.9% (lung). But 1-year mortality was high across the board at 80.0% in breast cancer patients, 78.6% (prostate), 80.9% (colon), and 83.2% (other).

Survival time was usually short, at just 54 days for those with lung cancer and 110 days for patients with other cancers. The longest survival times were in breast (172 days), prostate (149 days), and colon (142 days) cancers.

Dr. Colloca reported no conflicts of interest.

Severe comorbidity doubles death risk in multiple myeloma

Elderly patients with multiple myeloma and severe comorbid disease are more than twice as likely to die than were those with no comorbidities, data from a single-center, retrospective study show.

Mild or moderate comorbidities did not seem to influence overall survival significantly in the 179-patient study. The HR for death in patients with severe comorbidity compared with none was 2.36 ($P = 0.01$), which was associated with a median overall survival of 15.1 months.

Median overall survival was 43.1 months for those with no comorbidities and 31.5 and 35 months, respectively, in those with mild (HR, 1.38; $P = 0.26$) or moderate (HR, 1.5; $P = 0.19$) comorbidities.

Lead author Dr. Tanya M. Wildes of Washington University in St.

Louis, Missouri, noted that although the severity of comorbidities is associated with poorer survival in older adults with multiple myeloma, comorbidities are not currently incorporated into any staging systems for the disease. The research is part of a wider project that is looking at the value of performing a geriatric assessment to help predict which elderly patients with hematologic malignancies may be able to undergo standard cancer treatment or require additional monitoring for adverse events or more supportive care.

In the current study, Dr. Wildes and her colleagues identified all patients who were diagnosed and treated for multiple myeloma at Barnes-Jewish Hospital, St. Louis, between January 2000 and March 2010. Demographic, clinical, and survival data were obtained, with concomitant conditions graded using the Adult Comorbidity Evaluation (ACE) 27 index as none, mild, moderate, or severe. The primary endpoint of the study was overall survival, the duration of which was calculated from the date of diagnosis until the time of last follow-up.

The median age of patients at baseline was 69 years (range, 65–91 years). There was a similar percentage of men (48.4%) and women (51.4%), and 75% of the population was white. Most of the remainder was black (23.5%). According to the ACE-27 index, 41.3% of patients had mild, 24.6% had moderate, and 15.6% had severe comorbidities. The remaining 18.5% had no comorbidities.

“The challenge with multiple myeloma is that some of the comorbidities may be disease related as opposed to patient’s underlying comorbidities,” Dr. Wildes noted. That would require reviewing the patients’ medical records, which was not done in the current evaluation of this data set but is something that the researchers plan on looking at next.

“These are hypothesis-generating

data at the moment,” Dr. Wildes said. Further study to evaluate the impact of comorbidities on survival in multiple myeloma and their influence on patients’ tolerance of therapy and treatment decisions is needed.

Dr. Lazzaro Repetto of the Istituto Nazionale di Riposo e Cura per Anziani at the Istituto di Ricovero e Cura a Carattere Scientifico in Rome said that, on average, three comorbidities can be expected in a patient aged 65 years or older. Speaking at separate session during the meeting, Dr. Repetto said common comorbidities in elderly cancer patients included cardiovascular disease, renal insufficiency, diabetes, dementia, depression, anemia, osteoporosis, arthritis and arthrosis, and chronic obstructive pulmonary disease. All of these comorbidities may have an impact on survival.

Indeed, other research presented by a Danish team showed that colorectal and lung cancers in particular were associated with a high number of comorbidities when compared

with the frequency of comorbidities in the general elderly population. A high comorbidity burden was also linked to reduced overall survival, but only in those with lung cancer, reported Dr. Trine Lembrecht Jørgensen of Odense (Denmark) University Hospital and associates.

Dr. Repetto noted that the presence of comorbidities can alter treatment decisions and influence the type of treatment offered, though he advised that although it is important to assess comorbid disease, it should always be part of a wider geriatric assessment—including measures of cognition, emotional and physical functioning, medication use, socioeconomic and social support factors, and the patient’s wishes. “Using the geriatric assessment we can personalize treatment and optimize the balance between benefit and risk of our decisions,” Dr. Repetto suggested.

Dr. Wildes’ research was supported by a grant from the National Cancer Institute. Dr. Wildes and Dr. Repetto had no conflicts of interest.

Half of older cancer patients have unrecognized medical problems

About half of older cancer patients have unrecognized medical problems that may need to be addressed, according to the results of a prospective, multicenter study being conducted in Belgium. Initial findings from the ongoing study of 1,347 elderly individuals with a mean age of 77 years and a variety of malignancies indicate that 51.4% of patients assessed using a systematic battery of geriatric screening tests had additional problems.

The additional problems reported were: reduced physical functioning (20.4%), nutritional deficiencies cou-

pled with fatigue (19.2%), falls (16.6%), depression (14.3%), pain (12.6%), cognitive impairments (8.3%), and a lack of social support or problems linked to their social status (5.3%).

“Forty-two percent of physicians were not aware of the geriatric assessment results at the time of treatment decision,” said Cindy Kenis, RN, of the University Hospitals Leuven (Belgium). Ms. Kenis emphasized the need for better communication between healthcare professionals who treat elderly patients, specifically between geriatricians and oncologists.

The goal of the study is to look at

the utility of a systemic geriatric assessment at 10 institutions in patients aged 70 years or older who have one of six specific tumor types. Currently, almost 39% of study participants have breast cancer; about 22%, colorectal cancer; 14%, hematologic malignancies; nearly 12%, lung cancer; about 8%, prostate cancer; and roughly 5%, ovarian cancer.

Nearly two-thirds of the patients being evaluated are women, with 65% undergoing systematic geriatric assessment at diagnosis and 35% at progression of their malignant disease.

Patients in the study were first screened with the G8 questionnaire, an eight-item tool that can be easily used by oncologists. If the G8 score was ≤ 14 out of a total of 17, indicating some possible impairment, a full geriatric assessment was performed. This was done in 72.5% of the study population.

The full geriatric assessment includes the evaluation of Activities of Daily Living, Independent or Instrumental Activities of Daily Living, fall history, Mobility-Tiredness questionnaire, the Mini-Mental State Examination, the four-item Geriatric Depression Scale, the Mini Nutritional Assessment, the Charlson Comorbidity Index, and polypharmacy. Physicians also completed a questionnaire about their awareness of the results of geriatric assessment and treatment plans.

The results of the geriatric assessment led to interventions being planned to address previously unknown problems in a third of patients, with treatment decisions influenced in 15.5%.

Dr. Stuart M. Lichtman of the 65+ clinical geriatrics program at Memorial Sloan-Kettering Cancer Center in New York said that although all of these assessments were used in the study, which may have some oncologists reeling from the additional work involved, geriatric assessment did not need to be as complicated in practice.

A variety of tools are available to physicians, but the key thing is to be aware and to ask a few simple questions.

Ms. Kenis agreed with his observations in an interview. "One of the main things is that we have to do an assessment, and that we don't just perform the assessment, but we actually do something with it."

The study's findings support a

"three-step" approach in geriatric oncology, Ms. Kenis said: "You have to screen, you have to perform a geriatric assessment, and you have to do something with the results."

The study is supported by the Belgian government as part of the National Cancer Plan. Ms. Kenis and Dr. Litchman had no relevant financial disclosures.

Radionuclide therapy alleviates bone pain in prostate cancer

Radionuclide therapy can alleviate painful bone metastases in 63%–75% of men with prostate cancer, reducing the need for narcotic analgesics, according to the results of an 841-patient, retrospective, single-center study.

Investigators concluded that based on their experience at Hôpital René Huguenin in Saint-Cloud, France, treatment with strontium-89 chloride (Metastron) can be suggested as a "valuable supplement" to other treatments currently used.

"Bone metastases are present in more than 90% of patients who die from prostate carcinomas," Dr. Alain Pecking told attendees at the meeting. In addition to pain, metastases in the bone can lead to fractures and neurologic symptoms and can compress the spinal cord, he said, all of which can have a significant impact on the patient's ability to function normally and can increase his or her reliance on others to perform daily tasks.

For the past 18 years, Dr. Pecking, of the department of nuclear medicine at Hôpital René Huguenin, has been using radionuclide therapy with strontium-89 chloride to treat patients with painful bone metastases. A bone-targeting, beta-emitting radionuclide, strontium-89 is deposited in metabolically active regions of bone. It has a long half-life (more than 50

days); after a single infused dose of 148 MBq—the equivalent of about 9 Gy of irradiation—about 80% is retained in the tumor at 100 days. The rationale for using strontium-89 is that many patients suffer from painful bone metastases despite using current therapies, which includes narcotic analgesics, hormonal treatments, chemotherapy, bisphosphonates, and external-beam radiotherapy.

To look at the effects of radionuclide therapy on pain caused by multiple bone metastases secondary to prostate cancer, Dr. Pecking and his colleagues reviewed the medical records of men who were treated with strontium-89 at their institution. All participants were using narcotic analgesics at study entry, and the aim was to see whether strontium-89 therapy could reduce the need for their use.

The researchers studied the records of 841 patients with a median age of 73 years. Dr. Pecking reported that if there was a partial response or if the patient relapsed after a complete response to strontium-89, a second infusion was given to 268 men (median age, 71 years) and a third to 86 men (median age, 70 years). Patients who received one or two infusions had 12–16 metastatic sites, of which about 4 were painful, whereas those who needed three doses had about 7 painful sites.

A complete or global response was defined as the disappearance of more than 80% of all painful metastatic bone sites and a significant decrease in use of narcotic analgesics. A partial response was defined as a reduction in pain of more than 40% without any significant reduction in daily use of narcotic analgesics. A slight change, no change, or increase in use of narcotic analgesics was regarded as treatment failure.

“From one infusion [of strontium-89] you have 63% good responses, and after two courses you have 75%,” Dr. Pecking said. A “good” response equated to the number of complete plus partial responses,

which for one infusion was 12.6% and 50.4%, respectively, and for two infusions, 21.4% and 53.7%. The number of complete and partial responses after three strontium-89 doses was 15.1% and 43%, respectively.

The time to response was 11 days following one infusion, 14 days after two infusions, and just over 15 days after three infusions. The duration of the pain-easing effect was longest (158 days) after one infusion, decreasing to 138 days after two and 101 days after three infusions.

Pain was a common side effect of treatment, occurring in just under a quarter of patients during the first 15 days after an infusion.

Prostate-specific antigen levels also spiked after the first infusion in 681 patients (81%), but this is not a problem, said Dr. Pecking. “It is necessary to explain this phenomenon to the patient and to his medical doctor, but it is not a contraindication to the treatment.”

Although not without side effects, strontium-89 was generally well tolerated, he added, noting that it’s important to remember that other treatments used currently also have side effects such as fatigue, nausea, constipation, and anorexia.

The Curie Institute financed the study. Dr. Pecking had no conflicts of interest.

From the 2011 annual meeting of the Radiological Society of North America

Advances in imaging aid detection of cancer

The following reports are based on presentations at the 2011 annual meeting of the Radiological Society of North America, held November 27–December 2, 2011, in Chicago.

Family history data support annual mammograms in 40s

SUSAN BIRK

Women aged 40–49 years with and without a family history of breast cancer had almost the same rates of invasive disease in a retrospective analysis of data on more than 1,000 patients diagnosed over a 10-year period at a single site.

The finding adds weight to the American Cancer Society's recommendation in favor of annual screening mammograms for women beginning at age 40, said principal author Dr. Stamatia V. Destounis of Elizabeth Wende Breast Care LLC in Rochester, NY. Dr. Destounis presented the results of her study in a press briefing.

A study presented at last year's meeting by researchers at the London Breast Institute of the Princess Grace Hospital indicated that annual mammograms could reduce by half the risk of mastectomy in women who were diagnosed with breast cancer between the ages of 40 and 50 years.

Both studies challenge the recommendation against routine annual mammography for women under the age of 50 made in 2009 by the US Preventive Services Task Force.

"These conflicting recommendations have led to confusion among patients and physicians," Dr. Destounis said. In the present study, she and her

colleagues analyzed data on women between the ages of 40 and 49 years who underwent screening mammography at the center between 2000 and 2010.

In all, 1,116 cancers were found in 1,071 patients aged 40–49 years. Of those patients, 373 were diagnosed by screening mammography, and of the 373, 144 (39%) had a family history of breast cancer, 228 (61%) did not, and 1 patient did not know her family history. (A total of 7 patients with and 16 patients without a family history of breast cancer also had a personal history of breast cancer.) Among women with a family history, 32% (46) had a first-degree relative with a premenopausal history, 38% (54) had a first-degree relative with a postmenopausal history, and 31% (44) had a second- or third-degree relative with a pre- or postmenopausal history of the disease.

The incidence of invasive breast cancer was virtually the same—63% (91) and 64% (146), respectively—in women with and without a family history. The incidence of noninvasive disease in the two groups was also similar, at 37% and 36%, respectively. Those with and without a family history shared similar rates of lymph node metastatic disease (31% and 29%) as well. "Family history did not seem to [affect] the rate of inva-

sive disease in our patient cohort," Dr. Destounis said.

The following lesions were found in women with and without a family history, respectively: mass (42, 86), microcalcification (69, 97), mass with calcification (21, 18), architectural distortion (11, 18), and asymmetry (1, 9).

All 144 patients with a family history of breast cancer and 227 of 228 patients in the group without a family history proceeded to surgery. One patient had metastatic disease and opted for no surgery or treatment.

In women with and without a family history, 63% and 68%, respectively, underwent a lumpectomy. Some of those patients did not have clear margins after surgery and went on to mastectomy. In all, 38% (54) of women with a family history and 31% (71) women without a family history underwent mastectomy.

Since no difference in the rate of invasive breast cancer between women with and without a family history was found in this population, "the recommendation should be that women in their 40s have a screening mammogram yearly," Dr. Destounis said. She and her colleagues are currently collecting additional data on breast density, demographics, and survival rates for this patient group.

Dr. Destounis has been an investigator for Siemens AG, Fujifilm Holdings, Hologic Inc., and Koning Corp. She has also served as an advisory board member for Philips Electronics and Matakina International Ltd.

Mismatch between breast and mammogram detector size results in excess irradiation

PATRICE WENDLING

A mismatch between breast size and detector size during mammography resulted in significantly higher radiation doses for women with large breasts in a study of 886 patients. On average, women with large breasts screened on a small detector received almost 5 mGy of irradiation, which exceeds the American College of Radiology guidelines of 3–4 mGy or less for a standard two-view mammogram.

When a mismatch occurs, women with large breasts receive significantly higher doses of irradiation than do women with small breasts or their counterparts with large breasts correctly matched to a large detector, Dr. Cathy Wells said when presenting the award-winning study.

“Women with large breasts should be imaged with a large detector to avoid an unnecessary increase in radiation dose,” she urged.

The quality assurance study involved 886 women who presented for screening or diagnostic mammography during a 6-week period in late 2009. The exams were performed with a phosphor charge-coupled device (CCD) detector, which is available in preset sizes (large or small) due to manufacturing constraints, she said. Insufficient data for 22 patients left 426 screening and 438 diagnostic patients evaluable for analysis.

A sizeable number, or almost 20% of patients, were affected by a mismatch between breast and detector size, said Dr. Wells, who completed the study at Beth Israel Deaconess Medical Center and is now a breast imaging fellow at Massachusetts General Hospital, both in Boston.

The percentage of mismatches varied from 10% of screening patients

with large breasts, defined as a C cup or larger, to 27% of screening patients with small breasts imaged with a large detector. A mismatch occurred in 22% of diagnostic mammography patients with large breasts and 17% of diagnostic patients with small breasts.

Despite the sizeable number of mismatches in the study, not all women will be faced with this problem when they arrive for their mammogram, Dr. Wells said in an interview. The phosphor CCD detector is one of four types of digital detectors currently available in the United States and, to her knowledge, the only type

‘Women with large breasts should be imaged with a large detector to avoid an unnecessary increase in radiation dose.’

that has such size constraints. In addition, not all imaging centers use this detector type.

Some centers, including her own, have both large- and small-sized detectors available, although there can be a wait for the proper size, she noted. Women can choose to wait or be imaged with a different detector after a discussion with the technologist.

“The best option for women to ensure a correct match between breast size and detector size would be to talk with the technologist who performs the actual mammogram, [as] the scheduler or person at the check-in desk will likely not know the answer,” Dr. Wells said. “Women could

ask the technologist whether the detector comes in different sizes, since not all do, and if so, whether they are correctly matched.”

Screening mammogram patients with correctly matched breast and detector sizes received an average mean glandular dose per breast of 3.3 mGy, compared with 4.9 mGy for mismatched patients with large breasts ($P < 0.05$). The higher radiation dose correlated with a significant increase in number of views obtained in mismatched patients with large breasts (mean, 5.9 views), compared with both large-breast patients imaged on a large detector (4.6 views) and small-breast patients imaged on a small detector (4.7 views; $P < 0.05$), Dr. Wells said. Small-breast patients mismatched to a large detector underwent a similar number of views (mean, 4.6 views) but actually received slightly less irradiation (mean, 2.9 mGy; $P < 0.05$).

During diagnostic mammograms, the radiation dose was again significantly higher among mismatched patients with large breasts, compared with the correctly matched large- and small-breast groups (8.2 mGy vs 6.7 mGy, respectively; $P < 0.05$), but it did not seem to be related to the number of views obtained, she said, adding that other factors must be at work. Several variables contribute to radiation dose, but in this case, the most likely culprit is compression thickness, Dr. Wells said. “It might be more difficult to adequately compress a large breast with a small detector, resulting in a larger radiation dose. We hope to analyze the data again to answer this question.”

Dr. Wells reported no conflicts of interest.

Multiparametric MRI helps identify prostate cancer patients for surveillance

PATRICE WENDLING

Multiparametric MRI was superior to National Comprehensive Cancer Network (NCCN) guidelines in correctly classifying patients with prostate cancer as active surveillance candidates in a retrospective study of 126 men.

NCCN guidelines misclassified 22 of the 126 patients, compared with 12 who were classified using multiparametric magnetic resonance imaging (MP-MRI). When MP-MRI was added to the NCCN criteria, however, only five patients were misclassified, Dr. Baris Turkbey reported in an award-winning paper at the meeting. “Presently, MRI is not in any urology guideline, but we want to change that. Our goal is to create [a National Cancer Institute] prostate cancer nomogram that includes multiparametric-MRI, and our scientists are close to finishing it.”

Dr. Turkey, a fellow in the division of cancer treatment and diagnosis at the National Institutes of Health in Bethesda, Maryland, and his colleagues, evaluated 126 men with biopsy-proven prostate cancer who underwent 3T MP-MRI of the prostate and subsequent radical prostatectomy at a median of 48 days. Their mean age was 59 years and mean prostate-specific antigen (PSA) level, 6.67 ng/mL.

MP-MRI images were obtained of the largest and most aggressive lesion using T2-weighted MRI, diffusion-weighted MRI, MR spectroscopy, and dynamic contrast-enhanced MRI. Each dominant lesion was then assigned an MP-MRI score of low (at least two positive sequences), moderate (three positive sequences), or high (four positive sequences).

Patients were eligible for active surveillance on MP-MRI if they had a

dominant tumor of < 0.5 cm³ without extracapsular extension or seminal vesicle invasion and a low imaging score. The NCCN criteria for active surveillance is T1c disease, Gleason score of 6 or lower, fewer than three positive biopsy cores, PSA level < 10 ng/mL, and PSA density < 0.15 ng/mL/g.

Based on histopathologic findings, 14 of 126 patients were eligible for active surveillance, with the remaining 112 candidates for active whole gland treatment. NCCN guidelines wrongly classified 5 of the 14 active surveillance patients and 17 of the 112 active treatment patients, whereas MP-MRI wrongly classified 1 active surveillance and 11 active treatment patients. The sensitivity, specificity, and

overall accuracy of the NCCN guidelines were 64.3%, 34.6%, and 82.5%, respectively ($P = 0.00002$), compared with 92.8%, 54.2%, and 90.5% with MP-MRI ($P < 0.000001$).

Dr. Turkbey noted that the study was limited by using a relatively simple nonweighted MP-MRI scoring system and by comparing MP-MRI with NCCN guidelines only. The researchers are currently evaluating a system in which the various parameters are weighted to obtain better predictions.

Dr. Turkbey reported no conflicts of interest. A coauthor reported serving as a researcher for Koninklijke Philips Electronics, General Electric, Siemens, Hoffman-La Roche, and iCAD.

Tomosynthesis offers detection benefits in dense-breast cases

PATRICE WENDLING

The addition of tomosynthesis to full-field digital mammography improved cancer detection and reduced recall rates in women with dense breasts in a study of 293 patients.

“Both clinically and in trials, we’ve seen that tomosynthesis offers benefit for all women, but there is a particular benefit—the increased gains are more—for women with dense breast tissue,” said Dr. Elizabeth Rafferty of Massachusetts General Hospital, Boston. “That underscores where we may start our triage efforts with limited resources.”

Dr. Rafferty reported on an enriched case set of 69 biopsy-proven cancers, 74 benign biopsies, 50

recalled screening cases, and 100 negative screening cases, all with a BIRADS density score of 3 (heterogeneously dense) or 4 (extremely dense). Calcification was present in 25% and noncalcification in 75% of cases. Eight radiologists read the cases in two separate sessions separated by a month, with half of the cases read in each mode for each reading session. Identification of the lesion location and type and initial BIRADS score (0, 1, 2) were used to determine the recall rate. A probability of malignancy score from 0% to 100% was used to calculate the receiver operating characteristic area under the curve (AUC).

The difference in the AUC between

standard full-field digital mammography (FFDM) plus tomosynthesis and FFDM alone was significantly higher at 8.3% for all cases (AUC, 0.940 vs 0.857, respectively; $P < 0.0001$), 4.1% for calcification cases (0.818 vs 0.777; $P = 0.048$), and 11% for noncalcification cases (0.977 vs 0.867; $P = 0.0001$), reported Dr. Rafferty, director of breast imaging at Massachusetts General Hospital in Boston.

The recall rate for all cancer cases was 9.7% higher for FFDM plus tomosynthesis versus FFDM alone. Specifically, it was 3.8% higher for calcification cases and 14.3% higher for noncalcification cases.

Seven of the eight readers increased their cancer detection rate using FFDM plus tomosynthesis, and one reader had the same detection rate on the two modalities. For six of

the seven readers, the improvement in cancer detection was statistically significant, she said.

For non-cancer screening cases, the recall rate for FFDM plus tomosynthesis was 23.3%, compared with 33.9% for FFDM alone, representing a 31% reduction in the non-cancer recall rate.

Six of the eight readers had significant decreases in their screening recall rate using the combined imaging modality, and two had no significant change.

“In women with dense breast tissue, tomosynthesis, when added to FFDM, seems to offer particular value both in terms of sensitivity as well as specificity of the examination,” Dr. Rafferty said. She added that the numbers were too small to identify a difference in performance with FFDM plus tomosynthesis between

dense and extremely dense breasts.

In response to a question about whether she would recommend using tomosynthesis in lieu of screening ultrasound, Dr. Rafferty replied that “in terms of the positive predictive value of screening ultrasound, I think that screening mammography, or some form of screening mammography, is going to remain the mainstay...but in terms of our diagnostic evaluation, ultrasound has become an incredibly important tool in the diagnostic evaluation. Tomosynthesis examination plus ultrasound has become [for me, and perhaps others] a kind of go-to regimen instead of using additional views. The two are very complementary.”

Dr. Rafferty reported no relevant financial disclosures. A coauthor reported serving as a patent holder and employee of Hologic Inc.

Bevacizumab approval revoked for metastatic breast cancer

Elizabeth Mechcatie and Lisa LaMotto

The approval of bevacizumab (Avastin) as a treatment for metastatic breast cancer has been withdrawn by the US Food and Drug Administration (FDA). The agency's commissioner, Dr. Margaret Hamburg, said November 18 that she had decided on the withdrawal because bevacizumab has not been shown to be safe and effective as a first-line treatment for metastatic breast cancer.

"This was a difficult decision. The FDA recognizes how hard it is for patients and their families to cope with metastatic breast cancer and how great a need there is for more effective treatments. But patients must have confidence that the drugs they take are both safe and effective for their intended use," Dr. Hamburg said. "After reviewing the available studies, it is clear that women who take Avastin for metastatic breast cancer risk potentially life-threatening side effects without proof that the use of Avastin will provide a benefit in terms of delay in tumor growth that would justify those risks. Nor is there evidence that use of Avastin will either help them live longer or improve their quality of life." Her decision is explained in a 69-page opinion.

Dr. Hamburg emphasized in a press briefing that there is no identified subset of women for whom benefit from the drug can be demonstrated and that no study has shown an improvement in quality of life or survival in metastatic breast cancer, but serious life-threatening adverse events have occurred, including myocardial infarction, heart failure, severe hypertension, and hemorrhage. She en-

couraged Genentech, the drug's manufacturer, to consider other studies "to identify if there are select subgroups of women suffering from breast cancer who might benefit from this drug."

Bevacizumab is approved for other types of cancers and will remain on the US market. In those cases, the benefit has been significant enough to balance the risks, Dr. Hamburg said.

Genentech issued a statement that said the company was disappointed with the outcome but remained committed to women with metastatic breast cancer and would "continue to provide help through our patient support programs to those who may be facing obstacles to receiving their treatment." The company said that despite the agency's decision, it planned to start a new phase III study of bevacizumab in combination with paclitaxel in women with previously untreated metastatic breast cancer to evaluate "a potential biomarker that may help identify which people might derive a more substantial benefit from Avastin."

Genentech had hoped to retain the approval for metastatic breast cancer while that study was being conducted, but Commissioner Hamburg was not swayed by that argument.

Lead-up to the withdrawal decision

The FDA granted an accelerated approval to bevacizumab in combination with paclitaxel as a first-line treatment for metastatic breast cancer in February 2008, based on an open-label study that found a survival advantage for the combined treatment compared with paclitaxel alone.

Studies confirming the beneficial effects are a condition of accelerated approvals. In this case, though, two follow-up studies failed to confirm the benefit. The FDA concluded that bevacizumab had an unfavorable risk-benefit profile for the breast cancer indication and decided to withdraw approval of the breast cancer indication.

In an unprecedented move, Genentech appealed the decision and requested a hearing, which was held in July 2011. At that meeting, the FDA's Oncologic Drugs Advisory Committee unanimously voted that approval for the breast cancer indication should be withdrawn because clinical trials did not show an improvement in overall survival or any clinically meaningful improvements in progression-free survival. The final decision was left to Dr. Hamburg.

Use of bevacizumab for metastatic breast cancer won't stop

Although Genentech can no longer include metastatic breast cancer on its label or openly promote it, it will not stop physicians from prescribing it to patients whom they think might benefit from its use. Bevacizumab previously commanded about 55% of the HER2- breast cancer marketplace, but that share has dropped precipitously since the FDA's Center for Drug Evaluation and Research first voiced concerns about the drug's efficacy, and the proportion now stands at 20%. The company has indicated that off-label use is expected to continue at that level.

The chief repercussion of taking

the breast cancer indication off the bevacizumab label is coverage from insurers—namely, that they are no longer required to give any coverage at all for the drug. In late 2010 and early 2011, several regional plans revoked coverage, including the Blue Cross and Blue Shield insurers Regence, which covers 2.5 million members across Idaho, Oregon, Utah, and Washington; Excellus (about 1.9 million members in Rochester, NY); and Dakotacare (about 120,000 members in South Dakota). Blue Shield of California (3.3 million members) originally stated that it would discontinue coverage for the drug in breast cancer

patients but then revised its policy to grandfather in any patients who were already taking the drug and to provide coverage only for new patients whose case had been reviewed by two oncologists and deemed medically necessary.

CMS released a statement on November 18 saying that it would continue coverage for breast cancer patients. “CMS will monitor the issue and evaluate coverage options as a result of action by the FDA but has no immediate plans to change coverage policies,” the agency indicated.

Despite the varying levels of coverage from insurers, Genentech will

no longer include breast cancer patients taking bevacizumab in its cap on costs for patients, which provides an annual limit on the amount a patient must pay toward treatment; beyond \$58,000, Genentech covers the cost. “We are still able to provide many of our patient support services to people receiving Avastin for breast cancer, so they should still call us if they are facing obstacles receiving their treatment as a result of [the FDA’s] decision,” Genentech said in a statement.

Bevacizumab is still approved for treating metastatic breast cancer in more than 80 countries.

Restricted access requirements dropped for romiplostim, eltrombopag

Shirley Haley

The FDA has announced that it would no longer require healthcare professionals, hospitals, specialty care facilities, and patients to enroll in a restricted access program to be able to prescribe or receive the thrombocytopenia treatments romiplostim (Nplate) and eltrombopag (Promacta) and that physicians will no longer be required to complete periodic safety forms for patients receiving these drugs.

Pharmacies also will no longer be required to enroll in the programs or verify prescriber and patient enrollment before dispensing eltrombopag, an oral therapy covered under Medicare Part D.

Amgen, the manufacturer of romiplostim, is hoping that the revision to the Risk Evaluation and Mitigation Strategies (REMS) will help it get off of the Centers for Medicare & Medicaid Services (CMS)’s list for a potential Medicare National Cover-

age Determination (NCD). Modified REMS for the two drugs will now include a communications plan to inform healthcare professionals about changes to the risk-management program and to reinforce safety risks associated with each product. The patient medication guide will be separated from the REMS but continue as part of the drugs’ labeling.

The changes came after additional information was submitted under the REMS assessment process. The FDA has already shown a willingness to modify the programs based on incoming information, such as that for golimumab (Simponi).

REMS review led to changes

The FDA approved romiplostim and eltrombopag in 2008 to treat adults with chronic immune thrombocytopenia—a rare autoimmune-mediated blood disorder that results in a low platelet count and associated

bleeding risk—who have not responded to corticosteroids, immunoglobulins, or splenectomy. The drugs work by stimulating the bone marrow to produce the needed platelets, but the process is not without risk.

Since the approvals, the agency has monitored bone marrow changes of collagen deposition (reticulin), risk of blood clots, risk of developing blood-related cancers resulting from bone marrow stimulation, and the increased risk of low blood platelet count or bleeding after discontinuation. Eltrombopag also carries a boxed warning concerning the risk of liver toxicity. In addition to the reports required by the REMS, Amgen and GlaxoSmithKline have submitted data from ongoing clinical trials to clarify the safety profiles of their therapies.

The agency based the new labeling on both long-term safety data submitted from those trials and a

determination that causality of adverse events in the individual case safety reports collected through the REMS was difficult to assign when the side effects of the therapies were mixed with the underlying medical conditions of the patients.

GlaxoSmithKline “worked with FDA on the specifics of the change for a number of months, with both sides seeking to ensure changes would be in the best interests of patients and healthcare providers,” the company said in response to queries about the process.

Although REMS continue to be “vital tools” for the FDA, “the agency

remains committed to exercising a flexible and responsible regulatory approach” to ensure the programs are effective and efficient and not “resulting in an unnecessary burden on healthcare professionals and patients,” Center for Drug Evaluation and Research director Janet Woodcock said in a statement.

Will romiplostim sidestep NCD?

CMS put romiplostim on its list of potential NCD topics even before it was approved, expressing safety concerns regarding thrombopoiesis-stimulating agents because they

lacked long-term safety data. Amgen has argued that romiplostim’s comprehensive REMS program—the first to include a mandatory patient registry—and lengthy list of postmarketing safety studies precluded the need for CMS to consider coverage restrictions. It seems that Amgen was able to convince the FDA to drop some of the most arduous restrictions because of the most recent REMS assessment, which was based on completed phase IV clinical studies. Amgen’s recent comments on CMS’ NCD topics list argue that the FDA’s reconsideration of the risk profile should lead the government payer to reconsider as well.

Asparaginase *Erwinia chrysanthemi* approved for acute lymphoblastic leukemia

Michele G. Sullivan

The FDA has granted orphan-drug status to asparaginase *Erwinia chrysanthemi* (Erwinaze) for use in patients with acute lymphoblastic leukemia (ALL) who are unable to continue treatment with *Escherichia coli*-derived asparaginase (Elspar) or pegaspargase (Oncaspar) due to hypersensitivity.

The new drug is derived from *Erwinia chrysanthemi*, a Gram-negative bacillus related to *E. coli*. It works by the same mechanism as the two previously approved agents, by breaking down asparagine in the circulation. Unlike normal cells, leukemic cells cannot synthesize asparagine and therefore die when deprived of an outside source of this essential amino acid.

“The approval of Erwinaze underscores the FDA’s commitment to the

approval of drugs for conditions with limited patient populations with unmet medical needs using novel trial endpoints,” Dr. Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research, said in a statement.

According to the prescribing information, asparaginase *Erwinia chrysanthemi* is indicated as part of a multiagent treatment regimen for patients who have developed allergic reactions to *E. coli*-derived asparaginase. The recommended dose of asparaginase *Erwinia chrysanthemi* is 25,000 IU/m² IM for each scheduled dose of asparaginase. When substituted for pegaspargase, 25,000 IU/m² of asparaginase *Erwinia chrysanthemi* should be administered IM three times a week for six doses for

each planned dose of pegaspargase.

FDA approval of the drug was based on a single-arm, open-label clinical trial of 58 patients with ALL who had to discontinue treatment with pegaspargase after developing allergic reactions to it. The main outcome measure was the proportion of patients who attained sustained serum asparaginase activity levels of ≥ 0.1 IU/mL, which is known to result in depletion of asparagine to levels that predict clinical efficacy in ALL. In the trial, all 48 evaluable patients met the predefined endpoint at 48 or 72 hours after receiving their third dose of asparaginase *Erwinia chrysanthemi*.

Safety data came from this study and a larger expanded access program that enrolled 843 patients with ALL or lymphoblastic lymphoma who had

developed hypersensitivity to *E coli*-derived asparaginase. The most common side effect associated with asparaginase *Erwinia chrysanthemi* was systemic allergic reactions (17%), the prescribing information notes. Other frequent side effects included pancre-

atitis (4%), coagulation abnormalities (3%), abnormal liver function (4%), and fever (3%). Hyperglycemia, nausea, or vomiting was reported in 2% of patients, and hyperammonemia, abdominal pain, diarrhea, headache, or seizure occurred in 1% each. These

side effects and their incidence are similar to those reported in patients receiving *E coli*-derived asparaginase, according to a FDA press release announcing approval of the new drug.

EUSA Pharma Inc. of Langhorne, Pennsylvania, manufactures the drug.

Packing a punch into your PowerPoint presentations

John J. Fried

Many PowerPoint presentations are mind-numbingly boring—and often useless—because some basic guidelines are overlooked during their preparation. As a result, the software ends up failing both the presenter and the audience. It doesn't have to be that way, though. If you use PowerPoint properly, it can enhance your talk, amplify your ideas, and help you deliver your message with maximum impact to an audience that remains engaged—and awake.

How can you make PowerPoint your friend? Here are five guidelines to keep in mind the next time you prepare to use this presentation software program.

Make an outline

All too many people who have to prepare a talk will sit down at the computer, fire up PowerPoint, and start creating the presentation. The probable result is an uninformative assault on your audience's senses.

There is a better approach. Remember a crucial lesson from your 10th-grade English class: Outline. Outline. Outline. You don't necessarily have to go through the classic alphanumeric outline of I A, B, C; 2 A, B, C, and so on, because PowerPoint has an outline tool that may be useful to you. Better still, you could sketch out—in a Word document—some single-sentence topics as well as ideas for illustrations. Then, by using Word's handy cut-and-paste functions, you can easily shift the order of the topics until you have them in an effective sequence.

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Another option is to use index cards or Post-it notes on a wall or whiteboard to create the outline. Those are easy to rearrange as you work your way through organizing your presentation.

Supplement content, don't reiterate it

This is probably the No. 1 PowerPoint sin: using the program to duplicate, often word for word, what you are saying. That is problematic because the brain processes auditory and visual input in different channels. And because those channels are independent of each other, it is a good bet your listeners will have trouble paying attention to your talk *and* your slides at the same time. Some members of the audience will listen with rapt attention to your talk and ignore the slides, meaning you will have wasted time creating the presentation, whereas others will read the slides and ignore your speech, meaning they will likely lose out on impromptu clarifications and interesting ad libs.

The more effective approach is to use slides to convey information that will substantiate or expand on your ideas. Are you describing a set of reactions to a drug you observed among a select group of patients in your practice? Then say so, telling the audience a bit about the patients and the medication. *Then* use a slide to list the most prevalent reactions or to present a statistical analysis. Keep quiet for a moment while the audience assimilates what you have presented visually. Some PowerPoint mavens even suggest that once you have allowed a slide to make its point, you can ensure

you regain the audience's attention by having the screen go dark while you continue your talk. On a PC, pressing the B key will do the trick, and pressing it again will retrieve the presentation.

Bonus tip: The sudden emergence of a screensaver during your talk can be disruptive, and a computer's sudden desire to slip into sleep mode or hibernate during your talk could completely destroy it, so disable those functions before you start talking.

For all to see...

Remember that the words on the slides may have to be read by everyone, including those at the back of the auditorium or lecture room. So although PowerPoint gives you scores of sexy and fun fonts to choose from, stick to one that is clean and simple to use. Sans serif typefaces such as Arial and Calibri are good. For headlines, use a larger font size and opt for a somewhat smaller font size for your regular text (Figure 1).

What about color? This is tricky because there are so many choices and combinations, so keep it simple; less is more (effective). Certain color combinations are easier to read because they provide a reader-friendly contrast. In general, cool colors—blue and green—tend to be better background colors, and warm colors—yellow, orange, and red—work better for text. If the room you are presenting in is going to be dark, you should opt for a darker background with light text; for a light room, you should use a light background with black or darker text. And remember that the combination might look different when

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the slides are projected, so make sure you do a test run before you settle on a color combination. It's a good idea to echo the text and background colors in your graphics as well so that the presentation ties together as a visual whole.

Bear in mind that a small percentage of men have some form of genetic color blindness and that the condition can also be triggered with aging and by eye problems (glaucoma, macular degeneration, or cataracts), eye injuries, or medication side effects, all of which affect how these individuals perceive certain colors, especially the red-green combination. As such, it is probably a good idea to limit the use of the red-green combination.

Keep it simple

Perhaps the best way to ensure that your audience will get little out of your presentation is to overload each slide with umpteen bullets, each one bearing enough text to fill *War and Peace*. Faced with such an overload of reading material, even slide-loving listeners will be discouraged before they reach the second bullet (Figure 2). The better approach is to populate each slide with three, maybe four, bullets. Keep the sentence length to a line or a line and a half (Figure 3).

The same keep-it-simple rule applies to graphics. If you must use complicated graphics, spreadsheets, or tables, by all means put them on slides. And include those slides only in the version you'll post online or in the printouts of the presentation that you place on the table at the back of the auditorium. That way, those who truly want or need the information will have time to puzzle out what those slides are trying to tell them.

Prepare, prepare, prepare

This could be the toughest part of your task. After working late into the night on your presentation, the temptation is strong just to give it a quick look-over. However, let one factual or

Use Sans Serif Fonts

- They aren't fancy, but they are easy to read.
- Sans serif fonts include **Calibri**, **Arial**, **Verdana**, and **Tahoma**.
- Use 44- to 48-point fonts for headlines, but smaller font sizes (32 or 36, for example) for text.

FIGURE 1 Choose fonts and colors wisely and consider the lighting in the room where your presentation will be viewed (compare Figure 3). If the room will be dark, choose a dark-blue or dark-green background and white or light-colored type. Once you pick a type face (we've used Calibri here), stick with the same font throughout all of your slides. Another way to avoid having your slides look like ransom notes: Choose one size for your headlines and a smaller size for your bullet points and other text and use it repeatedly.

This Is a Mind-Numbing Slide

Too many bullets, too much text

- Oral anticancer and supportive care agents administered to cancer patients are costly and are associated with large copayment requirements or are often not fully reimbursed by private health insurers or Medicare.
- A systematic review of PAPs found improvements in disease indicator outcomes for patients with common chronic diseases who access these programs. However, knowledge about the use of PAPs among cancer patients is limited.
- Cancer patients eligible for PAPs at MDACC include those who are uninsured, those who are underinsured, those whose pharmacy benefit limits have been reached, and those whose private health or government insurance has denied coverage of certain oral medications.
- Approval for this study was obtained from the MDACC Institutional Review Board.
- Prescription data were extracted from a pharmacy administrative dispensing database.
- We extracted patient billing charge per medication fill in dollars by the date of pickup in the outpatient pharmacy.
- In comparison to PAP nonusers, PAP users were, on average, younger (48 vs 52 years), indigent (73% vs 19%), white (50% vs 43%), and covered by Medicaid or were uninsured (75% vs 20%). PAP users also had more prescriptions fills (median = 30 vs 20) during the study period at the institution.

FIGURE 2 Slide overload—too many bullets and too much text—is perhaps the most common error people make when preparing a PowerPoint presentation—and one of the easiest to avoid. Each of these bullet points could easily fill an entire slide and be more memorable because of it. The same rule applies to graphics; keep them simple and uncluttered. It doesn't cost any more to create 50 slides than to create 10; don't be afraid to stretch out your bullet points and numerical data over several slides to get your message across to your audience. They will be more alert and thank you for it with their attention.

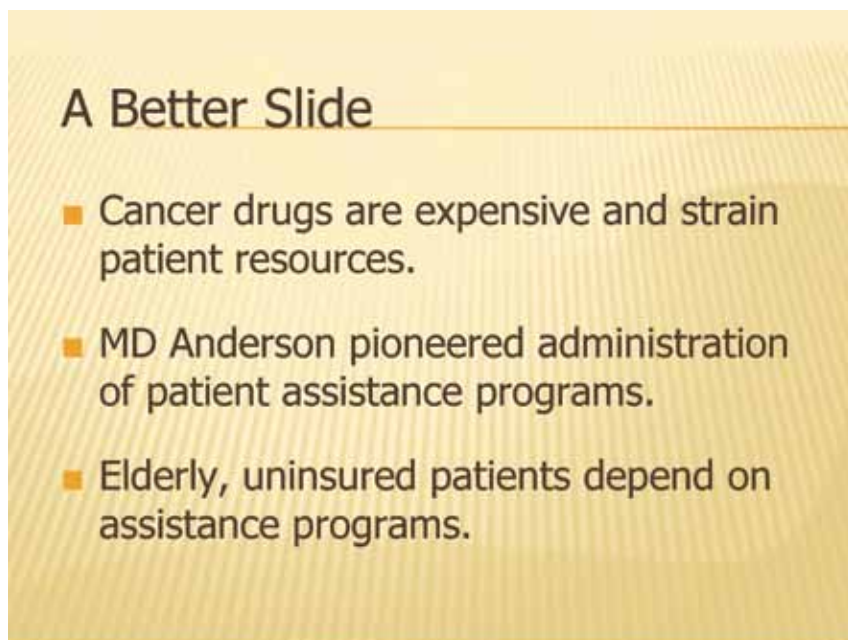


FIGURE 3 Here's an example of an effective slide from a PowerPoint presentation prepared for viewing in a well-lit room. Note the light background, dark type, consistent type face (Tahoma) and size (44 points for the headline and 34 points for the text), and sparse amount of text; no more than eight words are included in each bullet point. To liven things up a little without distracting the reader, the presenter underscored the headline with a thin orange-colored rule and used matching solid orange bullets.

typographical error or a sentence with funny syntax make its way into your presentation, and it could puncture the credibility of your entire talk. Even after you are sure you have read the

presentation carefully on the monitor and have run it through PowerPoint's spelling and grammar checker, print it out and read it again, word for word. I have been writing on computers for

30 years and am still amazed how, after repeatedly applying a gimlet eye at my copy on the monitor, I find typos, grammatical errors, and evidence of sloppy logic when I review a hard-copy version of my work. Even after you have scrutinized your slides on paper, don't be satisfied. Have someone whose knowledge of English you trust edit and proof your work.

After your slides have been thoroughly vetted, get access to a projector and a large conference or lecture room. Stand way in the back and study each slide as it appears on that far-away wall. If you were in the audience, would you be satisfied with what you are seeing?

When you are satisfied with your presentation, call or e-mail the tech support people at the venue where you will be making your presentation. Tell them what kind of a laptop you have and ensure that the right projector and a set of cables will be available for your use. And, oh yes, put a copy of your presentation on a DVD or a USB flash drive. If your laptop goes south, you can use that backup to run your now-brilliant PowerPoint effort from someone else's computer.

Oncology drugs hardest hit by shortages

Alicia Ault

Five therapeutic areas account for two thirds of the drug shortages in the United States, with oncology taking the hardest hit. The shortages might affect as many as a half-million cancer patients, according to a November 14 report from the IMS Institute, a division of the healthcare analytics firm IMS Health.

IMS reviewed information for 168 drug shortages reported to both the US Food and Drug Administration (FDA) and the American Society of Health System Pharmacists (ASHP). The data give more of a real-time snapshot of what's happening in the supply chain because they use invoice and purchasing data, said Bona Benjamin, ASHP director of medication use quality improvement, who discussed the report at the November 12–15 interim meeting of the American Medical Association (AMA) House of Delegates in New Orleans, Louisiana.

The institute found that more than 80% of the 168 products in short supply are generics and that more than 80% are injectables. A total of 16% are oncology products, 15% are anti-infectives, 12% are cardiovascular products, 11% are central nervous system products, 9% are for pain, and 9% are vitamins and nutritional.

There is no doubt that oncology is a problem area, said Ms. Benjamin, who is the liaison between ASHP and the FDA. "With the recent escalating oncology drug shortages, I've received many, many very distressing calls from patients who are not able to get the drugs they need."

Overall, 232 drugs have been in short supply this year, Ms. Benjamin said, adding that the number could reach 300 before year's end. In

oncology, there were few shortages for many years. The number jumped in 2010 to 24 shortages. There have been 20 so far in 2011, the vast majority of those shortages have been injectables, she said.

Dr. Chris Nunnink, delegate to the AMA House of Delegates from the American Society of Clinical Oncology, said that shortages were not only threatening patient care but also hastening the shift from office-based to hospital-based practices.

Profit margins are slim and declining; shortages are exacerbating that and making new physicians think twice about starting their practices, he said.

Patients often end up having to pay more out of pocket for the available alternatives, he said. And, sometimes standard chemotherapy drugs just aren't available. "I have to say I don't have Taxol," said Dr. Nunnink of the Vermont Cancer Center in Colchester. "To have that conversation with a patient is just incredibly frustrating."

The IMS report concluded that manufacturing issues are largely responsible for the shortages. Companies that get into trouble with the FDA concerning their drug quality either have to suspend manufacturing or stop producing the drug altogether. Also, many companies have not been prepared to meet the demand for their products, in particular the generic injectables.

Manufacturing and supply of many key products are concentrated with a few companies, the IMS report found. Although there are 100 suppliers of the 168 products studied, half of those products have only one or two suppliers. Thirteen companies have stopped supplying products on

the shortages lists within the past 2 years.

Ms. Benjamin said that 23 of the drugs have only two suppliers, and two thirds of the products have three or fewer suppliers. If one supplier is hobbled by a production issue, often the other two cannot meet the additional 30% demand, she said. This was the case for propofol; there were shortages for a year because one manufacturer ceased production. The FDA ended up allowing importation from Germany.

The IMS report also found lots of volatility in supply—for some drugs, from particular manufacturers, and in state-to-state distribution. The report broke products into three categories: increasing supply, stable supply, and declining supply.

The declining supply group had decreases of more than 20% when compared with a 3-year base period that ended in 2009. Ms. Benjamin said that for the 75 products in the declining supply group, the amount available for use dropped by half over a 5-year period, from 16 million dosing units to 8 million.

But there are anomalies in every category. Cisplatin was considered to be in stable supply, with a total average supply of 40,000 units, said Ms. Benjamin. But there has been great fluctuation with the availability from each manufacturer—and many supply contracts dictate where purchases can be made. Teva Pharmaceuticals stopped producing cisplatin in 2010. It took a while for the remaining two manufacturers to ramp up production, so some hospitals and physicians could not get enough, Ms. Benjamin said.

The IMS report also found that the per capita supply of injectables

has fallen more than 30% in 13 states. That state data are not easy to understand, Ms. Benjamin said, noting that in some states with high per capita use, there were no problems with supply.

The ASHP is aware that hoarding and stockpiling are occurring, she said, adding that some institutions and physicians are using their supplies to their advantage, selling them on the gray market. "We've heard about doctor theft, selling out the back door of the hospital.... Lots of egregious practices."

Her organization does not approve

of such sales and also cautions physicians and hospitals against buying products from gray market sellers, she said.

Like the ASHP, the FDA, and several legislative proposals in Congress, the IMS Institute proposed that an early warning system be established to require prompt notification of shortages. The institute suggests establishing volatility indexes and borrowing demand forecasting and predictive modeling tools from the financial industry to help manage shortages more closely.

Ms. Benjamin said that the drug

industry appears to be stepping up in the wake of President Obama's October 31 Executive Order calling for more voluntary reporting. The FDA told ASHP representatives in a recent meeting that more companies have been communicating with the agency about shortages, she said.

She also noted that two more Senators signed on as cosponsors to a drug shortages bill introduced by Amy Klobuchar (D-MN), the Preserving Access to Life-Saving Medications Act. On November 10, Sen. Klobuchar called for a Senate hearing on the shortages issue.