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August 25, 2013 * Vol. 35 * No. 16

oncology-times.com

Oncology Times

Lippincott Williams & Wilkins
Wolters Kluwer Health

The Independent Hem/Onc News Source

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Survey: Most Oncologists Avoid the Word 'Cure' in Discussions with Patients

BY KURT SAMSON

In what is believed to be the first such study to give quantitative as well as qualitative data on this topic, oncologists said both that their patients are hesitant to ask whether they are cured, and that they as cancer care clinicians try not to use the word with patients. The implications are many, those interviewed for this article said, and open up multiple avenue of research. *Page 24*

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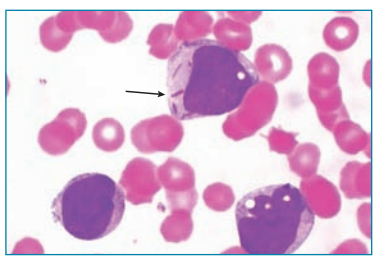

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PERIODICALS

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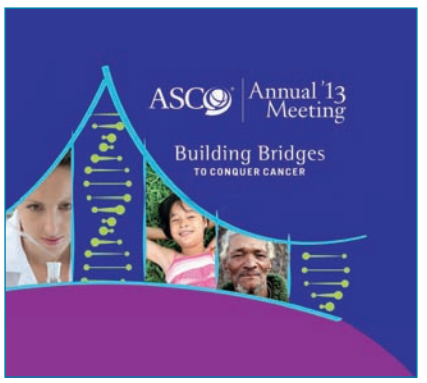
For Patients with Sentinel Node-Positive Early Breast Cancer, RT as Effective as and Less Toxic than Complete Surgical Axillary Clearance

BY PETER GOODWIN

CHICAGO—In women with early breast cancer who were clinically node negative but with a positive sentinel node, complete axillary clearance was not found to be superior to use of radiotherapy, which also had the benefit of being less toxic. The final analysis of the European Phase III EORTC AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery?) trial, were reported here at the American Society of Clinical Oncology Annual Meeting (***Abstract LBA1001***) by Emiel J.T. Rutgers MD, PhD, a surgical oncologist at the Netherlands Cancer Institute.

The results also showed that patients treated with radiotherapy were only half as likely to develop lymphedema as were those having surgery.



The aim of the study, he explained in an interview, was to see if there was a way to lessen the toxicity of surgical clearance of lymph nodes when metastases are found in the sentinel node but were not detectable clinically: "When we designed the study 12 years ago axillary clearance was dogma for these patients," he said, noting, though, that there was also recent interest in looking at other approaches to treating sentinel node positivity.

The researchers were concerned about the high level of side effects from lymph node surgery—particularly obstruction of the lymphatics of the arm, which usually necessitates lifelong treatment to manage lymphedema necessary.

The study included 4,806 patients with clinically node-negative early breast cancer, 3,382 of whom had no or only minimal metastasis and were allocated to follow-up. A total of 744 of the remaining 1,425 patients were allocated to surgery and 681 patients to radiotherapy. No significant differences in five-year overall survival (92.5 and 93.3 percent) emerged between the two treatment groups. Disease-free survival rates were also similar (82.6 and 86.9 percent).

The rate of cancer recurrence in the axilla was very low in both groups: 0.54 percent (4/744 patients) for surgery and 1.03 percent (7/681) for radiotherapy.

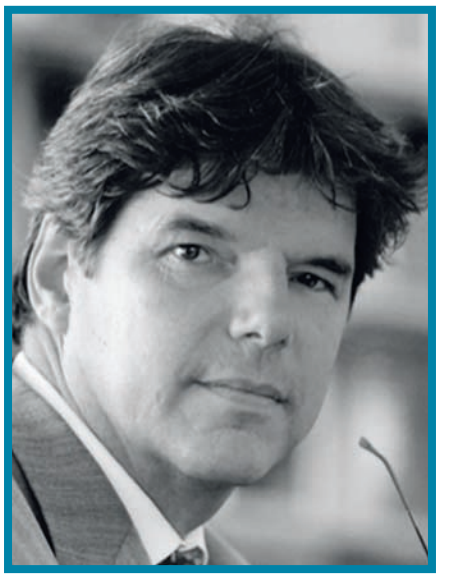
Arm edema (measured as any incidence of any symptom and/or treatment) was double—at 28 percent—in the group allocated to complete axillary dissection as compared with 14 percent in those treated with radiotherapy.

In terms of quality of life and shoulder movement impairment there were no significant differences between the study arms. "Radiotherapy to the axilla is a good alternative to surgical removal of the lymph nodes," Rutgers said. "If treatment is deemed necessary [in T1/T2 N0 breast cancer] radiotherapy is better than surgery."

Long-Term Toxicity

With a median follow-up of only 6.1 years, however, the long-term toxicity comparison remains to be determined, but Rutgers said he was fairly confident that those results will still favor radiotherapy. "In the long run the downside of using radiotherapy could be a small risk of damage to the nerves to the arm—plexopathy—and radiation-induced sarcomas," he said. But there has been no sign of such nerve damage yet, he noted, estimating that even if there was, the incidence of serious damage was not likely to exceed one percent of serious damage at 10 years.

Lymphedema, on the other hand, was a different situation: "Lymphedema in the long run is associated with serious side effects and very rare but serious sarcoma of the arm, and if you prevent lymphedema, you may prevent that serious side effect in the long run."



EMIEL J.T. RUTGERS MD, PHD: "In early breast cancer, complete axillary dissection is obsolete."

Clinical Recommendations

For cancer doctors the recommendation is quite clear, he said: "First, do sentinel node. Second, think what you do with the outcome—if it's negative, do nothing; if positive—if there is a small primary tumor—you can refrain from any axillary treatment. If there's more involved tumor, then radiotherapy is now the standard of care instead of a axillary clearance.

In early breast cancer, axillary clearance—complete axillary dissection—is obsolete."

The moderator of a news conference that included the study, Andrew D. Seidman MD, of Memorial Sloan-Kettering Cancer Center, and a member of ASCO's Cancer Communications Committee, noted that big steps have been made recently in the treatment of early breast cancer: "In the last few years we're re-thinking the local-regional management of breast cancer, with less surgery and perhaps now an increased

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"Axillary lymph node dissection and axillary radiotherapy after a positive sentinel node biopsy provide excellent and comparable regional control, but patients treated with radiotherapy were only half as likely to develop lymphedema."

Hear More!

Emiel Rutgers expands on his remarks in a podcast in the iPad edition of this issue.

→SLEDGE

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"Were the succession of stars endless, then the background of the sky would present us a uniform luminosity, like that displayed by the Galaxy—since there could be absolutely no point, in all that background, at which would not exist a star. The only mode, therefore, in which, under such a state of affairs, we could comprehend the voids which our telescopes find in innumerable directions, would be by supposing the distance of the invisible background so immense that no ray from it has yet been able to reach us at all."

A good enough answer, I would have thought, but there's another. The Big Bang, some 13.7 billion years ago, was associated with intense heat and, the astronomers say, light brighter than the sun. But most of that radiation has now redshifted to microwave wavelengths. Have you ever seen a microwave when you pop up some Orville Redenbacher? Me neither: my rods and cones aren't built for them.

If you want to see a brief, nifty explanation of Olbers' Paradox, go to this YouTube video: **http://www.youtube.com/watch?v=gxJ4M7tyLRE**

Olbers' Paradox is resolved by Edgar Allen Poe and Orville Redenbacher popcorn, which I for one find a deeply satisfying outcome. It would be even more troubling if the sky was bright all night long: I would never sleep.

Added Cetuximab Extends Survival in Patients with KRAS Wild-Type Colorectal Cancer

BY PETER GOODWIN

A total of 592 patients with KRAS wild-type metastatic colorectal cancer received either cetuximab or bevacizumab to supplement their first-line FOLFIRI chemotherapy, showing a 23% reduction in the risk of death and 3.7-month extension of life for those receiving cetuximab.

CHICAGO—Patients with metastatic KRAS wild-type colorectal cancer lived longer if cetuximab was added to their chemotherapy rather than bevacizumab, according to the results of a Phase III study from Germany reported here at the American Society of Clinical Oncology Annual Meeting (***Abstract LBA3506***).

Volker Heinemann, MD, Professor of Medical Oncology and Director of the Comprehensive Cancer Center at Klinikum der Universität in Munich, presented the data from the study, KRK-0306 (FIRE-3), showing that patients receiving cetuximab lived 3.7 months longer.

He emphasized that recruitment was restricted to patients with the non-mutated form of the KRAS gene (60 percent of all colorectal cancer cases), based on the discovery in 2008 that mutant KRAS disables cetuximab in colorectal cancer. Bevacizumab, on the other hand, is unaffected by KRAS status and is an effective and licensed treatment for all patients.

"It became clear that cetuximab—as an anti-EGFR [epidermal growth factor receptor] agent—is active only in patients with KRAS wild-type tumors. For this reason we could include only such patients in the trial, he said in an interview. "Cetuximab targets the EGF receptor, which is involved in cell growth, while bevacizumab targets vascular endothelial growth factor—i.e., it targets blood supply to the tumor."

The FIRE-3 study investigated whether cetuximab could be superior to its sister targeted agent in the subgroup of patients who are sensitive to it; the updated results from FIRE-3 provide the first Phase III evidence that it is.

A total of 592 patients with KRAS wild-type metastatic colorectal cancer (median age of 64) were randomized to receive either cetuximab or bevacizumab to supplement their first-line FOLFIRI chemotherapy (leucovorin, fluorouracil, and irinotecan). Median overall survival times were 25 months in patients receiving FOLFIRI plus bevacizumab vs. 28.7 months in patients receiving FOLFIRI plus cetuximab, with a hazard ratio of 0.77, which is equivalent to a 23 percent reduction in the risk of death and 3.7-month extension of life.

In the intention-to-treat (ITT) analysis, progression-free survival was similar between the two arms: 10.3 months with bevacizumab versus 10.0 months among patients receiving cetuximab. Objective response rates and complete remission rates were also similar: 62 and 4.4 percent, respectively, with cetuximab vs. 58 and 1.4 percent with bevacizumab.

But when patients who did not actually receive their allocated treatment were excluded, a statistically significant superiority in response rate emerged in favor of cetuximab: 72.2 vs. 63.1 per cent, p = 0.17, which Heinemann said could be driving the observed extension of overall survival in patients on cetuximab in the ITT analysis: "The finding was that with regard to the primary endpoint of the objective response rate, there was no difference in the ITT population, while in patients assessable for efficacy there was a significant difference between the cetuximab and bevacizumab arms."

To qualify as "assessable," patients needed to have received enough of the allocated treatment and have been assessed by computed tomography. "If you look at the efficacy of a treatment with regard to response rate you want to make sure that patients also actually received your agent and didn't drop out before," Heinemann explained. "For that reason we decided to look at patients who had received at least three cycles of treatment and also had one CT imaging, which could demonstrate for us the efficacy of that agent."

Explaining the mechanisms of action, VOLKER HEINEMANN, MD, said cetuximab targets the EGF receptor, involved in cell growth, while bevacizumab targets vascular endothelial growth factor—i.e., the blood supply to the tumor.

Toxicities for either of the targeted agents was "as expected, and manageable," he said, with both arms equivalent overall. The two agents gave different toxicities, but this was not considered to change the overall iatrogenic morbidity rates.

Heinemann noted that the FIRE-3 findings are consistent with earlier smaller Phase II studies such as the PEAK trial (**clinicaltrials.gov/ct2/show/NCT00819780**), which provided preliminary indications of a survival benefit

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→AMAROS

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consideration for the role of radiotherapy for local control."

Only for Defined Population

Asked for her opinion for this article, Pat Price, MD, Visiting Professor of Oncology at Imperial College in London and Chairperson of the UK's Action Radiotherapy charity, said that for this defined population of women (T1/T2 breast cancer, clinically node-negative with positive sentinel node biopsy) the AMAROS findings are grounds for change: "For this small group of patients surgery would not necessarily be the right option," she said.

"Axillary surgery will still be required for other groups of patients and there's a lot of work to be done about selecting those who need axillary node clearance, or perhaps those who don't need any surgery or radiotherapy at all."

Price said she was impressed by the size of the AMAROS study but had some reservations about the current definitions of lymphedema, which she said has been poorly studied and still needs to be researched: "We've got some very crude measurements and definitions of it. We don't even understand the mechanism."

"Axillary surgery will still be required for other groups of patients and there's a lot of work to be done about selecting those who need axillary node clearance, or perhaps those who don't need any surgery or radiotherapy at all."

Still, she called the reduction of lymphedema "startling"—"That's really important, because lymphedema is a huge problem—long term—for patients, and takes up a lot of health care costs—and there is also the worry that patients have about lymphedema. Since we've been doing more clearances, lymphedema has become a bigger problem. So if we can reduce this, this will be fantastic for women."