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Team Approach Reduces Local Regional Relapse

BY ROBERT H. CARLSON

MIAMI BEACH—Patient selection, operative technique, and careful assessment of excised tissues clearly are keys to reducing risk for positive surgical margins and local regional relapse in the conserved breast. But the most important factor appears to be the quality of the surgical team and the hospital where the patient is treated.

So said Benjamin O. Anderson, MD, Director of the Breast Health Clinic at the Seattle Cancer Care Alliance and Professor of Surgery and Global Health Medicine at the University of Washington and Fred Hutchinson Cancer Research Center, speaking here at the Miami Breast Cancer Conference.

In his presentation, "Surgical Strategies for Reducing the Likelihood of Local Regional Relapse in the Conserved Breast," he described a study from the Netherlands that pointed to a well-prepared surgical team as being most important in reducing positive margins, undesired reexcisions, and potentially increased local relapse rates (***Nederend et al: Br J Surgery 2014;8:949-958***).

The population-based screen series studied the outcomes of 417,013 screening examinations from 1997 to 2011, among women age 50 to 75. The treatment of women with breast cancer apparently did change in the Netherlands during that time: While overall the rates of breast-conserving surgery remained stable at 6.1 per 1,000 screened women, the rates of mastectomy doubled, from 0.9 to 1.9 per 1,000 screened women.

But the positive invasive margin rates decreased, from 19.6 to 7.6 percent—"So people seemed to be learning how to do better in terms of getting clear margins," Anderson said.

Most interestingly, he said, there was marked variation among the hospitals. The researchers looked at the common risk factors associated with getting positive margins, such as whether the cancer presented on the mammogram or in between mammograms, was low tumor grade, a T2 or T3 tumor, and had microcalcifications.

But the top factor that most predicted positive margins was the hospital that the surgery took place in, followed by the lobular histology and whether there was extensive ductal carcinoma in situ.

"The number one determinant of whether you had positive margins was the system—it was the surgeons and everybody who is with the surgeon; that's what makes the difference," Anderson said. "This means a team-based approach. It's the surgeon working with the radiologist, with the pathologist, those two talking to each other, and all of us working with radiation oncologists and medical oncologists to make this a comprehensive approach— that's what optimizes these outcomes."

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Preoperative Imaging Extent of Disease

Imaging correlation based on careful extent-of-disease workups is another critical factor in good surgical planning and execution, Anderson continued. How the mammogram and ultrasound are reviewed is extremely important.

"The big topic here is the use of MRI. Are we improving outcomes with the use of MRI?"

He reviewed the COMICE (Comparative effectiveness of MR imaging in breast cancer) randomized trial (***Turnbull et al: Lancet 2010;375:563-571***), which he called a big disappointment. The study randomized women to

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have or not have preoperative magnetic resonance imaging (MRI), but no benefit was found for the use of MRI in terms of needed reoperations.

The MONET (MR mammography of nonpalpable breast tumors) trial followed (***Peters et al: Eur J Cancer 2011;6:879-886***), which tested MRI after core needle biopsy.

"Not only did they not see improvement in outcome, but they ended up having more reexcisions in the patients who had the MRIs than the patients who didn't," Anderson said. "So is there evidence that MRI improves outcome by virtue of extent of disease workup? The answer is no."

He said that at his institution, MRI is routinely used for the evaluation of the extent of disease: "I have to say that, as I was preparing this talk, I asked myself are we actively thinking this through, are we really improving outcome?"

He said, "I like the pictures, I find them very helpful for planning how I'm going to do my resection, particularly oncoplastic resections. It shows you the shape, it shows you the extent. But we do not have trials that have shown the benefit of this."

He extended a plea to high-volume groups that have the opportunity to research MRI planning: "Tell us: Can you show us benefit, at least on an individual basis?"

Oncoplastic Techniques Classified

Oncoplastic surgical technique is a separate topic from local regional recurrence, but Anderson said it should be part of standard practices since it improves oncologic outcome as well as cosmetic outcome. "Oncoplastic resection techniques are among the most valuable approaches that surgeons can use, to simultaneously increase surgical resection volume and improve cosmetic outcome.

"By using approaches where we move tissue on the chest wall, we can preserve the shape and appearance of the breast much better than in prior years when we just made an incision, scooped something out, and hoped it worked out."

He added that oncoplastic resections require careful radiographic evaluation, particularly of the specimens.

Anderson credited Krishna Clough, MD, of L'Institut de Sein in Paris, France, for his work in standardizing oncoplastic procedures with a classification approach and a quadrant-per-quadrant atlas (***Clough et al: Ann Surg Oncol 2010;5:1375-1391***).

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Anderson illustrated this approach with the case of a woman who needed a breast reduction and had a cancer at the same time. "A very large volume of tissue could be removed by virtue of using this one particular type of approach, so we can get much more tissue out of the breast, preserve cosmetic outcome, and do well oncologically."

He also cited a 2013 study of 162 patients who received a quadrantectomy because of breast cancer and 106 breast cancer patients with macromastia who underwent breast-conserving surgery via bilateral reduction mammoplasty (***Gulcelik et al: J Breast Ca (Korea) 2013;2:193-197***). The authors reported that bilateral reduction mammoplasty has some advantages as compared with the standard conventional breast-conserving surgery techniques without having any unfavorable effects on surgical margin confidence, local recurrence, or survival rates.

Role of Surgical Margins

The joint consensus guideline of the Society of Surgical Oncology and American Society for Radiation Oncology on margins in invasive breast cancer, co-chaired by Monica Morrow, MD, for SSO and Meena Moran, MD, for ASTRO (***JCO 2014;14:1507-1515; OT 4/10/14 issue***) has had a profound impact on breast surgery, Anderson said.

"This was a very extensive analysis, and I think across the U.S. it's really changing practices. They confirmed that true positive margins are a problem, approximately doubling the rate of local recurrence."

The guideline concluded that a positive margin—defined as ink on invasive cancer or ductal carcinoma in situ—has a twofold increase in ipsilateral breast recurrence, and that radiotherapy, systemic therapy, or favorable biology do not make up for that lack of surgical technique.

However, negative margins—defined as no ink on the tumor—does optimize local control, Anderson said, but wider margin width does not significantly improve local control, at least in the setting of standard radiation treatment.

"The routine practice of obtaining margins more widely clear than no tumor on ink is not indicated," he said. "We have changed at our center, and we have not seen deficits."

Novel Technology Does Not Replace for Standard Assessment

The MarginProbe intraoperative assessment device was approved by the Food and Drug Administration in January 2013, noted Anderson, who served on that FDA panel. The device uses radiofrequency spectroscopy to characterize human tissue in real time, measuring differences in dielectric properties between normal and malignant breast tissue.

"The manufacturers are now publishing evidence [***Schnabel et al: Ann Surg Oncol 2014;5:1589-1595***] that it does seem to be able to detect positive margins," Anderson said.

But the FDA approval statement points out that the device is not a replacement for

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Deciding When Neoadjuvant Endocrine Therapy is OK for Patients with Operable Breast Cancer

BY ROBERT H. CARLSON

MIAMI BEACH—The indications for neoadjuvant endocrine therapy in patients with operable breast cancer have been the subject of much debate. "There is some reluctance in the U.S. to embrace this concept as wholeheartedly as people in other parts of the world," said William Gradishar, MD, Professor of Breast Oncology and Director of the Center for Women's Cancer Care at Lurie Comprehensive Cancer Center at Northwestern University Feinberg School of Medicine, speaking here at the Miami Breast Cancer Symposium.

He said that neoadjuvant endocrine therapy would be suitable for patients with estrogen receptor (ER)-rich cancers (Allred 7+8) and older postmenopausal women, as well as younger women with significant morbidities.

In the U.S., the use of neoadjuvant, or primary systemic, therapy has largely been limited to chemotherapy alone, or more recently to anti-HER2 therapy combined with chemotherapy for tumors that overexpress HER2 and are not candidates for immediate surgery, he said.

"Neoadjuvant chemotherapy with or without HER2 therapy is increasingly successful in producing pathologic complete responses (pCRs), but only in ER-positive and HER2-positive cancers."

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Endocrine agents are the less commonly used as a systemic approach for patients with ER-positive breast cancer, an approach that has been used mainly for patients who are not considered candidates for chemotherapy based on age or comorbidities.

Neoadjuvant endocrine therapy has largely been limited to this medically infirm patient population, but more recent data have begun to broaden the patient population who are appropriate for this approach, he said.

"The concept of neoadjuvant endocrine therapy may be forced upon us as endocrine therapies are being partnered with some of the new targeted therapies, such as mTOR inhibitors and PI3-kinase inhibitors."

Pathologic CR May Not Be Holy Grail

Gradishar said the notion that a pathologic complete response to neoadjuvant therapy may confer long-term benefit is the "Holy Grail" upon which every drug approval has been linked.

"A concept we often grab onto in the U.S. is that we want to make the tumor shrink, we all want to make it go away, but it is not fully appreciated that pCR is not as important in predicting the outcome of ER-positive cancers," he said, adding, though, that studies nonetheless routinely show that a pCR is better than not having one.

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standard histopathologic measurement, as well as other limitations, Anderson cautioned, noting that the study data show a 26 percent reduction in the number of patients who need a reexcision.

"However, the control group had a 41 percent reexcision rate, so that 26 percent reduction took them down to 30 percent. I think most of us would consider those numbers terribly high. In our center our reexcision rate is around 16 to 18 percent. So the benefit in that setting might be a little different than one would see."

Biology Counts

Emerging evidence suggests that the most important predictor of local recurrence may in fact be biological, Anderson said. Local-regional recurrence correlates with biological factors, but more extensive surgery does not overcome aggressive biology: "Aggressive surgery does not overcome aggressive biology. What is really needed are better drug treatments to manage this," he said.

And adjuvant radiotherapy and systemic treatments have local as well as distant influence on recurrence risk. "The 'wider is better' paradigm for surgical margins may be incorrect, at least in the era of effective adjuvant therapies."