Ann Surg Oncol (2013) 20:3153–3157
DOI 10.1245/s10434-013-3179-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – BREAST ONCOLOGY

How Genomics, Research, Ethics and Advances Translate into Improved Care for Breast Surgery Patients

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We are excited to present the fourth annual issue in the *Annals of Surgical Oncology* dedicated to manuscripts from presentations at the 14th annual meeting of the American Society of Breast Surgeons (ASBrS). A first for this year's meeting was invited submission of brief video presentations of "How I do it," which were presented at the meeting; several of these have been published in the online edition of the ASO, so take some time to look over these videos that outline techniques in breast surgery that may be different from the way that you approach the procedure or outline new procedures.

The meeting in Chicago was attended by more than 1,300 attendees. The theme of this year's meeting was GREAT—Genomics, Research, Ethics, Advances, Translate—and it was truly a great meeting. Herein, we review how these topics relate to the breast surgeon.

GENOMICS

The Human Genome Project, which was completed in 2003, resulted in the identification of the ~20,000–25,000 genes in human DNA, and the result has been a rapid and expansive permeation of genomic analysis, diagnostics, and prognostic markers in every specialty of medicine.[1] The impact on the field of surgical oncology, and specifically breast cancer, has been astounding. There are multiple potential ways in which this genomic information may translate ultimately to improved patient care and outcomes. It is not surprising, therefore, that many of the posters and oral presentations at the annual meeting specifically addressed various aspects of this genomic revolution. One potential role for genomic analysis is in the identification of unique tumor receptors or pathways that allow for targeted therapy development. Trastuzumab, a monoclonal antibody that inhibits the HER2/neu receptor, is now in widespread use for the treatment of breast cancer. It represents a success story in targeted therapy development, conferring an improved survival when used in the setting of HER2/neu amplified breast cancer.[2]

In addition to targeted therapy approaches, genetic analysis for cancer predisposition also is possible. Although *BRCA* mutations have gained widespread publicity with actress Angelina Jolie's disclosure of her mutation and decision for prophylactic mastectomy, there are other autosomal dominant mutations, such as PTEN, p53, E-cadherin, and STK11, which also can be associated with inheritable breast cancer.[3] A thorough family history is vital in order to identify patterns that may warrant testing beyond that of BRCA1/2.

One of the fastest growing areas of oncology-driven molecular tools is in the development of molecular diagnostics for prognostication. A recent prospective study evaluated the impact of the 21-gene recurrence score on treatment decisions in early-stage breast cancer.[4] Overall, the authors found that 33 % fewer patients received chemotherapy based on the recurrence score result compared with patients recommended chemotherapy pretest, including 29 % who were node-negative and 38 % who were node-positive.[4] Standard clinicopathologic features provide the foundation for treatment decision-making, but the addition of molecular prognostics can further define the approach and potentially avoid toxic side effects of treatment in patients who would not otherwise benefit.

Finally, vaccine development also is a fertile area of genomic investigation. Dr. Brian Czerniecki and his group reported their results of a HER-2 pulsed autologous dendritic cell vaccine administered in patients with ductal carcinoma in situ (DCIS) HER-2 expressing breast cancer

Published Online: 22 August 2013

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before lumpectomy.[5] Despite equivalent immune responses in both ER-negative and ER-positive DCIS, the HER-2 vaccine resulted in more complete pathologic responses in patients with ER-negative DCIS. They concluded that these vaccines may reduce recurrence in ER-negative DCIS where no adjuvant therapy currently exists.[5]

The genomic revolution and the molecular tools that continue to be developed promise enormous potential for personalized patient care and prevention strategies. As breast surgeons, we need to be leaders in understanding the technologies, interpreting the results, and determining their utility in clinical practice.

RESEARCH

In this issue, we present some of the papers from the oral scientific presentations, which covered a broad range of topics. More than 180 abstracts were submitted for the meeting and more than 60 papers submitted for this edition of the journal. Our previous editorials have discussed minimal invasive approaches to breast cancer and sentinel node surgery.[6,7] Patient selection is critically important as we look to be less invasive in our surgical management and more selective in use of adjuvant therapies. Several papers in this issue address patient age as a criteria to incorporate when selecting how aggressive to be and which therapies some patients may be able to avoid without significant impact and we have highlighted them here. However, we also must remember that tumor biology outweighs age alone, as highlighted throughout the studies below.

Axillary Surgery

The majority (>85 %) of women older than age 70 years with clinical stage I estrogen receptor-positive breast cancer still undergo axillary staging at the time of their definitive breast surgery. Despite surgeon interest in minimizing axillary surgery, this percentage has stayed steady from 2004 through 2010 in the National Cancer Center Database, although over the same time period the percentage of patients with three or less lymph nodes examined has steadily increased from 45 % in 2004 to 59 % in 2010, reflecting more sentinel node surgery and less axillary dissections. Extreme patient age does feature in the decision making as rates of axillary nodal examination decreased from 83.2 % in women age 80–85 years to 66.5 % for those aged 86–89 years and decreased to 46 % for those ≥90 years of age.[8] Surgical therapy should be tailored to those patients where it can provide therapeutic benefit or guide adjuvant treatment decision and is not needed for those where its use will not alter further treatment recommendations or outcomes.

Adjuvant Breast Radiation Therapy

CALGB 9343 study demonstrated that radiation therapy may not be needed for all elderly women (≥70 years) with stage I disease undergoing breast conservation and these recommendations were included in the National Comprehensive Cancer Center guidelines in 2005. Over time, use of adjuvant radiation therapy in elderly patients has been declining slowly, although from the data presented from the City of Hope in this edition did not find a significant acceleration in this trend when evaluating the Surveillance, Epidemiology and End Results (SEER) despite the reporting of the CALGB trial results.[9]

The Italian multicentre trial decreased the age requirement even lower and compared adjuvant radiation versus no radiation in women aged 55–75 years. With 108 months follow-up, this study showed no difference in local recurrence rates, distant disease-free survival, or overall survival between the groups treated with or without whole breast irradiation.[10] However, one major thing to realize is that the breast surgery in these cases was quadrantectomy, which involves resection of the tumor with large margins, which is different to the usual lumpectomies performed in the United States and therefore these results may not be easily translated to all practices.

Postmastectomy Radiation Therapy

Indications for postmastectomy radiation (PMRT) continue to be an area of significant debate. The Memorial Sloan Kettering Cancer Center presented their data on use of PMRT in patients with T1 or 2 breast cancers and 1–3 positive nodes. They showed that using clinicopathological criteria to determine who received PMRT and who did not that 15 % of patients received PMRT.[11] Patients who received PMRT were younger, had larger tumors, higher histologic grade, higher number of positive nodes and larger lymph node metastases, presence of lymphovascular invasion, and extracapsular extension. The 5-year locoregional recurrence was similar in the two groups. The significant predictors of locoregional recurrence were young age (age ≤50 years) and presence of lymphovascular invasion. Young age is known to be an independent predictor of recurrence and poor survival. In another presentation at the meeting, women younger than age 35 years diagnosed with breast cancer who were treated with mastectomy in Ontario were reviewed; 38 % received PMRT and there was no difference in locoregional or distant recurrence between those with and without PMRT.[12] These studies reassure us that using clinicopathologic factors to guide adjuvant treatment decisions remains effective and that these factors are multiple, including age, tumor biology, and pathologic factors in the equation.

Hormone Receptor-Negative Disease in the Elderly

The premise that underlies the possible ability to avoid adjuvant radiation and/or adjuvant hormonal therapy in women older than age 70 years is that these women have a) less aggressive disease and b) less time for recurrence between diagnosis and death from other causes. However, elderly women with hormone receptor-negative disease are more likely to die from their breast disease than from cardiovascular disease.[13] This reflects that tumor biology plays a larger role than age alone and should be considered in all patients regardless of age. The study by Weiss et al.[13] also found that women older than age 80 years with hormone receptor-negative disease are more likely to die from breast cancer than younger women and this is potentially due to lack of use of chemotherapy in older women.

ETHICS

Ethics, also called moral philosophy, seeks to resolve questions dealing with human morality. In the medical profession, we have long subscribed to a philosophy centered on the benefit to the patient. As physicians, we recognize our responsibility primarily to our patients and also to society and other health professionals. The principles of medical ethics outline that physicians should: be dedicated to providing competent medical care; uphold standards of professionalism; respect the law; respect the rights of patients, colleagues, and other health professionals; continue to study, apply, and advance scientific knowledge; be free to choose whom to serve and the environment in which to provide medical care; recognize responsibility to participate in activities to improve community and better public health; regard responsibility to the patient as paramount; and support access to medical care for all people.[14]

As surgeons, our relationship with patients is unique. My favorite quote of the meeting was delivered by Dr. Peter Angelos, quoting from "Forgive and Remember, Managing Medical Failure" by Charles Bosk. "When the patient of an internist dies, his colleagues ask the natural question, 'What happened?' However, when the patient of a surgeon dies, his colleagues ask, 'What did you do?'"[15] Taking this one step further, in truth we each individually reflect and ask "What did I do?; What should I have done differently?"

As surgeons and physicians working with industry and trialing or developing medical products, what is the balance between advancing the care of our patients and being an entrepreneur with a conflict of interest? Collaboration with industry can degrade public trust, especially when viewed that the collaboration compromises professionalism. Even industry-sponsored continuing medical education may be viewed as biased product promotion. However, the medical products industry spans companies of varying sizes and varying interests and incentives. The onus remains on the physician to ensure they remain committed to believe the best science and ensure their actions are ethical.

When reviewing the literature and defining our practice patterns, there can be a balance between what is best for the clinical practice and what is best for the individual patient. We draw your attention to a great debate session on margins after breast conservation surgery and whether this should be used as a quality metric for breast surgery. Drs. Degnim and Landercasper have summarized their debate in this edition, and there remains the potential for a future statement from ASBrS on this question. From an ethical perspective, this issue is challenging as surgeons vary on their indications for reexcision as well as their reexcision rates. Many surgeons may not accurately know their individual reexcision rates. Taking a wider margin than necessary negatively impacts cosmetic outcome, whereas not reexcising positive margins will leave patients at higher risk of recurrence. If we are judged on this metric, this may promote mastectomy over breast conservation. It is important to establish reasonable limits and understand the differences in surgical practices, patients' preferences, tumor biology, and tumor and breast size as we consider this topic.

As outlined in an article by Dr. Peter Angelos in this edition, the ethical challenges of clinical trials are complex and even more complex in relation to surgery, because "placebo" carries its own challenges. In the pharmaceutical trials placebo drug is frequently used; however, what is the placebo for surgery? A sham operation? Is that ethical? How much true equipoise is there around cancer surgery?

ADVANCES

There are many examples of the pioneering advances that have been made in the diagnosis and management of benign and malignant breast diseases that continue to push our field toward equally effective but less invasive approaches where side effects and impact on overall quality of life can be minimized. This theme of "advances" was placed center stage at our annual meeting with the opening lecture by Professor Umberto Veronesi. His review of the surgical revolution from the days of the Halsted radical mastectomy to our current models of breast conservation and skin-sparing (±nipple-sparing) mastectomy highlight the impact that breast surgeons have had on the overall landscape of our field. In the current issue, Coopey and colleagues report their experience with nipple-sparing mastectomy and concluded that the eligibility at

their institution has increased over time to include women with higher body mass index and larger breasts.[16] Despite this, they observed no increase in nipple loss due to ischemia and the rates of positive nipple margins actually decreased over time.[16] Thus, one would expect that the number of women being offered this approach has similarly increased across institutions and is likely to continue to increase over time. The method of localization utilized for surgical resection of nonpalpable breast lesions also is evolving. In a randomized trial comparing radioactive seed localization to standard wire localization, there were no differences in positive margin rates between the two groups, but the mean operative time was shorter for the radioactive seed localization group.[17] Furthermore, patients' pain rankings were significantly lower for the seed localization group.

The method of adjuvant radiation therapy also has witnessed significant advances during the past decade. Multiple, randomized, clinical trials and meta-analyses have demonstrated the effectiveness and safety of whole breast irradiation (WBI).[18,19] However, there has been increased use of accelerated partial breast irradiation (APBI) and intraoperative irradiation (IORT). As a result, the American Society for Radiation Oncology has developed a consensus statement regarding patient selection criteria and best practices for the use of APBI, defining those that are "suitable" for APBI outside of a clinical trial, a "cautionary" group for whom concern should be applied when considering APBI outside of a clinical trial, and an "unsuitable" group for whom APBI is not recommended outside of a clinical trial.[20] Our own society also has published a consensus statement on the use of APBI that mirrors these recommendations, and several publications have demonstrated the outcomes observed from our registry data.[21–25] These recommendations can provide guidance for the use of APBI, and potentially for IORT as well, but frequent updates are likely needed as the knowledge from ongoing investigations accumulates.

An area of growing interest and research is that of survivorship issues. While we all strive to affect a cure in our patients, the side effects of treatment can impact our patients' lives in many different ways. The advances being made to address and minimize these adverse events are numerous. Fertility preservation for women who desire this option can be safely accomplished with ovarian stimulation with gonadotropins and letrozole. Although patients who pursue fertility preservation have been shown to have a longer delay between time of surgery and initiation of chemotherapy (45 vs. 33 days, $p < 0.01$), there was no difference in their overall survival or recurrence risk.[26] Lymphedema often is a debilitating complication following breast cancer treatment. Minimizing the surgical extent of lymph node removal with the use of sentinel lymph node biopsy in patients with clinically node-negative disease and low-volume pathologic disease has been profound. New advances are emerging to further decrease the incidence of lymphedema and to treat those patients who do develop swelling. Axillary reverse mapping (ARM), whereby blue dye is injected into the upper arm to identify and preserve lymphatics draining the arm during sentinel lymph node biopsy, has been proposed as a method to decrease and prevent lymphedema development.[27] Newer surgical approaches of lymphatic venous anastomosis and lymph node transplant for patients with chronic lymphedema also are being investigated.[28]

Advances in technology are not limited to the treatment of malignant disease alone. Benign breast diseases make up a large proportion of our practice as breast surgeons. Nipple discharge is a common presenting complaint and we are faced with the dilemma of how best to evaluate and manage a patient who presents with pathologic nipple discharge. The majority of such patients will ultimately be found to have benign disease, with papillomatous lesions being most common. One of the accepted video presentations published online for this special issue illustrated the use of an interventional ductoscope that allowed the surgeon to visualize and remove the intraductal lesion of interest using a basket extraction device.[29] The ability to avoid surgical incisions, especially for patients with benign lesions, is an area of active interest for many breast surgeons.

TRANSLATE

The challenge remains: How do we take the Genomics, Research, Ethics, and Advances we have learned and *Translate* them to our individual practices so that we can improve our patients' outcomes? Medical knowledge and technology have advanced at exponential rates during the past several decades. This is not unique to breast surgery. As a result, breast surgeons have more to know, more to manage, more to do, more to watch and follow-up, and more people to coordinate than ever before. However, we are in a unique position where we are able to develop relationships with our patients where knowledge and information are shared and our patients are able to retain a source of control over the decisions they choose without compromising outcomes. Our role is to provide the best evidence-based data for that decision-making, customize it according to the individual needs and values of the patient, and provide the transparency necessary so that sound, safe decisions are made in a multidisciplinary environment. The content of our 2013 annual *GREAT* meeting and the research contained in this special issue should provide the framework for successful translation!

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