How close are we to individualized treatment of breast cancer?

Lawrence J Solin* speaks to Natalie Harrison, Commissioning Editor: Lawrence J Solin is Chairman of the Department of Radiation Oncology at the Albert Einstein Medical Center in Philadelphia (PA, USA). Dr Solin received his undergraduate and medical degrees from Brown University in Providence (RI, USA). He completed his residency in Radiation Oncology at the University of Pennsylvania and Thomas Jefferson University, both in Philadelphia. He is a coeditor of the book *Breast Cancer Management and Molecular Medicine: Towards Tailored Approaches*. He is Professor Emeritus at the University of Pennsylvania in Philadelphia (PA, USA) and has concentrated his research interests on breast-conservation treatment with radiation for early-stage breast cancer. Dr Solin has contributed over 170 peer-reviewed publications to the medical literature, has presented more than 170 invited national and international lectures, and serves on nine journal editorial boards. His recent research has focused on the use of breast-conservation treatment with radiation for ductal carcinoma *in situ* (DCIS), long-term outcomes after breast conservation treatment for invasive breast carcinoma and for DCIS, technical approaches to radiation treatment delivery, and biologically defined subsets of breast cancer. He also maintains an active clinical practice in the area of radiation treatment for breast cancer. At last year's San Antonio Breast Cancer Symposium (TX, USA), Dr Solin presented the results of a prospective validation study of the DCIS score from the ECOG E5194 trial, in which a quantitative multigene reverse transcription PCR assay was found to be capable of quantifying recurrence risk in selected patients with DCIS, who were treated with surgical excision without irradiation, thereby providing a new clinical tool for individualized selection of treatment for patients with DCIS.

Q What sparked your interest in radiation oncology & how have your research interests evolved since completing your residency?

My interest in oncology began in medical school (Brown University, RI, USA). Because I have always enjoyed mathematics and physics, radiation oncology seemed like a natural fit. At the time, radiation oncology was far less sophisticated than it is now and was early in its development in the oncology community.

I started my research interests in my residency (University of Pennsylvania [PA, USA] and Thomas Jefferson University [PA, USA]) when breast-conservation treatment was a new and developing field. It has become far more sophisticated since then – we now understand much more about breast cancer in general, and radiation oncology and breast conservation in particular. It has been exciting to observe and take part in these developments throughout my career, and much of my work still revolves around breast-conservation treatment.

Two key things have changed over time: one is refinement – moving towards more

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tailored, more individualized treatments. Although that is a buzzword, it really is true in the clinic. The second is the application of scientific breakthroughs and new technologies to clinical practice. Recently, for example, we have been looking at some molecular components of breast-conservation treatment, which is fascinating because we know that molecular signatures have played such a key role in systemic-therapy management. Now we are starting to apply that knowledge to local–regional management as well. It is an exciting development and I am fortunate to be a small part of it.

Q Your current research focus is on breast-conservation treatment with radiation for early-stage breast cancer. What, in your opinion, have been the most significant research developments in this field in the past few years?

There have been several: one is the increasing technical sophistication of radiation delivery, which has had a huge impact; I also believe that tailoring treatments based on individual patient characteristics has been a major advance.

Many physicians who are not radiation oncologists may not be aware of the large gains that have taken place in the technical delivery of radiation for breast-conservation treatment – the sophistication and advantages of delivery today are just spectacular. For example, in contemporary breast-conservation treatment, we now use intensity-modulated radiation treatment (IMRT) techniques that substantially reduce the acute toxicity, the long-term toxicity and the side effects of treatment.

In terms of acute side effects, skin toxicity is reduced with IMRT techniques. In the scheme of cancer, that may not seem like a big advance, but for the patient who has this toxicity, this is one thing that we can do to make that patient's quality of life better.

The long-term side effects associated with these techniques are also substantially reduced, such as the avoidance of cardiac damage and lung toxicity. These are dramatic factors for patients in terms of improving their outcomes.

Q The book you coedited, *Breast Cancer Management & Molecular Medicine: Towards Tailored Approaches*, claimed that individualized treatment was no longer a dream, but the main goal for current research. How much closer are we to that dream now than in 2007?

I think that we are substantially closer. First, we now have biomarkers that are routinely used for systemic therapy treatment decisions. One of the things that I have been working on recently is to try and see how much we can apply these molecular biomarkers towards local–regional treatment.

Second, we come back to the technical approach to individual radiation delivery, which is much more sophisticated now than it was 5 or 10 years ago. The technical delivery has become much more individualized and refined – it is light years beyond where it was 5 or 10 years ago, and there is no question that in the next 5 years, it will become only more sophisticated. Now that we have the ability to sequence individual genes, we will be better able to identify and tailor treatment to risk. Once this becomes widespread, I think it will have a huge impact on the management of breast cancer.

Q Are there any approaches to identifying which women would benefit most from radiation therapy?

We have actually been working on two or three different approaches. One approach is to try to identify patients for whom we can avoid radiation – that is, those who are at a sufficiently low enough risk after surgery. This was explored in our recent 2011 CTRC–AACR San Antonio Breast Cancer Symposium abstract, the goal of which was to see if we could identify women who did not need radiation – that is, to use a prognostic approach [1].

Next will be a predictive approach, and the question will be can we identify patients who will gain most from adding radiation treatment. Then the next question, of course, will be can we improve on the markers we currently have available for those prognostic and predictive approaches?

Q In your opinion, what are the biggest challenges facing radiation oncologists today?

That is a really interesting question. I think the challenges for us are, first, to optimize our radiation treatment technology, and I think that we have already done a fine job of that.

Next is to maximise the integration of radiation with other therapeutic modalities and to examine molecular biomarker panels/genes for molecular approaches that can help us identify the patients who may not need radiation and the patients who would benefit most from radiation.

Another important challenge is to find ways to get the radiation therapy out into the wider global community, where radiation may not be available. At present, the gains of radiation treatment are not available to all women internationally.

Q How do you see the field of breast radiation oncology progressing in the next 10 years? How important will the integration of other therapies be in this?

I think there are a couple of interesting ways one could think about this. Right now there are some wonderful panels of molecular markers that work in the systemic arena. I think that those panels will be helpful; however, they may not be ideal in the local therapy setting. For example, the panel that I just presented at San Antonio [1] is, although similar, not exactly the same as the panel of biomarkers that is most useful for treating systemic disease. There is going to be both some overlap and also some differences, and one of the challenges that we face will be trying to sort these out these differences.

In the real world, systemic biomarker panels get developed first, and now we are just breaking ground with implementing biomarker panels for local treatment. The challenge is to see which of those biomarkers work and which do not. For example, in our panel, we found that of the 21 genes in the Onco*type*® DX panel for systemic disease, only 12 genes were important for local-treatment risk. So the challenge is to make those transitions and advances because clearly the 21-gene panel is not

ideal for local treatment, and that takes a lot of hard work.

In the San Antonio presentation, we found that it was a subset of the systemic panel, but I think that 5 or 10 years from now it might not necessarily be a subset of the systemic panel, but a partially overlapping set. Instead of just 12 genes, it might be those 12, plus some other genes, which were not included in the original panel of 21.

Q There is a lot of controversy surrounding ductal carcinoma *in situ* (DCIS). Why do you think this is the case?

DCIS is a fascinating disease to study. It is usually discovered on routine mammography screening, so we see a lot of these patients. The issue here is that we know that DCIS is a marker for the development of subsequent invasive cancers in some women, but not in all women. So the challenge is to identify who needs treatment after surgery, and who does not.

For every DCIS patient, the question is what type of treatment is needed after surgery – radiation, hormones, both, or neither? The controversy here is that most women do not go on to develop bad cancers, and we therefore overtreat many to benefit the few.

The ultimate objective is to find better markers that highlight who is at risk of developing invasive cancer, who is at risk of the tumor spreading and who is going to benefit from treatment. For example, we know that we use hormonal therapy only if a patient is hormone receptor-positive. However, we do not know which subset of patients gain most from adding radiation after surgery.

The San Antonio presentation was the first time we learned who might not need radiation, which represents a major step forward in the management of DCIS.

Q How would you predict things will be different in 10 years for a patient going to the clinic compared with how they are today?

In the future I think we will have a more sophisticated understanding of the biology of breast cancer at the molecular level, and that we will use that knowledge to individualize therapy for our patients. I also think that we will have far more sophisticated diagnostic capabilities that will give us a deeper understanding of patients' spread of disease at initial presentation, both within the breast and at distant sites.

Right now, for example, in many patients we treat the whole breast just because it is at risk – possibly imaging tools in the future could tell us which patients have disease in the breast that warrants radiation treatment and which patients do not. There is excitement in the radiology field that there will be better anatomic definition of disease that will help to guide local therapies. I think that another development that will happen is that once we have more molecular targets, we will have more molecular therapies, such as monoclonal antibodies.

In the future, all of those advances will be very important. This is a really exciting time to be involved in breast cancer research – the explosion of information has been unprecented, and it has greatly benefited the patients. In the future, the trend is not only going to continue, but also to accelerate.

Q Do you have any final points you would like to share?

Most importantly, the patients have gained a lot from all of these advances. The goal of research is to help patients, and for breast cancer, there is no question that the research developments have had a huge, positive impact on patient care on many different levels.

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Reference

1 Solin LJ, Gray R, Baehner FL *et al.* A quantitative multigene RT-PCR assay for predicting recurrence risk after surgical excision alone without irradiation for ductal carcinoma *in situ* (DCIS): a prospective validation study of the DCIS Score from ECOG E5194. Presented at: *2011 CTRC–AACR San Antonio Breast Cancer Symposium.* San Antonio, TX, USA, 8 December 2011.