INTERVIEW

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Breast cancer: the pathologist's point of view

Kimberly Allison* speaks to Alisa Crisp, Commissioning Editor:

Kimberly Allison is Associate Professor in Pathology at the Stanford School of Medicine (CA, USA). She trained at the New York Medical College (NY, USA) and the University of Washington Medical Center (WA, USA). She has clinical expertise in breast pathology and her research interests include how standards should be applied to breast cancer diagnostics (such as HER2 testing), the utility of molecular panel-based testing in breast cancer and identifying the most appropriate management of specific pathologic diagnoses. She is also

the author of *'Red Sunshine'*, a memoir about her personal experience with breast cancer, a topic that she speaks about to both patient and healthcare audiences.

Q How did you initially get into the field of breast cancer?

It was almost by accident actually; I trained in breast and gynecological pathology as part of my fellowship. We did not have a traditional fellowship at the University of Washington in this field at the time, but it was an area that I was interested in and so I tailored my general surgical pathology fellowship to breast and gynecological training. I then focused on breast and gynecological pathology. Then, our main breast pathologist, the director of the Breast Pathology Service, left unexpectedly and after just 2 years, I suddenly became the new director of breast pathology. Two weeks later, I was diagnosed with breast cancer. This was a shock because I did not enter the field because I had a family history of breast cancer. I did, however, like the field of breast cancer pathology because I felt that it was an area where every detail in one's report could make a clinical difference in terms of what treatment a woman was getting; in that sense, it felt like what we were doing was very important. In other areas of pathology, pathologists are more drawn to the mystery of what the

diagnosis is: for example in gynecological pathology, there are mysterious ovarian tumors and your main focus is the fact that you need to figure out exactly what they are. By contrast, in breast cancer, your aim is more describing the details: is it close to the margins? Is it expressing hormone receptors? What grade is it exactly? How big is it exactly? Has it spread to the lymph nodes? Some pathologists do not actually enjoy breast pathology, but especially after I was diagnosed, I became a lot more interested in how every little detail in our report was impacting management. Therefore, having been a breast cancer patient, I am now much more passionate about the disease.

Q In your opinion, how important is the role of the pathologist in defining the treatment of breast cancer?

The breast cancer reports are probably some of the longest reports that you will find in pathology because there are so many specifics that can make a difference in treatment algorithms. Everything from the Nottingham grade to the exact size of a metastasis to a lymph node can make a difference between using chemotherapy

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*Stanford School of Medicine, 291 Campus Drive, Stanford, CA 94305, USA; allisonk@stanford.edu

or not, doing an axillary dissection or not, choosing mastectomy versus lumpectomy and deciding which type of surgery and type of targeted therapy to use, such as HER2-targeted and hormone receptor-targeted therapy. For breast cancer, pathology has really made the treatment personalized; thus, it is really important to get the details right because your entire treatment plan is going to be based on what is said in that pathology report. Therefore, I always encourage patients to make sure that they have asked their oncologists or surgeons details about their pathology report, or maybe even ask if a second opinion is something that they would recommend, because those details are so critical in the next steps and treatment planning.

Q Some of your research has been in molecular panel-based testing for breast cancer – how far do you think this is from the clinic?

There are some molecular panel-based tests that are already commercially available and are used by clinicians fairly routinely. Oncotype DX is one of them: it is used when the oncologist and the patient are debating the utility of chemotherapy in lower-risk breast cancers, in order to try and avoid chemotherapy, but it is an expensive test, as it costs approximately US\$3500. The test is only carried out in one commercial laboratory. I think there is certainly some utility to additional testing in the right clinical situation. My research was basically looking at the utility of Oncotype DX testing and how we can predict the results from the traditional pathological factors that we have in our routine pathology reports. Our question was: 'do we need to be ordering this expensive testing on every patient that is considered low risk or can we stratify those patients just using traditional pathology reports?'. We found that it was probably most useful in the very gray areas, whereas the patients in whom you might expect a low recurrence score from Oncotype DX, such as Nottingham grade 1 cancers with strong PR and ER expression and low proliferation rates, usually come back as low risk by the oncotype recurrence score and

are thought to not benefit from chemotherapy. However, our argument was that you could predict the low recurrence score really well when the PR expression was high and the Nottingham grade was low, and you could avoid the testing and just assume that you would get a low risk recurrence score.

The other issue is that this molecular panel-based testing is, in a way, a step forward because you are using multiple markers at the same time and a lot of them are very proliferation-driven. We do our mitotic counts and sometimes we use markers, such as MIB1 or Ki-67, to look at proliferation in the traditional pathology, but the molecular panel-based test uses multiple markers and, in a way, that is a step forward.

It is important not to view these tests as the new gold standard, just because they are molecular panel-based, because there are pitfalls with them and I think it needs to be emphasized that it is only one piece of the puzzle. If you have pathological factors that really contradict a result from a molecular-based panel, it is time to take a step back. I think it is the pathologist's job to really look at all of those results and come up with some conclusion or recommendation about whether the testing needs to be repeated or if there is an explanation for why a molecular panel-based test may have resulted in a higher score than was expected based on the histology. For example, there may be a lot of intermixed inflammation, which can increase proliferation rates if you are not doing an *in situ* test, but rather a molecular test instead, because that will become part of the proliferation index.

There are also other molecular-based panels, such as MammaPrint, which you can now do in paraffin-embedded tissue, so I have seen our clinicians use this a little more frequently than they used to when it was only in fresh tissue. The utility of those tests is still being vetted in prospective trials and we will see whether it continues to be a standard of care in the long term, but it has definitely already been integrated into a lot of clinical practice models of breast cancer treatment; specifically, it is most useful in decision-making

concerning the low-risk hormone receptor-positive cancers in terms of whether to skip chemotherapy or not. Therefore, although there are pitfalls with molecular panel-based testing, they can add a lot to the picture.

Q What do you think we need to improve in order to increase the utility of these tests in the clinic?

The tests that have been most successful can be performed in paraffin-embedded tissue and not in fresh tissue, so that, after all of the final pathology reports are in, you can really identify which block is the most representative of the cancer. The only aspect pathologists may hesitate over is that when you carry out a molecular panel-based test, it is not an *in situ* test; you are grinding up tissue, so the tissue must be pure and representative. For example, you cannot include ductal carcinoma *in situ* because you want it to be a pure invasive cancer. You do not want to include any inflammation or biopsy site reaction in it and so I think the companies that are performing the molecular panel-based testing should continue to microdissect out invasive cancers, or perhaps develop more *in situ* methods; that is one of the advantages of immunohistochemistry, because you can see what you are staining visually and you can be sure that you are looking at, for example, hormone receptor expression in the invasive cancer, not in the ductal carcinoma *in situ* or some background tissue. In the future, I think it would be wonderful to have new multimarker testing methods that are based *in situ*. I also think that we will do more searching for specific mutations or genetic abnormalities in the future, which is already beginning to happen. We already look for gene amplifications in *HER2* through FISH, but I think there may be other markers that we can start to use as a panel; that is, looking for more specific, perhaps less common mutations in breast cancers and in cancers across the board. The same mutation that may be present in a melanoma that has a targeted therapy may be present in one individual's breast cancer, so I think we will have more panel-based genetic

molecular testing that can cross the spectrum of cancer types in the future. However, it is going to cost a lot – I think that this is also one of the greatest challenges.

Q How likely do you think truly personalized medicine is for breast cancer?

I think we are already there in a lot of ways – we have already started to personalize breast cancer treatment. We test every breast cancer for hormone receptor expression, so we know we can put patients who are hormone receptor-positive on hormone-targeted therapies. We also test every breast cancer for *HER2* overexpression or gene amplification, and there are great targeted antibody therapies, so from this standpoint, that is very personalized. Following that, proliferation-based markers and Nottingham grade are used to look at the biology in order to answer questions such as: is it a high-grade process that is aggressive? Are they going to benefit from chemotherapy? Do you need some additional molecular panel-based testing in order to determine whether that patient is going to benefit from chemotherapy at all?

Because we have learned how to personalize medicine in a lot of ways, breast cancer reporting has become very detailed. This has resulted in the reporting becoming more regulated because the pathology is really what is creating personalized therapeutic options for breast cancer patients, and I think that will only continue. I think we will get more specific with our testing and our targets. Having said that, I also think that what we know regarding data from the Cancer Genome Atlas and other big datasets is that there are not many more major common targets. A lot of the additional targets are present in less than 10% of all breast cancers, and so it does not appear that we are going to have another major new target that we can personalize medicine to, but there may be many less common ones. Therefore, the pathology report is basically your personalized recipe for what therapies you are a candidate for, and this is only going to get more and more personalized as we move forward into a more molecular era.

Q You have previously said that holidays should be prescribed to patients after a cancer diagnosis, are there any other ways in which you think attitudes to cancer treatment need to change?

I remember in an ASCO newsletter somebody picked up on that in my book – that my white blood cell counts went up after I went on vacation and so they inferred that everybody should get holidays after cancer treatment! However, I think that one of the big lessons I learned from going through cancer treatment myself was that I knew what targeted therapies were available to me and I knew what medicine I needed to take in order to have the best chance of curing my cancer; nonetheless, what I did not anticipate was all the different ways that I needed to heal as an individual. Oncologists are rarely trained in this aspect. I think physicians in general are not really thinking or trained to think about other ways that patients can heal, and with that I mean ways that can make a big difference mentally, whether your prognosis is excellent or poor. There are patients who really want to be involved in their healing and there are many ways to encourage patients and exploring those can really help – whether it is offering lists of support groups or finding new spiritual ways of dealing with their new-found mortality or just encouraging them to use the opportunity of a cancer diagnosis to really take stock of all the different ways that they can heal as an individual. I started doing yoga and meditation and those were great activities for me and although it is not a recipe for everybody, I think that finding ways to heal yourself is critically important to avoid experiencing some of the aftereffects of cancer treatment and, psychologically speaking, the cancer diagnosis, because that can do a lot of damage. Finding healthy ways to heal is important.

Q What messages do you want clinicians to take from your book 'Red Sunshine'? Are there any other ways clinicians should change their approach to managing patients?

It is definitely worth thinking about the whole patient and encouraging them to

think this way, presenting the available resources so that the patient can go and see a naturopath or a support group or get help with her financial situation; having all those options available is really important to succeed in terms of treating and healing from cancer. I also think that my book is really about me stumbling through all those different processes and realizing what worked for me and helped me heal after and during the whole process. These days, patients have many less toxic treatments out there; encouraging patients to keep living their lives to the fullest extent possible during cancer treatment is a big mental shift that I had to make. I thought: "OK, I'm going to be going through chemotherapy, I'm not going to be able work or play with my kids or do all these things that I consider the richness of my life," but in reality, treatments are less toxic and there are better treatments for side effects, and by considering other ways of staying whole and healing. I think you can really live through cancer treatment with rich and full lives today, and that is something patients need to hear when they first get diagnosed.

Q In what ways has your diagnosis changed the way you manage patients/work?

It has not really changed the decisions I am making at the microscope; I am not changing what facts I see on the slides, but I am definitely training my residents to know the impact of their histologic diagnoses, and to be cognisant of turnaround times so that they consider the anxiety involved; there is probably somebody crying at home waiting for this result so you need to ensure that you provide the patient with a fast and accurate answer. Many pathologists do not necessarily learn this during their training because they are focusing more on what they see on the slides and what markers are expressed and they are not necessarily learning what impact that has on the patient. For example, questions need to be asked, such as: how is that going to change her treatment options if you say that the tumor is 2.5 cm instead of 1.9 cm? How accurately do you think you have sized that cancer or that close margin and how

close is it exactly? Do you know the distance from the margin that the surgeons will go back for? Considering these questions is not necessarily going to change the facts but I think it is really important to know their relevance so that when borderline cases occur, you have insight into the impact it will have if you are on the fence about something, or whether a second opinion is needed.

My diagnosis has also changed my practice in that I see patients more often than I used to, because I actively seek it out, so if a patient has a question about the pathology that their oncologist thinks might be better explained by the pathologists themselves, I am happy to see patients in my office and explain the reports or actually look at the slides with them. I have had patients who just want to see what they have been diagnosed or confronted with, in addition to knowing more information or having specific questions answered about their pathology.

From a personal standpoint, because I have been there and I am willing to talk about my experience, I like to mentor patients through the process, especially during the early stages, because I think that is the most terrifying time; right after diagnosis and at the time when your definite treatment plan may not have been decided, you have been given what feels like a death sentence in a lot of ways. I strive to shine some light on that and decrease the fear involved.

Q What research projects are you currently working on?

One of the projects I am excited about right now is looking at new thresholds for *HER2* testing by FISH, so that when

we look at the gene amplification status of breast cancers, we basically look at all the cells present and we take an average score across them. Most of the time, cases are straightforward – the majority of the cases are clear-cut. However, there are approximately 5–10% of cases that fall in a borderline zone, known as ‘equivocal’ or indeterminate, and I want to know more about the reasons behind this. I like to look deeper at what the reasons are underlying that borderline nature of the result and one of the issues that I am particularly interested in is *HER2* heterogeneity and how there may be minor populations of *HER2*-amplified cells, either in clusters or very intermixed in the cell population, and particularly when these should be considered to be clinically relevant, and a potential action could be to offer *HER2*-targeted therapy.

Q How do you see the field of breast cancer pathology changing in the near future?

I believe that we are going to learn more about who not to treat. We are already starting to do that. Breast cancer is common and the most common type is a very low-risk, slow-growing, hormone receptor-positive form of the disease. There has been a lot of talk in the press of overdiagnosis because we screen a lot, but what we are going to learn is that we can also treat less. Therefore, we do not need to offer chemotherapies to patients with low-risk disease just because we have one feature that we are worried about. This will really change survivorship in a lot of ways. I hope that, in the future, we may get better at risk prediction for patients so that we will know whom to be screening

more thoroughly – right now, we are not very good at that. Perhaps there will be new molecular or genetic markers that we can use to try to take stock of patients when they hit 40 years of age in order to figure out who would benefit the most from screening to prevent the higher-risk disease. Then, I really hope that we end up developing more cures; we have made so much progress in localized disease, but I really hope that we make even more progress in stage IV disease, so that we can actually develop true cures for this stage of disease. This stage is, of course, what we try to avoid with early detection, but there will always be a certain population that will present with stage IV disease, and this is considered incurable at this point. However, we are finding more women that we have been able to achieve long-term disease control at stage IV and I hope that this will continue. In the future, I think there will also be development in finding and using multiple drug targets.

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