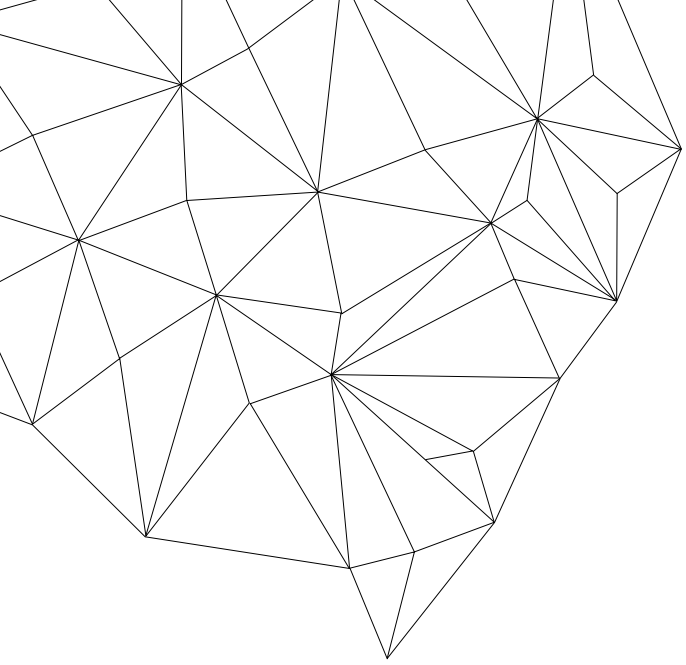

MORE PRECISE, LESS AGGRESSIVE

To know more is one of the main goals of the new methods in treating cancer patients. Lymph node status is one of the most important prognostic factors and plays a key role in surgical and therapeutic decision-making

Plain speaking in Barcelona: Pathologist Vicente Peg Cámara PhD, Gynaecologist Mar Vernet Tomas PhD and Radiation Oncologist Manel Algara López PhD

The reliable analysis of lymph node tissue and accuracy is crucial for a precise determination of the metastatic tumour burden and optimal staging as shown, for example, in the management of breast cancer. We invited Mar Vernet Tomas, MD, PhD, Chief of the Gynaecologic Oncology and Breast Diseases Section from Hospital del Mar, Barcelona, Manel Algara López, MD, PhD, Chief of the Radiation Oncology Department, also from Hospital del Mar, and Vicente Peg Cámara, MD, PhD, Pathology Department, Hospital Universitari Vall d'Hebron, Barcelona, to talk about the relevance of sentinel node analysis, the different challenges faced by the medical departments and the future of axillary management.

As you know, axillary management has changed significantly over the past few years. What are the main changes and challenges regarding the sentinel node technique today?
DR PEG: We have experienced radical changes: first, in the way we approach it, because anatomy is becoming increasingly molecular. The molecular approach has allowed us to give a definitive diagnosis in 100% of cases for the first time. Before, when a node was diagnosed positive, we were sure it was positive, but when it was negative, we could be wrong or simply not see what was there. Now, we are sure of what we are seeing. So, for reasons I am sure we'll cover later on, we provide more information than just 'positive or negative'. The clinical management is a different story, but for us, this has first of all meant changing the way we work and secondly, the ability to provide more information with greater confidence.

Dr Vernet, from a gynaecological point of view, what are the changes and challenges regarding the sentinel node?
DR VERNET: Well, all this translates into more precise patient treatment and follow-up. We give more precise and less aggressive treatments. We want to know more. Not just whether the sentinel node is positive or negative, but how positive or how negative it is. We are evidently moving towards a more accurate medicine with which we can make decisions that will affect survival because we are honing in more. The sentinel node technique is obviously along these lines: the lines of precision, of treatment individualisation, of knowing exactly what we have and consequently what we must do.
DR ALGARA: That is basically it. The sentinel node has allowed us to define micrometastasis and macrometastasis. The next step is to better define these, which will eventually lead us to the right treatment: more local treatment or more systemic treatment. Recent studies have totally revolutionised axillary treatment. We have gone from always operating to not operating in many cases with a positive sentinel node. Molecular analysis may also help us decide whether radiation therapy is necessary or not.

Regarding these new methods, what are the main benefits of molecular techniques, and what are the main differences with histopathology?

'We are evidently moving towards a more accurate medicine with which we can make decisions that will affect survival'

DR MAR VERNET TOMAS, CHIEF OF THE GYNAECOLOGIC ONCOLOGY AND BREAST DISEASES SECTION FROM HOSPITAL DEL MAR, BARCELONA

DR PEG: I think that the main, fundamental, difference is that we analyse the entire lymph node. Because if there is one thing pathologists are undoubtedly sticklers for, it is reproducibility. Ours is a very subjective speciality, and it is true that, in very clear cases, many of us agree, and in cases that are not that clear, we agree less, but there is always a certain degree of personal bias in the interpretation. Molecular technology offers reproducibility, as anything automated does. But it also provides us with more information. We measure metastasis. When we slice a lymph node, we never know if what we see is the maximum diameter, because we analyse a very small portion of it. So we analyse it in its entirety, we measure it in a much more reproducible manner. And on top of that, it provides clinical information and prognosis, which used to be much more difficult to obtain. Another question is what clinicians do with that information. They can judge how important it is, but from our point of view, we overcome one of those major hurdles pathologists deal with: reproducibility.

Dr Vernet, the concept of sentinel node is emerging in other cancer entities, such as gynaecological cancers. In that case, what kind of information do you expect from the pathologist today in order to decide on the surgical approach?
DR VERNET: To give a less invasive treatment that is just as effective as a more invasive treatment. Obviously, the more precise and reproducible the information given by the pathologist, the more homogeneous our therapeutic decisions will be, and the indications will be better. This is equally valid for onco-gynaecological diseases such as breast cancer. For us, it is fundamental to observe, standardise and use reproducible techniques.

How can precise staging be preserved when axillary dissection is being increasingly avoided and we are obtain infomation only from the sentinel node?

DR PEG: The number of axillary clearances has decreased. Therefore, all or many cases will be staged 'pN' based on the 'sn'. It is true that TNM takes this into consideration; it can be done only as a function of the result of the sentinel node. However, in any case, the usual TNM staging as we know it now will disappear.

DR VERNET: I am not sure. It is as if medicine is going a bit that way. I do not think that this issue is closed because if we look at precision medicine and we keep talking about individualisation, and then we don't care that, with some patients, we don't know whether there are three, four, five, or six positive nodes, well, that means we're not really individualising all that much. Because if I individualise, as we said before, based on the tumour phenotype, and then I do not care what is in the axilla, it is not that clear to me that it is not important. It seems that now it is fashionable to ignore it, but to me it is not that clear.

DR ALGARA: But if you have a test that tells you that the sentinel node has a high tumour load, perhaps it is not important to know whether there are seven or eight. Perhaps that is enough. We will see, maybe that is where the road will lead.

DR VERNET: I think that this is a complex equation with several different characteristics. What response to systemic treatment does such a phenotype with such a tumour load have; what response does radiotherapy give in any phenotype with a certain tumour load; and up to what point will surgery be necessary to reduce the tumour load. This is a more complex equation, I think, than what we are currently considering.

Dr Algara, in a scenario with fewer lymphadenectomies despite a positive sentinel node, what is the specific challenge for the radiation oncologist?

DR ALGARA: The challenge is to know whether to treat or not. Despite all the studies, Z0011 does not tell you what to treat or not to treat because in one treatment arm, 70 per cent received radiation therapy. Therefore, the challenge is to know really whether patients with low tumour load need or do not need axillary radiation. There is one study going on right now – OPTIMAL. We use the criterion of 15,000 copies of OSNA-determined total tumour load. We irradiate all or just a part.

And what is the implication of this in clinical practice? Do you think a personalised treatment for the patient is really possible?

DR ALGARA: Yes, radiotherapy increasingly allows us to personalise a lot because this issue of axillary radiation has been discussed for a long time now. Twenty years ago, we would not have had this discussion because whenever the breast was irradiated, the axilla was too. Nevertheless, this was when we planned everything in 2D. Currently, 3D techniques with modulated intensity and volumetric techniques allow you to adapt much better to the volume to be irradiated. So, I have to know whether I need to include the axilla or not. Additionally, partial radiation techniques are becoming increasingly common. Therefore, it is much more complicated to include the axilla in the treatment volume when you intend to irradiate only a part of the breast, than when you irradiate the whole thing. Axillary treatment can be surgery or radiation – the outcomes are the same. The role of the sentinel node is that you can be sure that there is or there is not complete remission, and that increasingly determines treatment. So far, even if there is complete remission, we still do everything, but in a matter of months or years, we'll stop doing things after complete remission. And also, in conjunction with molecular methods, for we trust molecular methods more than a microscope.

DR VERNET: Well, it is the pathologist we trust, right?

DR PEG: Let me qualify this: neither the microscope nor the pathologist, but the cut. Many of our failings were due to inaccurate location of the metastasis.

DR ALGARA: Because you cannot look at everything. When we did 2D radiotherapy, you could only see what was going on in one plane. Then the woman developed dermatitis four centimetres above. Of course: no one had made any calculations for that area! What molecular methods do is look at everything. They know what has happened in this node – and that is critical, because as I say, currently we continue doing everything, but we will stop doing certain things. We will probably operate less or irradiate less. One of the two local treatments will decline.

DR VERNET: Or both, as they become positive and respond to systemic treatment...

We know that OSNA and the number of copies of CK19 mRNA have also shown to be of prognostic value in the PLUTTO trial mentioned by Dr Peg. How is the issue of units of breast pathology taken into consideration for treatment decisions?

DR ALGARA: Very much little by little.

DR PEG: Just yesterday, I was talking with the hospital oncologist – I am going to start presenting it at an internal discussion forum as a possible marker. But for all practical purposes, in reality, very slowly.

How would you envisage using this kind of more elaborate diagnostic information on a broader level in the future?

DR PEG: In the near future, SLN can't be only a matter of positive or negative results, but there will be a need for more information like that which we can already get from the primary tumour. At that point, I am sure that molecular methods will continue to help us to make better decisions.

DR ALGARA: Essential. Treatments will become more and more personalised. This is the reason why information should be more detailed, accurate and reproducible.

DR VERNET: I see it as becoming an indispensable and routine tool in breast cancer treatment.