Redefining the role of pathology

How Giuseppe Viale embraced the new responsibilities of the molecular era

➜ Simon Crompton

In the era of personalised therapies, complete and accurate pathology reports are vital. Helping pathologists rise to their new responsibilities, and ensuring they are given the opportunity to play a full role, has been a mission for Giuseppe Viale, a leading Italian pathologist whose career has spanned the transition from microscope to molecular imaging.

Pathologists are meant to be retiring types, locked away in white rooms poised above their microscopes, feeding their findings through to physicians but rarely involved with patients. Not Giuseppe Viale.

He's confident, gregarious and influential, and when he shows me the certificates on the wall of his office in the European Institute of Oncology buildings in Milan, he emphasises he's not doing it to show off. "This is what matters," he says, pointing to the citations that are for his contribution to "cancer treatment" and "cancer therapy" – not simply pathology. Giuseppe Viale, known as 'Beppe' to his friends, has brought pathology out of the white rooms and onto an equal footing with oncology.

A Fellow of the Royal College of Pathologists and a leading light in the Breast International Group since 2002, he was among the first pathologists to introduce immunohistochemistry (detecting antigens in cells through the use of antibodies) into oncological pathology at the end of the 1970s. In 1994 he was instrumental in setting up the Division of Pathology at the European Institute of Oncology, where he is director.

When I first spy him in the pathology department, it's clear straight away that force of personality as well as professional skill has played its part in his achievements. He's talking intently to a student in a corridor, hands on her shoulders, imparting some light-hearted words of wisdom. Everywhere he moves in the institute people know him and greet him. Viale has an easy charm, mixing strong opinions with self-deprecating humour, and it is easy to see how he wins over students, oncologists and decision makers alike.

As he tells me the story of his career, he admits

that some of what he tells me is also regaled to his students – as the University of Milan's professor of pathological anatomy and histology, he supervises the budding pathologists of the future. The sum of his tales are an essay in good pathology.

Two revolutions

He has been in Milan since beginning his medical training there in 1969. During that time he has witnessed two revolutions in cancer pathology. The first came at the end of the 1970s. Until then, cancer pathology had been based almost entirely on observing the morphology of cancer tissue under a microscope. But then immunohistochemistry became widely introduced, allowing individual cell components to be identified. This opened up the way to biological tissue characterisation and the identification of important markers.

"We were among the first in this country to break into immunohistochemistry in oncology," says Viale. "At the beginning it was used diagnostically to differentiate different tumour types, but then we used it to identify markers that were not only diagnostic but enabled us to look into prognosis and predict the response to therapy." This revolution, he says, was largely a technical one, resulting from the discovery of new techniques to extract biochemical information from formalin-fixed tissue samples. But it still led to enormous improvements in treatment and life expectancy.

The second revolution was an oncological one. Until the late 1990s, says Viale, prescriptions of systemic treatments were mainly informed by tumour size and number of metastases. Then the oncological community began to distrust this approach – clearly something was wrong with it when small tumours with no metastases were killing people within three months, and people were also surviving large tumours with many metastases. So the quality of the cancer cells, not the quantity, and the biological features that would predict responsiveness to therapy became the focus of attention.

"This, to me, was the most important revolution in oncology," says Viale. "There was this important change where systemic treatment became based on expected responsiveness of the tumour."

At the same time, through immunohistochemistry, pathologists were now able to measure

oestrogen receptors and *HER2* status. Then, around 2004, targeted therapies such as Herceptin (trastuzumab) started to become available, so that markers like *HER2*, which had previously been used for diagnosis and prognosis, became specific targets for interventions.

All this made the information provided by the pathologist more directly important to patient welfare than ever before. "There are three pillars to build a systemic treatment: the pathologist's report, the patient's preferences and the oncologist's opinion of what is best for the patient. But the pathologist's report is absolutely essential to support the other two."

There is a problem, however. Nationally and internationally, the potential impact of modern pathology in oncology is not always fulfilled. Viale says there are worrying variations in practice and standards, often because pathologists are too isolated.

Dangers of isolation

"Let us divide pathologists into two groups," he suggests. "There are those active in multidisciplinary teams, say in cancer institutions, and those who are not. The second group don't see the full picture of a tumour that has to be treated according to biological features, the presence of specific targets, within the context of the tumour burden, within a given person in a given time and given resources. So for them, the diagnosis of cancer, 'yes' or 'no', is the peak of their activity. Some don't actually care about staining for oestrogen receptors or *HER2*."

This is one reason for disturbingly high rates of erroneous pathology reports. Viale says that looking at *HER2* status assays across the world, around 15–20% can be expected to be false. "Unfortunately this discordance rate implies that quite a large number of patients, today, in 2011" (he bangs the table with his finger pointedly) "are mistreated because of an inaccurate assessment of the predicted parameters of breast cancer."

The reasons for variability can sometimes be traced to technical faults in the ways assays are run. This can be minimised with modern automated immunohistochemistry stainers and approved reagents. But more significantly, variation comes because of the very nature of pathology: it is observational and subjective, and two pathologists looking at the same slide may interpret it differently.

"To minimise this is much more difficult," says Viale, "because it depends on experience, expertise, the number of cases you have seen, the clinical feedback you get, whether you participate in quality control." The problem is widespread even among western countries – so much so that when patients are referred to the European Institute of Oncology for a second opinion (there are around 2500 such referrals every year), the oncologists there do not trust the original pathology reports and ask Viale's department to carry out their own. "If you are not confident in data how can you be confident in your prescription?" he asks.

Equally, he points out, how can you have a clinical trial looking at tailored treatments for specific breast cancers if you are not confident that the right patients, with the right pathology, are being selected

The next generation. Viale allows students to share his office because learning about roles, responsibilities and interactions is as important as the purely medical side of the job

Viale is confident that this kind of double-checking will lead to pathology standards being driven up worldwide

for the trial? In large multicentre, international breast cancer studies it is now becoming mandatory that local pathology samples and reports are sent to a central facility for checking, and Viale is confident that – in breast cancer now, and other cancers to follow – this kind of double-checking will increasingly lead not just to benefits for the patient, and not just to more significant trial results, but also to pathology standards being driven up worldwide. Viale's own laboratories at the Institute have had this central checking role in many major international trials. "We can force improvement," he says.

He explains what he means with a story. In a recent breast cancer trial involving more than 10,000 women across the world, Viale's laboratory discovered a very high discordance rate of more than 14% in one European country where more than 100 centres participated. "This was most unexpected by the oncologists there. So we worked together with the pathologists in that country, looking into results from all their centres, and discovered that in a handful of centres the discordance rate was more than 50%, bringing the whole national rate out of scale.

"So they went back to them internally, and they are now acting on it. We are happy to talk to any of the centres involved in trials about the way they are working, because this is a good way of having international quality control, which may lead to improvements in leading centres."

Learning lessons

Viale's belief in the importance of pathologists working as part of a team have been forged by influential figures through his career. He was born in Turin in 1952, an only child. His father died of melanoma when he was just 10, leaving his mother – a figure Viale clearly admires for her enterprise – to pick up and run the car-painting business he had just set up. Driven by ideas of helping people, Viale started medical school at the University of Milan and knew straight away he wanted to be a pathologist.

"I wasn't interested in collecting symptoms, like many of my colleagues. I wanted to know, 'Why? Why fever? What is the mechanism?'" In his second year of study, he started performing autopsies at a general hospital in Milan on Saturday mornings, wanting to know about the feeling and consistency of organs, not just what he read in books. "It said in the books that liver had a 'parenchymatous' consistency, but what did that feel like?"

His professor of pathology during university training was Guido Coggi, whose inquiring lectures further inspired Viale. He joined Coggi as an intern at the university's pathology institute at Ospedale San Raffaele, Milan, and remained with him after qualification for 20 years. In 1994 Viale became professor of pathological anatomy and histology at the University of Milan – and then came an additional role: director of the Division of Pathology and Laboratory Medicine at the European Institute of Oncology. His move into cancer was down to the influence of another giant in his career, Umberto Veronesi.

Veronesi had just set up the European Institute, and phoned the university to see if there were any bright young pathologists available. Viale remembers how Coggi, despite being highly dependent on Viale to run his own department, instantaneously told him he should take the job. "This was so instructive. The greatness of the man was to be able, in 10 seconds, to figure out that, for the sake of my career, I had to move." It's a valuable lesson that Viale often tells others. There are two more pieces of instruction from mentors that Viale mentions as key to his career.

One came during his interview for the job with Veronesi. Viale expressed surprise that Veronesi should want a pathologist like himself to head the new Department of Pathology and Laboratory Medicine – normally such roles went to the laboratory medicine side. "He said, 'Listen, this is a cancer centre, and what I know is that a cancer centre is only as good as its pathology department.' It is absolutely true."

He immediately warmed to Veronesi's understanding of the treatment issues that needed to be tackled for the good of patient welfare, and the need for extra resources to research those issues.

But the third lesson initially came as a jolt to his confidence. It was from oncologist Aron Goldhirsch, director of the Department of Medicine at the European Institute – "another giant in my career". A few months after Viale arrived at the Institute, "most likely a reasonably good general pathologist," Goldhirsch came into his office. "He said, 'Listen, I have a problem. This is your pathology report. But it does not tell me how to treat this lady. So I told her, she should come to you and you should treat her.' I thought, 'Are you crazy?' But that was his message – that the oncologist was always searching the pathology report for data that would inform the systemic treatment, and there was something inconsistent in this report that made interpretation impossible. This was fantastic because it taught me what it is to be a breast cancer pathologist."

Goldhirsch involved Viale in the International Breast Cancer Study Group, and he became co-chairman of its Central Pathology Office in 2002. This work drew him into the Breast International Group – he became a member of its executive in 2004. During the past decade he has had a central role in some of the most important recent breast cancer trials. These include the HERA trial into the use of trastuzumab in the adjuvant treatment of *HER2*-postive breast cancer.

He is on the steering committee of the ALTTO trial, a worldwide study involving more than 8000 patients to evaluate the effectiveness of a new therapy, Tyverb (lapatinib), in treating early breast cancer following surgery. He is also on the steering committee and lead pathologist of the MINDACT trial, which is run by the EORTC and aims to demonstrate how molecular profiling can be used to assign risk and determine whether breast cancer patients without lymph node involvement, or with between one and three nodes positive, need to receive adjuvant chemotherapy or not. He has authored 328 articles in international journals and written 36 chapters in books.

Through all this, and with his responsibilities for supervising young researchers and fellows, Viale admits that he has little time for relaxation – apart from spending as much time as he can tending to his vegetable patch.

His family is fortunately understanding. His wife is a biologist who works alongside him at the European Institute – they met whilst working together under Coggi to develop immunohistochemistry staining techniques, and Coggi was insistent that she should go with him when he moved to the Institute. They have two grown-up daughters, aged 22 and 21, the eldest in her fifth year at medical school, the other working to be a script writer. And he still regularly sees his mother, now 91 and still living in Milan, having retired after 30 years of running her business.

Passing on the lessons

It is the power of people – as a motivating force and as interpreters of scientific data – that Viale continually re-emphasises. Science is nothing without them. He shows me his office, which contains three desks with three microscopes, and which he always shares with the two youngest students he is supervising. "I spend around 12 hours here every day, but when I leave, although I'm happy to see my family, I'm sorry to leave my students. Their enthusiasm is so fantastic."

As students discuss with him what they are examining, and as they listen to Viale's phone conversations with oncologists and surgeons, he can give them some insight into what pathology in cancer really means, passing on the sorts of advice that he received from his own mentors.

"Hopefully, what they're exposed to daily is that behind the microscope is a patient. They should always keep in mind that making the pathology diagnosis is not something unrelated to a patient, a family, a history, to a problem with systemic therapy, indication from a surgeon, whatever. If you want to do something useful for the patient, you need to insert the pathology diagnosis into a wider context.

"He said, 'I have a problem. This is your pathology report. But it does not tell me how to treat this lady'"

"It is dangerous to think, 'This tiny piece of the problem is my responsibility and the rest is not my business'"

What I'm trying to teach them is that it is very dangerous to have the attitude: 'This tiny piece of the problem is my responsibility and all the rest is not my business.' So if the diagnosis is difficult, open the medical charts, talk to the treating physician, ask the relatives – be proactive."

Viale wears the pathologist's white coat proudly, because he believes it sends an important message to patients and others he is working with. "They see someone who is looking and acting like a doctor. That is important, and reassuring," he says.

So as we talk about where pathology is heading, and the increasing potential of new techniques to take objective readings that could rule out the human error that he knows can prove so devastating to patients, he is also adamant that pathologists should never be mere "machines of the clinical laboratory".

Yes, efforts to improve accuracy in pathology have already brought down international variance rates in the assessment of oestrogen receptors and *HER2* status from around 21% to 15% in a decade, and new genomic and proteomic techniques, which rely on objective testing rather than subjective observation, could bring this rate close towards zero. In 20 years time, says Viale, blood tests may provide as much information as a tumour sample. In theory, pathology itself could become redundant.

"But honestly, I believe that in the next few years, pathologists will not be replaced by these tests. We need these techniques to add to what we have, not replace them. We need as comprehensive a picture as possible of the tumour."

It may be always necessary to accept some variance rate, he says. What is important is to offer minimum standards and constantly encourage improvement. The best way to do this is to adopt a multidisciplinary approach in all cancer centres and involve as many patients as possible in clinical trials. But he realises that this can be politically difficult in many countries where professional hierarchies are deeply embedded.

As he shows me out of his office at the end of the interview, past all those certificates on the wall, he comments in passing that he can't remember a pathologist being on the cover of *Cancer World*. I realise that despite all his self-mocking humour, Viale is extremely proud of what he has done to raise the profile of his profession. He enjoys the status and influence he has attained through hard work, and greets and chats with friends and colleagues as we pass down to the Institute's reception, finding me a taxi driver he knows well to take me back to my hotel.

As I head off out of the doors, I hear him jokingly call after me, "Remember, I want the cover!" Beppe Viale has established himself as on equal terms with oncologists, and wants the world to know it.

Family time. Patrizia, Viale's wife, works as a biologist at the European Institute of Oncology, daughter Giulia (left) is at medical school, while Elena is working to be a script writer