

# Vincenzo Valentini:

## putting knowledge to work

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Patients are being let down by a failure to integrate the knowledge we have to get the best possible results for each individual patient and for cancer patients as a whole. Vincenzo Valentini, the ESTRO president with a talent for maths, believes we must do better.

**T**he paradigm of personalised medicine has ushered in a potentially endless stream of new variables that can predict outcomes and response to treatments – far more than any doctor could hope to manage on their own. While high-quality multidisciplinary working among specialists is essential, it is not enough. New tools and approaches are needed that help oncologists integrate all the relevant knowledge and information to guide their decisions.

A European leader who is on top of this agenda is Vincenzo Valentini, current president of the European Society of Therapeutic Radiation Oncology (ESTRO), and chair of radiotherapy at Gemelli hospital in Rome, which sees more cancer patients than any hospital in Italy and is part

of Università Cattolica del Sacro Cuore.

Not only has he been designing educational computer tools for many years, he is now at the forefront of a movement to introduce decision-support systems that address the daunting complexity facing oncologists. As ESTRO president, he is also driving the society's ambitious vision introduced in 2012 – with education and multidisciplinary at its heart – and is reaching out to other parts of the cancer community in an effort to get a more coherent voice for oncology in Europe.

At the centre of his message is what Valentini calls 'knowledge-based oncology', which, as he explains, is not the same as evidence-based medicine. "Evidence-based oncology takes into account prospective studies on defined populations of patients, and doctors try to apply them to individual

patients on the basis of their understanding of patient features and of the study outcomes, taking for granted that they are uniform. Knowledge-based oncology aims to offer a decision model from heterogeneous data – clinical, biologic, imaging, treatment, demographic – to predict the outcome, and can offer a more transparent and reproducible system.”

The implications of getting this right for oncology are profound, adds Valentini. By 2020 or so he expects that there will be many thousands of variables that will predict survival, whereas the number of variables that doctors can handle on their own can be counted on the fingers of one hand. “So why not use the databases of information we already have in hospitals – imaging, blood, tissue, clinical records and more – to identify the more important predictors of survival and tailor the treatment?”

Such predictive modelling from large databases is one inevitable and challenging part of the future for personalising treatment for patients, says Valentini. It will integrate data on a patient’s clinical features with information derived from continuous monitoring of how the disease is responding to ongoing treatments, which will be adapted accordingly. Data from imaging will be key. “We need to put together variables we are not accustomed to integrating,” he says, pointing to the use of mathematical models such as nomograms – graphical calculators – that help make sense of wide sources of data for decision support.

While there is rapid growth in such tools, we are only at the beginning, says Valentini, who notes that the ‘big picture’ for this could hardly be bigger. The economic challenge of finding more cost-effective ways to deliver high-quality healthcare, as well as the medical challenge of rapidly filling the gaps in translational research and realising the promise of personalised medicine both depend on our ability to integrate large amounts of different types of information. While other branches of medicine are also contributing to the explosion in data, oncology stands out as requiring the data

crunching of a wide range of rapidly growing inputs, from cell biology to patient experience.

That there is a long way to go is also evident from the lack of true multidisciplinary teamwork that could make more sense of complex situations, he notes. This is driven partly by what he sees as a lack of ethics in healthcare. “As a profession we need a clear ethical framework that respects the patient, but this can be diluted by focusing too much, for

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example, on attracting specialist surgeons.” This can lead to cutting costs in other important areas, leading to poorer outcomes overall, he says. For instance, he adds, it is notable that, despite strong evidence, opportunities are being missed to integrate radiotherapy to spare extensive surgery in tumour sites such as head and neck, breast, cervix and prostate.

It was a development in Valentini’s own specialist area of rectal cancer that first convinced him of the need to work in a much more integrated way. “When we saw the first rectal and anal cancer patients who showed no more tumour after chemo-radiotherapy, that set us on the course of thinking about how we could work with other disciplines. We had been giving chemotherapy ourselves, like clinical oncologists do in the UK. We could also see that the surgical approach could change with chemo-radiotherapy. Our experience with imaging and data management put us in a good position to support the first multidisciplinary teams and become care drivers for patients at Gemelli at a time when this was not at all usual in Italy or Europe.” Valentini’s now 17-strong radiotherapy department continues to be the organiser of oncology care, he says.

To promote this more joined-up approach at a wider European level, Valentini is spending a lot of time not just with the top-level networking expected from the president of ESTRO, but also at the front-line of other disciplines, addressing European cancer surgeons and medical oncologists at their respective conferences. He does this, he stresses, in a non-confrontational way, taking a problem-solving learning style he has implemented for ESTRO and his own university hospital, both face-to-face and in particular in computer-based learning.

Understanding the problems faced by other specialists is critical to getting messages across about multidisciplinary working, he believes. “In the 1980s I had the opportunity to do intraoperative radiotherapy, so I could see first hand the difficulties surgeons have in removing tumours and preserving

functionality. We tend to see things from the perspective of our own tools and not how we can integrate with others. I find surgeons are much more receptive if you appreciate the challenging problems they have in things like the risks of bleeding when operating in the pelvic area, when putting the case for radiation to reduce recurrence rates. If you just start by saying, ‘I do organ-sparing radiotherapy,’ you have less chance of being listened to.”

Valentini recently put in a long spell as secretary of the International Society of Intraoperative Radiotherapy (ISIORT) and he has certainly been listened to by ESSO (the European Society of Surgical Oncologists), which has given him honorary membership – “I’m the first non-surgeon it has honoured in this way and it is an acknowledgment that I can speak their language,” he says.

Patients, he adds, are wanting not only cures now but the best quality of life, given that many will live a long time. “We need to be ready to manage the best combination of treatment for them,” he says, noting too that not only is there a mounting challenge of making decisions for so many variables, but there is also little evidence to prove the merits of multidisciplinary working. One paper he cites is on the impact of multidisciplinary team management in head and neck cancer, by a group in Australia. They report that ‘robust evidence’ that shows improvement in outcomes is lacking, leading to scepticism about the multidisciplinary team approach and its costs. Their own findings show a significant increase in survival when multidisciplinary teams are used – but also that a ‘surprisingly high’ proportion of patients are still being managed by a variety of disciplines working independently.

One consequence, says Valentini, is that some patients undergo unnecessarily extensive surgery: there is strong evidence, for example, that radiochemotherapy can cure patients without extensive surgery in cancer of the larynx, leaving patients with less damage to their vocal chords.



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At Gemelli there are some 12 tumour board meetings each week and, significantly, in attendance are imaging professionals trained to work on particular cancers as well as the technology, such as PET/CT, MRI and ultrasound. Valentini cannot stress enough how important imaging is becoming, both in molecular imaging within the best laboratory of all – the human body – and with the sophisticated hybrid radiotherapy and imaging set-ups that allow for repositioning of patients day to day and for movements when therapy is delivered.

He is particularly excited about the potential for ‘radiomics’ – using radiology, including sophisticated CT and MRI scanning, to guide treatment decisions by providing a picture of the cancer’s biology and genomic expressions. As he notes, this sort of imaging has two big advantages over molecular testing from biopsies – it can provide information about the whole tumour and, as it is not invasive, it can be repeated to capture changes in tumour biology in response to treatment and progression of the disease (for more on this Valentini

suggests recent papers on radiomics by Lambin et al. *EJC* 48: 441–446, and on tumour heterogeneity by Gerlinger et al. *NEJM* 366:883–892).

Again this is about adding more information to address the many variables that cancer has in the body, to both improve the chances of correct decisions for using targeted drug therapy and enable doses of radiotherapy to be targeted to areas of tumours that are, for example, more resistant to treatment. “Understanding tumour behaviour using imaging is the frontier and I trust this much more than what we do in the laboratory,” says Valentini, who adds that in a few years’ time we will see considerable advances in the contribution of imaging at the molecular level.

What a new approach to decision support needs is validation, and Valentini is leading a project called VATE – ‘validation of high technology based on large database analysis by learning machine’ – which is using dose distribution data from radiomics along with clinical data and reference databases for outcome prediction. “I refer to this kind of work as

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‘reverse angle’ because we are coming at problems from an opposite direction,” he says.

A typical type of question where more decision support is needed, he says, is in rectal cancer patients, to determine which patients are at high risk and which at low risk of local and metastatic recurrence, so that adjuvant chemotherapy and close follow-up can be given to the right people. Conventional controlled trials have not been able to distinguish those at early risk of an aggressive recurrence from those whose cancer may recur much later. With colleagues he has published just such a model, using nomograms based on data from large European clinical trials. For more on this see *JCO* 29:3163–72 and also [www.predict-cancer.org](http://www.predict-cancer.org), a project at MASTRO Clinic, a radiotherapy centre in Maastricht, Netherlands, which is one of several organisations developing prediction systems, and with which Valentini and others are collaborating. A paper on multifactorial decision making in radiation oncology has recently been accepted by *Nature Reviews Clinical Oncology*, led by Philippe Lambin at MASTRO.

For radiotherapy in early-stage treatment, says Valentini, there is an ongoing process of refining and extending gains that have led to fewer side-effects and better quality of life in rectal, breast, lung, head and neck, and particularly prostate, cancers as newer techniques are able to deliver safer, better-targeted dose volumes. But there is so much more to the field – he picks out a growing interest in treating metastatic disease, including using radio-surgery to consolidate remission after chemotherapy, to remove residual tumour and avoid going to second- and third-line drug treatments.

“We want some patients to avoid always being under treatment and to use a ‘stop and go’ strategy we see now being applied in colon cancer,” he says. An ESTRO forum in April will devote a day-long session to this topic. Giving radiotherapy to older people who cannot tolerate chemotherapy is allied to this, he adds. At Gemelli, there is also provision

for people with advanced disease to stay in the hospital with their families for pain treatment with radiation. “We challenged the view of some doctors who thought it was too much trouble to send patients here and who would instead just escalate their opioid drugs,” says Valentini.

Valentini has spent his entire career at Gemelli and went into radiotherapy at an early stage.



“I wanted to work in a field with a strong relationship with people, and a good place to do that is where they have troubles. Psychiatry is an obvious choice once you are in medicine, but I had a very good mentor in Numa Cellini [a leading Italian radiotherapist], who suggested cancer, and I’ve never looked back. If you have a good mentor you have a good chance of being a good doctor, and what’s more, he was no English speaker and let me be the ‘foreign minister’ for the department.”

He was in post when the first CT machine arrived, and being mathematically minded – maths could have been an alternative career – he worked on one of the first computerised treatment plans for using CT scans, and also developed a data manage-

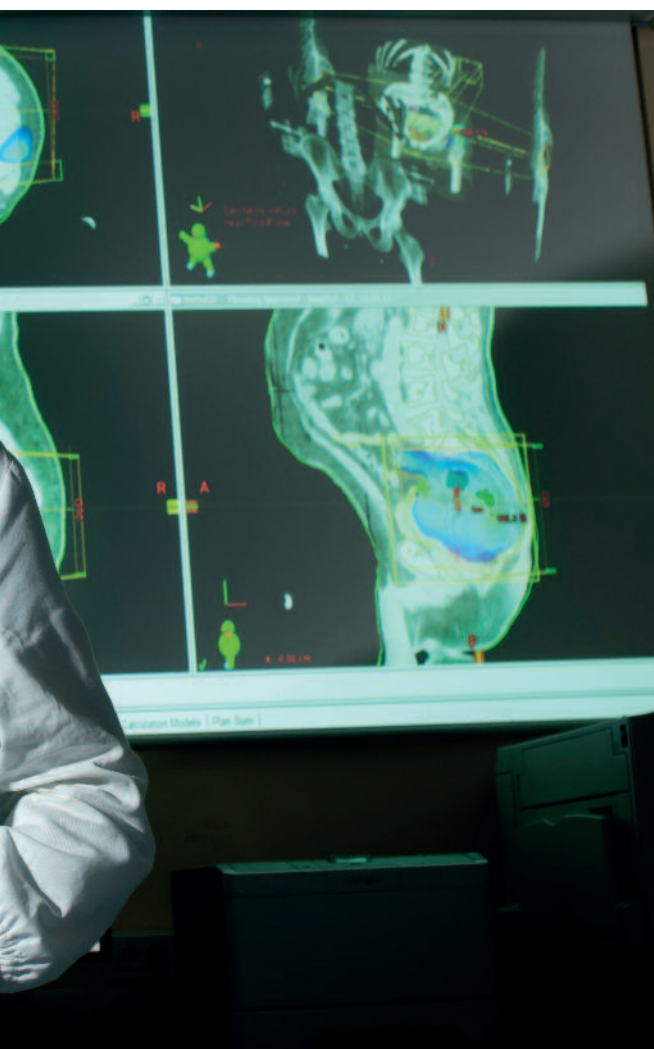
ment system. Out of the computing work also came a strong interest in education, and by the mid-1980s he was instrumental in introducing a computerised learning system for radiotherapy, segmenting knowledge into ‘learning objects’ for use by department staff and students at his medical school.

Valentini has a special interest in medical ‘e-learning’, using problem-solving techniques and tailoring content to specific audiences such as clinicians, technicians and nurses. And it ties in with the large-scale decision-support systems he can see on the horizon, which could use very sophisticated technology such as neural networks.

This e-learning approach is now an important component of the ESTRO educational approach. Valentini is a core member of the education and training committee (chaired by Richard Pötter), and he is chair of Eagle (ESTRO Applications for Global LEarning), which has started online courses for rectal cancer, where more multidisciplinary working is becoming crucial. He has also helped develop Tiger (ESTRO’s educational programme on image guidance) and Falcon (on contouring), as well as new core curricula for the three main radiation oncology professionals – clinicians, physicists and technicians – jointly promoted by ESTRO and the European Board of Radiotherapy of the Union of European Medical Societies.

At ESTRO, he admits the vision he has produced with colleagues is very ambitious. “But you won’t take any steps unless you set your sights high. I feel that we have achieved a much stronger voice in European oncology, thanks in particular to our past president Michael Baumann, who went on to become president of ECCO. We have set our own house in order with activities such as promoting science with our meetings and our educational programmes. Refining our membership strategy will be a priority this year.”

ESTRO’s vision remains focused on improving access to radiotherapy and optimising care for patients in Europe and further afield, through international liaison. The lack of a coherent vision within the broader community of cancer societies, however, remains a worry, and Valentini says he is keen to find effective ways for ESTRO “to drive the priorities and activities for the ‘village of societies’ at the oncopol-icy level,” which he adds is no easy task. “One way we are doing this was to publish the ESTRO vision



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at our strategy meeting at our 30th anniversary meeting – we are challenging the other societies to set out their visions as we have done.”

Of a recent ECCO oncopolity meeting in Brussels, he comments: “It was light and shadows. It met many different perspectives, but with no clear strategy of what we have to prioritise and ask for from the European Commission on behalf of cancer patients and the scientific community.”

He is also keen to invite more people into the ESTRO ‘house’ by working more with the disciplines that are closely allied to radiation oncology, including the societies that represent radiobiologists, medical physics, nuclear medicine and, of course, radiology. As Valentini says, the separation of European radiotherapy from the more numerous and powerful radiologists may have been a necessity to build the speciality of radiation oncology, but closer cooperation is overdue given that there is now a vital role for both in cancer treatment and research. This lies in what is being termed ‘imaging theragnostics’ (of which radiomics is a part) – using imaging knowledge (gnosis) to drive therapeutic choices from planning to treatment to follow-up.

He is pleased to report that a first joint course on multidisciplinary cancer imaging was hosted at his own hospital in October 2012, run by ESTRO and the European School of Radiology (the education arm of the European Society of Radiology).

His aims for ESTRO in the near future include cementing the scientific and educational side of the vision, continuing for example with focused ‘topics of the day’ at meetings. Engaging young professionals is another priority. “We have a task-force that is setting achievement goals for young people over a year and we also run a school for future leaders,” he says. Membership is also an issue for 2013 – “We will introduce block membership for institutions and clarify benefits for the two main classes of members – those who want to buy services and others who want the honour of belonging to a society.”

Online education will be extended, but one product looks to need little change: ESTRO’s journal, *Radiotherapy and Oncology*, has the highest impact of all journals in the sector – well ahead of the US equivalent – thanks to editor Jens Overgaard, says Valentini. He adds that Europe is also more active in clinical trials and is making more advances in radiotherapy practice, although the US does introduce much new technology.

The US has though provided Valentini’s own department with what he considers to be a vital service – quality assurance – thanks to accreditation from the American College of Radiation Oncology (ACRO). “Ten years ago we looked for an external agency to assure our procedures but there were only general industrial bodies in Europe. So we went to ACRO as the first hospital outside of North America for its QA programme. We would of course like to do QA from ESTRO and it has been considered in the past – we may look at it again.” Most radiotherapy units in Europe are not externally accredited, he adds, but many do have good internal quality assurance programmes. “But we do need to formalise this more.”

While it is easier to measure what goes on in radiotherapy than it is in surgery, for instance, and Europeans tend anyway to be very cautious about implementing technology, Valentini says there are clear pressures now in some countries to compromise on support for expensive units. ESTRO, he adds, is continuing to survey national provision with its HERO (Health Economics in Radiation Oncology) project (see also *Cancer World* September–October 2011 for a report on this and other ESTRO activities at the time of its 30th anniversary).

What will be most difficult for his presidency, Valentini agrees, is building consensus in the ‘village’ of European oncology for his vision of ethical, multidisciplinary working that best serves the patient. “But we Romans were good at developing a language of values and a moral and political framework for Europe – and that was without the Internet.” ■