Personalising treatments

how molecular imaging can help

Molecular imaging specialists are ready to break out of their research huddles and take their place at the heart of clinical decision making. But can they convince clinicians to welcome them in? **Anna Wagstaff** investigates.

We're in the age of precision medicine. But to the great majority of people with cancer it still doesn't feel that way. Patients and their doctors trying to decide on the best treatment options are still having to gamble on risk–benefit calculations drawn from very broad patient populations, without the personal prognostic and predictive information they need to tell them what their cancer will and won't respond to or how aggressive the treatment needs to be.

As a result, many are still being overtreated, undertreated, or wrongly treated.

The huge research effort invested in developing personalised medicine is in many ways further confusing the picture.

While new generations of 'targeted therapies' are coming onto the market in a steady stream, few of them come with instructions specifying who will and who won't respond, or how they can best be integrated within existing treatment pathways. Immunotherapies, the latest big hope, seem to work in only two in ten of their target population – more commonly only one in ten.

Doctors and patients accordingly find themselves with more options but little guidance on how to choose between them, what combinations work best, and how to time and sequence moving from one to the next.

Now an offer of help is coming from a surprising source, far from the molecular biology labs that have spawned the genomics, proteomics, metabolomics, transcriptomics and other specialist research fields that have so far dominated the precision medicine scene.

The imaging community – specifically specialists in molecular imaging – believe that they can help find answers to many treatment uncertainties, and they are reaching out to the clinical community to see what can be achieved by working together.

Molecular imagers come from two specialties. Nuclear medicine physicians scan using probes labelled with radioactive isotopes to visualise what is going on inside the body. These are the people who brought us PET scans, which use radioactive tracers to reveal the anatomic distribution of cells with a distinctive biology, such as a high metabolic rate, upregulation of different receptors, or hypoxia – all important information for tailoring cancer treatments. The advent of PET–CT scanners made it possible to combine the biological information from the radiotracers with the anatomical precision of CT scans.

Then there are MRI specialists, who in recent years have been pushing the boundaries of their field to provide biological information based on the behaviour of cells when subjected to different magnetic resonance sequences and techniques. While some of these techniques are so sophisticated they will probably only ever be used in a translational research setting, others, particularly diffusion-weighted MRI, can give information about cell density, cell membrane permeability, and hypoxia which could well play a role in tailoring treatments.

Technological developments over the past 20 years have brought the two specialties together, as Wim Oyen, professor of nuclear medicine and molecular imaging at the Institute of Cancer Research, in London, explains.

"PET comes from biology, MRI from anatomy. There is more and more biology coming into MRI and more and more anatomy coming into PET. So they are coming together and provide complementary information. The good thing is that they are talking to each other and developing the technology that helps us image the patient in the most appropriate way."

Good news indeed. But Oyen is well aware that if molecular imaging is to realise its true potential in improving the quality of patient care, the key conversations will be with the academic clinical community. In his capacity as Congress President of the European Association of Nuclear Medicine, he is leading a major charm offensive.

"We are very actively seeking collaboration with clinical societies," says Oyen. "For our annual congress in Barcelona in October we have invited something like 20 clinical societies for joint symposia and discussions, to get clinicians on board about what we can do, and to get our community on board about what clinicians really want from us."

They are reaching out to the clinical community to see what can be achieved by working together

To make sure everyone gets the message, these discussions will take place under the motto, "Go clinical!"

Oyen is aware that imaging specialists have a bit of an image problem themselves. They've gained a bit of a reputation among clinicians for being so proud of the truly impressive power of their technology that they have lost sight of what doctors and patients really need.

Radiomics – biological information *in vivo*

The ability of PET, CT and MRI techniques to visualise different aspects of tumour biology has spawned a new field of research which explores what information from an image can reveal about the prognosis of a tumour and its likely response to different types of therapy.

While genomic and other approaches that rely on tissue or liquid biopsy provide comprehensive 'snapshots' of biological indicators of cancer, imaging can take this information a step further, showing the activity of these markers *in vivo*, in tumours and the microenvironment, and how their activity changes over time.

Research conducted in the Netherlands and the US, for example, recently demonstrated that radiomic information mined from CT scans of 440 patients with cancers of the lung and head and neck correlated with both genomic information and survival (*Nat Commun* 2014, 5:4006).

Fair comment, he says. "A lot of imaging, I must admit, is done just because you can." In some cases the net impact on patient management has been decidedly questionable.

"They don't want a pretty picture that is nice to look at but has no relevance to patient management"

"When we first started looking at FDG-PET for example, one of the things we noticed was that we picked up a lot of little signals in the colon. We reported it and it turned out to be polyps, and we did it again and again, to a level that the clinicians got annoyed, because they had to do all these colonoscopies for something that is really not a colon cancer. Their patient had a lung cancer that required treatment, yet the treatment was postponed because a colonoscopy had to be done first."

It was all part of a learning curve, says Oyen. Today PET–CT continues to play an important role in selecting patients for lung cancer surgery, but the guidelines for reporting have been refined. Signs of polyps are now flagged up as a minor finding that might merit attention once the lung cancer has been resolved.

Oyen learnt from the experience about the importance of working hand in hand with the clinical community to develop the clinical use of imaging.

"They don't want a pretty picture that is nice to look at but has no relevance to patient management. They are looking for a pretty picture that is obvious for them to assess the information, and has a positive impact on patient management and patient outcomes. And that discussion is something that we have to do together." He says the offer they should make to clinicians is: "This is what we can do: what unmet needs do you have that we may be able to help with?"

This is pretty much the conversation that developed with a group of lymphoma specialists in the early 2000s. It's been such a success that lymphoma is being used as a showcase to raise awareness of what imaging can achieve when it addresses clinical uncertainties in an evidence-based way.

Assessing treatment response

Hodgkin's lymphoma is curable in more than eight out of 10 patients – it was the first cancer to be cured by radiotherapy, back in the 1950s, and the first to be cured by chemotherapy, in the 1960s. But treatments can be debilitating, and come with serious long-term effects – studies have shown that, on average, survivors lose 40% of their 'expected work efficiency' for the rest of their lives. This is a particular problem because the majority are diagnosed before they reach 40, many in their teens or twenties.

Finding ways to limit the damage by giving each patient no more treatment than they really need has therefore been a priority for Hodgkin's specialists, which is one reason why, when the first PET–CT scanners arrived in hospitals in the early 2000s, it was used very early in patients with Hodgkin's.

Martin Hutchings, nuclear medicine physician turned clinician, based at Copenhagen's Rigshospitalet, was among the early pioneers. At the time, says Hutchings, CT scans were the mainstay for staging and for assessing treatment response during and after treatment, but it was often hard to tell whether visible lesions represented active tumours or just scar tissue.

"Thousands of publications looked at the value of PET and PET–CT in staging and interim and end of treatment response assessment, and it was invariably found to have a higher accuracy," says Hutchings. Higher accuracy does not automatically benefit patients, he is quick to point out. Indeed in situations where low-risk disease is already being overtreated, using ever more sensitive techniques can exacerbate the problem. In this particular setting, however, studies showed that some patients do indeed benefit in a number of ways. The higher precision provides a more accurate idea of how far the disease has spread, improving the selection of patients for systemic therapy alone, or combined with radiotherapy (only used for more local disease due to the severity of side effects).

It also gives a better idea of response to treatment, and turns out to be highly prognostic. "When you scan a patient after treatment, the results of the PET–CT says more about the long-term outcome of the patient than the original CT scans did."

Hutchings' own studies, published in 2006, provided the key evidence to show that the results of PET–CT during and after treatment strongly predict for progression-free survival and overall survival. "Using PET–CT early during treatment, if the scan was negative, patients did extremely well – almost 100% long-term progression-free survival, and if it was still positive, they did pretty poorly, 70–80% failed in the first year."

This information is particularly valuable in assessing response at the end of treatment. "You want to know if the patient is in complete response, which means that in many cases the patient is likely to be cured, or whether there is unsatisfactory partial response, which might call for additional treatment or maintenance treatment, or a very close surveillance scheme."

Do no harm. Using PET–CT to guide treatment of Hodgkin's lymphoma helps doctors minimise long-term damage to the health of their patients, many of whom are still young

In 2007 clinical guidelines were revised to incorporate the PET–CT scan after treatment as the key determinant for response assessment. In 2014 they were changed again to include PET–CT as standard of care for staging and the interim assessment as well.

Selecting for surgery

PET–CT has also been proving its value in assessing response to treatment among patients treated with chemoradiation for head and neck cancers that have spread to the neck nodes. Recent results from the UK PET–NECK trial show that complete response on PET scans following chemoradiation is as reliable as surgical dissection for confirming that the nodes are free of cancer.

This is great news, says Vincent Gregoire, a radiation oncologist at the Catholic University of Louvain in Brussels, who specialises in head and neck cancer. Most doctors, he says, have been using either palpation or CT scans to assess response to treatment, but both carry a considerable margin of uncertainty, with the result that many patients have to be referred for lymph node dissection to be certain.

Gregoire compares lymph node CT to looking at a dustbin from the outside and guessing whether it is full of rubbish or not. "PET will tell you," he says. One in five patients in this population need to have their lymph nodes removed after chemoradiation to prevent recurrence. PET can be used to identify those patients, sparing everyone else from surgery they don't need, which, as Gregoire points out, is good for patients and saves money.

It's not a major operation compared to some head and neck surgery, he says, but it requires four days in hospital and patients do pay a price. "The neck will be stiffer with neck node dissection after radiation than without, and

in some patients you may end up with more severe complications, affecting the swallowing function, for example."

Gregoire and his colleagues have been interested for many years in the potential of molecular imaging to better tailor treatments for patients with cancers of the head and neck, since treatment often impacts heavily on long-term quality of life.

Having gone almost as far as they can in tailoring their radiation beams to the three-dimensional contours of an individual tumour, they now want to see how far they can go in tailoring radiotherapy to each tumour's individual biology.

Gregoire mentions three biological parameters in particular: hypoxia can be visualised by PET using, for example, ^{18}F-fluoroazomycin arabinoside (FAZA); high cell density can be visualised using diffusion-weighted MRI; high metabolic rate can be shown by PET using ^{18}F-fluorodeoxyglucose (FDG). All are known to be associated with poorer prognosis, and all are typically distributed unevenly in clusters within a given tumour.

It is yet to be proven whether increasing the dose to areas of the tumour showing these biological properties does in fact benefit patients. This is more likely to be the case in head and neck cancers, where loco-regional control is key, says Gregoire, than for instance in breast, lung or prostate, where metastatic disease is the bigger problem.

Two years ago he applied to the EU research programme, Horizon 2020, to fund a trial that he hopes will show that dose escalation tailored to cell density or to hypoxic cells will improve outcomes. Sadly, he says, it was turned down, so for the moment the protocol is sitting on his hard disc, gathering virtual dust.

Reducing futile treatment

Across the city at another Brussels hospital, another potentially important molecular imaging protocol gathers dust on another hard disc, having also had its Horizon 2020 funding application rejected.

Alain Hendlisz, head of the department of digestive oncology at the Jules Bordet Institute, is leading a study that could help reduce the number of cancer patients needlessly exposed to adjuvant chemotherapy.

For the moment, the trial protocol is sitting on his hard disc, gathering virtual dust

This is a toxic therapy, with potentially long-term effects, that is given following curative surgery, to mop up tumour cells that may be lurking undetected. The great majority of people treated with adjuvant therapies gain no benefit – most would not have suffered a recurrence anyway, while in some the disease recurs despite the therapy because the leftover tumour cells do not respond to the treatment.

Finding ways to refine the selection of patients who really need adjuvant therapy is therefore a major unmet need and has been a big focus for translational research, spawning tools like Mammaprint and Oncotype DX, that use gene signatures to define risk of recurrence.

Hendlisz and his colleagues – who include Martine Piccart who led the MINDACT trials to validate Mammaprint – are now taking a slightly different approach. Before giving adjuvant therapy, they want to use PET–CT scans to check that the cancer is likely to respond.

The proposed trial is in patients with stage III colorectal cancer, for whom adjuvant therapy with the FOLFOX cocktail of cytotoxics is the standard of care. The idea is to administer one cycle of FOLFOX before the tumour is surgically removed, and then examine the response by comparing PET–CT scans taken before and after the chemotherapy.

Results from the PePiTA trial (Preoperative chemosensitivity testing as Predictor of Treatment benefit in Adjuvant stage III colon cancer), led by Hendlisz, suggest that selecting patients for adjuvant FOLFOX based on their PET response may decrease the proportion of patients given adjuvant therapy by 40–50% without increasing recurrence rates. But this now needs to be validated in a larger and longer trial – and that is where the funding problems kick in.

Building the evidence

As a leading figure in the community, Wim Oyen is all too aware of how many small exploratory studies have shown potential for helping personalise treatments, but have never broken out of the research setting into the clinic.

He accepts that the problem is not just funding, it's also about attitudes and awareness. Imagers need to recognise that clinicians want strong evidence that a given technique will improve patient outcomes.

"I am now pushing in the nuclear imaging community that we stop entertaining ourselves and convincing ourselves that we have such great innovative imaging techniques, but fail to take the final step into actual

widespread clinical use because the evidence falls short of what clinicians accept as evidence."

He points out that the settings where molecular imaging has really caught on – such as lymphoma, head and neck cancer, and also lung cancer – are where "trials were done in a way that oncologists accepted."

Clinicians, on their side, need to be more aware of the potential of imaging to help personalise treatment, says Oyen, and should do their best to integrate molecular imaging, alongside for instance immunohistochemical and genetic biomarkers, when developing new treatment strategies.

It can be very frustrating, he says, when opportunities to generate this evidence are missed. He cites the example of oesophageal cancer, where a series of trials done at the Technical University Hospital in Munich had shown that early use of PET–CT to assess response to neoadjuvant chemotherapy benefited patients, allowing those who didn't respond to move straight to surgery, thereby saving them from unnecessary delays and toxicity.

"Clinicians should do their best to integrate molecular imaging when developing new treatment strategies"

So far so good, but the standard of care then changed to chemoradiation. However, the trials comparing the two treatments failed to address the question of who benefits, and whether PET–CT could be used in the same way to identify patients who derive no benefit from this even more toxic neoadjuvant therapy, and would do better moving straight to surgery. We'll need a new trial to find out, says Oyen, but he can't see that happening anytime soon. "If the imaging had been in that original trial, you would have had the answer."

He understands that the cost – and complexity – of including imaging in such trials can be intimidating, but as he points out, investing in techniques to personalise cancer treatment not only benefits patients but saves money in the long run. It reduces the direct costs of unnecessary treatment, and by avoiding unnecessary long-term damage to the health, function and quality of life of survivors, it will yield much greater savings from health and social care budgets, while boosting tax receipts.

The question is, who will pay?

Funding research

Some countries are making some public money available for these sorts of studies. The PET–NECK trial, for instance, which showed PET–CT response monitoring can reduce the unnecessary use of neck dissection, was funded by the UK's National Institute for Health Research.

It included a cost-effectiveness analysis, which showed that, over the two-year minimum follow-up period, the per-person cost saving was £1492 (€1900) per person (*NEJM* 2016, 374:1444–54).

In Belgium, however, Gregoire claims that public funding for such studies is increasingly hard to come by. "We have a lot of difficulties in convincing the payers." The typical response from funding agencies, he says, is that this sort of imaging is commonly carried out, "so we shouldn't need funding, because it will be paid by health insurance or whatever."

While that may have been true a few years ago, says Gregoire, nowadays payers won't cover imaging unless it is in use as a routine part of standard care.

Hutchings reports that some of his European colleagues face similar

False economy?

Surgical dissection of neck lymph nodes can affect patients' range of movement and their ability to swallow.

A UK study, funded by public money, found that PET–CT helps avoid unnecessary neck surgery in patients with squamous cell cancers of the head and neck, while at the same time saving almost €2000 per patient within two years *(NEJM* 2016, 374:1444–54).

Many other studies to confirm the value of molecular imaging in guiding treatment decisions are being held up because they can't get funding.

problems "Even in rich countries like Germany, access to PET–CT has been very difficult, I know it's been really difficult both for the German Hodgkin's Study Group and also for the non-Hodgkin's study groups to build trials where PET–CT was part of the trial. They really have to negotiate every single scan, because it's not something that the health insurance agencies naturally pay for. And that's increasingly the way things are going."

"They really have to negotiate every scan, because it's not something insurances naturally pay for"

It is, of course, right and proper that healthcare budgets should not routinely pay for scans whose clinical value has yet to be demonstrated. However, sustainable health systems do need mechanisms to fund trials that could lead to better outcomes and lower costs, which is part of a wider conversation about promoting innovation.

A priority for Oyen, meanwhile, is to ensure that imaging studies are built into the development of all new treatments, so that by the time new drugs come to market, or new therapeutic strategies are adopted, the role that imaging may be able to play in defining who should receive the treatment and when is clear.

"The moment you know a drug is going to be developed, and you know you have something of a signal from molecular imaging, then you should run molecular imaging, not as a side study, which is usually underpowered, but as part of the main protocol, and run it in a way that you enrich the patient population that will benefit from your drug.

"I'm strongly advocating that we start doing research from day 1, to be in a position to identify these molecular imaging biomarkers, because when a drug comes to market it is too late, nothing will change anymore."

He emphasises that he is not trying set up molecular imaging biomarkers as some sort of competition to other types of biomarker that are more commonly investigated in early trials.

"I am totally agnostic about which type of biomarker. If a liquid biopsy is doing the job, that is fine. But so far, the discussion I've seen starts with an indication that something is happening, and then the next question is 'Where is it?' and then you need imaging again. So if a patient with a prostate cancer has a rising PSA, something seems not right, but is it in his prostate, or his lymph nodes or bones?"

The plea he makes is for "a more open mind" towards what genetics and immunohistochemistry can offer in combination with imaging. "I would like nothing more than if we could use, for example, liquid biopsies to preselect the patients on whom we have the most impact on management when we put them through imaging."

Key to moving forward will be convincing the EMA and FDA, the European and US regulators, to acknowledge imaging biomarkers – which is a conversation he and his fellow members on the board of the European Association of Nuclear Medicine are actively engaged in.

He says that being expected to generate the same level of evidence as some of the lab-based biomarkers is hard, because they do not have huge numbers of patients. "We'll have to do smart trials, with smart designs to get the answers."

There is also the question about whether companies are prepared to invest the additional time and money to do these studies.

This too is part of a wider conversation about whether there may be better ways for public and private sectors to work together to deliver personalised medicine, which the current business models seem unsuited for.

The challenge for Oyen and his colleagues is to ensure that the role molecular imaging can play in finding solutions features as an integral part of these conversations.

The plea he makes is for 'a more open mind' towards what genetics and immuno-histochemistry can offer in combination with imaging

That has to start by convincing clinicians that molecular imaging can help them with the specific uncertainties they face in tailoring treatments to patients. He is hoping that his overtures to the clinical community at the forthcoming EANM congress, combined with his exhortation to the imaging community to "Go clinical!" will be a step in the right direction.