

We hit the spot

The new techniques that could bring interventional radiologists to the multidisciplinary table

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Less invasive than surgery and less toxic than systemic therapy, will the fast-growing specialty of interventional radiology join the ‘big three’ as the fourth pillar of cancer care?

Looking at the specialists in the front-line of oncology, the ‘big three’ of surgeon, medical oncologist and radiotherapist are the dominant forces, and rightly so, as the recognised clinicians in cancer treatment. But other medical disciplines that work alongside them are also increasing their impact on clinical care, none more so than interventional radiologists, who not only are very active now in oncology but are also staking a claim to being among the leaders in new developments – and indeed the ‘fourth pillar’ of cancer care.

Radiology is most associated with diagnostic procedures that use the array of imaging techniques to examine

the body’s anatomical structures. But in the past few decades radiologists have also pioneered minimally invasive techniques that are now widely used in clinical practice, such as angioplasty and stents used to open blocked arteries, and embolisation for bleeding. Radiologists invented these procedures because they are imaging specialists, and image guidance is often needed to place devices such as catheters, needles, probes and stents. So successful have they been that some other specialists, such as cardiologists and neurosurgeons, now ‘own’ the techniques in their fields.

This doesn’t worry Brian Stedman, consultant radiologist at Southampton

University Hospitals NHS Trust, UK. “My feeling is that interventional radiology is in the front wave of medical technology – we often develop techniques that other specialities take on, such as angioplasty for heart disease and vascular treatments for aneurysms such as carotid and leg stenting, which have taken over from surgery. So surgeons have now trained in these, taken the workload off us and gone on to further develop the procedures. Meanwhile we will go on developing new techniques, some of which will stay in radiology because of their complexity or rarity.”

One major field where radiologists are now making their mark is oncology,

CT-guided biopsy. With the help of images taken approximately every second, this interventional radiologist can guide the needle to a precise target located deep in the patient's abdomen



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says Stedman. He himself is a specialist in abdominal radiology and a clinical lead for cancer services in his area, and he recently made the news for carrying out the UK's first 'chemo-bath' of the liver for two patients with metastatic melanoma of the eye.

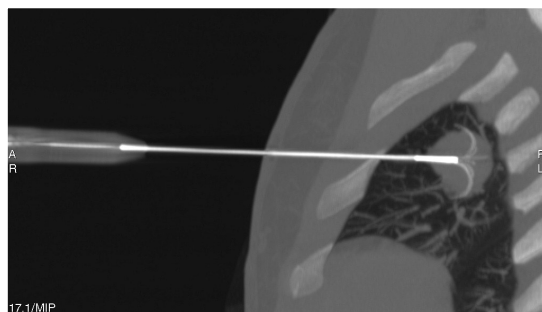
This technique – which isolates the liver for a short period during which chemotherapy is delivered directly to the organ – is not likely to be widespread given the rarity of both the tu-

mour and the expertise needed to carry it out. But for Stedman it points to a key concept in the delivery of drugs. "I think in 20 or so years' time we may look back and see giving systemic chemotherapy as odd. Why inject drugs into a vein for the whole body when you want an effect only in one organ such as the lung, kidney or brain?"

Liver perfusion is just one of many techniques that now make up interventional oncology – a field which,

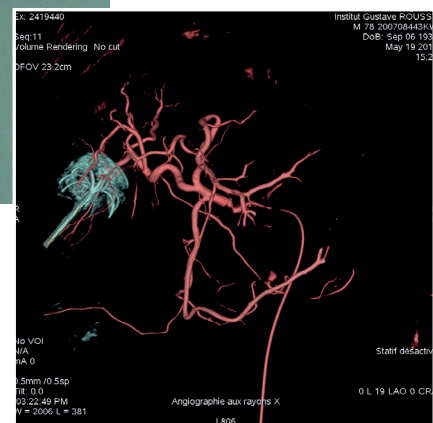
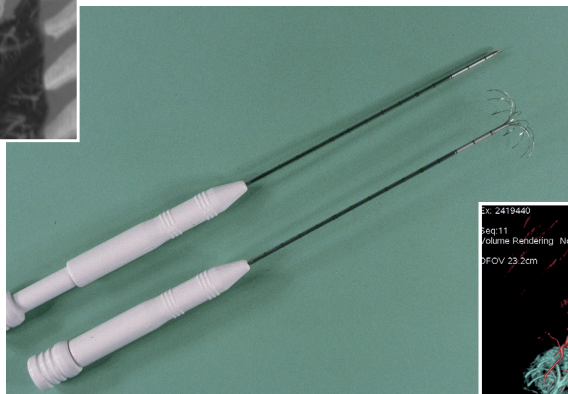
according to Andy Adam, professor of interventional radiology at the University of London (the first such position in Europe), is probably the fastest growing part of his specialty. Adam, who is based at London's Guy's and St Thomas' Hospital, and has been president of the European Society of Radiology among other posts, explains that the early applications of interventional oncology were in supportive and palliative care, and included for

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Radiofrequency ablation needles (centre) are inserted into the tumour in a retracted position, and can then be opened up to deliver a radiofrequency current to multiple locations. The upper image shows this procedure being carried out in the right upper lobe of the lung. The lower image is a 3D-reconstruction of combined therapy to a

hepatocellular carcinoma – the blue colour shows tumour uptake of drug and contrast agent lipiodol, the red denotes the hepatic arterial tree



instance applying stents in the biliary tree for obstructive jaundice. “Such procedures have made a huge difference to people’s lives – a stent in the oesophagus can allow someone to eat, for example,” he says. Embolising neuroendocrine tumours – cutting off their blood supply – addressed symptoms such as severe flushing and diarrhoea that made patients’ lives miserable, he adds, and the effects, though short lived, were real. “Then drugs made this redundant – but it paved the way for new vascular procedures.”

Radiologists have also long performed biopsies where it is necessary to place a needle very accurately to take a sample, says Adam, and it is by extending the various techniques to curative settings that interventional radiology is now making its name in oncology. The basic idea is that radiologists can guide a needle or probe to almost any part of the body and then carry out local treatment directly to a tumour or its blood supply.

The two main treatment types in interventional oncology currently fall under the umbrellas of ablation and embolisation. Ablation of tumours is probably the most rapidly growing treatment area. Using energy such as radiofrequency and microwave, or freezing (cryo-ablation), radiologists guide probes directly into the tumour to deliver cell-killing treatment.

Embolisation also has several techniques – on its own, a radiologist can place a catheter in a tumour’s blood

supply and release embolic agents to block the blood flow. But there is also chemo-embolisation, which combines embolic agents with chemotherapy, and radio-embolisation, which adds radioactive beads to help kill tumours.

There are plenty of variations and other techniques that are attracting attention, such as high-intensity focused ultrasound (HIFU), an ablation method being trialled in prostate cancer; irreversible electroporation, an ablation technique using bursts of electricity that avoids heat damage to surrounding tissue; a technique that uses ultrasound to break up bubbles that release drugs; and the liver chemo-bath, which is more properly known as chemo-saturation or percutaneous hepatic perfusion.

But most of these procedures are recent and still in development. The challenge now is to generate an evidence base for interventional oncology, and for this growing field to find its way into mainstream practice. So far, procedures that are widely carried out are mainly limited to small tumours where the disease is not widespread – typically no more than three tumours <3 cm – in particular in the liver, kidney and lung.

A place in the mainstream?

Interventional radiologists are essentially acting as alternatives to surgeons – they aim to remove or reduce visible tumours. While taking on palliative care is a large part of their practice, they can also be involved in early-stage treatment, where multidisciplinary discussions are required. As with any expanding area of oncology, there are also key questions about combining treatments with other therapies such as radiation and drugs. It’s a challenging agenda, especially as there are not many interventional radiologists practising exclusively in oncology in Europe, and the field is fragmented. There are pockets of excellence, mainly at cancer centres and large teaching hospitals, but they often take different approaches to the same techniques, which makes comparisons difficult.

One practitioner who has helped to put interventional oncology on the map

De Baere expects to see radiofrequency ablation increasingly included in guidelines for small tumours

in France and elsewhere is Thierry De Baere, who is based at the country's largest cancer centre, Institut Gustave Roussy (IGR). He is head of an interventional radiology department dedicated to oncology – one of the few in Europe – and was originally trained as a radiologist, joining IGR 20 years ago.

“When I joined most practice was palliative care such as biliary and urinary stenting and embolisation, but a milestone was the first radiofrequency percutaneous ablation, which made us part of treatments with a curative intent. It was a key change because oncologists looked at our practice and saw that we could be involved not only with end-stage care.”

De Baere says radiofrequency ablation is now a standard option in the treatment of localised liver cancer (hepatocellular carcinoma) – the latest clinical practice guidelines from EORTC/European Association for the Study of the Liver (EASL) note that radiofrequency ablation can achieve greater than 90% complete response in small early-stage tumours, and the same is true also of another technique, injecting alcohol (ethanol) directly into these small tumours, which is particularly popular in the Far East in countries such as China and Japan. Both techniques can also be used in patients for whom surgery is not an option.

De Baere expects to see radiofrequency ablation increasingly included in guidelines for small tumours in other cancers. “For example, in renal cancer the first option is surgery, but there is a subgroup where there is a borderline situation for surgery and for whom there is a high success rate for

ablation. We are also treating metastatic disease as well of course, and there is a sort of competition between surgery and radiofrequency ablation for small lung metastases of less than two centimetres.”

Building the evidence

Much of the work is fairly new, with a flurry of activity in the past three to four years, adds De Baere. The next milestone is to provide more evidence that radiofrequency ablation really is as good as surgery, or at least very close to it, for small tumours. There are randomised trials that compare radiofrequency ablation with surgery in hepatocellular carcinoma, which have demonstrated no significant difference in overall and disease-free survival (and given ablation's less invasive nature it is the preferred first-line option in some centres). But there are no such studies yet in lung or kidney cancer and, as he notes, it is difficult to randomise patients, given the high volume needed, although various centres have tried to embark on these comparisons.

“Cohort studies and registry databases will give some lead on survival outcomes, but in any case the situation is not very different from surgery – there are no randomised studies that show surgery is better than something else,” says De Baere.

Adam adds that while the evidence in hepatocellular carcinoma is excellent, no one knows yet whether interventional techniques are actually better than surgery. He also notes another barrier to randomising patients – they will often prefer the far less invasive nature of interventional radiology. “The

choice could be between a simple one-hour procedure or a major operation with a hospital stay that could end up with someone losing a kidney and going into dialysis.”

In kidney cancer, he says, oncologists are now also referring patients with small tumours for radiological removal rather than adopting a ‘watchful waiting’ approach, given that, although smaller ones are usually relatively benign, they can metastasise if they grow.

Interventional technology is moving much faster than the evidence base, says Stedman. “Our probes used to be limited to the small area of damage they could cause. Now with modern technology such as microwave equipment and cryo-ablation we can kill quickly a bigger lump of tissue under image guidance. If a patient has four or five tumours in the liver, kidney or lung we can now treat them in one sitting – 10 years ago to kill one kidney tumour of 3–4 cm, it took a lot of probes and skill to get it right.”

Stedman agrees that good evidence is building for ablation of kidney tumours, and that the debate is moving to whether interventional procedures should be preferred as a first-line option. One key study he mentions, which is ongoing and could substantially raise the profile of interventional oncology, is FOXFIRE, a UK multicentre comparison of adding radio-embolisation to chemotherapy to treat colorectal cancer that has spread to the liver. (An international version of the trial is SIRFLOX, which includes patients in the US, and which has now closed.)

“This is a Formula One race in

oncology, as metastatic colorectal cancer is where many drug companies are eager to gain a foothold. The response rate of first-line chemotherapy has improved but, if radio-embolisation is effective as an addition, it will be a step-change in how interventional radiology is seen. It would be a big example in the front-line delivery of treatment for a common disease.”

This pivotal multicentre trial uses technology called Sir-Spheres, from Australian company SIRTex. These are microspheres labelled with yttrium-90 that are injected into the hepatic artery, which then lodge in the tumours’ vascular structures. Only centres with expert interventional radiologists can participate. Earlier studies have shown the effectiveness of just a single injection of the radioactive spheres.

As Stedman adds, the liver has the important feature of having two blood supplies, the hepatic artery and the portal vein, and normal liver tissue is supplied mostly from the portal vein, allowing agents to reach tumours through the arterial supply. This is also how the chemo-bath procedure he has carried out works.

“There have been no great treatment options for ocular melanoma that has spread to the liver – it is resistant to systemic chemotherapy, and surgical attempts to put clamps round the liver and then apply drugs are very invasive and do not work well. Now by placing balloon catheters above and below the liver to block the venous supply we can pour whatever we want into the hepatic artery without it being systemic.”

The agent used in this case is actually a mustard gas derivative (melphalan), which at the high doses administered would be highly toxic in the rest of the body, but attacks only melanoma metastases in all parts of the cell cycle and kills them, without affecting the normal liver. Stedman says the treat-

ment lasts about an hour, and the blood leaving the liver is directed outside the body and cleaned and put back into circulation via the jugular vein.

Commenting on the procedure, Peter Naredi, chair of surgery and a liver specialist at Sahlgrenska University Hospital in Gothenburg, Sweden, says: “Isolated liver perfusion for melanoma is something we started 20 years ago, and we are the referral hospital for Sweden. But we do the procedure as open surgery – interventional radiology is promising but has yet to prove it can replace open surgery. And I would instead choose liver embolisation with yttrium spheres as more innovative.”

A company named Delcath is marketing the liver chemo-bath system. While it does at present have only limited use in a small population of ocular melanoma patients, it could be applied in other cancers such as colon and breast. Stedman agrees it is not yet a ‘finished product’. It is also a complex technology requiring a high level of skill to place three catheters guided by X-ray fluoroscopy and administer the treatment. And as De Baere points out, technical complexity is a barrier to developing the field. “The reason radiofrequency ablation has become widely used is because you just need ultrasound to guide it,” he says.

Cost is also an issue, he adds, with expensive new technologies that may not find ready reimbursement by health systems in some countries. “We need to say to providers that paying for, say, radiofrequency ablation in kidney cancer means you can save money because you are not also paying for surgery.” Although much interventional oncology has been pioneered in Europe, superior reimbursement has meant the US is now generating about half of developments.

Adam also sounds a note of caution about pushing too quickly for new technology and procedures, as there

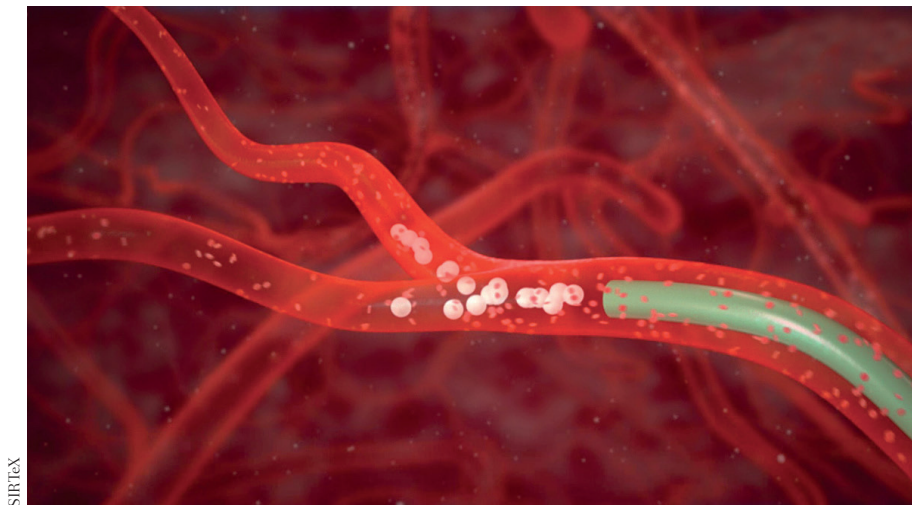
are not yet enough interventional radiologists with oncology expertise. “You cannot approach oncology as a technician – you have to spend time with patients discussing the options and following up your procedures. You can’t delegate this to others as they won’t have the knowledge about problems with treatments. You have to be a proper clinician like other oncologists.”

At the radiology/oncology interface

The main pathway into interventional radiology is from radiology itself, although there are some who transfer from surgery – Stedman for example – and some surgeons predominantly carry out interventional procedures. The workload for many in interventional radiology can be immense, and a big distraction from developing oncology interests. They are much in demand, for instance, in hospitals with emergency departments, while even in large teaching establishments such as his own, Adam says he cannot attend all the tumour board meetings he would like to, and has to prioritise where he feels the interventionalist’s voice is most needed to discuss treatment options. “I don’t attend kidney meetings now, because we have that well covered,” he says.

Stedman is a rarity – he is the clinical lead for the regional cancer network, a post historically held by surgeons, and he says others find it odd to have a radiologist in charge. “It’s a sign that interventional oncology is at the frontline of treatment.” It is logical to have radiologists playing a central role, he says. “When patients come into our network the imaging interactions are often the most important part of the pathway, with questions such as: is the tumour resectable? or is there another technology we can use for treatment?”

But he is not actually part of oncology, which can be problematic. “Some



SIRTEX

Blockade. These tiny radioactive spheres target the tumour to deliver local radiation therapy; trials are ongoing to see how effective they are used in combination with chemotherapy for treating liver metastases from colorectal cancer

patients are managed by me, some by oncology – but I don't have junior staff and a lot of oncologists don't know about the techniques or potential complications."

At IGR, De Baere's department does have three full-time staff, with another coming, plus two fellows. But the workload is going up by double digits each year – more than 3000 patients were seen by his team last year, many for biopsies as the demand for personalised testing for new biomarkers mushrooms (biopsies went up by 60% last year alone, he says).

Collaboration with oncology is clearly essential, and De Baere says that, because interventional oncology is limited to small tumours at present, this has restricted impact at the multidisciplinary table. He notes that medical oncologists are particularly receptive, because of the ability to down-

stage and treat people several times, helping also to give patients 'chemo holidays' from systemic drugs.

"But with surgeons we can be treating the same population and they need to accept that they don't need to operate on some small tumours – attitudes do vary by centre." Perhaps the most challenging partnership is with radiation oncologists, as there is again crossover with potential treatments such as brachytherapy, and there could be combined approaches. "This is a difficult field," says De Baere.

There are various local, national and international curricula and training programmes in interventional radiology, such as the European Interventional Syllabus from the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), which has also established the annual European Conference on Interventional

Oncology (ECIO), which will convene for the fourth time in June in Budapest, and has Adam and De Baere on its advisory board.

A key role for both CIRSE and ECIO is to look objectively at shortcomings in the evidence base, expand the curriculum, and network with other disciplines such as European radiation oncologists. "We have also set up a multidisciplinary committee with experts such as Liz Kenny, a radiation oncologist from Australia [based at the Royal Brisbane and Women's Hospital], who is a world expert on cancer services," says Adam. "We are not the fourth pillar of oncology yet – our disadvantage is we sit in radiology and it is hard for us to be heard. But our advantage is that we have highly effective procedures that are much less traumatic. We deserve to be there but it will take time."

And Kenny herself adds: "I think it is essential to have interventional oncology as the fourth pillar of cancer care. The potential to do good is high. To have this accepted, however, we need quality outcome data on patient benefit, including quality of life and costs associated with treatment. Interventional oncologists should also work within multidisciplinary teams and they need to develop a good understanding of the natural history of the cancers that they are involved with.

"With an evidence base, interventional oncology techniques are more likely to be incorporated into national and international guidelines and become mainstream options for people with cancer. But if its use is indiscriminate it runs the risk of falling into disrepute and this would be a tragedy." ■

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