Andreas Grüntzig’s beginnings started in peripheral arteries

Perhaps young cardiologists are not familiar with the fact that coronary balloon catheterization was developed by Andreas Grüntzig in peripheral arteries before he dared to apply this tool to the coronary arteries.

In 1964 the radiologists Charles Dotter and Melvine Judkins of Portland, Oregon, published in Circulation a new method to recanalize obstructed peripheral arteries by means of catheters.¹ They used telescoped angiographic catheters of increasing diameter to dilate the vessels. This technique was not readily accepted in the USA but, instead, produced the name ‘Mad Dotter’ for its inventor.

Notwithstanding the name, there were some other pioneers such as Eberhard Zeitler, a radiologist who stayed with the method in Germany and Andreas Grüntzig, a young German who enthusiastically picked up the technique from Zeitler. Grüntzig worked from 1973 to 1980 at the University Hospital of Zurich, initially in the angiology department of Alfred Bollinger.

Grüntzig quickly noticed the great disadvantage of the Dotter method. Because the entry puncture in the arterial wall equalled the desired diameter of the arterial lumen to be dilated, the catheters made a very large hole, or with a smaller entry, dilated the arterial lumen insufficiently. To avoid this, the idea of a balloon catheter was in the air. The very elastic softer Fogarty catheter was unsuitable for the purpose of compressing the plaque material (as was the proposed working hypothesis at the time), and carried a risk of disrupting the vessel wall at higher pressures.

The close proximity of the Swiss Federal Institute of Technology (ETH) in Zurich to the university hospital provided the solution, in the form of a so-called racked PVC polymer tube, having minimal compliance to high pressures. The only problem was to mount this material on a catheter.

Now comes the famous ‘kitchen table story.’² Grüntzig’s skilled lab technician Maria Schlumpf and her husband glued the narrow tubes of 4–5 mm diameter and 40 mm length to the top of a ‘Red Oedman’ catheter in Grüntzig’s little kitchen during the night hours. Through side holes the balloon could be filled with contrast fluid under high pressure, while the opening at the end was occluded by a guide wire with a metal olive at its tip. These prototypes were sterilized and successfully used on the first patients in 1974.

Grüntzig sought a professional producer for his instruments and found a small manufacturer of laboratory instruments operated by Hugo Schneider, who quickly made the peripheral balloon catheters commercially available. The author had the opportunity to work with Grüntzig during this crucial phase.

All patients were carefully examined non-invasively before and after the intervention, and followed during the years by Maria Schlumpf. Grüntzig had previously worked with the Life Table method at the Institute for Epidemiology at Heidelberg University, Germany, and so he introduced this method for the analysis of patency rates over time into the medical literature, a statistical method which is in common use today.

The results, which were presented at many vascular meetings in that manner, soon convinced other groups and led to a rapid breakthrough, even though harsh resistance arose from many vascular
surgeons. Figure 1 shows the three pioneers Dotter, Zeitler, and Grünzig together at a meeting in Nuremberg in 1978. The results of around 150 patients with peripheral arterial disease treated by Grünzig were summarized in his 1977 Habilitationsschrift (Figure 2).

Indications for the now so-called percutaneous transluminal angioplasty were initially short isolated stenotic lesions in the femoral and iliac arteries, which sometimes included even total occlusions in claudicants. The 95% primary success rates in the iliac arteries exceeded those in the femorals of 85%. Also, the 90% patency results at 1-year follow-up in the iliac arteries of the initially successful cases exceeded those in the femorals of 75%. Interestingly, the reduced patency occurred mainly during the first 6 months of follow-up and was not due to progression of atherosclerosis but to neo-intimal hyperplasia. More severe stages of peripheral arterial disease and longer or complicated lesions were rarely attempted and had inferior results. Today, any lesion can be approached percutaneously.

From 1975 onwards, in addition to work on peripheral arteries, Grünzig was working on the miniaturization of his equipment for the coronaries, initially in dogs. He presented his experimental results in Germany and the USA in 1976, substantiating them by robust statistical data from his peripheral work before he could triumph with his first human coronary results. The forecast of Dotter and Judkins that the carotid, renal, vertebral, and coronary arteries would be amenable to catheter intervention became reality. The further development of wires and catheters for almost every vascular region in the human body and stents and stent grafts, led to the revolution of vascular treatment we encounter today.

However, the experimental ground and clinical experience lay not in the delicate arteries of the heart, but in the larger vessels of the periphery.

Developments in the treatment of aortic aneurysms in 2014

Since the introduction of EndoVascular Aortic Repair (EVAR) for the treatment of abdominal aortic aneurysms (AAA) more than 20 years ago,1–3 the technique has evolved rapidly, from tubular grafts for fairly simple abdominal aortic anatomy, to bifurcated, fenestrated, branched, or parallel grafts for complex aortic aneurysms, no longer confined to the infrarenal abdominal aorta.

Not only technological but also material improvements have taken place during the last two decades, including smaller sized sheaths that need to enter the femoral artery and the advent of vessel closure devices. Such advances have brought about the development of complete percutaneous techniques to repair aortic aneurysms. This, in turn, has transformed EVAR into a procedure that can sometimes be performed as an outpatient operation.4

Already during the 1990s, endovascular tube grafts were demonstrated to be an applicable and successful means for the exclusion of descending aortic aneurysms.5 With modern technical solutions, EVAR has moved from the abdomen proximally to the thoracic aorta, enabling endovascular treatment of complex thoraco-abdominal pathologies. If the patient cannot be completely managed endovascularly, methods that combine endovascular and open techniques, hybrid procedures, have made possible the treatment of pathologies that would otherwise have required major open surgical procedures. In addition, patients previously deemed unfit for open surgery can now frequently be offered aneurysm repair by way of these less-invasive operations.

There is a wide spectrum of topics in the research field on aortic aneurysms and on methodological development. Many advances have been made during the last few years and reported or refined during 2014, particularly concerning image processing and reconstruction, and stent graft design. Moreover, EVAR simulation training, AAA screening and a randomized trial on repair strategy for ruptured AAA are additional subjects that attracted attention during the last year.

To reduce the radiation exposure and contrast load used for EVAR, image fusion and patient-specific rehearsal (PRS) have been shown to be very promising tools in 2014.6–8 However, computer-based simulation cannot yet be used for thoraco-abdominal or aortic arch aneurysm repair, as visceral aortic branches or aortic arch branches have not been completely incorporated into the software.

Figure 1 The clear clinical trend towards more endovascular procedures is reflected by a predominance of scientific publications on endovascular procedures in abdominal and thoracic aortic aneurysm treatment.
There is not only a change in favour of EVAR for simple thoracic or AAAs (Figure 1), but a growing number of patients with pathology of the aortic arch and/or the visceral aorta are nowadays also treated endovascularly. For such procedures dedicated endovascular grafts with fenestration(s) and/or branches for maintenance of aortic side-branch perfusion are used (Figure 2).

One of the most challenging and time-consuming phases of such procedures is the cannulation of the aortic side-branches and the introduction and deployment of the bridging stents or stent grafts—depending on whether a bare metal or covered stent is considered favourable in the particular situation. To face such difficulties, improved steering and navigation tools are required. In 2014, impressive and excellent experience in aortic arch and visceral aorta branches, as well as in pelvic branches was reported with the Magellan robotic system. This represents a major technical improvement.

In addition, a very promising innovation and potential game-changer in vascular surgery, a novel electromagnetic steering system for catheters, has been developed for ablation procedures (Figure 3). That device might be integrated into regular hybrid operating theatres or catheter labs in the near future.

Nearly 60% of all patients treated for AAA in Sweden in 2013 underwent EVAR. In elective repair, 649 of 1019 (64%) patients had endovascular repair, whereas in ruptured AAA the share was lower, 103/264 (39%). This may in part be due to the lack of a 24/7 on-call service for endovascular procedures in some hospitals. A similar trend has been observed in Switzerland. Even though elective EVAR is a fairly safe procedure, one should also keep in mind that the outcome of elective open repair has improved over time. In an attempt to further reduce aneurysm-related mortality, a regional screening programme was instituted in Sweden in 2006, and at present 95% of all Swedish 65-year-old men are invited to screening by way of ultrasound. A recent report demonstrated very low post-operative mortality after AAA repair in patients with screening-detected aneurysms.

In ruptured AAA, the option to carry out a less-invasive procedure under local anaesthesia would speak in favour of EVAR. However, EVAR requires preoperative imaging, and compliance with anatomical criteria, at least in centres that do not treat patients with complex aneurysms endovascularly. Until recently, branched and fenestrated stent grafts have had to be custom-made and thus

Figure 2 Patient treated with Nexus (Endospan) branched and fenestrated graft for symptomatic ductus botalli aneurysm. Additional left carotid-to-left subclavian artery bypass was performed to maintain antegrade flow to the left vertebral artery.

Figure 3 New electromagnetic steering system for human use that will soon be ready for clinical utilization.
ordered in advance. Off-the-shelf devices have been introduced during the last few years, with the potential to enable acute endovascular treatment of complex juxta- and suprarenal aneurysms or even thoracoabdominal aneurysms. In some centres, the ambition to treat most patients with ruptured AAA by way of EVAR has entailed more frequent use of parallel grafts for preservation of flow to the reno-visceral arteries in complex aneurysms. Using this method, an observational study from Zurich, Switzerland, and Örebro, Sweden, demonstrated excellent results.\(^1\)

In 2014, 30-day outcome of the Immediate Management of Patients with Rupture: Open Versus Endovascular Repair (IMPROVE) trial was published.\(^1\) The objective was to assess whether an EVAR strategy (in suitable anatomy) would reduce early mortality in patients with suspected ruptured AAA compared with open repair. It was designed as a randomized trial. In the primary outcome of 30-day mortality, no difference between the groups was reported. In sub-group analysis, women were found to benefit more from an EVAR strategy, due to high mortality in the open repair group among women. Moreover, more patients in the EVAR group were discharged directly to home. Many questions remain unanswered, such as if there are any differences between the two groups in the long run, and if that would infer any cost differences. We are anxious to see further results.

In conclusion, the year 2014 brought about important technical and methodological improvements and refinements, as well as epidemiological data on patients with aortic aneurysms. Elective repair of the standard infrarenal AAA, in most patients, has become a fairly safe procedure, and there is a trend towards a higher proportion of patients undergoing endovascular treatment.

Even complex pathologies of the suprarenal and thoracoabdominal aorta can be managed endovascularly, and patients previously considered unfit for surgery can be offered repair to a higher degree. With the new imaging processing techniques, both patients and surgeons are exposed to less radiation, and improved imaging together with preoperative simulation can even further reduce the contrast load. Further developments in basic science and pharmacology may be additional amendments to the technical progress. We look forward to an exciting 2015!

Conflict of interest: none declared

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Interventional treatment of venous thromboembolism

A review and update of treatments in 2014

Venous thromboembolism (VTE) encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT) and has an approximate annual incidence of 1 in 1000.\(^1\) Venous thromboembolism contributes to death in more than half a million cases each year in the European Union.\(^2\) Pulmonary embolism is a potentially life-threatening disease, particularly if systemic hypotension and right ventricular dysfunction are present.\(^3\)

Although DVT is usually not life-threatening, its long-term sequelae have been underestimated for many years. Up to 40% of patients develop the post thrombotic syndrome (PTS), which often reduces quality of life due to venous claudication, skin changes, and ulcers.\(^4\) The risk of PTS is greatest in patients with thrombosis of the ilio-femoral veins, or the inferior vena cava.

Of note, anticoagulation therapy is associated with poor venous patency rates and the majority of ilio-femoral DVT do not recanalize, despite therapeutic levels of anticoagulation therapy.\(^5\)

An early revascularization strategy in PE patients aims at restoring flow in pulmonary arteries, reversing right ventricular dysfunction, reducing the risk of circulatory collapse, death, and chronic thromboembolic pulmonary hypertension. In addition to anticoagulation with heparin, systemic thrombolysis is considered the standard therapy for PE patients at increased risk of death, but it is withheld in the majority of cases mainly due to the fear of life-threatening bleeding complications including intracranial haemorrhage.\(^3\) Catheter interventions have evolved as a promising alternative to systemic thrombolysis or surgical embolectomy.

An early revascularization strategy in patients with ilio-femoral DVT aims at restoring venous flow and preserving venous valvular function, thereby improving symptoms and signs of acute DVT and preventing the development of the post thrombotic syndrome.\(^6\) Catheter-directed thrombolysis followed by routine stenting of residual venous stenosis has replaced open surgical thrombectomy for the majority of ilio-femoral DVT cases.\(^7\)

Recommendations and techniques for interventional treatment of acute VTE are summarized in this article.
Recommendations on interventional treatment

Pulmonary embolism

The 2014 European Society of Cardiology (ESC) guidelines on the management of PE recommend systemic thrombolytic therapy in high-risk patients who present with cardiogenic shock or systemic hypotension. Owing to the risk of intracranial bleeding, systemic thrombolysis is no longer recommended as first-line therapy for haemodynamically stable patients at intermediate risk, i.e., in the presence of right ventricular dysfunction and a positive troponin test. Systemic thrombolysis is recommended as rescue therapy in intermediate-risk patients who suffer haemodynamic deterioration during the initial phase of anticoagulation treatment.

Catheter-directed treatment or surgical embolectomy should be considered for patients at intermediate or high risk, in whom systemic thrombolytic therapy is contraindicated or has failed.

Deep vein thrombosis

The 2012 guidelines of the American College of Chest Physicians recommend emergent thrombus removal by catheter intervention or surgical thrombectomy in patients with impending venous gangrene.

Methods of interventional treatment

Overall, interventional treatment options are classified into those with or without the use of thrombolysis.

Catheter interventions without thrombolysis

For patients with absolute contraindications to thrombolysis therapy, the following techniques of intervention therapy are performed:

1. Thrombus fragmentation
   This technique disrupts obstructing thrombus into smaller fragments by manual rotation of a pigtail catheter or by inflation of a balloon catheter. There is a risk of distal embolization and worsening haemodynamic status when used in patients with centrally located PE.

2. Rheolytic thrombectomy
   Rheolytic thrombectomy (AngioJet®, Boston Scientific, USA) uses the Venturi effect and is enabled by a high-pressure saline jet inside the catheter.

3. Suction thrombectomy
   Suction of thrombus using large-lumen catheters (8–12 French) is performed manually by inducing a negative pressure with an aspiration syringe.

4. Rotational thrombectomy
   Rotational thrombectomy by an 8 or 10-Fr Aspirex® catheter (Straub Medical, Switzerland) can be used to establish flow in thrombotic occlusions. It macerates and removes thrombus by an incorporated high-speed rotational coil.

5. Vacuum-assisted thrombectomy
   Vacuum-assisted thrombectomy (AngioVac®, Angiodynamics, USA) is another option for patients with massive vena cava thrombosis or PE who cannot receive thrombolytics due to high risk of bleeding. It includes an extra corporal veno-venous bypass with a 22-Fr suction cannula, a 16-Fr re-infusion cannula, and a filter.

Catheter interventions with thrombolysis

Catheter interventions with thrombolysis are the most commonly used techniques for the treatment of patients with PE and DVT.

Conventional catheter-directed thrombolysis

Thrombolytic agents, for example, recombinant tissue plasminogen activator (rtPA) at a dose of 1–2 mg/h for up to 24 h, are infused through side-hole catheters which are placed at the side of the thrombotic occlusion.

Pharmacomechanical thrombolysis

Pharmacomechanical thrombolysis refers to catheter-directed thrombolysis combined with a mechanical catheter technique. In addition to the thrombectomy mode, the AngioJet® system (Boston Scientific, USA) enables a high-pressure intrathrombus injection of thrombolytic agents (PowerPulse® technique).

Ultrasound-assisted thrombolysis is another type of pharmacomechanical thrombolysis which aims to accelerate thrombolysis success. It consists of a thrombolysis catheter with a microsonic core wire that uses high-frequency low-power ultrasound waves (EKOS Corporation, Bothell, WA, USA). In a randomized trial of PE patients at intermediate risk, ultrasound-assisted catheter-directed thrombolysis was superior in reversing right ventricular dilatation without an increase in bleeding rates compared with patients who received only anticoagulation.

Summary and perspective

Catheter intervention is an evolving and promising minimal-invasive therapy for patients with acute VTE. The most commonly used techniques for patients with PE and DVT are catheter-directed thrombolysis and pharmacomechanical thrombolysis. Various mechanical thrombus removal therapies are available for patients who cannot receive thrombolytic agents due to an increased risk of bleeding.
While most PE patients do well with anticoagulation therapy alone, catheter interventions may be considered for selected PE patients at intermediate or high risk. Since systemic thrombolysis should no longer be used as a primary reperfusion therapy for PE patients at intermediate risk, it is likely that many centres will offer catheter-directed therapy to their patients in the future.

Patients with acute ilio-femoral DVT are at risk of developing the post-thrombotic syndrome if managed conservatively with anticoagulation therapy alone. Catheter-directed thrombolysis followed by stenting of underlying venous obstruction has emerged as standard treatment in many centres.

**Conflict of interest:** none declared.

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**From academia to industry**

**Working in industry requires wanting to make medicines**

**Patrick Vallance, head of Research & Development at GlaxoSmithKline, discusses his move from academia to industry and advises dropping personal research interests**

Patrick Vallance MD FRCP FMedSci has never been one for career planning. The decision to leave academia for industry was made overnight, following dinner with the then chairman of Research & Development (R&D), Dr Tadataka (Tachi) Yamada, who said, ‘Why don’t you come and join GlaxoSmithKline (GSK)?’

At the time Vallance was head of the division of medicine at University College London, UK. He was practising as a general and cardiovascular physician, teaching at the university, and had his own research group. ‘I had very little to do with industry and all of my research money came from peer reviewed grants and other places’, he says.

Vallance’s clinical pharmacology background led to involvement with formularies and access to medicines, and Yamada had asked him to become part of the research advisory board for GSK. ‘I did that and it was a massive eye opener for me about what went on in industry, the quality of the science, the breadth of the science, and the potential to impact human health’, says Vallance. But he adds: ‘I still had no intention of joining industry’.

After the dinner with Yamada he went home and thought, ‘Am I going to spend the rest of my career trying to do something a bit like this in academia, trying to make chemicals and interfere with processes and write the occasional critical article about industry, or go in there and try and do something about it. I decided overnight that I would make the swap’. The decision came down to the observation that it’s not possible to make medicines in academia. ‘Medicines are made in industry and that’s what I wanted to be involved with’, says Vallance. ‘A process that allows you to go from an idea through to something which is going to be given to millions of people and improve lives of patients across the world’.

As head of R&D at GSK he is involved in the whole process of making medicines, from the very early stage of ideas through to approval. In common with academia, he works with smart scientists who are extremely motivated and enthusiastic. Vallance says: ‘It is in some ways a challenge of fostering individual and team creativity and delivery, which is a very similar thing to leading an academic department’.

He adds: ‘What’s different is it needs to be marshalled towards very clear, big outputs that need many, many people involved over multiple years’.

The science is much broader than at UCL, ranging from chemistry through to clinical science and crossing all therapy areas. ‘I know enough to ask the questions of people and push things a bit’, he says. Much of the job is about leadership. While the department at UCL was large, with 400 or so people, at GSK he leads 10 500 staff. People who come from academia sometimes don’t understand how important it is to get that leadership bit right’, says Vallance. ‘A lot of academia remains a very individualistic exercise. This is much more about getting teams working well together’.

He is also seeking to collaborate with scientists outside GSK’s own walls through the company’s ‘open innovation’ approach. It was developed to encourage innovation in diseases of the developing world, where there is no same potential commercial return and research has stalled. In 2010 GSK opened up access to its compounds that show activity against malaria and in 2012 did the same for TB.

When Vallance made the move to industry he thought he would miss seeing patients, but that has not been the case. He loved being a clinician, but explains: ‘I’d become so busy in that job I’m not sure I was giving it the time and attention that it deserved’.

And with so much going on at GSK he does not miss his personal research either. His lab at UCL was the first to show that nitric oxide controls vascular tone in humans and they identified a novel pathway that regulates nitric oxide synthesis. The group did a collaborative piece of work using a big general practice database which showed that risk of myocardial infarction is elevated...
for a short period following either a respiratory tract infection or a urinary tract infection.

‘Those are the things from my group which have stood the test of time and made some sort of difference’, says Vallance, adding that it is the students he misses most from academia—‘their excitement, curiosity, optimism, and naïveté.

For anyone considering a switch to industry, Vallance advises throwing yourself into it 100%. Second, if you are going in at a senior level, drop your personal research, and concentrate on what is happening in the company. Third, understand the complexity of the business.

He explains: ‘It is much more complicated than I’d realised in terms of the different sciences ranging from quality control science on the manufacturing requirements back down to the things that are more familiar such as the biology or the chemistry and biology interactions’.

He adds: ‘The interdisciplinary nature of it is something that you’ve got to embrace and take the time to understand. I’m not sure I did take enough time to really understand that initially’. In addition to wanting to be part of the process of making medicines, joining industry demands being ‘prepared to suppress individualistic ego credit’, says Vallance, who calculated that 3500 people at GSK played some part in one medicine that was approved recently. He says: ‘If you want personal, identifiable, individualistic recognition to the outside world this isn’t the right place to be’.

Not one for career planning, Vallance has no idea what he will do in future. ‘All I can say is I enormously enjoy what I am doing now’. ‘One of the really exciting things about this job is, particularly as you go earlier in the pipeline when everything’s a vision of the future, you can dream as to which of these are going to make it. That really motivates me’.

**STEMI and stroke: distant cousins at best**

Remember the old days? Shortly after the introduction of elective PTCA by Andreas Grünzig in 1978 the teams of cardiologists in Mainz and Kansas City began to treat patients with acute coronary syndromes (ACS). Emergency PTCA were troubled with thrombi, recoils and urgent surgery referrals (up to 10%) at the time. While high-dose unfractionated heparin (up to 20,000 IE!) and perfusion balloons were mostly futile the proof of principle survived. Today, fast-track PCI has become the undisputed first-line therapy in all STEMI and in the vast majority of NSTEMI patients worldwide.

The story of stroke reperfusion therapy initially runs parallel up to a point, and then it halts. Similar to STEMI trials conducted in the 1980s (GISSI, GUSTO, TIMI etc.), trials in stroke patients conducted in the 1990s (NIHDS) have demonstrated significant clinical benefits of systemic thrombolysis over standard therapy. However, contrary to the ACS concept of mechanical reperfusion therapy, in stroke patients this has not yet been validated. In fact, the recent trials comparing mechanical interventions and standard treatments (IMS III, SYNTHESIS Expansion, MR RESCUE) were all negative.

First, tolerance of ischaemia by brain tissue compared with heart muscle is far worse. Second, tolerance ischaemia by the brain is more individually variable, due to the enormous differences in preformed extra- and intracranial collaterals. Third, the vascular pathology associated with stroke is more varied with a significant proportion of embolic events and dissections. Fourth, the culprit lesion strategy is upset due to the multitude of cognitive and psychomotor functions of the brain with widely spread neuronal networks not necessarily supplied by a single vascular territory. Fifth, differences in large vessel occlusions associated with watershed infarcts and peripheral artery occlusions associated with central infarcts impact management strategy. Sixth, reperfusion haemorrhage is vastly more devastating in the brain, likely due to the associated vasoconstriction of the collateral channels and damage to the blood-brain barrier. Seventh, mechanical revascularization of cerebral arteries are technically more complex due to the excessive tortuosity of brain vessels, particularly in hypertensive and aged patients, the propensity to vasospasm, and greater vulnerability due to the thin media layer; compared with the coronary arteries. Consequently, due to the variability of the above factors, rather than a general (sweeping) indication for mechanical revascularization as is customary in ACS, in stroke patients’ individual suitability including assessment of the individual’s therapeutic window may be required for optimum selection.

To determine the role of mechanical revascularization in stroke management and to improve clinical outcomes, three key issues need to be urgently addressed. First, selection criteria for mechanical interventions need to be redefined, based on individual factors. Second, time to mechanical revascularization needs to be shortened. Third, procedural expertise of interventionists needs to be developed to perform demanding interventions rapidly and safely in all patients.

An interdisciplinary dialogue and consensus is required to establish standard protocols designed to determine the clinical value of mechanical reperfusion in stroke patients. Early involvement of cardiologists is critical to assure the quality of the ongoing process. The Prague-16 study (Widimsky et al. EuroIntervention 2014 May 20. pii: 20140325–07. doi:10.4244/EIJY14M05_12. [Epub ahead of print]) represents an important step in the right direction. [The full title ‘Direct catheter-based thrombectomy in acute ischaemic stroke performed collaboratively by cardiologists, neurologists and radiologists: the single-centre pilot experience (PRAGUE-16 study) has not yet been published in print].