

Interventional Oncology – Challenges from Asia

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EDUCATIONAL SESSION REVIEW

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Chair: Susumu Kanazawa

Speakers: Kiang Hiong Tay and Yasuaki Arai

The Role of Angio CT in Interventional Radiology: the Singapore General Hospital Experience

Kiang Hiong Tay

The Angio CT system is an angiography machine coupled with a computed tomography (CT) scanner to allow interventional radiologists to use the equipment independently of each other or simultaneously without the need to move the patient between rooms (Figure 1). It was first introduced in Japan in the early 1990s and although its use in Japan is well established, its availability around the rest of the world is limited. It was originally developed to facilitate the performance of transcatheter arterial chemoembolisation (TACE) in patients with hepatocellular carcinoma (HCC).

However, the versatility of this setup, which allows for multiple combinations of imaging options (CT $\pm$ fluoroscopy $\pm$ digital subtraction angiography [DSA] $\pm$ ultrasound), has led to its use in other procedures such as selective internal radiation therapy (SIRT), catheter-directed intra-arterial computed tomography angiography (IACTA), complex drainage cases and difficult embolization procedures, e.g. bronchial artery embolization, mesenteric artery embolization or translumbar sac puncture for endoleak embolization.



Dr Tay is Head of the Department of Diagnostic Radiology at Singapore General Hospital and Associate Professor at both Duke NUS Graduate Medical School Singapore and Yong Loo Lin School of Medicine in the National University of Singapore. As an expert in vascular and interventional radiology, Dr Tay has lectured extensively and published widely. He is currently Chairman of the Cardiovascular and Interventional Radiology section of the Singapore Radiological Society, as well as Honorary Secretary of the College of Radiologists, Singapore.

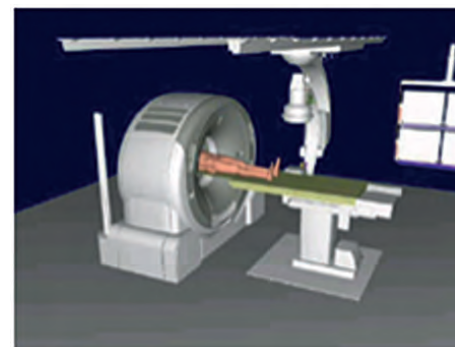
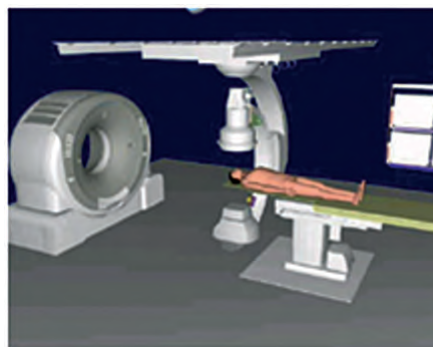


Figure 1. Angio CT suite where the computed tomography (CT) scanner and angiography machine share a common patient couch/table. The patient can undergo CT and angiography examinations without need to move between rooms.

Angio CT in SIRT - The Singapore General Hospital Experience

Since the installation of an Angio CT system in the Interventional Radiology Centre in Singapore General Hospital in 2008, hybrid procedures where both the CT and angiography components of the system were used during the procedure have accounted for 417 of 2247 (18.6%) procedures. Most of the hybrid procedures were to facilitate planning for SIRT (hepatic technetium-99m macroaggregated albumin [Tc-99m MAA] study) and for delivery of yttrium-90 microspheres during SIRT itself. There is good evidence to show that SIRT can have a positive effect on patient survival in HCC patients, even among those with advanced disease^(1,2) (Figure 2).

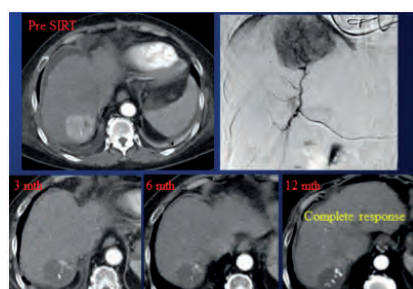


Figure 2. Example of complete response following SIRT in a patient with right hepatic lobe HCC.

The aim of SIRT in HCC is to deliver a high dose of radiation (≥ 120 Gy) directly to the tumor within the liver via the hepatic artery while minimizing the exposure to healthy liver tissue and the rest of the body. Radiation delivery is via injection of small inert resin (SIR-Spheres[®]) or glass (TheraSphere[®]) microspheres (measuring approximately 25 to 35 microns), loaded with the radionuclide yttrium-90 (⁹⁰Y)⁽²⁾. These small microspheres lodge within the peripheral neovasculature of tumors, where they deliver high-energy beta radiation over a limited range (mean penetration of radiation into tissues

is 2.4 mm), thereby confining the tumoricidal dose to the immediate proximity of the tumor and sparing the normal liver parenchyma. Unlike the larger particles used in TACE (100 to 500 microns in diameter), they do not occlude arteries to cause ischemia which is why portal vein thrombosis is not a contra indication for SIRT.

Dosing and administration of SIRT is complex and the complications observed can be severe if healthy bowel or lung tissue is exposed to radiation. Angio CT provides us with an invaluable tool to visualise the tumor's vasculature, helping to reduce the risk of injury to non-tumoral vessels. At Singapore General Hospital, we have also used this Angio CT technology to develop a novel, personalised, predictive dosimetric technique⁽³⁾.

The technique enables one to calculate the dose that should be given individually into each hepatic artery based on the DSA and IACTA data as well as the single photon emission computed tomography (SPECT)/CT data from the Tc-99m MAA scan. The formulae also predict the radiographic exposure to the tumor, liver, lung and elsewhere in the body. This calculation tool is now available on the Singapore General Hospital website (<http://www.sgh.com.sg/Pages/default.aspx>)⁽⁴⁾. In one study we used this technique to target 20 arterial territories in 10 patients with HCC, achieving a 100% tumor response rate⁽³⁾. Tumor size was decreased by 58% (95% confidence interval [CI], 40% to 72%). Median predicted mean radiation absorbed doses were 106 Gy (95% CI, 105 to 146 Gy) to tumor, 27 Gy (95% CI, 22 to 33 Gy) to non-tumorous liver, and 2 Gy (95% CI, 1.3 to 7.3 Gy) to lungs. Across all patients, tumor, non-tumorous liver and lungs received ≥ 91 Gy, ≤ 51 Gy and ≤ 16 Gy, respectively, via at least one target arterial territory.

As well as giving us confidence in identifying the liver and tumor blood supply, DSA in combination with IACTA

using Angio CT is also very useful for evaluation of the extrahepatic arterial anatomy (Figure 3). It is not uncommon for liver tumors to receive their blood supply from elsewhere in the body; extrahepatic collaterals to tumors have been identified in 25% of patients with HCC. The greatest risk of treatment complications comes from aberrant extrahepatic collaterals that supply both the liver and extrahepatic tissues. If unrecognized, inadvertent delivery of radioactivity to non-target areas can occur which will result in severe complications. Ulcers in the stomach or duodenum will occur if microspheres are shunted to the gastroduodenal artery (GDA) or aberrant bowel supply from hepatic arteries. Similarly, radiation dermatitis can occur when radioactivity reaches the anterior abdominal wall via a patent falciform artery⁽⁵⁾. Theoretically, acute cholecystitis could occur via transfer of microspheres into the cystic artery but we have not seen any cases of this.

To reduce the risk of non-target embolization, the Radioembolization

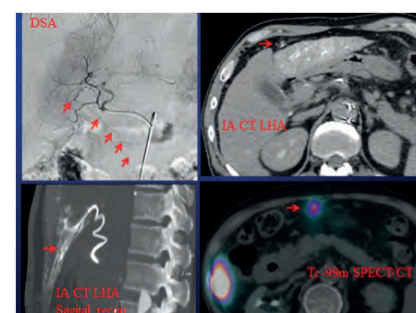


Figure 3. The falciform artery is important to identify for selective internal radiation therapy patients as non-target embolisation of the Y90 microspheres in this artery will lead to radiation dermatitis of the anterior abdominal wall. Our experience has shown that intra-arterial computed tomography angiography (IACTA) is superior to digital subtraction angiography (DSA) in depicting the falciform artery. LHA, left hepatic artery; SPECT, single photon emission computed tomography; Tc-99m, technetium-99m.

Brachytherapy Oncology Consortium guidelines published in 2006 recommend that all extrahepatic vessels originating from the hepatic arteries that supply the gastrointestinal tract should, under most circumstances, be embolised to prevent extrahepatic deposition of the ^{90}Y microspheres ⁽⁶⁾. In most cases, interventional radiologists will coil embolise up to 87% of GDA and bowel collaterals before injecting the microspheres ^(7,8). However, even with extensive coil embolization of aberrant hepatic branches supplying the gut, gastrointestinal ulceration has still been found to occur in at least 4% of cases ⁽⁹⁾. With Angio CT technology at the Singapore General Hospital, we are able to identify accurately the presence of extrahepatic enhancement on IACTA to predict non-target embolization to the bowel or abdominal wall and perform coil embolization as necessary. This reduces the need for prophylactic embolization of the GDA and bowel collaterals. In our experience our coil embolization rate is only 23% compared with 87% in some reports. Angio CT thus helps to reduce procedure time, enhance operator confidence and improve the safety of the procedure (Figure 4).

In summary, Angio CT at the Singapore General Hospital has led to a high success rate and low

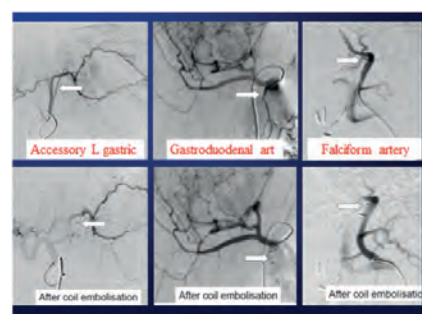


Figure 4. Coil embolization of gastric, gastroduodenal and falciform arteries prior to administration of radioactive microspheres to prevent non-target embolization.

complication rate in performing SIRT for the treatment of liver cancers. It has facilitated dose proportioning and accurate dosimetry, reduced the need for coil embolization of gastric and gastroduodenal arteries and improved confidence while delivering radio isotopes. Overall this leads to reduced procedure time and potentially improved patient safety.

Other applications of Angio CT at Singapore General Hospital

We capitalise on the ability to perform catheter-directed IACTA in our Angio CT suite for performance of difficult embolization procedures. For example, in bronchial artery embolisation for haemoptysis, there is often concern about non-target embolization of the spinal artery leading to paraplegia complication. We have in several cases used IACTA where there is uncertainty about spinal artery supply to prove or disprove the presence of spinal supply and take necessary precautions before proceeding to bronchial artery embolization. Similarly, in difficult bleeding gastro-intestinal tract (GIT) cases, we have demonstrated GIT bleeding on IACTA when conventional DSA failed to show the bleeding (Figure 5a). Translumbar sac puncture for embolization of endoleak is another procedure that benefits from Angio CT (Figure 5b).

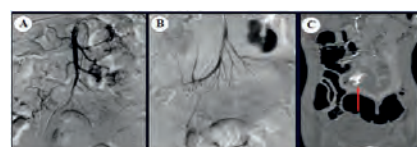


Figure 5a. This patient presented with hypotension due to massive lower gastrointestinal tract bleeding. Conventional mesenteric angiogram using digital subtraction angiography (A, B) was negative. Intra-arterial computed tomography angiography with catheter in the superior mesenteric artery (C) showed obvious contrast extravasation in the small bowel.

The puncture is performed accurately under CT fluoroscopic guidance and the embolisation is performed under DSA control following successful sac puncture.

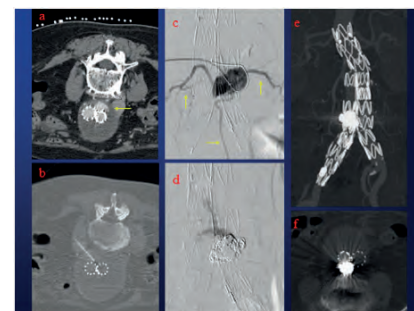


Figure 5b. Patient with type 2 endoleak from lumbar artery backbleed following aortic stent graft for abdominal aortic aneurysm. The patient was placed in a prone position and conventional contrast computed tomography (CT) of the abdomen was performed (a). Under CT fluoro guidance, translumbar sac puncture into the endoleak was performed (b). The embolization was performed under fluoroscopy and digital subtraction angiography control using a combination of platinum coils and glue (c,d). Post-embolization CT showed successful deposition of coils/glue within the endoleak, indicating a good result (e,f).

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Interventional Oncology – Towards New Horizons

Yasuaki Arai

As mentioned in Dr Tay's presentation, TACE was one of the first applications of Angio CT beyond its being a safe and easy method by which to obtain images for CT during arterial portography (CTAP) and CT during hepatic arteriography. To perform it effectively, it is important to confirm the main feeding artery of the tumor and to recognise that potentially the tumor has multiple feeding arteries. The technique has been enhanced by the development of superselective TACE which approaches the tumor from the distal portion of the feeding subsegmental hepatic artery to evoke strong ischemic effects on a small area of the liver ⁽¹⁾. This is achieved using Lipiodol® (semi-fluid iodised oil) which flows into the surrounding portal venules and hepatic sinusoids through the drainage route from the hypervascular HCC. This blocks the reversed flow from the hepatic sinusoids and portal venules to the peripheral portion of the tumor and daughter nodules before injecting a particulate embolus (such as gelatin sponge particles).

Angio CT can also be applied to non-vascular procedures. Angio CT can be used to replace ultrasound guidance in non-vascular cases making it possible to perform some interventions that would have been too difficult without this technology, and facilitating others (Figure 6).



Dr Arai is the Director of the Hospital and Chair of the Department of Diagnostic Radiology at the National Cancer Centre in Tokyo, Japan. He has published widely in the field of interventional radiology in oncology and has held the position of Associate Editor of the Journal of Vascular and Interventional Radiology. He is a member of several international societies for clinical oncology and interventional radiology and has served as Chair of the Japan Interventional Radiology in Oncology Study Group (JIVROSG).

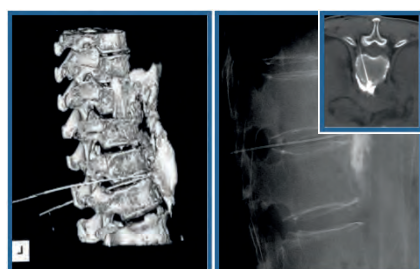


Figure 6. Celiac plexus block.

The tandem technique makes use of a guiding needle followed

by subsequent insertion of a treatment needle which allows the interventional radiologist to confirm the exact location of the treatment needle tip. This technique can be used to perform safe and accurate drainage of mediastinal abscesses after surgery for oesophageal cancer by inserting a fine needle under CT guidance followed by a drainage needle under fluoroscopic guidance ⁽²⁾. The imaging techniques can be used together to confirm the reverse flow of abscess

fluid from the drainage needle on aspiration leaving an empty cavity. The tandem technique can also be used to separate tumors from healthy tissue before treatment. This involves inserting a needle in between the tumor and the healthy organ, such as the stomach, inflating a balloon catheter to push them further apart and then inserting a second needle directly into the tumor to perform radiofrequency ablation, avoiding heat damage to stomach.

Evidence-based medicine

Many new tools and techniques have become available in the field of interventional oncology during recent years, but few have been adopted as standard of care due to a lack of controlled clinical trial data. To be implemented as a standard of care there must be rigorous safety data from phase I trials, demonstrated efficacy from phase II trials and evaluation of clinically meaningful outcomes compared with available treatments from randomized, controlled, phase III clinical trials. It is difficult to carry out well controlled clinical trials in interventional radiology because the treatments are dependent on technique, and it is hard to standardise approach due

to a lack of established methodology. However, it is important that these challenges are overcome with well-designed protocols. In addition to the use of standardized techniques, other key features that lead to successful clinical trials in this field are the existence of a common clinical question, recruitment of patients without delays and collaboration with other countries.

The Japan Interventional Radiology in Oncology Study Group (JIVROSG) was established to support an evidence-based approach⁽³⁾. It was set up in 2002 under a parent organisation, the Research Group for the Standardization of Interventional Radiology Indications and Techniques for Cancer Treatment, which was funded by a grant-in-aid for cancer

research from the Ministry of Health, Labour and Welfare in Japan. The aims of the group are to: evaluate scientifically the applications of interventional radiology for cancer treatment via clinical trials; develop better treatments; and standardise treatment methods. In the last 10 years the JIVROSG has investigated many valuable clinical trials of various treatments and cancers (see Table 1 for selected examples).

Cost of treatment

Advances in medical technology are increasing the cost of care for most fields of medicine, and oncology is no exception. While new drugs offer survival benefits over older treatments, albeit modest gains in

Table 1. Clinical trials of the Japan Interventional Radiology in Oncology Study Group (JIVROSG).

Protocol number	Phase	Treatment	Condition
JIVROSG-0201	I/II	Transhepatic peritoneal-venous shunt	Persistent ascites
JIVROSG-0202	I/II	PVP	Painful bone metastases
JIVROSG-0203	I/II	RFA	Lung cancer
JIVROSG-0204	I/II	RFA	Painful intrapelvic tumor
JIVROSG-0205	I/II	Percutaneous trans-oesophageal gastro-tubing	Upper GI obstruction
JIVROSG-0206	I/II	Stent therapy	Colonic stenosis
JIVROSG-0207	III	Covered vs bare stent	Malignant biliary obstruction
JIVROSG-0208	I/II	RFA	Painful bone metastases
JIVROSG-0301	I/II	Hepatic arterial GEM	Cholangio carcinoma
JIVROSG-0302	I/II	Uterine artery embolisation	Uterine fibroid
JIVROSG-0401	I/II	Cisplatin-TACE	HCC
JIVROSG-0402	II	Stent therapy	Superior/inferior vena cava syndromes
JIVROSG-0604	II	Epirubicin-Doxorubicin/Doxorubicin-Lipiodol-gelatin sponge TACE	HCC (Korea-Japan)
JIVROSG-0606	III	HAIC with FOLFOX	Liver metastases from CRC
JIVROSG-0701	I/II	Radiofrequency ablation	Renal cancer
JIVROSG-0702	II	RFA	Lung cancer
JIVROSG-0703	II	PVP	Painful bone metastases
JIVROSG-0704	I/II	RFA	Osteoid osteoma
JIVROSG-0803	III	Shunt	Persistent ascites
JIVROSG-0804	III	PVP	Painful bone metastases
JIVROSG-0805	III	Percutaneous trans-oesophageal gastro-tubing	Upper GI obstruction
JIVROSG-0806	III	Stent therapy	Colorectal stenosis
JIVROSG-0807	III	Stent therapy	Superior/inferior vena cava syndromes

CRC, colorectal cancer; FOLFOX, oxaliplatin, 5-fluorouracil and leucovorin; GEM, gemcitabine; GI, gastrointestinal; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; PVP, percutaneous vertebroplasty; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolisation.

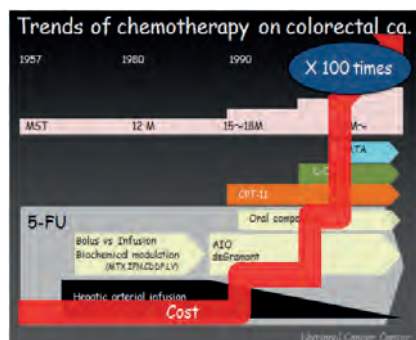


Figure 7. Cost of cancer treatment for colorectal cancer has increased 100-fold from 5-FU alone to modern combination chemotherapy.

some cases, they are more expensive, leading to an increase in cancer care costs of 15% per year ⁽⁴⁾. We estimate that since the introduction of fluorouracil in 1957, costs of chemotherapy for colorectal cancer have increased 100-fold (Figure 7). The median increase in survival time among HCC patients of 2.8 months with sorafenib treatment in the SHARP study ⁽⁵⁾ has an economic impact of \$6000 per month according to our calculations. A survey of cancer patients and their family members in the United States showed that as a result of increased treatment costs, 33% of families are experiencing difficulty paying for their care and 25% of people reported that they had used up all or most of their savings ⁽⁶⁾. In recognition of the fact that these rising costs are becoming a barrier to high-quality care for many cancer patients, ASCO set up the Cost of Cancer Care Task Force in 2007 ⁽⁴⁾ which published a Guidance Statement on the Cost of Cancer Care in the *Journal of Clinical Oncology* two years later ⁽⁶⁾.

Can we reduce costs?

Cost reduction is one of the most important global issues of medicine today. It is important to bear in

mind that there may be instances when techniques will work just as well without the most recent and expensive innovations. For example, since the introduction of uterine artery embolization (UAE) to treat symptomatic uterine fibroids in 1995, several types of embolic agents have been marketed in Europe and the United States, from the original nonspherical polyvinyl alcohol (PVA) to, more recently, tris-acryl gelatin microspheres (TAGMs) and spherical PVA particles ⁽⁷⁾. In contrast, since no embolic agents have been approved for UAE in Japan, only gelatin sponge is available to use as a substrate with this technique. Two studies in Japan (one carried out by the JIVROSG) have shown that gelatin sponge is as effective as embolic agents in alleviating symptoms and reducing volume reduction of fibroids at 1 year ^(7, 8). However, gelatin sponge costs a fraction of the price of the embolic agents; the approximate price of one vial of TAGMs (Embosphere®) is \$240, whereas that of a block of gelatin sponge (Spongel®) is \$2 ⁽⁷⁾. Given the variable use of each embolic material, the cost per procedure would be approximately \$960 for TAGMs and \$5 for gelatin sponge, approximately a 200-fold difference ⁽⁷⁾.

In summary, moving forward in the field of interventional oncology we need more evidence from clinical trials to demonstrate the meaningful value of our interventions in order for them to be implemented as standards of care. However, we must be aware of the costs of the latest innovations and must bear in mind that we may be able to use our skills and existing materials to achieve similar results. It is more important that we support treatment advances that can be made available across the world rather than the most expensive developments that are only available to patients in the richest countries.

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