QUEENSLAND COURTS

CORONERS COURTOF QUEENSLAND

FINDINGS OF INVESTIGATION

CITATION:	**Non-inquest findings into the death of TO**
TITLE OF COURT:	Coroners Court
JURISDICTION:	BRISBANE
DATE:	23/10/2017
FILE NO(s):	2015/4633
FINDINGS OF:	Ainslie Kirkegaard, Coronial Registrar
CATCHWORDS:	CORONERS; Selective Internal Radiation Therapy (SIRT), metastatic gastric carcinoma, previous Whipple procedure, increased risk of biliary sepsis, antibiotic prophylaxis

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Background

TO was a 73 year old man who died at the regional public hospital on 21 November 2015. He ordinarily resided at 368 Dungannan Road, Sandy Camp.

TO's death was reported to the coroner because of concerns he may have died from complications of selective internal radiation therapy (SIRT) for metastatic gastric carcinoma performed at a metropolitan private hospital on 18 November 2015.

SIRT is a treatment modality for tumours of the liver in which radioactive microspheres are inserted via a catheter into the blood vessel in the groin. The radioactive microspheres lodge within small vessels within the liver and exert their effect on tumour cells.

Preliminary independent clinical review

The then Deputy Registrar arranged for an independent doctor from the Department of Health Clinical Forensic Medicine Unit to review the private hospital records and advise whether there may have been an opportunity to have changed the outcome for TO.

The SIRT procedure was performed at the private hospital on 18 November 2015 by an interventional radiologist, Dr C, with ultrasound guidance. The post-procedure plan was for routine observations, analgesia and anti-nausea medication as required. TO experienced some pain and nausea following the procedure and remained an inpatient overnight.

The reviewing doctor noted TO was persistently hypertensive following the SIRT procedure. From the scant medical record available at this early stage in the investigation, this did not appear to have been investigated. Rather Dr C recommended follow up with TO's general practitioner.

TO developed a fever of 37.8 degrees on 20 November 2015. The reviewing doctor advised this is not unexpected in patients with this procedure as the dying tissue in the liver will cause fever. However, no investigation or examination of TO is documented in the then available medical record. TO was considered suitable for discharge home despite his persistently elevated blood pressure.

The patient discharge information sheet provided by the private hospital provides instructions to remove the groin dressing in two days and report any excessive bleeding, swelling, pain and fever to a doctor. It indicates TO was discharged on Panadol and no other medications.

TO returned home. The ambulance was called to the family home the next evening, 21 November 2015 as he had become very unwell. On assessment, he was noted to have a fluctuating level of consciousness, was jaundiced and hot to touch. He was tachycardic, hypertensive, febrile to 40.7 degrees, hypoxic and responsive. He demonstrated unusual positioning of his arm. His condition became more unstable

enroute to St Vincent's Emergency Centre Toowoomba with decreasing level of consciousness so the ambulance was rerouted to the regional public hospital emergency department.

On arrival in the emergency department TO was unresponsive, tachycardic, febrile, hypertensive and hypoxic. He was noted to be jaundiced and his liver was palpable externally. He demonstrated some adverse neurological signs with increased tone of the muscles of the left upper and lower limb. This was followed by a drop in blood pressure and oxygen saturation which was corrected by intubation. Initial blood gas analysis showed a metabolic acidosis, elevated lactate and potassium.

He was to be commenced on intravenous antibiotics and transferred for CT scans of the head, abdomen and chest. However, he became acutely unwell with loss of cardiac output. Unfortunately despite emergency resuscitation efforts TO was unable to be revived.

The treating team attributed his death to multi organ dysfunction and disseminated coagulation as a consequence of sepsis and haemorrhage.

Having considered the then available clinical information, the reviewing doctor was concerned that TO had been discharged home following "novel" therapy with persistent hypertension and recent fever, and no apparent consideration for referral to a physician in the hospital.

On this basis, the Deputy Registrar declined to authorise the issue of the proposed cause of death certificate.

Autopsy findings

Due to significant radiation exposure risks, a time limited external examination only and medical records review were performed at the John Tonge Centre on 27 November 2015. The final autopsy report issued on 28 June 2016. Post-mortem imaging excluded intracranial and intra-abdominal haemorrhage. The pathologist advised that without internal examination, the pathological process and cause of death could not be determined.

Statement of interventional radiologist, Dr C

I provided Dr C with an opportunity to respond to the issues raised by the reviewing doctor about the appropriateness of his management of TO.

Dr C helpfully explained the sequence of events by which TO came under his care:

- TO had been referred for consideration of liver directed therapies (SIRT) for metastatic gastrointestinal tumour by a consultant medical oncologist;
- TO had undergone a Whipple procedure performed at the Greenslopes Private Hospital on 12 June 2014 for a high risk gastrointestinal tumour. While there was no lymph node involvement or any evidence of lymphovascular or perineural invasion or any margin involvement, the medical oncologist had estimated an 86% chance of recurrence during long-term

follow up, based on the duodenal location of the tumour, its size (65mm) and the finding of 12 mitoses per 50hpfs;
- the plan was to give TO three years of adjuvant chemotherapy but he was completely unable to tolerate the chemotherapy agent. He was commenced on a surveillance protocol with three-monthly CT scans; and
- in October 2015, CT scan revealed new metastatic deposits throughout his liver. TO was noted to be pragmatic about the implications of this finding but eager to pursue any and all therapies. The medical oncologist commenced him on sunitinib.

Dr C first met with TO on 22 October 2015 for just over an hour. He says that consultation involved:

- his review of the CT images noting at least 40 new tumours (ranging in size from a few millimetres up to 23mm in diameter) which had appeared in the three months since the previous CT study;
- advising TO that while the "evidence for benefit" for this specific tumour was "not particularly robust", SIRT was a well proven, generally safe treatment used extensively for other metastatic tumours to the liver. He says he explained there had been several small trials which had shown significant survival benefit for SIRT treatment for gastrointestinal tumour but given Mr TO's disease was uncommon and usually responded well to chemotherapy, it had not been studied exhaustively;
- telling TO that given his tumours were very vascular (making them more likely to respond to treatment) and his disease seemed widespread and aggressive, he thought the whole liver in one sitting would be appropriate (and in keeping with normal practice) in order to attempt to slow down his disease progression – this was not offered as a cure but as a way to prolong his survival and slow down disease progression within the liver (but would not have any impact on any disease he might have outside the liver);
- advising TO the SIRT procedure is generally well tolerated by patients and usually has a minimal impact in terms of quality of life and time away from home – TO indicated he was interested in having this treatment;
- explaining the procedure in the following terms – it involved an initial work up in hospital as a day procedure with an angiogram to map the blood supply to his liver and then administration of a special tracer to the liver to assess for abnormal flow to the lungs. If satisfactory, the treatment would be performed as a separate procedure involving at least an overnight admission. This procedure would involve another angiogram, positioning a catheter into the arteries to liver and delivering millions of tiny radioactive particles to the liver. These particles would get lodged in the small arteries feeding the tumour, where they stay permanently and preferentially deliver their radiation dose over a 1-2mm radius, killing the tumour;
- warning TO to expect some nausea and lethargy for a few weeks or so after the procedure and that he would be given medications (analgesia, anti-nausea and anti-reflux) to help with these symptoms. He says he mentioned that some patients get some mild fever and mild abdominal pain/discomfort is common but usually settles quickly;
- explaining the general risk of angiography associated with accessing the vessel (dissection, embolus, haematoma, surgery). He says they also discussed TO's variant anatomy (part of the supply to the liver coming from

the superior mesenteric artery, as evident on CT scan) and the fact that the altered anatomy after his Whipple procedure could work in their favour in terms of reducing the risk of non-target embolisation to other organs, particularly the stomach and gallbladder;
- discussing the risk of non-embolisation and the possibility of injury to other structures particularly the small bowel, which could be serious; and
- talking about damage to the liver from the radiation that may rarely be fatal but tended to occur in people with significantly more extensive disease and with less physiological reserve.

Dr C says he told TO this was a relatively new procedure and that he was also new to it but had done other similar procedures before and would have a very experienced colleague, Dr W, with him. He recalls TO seemed happy with this. He declined Dr C's offer to speak to his family who were in the waiting room.

Dr C's decision to treat TO with this therapy was made after reviewing the CT imaging and discussing the case with Dr W.

The SIRT work up was performed on 4 November 2015. The procedure and day admission were uneventful. Dr C says he noted TO's blood pressure was elevated at this time – it varied from baseline 167/87 up to 196/98 at the start of the procedure to 150/81 at the end of the procedure. He advised that while this is elevated, it is common to encounter readings in these ranges during procedures. He did not consider it to be dangerously high or a contraindication to proceeding with the treatment.

The dose to be administered was calculated via the online SIRTEX dose calculator which uses volume measurements (whole liver volume and tumour volume based on the CT images), height and weight, Tc99 MAA lung shunt value (estimated to be at 4%) to estimate the dose required. The online calculator gave a dose of 1.6GBq which Dr W advised to increase to 1.8GBq, based on his observation that some activity always remains in the delivery system. Dr C says he divided the dose based on an estimation of the volume of liver supplied by the segment 5/8 artery from the superior mesenteric artery which was well demarcated via the common hepatic injection flat panel CT performed at the time of the work up.

Dr C described the SIRT treatment performed on 18 November as uneventful. He went through the consent process with TO again in the bed bay. Dr W was in the room observing the procedure. TO had been admitted under Dr W on this occasion.

Dr C describes the procedure as proceeding as follows:
- the right common femoral artery was accessed under ultrasound guidance with a 4 French sheath placed;
- the dose was delivered via a co-axial microcatheter from stable right and left hepatic artery and accessory right segment 5/8 vessels under fluoroscopic control, with no evidence of reflux or non-target embolization;
- he again noted TO's blood pressure was elevated from 212/93 (single reading) at the start to 163/91 at the end of the procedure – he interpreted the higher readings as reflecting anxiety and discomfort; and

- TO's blood pressure quickly settled to an acceptable level once he received some sedation – Dr C did not consider this to be a contraindication to proceeding with the treatment.

TO had pain in the post-procedure period which was expected and consistent with normal post-procedure events. It settled with some analgesia. He had some nausea and vomiting overnight. Dr W was contacted and ordered fluids and anti-emetics with good effect.

Dr C says he spoke with TO and the nursing staff and decided to keep him in hospital for another day to ensure his nausea settled to a manageable level.

TO tolerated breakfast the next morning and his pain continued to improve but he had ongoing nausea.

Dr C spoke to him prior to discharge on 20 November about follow up blood tests in one month. He says they discussed strategies for dealing with the nausea and maintaining a good oral intake. He says he told TO his blood pressure had been high over this admission and at the initial work up and he may need antihypertensive medication at some stage if it failed to return to normal once he was out of the hospital environment. He says he advised TO to follow this up with his general practitioner, which TO reportedly agreed to do.

Dr C acknowledges he was aware that TO was hypertensive and his blood pressure had fluctuated during both the workup and treatment admissions, and with some exceptions ranged from around 180 – 160 systolic. While this was high, it did not seem dangerously high and he did not consider it posed an imminent or short term danger to TO's health. Consequently, he felt this would be most appropriately dealt with in the outpatient setting by TO's general practitioner.

Dr C's statement did not address the reviewing doctor's concerns about TO having been discharged with a fever.

Private hospital clinical review outcomes

The care provided to TO at the private hospital was considered by the hospital's Quality Assurance Committee. I am advised that the committee members did not have any concerns about the care he received and did not recommend any system modifications.

Independent expert opinion

I obtained an expert opinion about the management of TO's SIRT and its contribution to his death from A/Professor Lourens Bester, an interventional radiologist from New South Wales with significant experience in performing SIRT since 2004.

A/Professor Bester explained that as at 2015, SIRT was no longer an experimental treatment as it had been in use for the treatment of colorectal cancer since obtaining regulatory approval in 2004. SIRT in secondary liver cancer is used mainly as a

salvage treatment when all chemotherapeutic agents used have failed. Consequently, most of the patients treated have limited life expectancy if they were offered best supportive care only but SIRT can improve their overall life expectancy substantially.

A/Professor Bester was satisfied TO satisfied the clinical criteria for suitability for SIRT.

He considered several factors that can influence the outcome of SIRT:

1. The patient's performance status – to meet the clinical criteria for SIRT, TO's ECOG needed to have been 0-2. Although this is not referenced in the medical oncologist's referral to Dr C, A/Professor Bester presumed the medical oncologist would not have referred him for treatment if he was outside this range.

2. Previous Whipple procedure with an increased risk of infection – TO had undergone this procedure in 2014. It can increase the infection risk when SIRT is performed as it creates direct communication between the bowel and the common bile duct. The biliary tree gets colonised by gram negative bacteria as a result of this communication and violation of the sphincter of Oddi.

3. Prophylactic antibiotic cover before, during and after SIRT procedure - A/Professor Bester advised that he normally administers Ciprofloxacin and Metronidazole before, during and after the SIRT procedure.

4. Tumour necrosis – SIRT causes necrosis of the tumour, a process that starts almost immediately post-SIRT. A/Professor Bester considered this may explain the slight rise in TO's temperature post-procedure (37.8). He describes a temperature of this level as not unusual post-SIRT. He considered that in TO's case, because of the previous Whipple procedure, biliary sepsis would have been in the differential diagnosis and for this reason antibiotic cover would have been appropriate.

5. He was satisfied TO did not go into liver failure post-SIRT as his liver function tests on 19 November 2015 showed only an increase in the bilirubin (25, up from 14) while the rest of the values were almost the same as pre-procedure.

6. Radiation Induced Liver Disease – this is associated with damage to the sinusoids in the liver and usually presents 6-8 weeks after SIRT. As such TO did not have time to develop this condition.

Noting that TO arrived at the regional public hospital emergency department with a temperate of 40.7 degrees and in shock, A/Professor Bester considered that TO died from gram negative septic shock which was facilitated by the Whipple procedure and the necrotic tumour tissue in the liver. He suggests the use of prophylactic antibiotics before, during and after SIRT may have prevented TO's death.

Dr C's response

I provided Dr C with an opportunity to consider and respond to the issues raised by A/Professor Bester. I received Dr C's further statement on 5 October 2017.

He performed the SIRT procedure on TO as the second of three proctored cases co-ordinated through the Sirtex company. His proctor was Dr W, who he describes as one of the most experienced and respected operators in Australia regarding radioembolisation of liver tumours ("perhaps second only to A/Professor Bester"), and the most experienced operator in Queensland.

Dr C explained that prior to performing the SIRT on TO, he had done what he felt was an extensive clinical literature review, concentrating predominantly on the technical aspects of the procedure, recognising potential anatomical pitfalls and the treatment of TO's tumour type, which was an uncommon type of primary tumour to treat with SIRT.

He acknowledges that despite this, he did not fully appreciate the significance of the previous Whipple procedure and the subsequently increased risk of sepsis. He described it as a reasonably uncommon scenario to perform this procedure on post-Whipple procedure patients. He explained SIRT as a palliative procedure associated with a small but real risk of procedure related death (citing about 1%) which he says had been discussed in his consultation with TO.

Dr C expected TO's synthetic function to be normal as he had only had a short burst of a poorly tolerated chemotherapy agent. TO's main issue was untreated rapidly progressive liver disease and not diffuse parenchymal liver disease.

Dr C had reviewed the case with Dr W after his initial consultation with TO – they reviewed the CT imaging, noting the extensive liver dominant disease and rapid disease progression and the post-surgical changes. He advises that no written protocols were available regarding antibiotics at their institution. They discussed the expected tumour response and decided to proceed with the workup.

Neither Dr C nor Dr W considered antibiotics at the time of the SIRT procedure or earlier. With the benefit of hindsight, and after considerable discussion with his clinical colleagues, Dr C agreed that the omission of antibiotic prophylaxis may have contributed to TO's death. He offered his sincere condolences to TO's family and apologised for this omission.

Findings required by *Coroners Act 2003*, s.45

Identity of the deceased: [de-identified for publication purposes]

How he died: TO died from complications of selective internal radiation therapy (SIRT) for metastatic gastric carcinoma performed at a metropolitan private hospital on 18 November 2015. This procedure was performed not as a cure but with the hope it may prolong his survival and slow down the rapid disease

progression within his liver. While TO met the clinical criteria for suitability for SIRT, his previous Whipple procedure increased his risk of sepsis. This increased risk was not appreciated by the interventional radiologists who performed and supervised the SIRT procedure so he was not prescribed antibiotic prophylaxis before, during or after the procedure. Unfortunately this risk subsequently manifested for TO causing him to become acutely unwell and die not long after being discharged home from the private hospital. I am satisfied that the interventional radiologist has since appropriately recognised the significance of TO's previous Whipple procedure in increasing his infection risk and acknowledged that the omission to prescribe antibiotic prophylaxis may have contributed to TO's death.

Where he died: Toowoomba Hospital, Toowoomba, Queensland

When he died: 21/11/2015

What caused his death:
1(a) Sepsis
1(b) Metastatic gastric cancer (treated with Selective Internal Radiation Therapy procedure)

I close the investigation.

Ainslie Kirkegaard
Coronial Registrar
CORONERS COURTOF QUEENSLAND
23 October 2017