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SDH Research and Clinical Trials Selective Internal Radiotherapy (SIRT) for Liver metastases in SDH Deficient GISTs

Dr. Ramesh Bulusu

Selective Internal Radiotherapy (SIRT) for Liver metastases in SDH Deficient GISTs

Ramesh Bulusu

Consultant Oncologist

Cambridge University Hospitals

United Kingdom

Clinical Lead PAWS GIST Clinic UK

Ancient quote from China—borrowed from Prof Tony Mok's talk at BTOG Belfast April 23

Quote #2: If you know the enemy and know yourself, you need not fear the results of a hundred battles.

This is another popular Sun Tzu *Art of War* quote. Sun Tzu advises you know your enemy. To know your enemy, first understand its strengths and weaknesses.

First, you should assess these five traits regarding *your* forces. Then, **assess these five traits for your enemy** to size up the competition. "If you know the enemy and know yourself, your victory will not stand in doubt."

- If you understand both your strengths and efficiency and those of your enemy, you can realistically compare the two and predict the likelihood of victory during conflicts.

- Knowing your enemy- what does it mean?
- Strengths & weaknesses
  - Cancer
  - Us—clinicians/researchers
- Biology
- Molecular mechanisms
- Achilles heel
- Our strengths???
- Our weaknesses ??

What is SIRT?
Selective Internal Radiotherapy (Radioembolization)

- Delivery of a radioactive substance in to the tumoural vascular supply via an intra arterial catheter placed under radiological guidance
- Rationale in treating liver metastases
  - High dose to the tumour, lower dose to the liver
  - Primary and secondary liver cancers derive 80-100% of their blood supply from hepatic arteries
  - Normal liver tissue blood supply– up to 30% derived from hepatic artery, rest from portal vein
  - Most commonly used radionuclide Yttrium-90.

- Well established for other liver cancers

^{90}Yttrium Radioisotope for SIRT

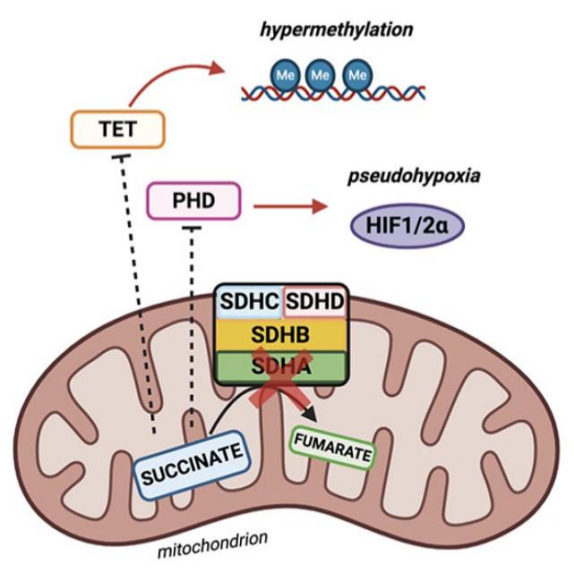
- One of the first pioneers to explore Yttrium SIRT was Dr Irving Ariel. Surgeon from New York
  - Radioactive isotopes for adjuvant cancer therapy; animal experimentation and preliminary results in human application. Arch Surg 1964; 89: 244–9
  - Nolan TR, Grady ED. Intravascular particulate radioisotope therapy: clinical observations of 76 patients with advanced cancer treated with 90-yttrium particles. Am Surg 1969;35: 181–8.

Yttrium-90 properties and microspheres

- 90Y is a beta emitter with a 64.2-h physical half-life
- 90Y microspheres entrapped in the microvasculature of the liver emit b-radiation with a mean energy of 0.94MeV, maximum energy of 2.26MeV
- Mean tissue penetration of 2.5mm and max 11mm.
- Two types of 90Y microspheres available
  - TheraSphere™ (glass microspheres; BTG, London, UK)
  - SIR-Spheres™ (resin microspheres; Sirtex Medical Limited, Australia)
- Glass microsphere 20-30 mic. Resin 20-60 mic dm
- 1-2 million microspheres are injected in average pt

SDH Deficient GISTs have defects in DNA repair mechanisms

- Succinate acts as an ONCOMETABOLITE
- Inhibits alpha-ketoglutarate dependent enzymes involved in dna demethylation leading to hypermethylated state
- Hypermethylation of the promoter region of the **MGMT** (O6-methylguanine-DNA methyltransferase) gene. MGMT is a critical DNA repair protein
- The hypermethylation silences the MGMT gene, results DNA repair problems in the tumour cells. SDH def cells become highly sensitive to DNA damaging agents



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nature genetics

LETTERS

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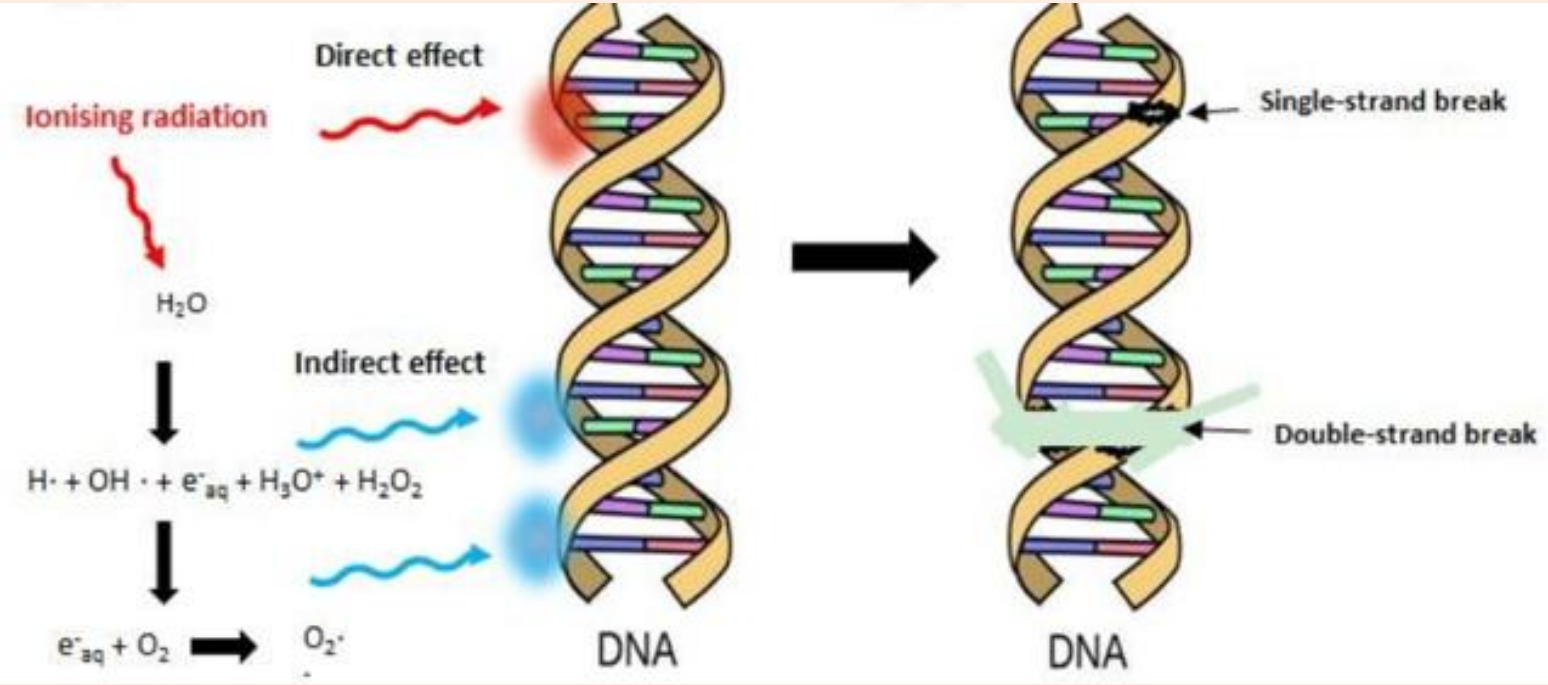
Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair

Parker L. Sulkowski[1,2], Ranjini K. Sundaram[1], Sebastian Oeck[1,3], Christopher D. Corso[1,4], Yanfeng Liu[1], Seth Noorbakhsh[1], Monica Niger[1,5], Marta Boeke[6], Daiki Ueno[6], Aravind Nambiar Kalathil[1], Xun Bao[7], Jing Li[7], Brian Shuch[6,9*], Ranjit S. Bindra[1,8,9*] and Peter M. Glazer[1,2,9*]

Most effective DNA damaging tool **ionising radiation**



Practical aspects of SIRT

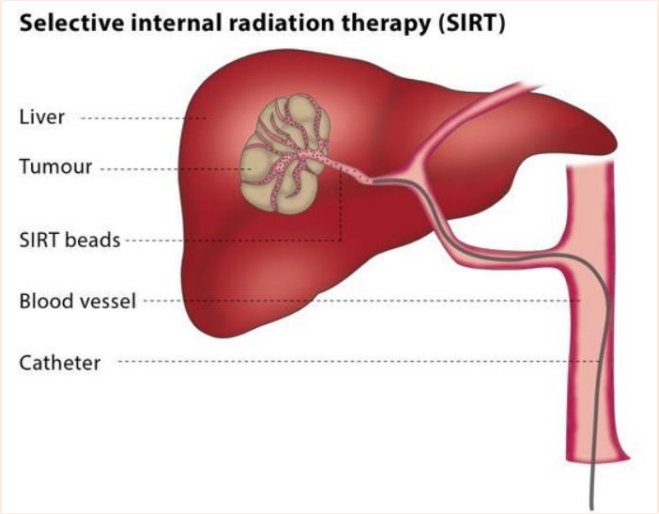
- Multidisciplinary
  - Oncologists, radiologists, nuclear medicine, interventional radiologists, medical physicists
- Suitability of patient and tumour criteria discussed in Multidisciplinary/Tumour Board meeting
- Standard inclusion and exclusion criteria
- Baseline bloods (FBC, Creatinine, LFTs)
- Informed written consent

Yttrium 90 Selective Internal Radiotherapy (SIRT) in SDH Deficient GISTs PAWS GIST UK Initiative

- Strong rationale for using Yttrium SIRT in SDH Def GISTS
- A potential option for patients with SDH Deficient GIST with liver only or liver predominant metastatic disease
- SIRT program established in 2018
- First patient in UK treated in 2018
- Clatterbridge Cancer Centre in Liverpool UK
- Close collaboration between PAWS GIST Clinic team, SIRT team and patient's local oncology team

SIRT-Two-part procedure

- Step 1
  - Feasibility and safety assessment with Technetium—99m labelled macro aggregated albumin (^{99m}Tc-MAA)
  - SPECT CT post ^{99m}Tc-MAA iv administration to check hepatic and extra hepatic uptake (lung uptake)
  - Liver→Lung shunt is calculated—if safe and no other concerns—proceed to Step 2
- Step 2
  - Treatment dose of Yttrium 90 delivered via hepatic artery to the one or both lobes of liver
  - Approximately an hour
  - Average absorbed dose to tumour is 80-120 Gy
  - Return to ward
  - Aftercare



Post SIRT Care of the patient

- Overnight stay as in patient
- Transient side effects
  - Nausea, liver pain, fatigue
  - Rarely lung symptoms—pneumonitis related to radiation
  - Gastric/duodenal ulceration related to radiation
  - Very rarely may require surgical intervention
- Supportive treatment
  - Prednisolone tapering dose for 2weeks
  - Cyclizine 50 mg oral 3 times a day as required
  - Omeprazole 20 mg twice a day for 4 weeks
- FBC, LFTs weekly for day 8, day 15 and day 28
- Repeat MRI liver with contrast in 10-12 weeks

Results: 90Yttrium SIRT dataset UK

- 11 patients evaluated for SIRT
- 7 SDH deficient GIST patients
- 1 KIT mutant GIST patient
- 3 screen failures (1 SDH def, 1 NF1, 1 KIT exon9)
- Median age 35 years (range 18-54)
- Female:Male 6:1
- SDHA mut 4, SDHC epimutant 3

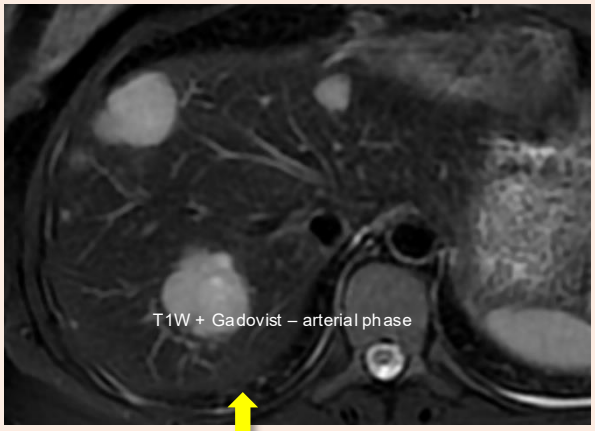
Results

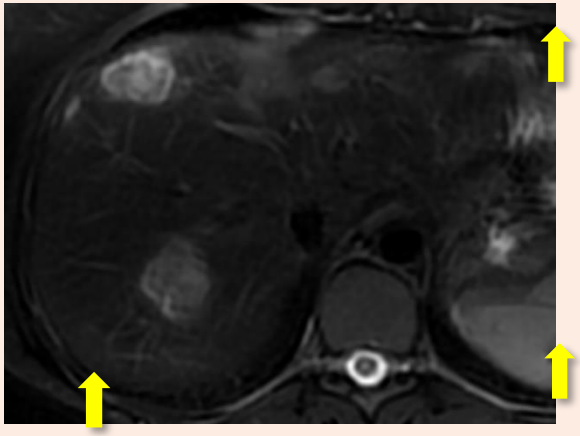
- Ongoing partial response in all patients
- Median FU 3 years
- Longest FU 7.5 years with ongoing no evidence of liver progression
- Manageable acute side effects
- No long term liver toxicities

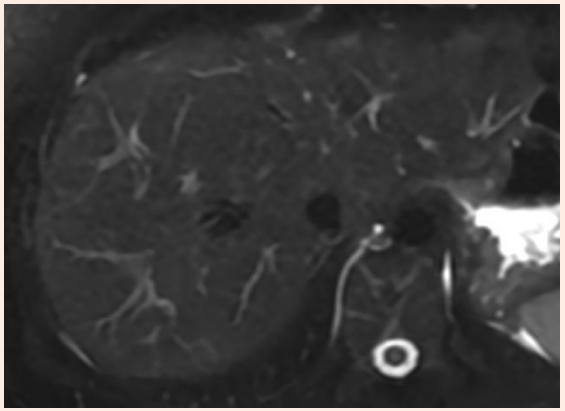
90Yttrium SIRT complications

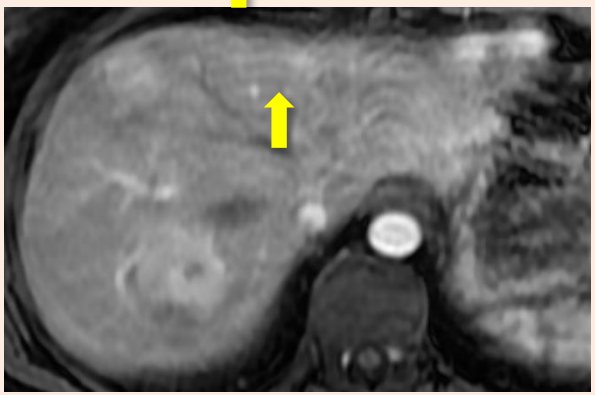
- Grade 1 nausea, fatigue 4 pts
- Grade 1-2 elevated ALT, Gamma GT 3 pts
- Gr anaemia -1 pt
- 1 pt ischaemic cholecystitis-cholecystectomy
- No bleeding complications
- No deaths related to procedure
- Well tolerated

Yttrium SIRT in SDH Deficient GISTS-Patient 2



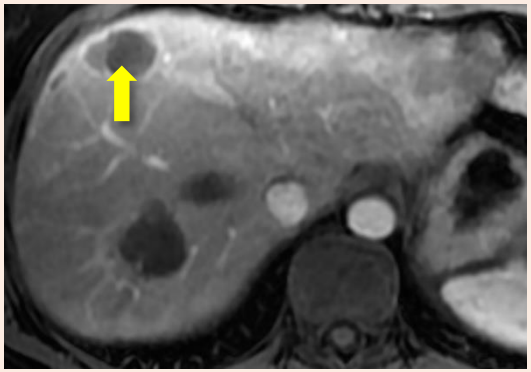






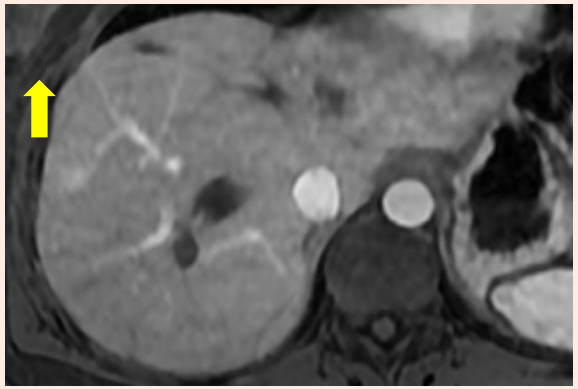
Baseline – Sep 2019

- Arterially enhancing metastases
- Hyperintense on T2W imaging



2/12 post SIRT – Dec 2019

- Features of necrosis
- Marked reduction in enhancement
- Size reduction, reduced T2 hyperintensity

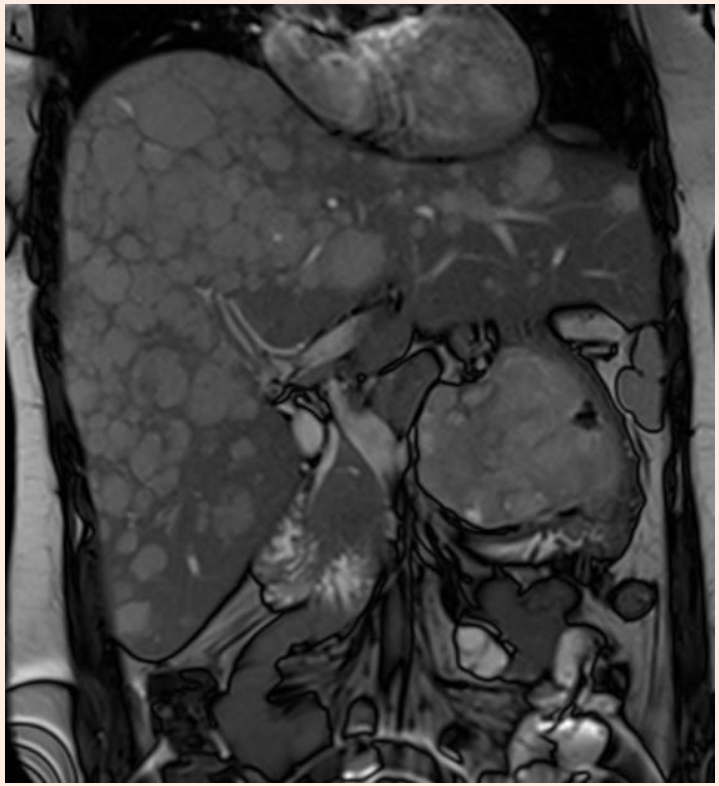


76 months post SIRT – Feb 2026

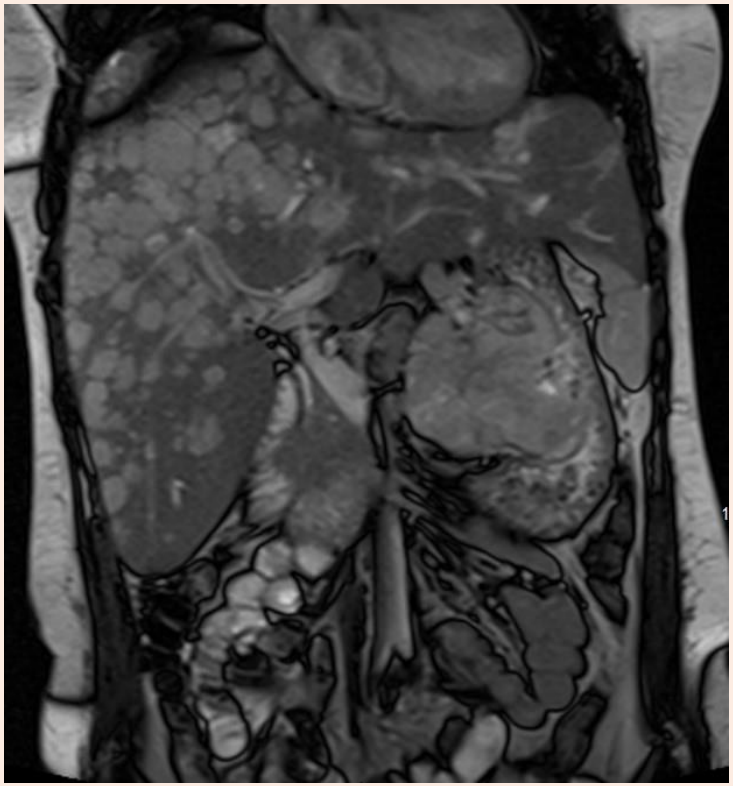
- Barely measurable residual lesions

Images courtesy Dr David Bowden CUHFT

Yttrium SIRT in SDH Deficient GIST patient 7



Baseline pre SIRT Oct 2025



12 weeks post SIRT May 26
2 stage procedure month apart

Conclusions

- Yttrium SIRT is a viable alternative to systemic therapy in patients with SDH Def GISTS
- **Durable responses**
- **SAFE**
- Acceptable and manageable toxicities
- Patients maintained good QoL post SIRT
- Joint manuscript between UK/Europe/USA researchers submitted
- Could be considered as an alternative to clinical trials


SDH-d
Gist
Gist
??
Gist
NF1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