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Stereotactic Ablative Body Radiotherapy for Locally Advanced (unresectable) non metastatic Pancreatic Cancer

Ganesh Radhakrishna

Outline of session

- Principles of Stereotactic Ablative Body Radiotherapy (SABR)

- Future developments on the horizon

  Promise of newer technologies

Principles of radiation therapy in Pancreatic tumours

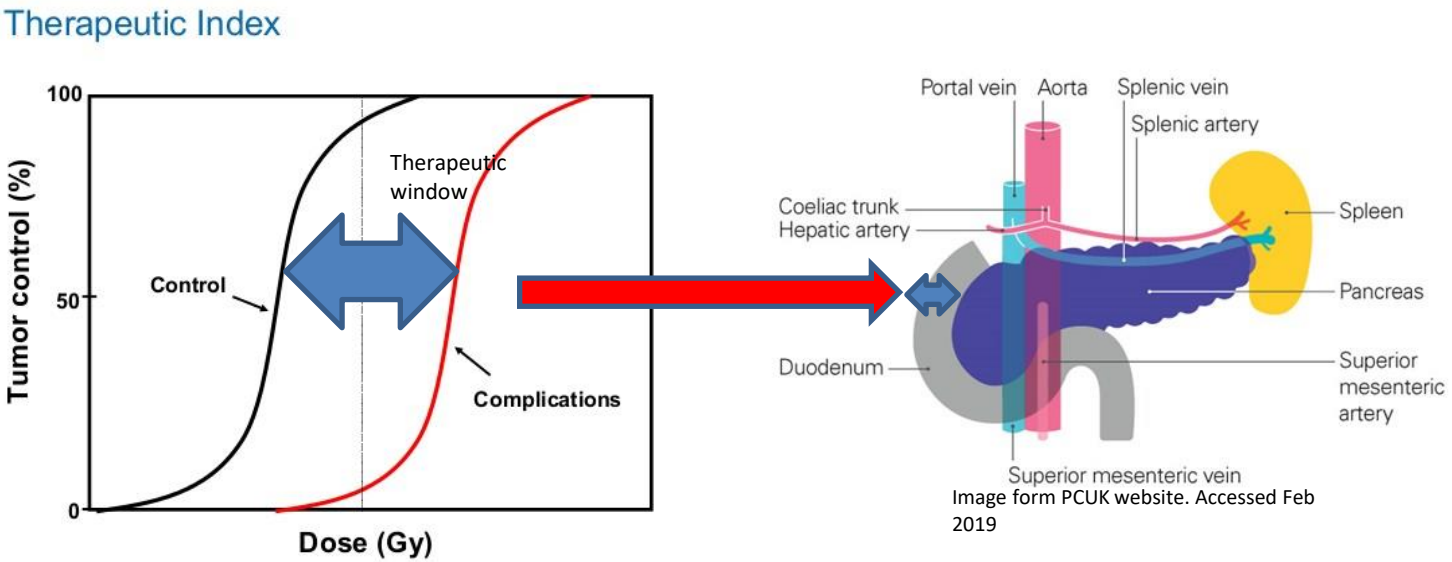

Image form PCUK website. Accessed Feb 2019

Linear Accelerators

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SABR

Stereotactic ablative body radiotherapy (SABR) refers to the precise irradiation of an image-defined extra-cranial lesion with the use of high radiation dose in a small number of fractions

UK SABR Consortium guidelines 2013

Core principles

- Image Guided RT = IGRT
  - Patient derived treatment volumes (personalised)
  - Adaptive Treatment (on line imaging)
  - Motion management
- High Dose to Target Volume
  - Increasing Biological effective doses (BED)
    - dose per treatment higher than conventional regimes (e.g. SABR)
- Maximal sparing of normal tissue
  - Dose sculpting

Pancreatic RT challenges

- Target Volume delineation
  - Difficult to visualise
  - Imaging underestimates tumour
- Organs at Risk
  - Close proximity
  - Narrow therapeutic index
- Motion

Potential benefits of SABR

- Longer freedom from treatment time / PFS
  Suker et al. EClinicalMed 17(2019)
- Improved tolerability / trend to improved OS
  CRISP metanalysis, Tcehelebi et al 2020
- Reduction in number of treatment visits
  Jones, C.M., *et al.* 2020
- Improved local control / symptom control
  Tangible benefit in reduction in pain
  Herman et al. Cancer April 2015
- Effects of SABR beyond primary disease control
  Griffin et al. IJROBP 2020. 107(4); 766-778

Clinical Commissioning Policy Statement: Stereotactic ablative body radiotherapy for patients with locally advanced, inoperable, non-metastatic pancreatic carcinoma

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Topic: Commissioning
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Stereotactic ablative body radiotherapy (SABR) is recommended to be available as a treatment option through routine commissioning for adults with locally advanced, inoperable, non- metastatic pancreatic carcinoma (LANPC) within the criteria set out in this document.

NHS E criteria

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Effectively patients currently receiving chemo RT over 6 weeks of treatment will be eligible

- Already established expertise in precision RT for HPB cancers
- Already established patient pathway

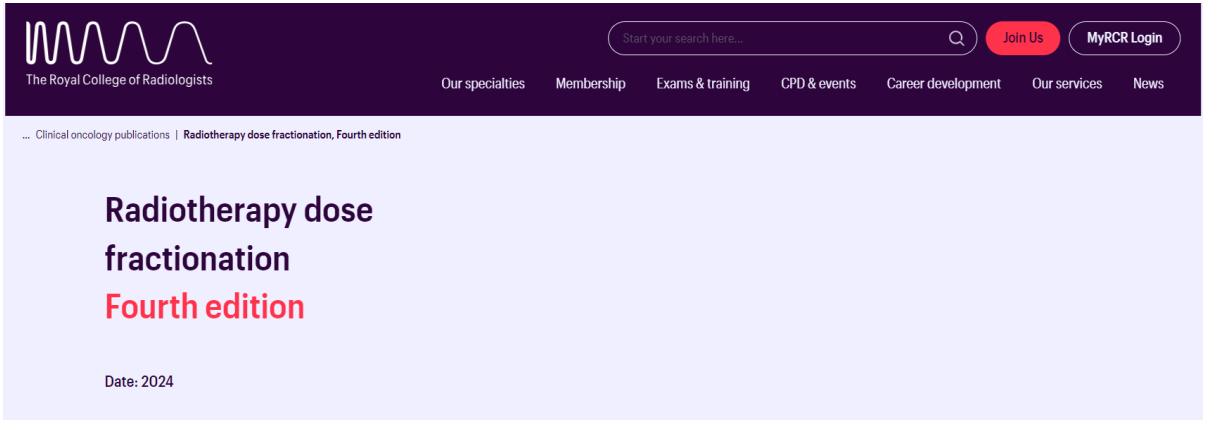
Key criteria

- Locally advanced non metastatic
- Minimum 3 months induction chemo and / or unable to tolerate SACT
- Who PS < 2
- Patients are suitable for pancreas SABR as determined by SABR and / or specialist HPB MDT

Roll out

- NHS E approval process
  - Approved protocol and workshops by RCR-SABR_C-RTTQA
  - Test case reviewed for outlining and plan by RTTQA team (2 clinicians and physics independently).
  - Benchmarked against a pre defined standard
  - First case treated in centre independently peer reviewed by RTTQA team
  - Ongoing review as indicated
  - 7 centres completed or partial approval

Guidelines

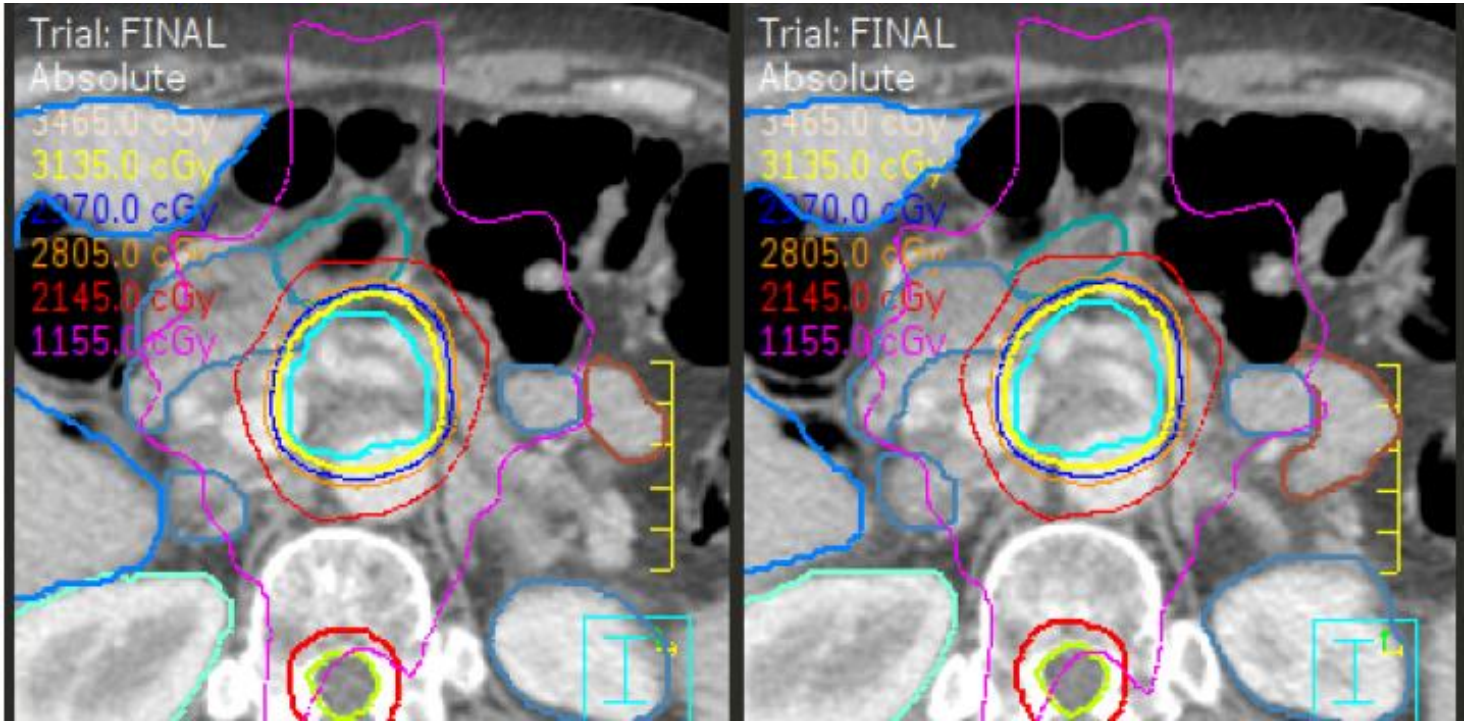


RCR guidelines: [Radiotherapy dose fractionation, Fourth edition | The Royal College of Radiologists (rcr.ac.uk)]

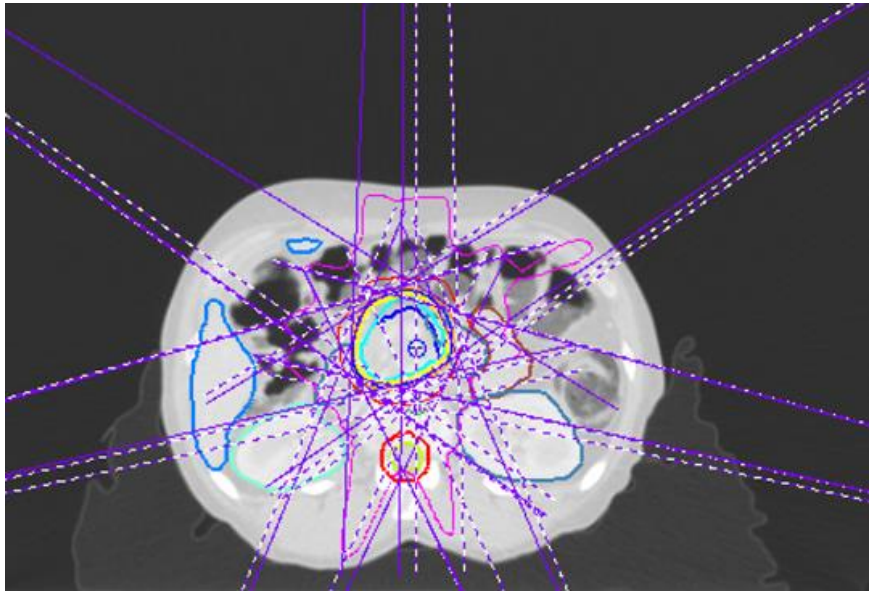
In progress

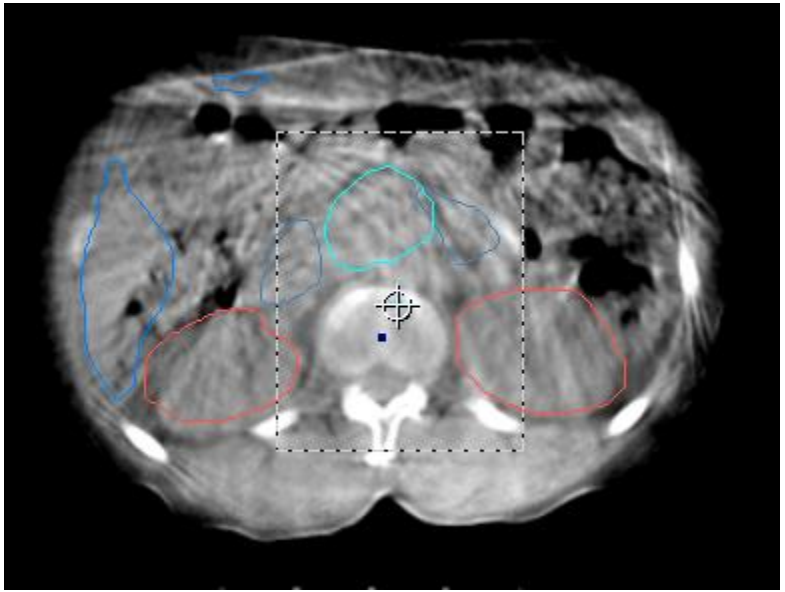
SABR-C guidelines update this year

SABR pancreas



SABR plan and on treatment verification





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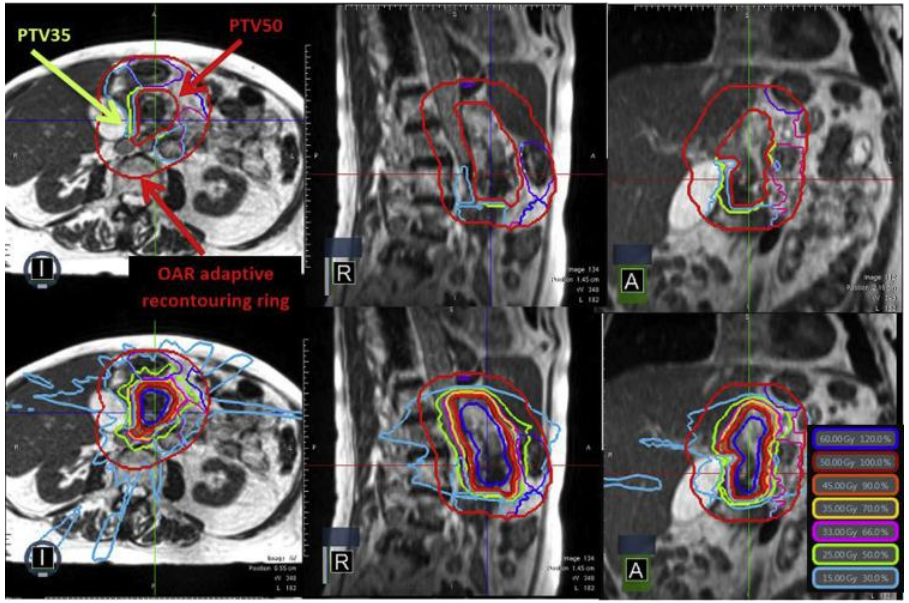
MR Guided Adaptive RT

IMPROVING THE THERAPEUTIC INDEX

MR_Linac

SMART

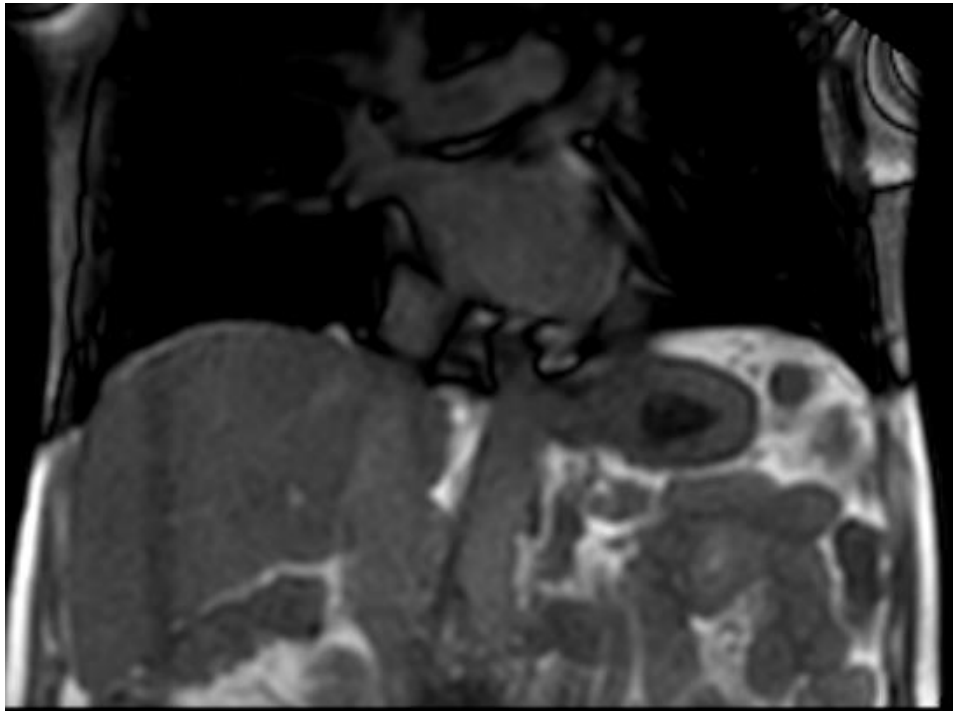
- Stereotactic MR Image guided Adaptive Radiation Therapy



Practical Radiation Oncology
Volume 11 Issue 2 Pages 134-147 (March 2021)
DOI: 10.1016/j.prro.2020.09.005

Respiratory motion GIF

bFFE coronal cine in free-breathing (FB)



Courtesy Mairead Daly

Physiological motion in BH GIFs

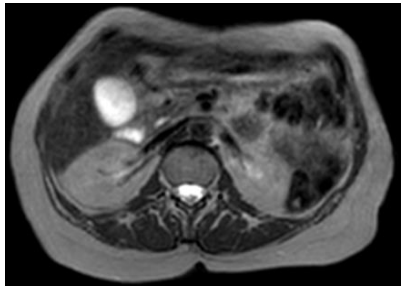
bFFE coronal cine in EEBH showing large peristaltic motion of pylorus and duodenum (fasted 2+hrs patient)

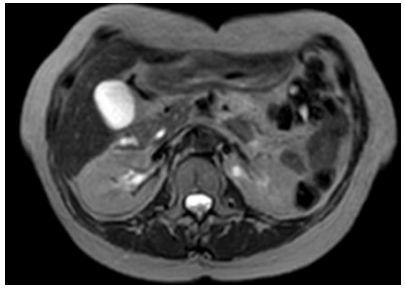
Courtesy Mairead Daly

Impact of motion and MR acquisition protocol on image

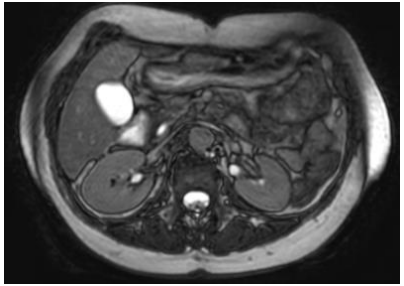
FB is more ‘fluff’

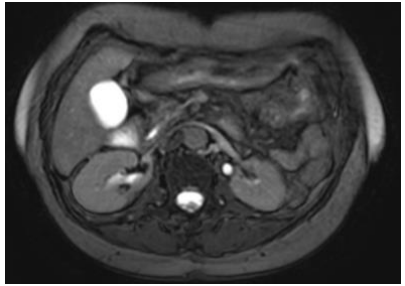
Imaging modalities

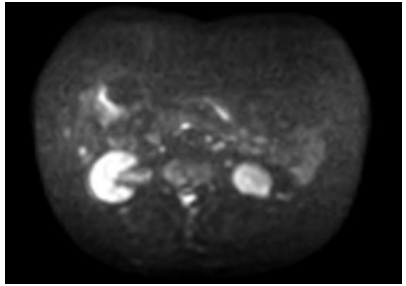

T2 3D Tra – free breathing


T2 3D Tra – abdominal compression


3DCT + IV contrast in EEBH


T2 3D Tra – bFFE 3D VANE


bFFE 3D VANE SPAIR


DWI

Courtesy Mairead Daly

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CLINICAL INVESTIGATION

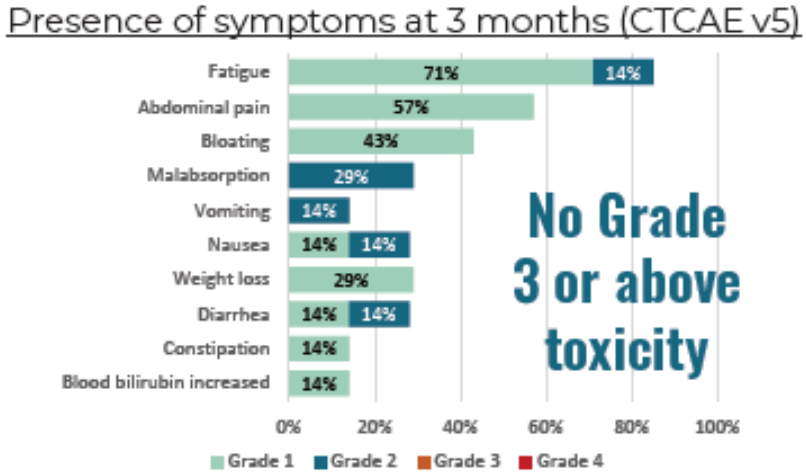
A Multi-Institutional Phase 2 Trial of Ablative 5-Fraction Stereotactic Magnetic Resonance-Guided On-Table Adaptive Radiation Therapy for Borderline Resectable and Locally Advanced Pancreatic Cancer

Parag Jitendra Parikh, BSE, MD,* Percy Lee, MD,† Daniel A. Low, PhD,‡ Joshua Kim, PhD,*
Kathryn E. Mittauer, PhD,§ Michael F. Bassetti, MD, PhD,‖ Carri K. Glide-Hurst, PhD,‖ Ann C. Raldow, MD, MPH,¶
Yingli Yang, PhD,¶ Lorraine Portelance, MD,# Kyle R. Padgett, PhD,# Bassem Zaki, MD,** Rongxiao Zhang, PhD,**
Hyun Kim, MD,†† Lauren E. Henke, MD,†† Alex T. Price, MS,†† Joseph D. Mancias, MD, PhD,‡‡
Christopher L. Williams, PhD,‡‡ John Ng, MD,§§ Ryan Pennell, PhD,§§ M. Raphael Pfeffer, MD,‖‖
Daphne Levin, PhD,‖‖ Adam C. Mueller, MD, PhD,¶¶ Karen E. Mooney, PhD,¶¶ Patrick Kelly, MD, PhD,##
Amish P. Shah, PhD,## Luca Boldrini, MD, PhD,*** Lorenzo Placidi, PhD,*** Martin Fuss, MD,††† and
Michael D. Chuong, MD§

*Henry Ford Health — Cancer, Detroit, Michigan; †City of Hope National Medical Center, Los Angeles, California; ‡Department of Radiation Oncology, University of California, Los Angeles, California; §Miami Cancer Institute, Baptist Health South Florida, Miami,

- Grade 3 toxicity = 0
- 1 year (from diagnosis) PFS= 80.1%; LC = 90%; OS = 93.9%

MRg ART in practice



Brocklehurst et al. The Royal College of Radiologists Open
Volume 1, Supplement 1, December 2023, 100043RCR Annual conference 2023

Current SABR trials

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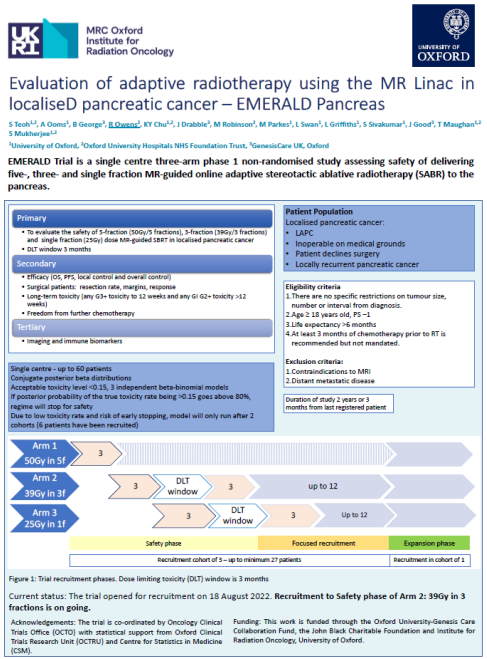


MRC Oxford Institute for Radiation Oncology

Evaluation of adaptive radiotherapy using the MR Linac in localiseD pancreatic cancer – EMERALD Pancreas

S Teoh[1,2], A Ooms[1], B George[3], R Owens[2], KY Chu[1,2], J Drabble[3], M Robinson[2], M Parkes[1], L Swan[1], L Griffiths[1], S Sivakumar[1], J Good[3], T Maughan[1,2], S Mukherjee[1,2]

[1]University of Oxford, [2]Oxford University Hospitals NHS Foundation Trust, [3]GenesisCare UK, Oxford

EMERALD Trial is a single centre three-arm phase 1 non-randomised study assessing safety of delivering five-, three- and single fraction MR-guided online adaptive stereotactic ablative radiotherapy (SABR) to the pancreas.

Primary
- To evaluate the safety of 5-fraction (50Gy/5 fractions), 3-fraction (30Gy/3 fractions) and single fraction (25Gy) dose MR-guided SBRT in localised pancreatic cancer
- DLT window 3 months

Secondary
- Efficacy (OS, PFS, local control and overall control)
- Surgical patients: resection rate, margins, response
- Long-term toxicity (any G3+ toxicity to 12 weeks and any GI G2+ toxicity >12 weeks)
- Freedom from further chemotherapy

Tertiary
- Imaging and immune biomarkers

Single centre - up to 60 patients
Conjugate posterior beta distributions
Acceptable toxicity level <0.15, 3 independent beta-binomial models
If posterior probability of the true toxicity rate being >0.15 goes above 80%, regime will stop for safety
Due to low toxicity rate and risk of early stopping, model will only run after 2 cohorts (6 patients have been recruited)

Patient Population
Localised pancreatic cancer:
- LAPC
- Inoperable on medical grounds
- Patient declines surgery
- Locally recurrent pancreatic cancer

Eligibility criteria
1.There are no specific restrictions on tumour size, number or interval from diagnosis.
2.Age ≥ 18 years old, PS ~1
3.Life expectancy >6 months
4.At least 3 months of chemotherapy prior to RT is recommended but not mandated.

Exclusion criteria:
1.Contraindications to MRI
2.Distant metastatic disease

Duration of study 2 years or 3 months from last registered patient

Figure 1: Trial recruitment phases. Dose limiting toxicity (DLT) window is 3 months

Current status: The trial opened for recruitment on 18 August 2022. **Recruitment to Safety phase of Arm 2: 39Gy in 3 fractions is on going.**

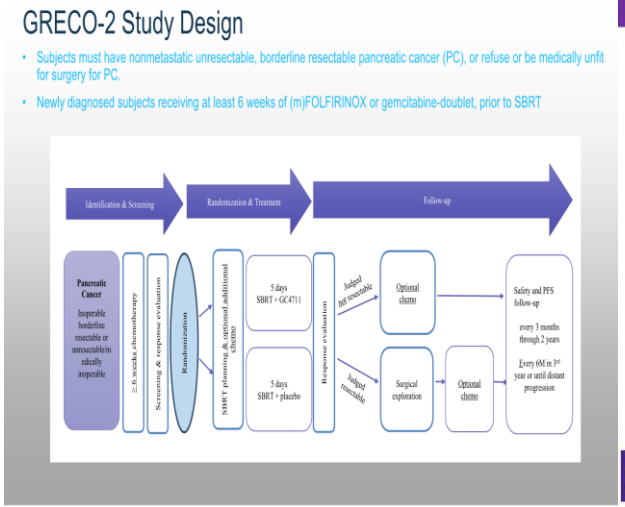
Acknowledgements: The trial is co-ordinated by Oncology Clinical Trials Office (OCTO) with statistical support from Oxford Clinical Trials Research Unit (OCTRU) and Centre for Statistics in Medicine (CSM).

Funding: This work is funded through the Oxford University-Genesis Care Collaboration Fund, the John Black Charitable Foundation and Institute for Radiation Oncology, University of Oxford.

Oxford University Hospitals NHS Foundation Trust

CANCER RESEARCH UK

GenesisCare



GRECO-2 Study Design

- Subjects must have nonmetastatic unresectable, borderline resectable pancreatic cancer (PC), or refuse or be medically unfit for surgery for PC.
- Newly diagnosed subjects receiving at least 6 weeks of (m)FOLFIRINOX or gemcitabine-doublet, prior to SBRT

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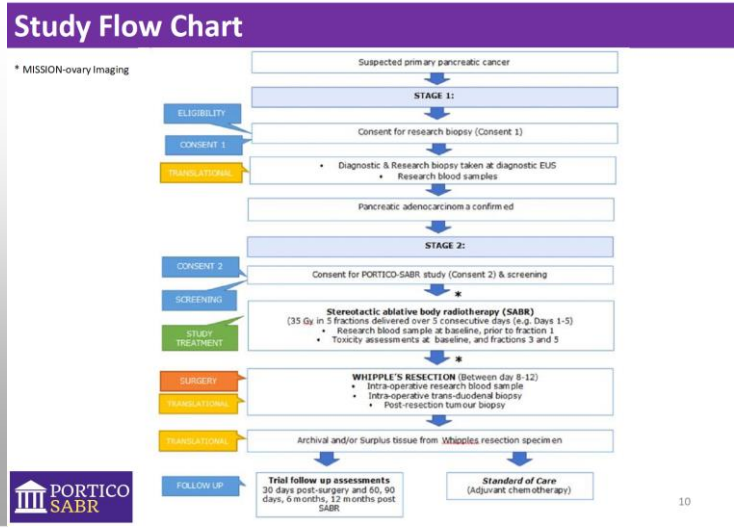

Study Flow Chart

* MISSION-ovary Imaging

PORTICO SABR

10

Schema courtesy Somnath Muyherjee – CI EMERALD trial Oxford and A Thankamma –CI PORTICO SABR Cambridge

GRECO-2 UK CI – James Good/ Rob Owen

Trials Update

- EMERALD – closed and in analysis. Patients recruited to all fract schedules
- GRECO 2 – futility end point reached so stopped early and not for further drug BUT continue SABR
- PORTICO – completed full recruitment. Analysis in progress. Translational analysis in AZ labs – Boston US

Summary

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- SABR is safe, convenient and efficacious
- Should be available to all patients – consider referral pathways in your network
- SABR requires further study with meaningful end points to refine its role in the patient pathway

Acknowledgements

- Patients and carers
- PCUK team
- Ex - NCRI Pancreatic Group
- UK HPB Medical and Clinical Oncology community
- PACT – UK Team
- MR-Linac research team and Momentum/ MR Bio trials team
- Pancreatic Technical RT teams at the Christie, Royal Marsden and Leeds

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