

MRI-guided
stereotactic
ablative
radiotherapy
for patients
with localised
pancreatic
cancer

GenesisCare Foundation Compassionate Access Programme

Information for healthcare professionals

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Summary

Patients with localised pancreatic cancer have variable access to precision radiotherapy in the United Kingdom. The n-SARS-CoV-2 pandemic has further disadvantaged this patient group by reducing the availability and safety of surgery and chemotherapy. The GenesisCare Foundation **Compassionate Access Programme** will make available MRI-guided stereotactic ablative radiotherapy (SABR) on the ViewRay MRIdian platform, without cost, to NHS patients with localised pancreatic cancer. The programme will generate preliminary clinical and patient-reported outcome data on a UK patient cohort that will act as a pilot phase prior to dose escalation within an ethically-approved basket study; inform the design of subsequent randomised clinical trials; and help to embed SABR in UK oncology practice.



The ViewRay MRIdian platform is at the GenesisCare centre in Oxford. Transport and accommodation will be provided.

Background

Surgery offers the only chance of curing pancreatic cancer, but most patients present with inoperable disease. Only 20% cases are resectable at presentation, and a proportion of these patients have medical comorbidities that make surgery high risk. Those with metastatic disease are typically offered chemotherapy or best supportive care. There is also an intermediate group, with borderline resectable (BRPC) or locally advanced pancreatic cancer (LAPC), where downstaging neo-adjuvant treatment can facilitate a resection to clear margins¹. In some patients, local (rather than metastatic) disease is the primary determinant of outcome. The definition of these clinical entities varies between institutions, and the optimal combination of systemic therapy and local therapy in the neo-adjuvant setting has not been defined². Similarly, the optimal regimen of radiation therapy remains uncertain. Conventionally fractionated chemo-radiation has been shown not to improve overall survival in comparison with chemotherapy alone³. There is however emerging evidence of a dose response relationship, proving that escalated radiation doses are associated with improved local control and overall survival. Therefore, delivering ablative doses of radiation using shorter treatment schedules given the high propensity for metastatic spread minimises the burden of treatment making it very attractive for patients⁴.

These considerations have been magnified by the n-SARS-CoV-2 pandemic. Access to surgery, systemic therapy and radiotherapy in the National Health Service (NHS) have all been adversely affected, with significant regional disparities emerging. There are some indications that peri-operative mortality in people with latent COVID-19 infection is increased⁵. Stereotactic ablative radiotherapy (SABR) for localised or locally recurrent pancreatic cancer is not funded by the NHS, and so to maintain access to a radiation therapy option that minimises hospital footfall, a consensus paper has recommended a hypofractionated radiotherapy regimen of 25–30 Gy in 5#, delivered using intensity modulated radiotherapy (IMRT) rather than unfunded stereotactic techniques⁶. The radiation dose to the stomach or duodenum is the usual limiting factor in pancreatic cancer radiation therapy, and this tolerance dose can usually be met by limiting the overall prescribed dose.

Whilst IMRT delivers a comparatively homogenous radiation dose to the target volume, SABR techniques facilitate a deliberate heterogenous dose distribution across the target, such that the radiation tolerances of surrounding organs at risk (OARs) and normal tissues can be respected, whilst as much of the tumour as possible receives a higher radiation dose. Whilst single fraction SABR has been associated with high rates of toxicity, fractionated approaches have shown excellent tolerance and local control, but with modest survival rates, albeit possibly superior to conventional fractionation⁷. A further retrospective institutional study showed the safety of delivering a moderately hypofractionated regime (67.5 Gy in 15 fractions) to tumours >1 cm away from luminal structures, with these patients having a significantly improved overall survival at three years of 31% in comparison to 9% for patients receiving a lower

biological effective dose⁸. This approach can also be used to treat tumours adjacent to OARs with careful considerations to the technical aspects of radiation delivery^{9,10}.

MRI-guided radiation therapy has emerged as a promising modality by which to achieve accurate radiation dose escalation¹¹. The benefits of treatment on the ViewRay MRIdian platform derive from its three technological innovations. Firstly, patients undergo reimaging with MRI at each treatment fraction. The soft tissue definition made possible by this step greatly exceeds that which is possible using the cone-beam computed tomography (CBCT) imaging on conventional linear accelerators, giving the treating physician greater precision and therefore confidence in addressing intra and inter-fraction anatomical variability. Secondly, the MRIdian planning system is able to generate, while the patient is in the treatment position, a new radiation plan that accounts for these anatomical variations. Thirdly, the system can detect the movement of the tumour with respiration, gating the radiation beam accordingly. These three elements of so-called adaptive SABR facilitate radiation dose escalation, whilst still respecting the radiation tolerance of normal tissues and surrounding OARs.

A recent retrospective multi-institutional analysis of 44 patients with LAPC treated on the MRIdian platform demonstrated that dose escalated SABR has the potential to improve overall survival compared with standard doses¹². All patients were treated on MRIdian, but dose, fractionation and planning approach varied between patients and institutions. Those treated to a BED10>70 Gy were deemed to have received high-dose therapy, whereas those receiving 70 Gy had received standard dose therapy. Of the high dose group, 83% underwent daily treatment adaptation, compared to 15% of the standard group. Importantly, grade 3+ toxicity was 7% in the standard dose/low adaptation group (and was seen in patients receiving concomitant gemcitabine), whereas no grade 3+ toxicity was seen in the high dose/high adaptation group. Median follow up was 17 months. At two years, 49% of the high dose group was alive, compared with 30% of the standard dose group (p=0.03). Local control was not statistically improved. On multi-variate analysis, only radiation dose and duration of induction chemotherapy were correlated with overall survival.

This data led to the prospective phase II study of stereotactic MR-guided on-table adaptive radiation therapy (SMART) study for patients with borderline or inoperable locally advanced pancreatic cancer, led by the Henry Ford Cancer Institute in Detroit and sponsored by ViewRay (NCT03621644). The primary endpoint of the study is grade 3 or greater toxicity at 90 days when delivering a dose of 50 Gy in 5#. Secondary endpoints are overall survival at two years, distant progression free survival at six months, and changes in patient-reported quality of life at three and 12 months.

In summary: standard dose SABR deliverable on conventional radiotherapy machines improves tumour control but may not improve survival, whereas the safe dose-escalated SABR that is made possible by MR-guidance may improve survival, without compromising quality of life.

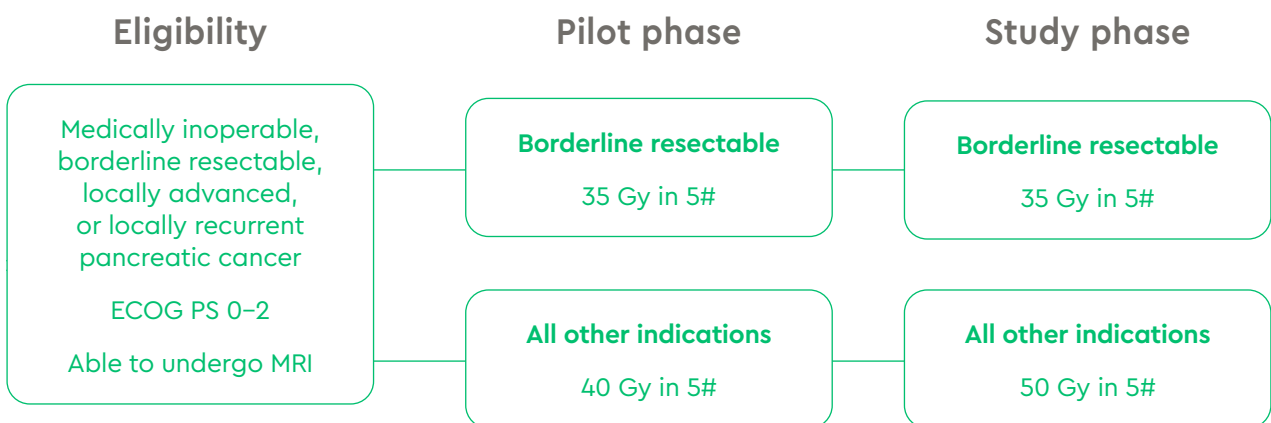
Rationale

GenesisCare is committed to building the evidence base for precision radiotherapy and MRI-guided SABR by making these techniques available to as many patients as possible. Those with medically inoperable, borderline operable, locally advanced and locally recurrent pancreatic cancer, particularly during the viral pandemic, have been identified as a group likely to derive clinical benefit. The goals of the GenesisCare Foundation **Compassionate Access Programme** are three-fold:

- To provide access to MRI-guided SABR to patients for whom other local therapies may not be available, or where hypofractionated radiotherapy is preferred, free of cost
- To build UK experience in delivering high quality SABR for this disease, with a commitment to sharing this expertise with the NHS oncology community
- To generate prospective clinical and patient-reported outcome data, and to act as a bridge to randomised comparisons of multi-modality treatment regimens incorporating MRI-guided SABR with existing standards of care

The pilot phase will not exist within a trial framework, but patients will be treated according to the defined eligibility and exclusion criteria set out below, and according to a radiotherapy treatment protocol aligned to international best practice in MR-guided SABR and the published literature outlined in the introduction. Clinician and patient-related outcome data will be recorded.

A full trial protocol is in preparation (A Study to Evaluate Feasibility, Clinical Benefit, and Prediction of Outcome using Adaptive Radiotherapy and Functional Imaging using the MR Linac, IRAS ID 279946. EMERALD: Evaluation of adaptive radiotherapy and imaging using the MR Linac for feasibility, clinical benefit and prediction of outcome in Different cancer types). Full dose escalation to 50 Gy in 5# will only proceed under the auspices of the study protocol.



Who is eligible for the Programme?

Patients with medically inoperable, borderline resectable, locally advanced or locally recurrent pancreatic cancer, without any evidence of metastatic disease, constitute the group potentially eligible for the programme.

■ Inclusion criteria

- Histologically/cytologically proven pancreatic malignancy. Where not available, NHS MDT consensus confirmation of likely malignancy is required
- Locally advanced, unresectable, or borderline resectable disease (abutment of superior mesenteric artery, coeliac axis, superior mesenteric vein, or portal vein); or locally recurrent disease after previous pancreatectomy; or medically inoperable disease
- ECOG performance status 0–2
- No contraindication to MRI
- Life expectancy >6 months
- Recovered from the effects of previous treatment with a minimum of two weeks break between previous treatment and first SABR fraction
- Axial imaging of the thorax, abdomen, and pelvis within six weeks of referral date, excluding metastatic disease; FDG PET is not mandated but is strongly preferred
- Adequate organ function as follows: haemoglobin > 90 g/L, absolute neutrophil count > $1.5 \times 10^9/L$, platelets > $80 \times 10^9/L$, bilirubin < 3.0 times upper limit of normal range, INR < 1.3 or correctable with vitamin K, AST or ALT < 5.0 times normal range, Creatinine < 200 $\mu\text{mol/L}$

Patients with operable disease are excluded, as they generally have the option of bridging chemotherapy within the NHS if surgery is not immediately available. It is preferred, but not mandated, that all patients referred have had at least three months of chemotherapy prior to SABR.

■ Exclusion criteria

- Frank invasion of adjacent gastrointestinal structures, as evidenced clinically and/or radiologically
- Patients with active hepatitis or clinically significant liver failure (encephalopathy, oesophageal varices, portal hypertension), or patients with chronic active gastro- duodenal ulcer disease
- Prior overlapping abdominal radiotherapy. Prior breast, pelvic and lung radiation is permitted, as long as no overlap occurs
- Therapeutic anticoagulation is a relative contra-indication

What is the referral and treatment process?

All patients must be referred by their local oncologist or surgeon on the Pancreas SABR Referral Form, an editable pdf being available from:

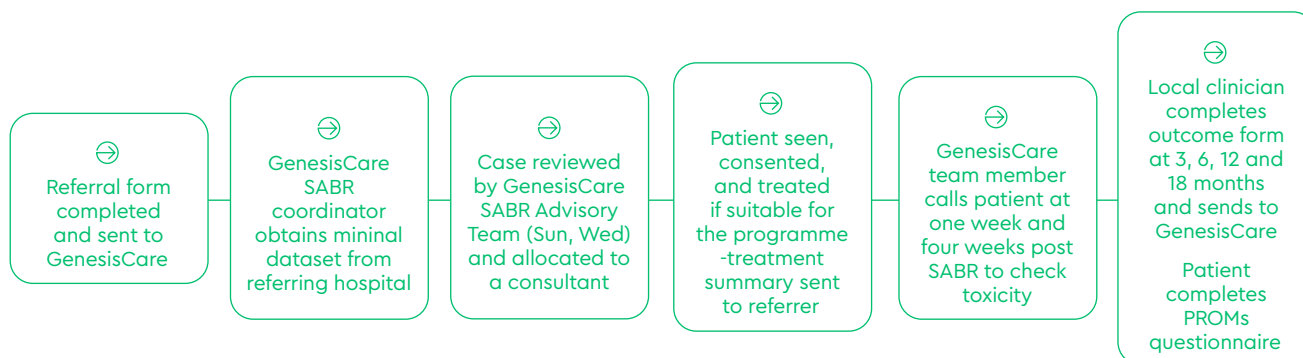
pancreas@genesiscare.co.uk

The minimal dataset consists of the fully completed referral form, a histology report confirming malignancy or an MDT report stating the diagnosis on the balance of probability, and the most recent whole-body axial imaging report. The GenesisCare SABR Coordinator obtains relevant imaging and this, along with the clinical details, is reviewed by a twice-weekly online SABR Advisory Team meeting. If the application is approved, the patient is then seen at one of our Pancreas SABR Hubs by a clinician with extensive SABR experience.

Pancreas SABR Hub	Consultant Clinical Oncologists
GenesisCare, Oxford	Dr James Good Dr Andrew Gaya Prof Somnath Mukherjee
GenesisCare, Birmingham	Dr James Good
GenesisCare, Cambridge	Dr Alexander Martin
GenesisCare, Nottingham	Dr Luis Aznar-Garcia

If the patient meets the eligibility criteria, they are then booked to undergo simulation and treatment at GenesisCare in Oxford. They are followed up four weeks after completing treatment by the SABR Hub clinician, before being returned to the ongoing care of their referring clinician in the NHS. Full details of the treatment delivered will be provided. The process is shown in figure 1:

Fig 1. ViewRay MRIdian Patient Treatment Journey



Supporting patients with travel and accommodation

All patients accepted into the GenesisCare Foundation **Compassionate Access Programme** can access the complementary driver service, removing the burden of travel for the patient and their families. The service is available for each journey to and from the Oxford centre for both the planning scan and treatment. All UK patients are eligible for this complementary service, enabled by the generous support of our partners at Pancreatic Cancer Research Fund. Patients travelling beyond 75 miles to the Oxford centre can opt to access accommodation support from the night before their treatment until their treatment completes. GenesisCare will coordinate all travel and accommodation for all patients.

An experienced MRIdian team

Adaptive, MR-guided SABR at GenesisCare is a fully consultant-delivered service. At every treatment fraction, the patient undergoes planning MR, recontouring of tumour and OARs, and replanning to maximise tumour coverage and minimise OAR dose. The team has treated >100 patients in the first seven months of operation, including many patients with complex abdominal targets. A summary of the adaptive workflow is shown in figure 2.

What outcome data will be collected?

The primary purpose of the GenesisCare Foundation **Compassionate Access Programme** is to make precision radiotherapy available during the COVID-19 pandemic, and its aftermath. Patients are under no obligation whatsoever to participate in the collection of PROMs, and referrers are under no obligation to provide follow up data.

The secondary purpose, however, is to generate a body of data that will inform the development of clinical trials aimed at establishing a definitive role for SABR in the management of pancreatic cancer. As such, we aspire to collect the following data on all patients treated within the Programme.

Patient-reported quality of life using the EORTC QLQ-C30 and QLQ-PAN26 tools at baseline, four weeks, three months, six months, 12 months and 18 months.

- Clinician-reported toxicity according to CTCAE version 4.0 criteria
- Six-month and 12-month local control, as defined on local imaging
- Overall progression-free survival, as defined on local imaging
- Overall survival at 18 months
- Investigational imaging biomarkers of local control (details to be confirmed)

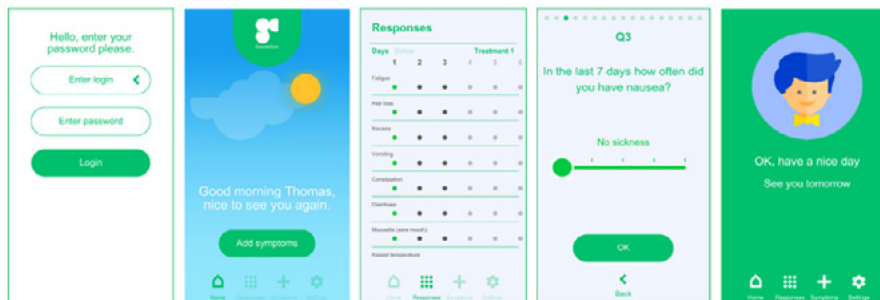
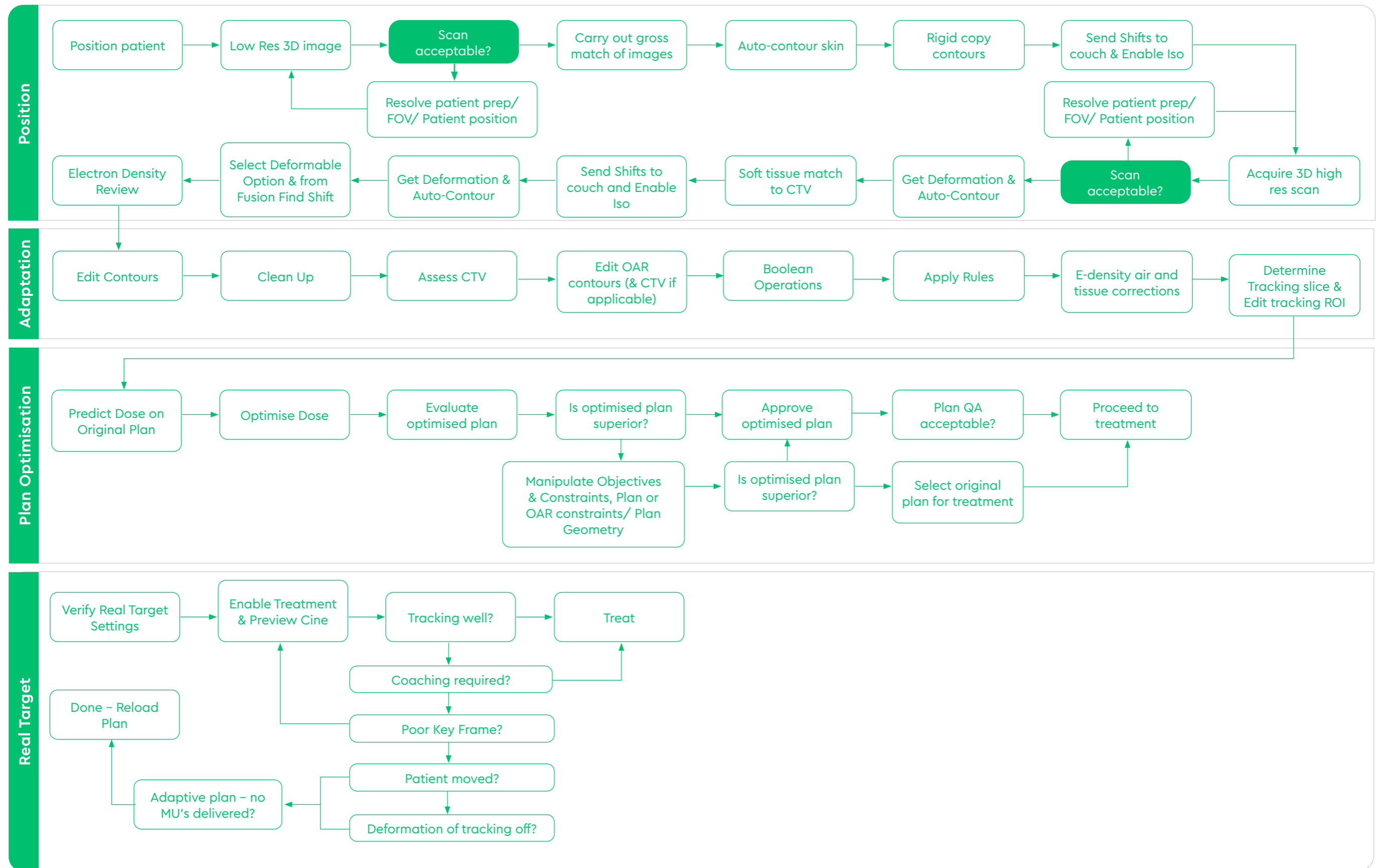


Fig 2. ViewRay MRIdian Adaptive Treatment Workflow



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About the sponsors



The GenesisCare Foundation is an independent health promotion charity born from the philanthropic vision of GenesisCare. Its mission is to seek out and support life-changing improvements in cancer and cardiac care, in order to create profound impact at scale for both individuals and communities. It does so by investing in research that has the power to radically improve patient outcomes and by enabling access to innovative care. Chaired by Dan Collins, Founder and CEO of GenesisCare, the Board which governs the Foundation is comprised of experts in their fields who share a passion for philanthropy. Learn more at genesiscare.com/au/genesiscare-foundation



Pancreatic Cancer Research Fund is the only national charity dedicated exclusively to funding pancreatic cancer research. With this single-minded focus, its mission is to defeat pancreatic cancer by funding and promoting innovative, world-class research into the disease – research that will lead to the development of more effective detection, diagnosis and treatments and improved survival for patients.



ViewRay is re-envisioning radiation therapy to conquer cancer with the MRIdian® MR-Guided Radiation Therapy System. MRIdian allows clinicians to see as they treat, adjusting the beam to allow for movement and anatomical changes. The ability to target the tumor while sparing the healthy tissue brings a new level of control and confidence to stereotactic ablative radiotherapy. In routine clinical use throughout the world, MRIdian is revolutionising radiation oncology and changing the paradigm in patient care.

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Oxford University is world-famous for research excellence, innovation, and home to some of the most talented people from across the globe. Its work helps the lives of millions, solving real-world problems through a huge network of partnerships and collaborations. The Oxford Institute for Radiation Oncology is one of the world's leading centres for radiotherapy-related research and has established a 10-year partnership with GenesisCare, which enables the treatment of NHS patients on the ViewRay MRIdian® as a platform for state-of-the-art treatment and research thanks to a generous donation from the John Black Charitable Foundation.



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