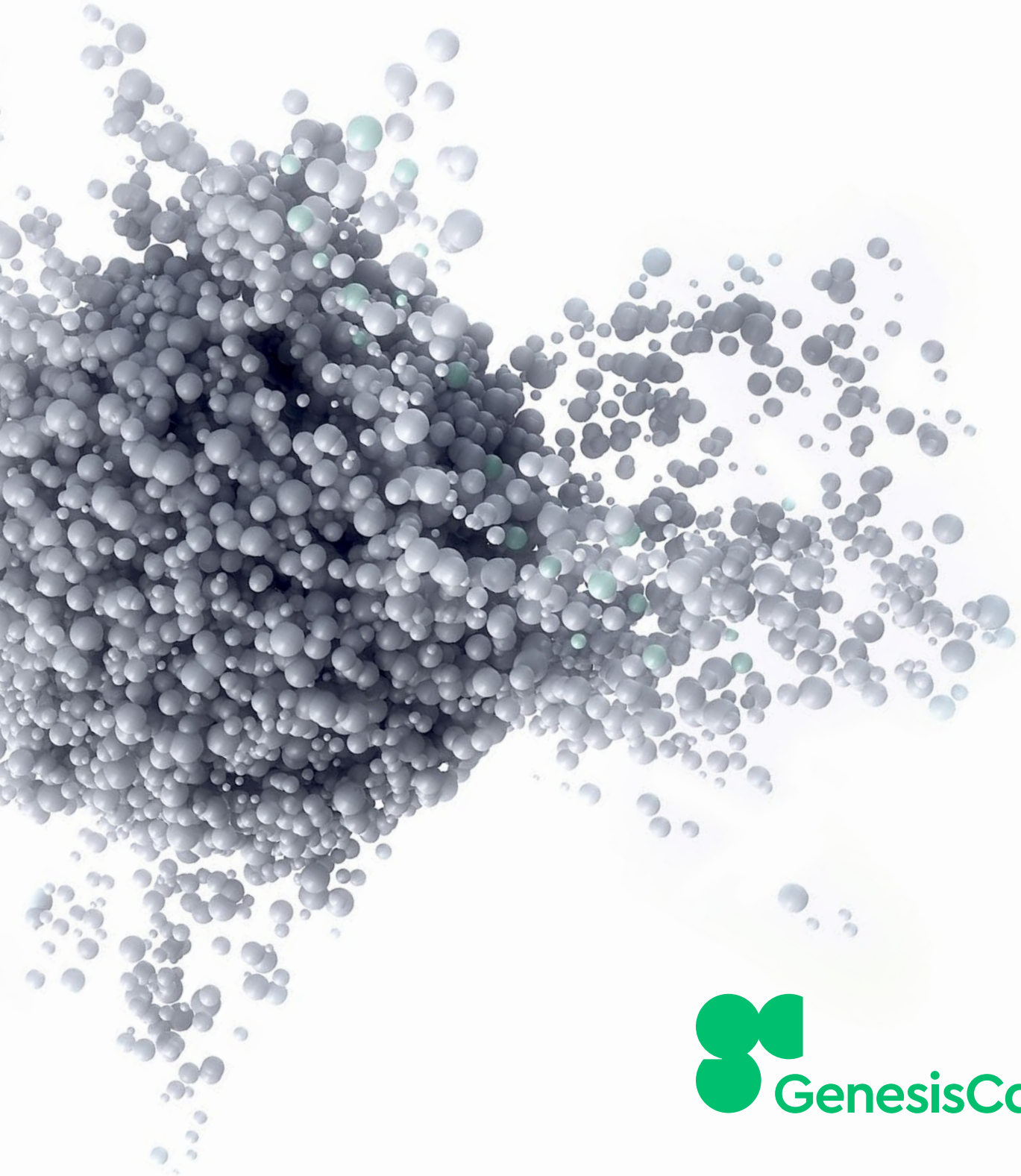
Stereotactic ablative radiotherapy

Evidence summaries

Oligometastatic and Oligoprogressive disease

Spring 2022 · Issue 1



GenesisCare

SABR-COMET and other trials have given us randomised evidence that SABR improves overall survival for oligometastatic disease with acceptable toxicity when added to standard therapy

Dear Colleagues,

The use of stereotactic ablative radiotherapy (SABR) in the treatment of both primary and metastatic cancers has been increasing steadily over the last 20 years. It is now an established treatment for selected primary cancers of the lung, liver, pancreas, kidney and prostate, and for patients with metachronous oligometastases.

There is also growing use in the context of synchronous oligometastases, and for patients with oligoprogression on systemic therapy.

In the context of advanced, metastatic disease the role of SABR is well established.

In the oligometastatic disease setting, the recently published long-term outcomes of the SABR-COMET trial has demonstrated the significant benefits SABR can offer to patients with a limited number of sites of metastatic disease.

Prior to this study there has been over two decades of non-randomised published data highlighting the potential benefits of an aggressive ablative strategy in the management of selected oligometastatic cancer patients.

These SABR studies have prompted acute interest in the approach to oligoprogressive and oligometastatic disease and the opportunity to improve outcomes for these patients. It has led to the creation of more randomised trials designed to answer the specific question: does the use of SABR in oligometastatic cancer lead to improvements in patient outcomes.

This brochure introduces the SABR-COMET trial results and summarises the key trials and ongoing studies that are defining the role of SABR.

If you would like any more information about SABR treatment or about how to refer patients to GenesisCare for SABR, then please contact your local Referrer Engagement Manager who will be able to put you in touch with a member of the SABR Advisory Team (SAT) and can provide you with advice on how to become credentialled.

SABR Clinical Reference Group
GenesisCare UK

Contents

SABR

Patient selection, patient choice

Patient selection is a key determinant of successful treatment outcomes. It is hoped and anticipated that data from SABR-COMET-3 and SABR-COMET-10 will provide more definitive data guiding patient selection. In the meantime, doctors and patients need to make treatment decisions with the data currently available.

At GenesisCare we provide evidence-based medicine and are committed to helping to build the body of evidence for SABR, notably through our partnership with the University of Oxford to increase trial access to MRI-guided SABR.

As a patient-centric organisation, we are also motivated by the opportunities SABR presents to improve patient experience and quality of life. The case studies in this publication highlight the opportunity to improve the experience of people with oligometastatic disease, taking into account personal preferences.

This illustrates the three core principles of our SABR service at GenesisCare.

- **Improving patient outcomes** – A growing body of evidence indicates SABR can improve outcomes for patients with oligometastatic lesions
- **Improving patient experience and quality of life** – SABR potentially offers patients an improved treatment experience – with fewer visits needed, treatment completing over a shorter time period and generally low toxicity (in comparison to other available treatment options)
- **Patient choice** – Ultimately the decision to go ahead with SABR is the choice of the patient, made in conjunction with their treatment team. The decision needs to be as informed as possible but also recognise the importance of the patient's personal objectives and wishes

"GenesisCare is one of the largest global private providers of SABR treatment, delivering evidence-based treatment to 400 private and NHS patients a year in the UK, on a variety of advanced treatment platforms."

GenesisCare

Definitions

SABR, otherwise known as stereotactic body radiotherapy (SBRT), refers to the precise irradiation of an extracranial lesion using a small number (typically one to five) of high-dose fractions. It harnesses the power of large doses of radiotherapy, improving the chance of tumour ablation compared to conventionally fractionated radiotherapy. Whilst these large doses are also potentially more damaging to normal tissue, the exquisite precision of modern equipment means that this treatment can be delivered safely. MR-guidance maximises the chance of delivering an ablative dose to tumour in challenging anatomical locations whilst respecting the tolerance of normal tissues. It also makes it possible to treat multiple tumours in the liver, for example, and facilitates safer re-irradiation.

Definitions – SABR

At GenesisCare, we use the term SABR to refer to stereotactic ablative radiotherapy. SABR delivers high dose, hypofractionated radiotherapy doses with high precision to small tumour targets. Elsewhere, SABR is also described as:

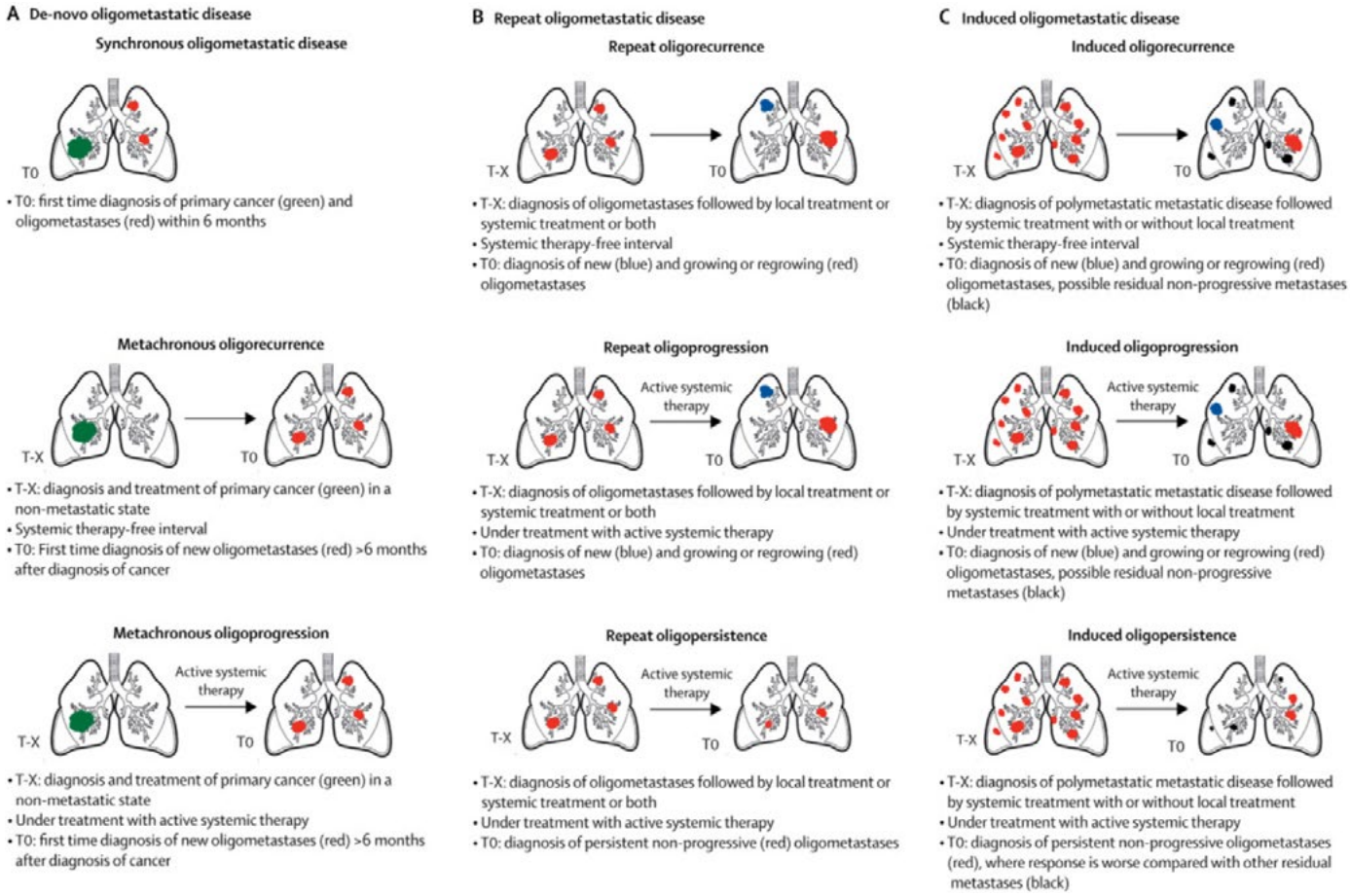
- SBRT – stereotactic body radiation therapy
- MDRT – metastasis-directed radiotherapy

Definitions – disease state

There has been plenty of debate in scientific literature about the definition of terms such as oligometastatic and oligoprogression. At GenesisCare, we use the following definitions:

- Oligometastatic disease – development of up to five metastases
- Oligoprogression – progression at a limited number of sites after achieving controlled, stable disease that has responded to treatment
- Synchronous – metastasis identified within six months of primary tumour
- Metachronous – metastasis identified more than six months after primary tumour

GenesisCare also follows the latest consensus recommendation from the European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer[1]



Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Overview of SABR-COMET Phase II trials

A number of studies have been published in recent years demonstrating the benefits of SABR treatment to patients with oligometastases. Until recently however, data comparing the benefits of SABR with standard treatment were lacking. The SABR-COMET trial is the first randomised, controlled trial to compare the effects of SABR treatment plus standard of care with standard of care alone on oligometastatic disease.

SABR-COMET – a ground-breaking Phase II trial for oligometastatic disease

The concept of oligometastatic disease, first defined in 1995[2], suggests that patients with a limited number of metastases can have improved outcomes if all metastatic sites are ablated. In recent years, a growing number of published studies have demonstrated benefits and better-than-expected survival in patients with oligometastases treated with ablative therapies including SABR. Interest in and use of SABR continues to increase, based on the growing bank of evidence of effectiveness as well as a generally low toxicity profile. In addition, the convenience of the treatment regimen and subsequent potentially lower impact on patients' quality of life in comparison with other treatments is an important consideration.

As published data on SABR have generally been from observational studies, there have been concerns that any benefits may have been impacted by selection bias. The SABR-COMET (Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases) trial is significant in that it is the first randomised, controlled trial to compare outcomes of SABR treatment plus standard of care with standard of care alone in oligometastatic disease.[3] The results suggested that SABR can improve long-term outcomes in patients with a limited number of metastases. This interpretation has been further reinforced since by the publication of long-term results. Whilst Phase III trials are ongoing, the published SABR-COMET reports remain the most comprehensive data available to guide treatment decisions for the use of SABR in oligometastatic disease.

Study design

SABR-COMET[3] was a randomised, open-label Phase II study carried out at 10 hospitals in Canada, the Netherlands, Scotland and Australia. Patients had all had definitive treatment for a primary tumour at least three months before enrolment and between one and five metastatic lesions. Patients had no more than three metastases in any one organ. A total of 99 patients were randomised to receive palliative standard of care (control group) or standard of care plus SABR to all metastatic lesions (SABR group) in a 1:2 ratio. The sample size was chosen based on the ability to detect a six month improvement in median survival using a two-sided α of 0.20 and a power of 80%, based on an estimated median survival of nine months in the control group and assuming 5% of patients would be lost to follow-up. Patients were seen every three months for two years and then every six months until year five. The protocol was later amended so patients would continue to be seen every year until year 10. SABR-COMET is due to end in June 2026.

Patients were stratified by the number of metastases (one to three, or four to five). The primary endpoint was overall survival. Secondary endpoints were quality of life, toxicity, progression-free survival, proportion of patients with lesional control and further chemotherapy or systemic therapy.

Radiotherapy was delivered in the control group to the standard principles of palliative radiation. The goal was to alleviate symptoms or prevent anticipated complications of progression. Treatment fractionations varied from 8 Gy in one fraction to 30 Gy in 10 fractions.

In the SABR group, SABR was delivered to all sites of metastases, with the goal of achieving disease control whilst minimising potential toxicities. Allowable doses ranged from 30 to 60 Gy in three to eight fractions. Single fractions of 16 to 24 Gy were allowed for metastases in the brain and vertebrae. The choice of systemic therapy was as indicated and at the discretion of the medical oncologist in both groups. Patients in the SABR group who developed new metastases were able to have further SABR at those sites as salvage.

SABR-COMET baseline demographics

	Control group (n=33)	SABR group (n=66)
Median age	69 (64-75)	67 (59-74)
Men	19 (58%)	40 (61%)
Women	14 (42%)	26 (39%)
Site of primary tumour		
Breast	5 (15%)	13 (20%)
Colorectal	9 (27%)	9 (14%)
Lung	6 (18%)	12 (18%)
Prostate	2 (6%)	14 (21%)
Other	11 (33%)	18 (27%)
Number of metastases		
1	12 (36%)	30 (46%)
2	13 (40%)	19 (29%)
3	6 (18%)	12 (18%)
4	2 (6%)	2 (3%)
5	0 (0%)	3 (5%)
Location of metastases		
Adrenal	2/64 (3%)	7/127 (6%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)
Lung	34/64 (53%)	55/127 (43%)
Other	5/64 (8%)	4/127 (3%)
Brain	3	1
Lymph nodes	1	3
Para-renal	1	0

Fig 1: Long-term progression-free survival in overall population

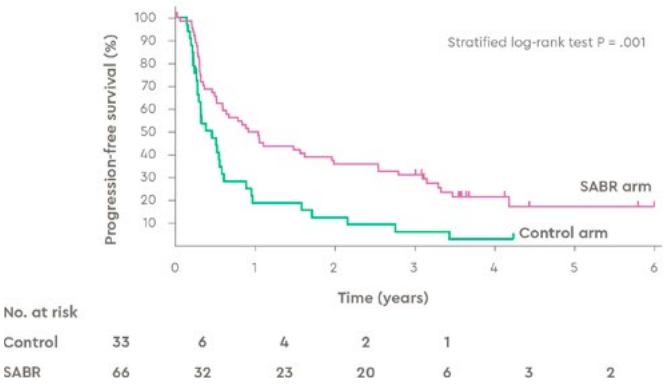
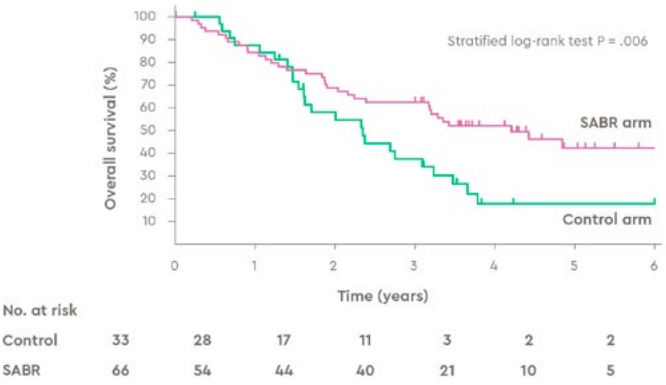


Fig 2: Long-term overall survival in overall population



Key results

Initial results from SABR-COMET were published in 2019[4], showing a 13 month increase in overall survival in the SABR group and a doubling in median progression-free survival. Due to a larger number of patients than expected reaching five-year survival, follow-up was extended and longer-term data were published in June 2020 (Figures 1 and 2).[5] The longer-term data showed the effects of SABR on overall survival to be larger in magnitude than previously reported, with a median overall survival benefit of 22 months (28 months in the control group versus 50 months in the SABR group), compared with 13 months in the initial analysis. As well as providing evidence of improved outcomes, the study authors also indicated that the data showed the strongest clinical evidence to date in supporting the concept of the oligometastatic state.

The most common radiation fractionation doses in the SABR group were 35 Gy in five fractions (39 targets), 60 Gy in eight fractions (19 targets) and 54 Gy in three fractions (16 targets). In the initial report, two patients had received salvage SABR for new metastatic sites and two other ablative therapies. As reported in the longer-term data, since then one patient in the control group received SABR for a solitary liver lesion that had initially responded to targeted therapy but progressed with no new sites of disease. Nine patients in the SABR arm received salvage SABR for new metastases, including three of the 10 patients who survived beyond five years.

Safety

SABR was well-tolerated by the majority of patients, with adverse events of grade 2 or above in three (9%) of the control group and 19 (29%) of the SABR group. There were three deaths in the SABR group that were possibly, probably or definitely related to treatment (one due to radiation pneumonitis, one due to pulmonary abscess and one due to subdural haemorrhage after surgery to repair a SABR-related perforated gastric ulcer). There were no treatment-related deaths in the control group.

"SABR-COMET represents the most comprehensive data available to guide SABR treatment in oligometastatic disease."

GenesisCare

SABR-COMET study outcomes

	Initial results[4]		Long-term results[5]	
	Control group	**SABR group**	**Control group**	**SABR group**
Follow-up (median)	25 months	26 months	51 months	
Death from any cause (n)	16 (48%)	24 (36%)	24 (73%)	35 (53%)
Overall survival, median (95% CI)	28 months (19-33)	41 months (26-not reached)	28 months (18-39)	50 months (29-83)
	Stratified log rank p=0.090		Stratified log rank p=0.006	
5-year overall survival, (95% CI) Stratified log rank p=0.006			17.7% (6-34%)	42.3% (28-56%)
Progression events (n)	28 (85%)	39 (59%)	29 (88%)	45 (68%)
Progression-free survival, median (95% CI)	6.0 months (3.4-7.1)	12 months (6.9-30.4)	5.4 months (3.2-6.8)	11.6 months (6.1-23.4)
	Stratified log rank p=0.0012		Stratified log rank p=0.001	
4-year progression-free survival (95% CI)			3.2% (0-14%) (last patient censored)	21.6% (12-33%)
5-year progression-free survival (95% CI) p=0.001			Not reached	17.3% (8-30%)
Proportion of patients with lesional control	49%	75%	46%	63%
Quality of Life assessment - FACT-G score at 6 months, mean (SD) p=0.99	82.5 (16.4)	82.6 (16.6)	No significant differences reported	
Adverse events				
Grade 2 or higher	3 (9%)	19 (29%)	No new events reported	No new events reported
Grade 5 treatment-related events	0 (0%)	3 (4.5%)		
Received palliative systemic therapy	19 (58%)	34 (52%)	21 (64%)	36 (55%)
Received palliative radiotherapy	21 (64%)	13 (20%)	23 (70%)	16 (24%)

Limitations of SABR-COMET – controversies and future directions

As a Phase II trial, the limitations of SABR-COMET were recognised by the study authors. For example, there has been some concern about an imbalance in the study groups at baseline, with more patients with prostate and breast cancer (who may be expected to have a better prognosis) or with a single metastasis in the SABR group. However, post-hoc sensitivity analysis excluding patients with prostate cancer showed five-year overall survival of 33.1% (95% CI 20–47%) in patients treated with SABR compared with 16.2% (95% CI 5–32%) in the control arm. Data from Phase III trials will further explore some of the questions raised due to the limitations of SABR-COMET.

Ongoing research: SABR-COMET-3 and SABR-COMET-10 Phase III trials

Whilst the data from SABR-COMET are strongly indicative of a treatment benefit of SABR, data from ongoing Phase III trials are needed to further prove a survival benefit as well as define the maximum number of metastases where SABR leads to improved outcomes.

Due to the encouraging results reported from SABR-COMET, two larger Phase III trials have now commenced: SABR-COMET-3 (Stereotactic Ablative Radiotherapy for the comprehensive treatment of 1–3 oligometastatic tumours)[6] and SABR-COMET-10 (Stereotactic Ablative Radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumours)[7], researching overall survival in patients with 1–3 or 4–10 metastases, respectively. By stratifying patients by the number of metastases present at baseline, it is anticipated that data from these trials will provide further guidance in identifying patients most likely to benefit from SABR.

Summary of ongoing Phase III trials: SABR-COMET-3 and SABR-COMET-10

	Study start date	Study end date (due)	
SABR-COMET-3	Nov 2019	Dec 2028	• Compares standard of care (SOC) vs. SOC + SABR • 297 patients in 1:2 ratio • 1-3 metastases • Primary endpoint: overall survival • Secondary endpoints: side effects, progression-free survival (PFS), quality of life (QoL), health-related QoL (HRQoL), resource utilisation, correlation between candidate biomarkers of oligometastatic disease (blood-derived) and oncologic outcomes
SABR-COMET-10	Feb 2019	Jan 2029	• Compares SOC vs. SOC + SABR • 159 patients • 4-10 metastases • Primary endpoint: overall survival • Secondary endpoints: PFS, time from randomisation to development of new metastatic lesions, QoL, toxicity, overall survival at study midpoint

Other key trials

Name of trial	Author, year	Phase	Trial overview	Patients	Primary site	Metastases	Status
CORE (Conventional care versus Radioablation (stereotactic body radiotherapy) for Extracranial oligometastases)	Khoo V et al. 2018[8]	II / III Follow-up 5 years	Multicentre, non-blinded, parallel group randomised control trial Primary outcome: progression-free survival time Secondary outcomes: feasibility of recruitment, feasibility of SBRT delivery, overall survival, local lesion control, toxicity, QoL	245 patients randomised to receive standard care or standard care + SBRT	Breast, prostate or NSCLC	One to three extracranial metachronous	Recruitment started Nov 2016 Estimated primary completion date Oct 2024
STOMP (International randomised study of prostatectomy vs stereotactic body radiotherapy (SBRT) and conventional radiotherapy vs SBRT for organ-confined prostate cancer)	Ost P et al. 2018[9]	II	Multicentre, randomised Primary outcome: androgen deprivation therapy (ADT)-free survival	62 patients randomised to surveillance or metastasis-directed therapy (MDT – surgery or SABR))	Prostate	One to three extracranial	Completed May 2017 At three years, median ADT-free survival was 13 months in surveillance group vs. 21 months in MDT group QoL similar at three months and one year. Six patients with grade 1 toxicity in MDT arm, no grade 2-5 toxicity
PACE (Prostate Advances in Comparative Evidence)	Brand D et al. 2019[10]	III Follow-up 10 years	Multicentre, international, randomised controlled study Primary outcome: biochemical progression-free survival Secondary outcomes: toxicity, QoL, overall survival, progression-free survival, commencement of androgen deprivation therapy	Three cohorts (independently powered randomised sub-trials): PACE-A: 234 patients. SBRT vs. surgery PACE-B: 874 patients. SBRT vs. radiotherapy (no hormone therapy) PACE-C: 1,182 patients. SBRT vs. radiotherapy (+ six months hormone therapy)	Prostate	None	PACE-B and C now closed to recruitment PACE-B results show no difference in acute GI and GU toxicity between SBRT and conventional radiotherapy arms. Grade 2 or higher GI toxicity at 2 years 4.2% (radiotherapy) vs 3.7% (SBRT). Grade 2 or higher GU toxicity at 2 years 5.8% (radiotherapy) vs 11.8% (SBRT)
ORIOLE (Randomised Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer)	Phillips R et al. 2020[11]	II	Randomised Primary outcome: progression at 6 months Secondary outcomes: toxicity, local control, progression-free survival, QoL, ADT-free survival	54 patients randomised 2:1 to SABR or observation	Prostate	One to three bone or soft tissue	Primary completion Aug 2018, estimated completion Apr 2023 Progression at six months in 19% of SABR group vs. 61% of observation group. Progression-free survival 5.8 months vs. not reached. No toxic effects grade 3 or above observed
Maintenance chemotherapy vs. SABR + maintenance chemotherapy for Stage IV NSCLC	Iyengar P et al. 2018[12]	II	Single institution, randomised Primary outcome: progression-free survival Secondary end-points: toxicity, local and distant control, patterns of failure, overall survival	29 patients: 15 maintenance therapy vs 14 SABR followed by maintenance therapy	Stage IV NSCLC	One to five (up to three in the liver and up to three in the lung)	Trial stopped to accrual early after interim analysis found significant improvement in progression-free survival in SABR arm (9.7 vs. 3.5) Toxicity similar in both arms
Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study	Gomez D et al. 2019[14]	II	This phase II randomised, multicentre trial enrolled stage 4 NSCLC patients (≤3 metastases) with no progression at three or more months after first-line systemic therapy Long-term results showed that this PFS benefit was durable; after a median follow-up of 38.8 months the median PFS was 14.2 months in the LCT arm versus 4.4 months in the standard arm, whilst median overall survival was 41.2 months versus 17 months, respectively This study represents the first multicentre, randomised trial of LCT for selected oligometastatic NSCLC to demonstrate that aggressive consolidation therapy (surgery or SABR) leads to a PFS benefit	49 patients randomized to maintenance therapy/ observation vs local consolidative therapy (LCT) with surgery or SABR	Stage 4 NSCLC	≤3 in: Spleen Brain Bone Lung Lymph nodes Adrenal Liver Cervical lymph nodes Spinal Kidney Abdominal	Completed Mar 2022 The study closed early after only 49 patients were enrolled when interim analysis found median PFS in the LCT arm to be 14.4 months compared to 3.9 months in the standard arm
SARON (Study protocol for the SARON trial: a multicentre, randomised controlled phase III trial comparing the addition of stereotactic ablative radiotherapy and radical radiotherapy with standard chemotherapy alone for oligometastatic non-small cell lung cancer)	Conibear J et al. 2018[15]	III	This large, randomised controlled, multicentre, UK phase III trial is currently recruiting patients from 30 UK sites with oligometastatic NSCLC (1-3 sites of synchronous oligometastases) to investigate the feasibility of adding SABR and radical radiotherapy (RRT) following standard chemotherapy Primary outcome: overall survival	340 randomised to standard chemotherapy only (control) vs standard chemotherapy plus SABR/RRT to primary tumour and SABR/SRS to oligometastases	NSCLC	One to five synchronous oligometastases (up to a maximum of three organs)	Ongoing (started in 2016) Estimated primary completion date August 2022
HALT (Targeted therapy with or without dose intensified radiotherapy for oligoprogressive disease in oncogene-Addicted Lung Tumours	McDonald F et al. 2017[16]	II/III	This randomised controlled, multicentre phase II/III trial is currently recruiting patients with advanced NSCLC and oligoprogressive disease, which developed after becoming resistant to targeted TKI inhibitor treatment	110 randomised to targeted therapy (control) vs SABR plus targeted therapy	NSCLC	Unknown (recruiting)	Ongoing (started in 2017) Estimated primary completion date has passed – Nov 2021

References:

1. Guckenberger M, Lievens Y, Bouma A, Collette L, Dekker A, deSouza N et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. The Lancet Oncology. 2020;21(1):e18-e28.

2. Hellman S, Weichselbaum R. Oligometastases. Journal of Clinical Oncology. 1995;13(1):8–10.

3. Palma D, Haasbeek C, Rodrigues G, Dahele M, Lock M, Yaremko B et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): Study protocol for a randomized phase II trial. BMC Cancer. 2012;12(1).

4. Palma D, Olson R, Harrow S, Gaede S, Louie A, Haasbeek C et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. The Lancet. 2019;393(10185):2051–2058.

5. Palma D, Olson R, Harrow S, Gaede S, Louie A, Haasbeek C et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. Journal of Clinical Oncology. 2020;38(25):2830–2838.

6. Olson R, Mathews L, Liu M, Schellenberg D, Mou B, Berrang T et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 1–3 Oligometastatic tumors (SABR-COMET-3): study protocol for a randomized phase III trial. BMC Cancer. 2020;20(1).

7. Palma D, Olson R, Harrow S, Correa R, Schneiders F, Haasbeek C et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. BMC Cancer. 2019;19(1).

8. Khoo V, Hawkins M, Ahmed M, Kirby A, van As N, McDonald F et al. A Randomised Trial of Conventional Care versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases. Clinical Oncology. 2018;30(6):e64.

9. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. Journal of Clinical Oncology. 2018;36(5):446–453.

10. Brand D, Tree A, Ostler P, van der Voet H, Loblaw A, Chu W et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. The Lancet Oncology. 2019;20(11):1531–1543.

11. Phillips R, Shi W, Deek M, Radwan N, Lim S, Antonarakis E et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer. JAMA Oncology. 2020;6(5):650.

12. Iyengar P, Wardak Z, Gerber D, Tumati V, Ahn C, Hughes R et al. Consolidative Radiotherapy for Limited Metastatic Non–Small-Cell Lung Cancer. JAMA Oncology. 2018;4(1):e173501.

13. Chmura S, Winter K, Al-Hallaq H, Borges V, Jaskowiak N, Matuszak M et al. NRG-BR002: A phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer (NCT02364557). Journal of Clinical Oncology. 2019;37(15_suppl):TPS1117-TPS1117.

14. Gomez D, Tang C, Zhang J, Blumenschein G, Hernandez M, Lee J et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. Journal of Clinical Oncology. 2019;37(18):1558–1565.

15. Conibear J, Chia B, Ngai Y, Bates A, Counsell N, Patel R et al. Study protocol for the SARON trial: a multicentre, randomised controlled phase III trial comparing the addition of stereotactic ablative radiotherapy and radical radiotherapy with standard chemotherapy alone for oligometastatic non-small cell lung cancer. BMJ Open. 2018;8(4):e020690.

16. McDonald F, Guckenberger M, Popat S, Faivre-Finn C, Andratschke N, Ridell A et al. Targeted Therapy With or Without Dose-intensified Radiotherapy in Oligoprogressive Disease in Oncogene Addicted Lung Tumours. Clinical Oncology. 2018;30(6):e64-e65.

Case studies

GenesisCare is an established provider of specialist SABR treatment. We have invested in a network of lead centres that offers world-class technology, including sophisticated imaging, motion monitoring and the UK's first MRIdian, for real-time adaptive planning and delivery. A selection of our most interesting SABR case studies across a diverse range of oligometastatic cancers are detailed here. GenesisCare is collecting outcome data for all of these patients and looks forward to publishing these in the coming months and years.

SABR to oligoprogressive nodal cluster around the coeliac axis originating from colon cancer primary

Dr Andy Gaya

Case presentation

We illustrate the case of a fit male in his mid 60s working in the oil industry previously treated with surgery and adjuvant chemotherapy for a HER2 strongly positive MMR proficient colon cancer, who relapsed with nodal disease above and below the diaphragm.

Challenges of presentation and choice of treatment

A few months following complete radiological and metabolic response of his nodal disease to further chemotherapy he developed oligoprogression in a small nodal cluster around the coeliac axis (see Figure 1). This was not amenable to surgical resection. Stereotactic radiotherapy was recommended to the site of oligoprogression to delay any change in systemic therapy, and the patient was determined to pursue this approach. Cyberknife was declined due to the risks associated with fiducial marker insertion in this location. Conventional non-gated linac SABR would be possible but dose would have to be restricted significantly to meet organ at risk tolerance of the surrounding liver, stomach and small bowel. Due to the proximity of normal tissues, irregular daily variations in stomach and bowel position, and significant respiratory motion, MR-linac guided SABR was recommended.

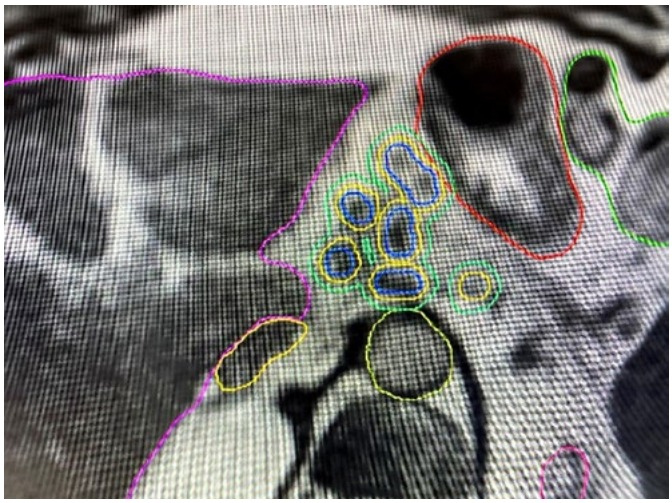


Fig 1: Oligoprogression in a small nodal cluster around the coeliac axis

SABR treatment

With automatic respiratory gating, daily recontouring of target and organs at risk, and adaptive replanning and reoptimisation a potentially ablative dose of 40 Gy in five fractions was achieved.

Results and follow-up

Treatment was very well tolerated with only mild (grade 1) nausea and fatigue. Without MRL, one would have to question the value of "low" dose SABR in this location. This patient was treated with confidence and as a result has been able to delay a change in systemic therapy for significantly longer, thus improving quality of life. Results from the SABR-COMET trial and others also suggest that SABR to oligometastatic disease may improve survival over and above standard of care systemic therapy – 42% vs 17% 5 year overall survival.

"This patient was treated with confidence and as a result has been able to delay a change in systemic therapy for significantly longer, thus improving quality of life."

Dr Andy Gaya

SABR to retroperitoneal metastases and iliac lymph node oligoprogression

Dr Andy Gaya

Case presentation

A 47-year-old lady with an adenocarcinoma of unknown primary presenting with a mass of retroperitoneal nodes around the coeliac axis, and small volume para-aortic (PA) and iliac nodes. Immunohistochemical profile suggested hepatobiliary origin. Molecular profiling revealed microsatellite instability high, mismatch repair deficient, tumour mutation burden high (19 mutations / MB), BRAF V600E mutation. FOLFIRINOX was commenced with a partial response after four cycles but was very poorly tolerated.

Challenges of presentation and choice of treatment

Despite dose reductions, grade 3 fatigue meant treatment had to be stopped as it was affecting her ability to care for her two young children, as well as perform her part-time job. Single-agent nivolumab was commenced (due to her microsatellite instability and high tumour mutation burden) and was well tolerated with just grade 1 fatigue, and temporary autoimmune arthropathy which settled and didn't return following two weeks of prednisolone. Imaging showed ongoing partial response over the course of 14 months. Due to ongoing coeliac plexus pain, MRI-guided stereotactic radiotherapy was undertaken to the large nodal mass.

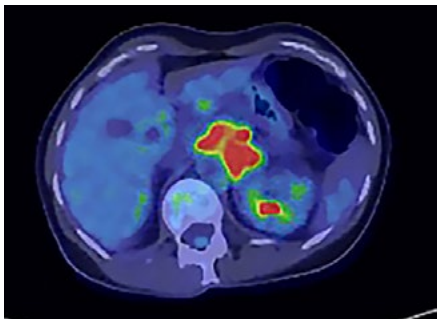


Fig 1: Pre-treatment – large retroperitoneal nodal mass

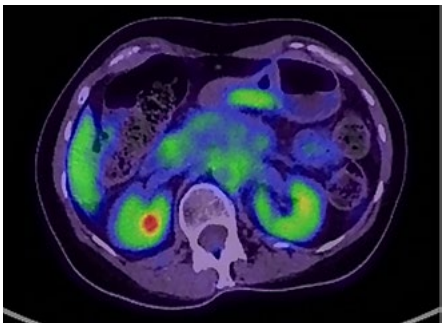


Fig 2: Post SABR treatment

SABR treatment

A SABR approach (40 Gy in five fractions) on the MR-linac was used due to minimal systemic disease elsewhere. Nivolumab continued four-weekly.

Results and follow-up

A few months later, imaging showed a complete metabolic response on PET with abscopal response in the PA and iliac nodes. The patient experienced grade 2 fatigue and nausea lasting one month after treatment. More recently, the patient developed oligoprogression in iliac nodes and then left adrenal gland, and received further SABR alongside nivolumab.

Latest imaging shows ongoing complete metabolic response following SABR treatment. The patient is currently leading a normal life with her husband and children nearly four years from diagnosis, with barely any impact from the nivolumab or previous SABR on her quality of life.

SABR to oligoprogressive subdiaphragmatic lymph node originating from renal cell carcinoma primary

Dr Philip Camilleri

Case presentation

A 52-year-old female with metastatic renal carcinoma. At the time of referral for stereotactic ablative radiotherapy (SABR) she had oligoprogressive disease in a single lymph node beneath the right diaphragmatic crus (figure 1).

The patient was initially diagnosed in October 2018 when she also underwent an open right radical nephrectomy confirming the presence of renal clear cell carcinoma with rhabdoid change, stage T3bNxMx. Further investigation revealed the presence of multiple pulmonary metastases and she was commenced on nivolumab and ipilimumab immunotherapy treatment. Her metastatic disease had been completely controlled with no evidence of growth until a routine check CT scan identified an enlarging right upper abdominal node adjacent to the right diaphragmatic crus. At the same time, she developed right upper abdominal pain which was thought to possibly be due to the nodal growth but also possibly due to gallstones which she was also known to have.

She was otherwise enjoying an active lifestyle which had been mostly unchanged by her disease.

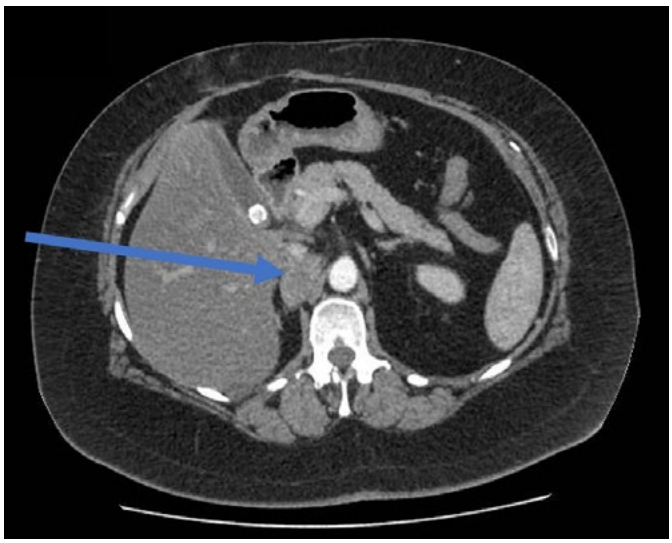


Fig 1: Pre-treatment CT scan showing right upper abdominal node measuring 25 mm on 10th January 2020

Challenges of presentation and choice of treatment

Radiotherapy was an option to achieve local disease control. However, this was a complex case due to the close proximity of the liver and small bowel, and the movement of these organs at risk (OARs) with respiration.

The opportunity to treat this patient with SABR using the MRIdian MRI-guided system was reviewed with the SABR Advisory Team at GenesisCare.

With its integral MR scanner and real-time imaging, MRIdian offers the capability of good soft tissue visualisation in the upper abdomen as well as allowing clinicians to account for the location of small bowel and other significant OARs, adapting the radiotherapy plan on a daily basis. This adaptive radiotherapy, together with the breath-hold and automated beam gating function of MRIdian, allows a high dose to be safely delivered to the target.

SABR treatment

Stereotactic ablative radiotherapy (SABR) treatment on the MRIdian MR-linac was prescribed at 40 Gy in three fractions as it was felt to involve partial re-irradiation. Treatment sessions were carried out on alternate days and were completed at the end of February.

The dose prescribed was in line with the UK SABR consortium guidance for stereotactic radiotherapy to involved nodes.

At each session the plan was recontoured and the daily plan was adapted to match the position of the target node as well as the surrounding organs at risk, specifically the small bowel and liver. This was important to ensure the dose to organs at risk was kept to an absolute minimum. The patient was also required to use the breath-hold visualisation, to enable the automated beam gating. Each treatment session took approximately 45 minutes, including contouring and plan adjustment.

Results and follow-up

The patient noted very few treatment side effects. She had grade 1 fatigue lasting two weeks and no nausea, vomiting or bowel disturbance.

Patient-reported outcome measures (PROMs) are collected from baseline and show that although she had recorded moderate fatigue prior to her SABR treatment and on the day of her final fraction, four weeks and three months post treatment she recorded no fatigue.

Other PROMs show no change from baseline in pain, gastric symptoms, intestinal symptoms, sexual functions or emotions.

A follow-up CT scan at 10 weeks after SABR treatment showed a reduction in size of the node.

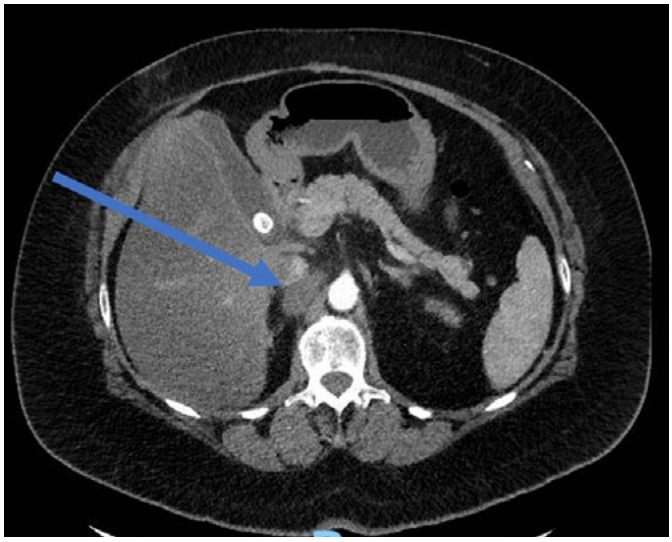


Fig 2: Post-treatment CT scan (19 mm) on 12th May 2020 10 weeks after completion of SABR

SABR using the MRIdian MR-linac allowed safe delivery of a high dose, while limiting toxicity to OARs. In the event, this was found to be a straightforward treatment approach. The patient was delighted to have completed her treatment so quickly and with almost no effects apart from mild fatigue.

"SABR using the MRIdian MR-linac allowed safe delivery of a high dose, while limiting toxicity to OARs."

Dr Philip Camilleri

SABR to liver metastasis originating from a gallbladder primary

Dr Andy Gaya

Case presentation

A 60-year-old male with primary gallbladder adenocarcinoma and comorbidities of NASH cirrhosis with mild portal hypertension. He had a radical cholecystectomy and wedge resection of adjacent liver – pT2b N0 (0/9) R0. No adjuvant chemotherapy was offered.

Challenges of presentation and choice of treatment

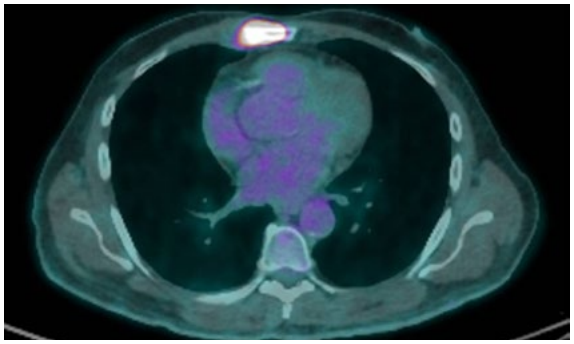
Six months later, at routine follow-up, he had developed a solitary liver metastasis and a paracardiac node. Gemcitabine + carboplatin was given with progression after three cycles.

SABR treatment

He received six cycles of second-line FOLFOX chemotherapy with a partial response followed by CyberKnife SABR to his liver metastasis (60 Gy in five fractions) and proton beam therapy to the paracardiac nodes (70 Gy in 20 fractions) – protons were used to spare heart dose. He completed the balance of FOLFOX chemotherapy and returned to his home country.

Results and follow-up

His post-treatment scans noted a 9 mm internal mammary node which was kept under surveillance. Six months later, interval scans showed slow progressive disease in the right internal mammary node with invasion to the posterior aspect of adjacent sternum. There were no new sites of disease. He received further SABR treatment using MRI guidance to the internal mammary chain (IMC) node (40 Gy in five fractions) which was his sole site of disease. There has been no liver recurrence.



He continued throughout both courses of radiotherapy to maintain an excellent quality of life with fatigue the only noticeable toxicity, which quickly settled. Two years later, the patient remains with oligometastatic disease and no evidence of more widespread progression.

Fig 1: Parasternal/IMC nodal deposit

SABR to liver metastases originating from a caecum primary

Dr Rafiqul Islam

Case presentation

A 73-year-old male presented in 2019 with a primary cancer of the caecum, liver, perihepatic nodal and possible lung metastases. Although liver metastases were resectable at presentation, it was not offered due to the presence of perihepatic nodal disease. Therefore, he went ahead with a right hemicolectomy for his locally advanced primary caecal cancer. He started FOLFIRI plus Bevacizumab in July 2019 and tolerated chemotherapy very well and has managed to enjoy a good quality of life over the intervening two years. In September 2021 he remained well but unfortunately his restaging CT scan showed a total of five liver lesions. Although three were existing metastases, two of the metastases were new, confirming oligoprogressive disease (figure 1).

Challenges of presentation and choice of treatment

The CT did not reveal any sites of progression elsewhere. Following discussion at the GenesisCare SABR MDT I had offered him MR-guided SABR to all of the liver metastases. He was also keen to be able to continue on his current systemic therapy.

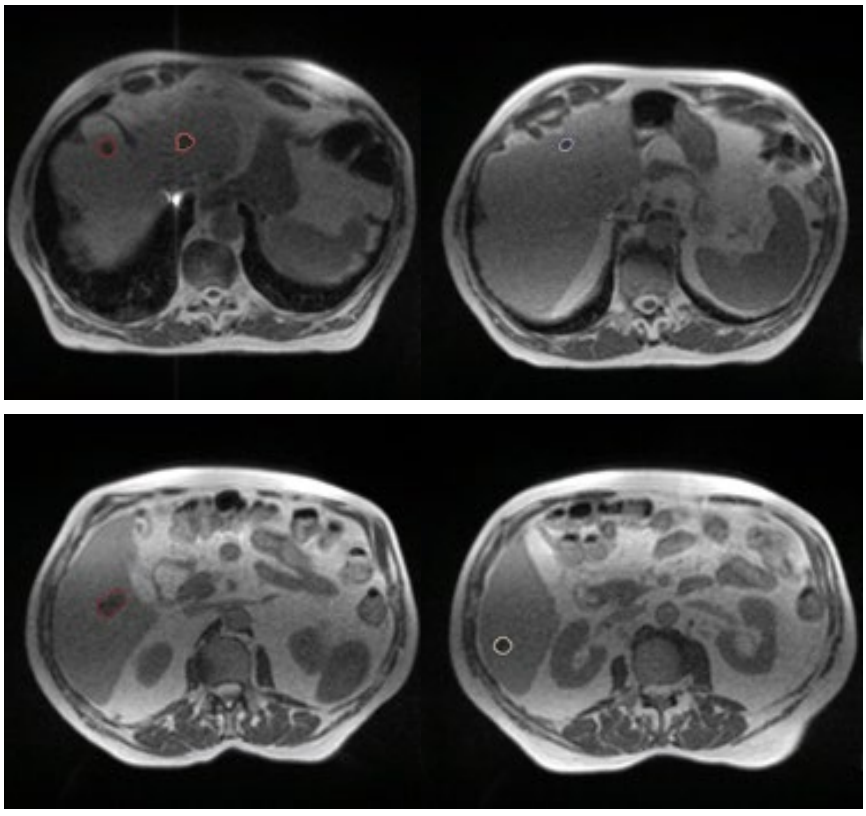


Fig 1: MR images of liver metastases

SABR treatment

The SABR referral process at GenesisCare is swift and collegial and the high level of clinical governance in place is reassuring, given the complexity of this form of treatment. The advantages of the MRIdian platform in allowing daily GTV and OAR recontouring, plan reoptimisation and respiratory gated treatment delivery, maximised target coverage and minimised dose to normal liver. At simulation the GenesisCare physics team noted that all the lesions were moving synchronously, and all five lesions were therefore planned to be treated simultaneously in one plan. GTV was defined using a contrast enhanced diagnostic MRI. A CTV was created from his GTV by adding a uniform 3 mm margin, which was then adjusted to obey the liver contour. The final PTV was created by adding an isotropic 5 mm margin to the CTV except for CTV3 where a 3 mm margin was used as this was going to be used as the index lesion for MRL treatment tracking and therefore did not warrant a 5 mm margin.

He was treated with 45 Gy in five fractions delivered on alternate days. The plan achieved all mandatory constraints including mean liver dose of less than 15 Gy. Treatment was planned (figure 2) and delivered, with daily adaptation, consistently achieving coverage as planned, while respecting the dose constraints of the OARs (figure 3). During treatment delivery, any movement of the index PTV3 outside of a tightly defined 'treatment reticule' resulted in a pause in treatment until target re-entered the reticule. This gave us confidence that the entire planned dose was delivered to the targets. Overall, the process was straightforward and the patient was supported throughout by the onsite MR-linac team.

Results and follow-up

Apart from grade 2 fatigue, he has not experienced any further toxicity. He was reviewed at two weeks post treatment and will have a response assessment scan in eight weeks.

He was also GenesisCare's 400th MRIdian patient and was very pleased with the care and compassion provided by the whole GenesisCare Cromwell team.

"The treatment itself was painless, the main side effect being tiredness. GenesisCare has been fantastic and their care has gone beyond my treatment and extended to my direct family."

GenesisCare patient

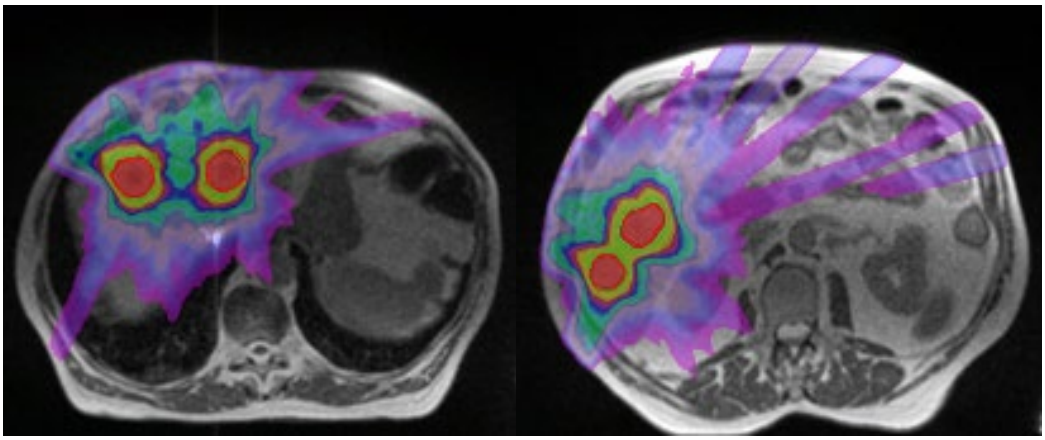


Fig 2: MR images of SABR plan with isodoses

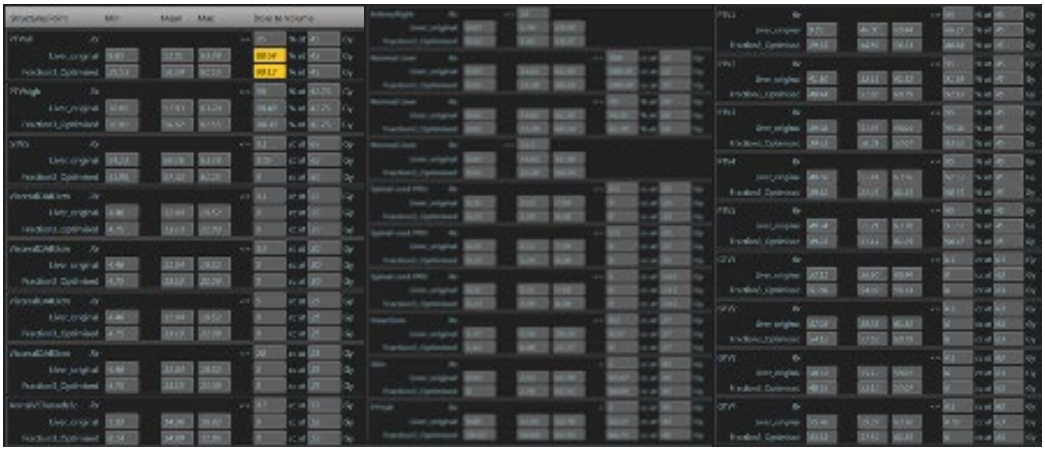


Fig 3: Base plan compared to adapted fraction no 3

This case report illustrates the flexibility of the MRIdian platform in delivering ablative radiotherapy to complex targets, putting the service at the forefront of modern cancer medicine in the UK.

SABR to liver metastases originating from breast primary

Dr James Good

Case presentation

A 64-year-old lady with a history of HER2 negative ER+ breast cancer. She initially presented with stage pT2N1M0 disease and had previously undergone wide local excision and post-op radiotherapy, chemotherapy and endocrine therapy. She relapsed with three liver metastases on FDG PET and MRI and on the basis of the SABR-COMET trial results, and a preference to avoid surgery, was referred for stereotactic ablative radiotherapy (SABR).

Challenges of presentation and choice of treatment

The challenge here was the number of metastases. Two of them were in a position not amenable to percutaneous radiofrequency ablation and given that breast cancer can recur in other tissues as well as liver, surgery was likely not to be the optimal approach. The lesions were positioned in different segments of the liver, making it challenging to treat with conventional SABR due to the need for an internal target volume (ITV), leading to an increased mean liver radiation dose and therefore potentially reduced dose to the tumours.

SABR treatment

The patient accepted treatment on the MR-linac despite being apprehensive about the treatment time. The lesions were readily visible on the MRIdian planning scans with IV liver-specific contrast (figure 1). She completed treatment as planned, and we were able to deliver 50 Gy in five fractions to all three lesions. During the adaptive replanning process we could see that the gross tumour volumes (GTVs) were decreasing in size as SABR proceeded. She has also continued with second line endocrine therapy.

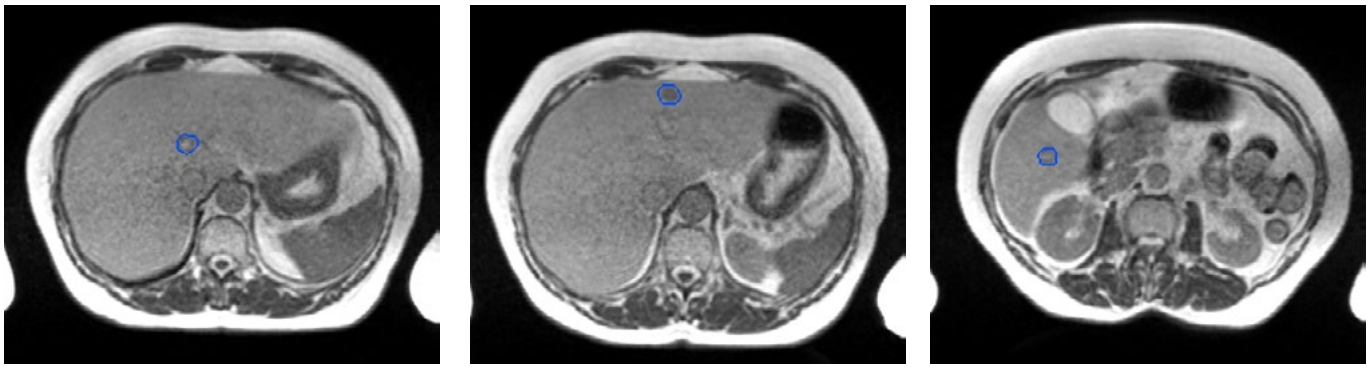
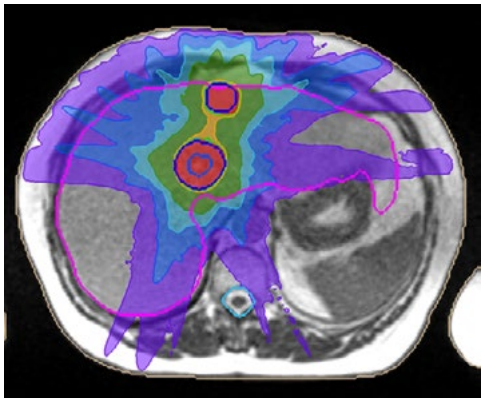


Fig 1: Pre-treatment MRIdian planning scans showing three small, scattered liver metastases



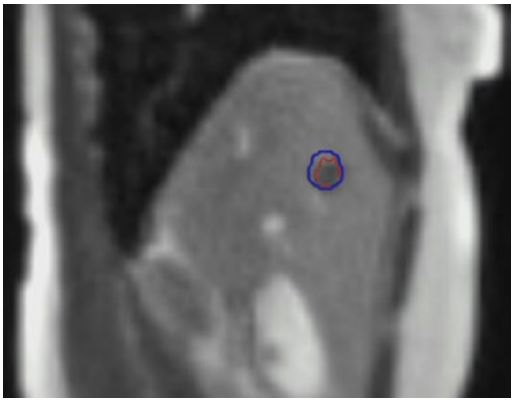
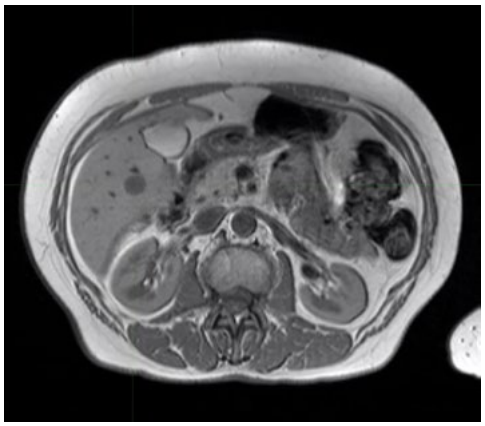


Fig 2: MRIdian SABR plan, showing tight dose distributions across two of the three tumours

Fig 3: Treatment tracking image, which empowered the patient to participate in her own treatment

Results and follow-up

The patient did develop some rib tenderness related to radiation dose to the most peripheral lesion, but this settled with simple analgesia and time. MRI scan at three months showed the tumours were almost completely clear and a further scan at six months showed no active cancer. The patient requires ongoing endocrine therapy to control her disease.



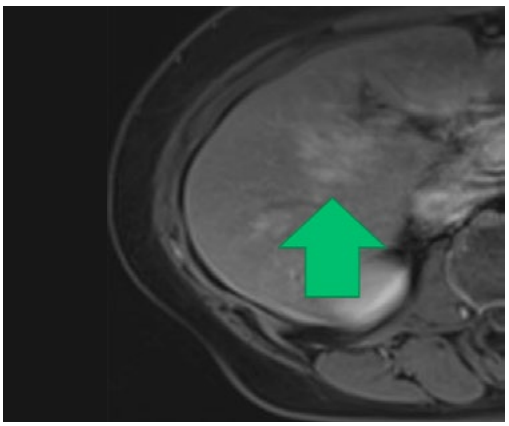


Fig 4: Post-treatment MRI scan, showing a well demarcated ablation zone

The improved soft tissue definition, beam gating and adaptive replanning made possible by MRIdian allowed an entirely non-invasive approach to ablating this lady's liver metastases. MRI-guidance added value through greater confidence in delineating and tracking gross tumour volumes, smaller treatment margins and maximising the ablative radiation dose.

SABR treatment to spinal oligometastasis originating from lung primary

Dr Veni Ezhil

Case presentation

A 67-year-old lady had a left upper lobectomy for pT1c pN1 adenocarcinoma of the lung in March 2019. Molecular markers and PD-L1 expression were negative.

She proceeded to adjuvant chemotherapy with four cycles of pemetrexed and cisplatin, which completed in July 2019.

Challenges of presentation and choice of treatment

PET-CT on follow-up in June 2020 showed a solitary 7 mm FDG avid lytic lesion in L3. This was not suitable for further evaluation with MRI due to a pacemaker and was not suitable for biopsy. Interval PET four weeks later showed an increase in size of the lesion to 9 mm with increase in FDG avidity.

SABR treatment

She received SABR to the solitary metastasis in L3, receiving 27 Gy in three fractions delivered on alternate days. Follow-up imaging showed a complete metabolic response at L3.

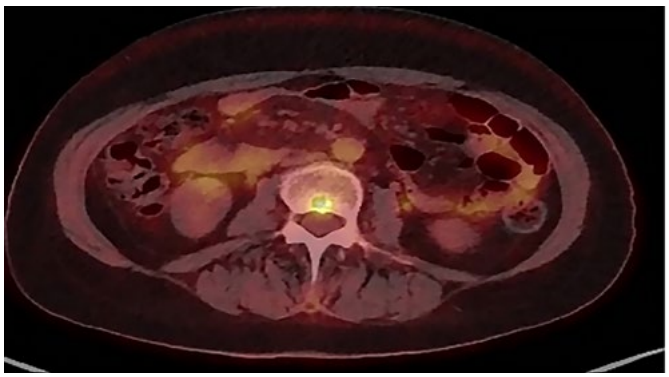


Fig 1: PET-CT showing solitary 7 mm FDG avid lesion in L3

Results and follow-up

Patient has since had no toxicity including pain, collapse or stress fracture. There has also been no recurrence at the site of SABR treatment. The patient relapsed in January 2022 with small lung metastases but no residual disease in L3. She has since started osimertinib as she has an exon 19 EGFR mutation, and has had a good response. The patient remains active with a performance status score of 1 (PS-1).

SABR to oligoprogression in the lung & SCF node originating from a NSCLC primary

Dr Veni Ezhil

Case presentation

A 56-year-old lady was diagnosed with EGFR mutation positive metastatic NSCLC. She presented with widespread lymphadenopathy and multiple lung and bone metastases in July 2018 and had a complete metabolic response to osimertinib on PET-CT in January 2019.

Challenges of presentation and choice of treatment

A repeat PET-CT in September 2020 showed oligoprogression in three lung nodules in the right middle lobe and a left SCF node.

SABR treatment

She received SABR to the lung nodules (60 Gy in eight fractions) and left SCF node (30 Gy in five fractions) with good response and continues osimertinib with no further progression to date.

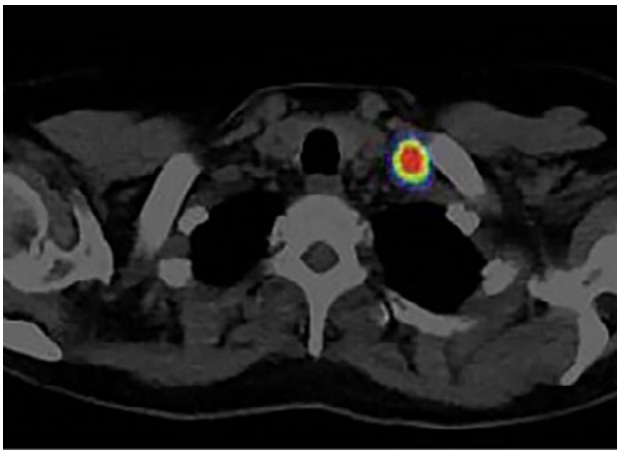


Fig 2: Left SCF node on FDG PET

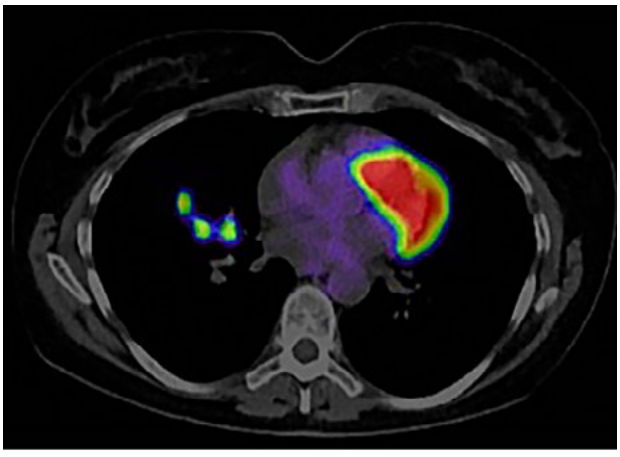


Fig 3: Right middle lobe nodules on FDG PET

Results and follow-up

The patient has had no recurrence or toxicity to either site of SABR treatment. Her primary has since progressed in March 2021 and the patient subsequently received 4 cycles of chemotherapy. Further progression with bone metastases occurred in January 2022. The patient has now received palliative radiotherapy to her right pelvis and L5. The lady has been referred to The Royal Marsden NHS Foundation Trust for treatment in a clinical trial.

SABR to peripheral lung oligoprogression originating from a lung primary

Dr Tim Sevitt

Case presentation

A 65-year-old lady was diagnosed with metastatic carcinoma of the lung in 2018 when she presented with shortness of breath and cough. After investigation she was found to have a T3N2M1a adenocarcinoma of the right lung with bilateral pulmonary nodules and a single rib metastasis. She was commenced on Carboplatin, Pemetrexed and Pembrolizumab in September 2018 but needed to stop after three cycles due to immune-related hepatitis and nephritis.

Although imaging in February 2019 suggested a response, she unfortunately progressed in July 2019 and was re-challenged with single agent Pembrolizumab. She has subsequently remained on this treatment with a good radiological response. Towards the end of 2019 she did receive a short palliative course of radiotherapy with 20 Gy in five fractions to the right hilar mass for symptom control.

This was tolerated well with good symptomatic effect.

Challenges of presentation and choice of treatment

In June 2021 she remained well however a PET-CT scan showed a growing, avid left upper lobe lesion (SUV 9.7) but no signs of progression elsewhere.

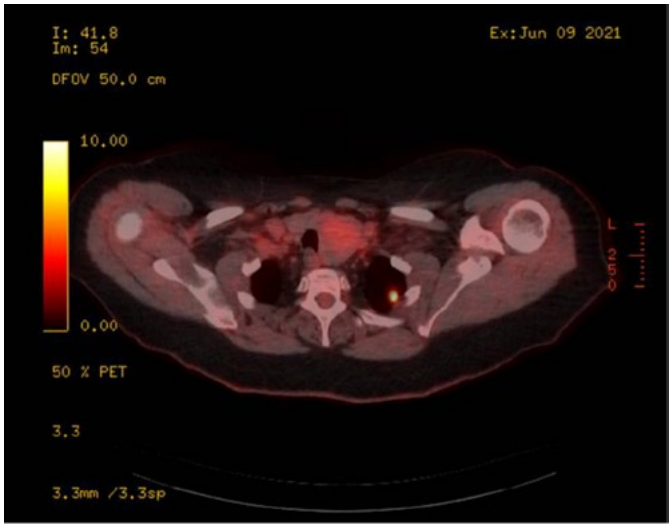


Fig 1: PET-CT scan showed the growing, avid left upper lobe lesion (SUV 9.7)

The images were reviewed in the local lung MDT meeting and the peripheral left upper lobe nodule was felt to represent oligoprogressive disease. For this reason, I considered her potentially eligible for simple SABR to the lung nodule to maximise her disease control. On discussion she was keen to go ahead with treatment.

SABR treatment

I completed a SABR Advisory Team (SAT) referral form and submitted it to the SABR MDT coordinator. Her case was subsequently promptly discussed by the SAT team and approved for treatment. The radiotherapy referral was then completed on the online Horizon referral platform and she was quickly scheduled for her pre-treatment and radiotherapy appointments. The overall process was very straightforward and supported throughout by the SABR and Maidstone clinical teams.

The peripherally located left upper lobe lung lesion was anatomically distant from the previous right-sided palliative radiotherapy field and was planned to receive 55 Gy in five fractions over two weeks. The plan achieved all the mandatory OAR constraints.

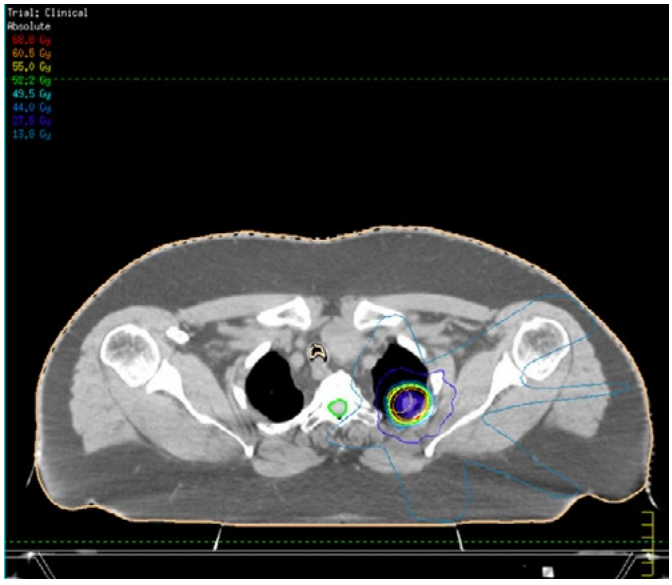


Fig 2: Axial CT image of SABR plan with isodoses

Results and follow-up

The treatment was safely delivered, and the patient did not experience any significant acute side effects. At four weeks after radiotherapy she had reported no side effects apart from some mild to moderate fatigue. At 12 weeks a CT scan showed stable appearances with no evidence of disease progression. Further imaging 10 months after treatment has shown scarring but resolution of the treated lung nodule.

SABR to iliac lymph node metastasis and mesorectal lymph node metastasis originating from a prostate primary

Dr Philip Camilleri

Case presentation

A 62-year-old man originally underwent radical prostatectomy in 2015 and then, following biochemical recurrence in 2018, had a PSMA PET scan which showed a solitary focus of avidity in a right external iliac lymph node.

Challenges of presentation and choice of treatment

He received SABR to the involved node with a good PSA response, and stayed off ADT. In 2020 his PSA started rising slowly again and a repeat PSMA PET scan showed avidity in a single mesorectal lymph node, adjacent to the rectum.

SABR treatment

This was once again treated with SABR and, in view of the location and previous pelvic SABR, this was delivered on the MR-linac.

Results and follow-up

There were no side effects from treatment and he went on holiday the following day. He remains off androgen deprivation.

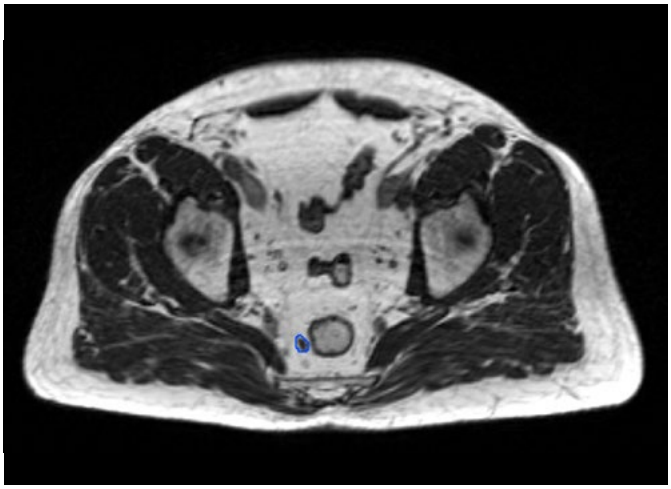


Fig 1: Case study 1

SABR to pancreatic metastasis originating from a renal cell carcinoma primary

Dr Nicola Dallas

Case presentation

I recently met an 81-year-old gentleman who had had a right radical nephrectomy in 2014 for a pT1b Nx M0 Grade 2 clear cell renal cell carcinoma. He had been treated and followed up in the NHS and was found to have an incidental 16 mm hyper vascular lesion in the pancreatic head on his five year surveillance CT scan, which had been delayed slightly due to the COVID-19 pandemic. With no other abnormalities identified, and a performance status of zero he had been referred to the upper GI team for further investigation and when biopsied this was confirmed to be a metastasis from his previous renal cell carcinoma, now six years since his original diagnosis and surgery.

Challenges of presentation and choice of treatment

He came to see me in my private clinic to discuss his potential treatment options and I requested a PET-CT scan which showed this to be a solitary site of disease.

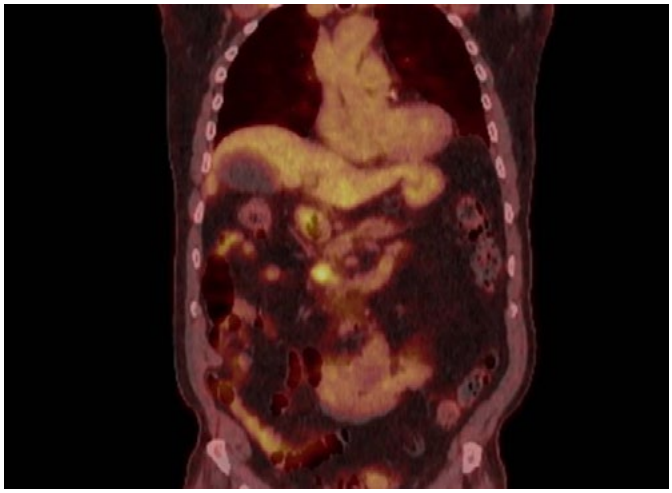


Fig 1: Fused coronal PET-CT image showing pancreatic metastasis

Given the insidious nature of this disease I knew immediately that I should consider potentially curative focal treatment. Being a pancreatic lesion, this type of complex SABR treatment is currently outside of my expertise, yet working with GenesisCare I am able to access this state-of-the-art treatment for my patients.

In addition, my work on the MRIdian MR-linac in Oxford has shown me first-hand the greatly improved soft tissue definition achievable on this machine. For a pancreatic lesion sitting adjacent to the duodenum this improved definition becomes invaluable, together with the ability to review and edit the target and the organs at risk for each fraction. It is then possible to reoptimize the plan for the daily anatomy, before treating the patient whilst tracking the tumour and gating the dose delivery. All of this increases the likelihood of delivering truly ablative doses to the target, whilst reducing the volume of normal tissue being irradiated.

SABR treatment

For my patient, I completed a SABR Advisory Team (SAT) proforma and supplied the required clinical data set. Two days later I received the review outcome accepting my patient for treatment and within two weeks he had met the treating oncologist and attended for treatment planning. He was subsequently been treated with a dose of 40 Gy in five fractions, treating on alternate days.

Results and follow-up

The patient tolerated the treatment well with no lasting side effects. At 18 months post-treatment, he is doing very well. A recent MRI showed stable appearances with no sign of persistent or recurrent disease. At the time of writing, he has not needed any further treatment.

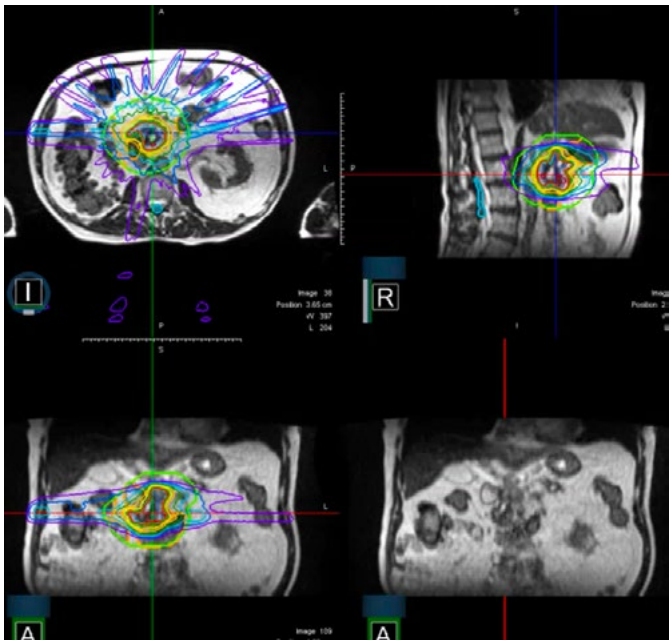


Fig 2: MRL plan

Access to SABR in the UK

In March 2020, the NHS published a commissioning policy[1] on SABR, stating that it should be made available as a routine treatment option to patients meeting specific criteria. Prior to this, access to SABR in the NHS had only been available through clinical trials and a Commissioning through Evaluation (CtE) process at a limited number of hospitals.

Under the current commissioning policy, access is limited specifically to patients with metachronous oligometastatic disease, defined as metastasis that develops more than six months after treatment of a primary cancer, with no more than three sites of metastases in no more than two of the bone, spine, lymph nodes, liver, adrenal gland and/or lung (the only exception to this rule is synchronous colorectal liver metastases that meet the other criteria). For patients with spinal metastases, a maximum of two sites in the spine can be treated with SABR. The policy working group estimated that of the estimated 140,000 patients diagnosed with metastatic cancer in England every year, approximately 2,200 will be suitable for SABR treatment in line with this policy.[1]

The decisions of the commissioning policy were based on an Evidence Review[2] and a Commissioning through Evaluation (CtE) programme carried out by the NHS.[3] It was concluded that as indicated in the treatment of metachronous, extracranial, oligometastatic cancer, the use of SABR is thought to:

- Prolong disease-free survival
- Delay the use of systemic treatment
- Improve quality of life
- Improve overall survival

In public consultation prior to the commissioning report[4], two respondents queried why the policy was to be restricted to patients with no more than three metastatic sites when oligometastatic disease had been defined for the purposes of the report as between one and five metastases. The panel responded that although some studies in the evidence review included patients with up to five metastases, the policy was aligned to the eligibility of the CtE programme.

Evidence review[2]

16 studies were included in the analysis of efficacy and safety. The SABR-COMET Phase II trials provided the strongest evidence of an effect on overall survival and progression-free survival. The effects on overall survival were corroborated by a prospective cohort study[5] with a median overall survival of 42.3 months.

Data on toxicity were available from 14 studies. Overall, the toxicity profile of SABR treatment was favourable with no grade 4 and grade 5 acute and chronic toxicity and very low rates of grade 3 events. The only exception was the SABR-COMET trial, where there were three grade 5 events as described previously.

NHS England concluded that the available evidence had shown:

- A significant benefit in survival following SABR, doubling overall survival to 13–14 months
- Although there was some toxicity, this is likely to be considered tolerable by patients

Additional benefit was demonstrated through local control. Some studies reported an improvement in quality of life.

The authors of the evidence review noted that a Phase III trial examining both survival and toxicity is required to provide definitive evidence of the overall benefit of SABR treatment. It is hoped that SABR-COMET-3 and SABR-COMET-10 will go some way to addressing these concerns.

Commissioning through Evaluation (CtE) study

The data from the evidence review were further supported by the NHS CtE scheme for SABR, carried out at 17 NHS radiotherapy centres between 2015 and 2019. Funding was provided for patients with extracranial oligometastatic cancer to access SABR within the NHS, whilst participating in a prospective, registry-based, single-arm, observational, clinical effectiveness and safety evaluation study.[3]

The objective of the CtE study was to assess clinical efficacy and safety of SABR in order to inform national treatment policy. SABR was administered based on the UK SABR Consortium guidelines with prescribed doses of 24–60 Gy in three to eight fractions. Whilst single-arm only, the CtE study is significant in that it included the largest cohort of patients (1,422) with oligometastatic disease treated with SABR in a real-world setting. Encouragingly, survival rates were higher than predicted and toxicity was low.

Key results

The median age of patients in the study was 69 years. 947 males (66.6%) and 475 females (33.4%) were enrolled. The most common site of primary tumour was prostate (28.6%), followed by colorectal (28.6%) and renal (10.1%). Patients had one (75.6%), two (19.6%) or three metastases (4.8%). Further baseline characteristics were provided in the published report.

Median follow-up was 13 months. Median overall survival time was not reached as it was longer than the last point of analysis at two years. Overall survival was better than estimated:

- At one year: 92.3% (95% CI 90.5–93.9) vs. an estimated 70%
- At two years: 79.2% (76.0–82.1) vs. an estimated 50%

Local control at one year was 86.9% (84.6–88.9%) and at two years was 72.3% (68.7–75.6%). Metastasis-free survival at one year was 84.0% (81.4–86.3%) and at two years was 52.0% (47.4–56.4%).

Differences in survival were seen according to the site of the primary tumour, with two-year survival ranging from 60.5% in patients with melanoma to 94.6% in patients with prostate cancer. In a univariate analysis, the number of metastases did not have an effect on overall survival, although it is important to note that in this study the maximum number of metastases was three.

Safety

959 patients reported a total of 2,410 adverse events. There were no deaths due to adverse events reported. The most common adverse event was fatigue (reported by 803 patients, 56.4%) and cough (228, 16.0%). Fatigue was also the most common grade 3 or higher adverse event (28, 2.0%). The most common grade 4 adverse event was increased liver enzymes (9, 1%). Quality of life was shown to be generally stable over time.

Discussion

The results from the CtE study were supportive of the efficacy findings of SABR-COMET as well as other trials. Unlike SABR-COMET, there were no grade 5 adverse events reported and the toxicity profile was generally favourable in line with other published studies.

References:

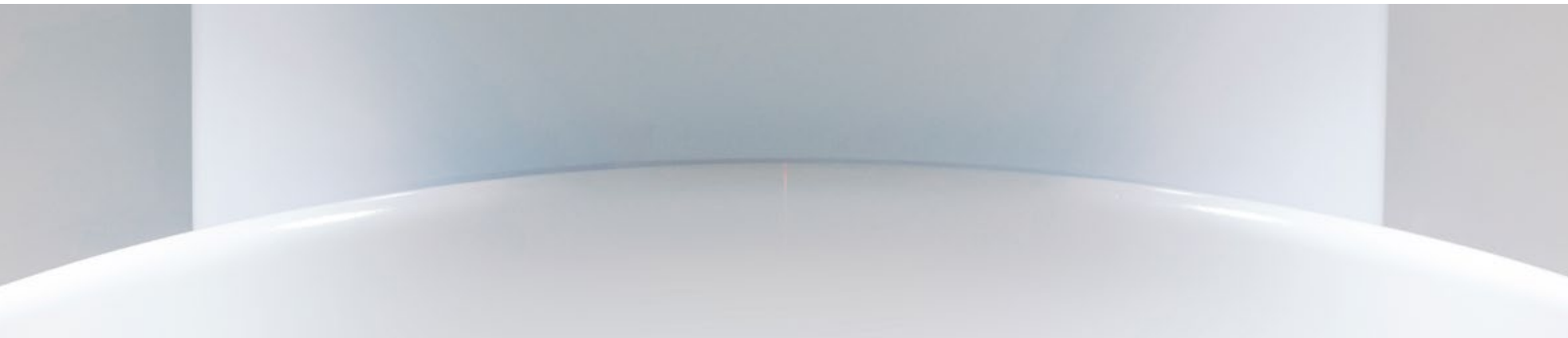
1. "Clinical Commissioning Policy Stereotactic ablative radiotherapy (SABR) for patients with metachronous extracranial oligometastatic cancer (all ages) (URN: 1908) [200205P]," March 2020. [Online]. Available: https://www.england.nhs.uk/wp-content/uploads/2020/03/1908-cc-policy-sbar-for-metachronous-extracranial-oligometastatic-cancer.pdf. [Accessed 6 May 2022].

2. King's Technology Evaluation Centre on behalf of NHS England Specialised Commissioning, "Evidence review: Efficacy, toxicity and cost-effectiveness of stereotactic ablative radiotherapy (SABR) in patients with metachronous extracranial oligometastatic cancer," May 2019. [Online]. Available: https://www.england.nhs.uk/wp-content/uploads/2020/03/1908-Evidence-Review.pdf. [Accessed 6 May 2022].

3. Chalkidou A, Macmillan T, Grzeda M, Peacock J, Summers J, Eddy S et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. The Lancet Oncology. 2021;22(1):98–106.

4. NHS England, "Consultation Report – Stereotactic ablative radiotherapy (SABR) for patients with metachronous extracranial oligometastatic cancer (all ages)," [Online]. Available: https://www.england.nhs.uk/wp-content/uploads/2020/03/1908-Consultation-Report.pdf. [Accessed 6 May 2022].

5. Sutera P, Clump D, Kalash R, D'Ambrosio D, Mihai A, Wang H et al. Initial Results of a Multicenter Phase 2 Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer. International Journal of Radiation Oncology*Biology*Physics. 2019;103(1):116–122.



Partner with us

GenesisCare is a global organisation and the UK's leading independent provider of innovative radiotherapy and cancer treatments. We collaborate with health professionals who share our vision of ensuring fast access to world-class cancer care. Our strategy is to invest early in new evidence-based modalities that hold potential for improved life outcomes.

GenesisCare is an established provider of specialist SABR treatment. We have invested in a network of lead centres that offers world-class technology, including sophisticated imaging, motion monitoring and the first MRIdians in the UK, for real-time adaptive planning and delivery.

Our service is led by a team of expert clinicians with extensive experience of this SABR modality for all tumour types and who oversee a nationwide rapid access pathway.

SABR Advisory Team and Clinical Reference Group

The role of the SABR Clinical Reference Group is to provide the necessary clinical oversight for a safe and effective SABR service across the GenesisCare network. This includes improved access to SABR treatments, introducing new clinicians to the SABR network, overseeing training and competency frameworks and contributing to the evidence base. In addition they drive the implementation of exciting and emerging radiation technologies, in particular the MRIdian for MR-guided SABR, with responsibility for the treatment network as well as academic collaboration with the University of Oxford.

Group members also comprise the SABR Advisory Team (SAT) who lead the multidisciplinary teams and assess all referrals through the eMDT.

Dr James Good

Clinical Director of Stereotactic Radiotherapy, GenesisCare UK
University Hospital Birmingham NHS Foundation Trust

Special interest: colorectal, HPB and head and neck cancers

Dr Alex Martin

Consultant Clinical Oncologist
Cambridge University Hospitals NHS Foundation Trust

Special interest: thoracic cancers and urological cancers

Dr John Conibear

Consultant Clinical Oncologist
Barts Health NHS Trust

Special interest: thoracic cancers and breast cancers

Dr Andy Gaya

Consultant Clinical Oncologist
Cromwell Hospital and The London Clinic

Special interest: upper and lower, GI and HPB cancers

Dr Veni Ezhil

Consultant Clinical Oncologist
Royal Surrey NHS Foundation Trust

Special interest: thoracic cancers and lymphoma

Dr Philip Camilleri

Clinical Director of Urological Cancers, GenesisCare UK
Oxford University NHS Trust

Special interests: urological cancers

Dr Sherif Raouf

Consultant Clinical Oncologist
Barts Health NHS Trust

Special interest: colon, gynaecology, lower and upper GI, and lung

GenesisCare SABR network

Simple SABR

Simple SABR means non-spine bone, peripheral lung, pelvic lymph node mets and simple re-irradiation* – this accounts for over half of the cases treated across the network to date.

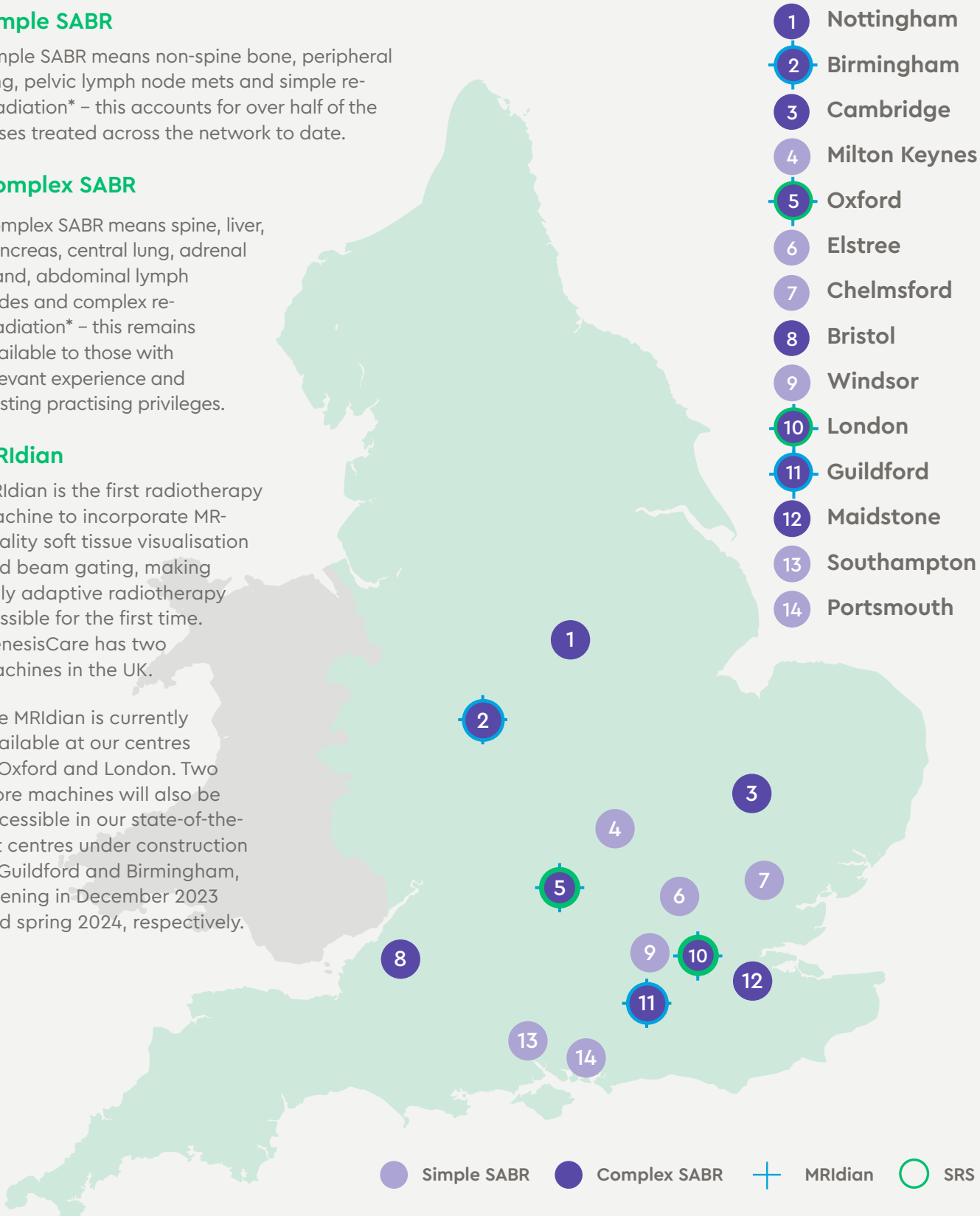
Complex SABR

Complex SABR means spine, liver, pancreas, central lung, adrenal gland, abdominal lymph nodes and complex re-irradiation* – this remains available to those with relevant experience and existing practising privileges.

MRIdian

MRIdian is the first radiotherapy machine to incorporate MR-quality soft tissue visualisation and beam gating, making truly adaptive radiotherapy possible for the first time. GenesisCare has two machines in the UK.

The MRIdian is currently available at our centres in Oxford and London. Two more machines will also be accessible in our state-of-the-art centres under construction in Guildford and Birmingham, opening in December 2023 and spring 2024, respectively.

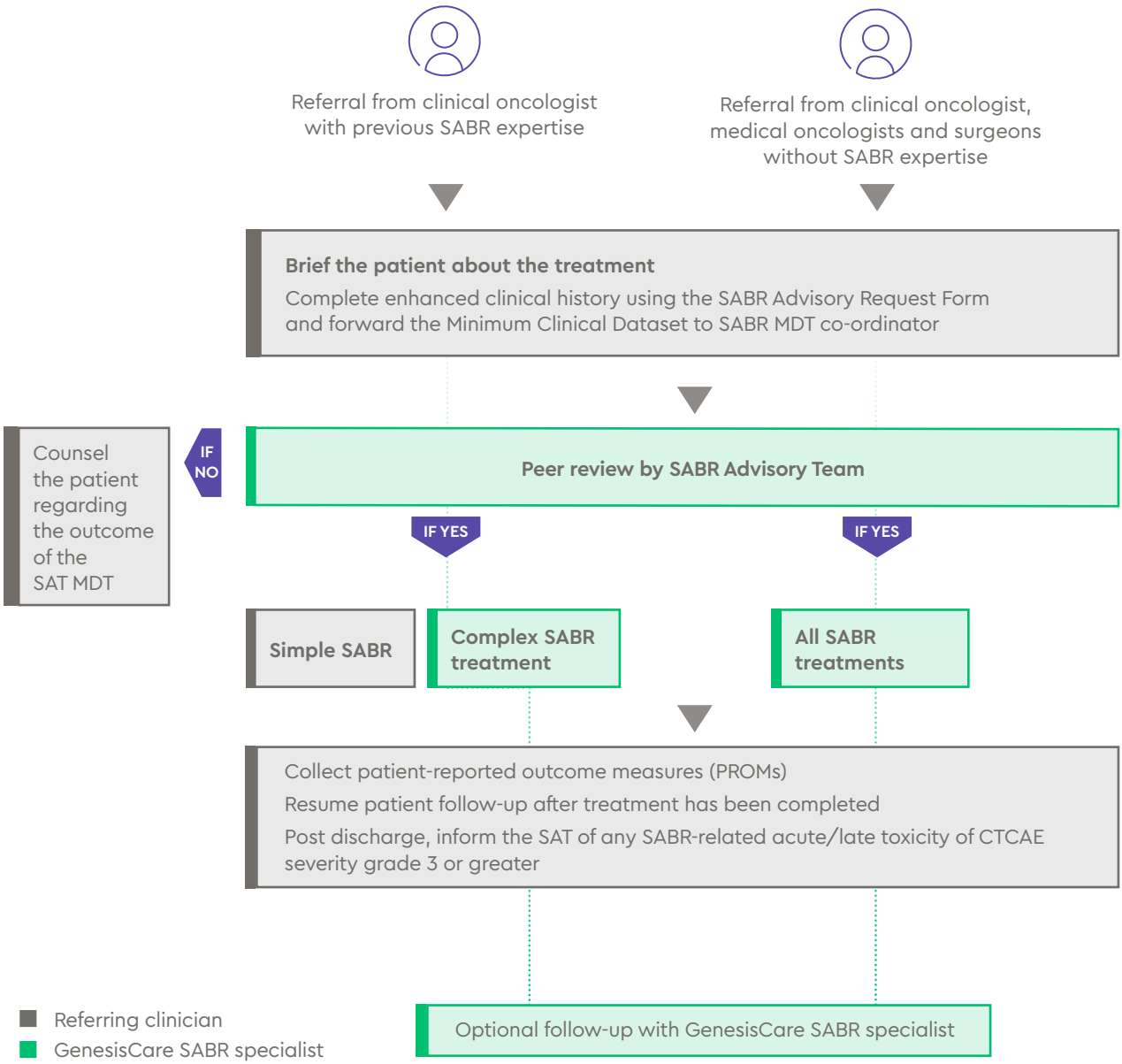


*Re-irradiation where critical OARs are not adjacent to the target may be treated in any GenesisCare centre.

Patient selection and referrals

Appropriate case selection remains an important aspect of SABR delivery. Within GenesisCare we have a national SABR Advisory Team (SAT) of experienced SABR clinicians who are available to provide informal advice and assistance. We also have a twice-weekly SABR MDT for the discussion of potential cases and for streamlining the treatment pathway.

Fig. The GenesisCare SABR referral and treatment pathway



Governance and safety

Prior to the planning CT scan, SABR referrals are initially reviewed within a GenesisCare MDT for suitability. Target volumes (GTV +/- CTV) are defined or approved by a competent SABR consultant. PTV margins for the case/treatment site are defined by SABR consortium guidelines. Peer review of planning outlines created by competent SABR consultants are facilitated, on request, by the SABR Advisory Team (SAT)

Treatment protocols and SABR consortium guidelines

Criteria for patient selection uses evidence-based guidelines, in particular the SABR Consortium Guidelines 2019, endorsed by The Faculty of Clinical Oncology of The Royal College of Radiologists.

Contact us

How to refer

GCLO.team@nhs.net

0808 301 9752

Website

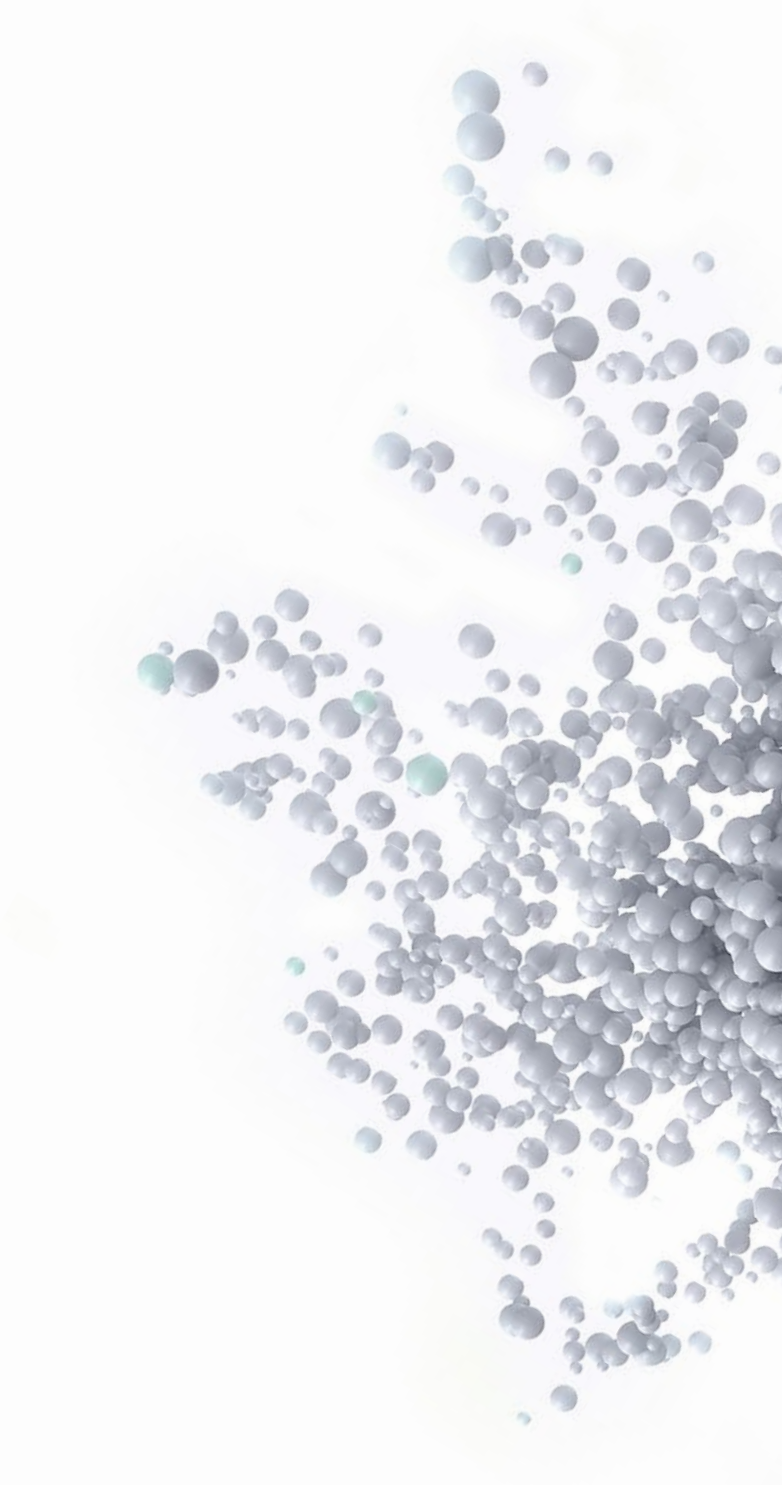
Visit our dedicated healthcare professionals website section for more details about our services, radiotherapy protocols, case studies and consultant teams.

genesiscare.com/uk/hcp

Practising privileges

If you would like to gain GenesisCare practising privileges, please contact:

REM@genesiscare.co.uk



genesiscare.com

GenesisCare is a trading name of
Genesis Cancer Care UK Limited.
UK_106.01D_V1_09.2023

GenesisCare