KiTEC

DRAFT

Commissioning through Evaluation:

Stereotactic ablative body radiotherapy (SABR) for patients with oligometastases report

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Contents

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Abbreviations

ACR	American College of Radiology
ADL	Activities of daily living
AE	Adverse events
ASTRO	American Society for Radiation Oncology
BED	Biologically equivalent dose
CI	Confidence interval
CEA	Carcinoembryonic antigen
CRC	Colorectal
CtE	Commissioning through Evaluation
DOB	Date of birth
DOD	Date of death
HES	Hospital Episode Statistics
HRA	Health Research Authority
IQR	Inter Quartile Range
ICER	Incremental cost-effectiveness ratio
KCL	King's College London
KiTEC	King's Technology Evaluation Centre
LC	Local control
MDT	Multidisciplinary team meeting
NICE	National Institute for Health and Care Excellence
NHS Digital	National Health Service Digital
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OS	Overall survival
PFS	Progression free survival
QALY	Quality-adjusted life of years
Patients	Pts
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RD	Research and Development

REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Side effects
SA	Sensitivity analysis
SABR	Stereotactic ablative body radiotherapy
SD	Standard deviation
TPN	Total parenteral nutrition
UK	United Kingdom

Authorship and acknowledgements

About KiTEC

KiTEC (King's Technology evaluation Centre) is a health technology assessment (HTA) organisation which is part of King's College London with experience in carrying out medical technology evaluations. Since 2011, KiTEC has worked as an External Assessment Centre (EAC) that carries out work for the National Institute for Health and Care Excellence (NICE) Medical Technologies Evaluation Programme (MTEP) and Diagnostic Assessment Programme (DAP). MTEP selects and evaluates innovative medical technologies (including devices and diagnostics) and helps the NHS adopt efficient and cost effective medical devices and diagnostics more rapidly and consistently. KiTEC uses specialist expertise to produce systematic reviews, meta-analyses, economic models, outcomes research, as well as services for horizon scanning, real world data analysis, data linkage and registry analysis. KiTEC works with a variety of stakeholders including the NHS, academic research groups, and private manufacturers of medical technologies.

Authorship

Dr Anastasia Chalkidou was project lead for the SABR CtE scheme. She was responsible for obtaining ethics and HRA approvals for the data analyses, worked on developing the study protocol, data dictionary, and active surveillance plan. She co-authored the executive summary and sections 1, 2, 3, 6, 7, 8 and 10 and contributed to sections to sections 4 and 9. AC collated and reviewed all sections of this report.

Thomas Macmillan carried out the literature searches for the clinical evidence and co-authored section 6 and appendices A and B and reviewed section 5.

Dr Kate Goddard interviewed the 17 centres for the providers' feedback and wrote section 9. She also co-authored section 6 and reviewed section 4.

Professor Janet Peacock, Fiona Reid, Dr Jennifer Summers, Saskia Eddy, Bola Coker, Dr Catey Bunce, Elli Bourmpaki, and Maria Elstad performed the CtE data statistical analysis and co-authored section 4 and 8. JP, BC, and FR also co-authored the active surveillance plan for the SABR CtE scheme. JP, BC, and FR contributed to the development of the study protocol and data dictionary. JP, SE, BC, and JS reviewed the executive summary and the conclusions. JP was the statistical analysis lead, and quality checked section 5.

Dr Mark Pennington, Dr Jin Huajie, and Dr Muralikrishnan Radhakrishnan produced the cost-effectiveness model and wrote section 5. MP was the health economics lead, co-authored the executive summary, conclusions of the report and quality checked section 6.

Professor Steve Keevil reviewed all sections, provided comments, and approved the final version prior to submission to NICE.

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Executive summary

Stereotactic Ablative Body Radiotherapy (SABR) is an emerging treatment that uses external beam radiation therapy to precisely deliver a high dose of radiation to a cancer lesion, using either a single dose or a small number of fractions. As a result, SABR is considered a more precise treatment than standard radiotherapy allowing the delivery of a high, biologically effective dose (BED) to the tumour while minimising the dose received by normal tissues, and thus could potentially minimise radiotherapy treatment toxicity and side effects (SEs). Metastatic cancer is diagnosed in approximately 140,000 patients in England per year. If not treated in time malignant tumours often spread by means of distant metastases. When cancer metastasises the most common sites it spreads to are lymph nodes, lungs, bones, and liver. Historically, the treatment of patients with metastatic solid tumours has been with palliative intent using chemotherapy aiming to delay disease progression and possibly extend life. Some metastatic cancers however, acquire their metastatic potential gradually and initially develop only a limited number of metastases (oligometastatic phase). Theoretically, if SABR was delivered during the oligometastatic phase, this might modify disease outcome in these patients.

In 2015 NHS England launched the Commissioning through Evaluation (CtE) scheme for SABR. The scheme, which is part of NHS England's Evaluative Commissioning Programme provided funding to treat patients with extracranial oligometastatic disease (estimated 1500 for the duration of the scheme) to access SABR within the NHS (National Health Service England 2014). This report summarises the findings of the scheme and all available published literature until May 2019 on the efficacy, safety, and cost-effectiveness of SABR in patients with oligometastatic disease.

Between 2015 and 2018, the CtE scheme collected outcomes from 1422 patients with oligometastatic disease recruited from 17 centres nationally. From these 1113 patients had their data also linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) registries. The median age of patients was 69 years, and most (66.6%) were men. The cohort was mainly comprised of patients with prostate (28.6%) and colorectal cancer (27.9%). The data analysis reported overall survival (OS) for patients with oligometastatic disease of 92.3% (95% CI: 90.5 to 93.9%) at 1 year and 79.2% at 2 years (95% CI: 76.0 to 82.1%). Both results were higher than the

actuarial survival[1] targets set at the beginning of the SABR CtE scheme (1-year target = 70%, 2-year target = 50%). However, it should be noted that for the 70% target it was assumed that the CtE cohort would include a small percentage of patients with breast and prostate oligometastatic disease. Although this was the case for breast cancer (5.5%), the CtE included a larger than estimated proportion of people with prostate cancer (28.6%), the highest for the whole cohort. Histology-based analysis of the CtE data provides further information on the possible impact of primary tumour histology with the 2-year OS ranging from 33.5% for oesophageal cancer to 94.6% for prostate cancer. There is additional evidence from the literature that the 1- and 2-year disease specific survival for patients with prostate oligometastatic disease is 100% (Ost et al., 2018). This can potentially have skewed the results towards a higher than anticipated OS.

The findings of the CtE scheme on the effect of SABR in OS of patients with extracranial oligometastatic disease is supported by good quality evidence from the literature. The main evidence comes from the SABR-COMET phase II RCT (Palma et al., 2019)[2] which included a similar cohort to the CtE scheme and compared SABR with standard care. The study concluded that the use of SABR in patients with controlled primary tumours and up to 5 oligometastases leads to an increase of approximately 13 months in OS (1-year OS of 86% and 2-year OS of 70%), with a doubling of progression-free survival (PFS). The study was adequately powered to detect a difference in OS between SABR and standard care, however, it was designed as a phase II RCT requiring a confirmatory phase III study to demonstrate if the OS and PFS advantage is true.

[1] The proportion of patients still alive at a predefined time point. For the SABR CtE scheme the overall survival at 1-year and 2-year post treatment were selected. All target rates set for the CtE were agreed by the working group by consensus, based on findings from a systematic review conducted in 2015. These targets were used to aid the interpretation of the survival and local control estimates observed in the CtE patients reported in the evaluation.

[2] Please note that throughout the document references to SABR-COMET or Palma et al. 2019 are used interchangeably.

The combined findings from the published literature and the CtE provide good[3] quality evidence that SABR significantly increases overall survival in comparison with standard care in patients with extracranial oligometastases in various locations.

The CtE data analysis also reported a local control (LC) rate for oligometastatic patients of 86.9% (95% CI: 84.6 to 88.9%) at 1 year and 72.3% (95% CI: 68.7 to 75.6%) at 2 years. Although the 2nd year LC rate was within range of the target set (2-year target = 70%) the first year LC rate was lower (1-year target = 90%). The results for LC reported by the CtE scheme are in the lower range as compared with the rest of the published literature. Contrary, to the rest of the studies, the CtE has not used RECIST[4] to calculate LC, therefore, the results are not easily comparable. The combined findings from the published literature and the CtE provide moderate quality evidence that SABR achieves high LC rates. There is further low-quality evidence from the published literature only, that the LC achieved with SABR is equivalent to that achieved by surgery (for pulmonary oligometastases) or radio frequency ablation (RFA for liver oligometastases).

The CtE data analysis reported grade 3[5] toxicity of 5.8% (95% CI: 4.7 to 7.2%) within the target set of 10%. It also reported grade 4[6] toxicity of 1.8% (95% CI: 1.2 to 2.7%) within the target of 5%. No grade 5 toxicity was reported. The majority of grade 4 events were related to increased levels of alanine aminotransferase and bilirubin levels and it is therefore, unknown if they resulted from clinically meaningful grade four toxicity. The results for adverse events reported by the CtE cohort are consistent with most of the published literature. The exception being the high incidence of grade 5[7] toxicity reported by the SABR-COMET RCT (4.5%) as a secondary outcome measure. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of OS achieved with standard care and active surveillance, the impact of severe toxicity is clinically important and

[3]The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence for each outcome included in the report.

[4] RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer patients improve (respond), stay the same (stable) or worsen (progression) during treatments.

[5] Defined as severe or medically significant but not immediately life-threatening toxicity resulting in hospitalisation or prolongation of hospitalisation, may also limit self-care or be disabling.

[6] Defined as toxicity resulting to life-threatening consequences that need urgent intervention.

[7] Defined as toxicity that causes the death of the patient.

should be investigated further in future studies and using real world data. The combined findings from the CtE and the published literature, provide low quality evidence that SABR may lead to an increase in severe toxicity in comparison with standard care.

There is low quality published evidence that treatment with SABR achieves equivalent quality of life (QoL) when compared to standard care or active surveillance. Literature addressing QoL focuses particularly on patients with prostate cancer, who have a relatively good prognosis. The original intention to quantify the impact of adverse events on QoL using the CtE data was not undertaken. This analysis had been specified conditional on the data being of sufficient quality. The analysis was judged inappropriate for the following reasons: there were concerns regarding the accuracy of the capture of the date of adverse events and whether this was sufficiently close to the date at which QoL was measured; it was unclear how data measured using the EQ-5D-5L had been entered into the database by centres; and the number of patients suffering a severe adverse event was low.

One of the factors influencing treatment decisions is whether treatment will affect patients' QoL; therefore, this outcome is clinically important and should be investigated further in future studies.

The main limitation of the current evidence (including the analysis of the CtE data) is that with the exception of the SABR-COMET RCT and 4 small retrospectively matched case series, the rest of the studies, including the CtE scheme, were non-comparative and so cannot inform the clinical efficacy and safety of SABR versus standard care. The retrospective case series studies that compare SABR with surgery or RFA have high risk of bias for patient selection and outcome detection and it is unknown if they are powered to detect differences between the two cohorts. The low numbers of patients and the high risk of bias do not allow robust conclusions to be drawn from the reported subgroup analysis.

The cost-effectiveness[8] analysis found that for adult patients with borderline resectable liver oligometastases who may be candidates for surgery, SABR results in more QALY gains and lower cost compared to surgery. This finding assumes that SABR and surgery lead to similar OS and LC over the duration of the analysis. Data from the CtE cohort indicates lower OS and LC rates with SABR when compared to published data on resection, and application of this data leads to the inference that

[8] Cost-effectiveness analysis is a form of economic analysis that compares the relative costs and clinical outcomes of two or more treatments. It is used to aid decisions about which medical care should be offered.

resection is the most cost-effective intervention. It should be noted however, that these studies usually recruited patients with better prognosis than studies with SABR. In the case of pulmonary metastases for example there is low quality evidence that SABR achieves equivalent results to surgery when the 2 groups have comparable characteristics. Therefore, inference from the sensitivity analysis must be treated with caution as most of the SABR cohort would not have been considered candidates for surgery and hence comparison of survival with patients undergoing resection is potentially compromised. The data indicate a potential for SABR to be cost-effective, if it can achieve similar survival to that achieved with surgery. Ultimately, a randomised trial would be required to provide robust evidence on the cost-effectiveness of SABR for patients with resectable liver oligometastases.

Further phase 3 trials are needed to confirm the benefit in OS in comparison with other metastases-directed treatments such as surgery and RFA, to define the maximum number of metastases that SABR can be used to treat and to investigate the impact on toxicity and quality of life. Further research should also aim to test the OS benefits for tumour-specific groups in an adequately powered phase 3 RCT. Ultimately, a randomised trial would be required to provide robust evidence on the cost-effectiveness of SABR for patients with resectable liver oligometastases.

1 Background

1.1 Stereotactic ablative radiotherapy

Stereotactic Ablative Body Radiotherapy (SABR) is an emerging radiation technology. The American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) define SABR as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extra-cranial target within the body, using either a single dose or a small number of fractions." SABR is a more precise treatment than standard radiotherapy. This results in the delivery of a high, biologically effective dose (BED) to the tumour while minimising the dose received by normal tissues, and thus could potentially minimise radiotherapy treatment toxicity and side effects (SEs). In addition, as the technique uses a smaller number of fractions (and, consequently, requires a smaller number of hospital visits) than standard radiotherapy, it may provide the opportunity for financial savings and improved patient experience. The technique requires specialist positioning equipment and imaging to confirm correct targeting.

1.2 Oligometastatic disease

Metastatic cancer is diagnosed in approximately 140,000 patients in England per year. If not treated in time malignant tumours often spread by means of distant metastases. When cancer metastasises the most common sites it spreads to are lymph nodes, lungs, bones, and liver. Historically, the treatment of patients with metastatic solid tumours has been with palliative intent aiming to delay disease progression and possibly extend life but not to cure the disease.

Anecdotal evidence from the 1930s, however, suggested that patients with metastatic disease may not be universally true as it was observed that in selected cases, survival beyond 5 years was reported after resection of the metastases (Palma et al. 2014). By the 1960s, it was established that long-term survival for patients with limited metastatic burden was associated with indolent tumour behaviour, manifested by a long disease-free interval between presentation of the primary tumour and development of metastases, a limited number of metastatic sites, and favourable tumour histology (Palma et al. 2014). In 1995 Hellman and Weichselbaum proposed the idea of an oligometastatic state (Hellman and Weichselbaum 1995). They suggested that some cancers gradually acquire their metastatic potential and initially develop a limited number of metastases

(oligometastatic phase). Theoretically, if SABR was delivered during the oligometastatic phase, this might modify disease outcome in patients. It is estimated that 2200 patients with extracranial oligometastatic disease (synchronous or metachronous[9]) would be suitable for SABR treatment annually in England (Policy Working Group consensus).

1.3 Commissioning through Evaluation programme

Despite the potential of SABR, there is limited evidence of its effectiveness except in early stage non-small cell lung cancer (NSCLC) and, therefore, extracranial SABR is currently only commissioned by National Health Service (NHS) England for this indication. To address the evidence gap, in 2015 NHS England launched the Commissioning through Evaluation (CtE) scheme for SABR. The scheme, which is part of NHS England's Evaluative Commissioning Programme provides funding for a limited number of patients to access medical treatments and technologies that are not routinely commissioned within the NHS (National Health Service England 2014). CtE enables patients to access promising new treatments, whilst new data is collected within a formal evaluation programme. Outcomes data are considered by NHS England in order to inform future review of clinical commissioning policy. The SABR CtE scheme included the following cohorts:

- Oligometastatic disease;
- Primary liver tumours (hepatocellular carcinoma);
- Re-irradiation of cancers in the pelvis and spine.

NHS England commissioned NICE and its External Assessment Centre (KiTEC) to lead data collection and evaluation of the SABR CtE (work package RX116). This report covers the oligometastatic disease cohort; results for the re-irradiation and HCC cohorts are reported in separate documents.

1.4 Aim of the project

To evaluate the clinical effectiveness, safety and cost-effectiveness of SABR in patients with extracranial oligometastatic disease.

[9] Synchronous metastatic disease is defined as the presence of metastases at the time of diagnosis. Metachronous disease is defined as the diagnosis of metastases more than 6 months after the diagnosis of primary cancer.

1.5 Stages

The project was carried out in two stages – a feasibility stage and a data collection and analysis stage, each with specific tasks and outputs. The purpose of the feasibility stage was to plan the data collection and analysis stage. The feasibility stage of the SABR CtE project started on in June 2015 and KiTEC completed the following tasks as part of that stage:

- Develop the variables/dataset required to capture essential information to answer NHS England's questions;
- Develop the interim data collection tool;
- Establish the roles and responsibilities for the project between KiTEC, NICE, NHS England and the clinical leads;
- Contact the centres that have commenced recruitment and establish the type of data they are collecting;
- Establish the governance requirements for the project and obtained REC, HRA and RD approvals.

KiTEC's overall goal for the second stage of the project was to oversee, co-ordinate and manage the data collection and to conduct the analysis. The results of this stage are reported in this document.

1.6 Database provider

The SABR CtE project required a centralised database to collect data from all of the participating clinical sites for the purpose of analysis. Following various discussions on this subject, it was decided that King's College London would hold the contract with the database provider. Following a successful competitive procurement process, UHB was selected as the database provider.

1.7 Project Scope

The scope for the SABR CtE scheme is outlined in Table 1 below.

Table 1: Project scope

Population	Patients with extracranial oligometastatic disease*
Intervention	SABR (8 fractions or fewer) to oligometastases (dose and fractionation dependent on site of metastasis and proximity to organs at risk).
Comparator	No comparator
Outcomes	• Overall survival • Local control† • Quality of life • Adverse events • Cost effectiveness
* Inclusion criteria are listed in section 1.7.1 † Local control is the proportion of patients for which the treated area does not increase in size at a defined follow-up point after beginning treatment. Local control is different to progression-free survival (PFS) that is the length of time during which the disease does not worsen, or the proportion of patients without worsening disease at a defined follow-up point after beginning treatment. Worsening of the disease usually means the development of metastases elsewhere in the body and/or an increase in the size of the treated lesion. There is significant variability on how different studies report this outcome. The CtE scheme assessed only local control and not PFS.	

1.7.1 Inclusion criteria

- Metastatic carcinoma with either a histologically or cytologically proven primary site or a male patient with a prostate-specific antigen (PSA)>50ng/mL and clinical evidence of prostate cancer.
- 1-3 sites of metastatic disease (defined after appropriate imaging) which can be treated with stereotactic radiotherapy using a radical radiation dose.
- A maximum of two sites of spinal metastatic disease.
- Maximum size of 6 cm for any single metastasis (5 cm for lung or liver metastases).

- Disease[10] free interval > 6 months; unless synchronous liver metastases from colorectal primary (see liver metastases section).
- No more than three oligometastatic sites treated in total per patient.
- Expected life expectancy > 6 months.
- WHO performance status ≤ 2.
- All patients to be discussed by stereotactic multi-disciplinary team (MDT) with presence of, or prior discussion with a disease site specific oncologist.
- All patients willing to attend follow up and have details collected on prospective database for a minimum of two years.

1.7.2 Recruiting centres

Seventeen sites were selected by NHS England to provide SABR treatments for patients with oligometastatic disease. The participating centres are listed below:

- **North Region**
  - Sheffield Teaching Hospitals NHS Trust
  - The Christie NHS Foundation Trust
  - The Clatterbridge Cancer Centre NHS Foundation Trust
  - Newcastle upon Tyne Hospitals NHS Foundation Trust
  - Leeds Teaching Hospitals NHS Trust
  - South Tees Hospitals NHS Foundation Trust
- **Midlands and East Region**
  - Nottingham University Hospitals NHS Trust
  - University Hospitals Birmingham NHS Foundation Trust

[10] Disease free interval represents metastasis free interval in this case. A cut-off of more than 6 months was used to separate metachronous from synchronous metastases.

- Mount Vernon Cancer Centre (North and East Hertfordshire NHS Foundation Trust)
- University Hospitals of Leicester NHS Trust

- **London Region**
  - The Royal Marsden NHS Foundation Trust
  - University College Hospitals London NHS Foundation Trust
  - Barts Health NHS Trust
  - Guys and St Thomas' NHS Foundation Trust
- **South Region**
  - University Hospitals Bristol NHS Foundation Trust
  - Oxford University Hospital NHS Trust
  - Royal Surrey County Hospital NHS Foundation Trust

2 Commissioning through Evaluation questions

NHS England required the following research questions to be addressed:

1. What is the 1-year and 2-year survival following treatment with SABR for the indications covered by the CtE scheme (presented as estimates with confidence intervals)? How do these survival estimates compare with the target outcomes (see section 4), in terms of superiority or non-inferiority?
2. Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?
3. What Adverse Events occur as a result of SABR in the CtE cohort of patients?
4. What is the patient experience of treatment with SABR for the clinical indications covered within the CtE programme?

5. What is the cost-effectiveness of providing SABR in three subgroups of patients covered within the CtE scheme (oligometastases (liver), re-irradiation (pelvis) & hepatocellular carcinoma)?
6. What are the outcomes by indication in the CtE cohort of patients? The cohort can potentially be stratified based on the location or histology of metastasis treated.
7. Are there any factors from the experience of provision within centres participating in the scheme that should be taken into account in terms of future service provision?
8. Are there any research findings that have become available during the course of the CtE scheme that should be considered alongside the evaluative findings of the CtE scheme?

3 Information governance

3.1 Ethics approval

To answer the NHS England's evaluation questions for this project the centres needed to collect routine clinical data, data on quality of life, pain symptoms, and patient experience using questionnaires and to store this locally, with standard NHS patient consent. This phase of the project was classified as an audit and all patient data were stored and viewed only by the patients' clinical team. KiTEC submitted a REC application for proportionate review at the North East - York Research Ethics Committee to gain permission to analyse these patient data in a non-identifiable format. The patients undergoing SABR as part of the scheme signed a standard NHS consent form to the treatment. The patients were consented separately to their treatment consent for their data to be analysed by KiTEC. Ethics approval for the project was obtained in August 2016 (REC reference: 16_NE_0285) and HRA approval was obtained in October 2016. Following that R&D approvals for all participating centres needed to be obtained separately.

The data flow between NHS Trusts and KiTEC was as follows:

1. Patient identifiable data were entered electronically at each NHS Trust site and were stored locally by the local clinical teams involved in patient care using an interim access tool (IAT) database developed by KiTEC.
2. Identifiable data from the IAT were subsequently uploaded from each centre to PROPEL the SABR national database developed by the database provider (UHB). The database can only be accessed from within the NHS by the clinicians involved in the project and each Trust will only be able to access its own data.
3. Patient anonymised data were subsequently send from PROPEL to KiTEC for analysis.

3.2 Data linkage approvals

Hospital Episodes Statistics (HES) is a data warehouse containing details of all admissions, outpatient appointments, and A&E attendances at NHS hospitals in England. Centres involved with SABR were submitting returns to HES monthly. The database provider submitted an application to NHS Digital to request data from HES and ONS. These patient records from HES/ONS were subsequently linked with patient level data captured in the PROPEL database. The purpose of this linkage was to enable accurate mortality data to be captured, as well as data on other diagnoses or procedures that patients may have

had at other departments (internal or external to the treating hospital), thus increasing the accuracy of the recording of both adverse event and mortality in the database. This process required UHB to collect non-anonymised patient data (NHS number as a minimum), as well to obtain access to equivalently non-anonymised HES/ONS patient records. On April 2018 the database provider submitted a formal application to NHS Digital (NIC-150435-R7X1Q) outlining the legal basis for linking the CtE collected data to non-anonymised HES/ONS patient records. After the application was reviewed by the IGARD[11] committee (the application was reviewed in 3 separate dates between September and November 2018) it was finally approved in November 2018, the database provider submitted the patient identifiers to NHS Digital on December 2018. Final data linkage between PROPEL and HES/ONS took place at the end of December 2018.

4 Analysis of CtE registry data

4.1 Statistical analysis plan

The data was analysed as per the SABR Data Analysis Protocol 17/02/2016 – Version 2.2 (please see appendix C).

4.2 Sample size

As this was a CtE project and not a clinical trial, a sample size calculation was not performed. The number of patients receiving SABR in England as part of the CtE scheme was fixed and dependent on the funding available from NHS England. This was estimated to be approximately 750 patients per year for the three indications (oligometastatic disease, re-irradiation, and hepatocellular carcinoma). For the total duration of the scheme (3 years), 2,250 people were expected to undergo SABR treatment for the three indications. Of this number, approximately 500 patients per year (total 1,500) were estimated to receive treatment for oligometastatic disease.

4.3 Database

Data for the CtE were collected on three different instruments:

[11] The Independent Group Advising on the Release of Data (IGARD) considers all requests for dissemination of confidential information by NHS digital, as defined in Section 263 of the Health & Social Care Act, through the Data Access Request Service (DARS).

4.3.1 Paper CtE monitoring form: July 2015 to May 2016

This instrument was provided by NHS England (see appendix C), and allowed for data collection at baseline and follow up clinical assessments as well as EQ-5D,(EuroQol Group 1990, Dolan P 1997, Feng Y et al. 2017) CTCAE (Common Terminology Criteria for Adverse Events),(U.S. Department of Health and Human Services 2010) and the Visual Analogue Pain score (Brief Pain Inventory).

4.3.2 KiTEC-developed interim access tool: June 2016 to May 2018

In line with information governance requirements, KiTEC developed an interim tool for hospital trusts to store data before sending it to the national database. The interim tool was developed using the specification from an agreed SABR data dictionary. It was developed using MS Access and allowed for data collection at the baseline, 4-6 week, 3-month, 6-month, 18 months and 24-month clinical assessments as well as EQ-5D, CTCAE, Visual Analogue Pain score, patient experience and radiotherapy parameters (Table 2 lists the data collected during each follow-up). The inclusion criteria allowed patients with up to three metastases to be included in the scheme, therefore, the tool allowed for details of up to three SABR treatments at baseline to be collected. Each provider site had their own interim tool and managed it in compliance with NHS information governance procedures. The interim tool was approved by each site's information governance department.

Table 2: Data collected at each follow-up appointment as part of the scheme.

TIME POINTS							
Forms	**Baseline**	**4-6 Weeks**	**3 Months**	**6 Months**	**12 Months**	**18 Months**	**24 Months**
Demographics	√						
Clinical Assessment - Baseline	√						
Clinical Assessment - Follow Up	√	√	√	√	√	√	√
EQ-5D	√	√	√	√	√	√	√
CTCAE	√	√	√	√	√	√	√
Pain Score[12]	√	√	√	√	√	√	√
Patient experience		√					
Radiotherapy planning details (Trt 1)	√						
Radiotherapy planning details (Trt 2)	√						
Radiotherapy planning details (Trt 3)	√						
Death		√	√	√	√	√	√

[12] Pain score data were collected as part of the wider SABR CtE scheme which also included patients receiving SABR for re-irradiation of cancers in the pelvis or spine, or for hepatocellular carcinoma. The pain score data were not analysed for patients with oligometastatic disease because they were not considered clinically relevant to this cohort.

4.3.3 UHB-developed PROPEL database: June 2018 to December 2018

This was created by UHB and mirrored the functionality of the KiTEC-developed interim tool with a few modifications. It was a web application based at UHB and was accessible only through the NHS N3 network. UHB performed the collation and migration of the KiTEC interim tools from the 17 sites. The PROPEL database had ethical approval and was managed by the UHB NHS IT department in compliance with NHS security procedures.

PROPEL also collected DICOM data as a separate project funded by NHS England – analyses are not provided as part of this CtE report.

4.4 Data extraction

Data were extracted from the UHB PROPEL database and were provided to KiTEC in pseudo-anonymised form along with a data dictionary (see Appendix D: Data dictionary for PROPEL). KiTEC did not have access to the paper CtE monitoring form or the data from the KiTEC-developed Interim tool used at each clinical site. Data extracts were provided by UHB in July 2018, September 2018, November 2018, January 2019 and the final data extract in February 2019. KiTEC fed back data quality issues to UHB after each extract except the final one.

Minor structural inconsistencies between the data dictionary provided by PROPEL and the data provided were resolved when possible through personal communication with UHB for the relevant variables for this current analysis. None of the inconsistencies resulted in data loss or affected the clinical outcomes included in this report.

4.5 Data management and HES-ONS linkage

On 21/12/2018, after obtaining the HES/ONS records from NHS Digital, UHB provided linked HES-ONS (Digital 2018, Digital 2018, Digital 2018) data for 1113 CtE patients who had consented for their identifiable data to be used. The linked HES/ONS data covered the period from 2015 to Oct 2018. To understand inconsistencies between data sources, UHB contacted seven centres, which had date of death (DOD) discrepancies between ONS (last updated 31/10/2018) and PROPEL (last updated 22/01/2019).

UHB provided KiTEC with the HES-ONS data, and KiTEC merged the HES-ONS data with the PROPEL data extract from UHB provided in February 2019 using the pseudo-anonymised patient identifiers in both extracts. The PROPEL dataset was provided in long format, and required extensive re-formatting by KiTEC to check for and address issues of duplication within patients' own data over the various assessment time points. Only after these extensive checks were completed could KiTEC merge the PROPEL data with the HES/ONS data.

In total, ONS contained 59 deceased patient records whereas PROPEL showed 62 patients as deceased among the consented cohort. Forty-two patients had the same DOD in both PROPEL and ONS databases. Sixteen patients were only recorded on ONS, potentially because the centres were unaware that the patient had died after the most recent follow-up assessment. Nineteen patients were only recorded in PROPEL. Of those, 14 patients were only included in PROPEL because ONS did not contain data after October 2018. The remaining 5 patients had no linked records in ONS, 3 of whom were verified using HES data and 2 whose demographic information was incorrect. Additionally, there were 3 instances of patients having their last appointment date recorded as after their DOD, though in these cases the centres confirmed that they were conducting telephone follow-up appointments and were informed by the patients' relatives about their death.

4.6 Data completeness

UHB and KiTEC using both the KiTEC- developed interim tool and the UHB PROPEL database conducted data completion explorations. The interim tool had an inbuilt aggregate report facility designed by KiTEC that provided percentage completion figures for patients who had records in the database. Data completion from the PROPEL tool used a similar aggregate report. The PROPEL tool also provided another report that allowed for patients who were missing from follow-ups. UHB reported to KiTEC that they had followed up data completeness and quality issues with centres.

Between September 2016 and January 2018 KiTEC monitored the completeness of the database mandatory fields using aggregate figures from the interim access tool. Centres were sent newsletters every two months showing their mandatory fields' completion rate.

From February 2018, UHB were responsible for monitoring both the completeness of the mandatory fields as well as the patients lost to follow up. UHB started sending Centres the mandatory field completeness newsletters in May 2018 and continued sending them every two months to Centres. UHB also monitored the completeness of patients being followed up. UHB reported regularly to

KiTEC through reports and teleconferences that they had followed up data completeness and quality issues with centres. Table 3 shows the final data completeness rates for each recruiting NHS Trust.

Table 3: Final data completeness rates achieved by each participating NHS Trust. Please note that due to the way data completeness was calculated it is provided for all three indications treated under the SABR CtE scheme.

Centre	Data completeness rate (%)
UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST	40
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST	98
UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST	95
SOUTH TEES HOSPITALS NHS FOUNDATION TRUST	90
THE CHRISTIE NHS FOUNDATION TRUST	89
UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST	97
THE CLATTERBRIDGE CANCER CENTRE NHS FOUNDATION TRUST	71
THE NEWCASTLE UPON TYNE HOSPITALS NHS FT	96
BARTS HEALTH NHS TRUST	91
GUY'S AND ST THOMAS' NHS FOUNDATION TRUST	83
ROYAL SURREY COUNTY HOSPITAL NHS FOUNDATION TRUST	97
OXFORD UNIVERSITY HOSPITALS NHS TRUST	65
NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST	96
LEEDS TEACHING HOSPITALS NHS TRUST	73
THE ROYAL MARSDEN NHS FOUNDATION TRUST	87
EAST AND NORTH HERTFORDSHIRE NHS TRUST	97
UNIVERSITY HOSPITALS BIRMINGHAM NHS FOUNDATION TRUST	96
Total	**Overall completeness: 87.7**

4.7 Statistical methods

KiTEC calculated summary statistics by CtE indication for demographics, of metastases, primary tumour histology, and patient experience questionnaire. Median follow-up time with inter quartile ranges (IQR) are reported where appropriate. Survival function estimates with 95% confidence intervals were estimated for one and two years from the start of SABR treatment using the Kaplan-Meier method, that takes into account differential follow-up times among the patient group. Where patients were still alive at the final documented clinical visit, they were censored at that date in the

analysis. Median OS and median local control failure are reported if within the two-year follow-up period.

The first occurrence of failure of local control was considered as the event.

These analyses were performed for each of the three CtE indication and reported only for patients with oligometastatic disease in this report. Kaplan-Meier survival curves were drawn with a 95% confidence interval for the curve.

Where there were fewer than 6 deaths in a group or subgroup of patients, Kaplan-Meier estimates were not calculated as they are considered unreliable (Peacock JL and Peacock PJ 2011). In these cases, indicative Kaplan-Meier plots have been given but without estimated survival.

To determine date of death, where available the HES/ONS date of death was considered the gold standard. This was therefore used when there was lack of consistency between the date of death reported in HES/ONS and the PROPEL database or when it was missing. HES/ONS data were only linked for patients who had consented. In order to maximise the number of patients who could be included, patients who had not provided consent for linkage with HES/ONS were included but their data were censored at the last point at which they were known to be alive.

Frequency of adverse events by type were calculated. Adverse events with a start date occurring prior to commencement of SABR treatment were excluded. Duplicated adverse events were also excluded. Data recorded outside of the CTCAE grading system were excluded. Adverse event toxicity variables based on anatomical treatment location, were not accurately provided in the PROPEL database nor did the data dictionary received from UHB reflect the PROPEL dataset. Therefore, it was not possible to assess the quality and accuracy of this variable in relation to the adverse event types. The following summary statistics were calculated for adverse events: percentage of patients with i) one or more adverse events overall, ii) with grade 3 adverse events and iii) with grade 4 or 5 adverse events. Please see appendix F for details of grade 5 adverse events. These were each calculated with a 95% CI using the exact binomial method to accommodate the very small frequencies.

The 'friends and family test' (https://www.england.nhs.uk/ourwork/pe/fft/), a short generic instrument, designed to provide some patient experience feedback was used to collect information for all SABR patients. This test has been widely used in the NHS. The frequencies have been given in this report with the percentages and 95% CIs for each category.

STATA version 15, plus STATA graph addition (Jann B 2018) and SPSS version 25 were used for analysis in this report.

4.8 Target survival rates

Target OS and LC rates were agreed by the working group by consensus, based on findings from a systematic review conducted in 2015. These targets were used to aid the interpretation of the overall survival and local control estimates observed in the CtE patients reported in the evaluation. The agreed targets for each outcome are listed in section 8.

4.9 Results

4.9.1 Data quality

KiTEC only assessed data quality of variables that feed into the outcomes assessed in this report as per the agreed Statistical Analysis Plan. Examples of some of the data errors identified by KiTEC in the variables utilised for the purposes of this report were:

- Incompatible SABR treatment/assessment dates.
- Follow-up assessment dates occurring before start of first SABR treatment.
- Follow-up assessments occurring on the same date as the first SABR treatment.
- Extensive duplication of data across time points.
- Over 70 patients who were missing dates of baseline or follow-up assessment.
- Multiple patients who only had baseline data and no follow-up.
- Dates of assessment occurring in non-chronological order.
- Adverse events which were non-compatible with CTCAE grades (see appendix F for discussion of Grade 5 adverse events).
- Patients whose start date for SABR treatment was the same day as their end date.
- Follow-up assessment dates occurring after death (HES/ONS or PROPEL listed death).
- Multiple patients with empty rows of data.

Only patients who contributed to the overall survival following SABR first treatment were included in the analysis. A total of n=84/1506 (5.6%) patients were excluded from all the analysis for the following reasons: missing CtE indication, patients with only baseline data available before the 1st February 2019 data extract cut-off, assessment dates in non-chronological order, no SABR start date,

no end date for SABR treatment, lack of follow-up data, SABR treatment start and finish on the same date (a minimum of 3 days is required), and follow-up occurred before the end of first SABR treatment.

4.9.2 Patient recruitment

Data were collected from 17 centres. Figure 1 shows the flow diagram for patient recruitment in the scheme. It should be noted that because centres screened patients through their MDT meetings, it is unknown how many patients were originally screened for eligibility.

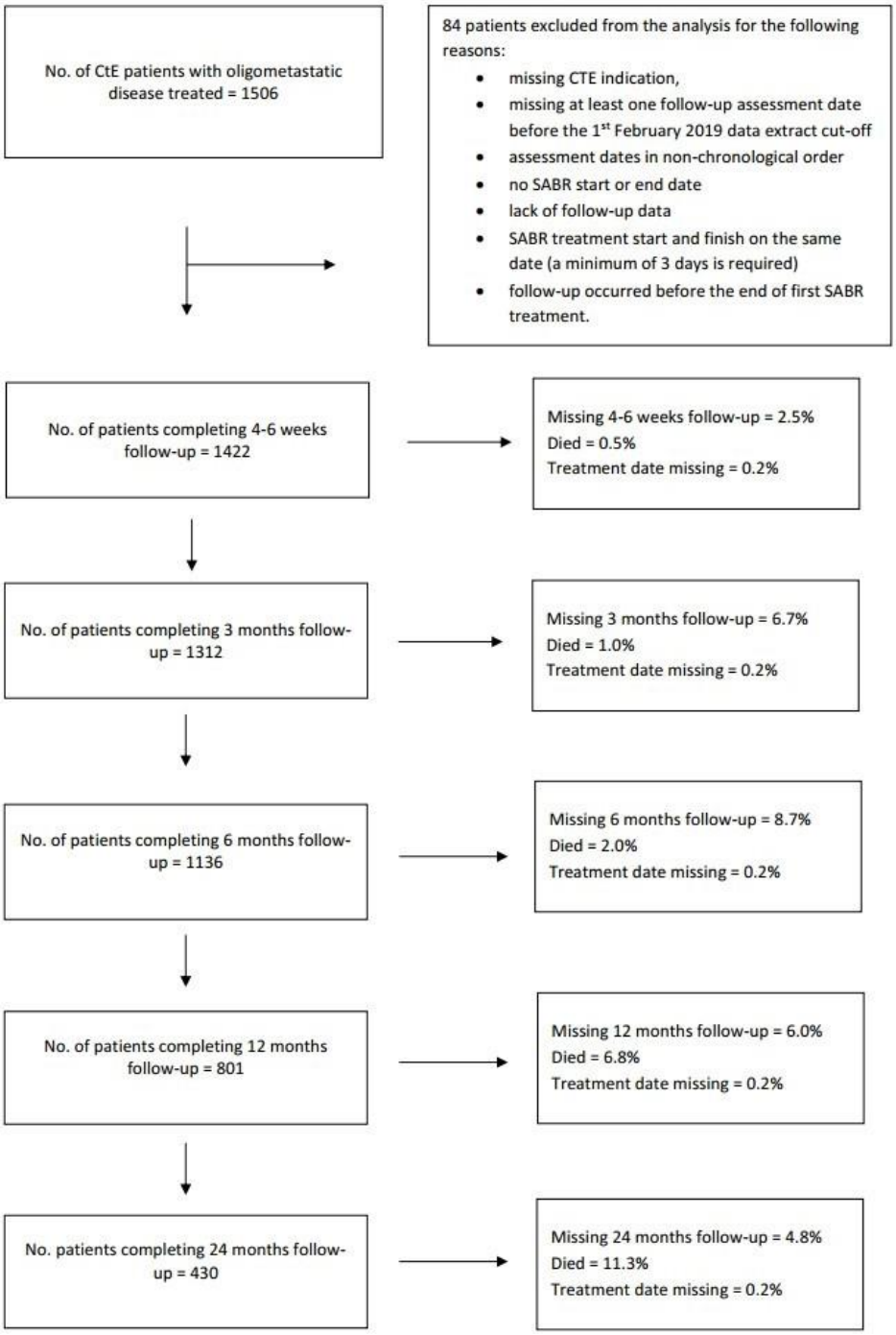

Figure 1: Patient recruitment flow chart.

4.9.3 Demographics

Baseline demographics and patient clinical information are in Table 4 and Table 5.

Table 4: Cohort demographics

	(n=1422)	
Age		
Age - N (%)	1422	100%
Age (years) – Median (IQR)	69	(62 to 76)
Sex		
Male - N (%)	947	66.6%
Female - N (%)	475	33.4%
Ethnicity - N (%)		
White - British	1094	81.8%
White - Irish	8	0.6%
White - Any other white background	23	1.7%
Mixed - White and Black Caribbean	1	0.1%
Mixed - White and Black African	0	0.0%
Mixed - White and Asian	0	0.0%
Mixed - Any other mixed background	1	0.1%
Asian or Asian British - Indian	10	0.7%
Asian or Asian British - Pakistani	2	0.1%
Asian or Asian British - Bangladeshi	2	0.1%
Asian or Asian British - Any other Asian Background	6	0.4%
Black or Black British - Caribbean	7	0.5%
Black or Black British - African	10	0.7%
Black or Black British - Any other Black background	4	0.3%
Other Ethnic Groups - Chinese	5	0.4%
Other Ethnic Groups - Any other ethnic group	13	1.0%
Not stated	152	11.4%
Total Ethnicity	**1338**	
Missing* Ethnicity	84	5.9%
*Missing % is based on overall number of patients in the specific category.		

Table 5: Baseline clinical characteristics

WHO performance status		
0 - Fully active, able to carry on all pre-disease performance without restriction	1000	71.1%
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	342	24.3%
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	64	4.6%
Total WHO performance status	**1406**	
Missing* WHO performance status	16	1.1%
Site of first metastases		
Lung	411	29.3%
Spine	132	9.4%
Bone	169	12.1%
Adrenal	41	2.9%
Pelvic	74	5.3%
Liver	135	9.6%
Nodes	439	31.3%
Total Site of first metastases	**1401**	
Missing* Site of first metastases	21	1.5%
Number of metastases		
1	1074	75.6%
2	279	19.6%
3	68	4.8%
Average number of metastases (SD)		1.3 (0.6)
Total Number of metastases	**1421**	
Missing* Number of metastases	1	0.1%
Prior systemic therapy		
Yes	850	59.8%
No	572	40.2%
Total Prior systemic therapy	**1422**	
Missing* Prior systemic therapy	0	0.0%

The baseline primary tumour diagnosis of patients with oligometastatic disease is reported in Table 6.

Table 6: Primary tumour diagnosis

	(n=1422)	
Primary Site - N (%)		
Head and neck (including thyroid)	39	2.7%
Lung cancer	64	4.5%
Breast cancer	78	5.5%
Prostate cancer	406	28.6%
Renal cancer	143	10.1%
Colonic cancer	233	16.4%
Oesophageal cancer	19	1.3%
Pancreatic cancer	13	0.9%
Gastrointestinal stromal tumour (GIST)	7	0.5%
Endometrial cancer	31	2.2%
Cervical cancer	8	0.6%
Melanoma	58	4.1%
Sarcoma	22	1.5%
Germ cell tumour	1	0.1%
Gastric cancer	6	0.4%
Bladder cancer	26	1.8%
Rectal cancer	164	11.5%
Anal cancer	14	1.0%
Transitional cell cancer (TCC)	0	0.0%
Penile cancer	3	0.2%
Ovarian cancer	17	1.2%
Cholangiocarcinoma	7	0.5%
Vulva cancer	1	0.1%
Urothelial cancer	10	0.7%
Hepatocellular carcinoma	6	0.4%
Other	46	3.2%
Total Primary Site	**1422**	

4.9.4 Overall survival analysis

Median follow-up time was 1.06 years (IQR 0.52 to 1.94). It was not possible to calculate the median overall survival time because it was past the two-year follow-up cut-off (see methods). Overall survival estimates at one and two years were calculated (Table 7) along with a corresponding Kaplan-Meier plot (Figure 2).

Table 7: Overall Survival Estimates

Survival interval	Probability of survival	95% Confidence Interval
One Year	92.3%	90.5 to 93.9%
Two Year	79.2%	76.0 to 82.1%

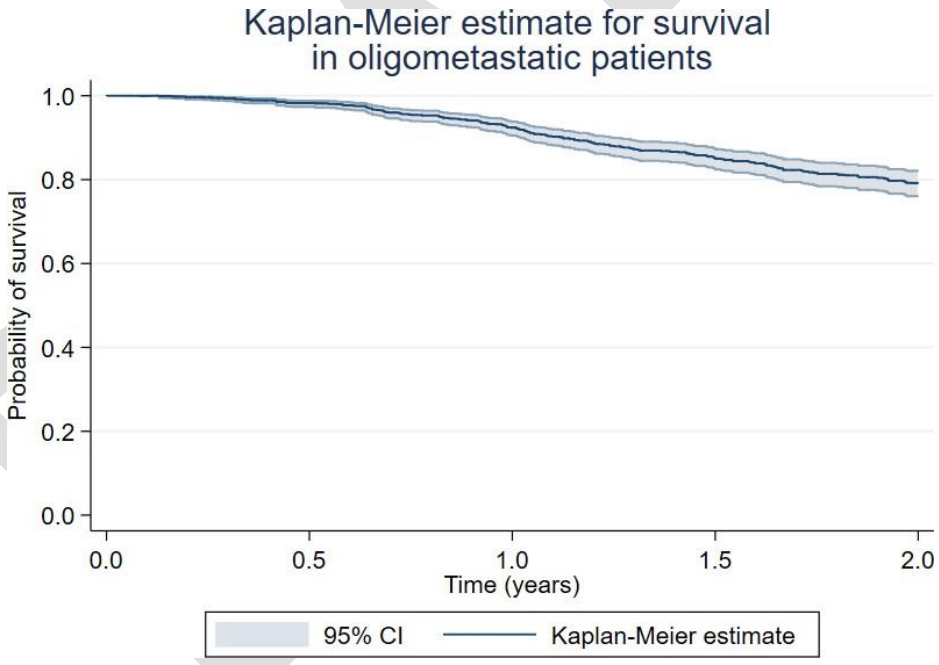

Figure 2: Kaplan-Meier estimate for overall survival

4.9.5 Overall survival analysis based on primary tumour histology

Overall survival estimates for patients with oligometastatic disease by baseline primary site are presented in Table 8.

Table 8: Overall Survival estimates[13] by primary tumour histology

Primary Site	Survival interval	Probability of Survival	95% Confidence Interval
Head and neck (including thyroid)	One Year	Not calculable	
	Two Year	64.7%	39.8 to 81.4%
Lung cancer	One Year	80.2%	67.1 to 88.6%
	Two Year	65.4%	50.6 to 76.7%
Prostate cancer	One Year	Not calculable	
	Two Year	94.6%	90.4 to 97.0%
Renal cancer	One Year	95.3%	89.0 to 98.0%
	Two Year	82.4%	70.6 to 89.8%
Colonic cancer	One Year	92.0%	86.6 to 95.3%
	Two Year	80.3%	71.8 to 86.5%
Oesophageal cancer	One Year	Not calculable	
	Two Year	33.5%	6.3 to 64.9%
Melanoma	One Year	Not calculable	
	Two Year	60.5%	38.0 to 77.0%
Rectal cancer	One Year	93.7%	87.2 to 97.0%
	Two Year	77.8%	66.5 to 85.7%
Other	One Year	Not calculable	
	Two Year	61.0%	37.1 to 78.2%

* Note that survival estimates are only provided when there are more than 5 events (deaths) (see methods)(Peacock JL and Peacock PJ 2011).

4.9.6 Local control analysis

Overall local control estimates at one and two years were calculated (Table 9) along with a corresponding Kaplan-Meier plot for with oligometastatic disease (Figure 3). It was not possible to calculate the median local control failure time because it was past the two-year follow-up cut-off (see methods).

[13] **Note that survival estimates are only provided when there are more than 5 events (deaths)Peacock JL and Peacock PJ (2011). Oxford Handbook of Medical Statistics. New York, United States of America, Oxford University Press.

Table 9: Overall local control estimates

Year of Local Control	Probability of local control	95% Confidence Interval
One Year	86.9%	84.6 to 88.9%
Two Year	72.3%	68.7 to 75.6%

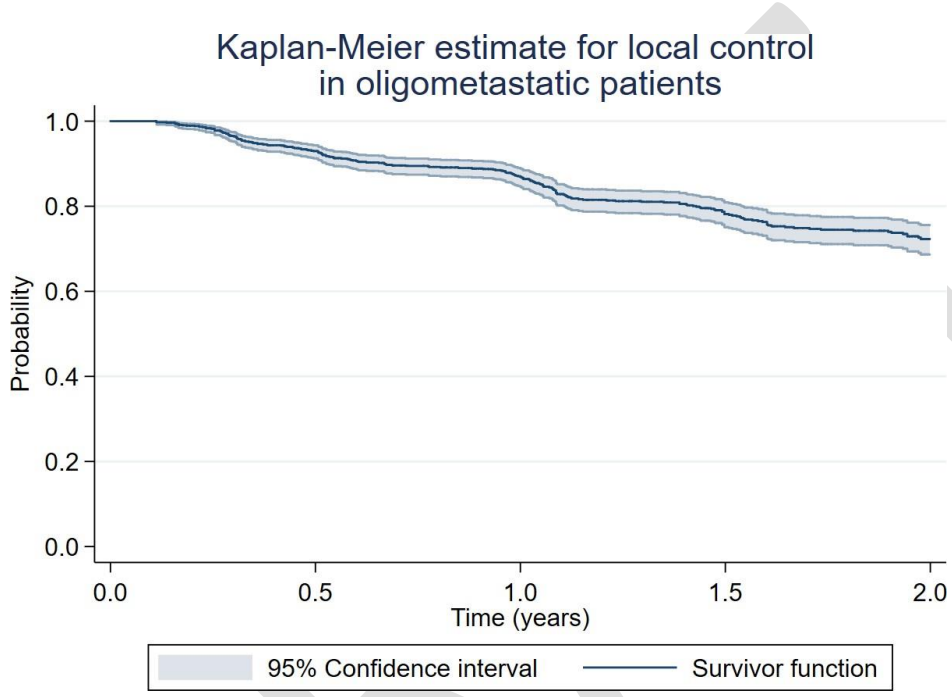

Figure 3: Kaplan-Meier estimate for local control

4.9.7 Adverse events

Total number of adverse events recorded across all patients is displayed in Table 10 and a summary of the percentages of patients with 1 or more adverse event reported is in Table 11.

Table 10: Frequency of Adverse Events

CTCAE grade	Total number of events recorded for all patients
Grade 1	3683
Grade 2	994
Grade 3	146
Grade 4	54
Grade 5*	0
All grades	**4877**

*Please see more information about the triangulation of grade 5 events in appendix E.

Table 11: Summary table for adverse events: percentage of patients with 1 or more adverse event reported

CTCAE grade	Number of patients with AE	Percentage of patients with AE	95% Confidence Interval
All grades (any AE)	959/1422	67.0%	65.0 to 70.0%
Grade 3	83/1422	5.8%	4.7 to 7.2%
Grade 4	26/1422	1.8%	1.2 to 2.7%

The following Table 12, provides a further break-down of all adverse events by CTCAE grade. Please note that empty grade fields reflect the CTCAE grading criterion, where there are not grading categories up to Grade 5.

Table 12: Total number of adverse events by CTCAE grade. The information provided is given as the total number of events experienced by all patients

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pericarditis	Grade 1 - Asymptomatic clinical or ECG findings	Grade 2 - Symptomatic pericarditis	Grade 3 - Pericarditis with physiological consequences	Grade 4 - Life-threatening consequences	Grade 5 - Death	
	29	10	2	1	0	**42**
Dysphagia	Grade 1 - Symptomatic, able to eat regular diet	Grade 2 - Symptomatic with altered eating/swallowing	Grade 3 - Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	84	45	3	0	0	**132**
GI haemorrhage	Grade 1 - Mild, intervention not indicated	Grade 2 - Moderate symptoms; medical intervention or minor cauterization indicated	Grade 3 - Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	14	0	3	0	0	**17**

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Gastritis	Grade 1 - Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Grade 2 - Symptomatic; altered GI function; medical intervention indicated	Grade 3 - Severely altered eating or gastric function; TPN or hospitalization indicated	Grade 4 - Life-threatening consequences; urgent operative intervention indicated	Grade 5 - Death	
	46	37	0	0	0	**83**
Upper GI ulcer	Grade 1 - Assymptomatic ulcer, intervention not indicated	Grade 2 - Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Grade 3 - Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Grade 4 - Life-threatening consequences; urgent operative intervention indicated	Grade 5 - Death	
	9	2	0	0	0	**11**
Nausea	Grade 1 - Loss of appetite without alteration in eating habits	Grade 2 - Oral intake decreased without significant weight loss, dehydration or malnutrition	Grade 3 - Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	*	*	
	173	49	3			**225**

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Vomiting	Grade 1 - 1 to 2 episodes (separated by 5 minutes) in 24 hrs	Grade 2 - 3 to 5 episodes (separated by 5 minutes) in 24 hrs	Grade 3 - >=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	17	2	2	0	0	**21**
Fatigue	Grade 1 - Relieved by rest	Grade 2 - Fatigue not relieved by rest; limiting instrumental ADL	Grade 3 - Fatigue not relieved by rest, limiting self care ADL	*	*	
	1541	374	37			**1952**
Spinal fracture	Grade 1 - Mild back pain; nonprescription analgesics indicated	Grade 2 - Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Grade 3 - Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Grade 4 - Life-threatening consequences; symptoms associated with neurovascular compromise	Grade 5 - Death	
	172	80	2	0	0	**254**
Myelitis	Grade 1 - Asymptomatic; mild signs (e.g., Babinskis	Grade 2 - Moderate weakness or sensory	Grade 3 - Severe weakness or sensory	Grade 4 - Life-threatening consequences;	Grade 5 - Death	

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	reflex or Lhermittes sign)	loss; limiting instrumental ADL	loss; limiting self care ADL	urgent intervention indicated		
	32	13	0	0	0	**45**
Cough	Grade 1 - Mild symptoms; nonprescription intervention indicated	Grade 2 - Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Grade 3 - Severe symptoms; limiting self care ADL	*	*	
	391	65	7			**463**
Pneumonitis	Grade 1 - Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Grade 2 - Symptomatic; medical intervention indicated; limiting instrumental ADL	Grade 3 - Severe symptoms; limiting self care ADL; oxygen indicated	Grade 4 - Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Grade 5 - Death	
	90	67	3	0	0	**160**
Duodenal/Gastric ulcer	Grade 1 - Assymptomatic ulcer, intervention not indicated	Grade 2 - Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Grade 3 - Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated;	Grade 4 - Life-threatening consequences; urgent operative	Grade 5 - Death	

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
			limiting self care ADL; disability	intervention indicated		
	6	1	1	0	0	**8**
Fever	Grade 1 - 38.0-39.0 degrees	Grade 2 - 39.1-40.0 degrees	Grade 3 - >40.0 degrees for <24 hours	Grade 4 - >40.0 degrees for >24 hours	Grade 5 - Death	
	10	2	1	0	0	**13**
Alanine aminotransferase	Grade 1 - >ULN- 3 x ULN	Grade 2 - 3 x ULN – 5*ULN	Grade 3 - >5.0 - 20.0 x ULN; >5 x ULN for >2 weeks	Grade 4 ->20 x ULN	*	
	10	2	30	30	0	**72**
Bilirubin	Grade 1 - >ULN- 1.5 x ULN	Grade 2 - >1.5 - 3.0 x ULN	Grade 3 - >3.0 - 10.0 x ULN	Grade 4 - >10.0 x ULN	*	
	7	3	36	22		**68**
Diarrhoea	Grade 1 - Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Grade 2 - Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Grade 3 - Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
			output compared to baseline; limiting self care ADL			
	115	38	2	0	0	**155**
Proctitis	Grade 1 - Rectal discomfort, intervention not indicated	Grade 2 - Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrument ADL	Grade 3 - Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	55	17	0	0	0	**72**
Rectal haemorrhage	Grade 1 - Mild; intervention not indicated	Grade 2 - Moderate symptoms; medical intervention or minor cauterization indicated	Grade 3 - Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	59	2	0	0	0	**61**
Haematuria	Grade 1 - Asymptomatic; clinical or diagnostic observations only;	Grade 2 - Symptomatic; urinary catheter or bladder irrigation	Grade 3 - Gross haematuria; transfusion, IV medications or hospitalization indicated; elective	Grade 4 - Life-threatening consequences; urgent radiologic or operative	Grade 5 - Death	

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	intervention not indicated	indicated; limiting instrumental ADL	endoscopic, radiologic or operative intervention indicated; limiting self care ADL	intervention indicated		
	40	9	1	0	0	**50**
Urinary frequency	Grade 1 - Present	Grade 2 - Limiting instrumental ADL; medical management indicated	*	*	*	
	355	14				**369**
Urinary incontinence	Grade 1 - Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Grade 2 - Spontaneous; pads indicated; limiting instrumental ADL	Grade 3 - Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	*	*	
	127	111	4			**242**
Urinary retention	Grade 1 - Urinary, suprapubic or intermittent catheter placement not indicated; able	Grade 2 - Placement of urinary, suprapubic or intermittent catheter	Grade 3 - Elective operative or radiologic intervention indicated; substantial loss of	Grade 4 - Life-threatening consequences; organ failure; urgent operative	Grade 5 - Death	

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	to void with some residual	placement indicated; medication indicated	affected kidney function or mass	intervention indicated		
	29	19	0	1	0	**49**
Urinary urgency	Grade 1 - Present	Grade 2 - Limiting instrumental ADL; medical management indicated	*	*	*	
	242	16				**258**
Bone pain	Grade 1 - Mild pain	Grade 2 - Moderate pain; limiting instrumental ADL	Grade 3 - Severe pain; limiting self care ADL	*	*	
	25	14	9			**48**
Fracture	Grade 1 - Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Grade 2 - Symptomatic but non-displaced; immobilization indicated	Grade 3 - Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	

Adverse Event Type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	5	2	0	0	0	**7**
Total of all Adverse Events	**3683**	**994**	**146**	**54**	**0**	**4877**

Note: Empty grade fields with * reflect the CTCAE grading criterion, where there are no grading categories up to Grade 5.

†The data dictionary was setup to map adverse events to the treated area. For example, a patient treated in the thorax would be mapped to upper GI toxicity reported as upper GI ulcer.

ADL = activities of daily living, ULN = upper limit of normal

4.9.8 Patient experience

The results of the patient experience question are in Table 13

Table 13: Patient Experience

	Number of patients (n=1422)		
Patient Experience - *How likely are you to recommend our SABR service to friends and family if they needed similar care or treatment?*			
	N	**Percent**	**95% CI**
Extremely likely	878	72%	69 to 74%
Likely	258	21%	19 to 23%
Neither likely or unlikely	26	2.1%	1.4 to 3.1%
Extremely unlikely	5	0.4%	0.1 to 0.9%
Don't know	60	4.9%	3.8 to 6.2%
Total	**1227**		
Missing*	195	13.7%	
*Missing % is based on overall number of patients in the specific category			

5 Cost-effectiveness analysis

5.1 Aim and objectives

The objective of the economic evaluation in this study was to determine whether SABR is a cost-effective intervention compared with RFA and surgery for patients with borderline resectable liver oligometastases[14].

5.2 Methods

5.2.1 Population & intervention

The base case for the analysis consisted of a hypothetical cohort of adult patients with borderline resectable liver oligometastases who may be candidates for surgery. When entering the model, this patient group will receive an initial treatment of surgery, RFA or SABR. Patients who experience local recurrence[15] after initial treatment may receive retreatment with the same treatment as initially given based on published retreatment rates. Patients who experience distant/regional[16] progression will receive palliative care.

5.2.2 Model structure

In order to compare the total cost and effectiveness of different treatment strategies, a decision analytic model was developed using TreeAge 2014 (TreeAge Software, Williamstown, MA). A Markov process was embedded in the model to model patients' possible prognoses after treatments, which are expressed in several mutually exclusive health states. In this model, nine mutually exclusive health states were included (Figure 1). Which health state the patient would be in depends on the patient's cancer progression status of oligometastases (no progression, local progression, or regional/ distant progression), the number of treatments that the patient received (initial treatment or retreatment), and whether or not the patient experienced severe adverse events (SAEs) of treatment, including abscess, would infection, transient respiratory failure and ileus (intestinal blockage). The definition of severe adverse events was adopted by Kim et al. (2011). The authors cite

[14] During the initial consultation for the CtE evaluation questions it was decided that only liver oligometastases would be analysed for cost-effectiveness.

[15] Local progression or local recurrence is defined as disease progression within the previously treated area. Local progression is reflecting changes associated with the local control outcome of the CtE scheme.

[16] Distant or regional progression is defined as disease progression outside the treated area, either in close proximity anatomically (regional progression) or remote to the previous treated area (distant progression).

references that used the CTCAE criteria to define severe toxicity. The cycle length is assumed to be one month; which means that every month, patients will either move from one health state to another, or stay within the current health state, corresponding to their change in health status. This model adopted a 5-year horizon.

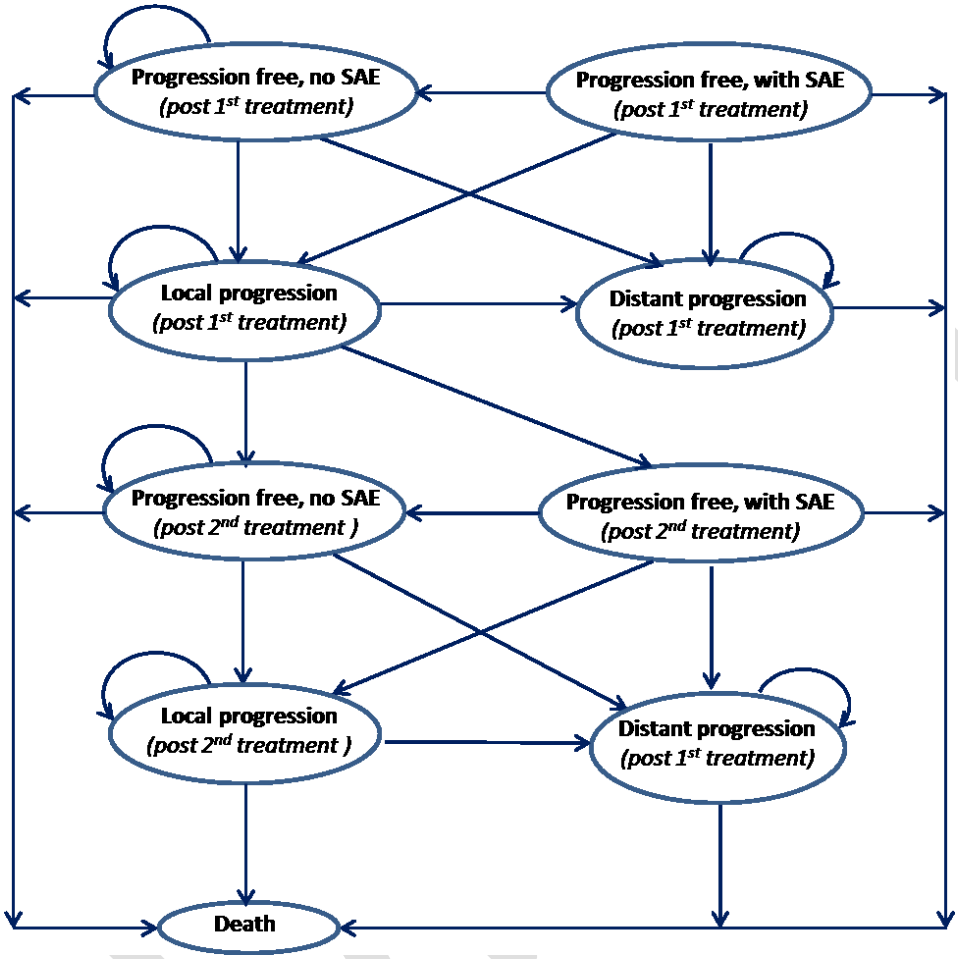

Figure 4: Markov model structure

5.2.3 Cost-effectiveness analysis

Each of the health states in Figure 4 is assigned a cost and outcome that patients accrue while in that state. The costs reflect the treatment that the patient is currently receiving (e.g. surgery, RFA or SABR) and the cost of any other resource use that may be required (e.g. treatment cost for SAEs). The effectiveness is expressed in terms of quality-adjusted life years (QALYs), which is a product of the quantity and quality of life. For each treatment, the overall costs and effectiveness are calculated on the basis of the total length of time patients spend in each health state over the time horizon. According to the National Institute for Health and Care Excellence (NICE) guideline manual (National

Institute for Health and Care Excellence 2017), costs and benefits incurred today are usually valued more highly than costs and benefits occurring in the future. Therefore, both costs and QALYs were discounted at an annual rate of 3.5%.

5.2.4 Input data

The clinical data used in the model were mainly obtained from published literature and the SABR CtE scheme. An initial search and scoping review of the literature was undertaken to assess the quality and availability of evidence on costs, survival and quality of life of patients receiving either surgery or RFA (where appropriate) for liver oligometastases. The following databases were searched: Ovid MEDLINE, Medline ahead of print and in-process, and Embase. The search terms are included in Appendix B. In addition, citations of key references were checked. After de-duplication, the initial database search retrieved 255 studies for liver oligometastases. After initial screening and exclusion of non-relevant studies there were 88 relevant studies for liver oligometastases. The search was updated on 23rd April 2019.The section below describes the key input data used in the model, including clinical data (section 5.2.4.1), cost and resource use data (section 5.2.4.2), and health-adjusted quality of life (HRQoL) data (section 5.2.4.3). A summary of all parameters used in the model, including their fixed values, ranges, distributions and sources, is reported in Appendix E.

5.2.4.1 Clinical data

This section describes the key clinical data used in the model, including cancer progression, mortality, probability of re-treatment, and probability of SAEs. In the base case analysis, SABR was assumed to confer no advantage for cancer progression or survival, in order to minimise the potential for bias arising from differences in patient populations across studies. This assumption was tested in structural sensitivity analysis, using data obtained from the CtE program and the best available literature. It should be noted that all probability data reported below are probability per cycle (per month), unless otherwise specified.

5.2.4.2 Cancer progression data

This section describes cancer progression data for patients after treatment, including initial treatment and retreatment. It was assumed that patients would be retreated a maximum of once if local progression occurred after treatment. In the base case analysis, it was assumed that all three interventions of interest (surgery, RFA and SABR) are equally effective in slowing cancer progression; in other words, the progression rates are the same for all patients, regardless of which intervention

they received. The progression data for patients after initial treatment, and after retreatment are presented in Table 14, and briefly described below.

Table 14: Cancer progression rates for treated patients and recurrent patients without retreatment

	Monthly transition rate
No progression to local progression	2.10% [a]
No progression to regional/distant progression	0.93% [a]
Local progression to regional/distant progression	3.58% [a]
a: Estimated from data in de Haas et al. (2010)	

Cancer progression data – published data for patients receiving initial treatment or retreatment

Since a recent systematic review (Wurster et al. 2017) found no difference in morbidity or mortality between patients who received repeated or single surgery, it was assumed that cancer progression rates are the same for patients receiving initial treatment or retreatment. In order to populate the model, the following transition probabilities between patients with different progression status are required: from no progression to local progression, from no progression to regional/distant progression, and from local progression to regional/distant progression. It was assumed that all three interventions of interest (surgery, RFA and SABR) are equally effective in slowing cancer progression; in other words, the progression rates are the same for all patients, regardless of which intervention they received. A few systematic reviews have published (Abbas et al. 2011, Kanas et al. 2012, Han et al. 2016) the long-term outcomes for patients with colorectal liver metastases; however none of them reported the transition probabilities of interest. Therefore, individual clinical trials were examined to locate the relevant transition probabilities. Of the 54 studies included in the review by Kanas, 27 studies had a sample size of over 100. The full-texts of these 27 studies were checked in detail. Although none of the 27 studies directly reported the transition rates of interest, two studies [de Haas et al. (2010) and Pawlik et al. (2005)] reported detailed recurrence outcomes after surgery which can be used to calibrate the transition rates of interest. The recurrence outcomes reported by de Haas et al. and Pawlik et al. are the proportion of patients who developed:

intrahepatic metastasis only, extrahepatic metastasis only, and both intrahepatic and extrahepatic metastasis. Based on the assumptions that intrahepatic recurrence is a proxy of local progression, extrahepatic metastases is a proxy of regional/distant progression, and for those who had both intrahepatic and extrahepatic metastasis, all of them developed intrahepatic metastasis before extrahepatic metastasis, the transition rates of interest can be estimated using data reported by de Haas et al. or Pawlik et al. The characteristics of both studies are presented in Table 15. de Haas et al.'s study was used in the base case analysis, because it has a longer follow-up period and larger sample size. Data from de Haas indicates a higher rate of progression than data from Pawlik. The monthly progression rates were estimated in a calibration exercise to match the data reported by de Haas et al., and are reported in Table 14.

Cancer progression data – recurrent patients who didn't receive retreatment

No published studies reported the progression rate for recurrent patients who didn't receive retreatment. Therefore, the progression rate for this patient group was calibrated based on mortality data for untreated patients with different cancer progression status, which is reported in Table 15.

Cancer progression data – data obtained from the CtE oligometastases scheme

Of the 135 patents in the CtE data with liver oligometastases, 34 patients were missing quality of life data at baseline and were excluded. For the remaining 101 patients, 25 developed local recurrence, and 36 developed regional/distant recurrence. Survival analysis indicates that the Weibull distribution gives the closest fit to the event rate for the transition from no progression to local recurrence, while the exponential distribution gives the closest fit to the event rate for the transition from no progression to regional/distant recurrence (monthly transition rate=3.99%). Due to the small sample size and short observation period, the data obtained from the CtE scheme was not used in the base case analysis and was only tested in the structural sensitivity analysis (Section 6.4.1).

Table 15: Characteristics of de Haas et al. (2010) and Pawlik et al. (2005)

Ref	Country	Follow-up year	Follow-up duration	Sample size	Recurrence outcomes (Percentage of patients)			
					No progression	Intrahepatic metastases only	Extrahepatic metastases only	Both intra and extrahepatic metastases
de Haas et al. (2010)	France	1990-2006	5 years	806	30.2%	22.8%	21.5%	25.6%
Pawlik et al. (2005)	US, Italy and Switzerland	1990-2004	2.4 years	557	59.7%	13.8%	14.7%	11.8%

5.2.4.3 Mortality data

This section describes mortality data for patients after treatment (including initial treatment and retreatment), and recurrent patients without retreatment. The mortality data for both patient groups are presented in Table 16, and briefly described below.

Table 16: Monthly mortality rate for patients with different progression status

	Monthly mortality rate
Patients with no progression	0.13% [a]
Patients with local progression	1.55% [b]
Patients with regional/distant progression	3.06% [c]

a: Calibrated from de Haas et al. (2010)

b: Calibrated from de Haas et al. (de Haas et al. 2010) and mortality rate for patients with no progression and regional/distant progression, as reported in Table 23.

c: Rees et al. (R2008)

Mortality data – Data obtained from published literature

Since a recent systematic review (Wurster et al. 2017) found no difference in mortality between patients receiving repeated or single surgery, it was assumed that mortality rates are the same for patients receiving either initial treatment or retreatment. In the base case scenario, it was assumed that mortality depends only on which progression status patients are at (no progression, local progression, or regional/distant progression), and does not directly depend on which intervention they received. The mortality rate for patients with no progression was calculated based on the calibrated cancer progression rates (Section 7.2.4.1) and progression-free survival reported by de Haas et al. (de Haas et al. 2010). de Haas didn't report mortality data for patients with regional/distant progression, therefore the mortality data for this patient group was obtained from Rees et al. (Rees et al. 2008). Rees et al. was chosen from all trials included in the systematic review conducted by Kanas et al. (Kanas et al. 2012), as this was the only UK study with a sample size over 100 which report separate mortality for patients with extrahepatic metastasis and intrahepatic

metastases. Mortality data for patients with local progression was estimated by calibration using the total mortality rate reported by de Haas, and mortality rates for patients with no progression or regional/distant progression (Rees 2008).

In the sensitivity analysis, it was assumed that patients who received different interventions have different mortality rates. The relative risk (RR) of RFA versus surgery was obtained from a recent systematic review and meta-analysis (Han et al. 2016) which compared the efficacy and safety of RFA with surgery for colorectal cancer liver metastasis. The meta-analysis indicated that patients treated in the RFA group had lower five-year overall survival (mortality relative risk: 1.361, 95% CI: 1.163-1.593) than patients treated by surgery. The 2-year mortality rates for patients who received SABR were obtained from the CtE scheme, while the 2-year onwards mortality rate for SABR was assumed the same as for RFA.

Mortality data – data obtained from the CtE oligometastases scheme

Of the 101 patients with liver oligometastases and baseline quality of life data included in the CtE cohort, 8 died during the study period and prior to progression of their disease. The exponential distribution appears to give the closest fit to mortality data (monthly mortality rate=0.90%). Due to the small sample size and short observation period, the mortality data obtained from the CtE scheme was not used in the base case analysis and was only tested in the structural sensitivity analysis (Table 20).

5.2.4.4 Probability of retreatment

This section describes the probabilities of receiving retreatment with the same treatment modality for patients who develop local progression after initial treatment. The probability of retreatment with surgery was reported to be 30.74% in a recent UK trial (Neal et al. 2017), with a range of 30.74 to 54.00% (Lee et al. 2015, Neal et al. 2017, Imai et al. 2018) tested in sensitivity analysis. The probability of retreatment with RFA has been reported by several studies (Wood et al. 2000, Aloia et al. 2006, van Duijnhoven et al. 2006, Berber and Siperstein 2008, Sgouros et al. 2011, Shady et al. 2016): 34.78% was used as the baseline value while a range of 18.18-66.67% was tested in sensitivity analysis. The probability of retreatment with SABR was assumed to be the same as for RFA in the base case analysis, with a range of 66.67-80.00% (Hoyer et al. 2006) tested in sensitivity analysis.

5.2.4.5 Severe adverse events (SAEs)

The probability of developing SAEs for patients who received different treatment is reported in Table 17. The probability of developing SAEs for patients who received surgery and RFA was calculated from data in Kim et al (Kim et al. 2011). The probability of developing SAEs for patients who received SABR was obtained from the CtE scheme (3/101, 2.97%). Three patients experienced a grade 3 or 4 toxicity within four months of treatment which was not present prior to treatment and after excluding changes in Bilirubin or ALT enzyme function. The latter toxicities were excluded as they were deemed less likely to impact on patient quality of life.

Table 17: Probability of developing SAEs for patients received different treatment

Treatment	Probability of SAEs	Source
Surgery	16.55%	Kim et al. (2011)
RFA	5.08%	Kim et al. (2011)
SABR	2.97%	CtE scheme

5.2.5 Cost and resource data

This model takes the perspective of the NHS and Personal Social Services (PSS), as recommended by NICE (October 2014). The financial year is 2016. The cost components considered in the model include: initial treatment (SABR, RFA or surgery), treatment for SAEs, outpatient follow-up, retreatment, and palliative chemotherapy for patients with regional/distant progression. The unit cost and resource use of each cost component is reported in Table 18. The total costs for patients who received different interventions were estimated by multiplying the unit costs with resources quantities. Unit costs were obtained from the NHS reference costs 2015-16 (Department of Health 2016) or the Unit Costs of Health and Social Care 2016 (Curtis 2016). Where appropriate, costs were uplifted to current values using Hospital Inflation Indices (Curtis 2016). The resource use for patients who received RFA or surgery were mainly obtained from published literature. The package price for SABR is £3,432 for 3 fractions and £4,856 for 5 fractions (NHS England 2015). Data from the CtE scheme showed that of 101 patients with liver oligometastases, 30 patients had 3 fractions and 71 patients had five fractions. Therefore, the weighted cost was calculated as £4,433 per patient.

Table 18: Unit cost and resource use data

Item	Unit cost	Resource use	Total cost
Surgery			
Surgical procedure	£6,272.87 [a]	1	£6,272.87
Additional bed days	£297.00 [b]	2.24 [c]	£665.28
		Total	£6,938.15
RFA			
RFA procedure	£3,714.06 [d]	1	£3,714.06
Additional bed-days	297.00 [b]	4.2 d [e]	£1,247.40
		Total	**£4,961.46**
SABR			
SABR	£4,433.00 [f]	1	£3,432.00
		Total	**£3,432.00**
Outpatient follow-up			
Outpatient attendance	£199.00 [g]	Every 3 months prior to disease progression	£199.00
Full blood count	£0.55 [h]	As above	£0.55
Liver function tests	£0.42 [h]	As above	£0.42
Carcinoembryonic antigen	£1.91 [h]	As above	£1.91
Abdominal CT	£94.96 [i]	As above	£94.96
		Total	**£296.84**
SAEs			
Treatment for SAEs	£557.49	N/A	557.49
Retreatment			
Retreatment	Assume to be the same as initial treatment		
Palliative care			
Palliative care for patients with regional/distant progression	£775.44 per month [k]	N/A	£775.44 per month

a. NHS Reference Costs 2015–16 (Department of Health 2016), HRG code GA05D: 'Very Major Open, Hepatobiliary or Pancreatic Procedures, with CC Score 0-2', including 4.16 elective inpatient bed days, 7 non-elective long stay bed days and outpatient procedure. The cost for HRG code GA05C 'Very Major Open, Hepatobiliary, or Pancreatic Procedures, with CC Score 3+' (£9,337.35) was tested in the sensitivity analysis.

b. Additional days are costed at inpatient excess bed-day cost of £297 per day, based on NHS Reference Costs 2015–16 (Department of Health 2016).

c. Average length of stay for patients who had a surgical resection in the study reported by Kim et al (2011) was 13.4 days. Therefore, the number of additional hospital bed days was calculated as: 13.4-4.16 (number of elective inpatient bed days) -7 (number of non-elective long stay bed days) =2.24.

d. Uplifted from Loveman et al. 2014 (2014).

e. Average length of stay for RFA in study by Kim et al. (2011) was 4.2 days.

f. The package price for SABR is £3,432 for 3 fractions and £4,856 for 5 fractions (NHS England 2015). The data from the CtE scheme showed that of the 101 patients with liver oligometastases, 30 patients had 3 fractions and 71 patients had five fractions. Therefore, the weighted cost was calculated as £4,433 per patient.

g. NHS Reference Costs 2015-16 (Department of Health 2016), currency code WF01B, service code 105: 'Hepatobiliary & Pancreatic Surgery Consultant-led: follow-up attendance non-admitted face to face'.

h. Uplifted from Loveman et al. (2014).

i. NHS Reference Costs 2015–16 (Department of Health 2016), HRG code RD20A: 'Computerised Tomography Scan of one area, without contrast, 19 years and over'.

j. Uplifted from Loveman et al. (2014).

k. Uplifted from Tappenden et al. (2007).

5.2.6 Health-related quality of life (HRQoL)

HRQoL describes that part of a person's overall quality of life that is determined primarily by their health status and which can be influenced by clinical interventions. Quantitative estimates of HRQoL known as utility weights are usually elicited on a scale on which 0 represents death and 1 represents full health. This model requires utility weights for four health states: progression free without SAEs, progression free with SAEs, local progression, and regional/distant progression. Utility weights currently applied in the model are reported in Table 19.

The baseline utility weight for the health state 'progression free, no SAEs' was obtained from the CtE scheme (0.86), while a range of values reported by published literature (0.65 to 0.90) were tested in sensitivity analysis (Krabbe et al. 2004, Mendez Romero et al. 2008, Wiering et al. 2011). The utility weights for the other three health states were derived from studies included in a systematic review of utility for patients with colorectal liver metastases (Loveman et al. 2014). The original intention to quantify the impact of adverse events on quality of life using the CtE data was not undertaken. This analysis had been specified conditional on the data being of sufficient quality. The analysis was judged inappropriate for the following reasons: there were concerns regarding the accuracy of the capture of the date of adverse events and whether this was sufficiently close to the date at which

quality of life was measured; it was unclear how data measured using the EQ-5D-5L had been entered into the database by centres; and the number of patients suffering a severe adverse event was low.

Table 19: Health states and their utility weight used in the model

Health state in model	Utility weight	Range	Source
Progression free without SAEs	0.86	0.65-0.90	Base case utility was obtained from the CtE scheme. Range of utility tested in sensitivity analysis was obtained from Wiering et al. (Wiering et al. 2010), Krabbe et al. (Krabbe et al. 2004), Romero et al. (Mendez Romero et al. 2008)
Progression free with SAEs	0.40	0.26-0.56	Romero et al. (Mendez Romero et al. 2008), Wiering et al. (Wiering et al. 2011) and Roberts et al. (Roberts et al. 2015)
Local progression	0.65	0.6-0.7	As above
Regional/ distant progression	0.19	0.15-0.4	As above

5.3 Sensitivity analysis

Three types of sensitivity analyses were conducted: structural sensitivity analysis, one-way sensitivity analysis of parameter uncertainty and probabilistic sensitivity analysis (PSA). Structural sensitivity analysis was undertaken to explore the impact of assumptions on cancer progression rates and mortality. The base case analysis assumes same cancer progression rate and same mortality rate for all three interventions. Three structural sensitivity analyses were undertaken to test the impact of using different cancer progression rates and different mortality rates for patients receiving alternative treatments:

(1) Assuming different cancer progression rate for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 13). The cancer progression rate for patients who receiving SABR was obtained from the CtE scheme: no progression to local recurrence (Weibull distribution, η=1.000, β=1.4928), no progression to regional/distant recurrence (exponential distribution

monthly transition rate=3.99%). The cancer progression rate for patients receiving RFA was assumed the same as SABR due to lack of data.

(2) Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) (de Haas et al. 2010). The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361 (Han et al. 2016). The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE programme (exponential distribution, monthly mortality rate=0.90%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who receiving RFA.

(3) Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) (de Haas et al. 2010). The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361. The mortality rate for patients receiving SABR was assumed the same as patients receiving RFA.

One-way sensitivity analysis was undertaken to explore the sensitivity of the results to variation in each of the parameters in the analysis considered singly. PSA was undertaken to capture the impact of joint uncertainty of multiple parameters simultaneously. PSA assigns to each input parameter a specified distribution and, by drawing randomly from those distributions, generates a large number of mean cost and effectiveness estimates that can be used to form an empirical joint distribution of the differences in cost and effectiveness between interventions. In this study, the main results of PSA were re-calculated 5000 times. The ranges and distributions tested in sensitivity analysis are reported in Appendix E.

5.4 Results

5.4.1 Base case and structural sensitivity results

The base case and structural sensitivity analysis results are presented in Table 20. In the base case analysis, it was assumed that:

(1) The cancer progression rates are the same for all patients, regardless of which intervention they received;

(2) Patient's mortality only depends on which progression status they are at (no progression, local progression, or regional/distant progression), and does not directly depend on which intervention they received.

Therefore, the only difference between different interventions are:

(1) Probability of developing SAEs;

(2) Probability of receiving re-treatment for those patients who developed local recurrence after the initial treatment.

The results of the base case analysis show that SABR dominates both surgery and RFA. This is likely to be because, of the three interventions tested, SABR is associated with lowest probability of SAEs, and the highest probability of receiving re-treatment. In structural sensitivity analyses, when it was assumed that different interventions are associated with different cancer progression rates and/or different mortality rates, SABR remained the most cost-effective intervention except under the scenario where it was assumed that different interventions are associated with different cancer progression rates (SA1 in Table 20). In this scenario surgery becomes the most cost-effective intervention.

Table 20: Base case and structural sensitivity analyses

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=£20,000 per QALY)	Ranking of NMB (WTP=£30,000 per QALY)
Base case results							
SABR	**16,863**	**2.5601**	–	–	**Dominating**	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
SA 1: Different cancer progression rates for patients receiving different interventions [1] *(base case assumes same rate for all three interventions)*							
SABR	21,746	1.5817	–	–	Dominated	2	2
RFA	22,399	1.5812	–	–	Dominated	3	3
Surgery	**19,775**	**2.5387**	–	–	**Dominating**	1	1
SA 2: Different morality rate for patients receiving different interventions. [2] *(base case assumes the same mortality rate for all three interventions)*							
SABR	**18,314**	**2.2408**	172	0.1017	1,692	1	1
RFA	18,142	2.1391	–	–	–	2	2
Surgery	21,898	2.2848	3,583	0.0440	81,479	3	3
SA 3: Different mortality rate for patients who received different interventions. [3] ***Mortality for SABR was assumed the same as RFA.***							
SABR	17,528	2.1396	–	–	–	1	1
RFA	18,142	2.1391	–	–	Dominated	2	3
Surgery	21,898	2.2848	4,370	0.1451	30,111	3	2

Abbreviations:
ICER: Incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY: quality-adjusted life of years; SA: sensitivity analysis; WTP: willingness to pay threshold.

Notes:
1. Assuming different cancer progression rate for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 20). The cancer progression rate for patients who receiving SABR was obtained from the CtE scheme: no progression to local recurrence (Weibull distribution, η=1.000, β=1.4928), no progression to regional/distant recurrence (exponential distribution monthly transition rate=3.99%). The cancer progression rate for patients receiving RFA was assumed the same as SABR due to lack of data.
2. Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) (de Haas et al. 2010). The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361 (Han et al. 2016). The mortality rates up to 2 years for patients

receiving SABR was obtained from the CtE programme (exponential distribution, monthly mortality rate=0.90%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who receiving RFA.

3. Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) (de Haas et al. 2010). The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361. The mortality rate for patients receiving SABR was assumed the same as patients receiving RFA.

5.4.2 One-way sensitivity analysis results

Forty scenarios were tested using one-way sensitivity analysis (Appendix E). The results show that under the NICE £20,000 per QALY willingness-to-pay threshold, the base case conclusion (SABR being the most cost-effective intervention) is robust to all scenarios tested except variation in the cost of SABR and RFA. A further goal-seeking analysis for these two cost parameters showed that in the following scenarios, RFA became the most cost-effective intervention under the £20,000 per QALY willingness-to-pay threshold:

1) when the cost of SABR is over £4,978 (base case value: £4,433);
2) when the cost of RFA (including inpatient stay) is below £4,417 (base case value: £4,961).

5.4.3 PSA results

The PSA results are shown in Figure 15. Assuming a willingness-to-pay threshold of £20,000 per QALY, the probability that SABR is most cost-effective is 56.84%. Assuming a willingness-to-pay threshold of £30,000 per QALY, the probability that SABR is most cost-effective is 56.86%.

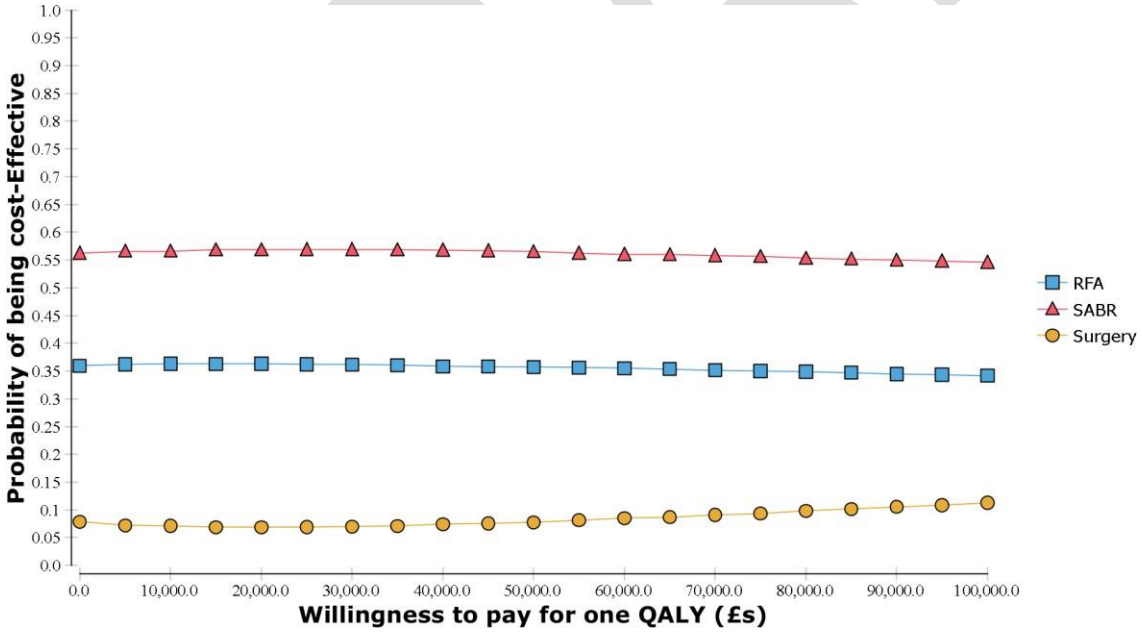

Figure 5: Cost-Effectiveness Acceptability Curve

5.5 Discussion

This section compares our findings with published economic studies and discusses the strengths and limitations of our analysis. The conclusion is presented in section 7.7.

5.5.1 Comparison with published studies

The literature search identified a number of economic analyses which compared alternative treatments for liver oligometastases. However, of those identified studies:

- The majority of them covered only one of the three interventions of interest (surgery, RFA and SABR) and therefore the conclusions cannot be compared with our study;
- Two studies covered two interventions of interest: RFA vs surgery (Loveman et al. 2014), and RFA vs SABR (Kim et al. 2016);
- None of them assessed all three interventions of interest.

Of the two published studies which assessed two interventions of interest, the first study is an health technology assessment (HTA) which compared surgery with RFA for patients with surgically resectable oligometastases in the UK (Loveman et al. 2014). This study conducted separate analyses for patients with different sizes of oligometastases:

- For patients with solitary metastases < 3 cm, the five-year survival rate was very similar for surgery and RFA. The cost-effectiveness analysis showed that compared with RFA, surgery results in higher cost and similar QALYs. Therefore, surgery was dominated by RFA.
- For patients with solitary metastases ≥ 3 cm, surgery was associated with better five-year survival compared with RFA (48% vs 34%). The cost-effectiveness analysis showed that compared to RFA, surgery results in higher cost and higher QALYs. The ICER of surgery was estimated to be £2,538 per QALY gained, which indicates that surgery is considered to be cost-effective under the NICE willingness-to-pay threshold (£20,000 to £30,000 per QALY gained).

The results of the HTA indicate that surgery is only more cost-effective than RFA if it is associated with a higher survival rate. This is consistent with our findings:

- In the base case analysis, when it was assumed that the cancer progression rate and mortality rate is the same for all patients regardless of which interventions they received, RFA dominates surgery;

- In the structural sensitivity analysis, when it was assumed that surgery was associated with better survival outcome (SA2 and SA3 of Table 20), surgery results in higher QALYs and higher cost compared with RFA.

Another published study compared SABR with RFA for patients with unresectable liver oligometastases in the US (Kim et al. 2016). This study found that compared with RFA, SABR resulted in $8,202 higher costs and 0.05 more QALYs, which is different from our findings (SABR resulted in lower costs and higher QALYs). This might be due to the use of different unit costs. In the study conducted by Kim et al, the cost of providing one course of SABR was estimated to be $13,000 (3-fraction), which is almost three times the cost of providing RFA ($4,397, including intervention cost and one day of hospitalisation). In our analysis, the cost of one course of SABR was estimated to be £4,433 (weighted by the number of fractions that patients received), which is less than the cost of providing RFA (£4,961, including intervention cost and 4.2 days of hospitalisation). In the sensitivity analysis, when the cost of SABR was increased to £4,961 or above, SABR results in higher cost and higher QALYs compared to RFA.

5.6 Strengths and limitations of the analysis

5.6.1 Strengths

There are three strengths of our study:

(1) To our knowledge, this is the first economic analysis which compares all three interventions for people with liver oligometastases: surgery, RFA and SABR.

(2) The clinical data for surgery and RFA were carefully selected from the best evidence sources identified from the literature review, while the clinical data for SABR were mainly obtained from the CtE scheme, with the published SABR data tested in sensitivity analysis. The unit cost and resource use data were obtained from published cost calculations based on reliable UK databases, such as NHS Reference Costs (Department of Health 2016) and PSSRU (Curtis 2016). The utility data were obtained from published studies which reported different utility for patients at different cancer progression status and with/without adverse events, with a wide range of possible values tested in sensitivity analysis.

(3) Extensive sensitivity analyses have been conducted to test the robustness of the base case conclusion under different assumptions and different sets of input data, including structural sensitivity analysis, one-way sensitivity analysis, and PSA.

5.6.2 Limitations

There are a number of limitations of the economic analyses presented here, the majority of which derive from limitations in the evidence base:

(1) Lack of clinical studies which directly compare SABR with RFA and surgery. Therefore, we had to use naive indirect comparisons to capture the relative effects between interventions. Differences in patient characteristics across studies can lead to significant bias and confounding. Data on surgical treatments may well reflect outcomes from a patient population with better prognosis than the patients included in the CtE scheme.

(2) Lack of clinical evidence about cancer progression rates for patients receiving alternative treatments. As a result, the progression rates used in the base case analysis were calibrated based on published data.

(3) Lack of clinical evidence about the mortality rate for patients at different cancer progression status. As a result, the mortality rates used in the base case analysis were calibrated based on published data.

However, in this study, the limitation related to parameter uncertainty has been partially mitigated by extensive sensitivity analyses.

5.7 Conclusion

This analysis found that for adult patients with borderline resectable liver oligometastases who may be candidates for surgery, SABR results in more QALY gains and lower cost compared to surgery. This finding assumes that SABR and surgery lead to similar overall survival and local control over the duration of the analysis. There is some evidence to support this. Data from the CtE cohort indicates lower overall survival and local control rates with SABR when compared to published data on resection, and application of this data leads to the inference that resection is the most cost-effective intervention. However, such inference must be treated with caution. Most of the SABR cohort would not have been considered candidates for surgery and hence comparison of survival with patients undergoing resection is potentially compromised. We sought the best available evidence on survival and local control after surgery for liver oligometastases, however these data probably reflect outcomes in a patient group with better prognosis than the CtE cohort. Our analysis indicates a potential for SABR to be cost-effective. This will depend on SABR achieving similar local control and overall survival rates to surgery or RFA. A randomised trial may be required to demonstrate such equivalence.

6 Evidence from the literature

6.1 Methods

6.1.1 Scope

The aim of the systematic review was to identify published evidence for the efficacy, toxicity, and cost-effectiveness of SABR in patients with extracranial oligometastatic cancer.

6.1.2 Search methods

A systematic search was undertaken based on the PICO document, which was formulated in collaboration with NHS England representatives, clinicians involved in the SABR CtE project, and KiTEC. The databases searched included Medline, Medline In-Process, Embase, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Controlled Register of Trials (CENTRAL). The search excluded conference abstracts and was restricted to articles from 2009 to the present (the searches were carried out on 8th March 2019). The full details of the search strategy are included in Appendix B. The searches retrieved 4791 records. Following de-duplication in EndNote X7, 3729 records were assessed for relevance according to the criteria outlined in Table 21.

Table 21: PICO table

Population and Indication	Patients who have extracranial oligometastatic cancer of any tumour type (metachronous disease†) with fewer than 5* metastases. Patients may have had or be having standard care, which differs depending on primary tumour site: systemic treatments (chemotherapy, hormone treatment or molecular targeted treatments) may be given alone or with local treatment of metastases.
Intervention	Stereotactic ablative body radiotherapy (8 fractions or fewer) to oligometastases (dose and fractionation dependent on site of metastasis and proximity to organs at risk).
Comparators	No treatment Palliative care alone Local treatment to oligometastases with conventionally fractionated radiotherapy, surgical excision, radio-

	frequency or microwave ablation and/or locally delivered chemotherapy either in combination or as single therapies.
Outcomes	<u>Critical to decision-making:</u> • Median overall survival • 1 year survival • 2 year survival • Local control at 1 year and 2 years (i.e. tumour regression/resolution OR no tumour progression within treatment field) • Progression free survival • Acute and late radiotherapy toxicity (including, but not limited to, fatigue, nausea, diarrhoea and bone fracture) • Quality of life • Adverse events <u>Important to decision-making:</u> • Cost effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials

Study design	Case reports, resource utilisation studies Studies with <30 patients
* Studies with a small % of patients with 5 lesions (<5%) were considered eligible for inclusion. † Metachronous disease was defined as the diagnosis of metastases more than 6 months after the diagnosis of primary cancer. In cases where this was not adequately reported the corresponding authors were contacted for further information. Patients eligible for the review who also had intracranial metastases were included.	

6.1.3 Data extraction and management

Two reviewers independently screened titles and abstracts of the citations identified by the search strategies. Full-text copies of all potentially relevant publications were obtained and independently assessed by each reviewer to determine whether they met the inclusion/exclusion criteria. Any disagreements were resolved by consensus. The data extracted included information on study design, population characteristics, comparators used, and outcome measures. Microsoft Excel software was used for data collection and management.

6.2 Results

6.2.1 Studies identification and selection

The 3729 abstracts identified after deduplication, were first assessed by title and abstract alone. Following the first sift, 166 records were identified as relevant, and the full texts of these articles were retrieved and reviewed. Following a second sift of the full-text articles, 17 fit the inclusion criteria and are included in this review. The sifting process was undertaken by two members of the KiTEC team and the results cross-matched for quality control. The PRISMA flowchart for study identification and selection is listed in (Appendix A: Prisma flowchart). Table 22, Table 23 and Table 24 list the methodological characteristics of all included studies.

6.2.2 Evidence summary tables

Table 22: Comparative studies

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Palma et al. 2019 NCT01446744 RCT Multicentre International (Canada, Netherlands, UK, Australia) Recruitment period 2012-2016 99 patients with oligometastases from various primary cancers (21% prostate*, 20% breast*, 14% colorectal*) 21% of the patients had prostate cancer in the SABR vs. 6% in the control group). 14% of the patients had colorectal cancer in the SABR vs. 27% in the control group. 95% of the patients had ≤4 metastases Median time to metastases: 2.4 years	Patients were randomised (2:1) to SABR (n=66) or standard care (n=33) The groups were well matched with the exception of a higher % of prostate cancer (21% for SABR vs 6% for the control group) and a lower % of colorectal cancer in the SABR group (14% for SABR vs. 27% for the control group). Total dose: SABR = 30-60Gy in 3-8 fractions, single fractions of 16-24Gy were permitted for brain or vertebrae metastases Palliative RT = 8-30Gy in 1-10 fractions Median 24 months follow-up.	ITT -Median OS = 28 months (95% CI 19-33) standard care vs. 41 months (95% CI 26-not reached) SABR, (HR 0.57, 95% CI 0.3-1.1, p=0.09) -1-year = 86% in both groups -2-year = 60% standard care vs. 70% SABR PFS: -Median = 6 months (95% CI 3.4-7.1) standard care vs. 12 months (95% CI 6.9-30.4) SABR, (HR 0.47, 95% CI 0.3-0.76, p=0.0012) -1 year = 22% standard care vs. 53% SABR -2 year = 15% standard care vs 40% SABR LC: 49% standard care vs 75% SABR, absolute increase 26% (95% CI 10-41)	**Appraisal:** Randomised. Due to the nature of the intervention, blinding was not possible. The study population and intervention are well matched to the CtE scope, with comparable % of prostate and colorectal cancer primary diagnoses. The groups were well matched with the exception of a higher % of prostate cancer (21% for SABR vs 6% for the control group) and a lower % of colorectal cancer in the SABR group (14% for SABR vs. 27% for the control group). The exact number of further cycles of systemic therapy, and the drugs used, could not be reliably ascertained as patients were often treated at other centres during the follow-up period. The study was adequately powered for the primary outcome, however, the overall survival outcomes were better than the a priori estimates of survival used in the sample size calculation. Progression was measured objectively using either PET or CT imaging. CI were reported. **Quality of evidence score:** 9 **Applicability:** high

Study Design and Population Characteristics	**Methodology**	**Results**	**Critical Appraisal Summary**
		Quality of life was similar between arms at baseline and remained comparable at 6-months. The only side effect experienced with standard care was fatigue. Patients receiving SABR had fatigue, dyspnoea, pain and Grade 5: 4.5% (3 deaths)	

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Ost et al. 2018 NCT01558427 RCT Multicentre Belgium Recruitment period 2012-2016 62 patients with oligorecurrent prostate cancer All patients had less than 3 metastases Mean time to metastases was approximately 6 months	Patients were randomised (1:1) to initial metastasis-directed therapy (SABR or surgery) or active surveillance In the metastasis-directed therapy group, SABR (n = 25) and surgery in 6 patients Total dose = 30Gy in 3 fractions Median 3 years follow-up.	ITT: Median ADT-free survival: -active surveillance = 13 months (80% CI, 12-17 months) -MDT: 21 months (80% CI, 14-29 months) (HR: 0.60 [80% CI, 0.40-0.90]; log-rank p= 0.11). Quality of life was similar between arms at baseline and remained comparable up to 1-year follow-up. Two patients that received SABR developed grade 1 toxicity in the MDT arm. No grade 2 to 5 toxicity was observed.	**Appraisal:** Randomised. Due to the nature of the intervention, blinding and concealment was not possible. The study population and intervention are well matched to the scope, however, 6 patients in the intervention group received surgery rather than SABR. The study was adequately powered for the primary outcome. Progression was measured objectively using either PET or CT imaging. Quality-of-life scoring was performed and scored using appropriate tools namely the EORTC QLQ-C30 supplemented with the QLQ-PR25. Toxicity was assessed using the CTCAE criteria. **Quality of evidence score: 9** **Applicability: Moderate**

(Lee et al. 2018) Retrospective case-control study Single-centre Korea Recruitment period unknown 51 patients with pulmonary oligometastases from various primary cancers (35.3% colorectal*) All patients had less than 3 metastases Mean time to metastases was approximately 30 months	21 patients received SABR and 30 had a metastasectomy Total dose = 60Gy in 3 fractions or 48Gy in 4 fractions Median follow-up: 14 months	OS: -1 year = 95% surgery vs 79.5% SABR -2 years = 81.8% surgery vs 68.2% SABR (p=0.534) LC: 1 year= 96.6% surgery vs 83.5% SABR 2 year = 91.5% surgery vs 75.2% SABR (p=0.163) PFS: 1 year= 51.1% surgery vs 23.8% SABR 2 year = 46% surgery vs 11.9% SABR (p=0.02) 85.7% of the SABR cohort developed radiation pneumonitis. Two patients experienced grade 1 and 2 rib fractures, one and two patients experienced grade 1 and 2 chest wall pain, respectively. In the surgery group: -1 patient experienced acute bleeding requiring surgical intervention. -1 patient had acute respiratory distress syndrome requiring intensive medical care -1 patient experienced grade 3 nausea and required fluid treatment.	**Appraisal:** Retrospective, no randomisation, blinding, concealment. The 2 groups were not well matched with SABR patients having larger tumours and higher incident of synchronous extra-pulmonary disease. It is unknown if the study was adequately powered, when the patients were recruited and the follow-up period was short. CI are not reported. **Quality of evidence score: 4** **Applicability: Low**

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Lodewegeset al. 2017 Retrospective case-control study Single-centre Netherlands Recruitment period 2007-2010 101 patients with pulmonary oligometastases from various primary cancers (57% colorectal*) 97% of patients had ≤4 metastases Mean time to metastases was approximately 16 months	42 patients received SABR and 68 had a metastasectomy Total dose = 60Gy in 3 fractions or 48Gy in 4 fractions Median follow-up: 7.6 years	OS: -1 year = 87% (95% CI 76-93) surgery vs 98% (95% CI 84-100) SABR -2 years = 74% (95% CI 61-82) surgery vs 86% (95%CI 71-93) SABR (p >0.05) LC: 1 year= 93% (95% CI 83-97) surgery vs 95% (95% CI 80-99) SABR 2 year = 91% (95% CI 79-96) surgery vs 95% (95% CI 80-99) SABR (p >0.05) PFS: 1 year= 56% (95% CI 43-66) surgery vs. 49% (95% CI 34-63) SABR 2 year = 35% (95% CI 23-46) surgery vs 27% (95% CI 14-41) SABR (p >0.05)	**Appraisal:** Retrospective, no randomisation, blinding, concealment. A small percentage of patients had more than 4 lesions. SABR was considered a second choice treatment after surgery and as result the groups had differences in the baseline clinical characteristics (in favour of surgery). The 2 groups well not well matched with SABR patients being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval. The authors used propensity scoring to account for the baseline differences among the 2 groups. The study did not report a sample size calculation. The study had long follow-up. **Quality of evidence score: 7** **Applicability: Low**

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Filippi et al. 2016 Retrospective case-control study Single-centre Italy Recruitment period 2005-2012 170 patients with pulmonary oligometastases from colorectal cancer The majority of patients had <3 metastases Mean time to metastases was more than 2 years	28 patients received SABR and 142 had a metastasectomy Total dose = 26Gy in 1 fraction or 45Gy in 3 fractions or 55Gy in 10 fractions or 60Gy in 8 fractions Median follow-up: SABR = 27 months Surgery= 46 months	OS: -1 year = 96% surgery vs 89% SABR -2 years = 82% surgery vs 77% SABR (p=0.134) The results of PFS are considered unreliable because different follow-up protocols were applied in the two cohorts. SABR: Toxicity: -Radiation pneumonitis grade 3 = 14.4% -Chronic chest pain grade 3 = 3.55 Surgery: No major complications and only one death within 30 days was observed among the surgical population.	**Appraisal:** Retrospective, no randomisation, blinding, concealment. A small percentage of patients had more than 4 lesions. The 2 groups were well matched, however, they were unbalanced in terms of numbers. The authors used propensity scoring to account for the baseline differences among the 2 groups. It is unknown if the study was adequately powered. The study had unbalanced follow-up between the 2 groups reducing the ability to detect differences between the 2 cohorts. **Quality of evidence score: 5** **Applicability: Low**

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Stintzing et al. 2013 Retrospective case-control study Single-centre Germany Recruitment period 2005-2011 60 patients with liver oligometastases from colorectal cancer The majority of patients had a single metastatic lesion Median time to metastases was 12 months	30 patients received SABR and 30 RFA Total dose = 26Gy in 1 fraction Median follow-up was 23 months	OS: Median = 52.3 (95% CI 31.1-73.6) RFA vs. 34.4 months (95% CI 19.9-48.9) SABR (p=0.06) LC: -1 year = 65% RFA vs 85% SABR -2 years = 61% RFA vs 80% SABR (p>0.05) Local PFS: Median= 6.0% (95% CI 1.9-10) RFA vs. 34.4% (3.4–65.4) SABR (p<0.001) No patient develop grade 3 or higher toxicity.	**Appraisal:** Retrospective, no randomisation, blinding, concealment. Baseline characteristics did not differ significantly between the groups. The study did not report a sample size calculation. It is unknown if the follow-up was consistent between the 2 groups. Confidence intervals were reported for some outcomes **Quality of evidence score: 5** **Applicability: Low**

Study Design and Population Characteristics	**Methodology**	**Results**	**Critical Appraisal Summary**
* The cancer types with the highest % representation in the sample Quality of evidence score: The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence included in the report. HR: Hazard ratio, ITT = intention to treat, LC = local control, OS = overall survival , 95% CI = 95% confidence interval			

Table 23: Non-comparative studies

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Sutera et al. 2019 NCT01345552 Prospective cohort Multicentre Ireland/US Recruitment period 2011-2017 147 patients with oligometastases from various primary cancers (21.8% lung* and 21.2% colorectal*) 97.2% of the patients had ≤4 metastases Mean time to metastases was not reported	All patients received SABR with changes in total dose and fractionation depending on treatment site. Total dose = 18-60Gy in 1-5 fractions Median 41.3 months follow-up.	OS: -Median = 42.3 months (27.4 - not reached) -1 year = 84% -2 year = 63% -5 year = 43% LC: -Median = not reached -1 year = 91% -2 year = 83% -5 year = 75% PFS: Median = not reported -1 year = 47% -2 year = 27% -5 year = 15% QoL did not change at treatment completion, 6 weeks, 3 months, and 9 months after treatment. At 6 and 12 months, patients were found to have statistically significant improvement in QoL. Adverse events are reported in the summary outcomes tables (table 8).	**Appraisal:** Non-randomised, single arm. Due to the nature of the intervention, blinding and concealment was not possible. The study population and intervention are well matched to the scope, however, the CtE had a higher population of patients with prostate cancer and lower % of patients with lung cancer. The study did not report a sample size calculation. Progression was measured objectively using CT imaging, however, the patients were followed-up every 6 months after the first post-treatment. This relatively raises concerns about detection bias. Quality-of-life was assessed and scored using an appropriate tool namely the 27-item Function Assessment of Cancer Therapy-General (FACT-G). The fact that changes in QoL were significant at 6 and 12 months but not 9 months questions the validity of the result. Confidence intervals were reported. **Quality of evidence score:** 7 **Applicability:** High

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Navarria et al. 2014 Prospective cohort Single centre Italy Recruitment period 2010-2012 76 patients with pulmonary oligometastases from various primary cancers (24% lung* and 38% colorectal*) Number of patients with ≤4 metastases not reported Median time to metastases = 24 months	All patients received SABR with changes in total dose and fractionation depending on treatment site. Total dose = 60Gy in 3/8 fractions or 48Gy in 4 fractions. The majority of patients received 48Gy in 4 fractions. Median 18 months follow-up.	OS: -Median = 20 months -1 year = 84% -2 year = 73% -3 year = 73% LC: -1 year = 95% -2 year = 89% -3 year = 89% PFS: -1 year = 83% -2 year = 70% -3 year = 70% No acute or late grade2+ pulmonary toxicity, chest pain or rib fracture was observed.	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. The study population and intervention are well matched to the scope, however, the CtE had a higher population of patients with prostate cancer and lower % of patients with lung cancer. The study did not report a sample size calculation. Progression was measured objectively using CT or PET imaging, however, not all patients were subjected to the same follow-up assessment raising concerns about detection bias. Confidence intervals were not reported. **Quality of evidence score:** 7 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Siva et al. 2018 U1111-1140-7563 Prospective cohort Single-centre Australia Recruitment period 2013-2014 33 patients with bone and lymph nodes oligometastases from prostate cancer All patients had ≤3 metastases Mean time to metastases was not reported	All patients received SABR with a single fraction of 20Gy Total dose = 20Gy in 1 fraction 2 years follow-up. Patients were followed-up with PSA, CT scans and NaF PET at 1 year.	OS: -1 year = 100% -2 year = 100% LC: -1 year = 97% (95% CI 91-100%) -2 year = 93% (95% CI 84-100%) PFS: -1 year = 58% (95% CI 43-77%) -2 year = 39% (95% CI 25-60%) Adverse events: The most common adverse event was grade 1 fatigue. There was no significant difference from baseline QoL	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. The study population and intervention are well matched to the scope. The CtE had a large population of patients with prostate cancer that matches the population included in this study. However, the presence of only bone and lymph nodes metastases may have favourably skewed the results for toxicity and OS in this study. The study was powered to detect a 15% acute grade 3 toxicity Progression was measured objectively using CT or NaF PET imaging. Confidence intervals were reported. **Quality of evidence score:** 7 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Warren et al. 2017 Prospective cohort Single-centre Australia Recruitment period 2013-2014 31 patients with liver oligometastases from various primary cancers (41% colorectal cancer*) All patients had ≤3 metastases Mean time to metastases was not reported All patients had Child-Pugh A liver function.	Total dose not reported but treatment was delivered in 3-6 fractions 6 months follow-up.	No grade 3+ acute or late toxicities Mean EQ-5D score at baseline was 0.857, which remained stable across the entire study period. The mean visual analogue related QoL score at baseline was 65.8 and remained unchanged throughout treatment and follow-up.	**Appraisal:** Non-randomised, lack of control. Due to the nature of the intervention, blinding and concealment was not possible. The study population matched the scope. However, the CtE had a higher population of patients with prostate cancer than the population included in this study. Compliance with QoL assessment reduced over time. This is a well-recognised problem in QoL research and minimises the validity of the results. EQ-5D is not a cancer specific QoL tool. It is unknown if the study was adequately powered to detect any of the clinical outcomes. Short follow-up duration. Confidence intervals were not reported. **Quality of evidence score:** 7 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Comito et al. 2014 Prospective cohort Single-centre Italy Recruitment period 2010-2013 82 patients with oligometastases (mixed pulmonary and liver metastases) from colorectal cancer All patients had ≤3 metastases Mean time to metastases was > 12 months for 76% of the patients	All patients received SABR with changes in total dose and fractionation depending on treatment site Total dose = 60Gy in 3 fractions, 48Gy in 4 fractions or 75Gy in 3 fractions Median 24 months follow-up.	OS: Median = 32 months -1 year = 85% -2 year = 65% -3 year = 43% LC: -1 year = 90% -2 year = 80% -3 year = 75% PFS: Median= 14 months -1 year = 56% -2 year = 40% -3 year = 40% The most common side effect was fatigue	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. The study population is matching the scope. However, the CtE had a higher population of patients with prostate cancer. The study did not report a sample size calculation. Short follow-up duration. Confidence intervals were not reported. **Quality of evidence score:** 6 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Kunos et al. 2012 Prospective cohort Single centre USA Recruitment period 2009-2011 50 patients with oligometastases from gynaecologic cancer (50% ovarian cancer*) 96% of the patients had ≤3 metastases Mean time to metastases was not reported	All patients received the same SABR treatment Total dose = 24Gy in 3 fractions Median 15 months follow-up.	OS: Median = 20.2 (95% CI 10.9 29.5) months LC: -1 year = 100% PFS: Median= 7.8 (95% CI 4.0-11.6) months The most common side effect was fatigue	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. Low BED (<100Gy) The study population is partially matching the scope. The CtE had a small population of people with gynaecologic cancer. The study did not report a sample size calculation. Short follow-up duration. Confidence intervals were reported. **Quality of evidence score:** 6 **Applicability:** Low

Study Design and Population characteristics	**Methodology**	**Results**	**Critical Appraisal Summary**
* The cancer types with the highest % representation in the sample Quality of evidence score: The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence included in the report. HR: Hazard ratio, ITT = intention to treat, LC = local control, OS = overall survival , 95% CI = 95% confidence interval			

Table 24: Registries

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Mahadevan et al. 2018 RSSearch registry NCT01885299 Retrospective cohort Multicentre International (USA, Germany, Australia) Recruitment period 2005-2017 447 patients with pulmonary oligometastases from various primary cancers (12.2% lung* and 44.3% colorectal*) Median number of metastases was not reported. Mean time to metastases was not reported	All patients received SABR with changes in total dose and fractionation depending on treatment site Median dose = 45Gy (12–60Gy) delivered in a median of 3 fractions Median 14 months follow-up.	OS: -Median = 22 months -1 year = 70% -2 year = 47% LC for BED≥100Gy: -Median = 52 months -1 year = 88%% -2 year = 77% There was no grade 3+ toxicity reported The most common toxicity was fatigue	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. Toxicity data was not available for all patients. The study population and intervention are matched to the scope of the CtE, however, the CtE had a higher proportion of patients with prostate cancer and lower % of patients with colorectal cancer. Recruitment period was over a decade starting from mid 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Follow-up duration was short. Confidence intervals not reported. **Quality of evidence score:** 5 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Ricco et al. 2017 RSSearch registry NCT01885299 Retrospective cohort Multi-centre International (USA, Germany, Australia) Recruitment period 2004-2015 447 patients with pulmonary oligometastases from various primary cancers (16.6% lung* and 25.7% colorectal*) Median number of metastases was 1. Mean time to metastases was not reported	Patients received SABR with changes in total dose and fractionation depending on treatment site Median dose = 50Gy (8–60Gy) delivered in a median of 3 fractions Median 13 months follow-up.	OS: -Median = 26 months -1 year = 74% -2 year = 60% -3 year = 33% -5 year = 22% LC: -Median = 53 months -1 year = 80% -3 year = 59% -5 year = 46% There was no statistical difference in LC rates based on primary tumour types.	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. The study population and intervention are matched to the scope of the CtE, however, the CtE had a higher proportion of patients with prostate cancer and lower % of patients with colorectal cancer. Recruitment period was over a decade starting from mid 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Follow-up duration was short. Confidence intervals not reported. **Quality of evidence score:** 5 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
Klement et al. 2018 DEGRO registry Retrospective cohort Multi-centre International (Germany, Switzerland) Recruitment period 1997-2014 637 patients with pulmonary oligometastases from various primary cancers (30.5% lung* and 21.9% colorectal*) 99% of the patients had ≤4 metastases. Median number of metastases was 1. Mean time to metastases was not reported	Patients received SABR with changes in total dose and fractionation depending on treatment site Median dose = 50Gy (8–60Gy) delivered in a median of 3 fractions Median 13 months follow-up.	OS: -Median = 23.5 (95% CI 21.4-26.6) months -1 year = 71% (95% CI 67%-75%) -2 year = 60% (95% CI 45%-54%) -3 year = 33% (95% CI 29%-39%) Main side effect was radiation pneumonitis.	**Appraisal:** Non-randomised, single armed. Due to the nature of the intervention, blinding and concealment was not possible. The study population and intervention are matched to the scope, however, the CtE had a higher % of patients with prostate cancer. Recruitment period was over a decade starting from late 1990s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Toxicity data was not available for all patients Follow-up duration was short. Confidence intervals were reported. **Quality of evidence score:** 5 **Applicability:** Low

Andratschke et al. 2018 DEGRO registry Retrospective cohort Multi-centre International (Germany, Switzerland) Recruitment period 1997-2015 474 patients with liver oligometastases from various primary cancers (13.3% breast* and 48.1% colorectal*) 100% of the patients had ≤4 metastases. Median number of metastases was 1. Mean time to metastases was not reported	Patients received SABR with changes in total dose and fractionation depending on treatment site Median dose and number of fractions not reported Median 15 months follow-up.	**Efficacy** OS: -Median = 24 months -1 year = 70% -3 year = 29% -5 year = 15% LC: -1 year = 77% -2 year = 64% -3 year = 56% **Toxicity** Acute up to 3 months post treatment (available for 73% of the patients): Grade 1-2 = 23% Grade 3 < 1% Grade 4-5 = 0 The most common side effects were fatigue, nausea, and diarrhoea. Chronic (available for 44% of the patients): Grade 1-2 = 10% Grade 3 = 1.4% Grade 4-5 = 0 The most common side effects were fatigue, nausea, liver enzyme elevation, jaundice, and diarrhoea.	**Appraisal:** Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population and intervention are matched to the scope, however, the CtE had a higher population of patients with prostate cancer. Recruitment period was over a decade starting from early 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Toxicity data, especially long-term was not available for all patients Follow-up duration was short. Confidence intervals were not reported. **Quality of evidence score:** 5 **Applicability:** Low

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
SABR CtE cohort Prospective registry Multicentre UK Recruitment period 2015-2018 1422 patients with oligometastases from various primary cancers (28.6% prostate* and 27.9% colorectal*) Nodal metastases = 31.3% Lung metastases = 29.3% Bone metastases = 12.1% Liver metastases = 9.6% WHO PS 0=71.1%, 1=24.3%, 2=4.6% Median age: 69 Men = 66.6% 100% of the patients had ≤3 metastases. Median number of metastases was 1 (75% of the patients had solitary metastases). Median lesion size: not reported Previous chemotherapy: 59.8%	Patients received SABR with changes in total dose and fractionation depending on treatment site Median dose and number of fractions not reported Median 12.72 months follow-up.	Median overall survival >24 months Actuarial OS: -1-year = 92.3% (95% CI 90.5-93.9%) -2-year = 79.2% (95% CI 76.0%-82.1%) Local control: -1-year = 86.9% (95%CI 84.6-88.9%) -2-year = 72.3% (95%CI 68.7-75.6%) Toxicity: -grade 3: 5.8% (95% CI 4.7-7.2%) -grade 4: 1.8% (95% CI 1.2-2.7%) -grade 5: 0%	**Appraisal:** Non-comparative cohort – no randomisation, blinding, concealment. Multicentre experience in a UK NHS setting increases the external validity of the results. This is a contemporary cohort with recruitment period starting from 2015, therefore, more comparable with current standards. Large patient cohort. Patients recruited into the CtE scheme were assessed for eligibility by a MDT team making sure that both clinical eligibility criteria but also technical feasibility aspects of the treatment were meet. LC was assessed qualitatively without using objective lesion size based measurements. This limits the generalisability of the results and introduces potential detection bias. The study did not report a sample size calculation. CIs are reported for most outcomes It was not possible to ascertain if patients received further treatment after SABR as patients were often treated at other centres during the follow-up period. The Kaplan-Meier analysis was based on the assumption that there was "no event" unless an event was recorded (for example death). As a result, the analysis relies on data completeness. Events cannot be accounted for patients who are lost to follow-up and we know from the providers' feedback that patients are often lost to follow-up because they become sicker due to disease progression. This increased the risk of detection bias within the CtE analysis. For OS this limitation is mitigated by the use of HES and ONS databases for data triangulation. Patients in the registry were linked to HES and ONS data, which provided a method to triangulate the mortality event rates, minimising detection outcomes and uncertainty. All centres taking part to the scheme had to undergo intervention a nationally assured training system for SABR treatment, ensuring not only consistency of the intervention across in a multicentre setting but also potentially increasing safety. **Quality of evidence score: 7** **Applicability: High**

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
* The cancer types with the highest % representation in the sample Quality of evidence score: The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence included in the report. HR: Hazard ratio, ITT = intention to treat, LC = local control, OS = overall survival , 95% CI = 95% confidence interval			

6.2.3 Studies outcomes tables

Table 25, Table 26, Table 27, Table 28 and Table 29 below report the overall survival, local control, toxicity, quality of life, and progression free survival results from the included studies.

Table 25: Overall Survival

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Palma et al. 2019 (SABR-COMET) RCT 25 N = 99	41 (95% CI 26-not reached)	Standard care 28 (95% CI 19-33)	0.57 0.3-1.1 P=0.09	Population similar to the CtE cohort

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Stintzing et al. 2013 Case control 23.3 N = 60	34.4	RFA 52.3	NR NR P=0.06	Heavily pre-treated population, single fraction SABR
Sutera et al. 2019 Cohort 41.3 N = 147	42.3 months (95% CI 27.4-not reached)	NA	NA NA NA	Contemporary cohort, population and intervention comparable to SABR-COMET and the CtE
Mahadevan et al. 2018 Registry 14 N = 427	22	NA	NA NA NA	Not contemporary cohort, only liver metastases, some patients received low BED
Klement et al. 2018 Registry 13 N = 637	23.5 months (95% CI 21.4–26.6)	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Andratschke et al. 2018 Registry 15 N = 474	24	NA	NA NA NA	Not contemporary cohort, only liver metastases, some patients received low BED

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Ricco et al. 2017 Registry 13 N = 447	26	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Navarria et al. 2014 Cohort 18 N = 76	20	NA	NA NA NA	Only treated patients with pulmonary metastases, high BED
Comito et al. 2014 Cohort 24 N = 82	32	NA	NA NA NA	Only treated patients with CRC and visceral metastases (liver and pulmonary), high BED
Kunos et al. 2012 Cohort 15 N = 50	20.2 (95% CI 10.9-29.5)	NA	NA NA NA	Only treated women with gynaecologic cancer, low BED
Palma et al. 2019 RCT 25 N = 99	-1 year =86% -2 year =70%	Standard care -1 year =86% -2 year =60%	NR NR NR	Population similar to the CtE cohort
Lee et al. 2018 Case control	SABR -1 year =79%	Surgery -1 year =95%	p=0.53	The 2 groups were not well matched with SABR patients having larger

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
13.7 N = 51	-2 year =68%	-2 year=82%		tumours and higher incident of synchronous extra-pulmonary disease. There were no significant differences in OS between treatment groups after dividing patients according to the presence or absence of synchronous metastases.
Lodeweges et al. 2017 Case control 7.6 years N = 110	SABR -1 year =98% (95% CI 84-100%) -2 year =86% (95% CI 71-93%) -3 year = 64% (95% CI 48-77%) -5 year = 45% (95% CI 30-59%)	Surgery -1 year = 87% (95% CI 76-93%) -2 year = 74% (95% CI 61-82%) -3 year = 63% (95% CI 51-73%) -5 year = 41% (95% CI 29-53%)	0.76 0.38-1.54 NR	SABR was considered a second choice treatment after surgery and as result the groups' baseline clinical characteristics were not well matched (in favour of surgery). The 2 groups well not well matched with SABR patients being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval. The authors used propensity scoring to account for the baseline differences among the 2 groups
Filippi et al. 2016 Case control	SABR -1 year = 89%	Surgery -1 year = 96%	1.28 0.58-2.82	The 2 groups were well matched, however, they were unbalanced in

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
27 N = 170	-2 year =77%	-2 year = 82%	p=0.54	terms of numbers. The authors used propensity scoring to account for the baseline differences among the 2 groups.
Sutera et al. 2019 Cohort 41.3 N = 147	-1 year = 84% -2 year = 63% -3 year = 50% -5 year = 43%	NA	NA NA NA	Contemporary cohort, population and intervention comparable to SABR-COMET and the CtE
Siva et al. 2018 Cohort 24 N = 33	-1 year = 100% -2 year = 100%	NA	NA NA NA	Only included prostate cancer patients. This patient cohort historically has better OS rates.
Navarria et al. 2014 Cohort 18 N = 76	-1 year = 84% -2 year = 73% -3 year = 73%	NA	NA NA NA	Only treated patients with pulmonary metastases, high BED
Comito et al. 2014 Cohort 24 N = 82	-1 year = 85% -2 year = 65% -3 year = 43%	NA	NA NA NA	Only treated patients with CRC and visceral metastases (liver and pulmonary), high BED

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Mahadevan et al. 2018 Registry 14 N = 427	-1 year = 70% -2 year = 47% -3 year = 30% -5 year = 5%	NA	NA NA NA	Not contemporary cohort, only liver metastases, some patients received low BED
Klement et al. 2018 Registry 13 N = 637	-1 year = 71% (95% CI 67%-75%) -2 year = 60% (95% CI 45%-54%) -3 year = 33% (95% CI29%-39%) -5 year = 20%	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Andratschke et al. 2018 Registry 15 N = 474	-1 year = 70% -2 year = 47% -3 year = 29% -5 year = 15%	NA	NA NA NA	Same as previously.
Ricco et al. 2017 Registry 13 N = 447	-1 year = 74% -2 year = 60% -3 year = 33% -5 year = 22%	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Abbreviations: BED, biologically effective dose; CI, confidence interval; CRC, colorectal cancer; LC, local control; OS, overall survival; RFA, radiofrequency ablation; RT, radiotherapy				

Table 26: Local control

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Lodeweges et al. 2017 Case control 7.6 years N = 110	-1 year =95% (95% CI 80-99%) -2 year =95% (95% CI 80-99%) -3 year = 90% (95% CI 70-97%) -5 year = 83% (95% CI 57-94%)	Surgery -1 year = 93% (95% CI 83-97%) -2 year = 91% (95% CI 79-96%) -3 year = 85% (95% CI 70-93%) -5 year = 81% (95% CI 65-90%)	0.8 (local recurrence) 0.24-2.65 > 0.05	Small lesions (mean size = 1.9 cm). However, lesion size did not influence LC (HR =1.03, 95% CI 0.73-1.45). LC was assessed with RECIST 1.1 and CT.
Stintzing et al. 2013 Case control 23.3 N = 60	-1 year = 85% -2 year = 80%	RFA -1 year = 65% -2 year = 61%	NR NR -1-year = 0.09 - 2-year = 0.20	Heavily pre-treated population, single fraction SABR. Average size lesions (mean=3.4 cm). Size and number of metastases matched between the 2 cohorts. CT or MRI was used for assessing LC.
Sutera et al. 2019 Cohort 41.3 N = 147	-Median = not reached -1 year = 91% -2 year = 80% -3 year = 75% -5 year = 75%	NA	NA NA NA	Contemporary cohort. Population, and intervention comparable to Palma et al., 2019. Small lesions (median=2.3 cm). LC was assessed with RECIST and CT.

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Mahadevan et al. 2018 Registry 14 N = 427	-Median = 51 months -1 year = 80% -2 year = 70% -3 year = 65% -5 year = 47%	NA	NA NA NA	LC was assessed with RECIST but imaging test used and frequency of follow-up not reported. Small tumours (<40 cm^3) had improved LC (p=0.0014). 1- and 2-year LC rates for BED10 ≥ 100 Gy were 87.5% and 77.2%, respectively, compared to 1- and 2-year LC rates for BED 10 < 100 Gy of 71.8% and 59.6% (p<0.0001). No difference in LC based on primary histology.
Ricco et al. 2017 Registry 13 N = 447	-Median = 53 months -1 year = 80% -2 year = 65% -3 year = 59% -5 year = 46%	NA	NA NA NA	LC was assessed with RECIST but imaging test used and frequency of follow-up not reported. Some patients received low BED. Improved LC was observed for lesions that received SABR doses of BED ≥100Gy. No difference in LC based on primary histology.
Andratschke et al. 2018 Registry 15	-1 year = 76% -2 year = 64% -3 year = 56%	NA	NA NA NA	Some patients received low BED. Different follow-up frequency and imaging modalities used between

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
N = 474	-5 year = 50%			centres. The size of the lesion and the BED affected LC.
Navarria et al. 2014 Cohort 18 N = 76	-1 year = 95% -2 year = 89% -3 year = 89%	NA	NA NA NA	Only pulmonary metastases, high BED. LC was assessed with RECIST using CT and/or FDG-PET/CT. No correlation between delivered doses and local control was present.
Comito et al. 2014 Cohort 24 N = 82	All -1 year = 90% -2 year = 80% -3 year = 75% High BED -1 year = 97% -2 year = 92% -3 year = 83% Low BED -1 year = 85% -2 year = 70% -3 year = 70%	NA	NA NA NA	Only CRC population, liver and pulmonary metastases, high BED. Mean lesion size was 3.3 cm. The difference in LC between the subgroup of lesions treated with ≥60 Gy (n = 58) and those irradiated with <60 Gy (n = 52) was statistically significant.

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Lee et al. 2018 Case control 14 N = 51	-1 year = 83.5% -2 year = 75.2%	Surgery -1 year = 96.6% -2 year = 91.5%	NR NR P=0.163	High BED. The tumour size in the SABR group was larger than in the surgery group (median 2.5 vs. 1.25 cm; p = 0.015). Details on follow-up and how LC was assessed are not reported.
Siva et al. 2018 Cohort N = 33	-1 year = 97% (95% CI 91-100%) -2 year = 93% (95% CI 84-100%)	NA	NA NA NA	LC was assessed using RECIST and CT and 18F-NaF PET imaging (at 12 months only).
Abbreviations: BED, biologically effective dose; CT, computerised tomography; CRC, colorectal cancer; CI, confidence interval; LC, local control; RFA, radiofrequency ablation; RT, radiotherapy				

Table 27: Toxicity

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Palma et al. 2019 RCT 25 N = 99	-Grade 2 = 16% -Grade 3 = 7% -Grade 5 = 5%	Standard care -Grade 2 = 6% -Grade 3 = 3% -Grade 5 = 0%	Absolute increase= 20% Grade 2/3 =5-34% Grade 5 = 1-10% NR	Toxicity was evaluated at each follow-up visit using the CTCAE version 4.0. The most common treatment related toxic effects of Grade 2 or worse in the SABR group were fatigue (n=4), dyspnoea (n=2) and pain (including muscle, bone, and other, total n=8). There were three treatment related Grade 5 events in the SABR group due to deaths from radiation pneumonitis (n=1), pulmonary abscess (n=1), and subdural haemorrhage after surgery to repair a SABR-related perforated gastric ulcer (n=1).
Ost et al. 2018 RCT 24 N = 62	-Grade 1 = 8% -Grade 2-5 = 0%	Active surveillance -Grade 1-5 = 0%	NR	Toxicity was assessed in the metastasis-directed therapy group using CTCAE for patients undergoing SABR and the Clavien-Dindo classification for patients who

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
				underwent surgery. Only 2 episodes (loose stools and muscle pain) of acute Grade 1 toxicity were observed with SABR.
Stintzing et al. 2013 Case control 23.3 N = 60	-Grade 1 = 6% -Grade 2 = 0% -Grade 3+ = 0%	RFA -Grade 1 = 8% -Grade 2 = 7.5% -Grade 3+ = 0%	NR NR NS	Heavily pre-treated population, single fraction SABR
Sutera et al. 2019 Cohort 41.3 N = 147	Acute: -Grade 2 = 7.5% -Grade 3 = 2% Late: -Grade 2 = 1.4% -Grade 3 = 1.4%	NA	NA NA NA	Contemporary cohort. Population and intervention comparable to Palma et al., 2019 Unclear how acute and late toxicity were defined
Warren et al. 2017 Cohort 6 N = 31	-Grade 1 = Unknown -Grade 2 = Unknown -Grade 3 = 0% -Grade 4 = 0%	NA	NA NA NA	Toxicity was assessed using CTCAE. No grade 3 or 4 acute or late toxicities nor classic or non-classic radiation-induced liver disease cases were reported.
Mahadevan et al. 2018 Registry 14	-Grade 1 = Unknown -Grade 2 = Unknown -Grade 3 = 0%	NA	NA NA NA	Toxicity data was not available from all centres for all patients.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
N = 427				
Klement et al. 2018 Registry 13 N = 637	-Grade 2 = 4% -Grade 3 = 1% -Grade 5 = 1 patient	NA	NA NA NA	Toxicity data was not available from all centres for all Patients. Toxicity was mainly associated with pneumonitis.
Andratschke et al. 2018 Registry 15 N = 474	Acute: Grade 1- 2= 23% Grade 3 < 1% Grade 4 = 0% Grade 5 = 0% Late: -Grade 1-2 = 10% -Grade 3 = 1.4% -Grade 4 = 0% -Grade 5 = 0%	NA	NA NA NA	Acute toxicity was scored according to the CTCAE criteria during and up to 3 months after SABR. Toxicity beyond 3 months (late) was graded using the RTOG/EORTC criteria. Acute toxicity data was available for only 73% of the patients. Grade 1–2 toxicity consisted mostly of fatigue, nausea, and diarrhoea. Chronic toxicity data was available for only 44% of the patients and consisted of fatigue, nausea, diarrhoea, liver enzyme elevation, and jaundice.
Navarria et al. 2014 Cohort	Acute: Grade 1-5 = 0%	NA	NA NA	Toxicity was assessed in the MDT group using CTCAE. It is unclear what

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
18 N = 76	Late: -Grade 1 = 80% (mostly radiological fibrosis in <25% of lung volume) -Grade 2 = 0% -Grade 3 = 0% -Grade 4 = 0% -Grade 5 = 0%		NA	cut-off the authors used to separate acute and late toxicity. No major pulmonary toxicity, chest pain or rib fracture occurred.
Comito et al. 2014 Cohort 24 N = 82	Acute -Grade 2 = 70% -Grade 3 = 0% -Grade 4 = 0% -Grade 5 = 0%	NA	NA NA NA	Acute and late toxicity were scored by the CTCAE criteria, however, the authors do not clarify the time frame for separating between acute and late toxicity. The most frequent side effects were fatigue (60%) and transient hepatic transaminase increase (25%) for liver metastases treatment. No patients developed RILD, chest pain or rib fracture.
Kunos et al. 2012 Cohort 15 N = 50	Acute and late -Grade 1 = 26% -Grade 2 = 50% -Grade 3 = 4% -Grade 4 = 2%	NA	NA NA NA	Acute (within a month after SABR) and late (after a month post SABR) toxicity were scored by the CTCAE criteria. The most frequent adverse events were grade 1 or 2 fatigue

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
				(20%) and grade 1 or 2 nausea (12%). The incidence of grade 3 or grade 4 possible SABR-related non-haematological toxicities was 6%. It is not possible to distinguish between acute and late toxicity events from the authors reporting of the results.
Lee et al. 2018 Case control N = 51	Radiation pneumonitis: -Grade 1 = 57.1% -Grade 2 = 23.8% -Grade 3 = 4.8% Rib fractures -Grade 1 = 9% -Grade 2 = 9% Chest wall pain -Grade 1 = 5% -Grade 2 = 9%	Surgery -1 patient experienced acute bleeding requiring surgical intervention. -1 patient had acute respiratory distress syndrome requiring intensive medical care	NR NR NR	There were differences in patients' baseline characteristics and toxicity profiles.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
		-1 patient experienced grade 3 nausea and required fluid treatment.		
Filippi et al. 2016 Case control N = 170	Radiation pneumonitis -Grade 1 = 21.4% -Grade 2 = 14.4% Chronic chest pain -Grade 2 = 3.5% -Grade 3 = 3.5%	One death within 30 days was observed among the surgical population. No other major complications were observed.	NR NR NR	Acute and late toxicity were scored by the CTCAE criteria. It is not possible to distinguish between acute and late toxicity events from the authors reporting of the results.
Siva et al. 2018 Cohort N = 33	-Grade 1 = 48% -Grade 2 = 15% -Grade 3 = 3% (vertebral fracture requiring spinal instrumentation)	NA	NA NA NA	The study estimated the sample size based on the assumption that grade 3 toxicity rate would be 10.5%, and the probability of no greater than 15% of patients in the sample suffering a grade 3 or higher acute toxicity would be 80%. The most common side effect was fatigue.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Abbreviations: CTCAE, common terminology criteria for adverse events; CI, confidence interval; MDT, multidisciplinary team; NA, Not applicable; NR, Not reported; RFA, radiofrequency ablation; RILD, Radiation-induced liver disease;				

Table 28: Quality of life

Quality of life				
Reference **Design** **Follow-up (months)*** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Palma et al. 2019 RCT 6 N = 99	82.6 (SD 16·6)	Standard care 82.5 (SD 16.4)	NA NA p=0.99	QoL was evaluated at each follow-up visit using the Functional Assessment of Cancer Therapy: General (FACT•G) tool. QoL was similar between arms at baseline and remained comparable at 6-months.
Ost et al. 2018 RCT 12 N = 62	Values not reported as results presented only on graphs	Active surveillance Values not reported as	NR NR NR	QoL was evaluated at each follow-up visit using the European Organization for Research and Treatment of

Quality of life				
Reference **Design** **Follow-up (months)*** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
		results presented only on graphs		Cancer (EORTC) Quality-of-Life Questionnaire QLQ-C30 and QLQ-PR25 tools. QoL was similar between arms at baseline and remained comparable at 1-year. The questionnaire completion rate was 97% at baseline, 89% at 3 months, and 84% at 1 year.
Sutera et al. 2019 Cohort 12 N = 147	NR	NA	NA NA NR	QoL was evaluated at each follow-up visit using the Function Assessment of Cancer Therapy-General (FACT-G) tool. QoL was similar between baseline, 6 weeks, 3 months, and 9 months after treatment. The fact that changes in QoL were significant at 6 and 12 months but not 9 months questions the validity of the result.

Quality of life				
Reference **Design** **Follow-up (months)*** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Warren et al. 2017 Cohort 6 N = 31	Mean EQ-5D-3L utility score at baseline = 0.857 (SD = 0.0258). Mean utility score at 6 months = 0.799 (SD = 0.0650)	NA	NA NA p > 0.05	QoL was evaluated at each follow-up visit using the EQ-5D-3L. QoL was similar between baseline and each follow-up up to 6 months.
Siva et al. 2018 Cohort 24 N = 33	Baseline = 77 (95% CI 70 - 84) 2 years = 69 (95% CI 61 - 77)	NA	NA NA NA	QoL was evaluated at each follow-up visit using the EORTC QLQ and BM22 tools. QoL was similar between baseline and each follow-up up to 2-years.
Abbreviations: CTCAE, common terminology criteria for adverse events; CI, confidence interval; MDT, multidisciplinary team; RFA, radiofrequency ablation; RILD, Radiation-induced liver disease;				

Table 29: Progression free survival

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Palma et al. 2019 RCT 25 N = 99	-Median = 12 months -1 year = 53% -2 year = 40%	Standard care -Median = 6 months -1 year = 22% -2 year = 15%	0.47 0.3-0.76 P= 0.0012	Population similar to the CtE cohort. Comparator was standard care. PFS was defined as time from randomisation to disease progression at any site or death.
Lee et al. 2018 Case control 14 N = 51	-1 year = 24% -2 year = 12%	Surgery -1 year = 51% -2 year= 46%	NR NR p=0.53	The 2 groups well not well matched with SABR patients having larger tumours and higher incident of synchronous extra-pulmonary disease. There were no significant differences in PFS between treatment groups after dividing patients according to the presence or absence of synchronous metastases.
Lodeweges et al. 2017 Case control 7.6 years N = 110	-1 year = 49% (95% CI 34-63%) -2 year =2 7% (95% CI 14-41%)	Surgery -1 year = 56% (95% CI 43-66%)	NR NR NR	PFS not defined. Comparator was surgery. The 2 groups well not well matched with SABR patients

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
		-2 year = 35% (95% CI 23-46%)		being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval.
Filippi et al. 2016 Case control SABR = 27 months Surgery= 46 months N = 170	-1 year = 58% -2 year = 25%	Surgery -1 year = 80% -2 year = 62%	1.28 0.58-2.82 p=0.54	PFS was defined as the time from the date of the treatment for lung metastases (SABR or surgery) to the date of progression (death or first local/distant recurrence) or of the last follow-up. The results of PFS are considered unreliable because different follow-up protocols and sample sizes were applied in the two cohorts.
Stintzing et al. 2013 Case control 23 N = 60	34.4 months (3.4-65.4)	RFA Median= 6.0 months (1.9-10)	NR NR p<0.001	The comparator was RFA. The study had unbalanced follow-up between the 2 groups reducing the ability to detect differences between the 2 cohorts.

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Sutera et al. 2019 Cohort 41.3 N = 147	-Median = 8.7 months (95% CI, 6.6-13.1) -1 year = 47% -2 year = 27% -5 year = 17%	NA	NA NA NA	PFS was defined as the time from completion of SABR to documentation of new distant metastases.
Siva et al. 2018 Cohort 24 N = 33	-1 year = 58% (95% CI 43-77%) -2 year = 39% (95% CI 25-60%)	NA	NA NA NA	PFS was defined based on imaging.
Navarria et al. 2014 Cohort 18 N = 76	-1 year = 83% -2 year = 70% -3 year = 70%	NA	NA NA NA	Only pulmonary metastases. PFS was not defined. Progression was measured objectively using CT or PET imaging, however, not all patients were subjected to the same follow-up assessment.
Comito et al. 2014 Cohort 24 N = 82	-Median = 14 months -1 year = 56% -2 year = 40% -3 year = 40%	NA	NA NA NA	Only CRC population, liver and pulmonary metastases. Progression included any intra- or extra-hepatic and pulmonary disease progression.
Kunos et al. 2012 Cohort	Median= 7.8 months (95% CI 4.0-11.6)	NA	NA NA	Progression was defined as distant disease relapse.

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
15 N = 50			NA	
Abbreviations: CRC, colorectal cancer; PFS, progression free survival; QoL, quality of life				

6.2.4 Evidence on clinical effectiveness

Median overall survival

Nine of the included studies reported median overall survival. One study was the SABR-COMET RCT (Palma et al. 2019) that compared SABR with standard of care in patients with oligometastatic disease from different primary tumours (please see Table 22), and one was a case-control study comparing SABR with RFA (Stintzing et al. 2013) for liver metastases. The rest of the studies were non comparative cohorts (Kunos et al. 2012, Comito et al. 2014, Navarria et al. 2014, Sutera et al. 2019) and 3 registries (Andratschke et al. 2018, Klement et al. 2018, Mahadevan et al. 2018). Figure 6 shows the median overall survival achieved with SABR for these studies.

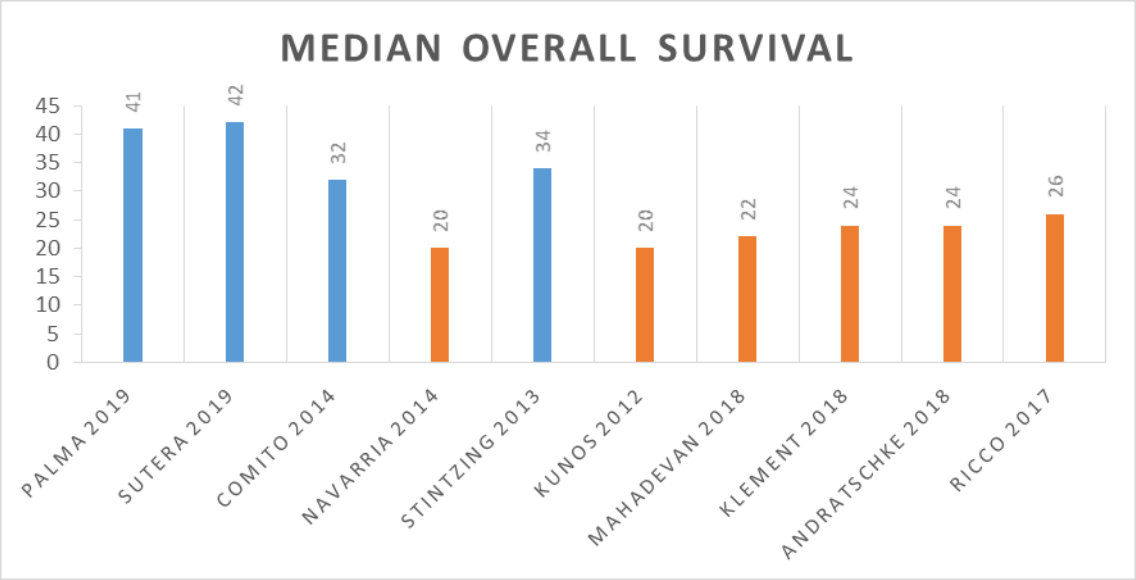

Figure 6: Median overall survival in months for patients treated with SABR. The studies are arranged based on recruitment dates starting from the most recent. All studies in orange had less than 20-months median follow-up time.

The shortest median OS reported was reported by (Kunos et al. 2012) at 20.2 months (95% CI 10.9-29.5), however, the study had a short follow-up (15 months), recruited only patients with gynaecological malignancies and some of the patients were treated with a low biologically equivalent dose (BED). Patients with oligometastatic disease are expected to have a longer survival as evident from the findings of Palma et al. (2019). In this study the

control group received standard of care and achieved 28 months median overall survival (95% CI 19-33 months).

The longest median overall survival was reported by (Sutera et al. 2019) at 42.3 months (95% CI 27.4 months-not reached). Similar findings were reported by Palma et al. (2019) at 41 months (95% CI 26 months -not reached). These two studies both recruited a contemporary cohort. They used comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various lesion locations, although there were differences in the individual proportions with a notably lower percentage of prostate cancer metastases for Sutera et al.'s (2019) study.

Some of the included studies referenced below reported the following variables influencing survival analysis[17]:

- Karnofsky Performance Status (Klement et al. 2018, Sutera et al. 2019).
- Primary diagnosis (Andratschke et al. 2018, Sutera et al. 2019).
- Metastasis size (Andratschke et al. 2018, Klement et al. 2018)
- Primary controlled (Klement et al. 2018)
- Solitary metastasis (Klement et al. 2018)

Actuarial overall survival

Twelve studies reported actuarial survival. One study was an RCT (Palma et al. 2019), three were case-control studies comparing SABR with surgery (Filippi et al. 2016, Lodeweges et al. 2017, Lee et al. 2018) for pulmonary metastases. The rest of the studies were non-comparative cohorts (Comito et al. 2014, Navarria et al. 2014, Siva et al. 2018, Sutera et al. 2019) and 3 registries (Andratschke et al. 2018, Klement et al. 2018, Mahadevan et al. 2018). Figure 7 and Figure 8 show the 1- and 2-year overall survival achieved with SABR for these studies.

[17] Only studies reporting multivariable analysis are included.

None of the studies reporting actuarial OS was adequately powered to detect a difference either from historically reported results or compared with a comparator (standard care, surgery, RFA). Studies reported mainly OS at 1- and 2-years post treatment.

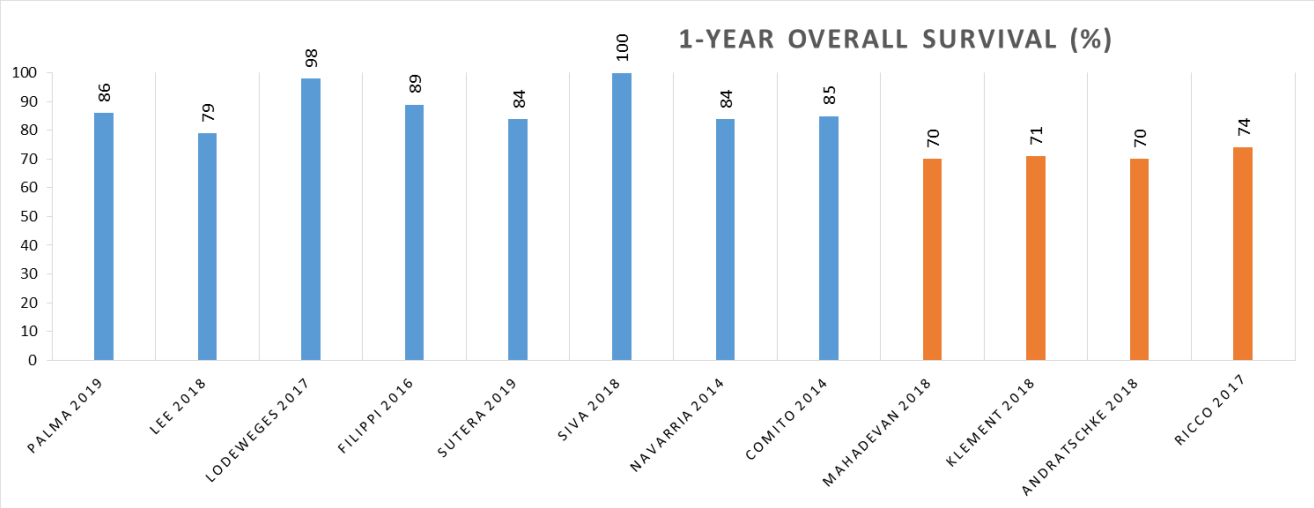

Figure 7: 1-year actuarial overall survival rates with SABR, in orange are results from registries.

The lowest rates for 1- and 2-year OS (approximately 70% and 47% respectively), were reported by the 4 registry analyses (Ricco et al. 2017, Andratschke et al. 2018, Klement et al. 2018, Mahadevan et al. 2018). These studies recruited patients for almost two decades starting in some cases from 1997, making the population, intervention and other aspects of the patient treatment and follow-up less comparable to a contemporary cohort. The highest 1- and 2-year OS was reported by Siva et al. (2018) a study that included only patients with prostate cancer and with bone/nodal metastases, all considered as good prognostic factors

for OS.

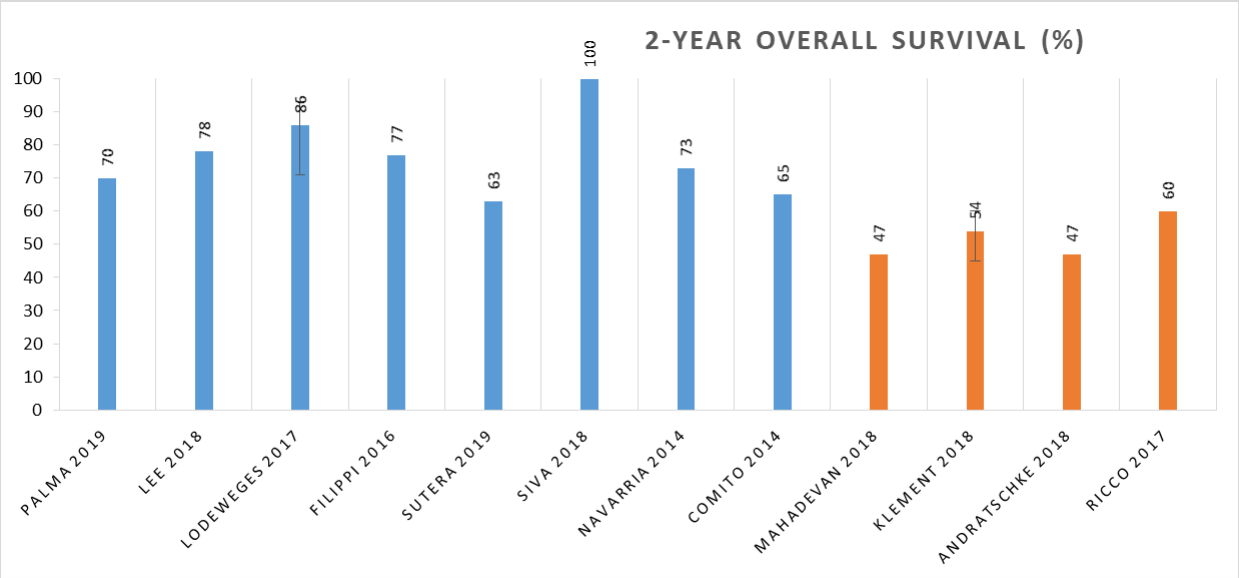

Figure 8: 2-year actuarial overall survival rates with SABR, in orange are results from registries. 95% confidence intervals are included when reported in the studies' results.

The best evidence on actuarial overall survival is provided by the Palma et al. (2019) RCT that reported OS of 86% and 70% with SABR and 86% and 70% with standard care. There is consistency between the results reported by Palma et al. (2019) and the rest of the evidence as the 1-year OS rates in the rest of the literature ranged between 70-100%. The differences in the included population, study designs and treatment received, could account for the outliers. The results were less consistent for the 2-year OS rates with rates between 47-100%.

Results of comparative studies

Three retrospective case-control studies compared SABR with surgery (Filippi et al. 2016, Lodeweges et al. 2017, Lee et al. 2018) for pulmonary metastases. All three studies reported equivalent results between SABR and surgery (metastasectomy). It should be noted, however, that these were retrospective case-control studies with small sample sizes and without estimated sample size calculations. The SABR cohorts included in these studies usually had more adverse prognostic factors such as having larger tumours and higher incidence of synchronous extra-pulmonary disease (Lee et al. 2018), being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval (Lodeweges et al. 2017). Two of the studies (Filippi et al. 2016, Lodeweges et al.

2017), used propensity scoring to account for the differences between SABR and the comparator.

The overall survival achieved with SABR reported from these studies is comparable to those of the largest international retrospective pulmonary metastasectomy analysis, according to which the 1- and 2-year survival rates for complete resection were approximately 85% and 70%, respectively (Pastorino et al. 1997). More recent studies have confirmed similar findings (Onaitis et al. 2009).

Local control

Ten of the included studies provided results on local control. Table 26 lists all studies that reported LC and Figure 9 shows the 1- and 2-year LC rates achieved with SABR for these studies. With the exception of the (Andratschke et al. 2018) study, which reported a 1-year LC of 76%, the rest of the studies reported values of 80-97%. In (Andratschke et al. 2018) the authors report a number of reasons for the relatively low LC in comparison with other studies, such as the recruitment of patients over almost two decades starting from the late 1990s, and the fact that some patients received low BED (which has been consistently associated with poor LC across the studies). Indeed, based on Andratschke et al's. 2018 subgroup analysis, the size of the lesion and the BED affected LC, and patients treated after 2003 had a better LC than patients treated in earlier years.

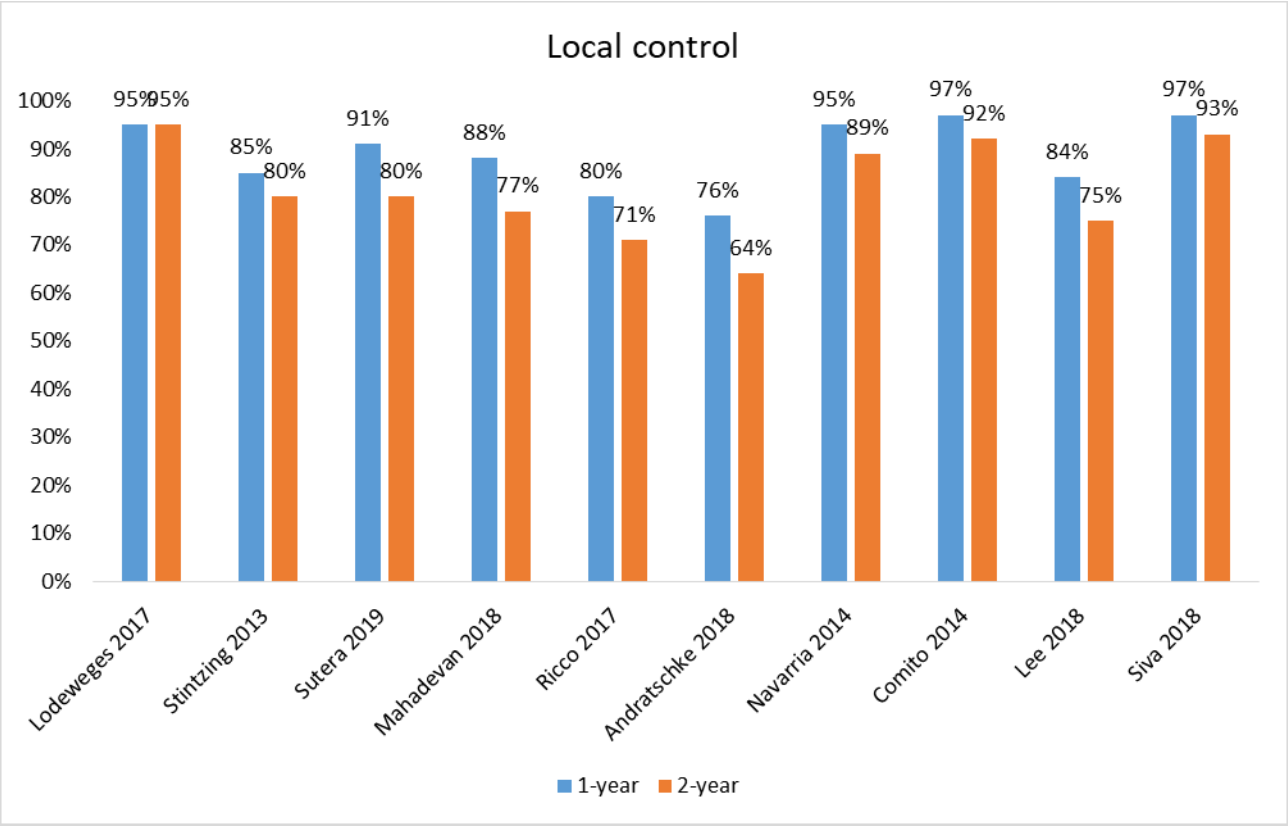

Figure 9: 1- and 2-year LC rates with SABR. When studies reported separate outcomes between radical and palliative radiotherapy doses the results for the high BED only have been included in the graph.

Results of comparative studies

Three studies were case-control studies comparing SABR with surgery for lung oligometastatic disease (Lodeweges et al. 2017, Lee et al. 2018) or RFA for liver lesions (Stintzing et al. 2013). In all three studies LC with SABR was not statistically significantly different to either surgery (Lodeweges et al. 2017, Lee et al. 2018) or RFA (Stintzing et al. 2013). However, all studies were retrospectively conducted with high risk of bias. Figure 10 shows the 1- and 2-year LC rates achieved with SABR versus surgery and RFA for these studies.

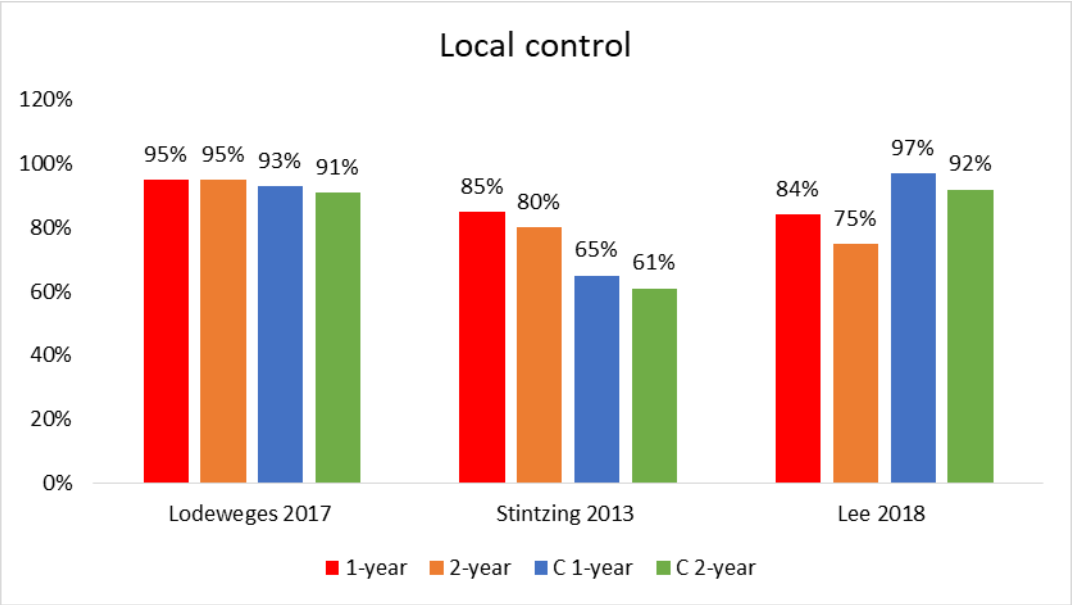

Figure 10: LC rates comparing SABR with surgery (Lee 2018, Lodeweges 2017) and RFA (Stintzing 2013). Red and orange columns show the 1- and 2-year LC achieved with SABR, respectively. Blue and green columns show the 1- and 2-year LC rates achieved with the comparator.

Effect of lesion size

In (Lodeweges et al. 2017) lesion size did not influence LC (HR =1.03, 95% CI 0.73- 1.45). However, overall the study included small lesions with a mean size of 1.9 cm. In studies including lesions with higher size variability such as (Ricco et al. 2017, Andratschke et al. 2018, Mahadevan et al. 2018) LC was better for tumours of smaller size.

Effect of dose

With the exception of (Navarria et al. 2014) a number of studies reported subgroup analyses which confirmed the impact of dose on LC. It should be noted, however, that in (Navarria et al. 2014) the authors used high radiotherapy doses (BED10 dose >100Gy) to treat all metastases resulting in very homogenous cohort that is difficult to separate with subgroup analysis based on dose.

Effect of primary histology

With the exception of (Andratschke et al. 2018), which found worse local control rates in patients with colorectal (CRC) metastases, all other studies that analysed results based on primary cancer diagnosis found no impact on LC of the histological type of disease (Ricco et al. 2017, Mahadevan et al. 2018). The above findings from the literature reflect the results

reported by a recent study (Guckenberger et al. 2016) that reported a strong association between dose and LC that was the similar between primary cancers and metastases.

Progression free survival

Ten of the included studies reported progression-free survival with SABR as a secondary outcome (please see Table 29). The studies used different definitions of progression depending on the histology, location of metastases and follow-up schedule, therefore, the results of PFS from the included studies are less reliable than those reported for OS and LC. One of the studies was an RCT (Palma et al. 2019), 5 were prospective non comparative cohorts (Kunos et al. 2012, Comito et al. 2014, Navarria et al. 2014, Siva et al. 2018, Sutera et al. 2019) and 4 were non-randomised comparative studies (Stintzing et al. 2013, Filippi et al. 2016, Lodeweges et al. 2017, Lee et al. 2018). The most significant evidence for this outcome is reported by Palma et al. (2019) with six months median PFS (95% CI 3·4-7·1 months) in the standard care group compared with 12 months (95% CI 6.9-30.4 months) in the SABR group (HR 0.47, 95% CI 0.30-0.76, p=0·0012). Although (Sutera et al. 2019) reported a lower median PFS of 8.7 months (95% CI 6.6-13.1) the 95% CI overlapped.

Quality of life

Five of the included studies reported quality of life (QoL) with SABR. Two of the studies were RCTs (Ost et al. 2018, Palma et al. 2019) and the rest were prospective non-comparative cohorts (Warren et al. 2017, Siva et al. 2018, Sutera et al. 2019).

With the exception of 1 study (Warren et al. 2017), all studies used cancer-specific questionnaires to assess quality of life. None of the studies reported a difference in QoL with SABR. More specifically, the RCT by Ost et al. (2018) found that QoL was similar at baseline and at 1-year post treatment, between patients with oligometastases from prostate cancer treated with SABR and those who were receiving active surveillance. This is a significant finding for this patient population with relatively good prognosis, as one of the factors influencing treatment decisions is whether treatment will affect quality of life. A prospective cohort study also reached a similar conclusion in this patient cohort, with no significant changes observed between baseline and up to 2 years post treatment.

The RCT by Palma et al. (2019) also found no difference in QoL between patients treated with SABR and those receiving standard care at 6 months post treatment. Sutera et al.

(2019) reached the same conclusion for a similar patient population with no major differences in QoL between baseline and 9 months after treatment with SABR.

Finally, a prospective cohort study (Warren et al. 2017) reported the QoL changes in patients with liver metastases only using the generic tool EQ5D. The mean utility score remained stable between baseline and at 6 months post treatment.

Although two of the studies contributing evidence for QoL are RCTs the current evidence is weak as QoL was not an adequately powered outcome in any of the studies. This is easily demonstrated in the case of Sutera et al. (2019) where changes in QoL were significant at 6 and 12 months but not at 9 months, which questions the validity of the result. All authors have noted that the lack of changes in QoL indicates that SABR does not significantly adversely affect QoL. However, it is common for patients whose health and subsequently QoL deteriorates to be lost to follow-up, resulting in detection bias and inability to accurately measure QoL outside an adequately powered phase 3 RCT.

Quality of life was a secondary outcome in all studies, therefore, none of them was adequately powered to detect a difference either from baseline or vs. a comparator (standard care or active surveillance). With the exception of (Siva et al. 2018) who reported QoL results for up to 2 years after treatment, the other studies captured only a relatively short post-treatment interval potentially failing to capture the effect of late toxicity on QoL. For some of the subgroups active surveillance is a common treatment strategy (such as with patients with prostate cancer) because of relatively good prognosis; one of the factors weighting in treatment decisions is whether treatment will affect their QoL. Unfortunately, the current literature cannot provide conclusive answers for this outcome.

6.2.5 Evidence on safety

Fourteen of the included studies provided results on toxicity. Two studies were RCTs (Ost et al. 2018, Palma et al. 2019), three studies were case-control studies comparing SABR with surgery for lung oligometastatic disease (Lodeweges et al. 2017, Lee et al. 2018) or RFA for liver lesions (Stintzing et al. 2013). The rest of the studies were non-comparative cohorts (Kunos et al. 2012, Comito et al. 2014, Navarria et al. 2014, Warren et al. 2017, Siva et al. 2018, Sutera et al. 2019) and registries (Ricco et al. 2017, Andratschke et al. 2018,

Mahadevan et al. 2018). Almost all studies used the CTCAE[18] criteria to record toxicity information. However, often the reporting was poor, failing to distinguish between acute and chronic toxicity. Table 27 shows the toxicity rates reported for SABR in these studies.

The 3 deaths reported in Palma et al. (2019) that were attributed to SABR were in 2 patients treated for pulmonary metastases and 1 patient treated for an adrenal metastasis. The first patient, had a prior non-small cell lung cancer (NSCLC) and a history of chronic kidney disease, and underwent SABR for two lung lesions and a liver lesion. All 3 lesions were treated within the expected normal tissue tolerance, meaning that they received a radiation dose that has low risk to cause toxicity. The patient developed symptoms of severe pneumonitis 2 months after SABR that did not respond to treatment and the patient died in hospital. The second patient with pulmonary metastases was treated for a single lung lesion. All normal tissue doses were within tolerance. Approximately 1 year later, he developed dyspnoea and left-sided chest pain, and was found to have a large pulmonary abscess at the treated location. Scans also showed widespread progressive disease. The patient was started on antibiotics but declined further treatment, and died in hospital. The third patient, was treated for an adrenal metastasis from colon cancer with a background history of Crohn's disease. The risk of gastrointestinal injury from SABR was high and discussed with the patient, and for that reason the gastric radiation dose was kept to a minimum. Several months after SABR, the patient was started on steroids for base of tongue swelling that proved benign. Shortly after starting steroids, the patient developed a perforated gastric ulcer requiring urgent operative intervention. Intra-operatively, the surgeon noted that the perforation occurred in the posterior gastric wall near the adrenal gland in an area of fibrosis, which corresponded to the area of treatment. In the post-operative period, the patient experienced an acute-on-chronic subdural haemorrhage and died (Palma et al. 2019).

With the exception of the SABR-COMET RCT (Palma et al. 2019) no other study reported Grade 5 toxicity with SABR. On the contrary, all previous studies reported a favourable toxicity profile with SABR in patients with oligometastatic disease with no Grade 4 and

[18] The CTCAE (Common Terminology Criteria for Adverse Events) criteria are a set of standardised criteria used to classify toxicity when a patient is undergoing anticancer treatment.

Grade 5 acute and chronic toxicity and very low rates of Grade 3 events. This finding highlights the significance of adherence to follow-up and avoiding bias during the collection of toxicity information. For example in all registry studies the retrospective data collection resulted in under-reported toxicity rates as noted by the authors of those studies. In the case control studies, patients who received different interventions had different follow-up schedules and often different toxicity profiles (Lee et al. 2018).

In the case of the second RCT by Ost et al. (2018), there were only 6 cases (17%) of G1 toxicity with metastasis-directed treatment. After removing the few cases treated with surgery, there were only two (8%) incidents of SABR-related toxicity, one associated with acute loose stools, and one with acute muscle soreness. No G2 or G5 toxicity was observed. The toxicity for all cases was well documented and assessed in the metastasis-directed treatment group without any patients lost to follow-up.

Treatment-related toxicity was a secondary outcome in all studies, therefore, none of them was adequately powered to detect a difference compared with a comparator (standard care, active surveillance, surgery, RFA). Evidence for an increase in severe toxicity with SABR is provided by the Palma et al. (2019) RCT that reported grade 5 deaths (4.5%, 95% CI 0-10%) with SABR but not with standard care. There is however, inconsistency between the results reported by Palma et al. (2019) and the rest of the evidence as no other study has reported grade 5 deaths with SABR. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care (Palma et al. 2019) and active surveillance (Ost et al. 2018) the impact of severe toxicity is clinically very important. The inconsistency between the toxicity results reported in Palma et al. (2019) and the rest of the literature, in combination with toxicity being measured as a secondary outcome in all studies results in low quality evidence for this outcome.

6.2.6 Subgroup analyses

It is not possible from the current evidence to discern any subgroups of patients who may benefit from SABR more than the wider population. There is weak evidence that local control with SABR is dependent on the size of the tumour and administered dose rather than primary tumour histology. Further research should assess the overall survival benefits for tumour-specific groups in adequately powered phase 3 trials.

6.3 Conclusions

Seventeen studies provide evidence relevant to the scope of this review. All evidence results described above are for an adult population. There is good quality evidence that SABR significantly increases median overall survival in comparison with standard care in patients with extracranial oligometastases in various locations. There is also moderate quality evidence that SABR results in local control and low quality of evidence that the result achieved with SABR is similar to that achieved by surgery (for pulmonary oligometastases) or RFA (for liver oligometastases).

Low quality evidence suggests that SABR may be linked to severe toxicity. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care and active surveillance, the impact of severe toxicity is clinically very important and should be investigated further in future studies and using real world data.

There is low quality evidence suggesting that the QoL after SABR treatment is equivalent to that experienced by patients receiving standard care or active surveillance. Literature addressing QoL focused particularly on patients with prostate cancer, who have a relatively good prognosis. One of the factors influencing treatment decisions is whether treatment will affect patients' QoL; therefore this outcome is clinically important and should be investigated further in future studies.

The main limitation of the evidence is that with the exception of the RCT by Palma et al. (2019) most studies were non-comparative and so cannot inform the clinical efficacy and safety of SABR versus comparators. In addition, most studies had a relatively short follow-up schedule. Although a short follow-up duration is appropriate for studying cancers with poor prognoses, in the case of oligometastatic disease is not appropriate and it can bias the reported survival analysis. The 4 retrospective case-control comparative studies have high risk of bias for patient selection and detection and are underpowered to detect differences between the two cohorts. Although some studies reported subgroup analysis, the low numbers of patients and the high risk of bias do not allow robust conclusions to be drawn.

The main implication from the available evidence is that the use of SABR in patients with controlled primary tumours and one to five oligometastases may lead to an increase of approximately 13 months in overall survival, with a doubling of progression-free survival.

The inconsistency between the reported toxicity results in the literature does not allow robust conclusions about the safety of SABR compared to standard care or other comparators.

In the future, phase 3 trials are needed to confirm the benefit in overall survival in comparison with other metastases-directed treatments such as surgery and RFA, to determine whether tumour sub-groups derive differing levels of benefit, to define the maximum number of metastases and to investigate the impact of SABR on toxicity and QoL.

7 Discussion

7.1 Summary of findings from primary data collection (CtE registry)

Between 2015 and 2018, the CtE registry collected outcomes from 1422 patients with oligometastatic disease recruited from 17 centres nationally. The median age of patients was 69 years, and most (66.6%) were men and had good performance status. The cohort was mainly comprised of prostate (28.6%) and colorectal patients (27.9%) and most of the patients had a solitary lesion of either nodal metastasis (31.3%) or lung metastasis (29.3%).

The analysis of people treated under the CtE scheme reported median OS >24 months. The data analysis reported OS for patients with oligometastatic disease of 92.3% (95% CI: 90.5 to 93.9%) at 1 year and 79.2% at 2 years (95% CI: 76.0 to 82.1%). Both results were higher than the actuarial survival targets set at the beginning of the SABR CtE scheme (1-year target = 70%, 2-year target = 50%). However, it should be noted that for the 70% target it was assumed that the CtE cohort would include a small percentage of patients with breast and prostate oligometastatic disease. Although this was the case for breast cancer (5.5%), the CtE included a larger than estimated proportion of people with prostate cancer (28.6%), the highest for the whole cohort. Histology-based analysis of the CtE data provides further information on the possible impact of primary tumour histology with the 2-year OS ranging from 33.5% for oesophageal cancer to 94.6% for prostate cancer. There is additional evidence from the literature that the 1- and 2-year disease-specific survival for patients with prostate oligometastatic disease is 100% (Ost et al., 2018). This can potentially have skewed the results towards a higher than anticipated OS.

The CtE data analysis also reported a LC rate for oligometastatic patients of 86.9% (95% CI: 84.6 to 88.9%) at 1 year and 72.3% (95% CI: 68.7 to 75.6%) at 2 years. Although the 2nd year LC rate was within range of the target set (2-year target = 70%) the first year LC rate was lower (1-year target = 90%). The results for LC reported by the CtE scheme are in the lower range as compared with the rest of the published literature. Contrary, to the rest of the studies, the CtE has not used RECIST to calculate LC, therefore, the results are not easily comparable.

The CtE data analysis reported grade 3 toxicity of 5.8% (95% CI: 4.7 to 7.2%) lower than the target set of 10%. It also reported grade 4 toxicity of 1.8% (95 % CI: 1.2 to 2.7%) within the target of 5% set originally. It should also be noted that the majority of grade 4 events were related to increased levels of blood biomarkers associated with liver toxicity, the alanine aminotransferase (ALT) and bilirubin. Both these biomarkers are indicators of liver damage and can increase not only because of treatment toxicity but also as a result of disease progression and abnormal liver function due to chemotherapy and other comorbidities. In addition, it is unknown if those events resulted in meaningful clinical toxicity for these patients. The results for adverse events reported by the CtE cohort are consistent with most of the published literature. The exception being the high incidence of grade 5 toxicity reported by the SABR-COMET RCT (4.5%) as a secondary outcome measure. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of OS achieved with standard care and active surveillance, the impact of severe toxicity is clinically important and should be investigated further in future studies and using real world data.

Finally, the analysis of the CtE data showed absence of severe toxicity with SABR confirming the results in the literature.

7.2 Results in the context of other studies

A literature review was performed to retrieve published evidence for patients undergoing SABR for extracranial oligometastatic disease. Seventeen studies provided evidence relevant to the scope of the CtE scheme. All evidence results described were for an adult population. Two RCTs SABR-COMET and Ost et al. 2018 provided evidence on the efficacy and safety of SABR in comparison with standard care and active surveillance, respectively. Four retrospective case-control studies provided evidence on the efficacy and safety of SABR in

comparison with surgery (3 studies) and RFA (1 study). The rest of the studies were non-comparative.

The findings of the CtE scheme on the effect of SABR in OS of patients with extracranial oligometastatic disease is supported by good quality evidence from the literature. The main evidence comes from the SABR-COMET phase II RCT (Palma et al., 2019) which included a similar cohort to the CtE scheme and compared SABR with standard care. The study concluded that the use of SABR in patients with controlled primary tumours and up to 5 oligometastases leads to an increase of approximately 13 months in OS (median OS = 41 months, 1-year OS of 86% and 2-year OS of 70%), with a doubling of PFS. The SABR-COMET RCT was adequately powered to detect a difference in OS between SABR and standard care, however, it was designed as a phase II RCT (Palma et al. 2019) requiring a confirmatory phase III study to demonstrate if the OS advantage is true. The combined findings from the published literature and the CtE provide good quality evidence that SABR significantly increases overall survival in comparison with standard care in patients with extracranial oligometastases in various locations.

With the exception of one retrospective registry analysis (Andratschke et al. 2018) study, which reported a 1-year and 2-year LC of 76% and 64% respectively, the rest of the studies reported values of 83-97% (1-year) and 71%-95% (2-years). A number of factors such as the variability in study design, lesion size and total BED delivered can affect local control and this partially can explain the variability in the observed LC rates. The CtE data analysis reported a LC rate within range of the available literature for oligometastatic patients of (86.9% at 1 year and 72.3% at 2 years). It is difficult to draw more specific conclusions about the comparability between the CtE analysis and the published evidence given the variability in study design. It is also not possible to draw robust conclusion about the comparability of the SABR CtE findings with the four retrospective case-control studies that compare SABR with surgery and RFA. As a result, the combined findings from the published literature and the CtE provide moderate quality evidence that SABR achieves high LC rates. There is further low-quality evidence from the published literature only, that the LC achieved with SABR is equivalent to that achieved by surgery (for pulmonary oligometastases) or radio frequency ablation (RFA; for liver oligometastases).

A high number of published studies (14 studies) provided results on toxicity as a secondary outcome. Almost all studies used the CTCAE criteria to record toxicity information. However,

often the reporting was poor, failing to distinguish between acute and chronic toxicity. For example in all registry studies the retrospective data collection resulted in under-reported toxicity rates as noted by the authors of those studies. In the case control studies, patients who received different interventions had different follow-up schedules and often different toxicity profiles (Lee et al. 2018). With the exception of the SABR-COMET RCT (Palma et al. 2019) severe toxicity with SABR in the published literature was low and absence of grade 5 events was noted by all authors. The SABR-COMET reported higher toxicity with SABR, and specifically grade 5 deaths (4.5%, 95% CI 0-10%) with SABR but not with standard care. The CtE analysis is consistent with the majority of the literature with low grade 3 and 4 toxicity and absence of grade 5 toxicity.

The main source of evidence for the effect of SABR on PFS is the published literature as the CtE did not report PFS results. The included studies used different definitions of progression depending on the histology, location of metastases and follow-up schedule, therefore, the existing PFS evidence are less reliable than those reported for OS and LC. The most significant evidence for this outcome is reported by Palma et al. (2019) with six months median PFS (95% CI 3·4-7·1 months) in the standard care group compared with 12 months (95% CI 6.9-30.4 months) in the SABR group (HR 0.47, 95% CI 0.30-0.76, p=0·0012). The positive effect of SABR on PFS will need to be verified with an adequately powered phase III RCT.

There is absence of outcomes in children in the published literature.

7.3 Strengths and limitations

7.3.1 Strengths of available evidence

The CtE registry had several strengths. Firstly, the scheme prospectively recruited and analysed the largest contemporary cohort of patients with extracranial oligometastatic disease. These patients were all recruited and treated in the NHS, bridging a gap in the literature for available evidence from a UK setting. Patients recruited into the CtE scheme were assessed for eligibility by a MDT team making sure that both clinical eligibility criteria but also technical feasibility aspects of the treatment were meet. All centres taking part to the scheme had to undergo intervention a nationally assured training system for SABR treatment, ensuring not only consistency of the intervention across in a multicentre setting

but also potentially increasing safety. In addition, patients in the registry were linked to HES and ONS data, which provided a method to triangulate the mortality event rates, minimising detection outcomes and uncertainty.

7.3.2 Limitations of available evidence

Most of the published evidence including the CtE come from non-comparative studies. The exception to this is the SABR-COMET RCT that compared SABR to standard care and 4 retrospective case-control studies that compared SABR with surgery and RFA. The combination of the SABR-COMET RCT and CtE data allows to draw some conclusions about the efficacy and safety of SABR compared to standard care. Contrary to standard care used in the control arm in SABR-COMET that was given with a palliative intent (chemotherapy or palliative radiotherapy), surgery, and RFA are performed with an intent to eradicate the disease locally similar to SABR.

The low reporting quality of most of these 4 retrospective comparative studies, the high degree of variability (study design and reporting) among them, and the absence of long-term follow-up means that evaluation of the CtE results with these published data is limited. All comparisons between the CtE outcomes and published data on use of surgery and RFA to treat patients with oligometastatic disease should be considered low quality and subject to considerable uncertainty. As a result, no robust conclusions can be reached about the efficacy and safety of SABR against surgery or RFA.

Other limitations with the registry include the following:

- The CtE only had a maximum of two years follow-up. As the SABR-COMET RCT showed patients receiving standard care have a median OS of 28 months. As a result, 2 years of follow-up does not allow the evaluation of long-term safety of and efficacy of SABR.
- The CtE included patients with multiple cancer types, however, often outcomes such as OS are influenced by the tumour's primary histology. Histology-based analysis of the CtE data provides further information on the possible impact of primary tumour histology with the 2-year OS ranging from 33.5% for oesophageal cancer to 94.6% for prostate cancer.
- It was not possible to ascertain if patients received further treatment after SABR as patients were often treated at other centres during the follow-up period.

- The Kaplan-Meier analysis assumed that there was "no event" unless an event was recorded (for example death). As a result, the analysis relies on data completeness. Events cannot be accounted for patients who are lost to follow-up and we know from the providers' feedback that patients are often lost to follow-up because they become sicker due to disease progression. This increased the risk of detection bias within the CtE analysis. For OS this limitation is mitigated using HES and ONS databases for data triangulation (see strengths above).
- For LC the CtE adopted a qualitative reporting method that was based on the absence or presence of any progression without using objective size measurements. This limits the generalisability of the results and introduces potential detection bias.
- The analysis of the adverse events results does not take into account the timing of the event it is therefore, not possible to separate between acute and late toxicity.

8 Answers to the CtE Questions

The following table (Table 30) contains KiTEC's response to the evaluation questions (based on Version 6.3, updated 22 December 2015)

Table 30: NHS England/NICE CtE Evaluation Questions

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
What is the 1-year and 2-year survival following treatment with SABR for the indications covered by the CtE scheme (presented as estimates with confidence intervals)? How do these survival estimates compare with the target outcomes, in terms of superiority or non-inferiority?	**Target:** OS rate of 70% at 1-year and 50% at 2-years with SABR. These estimates take into account both findings reported in the literature (average OS of 80% at 1-year and 60% at 2-years), and the imminent exclusion of breast and prostate patients from CtE (who have the best reported OS) as a result of the opening of the CORE trial.	The CtE data analysis reported OS results for patients with oligometastatic disease of 92.3% (95% CI: 90.5 to 93.9%) at 1 year and 79.2% at 2 years (95% CI: 76.0 to 82.1%). The 95% confidence interval for the CtE data is entirely above the actuarial survival targets set at the beginning of the CtE scheme (1-year target = 70%, 2-year target = 50%). However, it should be noted that for the 70% target it was assumed that the CtE cohort would include a small percentage of patients with breast and prostate oligometastatic disease. Although this was the case for breast cancer (5.5%), the CtE

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
		scheme included a large proportion of men with prostate cancer (28.6%), the largest group in the whole cohort. There is evidence from the literature that the 1- and 2-year disease specific survival for patients with prostate oligometastases is 100% (Ost et al. 2018). In addition, the majority of the CtE patients had solitary metastases and good performance status, both variables associated with good prognosis that may have contributed to the high OS rates. The findings of the CtE scheme on the effect of SABR in OS of patients with extracranial oligometastatic disease is supported by good quality evidence from the literature.
Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?	**Target:** A 1-year rate of 90% and 2-year of 70%. These estimates take into account	The CtE data analysis reported a LC rate of 86.9% (95% CI: 84.6 to 88.9%) at 1 year and 72.3% (95% CI: 68.7 to 75.6%) at 2 years.

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
	both findings reported in the literature, and clinical experts' consensus.	The CtE data confidence interval does not contain the target one-year local control rate of 90%, however, the CtE data confidence interval contains the target two-year local control rate of 70%. The results for LC reported by the CtE scheme are at the lower end of the range reported in the literature. Contrary, to the rest of the studies, the CtE scheme has not used RECIST to calculate LC, therefore, the results are not easily comparable.
What Adverse Events occur as a result of SABR in the CtE cohort of patients?	**Target:** Based on the published evidence and the accreditation scheme for all the NHS Trusts included in the CtE scheme, a target outcome rate for grade 3 toxicity of 10% and for grade 4-5 toxicity of ≤5% was proposed.	The CtE data analysis reported grade 3 toxicity of 5.8% (95% CI: 4.7 to 7.2%) within the target set of 10%. It also reported grade 4-5 toxicity of 1.8% (95% CI: 1.2 to 2.7%) within the target of 5%. No grade 5 toxicity was reported. The majority of grade 4 events were related to increased levels of

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
		alanine aminotransferase and bilirubin levels and it is therefore, unknown if they resulted in clinically meaningful grade 4 toxicity. The results for adverse events reported by the CtE cohort are consistent with most of the published literature. The exception being the high incidence of grade 5 toxicity reported by the SABR-COMET RCT (4.5%) as a secondary outcome measure. This finding is highly inconsistent with the previous literature on SABR that has not suggested an increase in severe adverse events especially grade 5 deaths.
What is the patient experience of treatment with SABR for the clinical indications covered within the CtE programme? The 'friends and family test' (https://www.england.nhs.uk/ourwork/pe/fft/),	NA	KiTEC report that 93% of CtE patients with oligometastatic disease, would be extremely likely/likely to recommend the SABR service to friends and family if they needed similar care or treatment.

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
a short generic instrument, designed to provide some patient experience feedback will be used to collect information for all SABR patients. This test has been widely used in the NHS.		
What is the cost-effectiveness of providing SABR in three subgroups of patients covered within the CtE scheme (Oligometastases (liver), Re-irradiation (Pelvis) & Hepatocellular carcinoma)? Cost-effectiveness will be assessed using a Markov model to synthesise evidence on SABR and from literature on relevant comparators over the time horizons specified. The Markov model will model the following four health states for SABR and comparators: • Progression free survival • Local progression	The following subgroup of patients and comparators were selected: Population: liver oligometastases Comparators: ○ surgery ○ radiofrequency ablation Time horizon: 5 years	This analysis found that for adult patients with borderline resectable liver oligometastases who may be candidates for surgery, SABR results in more QALY gains and lower cost compared to surgery. This finding assumes that SABR and surgery lead to similar overall survival and local control over the duration of the analysis. There is some evidence to support this. Data from the CtE cohort indicates lower overall survival and local control rates with SABR when compared to published data on resection, and application of this data leads to the inference that resection is the most

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
• Systemic progression • Death • Data for survival will be obtained from the SABR dataset and literature for comparators. In the absence of literature estimates distinguishing local and systemic progression, the health states will be combined. • Utilities will be estimated from the EQ5D of the SABR dataset and from literature for the comparators.		cost-effective intervention. However, such inference must be treated with caution. Most of the SABR cohort would not have been considered candidates for surgery and hence comparison of survival with patients undergoing resection is potentially compromised. We sought the best available evidence on survival and local control after surgery for liver oligometastases, however these data probably reflect outcomes in a patient group with better prognosis than the CtE cohort. Our analysis indicates a potential for SABR to be cost-effective. This will depend on SABR achieving similar local control and overall survival rates to surgery or RFA. A randomised trial may be required to demonstrate such equivalence.

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
What are the outcomes by indication in the CtE cohort of patients?	The cohort can potentially be stratified based on the location or histology of metastasis treated.	Histology-based analysis of the CtE data provides further information on the possible impact of primary tumour histology with the 2-year OS ranging from 33.5% for oesophageal cancer to 94.6% for prostate cancer. High OS was also reported for patients with colorectal and renal cancer.
Are there any factors from the experience of provision within centres participating in the scheme that should be taken into account in terms of future service provision?	NA	The providers' feedback reported that according to their experience, the programme was successfully implemented in their NHS Trusts, however, the centres noted the possible future need to expand the programme in order to cover demand.
Are there any research findings that have become available during the course of the CtE scheme that should be considered alongside the evaluative findings of the CtE scheme?	There are 3 prospective RCTs that will inform and potentially revise the target outcomes. These are:	The SABR-COMET and STOMP RCTs have now been published in full. The phase II SABR-COMET RCT reported a median overall survival of 41 months (95% CI 26-not

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
	○ The CORE trial (Aitken, K., M. Ahmed, M. Hawkins, et al. (2014). "A trial in design: CORE Conventional Care or Radioablation in the treatment of Extracranial metastases." Lung Cancer 83: S79.) ○ The STOMP trial (Decaestecker, K., G. De Meerleer, F. Ameye, et al. (2014). "Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): Study protocol for a randomized phase II trial." BMC Cancer 14(1).) and ○ The SABR-COMET trial (Palma, D. A., C. J. Haasbeek, G. B. Rodrigues, et al. (2012).	reached) and their finding is corroborated by a prospective cohort study by Sutera et al. (2019) with a median overall survival of 42.3 months (95% CI 27.4-not reached). Both studies recruited a cohort of patients that was recruited after 2010, resulting in comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various metastases locations, matching well with the population treated as part of the CtE scheme. The SABR-COMET RCT provides evidence for the superiority of SABR against standard of care, which includes palliative radiotherapy and chemotherapy. SABR-COMET also reported evidence of grade 5 adverse events (deaths) in the SABR cohort. As the study was

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's Response
	"Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial." BMC Cancer 12: 305.) This is expected to report outcomes in 2017.	designed as a phase II RCT an adequately powered phase III RCT is needed to confirm the advantage of SABR on OS, PFS and LC. The CORE trial has completed recruitment in Feb 2019 but has not yet produced results.

9 Providers' feedback

Participating SABR centres gave feedback about their experiences of implementing SABR in the NHS as a part of the CtE scheme. Telephone interviews were held with available clinicians, radiographers, physicists and data managers at all 17 provider centres.

9.1 Questions

The following broad, open ended questions were provided as prompts (adapted from the NHS Improvement Lessons Learnt guide):

- What are your thoughts on how successful the project has been?
- What were the key elements that worked well?
- What were barriers to success?
- If the service is routinely commissioned by the NHS, what would be the key learning points?

The following topics of interest were also suggested as topics for feedback: resources, quality assurance (QA), eligibility criteria, consenting, referral, and follow up pathways, dose constraint issues, and impact on capacity.

9.2 Feedback

9.2.1 Thoughts on the success of the CtE implementation within the centre

All centres felt that the project had been successful from the clinical perspective, particularly in light of the relatively short timeframe. Some centres suggested that clinical evidence increasingly demonstrated the advantages of SABR and described the CtE scheme as a "lifeline" for patients who would otherwise have not had access to the treatment. The CtE scheme was seen as beneficial for centres who would otherwise have a low volume of patients for SABR as it provided the opportunity to build the necessary skills and experience within a national framework.

Centres noted that, in general, patients undergoing SABR treatment expressed high satisfaction and would be very likely to recommend the service.

9.2.2 Key elements that facilitated success

Centres mentioned a number of factors as key to the success of the CtE scheme.

Multidisciplinary team (MDT)

All 17 centres highlighted that establishing a strong, specialised multidisciplinary team (MDT) was paramount. The MDT was described as the "nucleus" of a successful service and especially important when setting up and treating new anatomical sites. The MDT should ideally comprise of the following staff:

- Clinical lead
- Clinicians - site specialist oncologists and radiologists
- Dedicated radiographers to provide input for treatment delivery
- Physicists to provide technical input for treatment planning
- Dosimetrists (usually a radiographer or clinical technologist)
- SABR administrative coordinator

The structure of the MDT varied amongst centres. Most centres recruited a larger number of site-specialised staff to carry out SABR treatment as a small part of their role, for example, the lung cancer team would treat lung sites, or the urological team would treat the pelvic area. If resources are available, another option would be to recruit a smaller number of staff where SABR is a significant, specialist part of the role. Future SABR centres may decide on having a more organ-based SABR team or a more SABR treatment-specific team, depending on resources available. Centres suggested that a smaller, dedicated team was likely to be optimal in most situations. A smaller MDT at the outset can build up strong expertise that can be rolled out in the longer term to adapt to developing the service. A smaller, more visible team may also help raise the profile of the service and help develop pathways that are more consistent.

Most centres mentioned that frequent MDT meetings were helpful and held these weekly or fortnightly. In practise, the SABR MDT meeting was sometimes added on to other tumour-specific MDT meetings, but many centres felt that the complexity of SABR would warrant a dedicated group. Many centres discussed the importance of having a dedicated SABR/MDT administrative coordinator to organise the meetings and the additional clinical workload.

MDTs were often mentioned as bringing unanticipated benefits, including closer working ties between the different professions. Centres saw the increased intra-professional discussion about

patient eligibility as an opportunity for learning and breaking communication silos. Some centres noted that the scheme had encouraged improvements in image review training for radiographers.

Radiotherapy Trial Quality Assurance (RTTQA) approval/input:

All centres felt that the RTTQA process was very useful for providing a forum for discussion and advice. The process provided an external peer review and support network that all centres described as beneficial. The accreditation given by the QA process was also viewed positively from the departmental perspective and provided confidence that service standards were being maintained. In addition, it promoted the standardisation of practice for a service with complicated clinical pathways, which in turn helped clinicians manage and distribute their workload.

Centres felt that any newly commissioned service would benefit from new sites having access to a centralised QA service for benchmarking and approval. One centre suggested the service would benefit from having dedicated physicists to contact with technique or patient related queries. Another centre suggested that if not nationally, a similar QA process could be developed regionally with centres working closely in their cancer networks. Another centre mentioned this could involve cascaded training provided by more experienced centres, or a mentoring system.

Local education and promotion

Centres stated that it was important that the SABR service was well promoted within its catchment area, that there was a straightforward path for referral and that eligibility criteria were well understood. The methods of promoting the service varied depending on the pre-existing networks between the SABR site and referring centres but all aimed to ensure that there was adequate engagement with referring centres. Some centres noted that they already had very active and close relationships within their referral network, and little additional engagement was necessary. Other centres highlighted that intensive relationship building was key to the success of the project – this included the SABR team visiting referring centres, carrying out presentations and open days, and sending updates and newsletters. Some centres noted that the referral pathway should be made as simple and efficient as possible, for example using electronic referrals, SABR specific referral proformas and a dedicated email account as keys to engage potential referral centres. Centres also recommended advertising the SABR service at site specific MDTs to make sure all eligible patients are considered.

9.2.3 Key challenges to success

Resourcing

Centres spoke about challenges procuring adequate hospital staff and equipment resource during the CtE scheme.

Almost all centres noted the need for dedicated radiologist input at the MDT, in particular for mark-up issues (for example for delineation of treatment field or fiducial marker insertion), and that this was often difficult to procure. If the service was covering oligometastases at different anatomical sites, and therefore required site-specialised radiologists, many centres said they struggled to identify and include specialised radiologists for the MDT. Centres often mentioned that, in general, clinicians would ask radiologists for advice on an ad hoc basis but were not always able to do so in a timely manner, which sometimes produced delays in the process. Radiology input was particularly crucial at the start of a new service when the MDT was relatively inexperienced, for example, in providing advice on determining the volume and outline of tumours. Centres noted that ongoing training and development of radiology capability would be necessary. As a specific example, the setting up of processes to insert fiducial markers was noted by two centres as a consideration for interventional radiology departments wishing to introduce liver as a new treatment site.

Centres noted that certain anatomical sites also required greater staff resource. A number of centres mentioned particular challenges with liver SABR, which was noted as being harder to image and more challenging to contour than many other sites. In addition, if there were no liver-specialist radiologists then clinician presence was required during treatments. One centre mentioned that their dosimetrist reported it took a long time to plan a liver SABR patient.

Centres described how resourcing requirements changed through the lifecycle of the service. Many centres mentioned that lack of resource (staff and equipment time) were primarily a challenge until the services were better established and staff gained enough experience to streamline processes. For example, one centre said that the mark-up (requiring input from two doctors) would often be a bottleneck in treatment. The centre stated that having a dedicated MDT coordinator and using electronic care pathways now helps manage this process much more efficiently. The centre also noted that initially doctors attended all treatment fractions, which was challenging to organise. With increased experience, the service now has a local on call site-specific clinician available rather than requiring a doctor in attendance during all fractions, with the caveat that this can be an issue with less common SABR sites such as liver. The centre also explained that initially, treatments were

carried out first thing in the morning, as this meant fewer distractions, but with more experience the centre is more confident treating throughout the day which has alleviated some logistical issues.

Centres noted that individual SABR treatments are typically longer than conventional radiotherapy, and that this impacted linear accelerator (linac) time, especially as SABR treatments often require extra imaging or discussions. Centres mentioned the need for cooperation and the need for strong relationships between the MDT and the radiotherapy service.

Some centres mentioned that they had encountered resource challenges with MRI access. One centre noted "we're lucky we have our own dedicated MRI. I don't know what other centres would do if they didn't have that facility. MRI capacity needs to be thought about".

Staff training

Some centres discussed the challenges of providing training for enough staff to the required standard, noting that ongoing SABR training would be required to maintain competency. One centre described the necessity to maintain a balance between having a small enough team to maintain competency and expertise and also have enough flexibility in the system that if demand for treatment grew or staff were depleted due to holiday or sickness it did not impact the service. This may be an ongoing issue if new SABR indications are introduced and staff need to build up experience treating them.

The complexity of planning for treatment of multi-metastatic disease

Planning for metastatic tumours was posited as a resource challenge. One centre said that planning techniques to treat multi-metastatic targets often had to be developed "on the fly" to meet the unique technical requirements of individual patients. Despite the significant time expenditure, some centres mentioned that the organ at risk constraints for multi target treatments often could not be met. The same centres said that while the efficiency of planning treatment for this patient group has improved over time, multi-metastatic disease continues to provide a significant challenge to the planning team and represent a significant increase in complexity when compared to single target treatments.

Consent form

A new consent form was developed once the CtE scheme had started. Some patients who had already commenced SABR treatment needed to be reconsented. Many centres expressed dissatisfaction that the consent process was not established at the start and that reconsenting

was resource heavy. Centres noted it would be helpful to have all paperwork and databases ready from the outset or a new scheme. Most centres expressed overall satisfaction with the final consent form, however some suggested that changes could be made to enhance its usability. Some centres expressed dissatisfaction with the form, explaining that the consent form is not well designed for patients or staff, recommending that the design of the form would benefit from input from a consent writing workshop or patient information group.

Database

Some centres reported challenges with using the SABR CtE database recommending amendments, including the following:

- One centre noted an inability to record patients who are no longer appropriate for follow ups, for example, having gone to palliative care. It suggested an option for this in the database would be helpful to provide more detail.
- A centre mentioned there was a lack of choice for some of the systemic therapy options, suggesting it would be useful if there was an option to select 'other' and enter free text.
- One centre mentioned that a more comprehensive list of drugs would be helpful as the database only allowed a choice of certain drugs.
- A centre suggested that the following additions to the dashboard would be useful: the date that the follow up was carried out, highlighting areas with missing data, increasing drop down options for example, for the Gleason score (addition of 4+5 option) for prostate.
- One centre was concerned about the inability of the database to pick up significant toxicity.

Image transfer

Some centres mentioned that now the service is established (as part of the CtE scheme), the main barrier has been receiving all the necessary information and prior imaging for the referred patient. Centres suggested that having an efficient method of transferring this information, imaging in particular, would promote a successful service.

9.2.4 Feedback on other key topics

Inclusion criteria

All centres felt that the selection criteria were understandable but could be revised in light of new evidence. The following potential updates were suggested as examples:

- Some centres suggested that systemic treatment could be continued in addition to SABR treatment (the CtE eligibility criteria suggested that there should be no concomitant systemic treatment).
- Some clinicians mentioned there was evidence supporting the benefits of including synchronous metastases in future commissioning (as well as metachronous).
- Inclusion criteria could be further developed by considering efficacy and feasibility of SABR by disease site. The existence of a disease marker, for example in prostate or bowel cancer, was noted as helpful to enhance monitoring and therefore treatment effectiveness. One centre suggested the efficacy of SABR in breast cancer is more variable, however if the disease is restricted to a solitary node some clinicians suggested SABR would be effective. Some centres mentioned there may be a difference in efficacy between visceral versus bone metastases.
- Some centres suggested that it might be helpful to have some more information about lower size limits for tumours (in addition to the existing upper size limits in the criteria), explaining that in their experience, some metastases had been too small to treat (for example, due to difficulties with voluming).
- One centre suggested that if low volume metastases are commissioned then some clear guidelines would be needed on what would be considered a treatable number of lesions.

Most centres suggested expanding the indications from the CtE criteria as more evidence accumulates for the effectiveness of SABR.

Some centres suggested that disease definitions were not always clear within the CtE criteria but that these definitions are not well established more generally in the field. For example, some clinicians mentioned that the lack of clarity around definitions for re-irradiation or oligometastatic disease impacted referrals for SABR treatment. In oligometastatic disease, clinicians mentioned that there had been some uncertainty about the defined cut off of 3 metastases – whether this also includes oligoprogression. One centre explained it was unclear whether the cut off referred to 3 current metastases, or 3 metastases over a certain period of time. For example, the centre questioned that if a patient with colorectal cancer who had previously had successful surgery for primary and metastatic peritoneal disease then later developed a solitary lesion, it was unclear whether the multiple peritoneal metastases were considered as more than 3, therefore excluding the patient from SABR treatment.

Some centres strictly adhered to the inclusion criteria during the CtE scheme, and others built in some flexibility in terms of how criteria were applied to patients. For example, some centres noted that the definitions for radical treatment or oligoprogression were open to interpretation and therefore subject to debate at MDTs. Most centres agreed that if SABR was to be routinely commissioned it is important that some flexibility should be allowed for decision making on a patient-by-patient basis. One centre noted that an internal audit showed that concordance with the inclusion criteria increased over time.

Referral pathway

At most centres, eligibility was discussed at the tumour site MDT and patients were referred on to the dedicated SABR MDT which then made the final decision about whether to treat (the SABR MDT was described as the gatekeeper for the treatment). Other centres followed a different approach, promoting the SABR treatment more widely both within and outside the trust so individual oncologists and surgeons were able to refer a broader selection of potential patients to the dedicated SABR MDT. If SABR was routinely commissioned, one centre suggested that a patient centred approach should be used as the geography of different centres and the referral pathways for different disease types are likely to be varied.

Most centres agreed that ideally patients would be pre-screened at a tumour specific MDT before referring to the SABR MDT. Centres reported a highly variable rate of patient eligibility at the point of the SABR MDT meeting – from almost 100% to around half being considered eligible. This was often dependent on whether the patient had been pre-screened and how rigidly the eligibility criteria were adhered to.

Some centres discussed the use of a proforma developed by the SABR MDT. The proforma was provided to referring centres and tumour specific MDTs and was then populated and returned along with imaging. The proforma contained questions to gather information such as what treatment the patient had for the primary disease, when this was carried out, the number, and location of metastases, and patient performance status.

Follow up pathway

Most centres agreed that the follow up of patients as part of the CtE scheme was a resource-intensive undertaking. For centres with larger catchment areas this was more challenging as patients typically preferred not to travel back to the centre. Telephone follow ups were common, and centres reported that though these were preferred by patients, they varied in success. Centres felt that the

key to success was having strong administrative support to ensure patients were sent reminders, called on time or had their call rescheduled. In some places, follow up was carried out by the referring centre, in collaboration with the SABR centre.

One centre explained that if they wanted the patient to be followed up locally, they would send follow up criteria (using SABR consortium guidelines) which included a list of required investigations, along with a letter to the original carer. The nature of future (non-CtE) follow up depends on how a future service is commissioned and the level of detail required. Centres said follow up was an intensive process for the CtE scheme. If follow up was required with the same level of detail as CtE, centres felt this was a significant undertaking and would require additional funding.

Pathway standardisation

Most centres felt that some flexible standardisation of pathways would be helpful for clinical decision-making. One centre mentioned that standardisation may be particularly useful for patients with oligometastases. It expressed concern that this was a group of patients who would benefit from SABR treatment but may not be referred if inclusion criteria and tests to diagnose oligometastases are not well defined.

Dose constraint issues

All centres felt that they were able to meet the dose constraints in most cases. Centres reported that the constraints were reasonable but noted that occasional compromises needed to be made. The following specific anatomical areas of uncertainty were mentioned:

- The irradiation of the bladder (uncertainty over what alpha-beta ratio to use)
- Multiple lung metastases
- Bowel
- Heart

Centres described a number of tactics for compromise. One centre said: “During the planning, if we were exceeding a dose constraint we would either compromise the coverage, that was one tactic we had, or sometimes we would drop the dose slightly. Another tactic we had is sometimes we would change the fractionation. For example, for pelvic SABR cases, if they were re-irradiations and they'd had prior prostate radiotherapy it was almost impossible to meet the sacroplexus constraints”.

Some centres mentioned that it was helpful that the dose constraints were open to interpretation. One centre explained, for example, that in patients who had already received prostate radiotherapy, some may have already exceeded the tolerances allowed before SABR. It suggested that if dose

constraints were applied strictly in these situations then SABR would not be given to any patients who were due to be retreated. Flexibility must be built in so individual MDTs can discuss cases on a patient-by-patient basis.

Impact on capacity

Most centres said that capacity had not been a significant issue for them during the CtE scheme. For some centres it was because the SABR service had already been established (SABR was described as already being the standard of care for other indications). In other centres it was because the selection criteria were strictly adhered to and therefore a relatively low number of patients were treated. It was suggested that centres that had been more flexible with the criteria may have experienced more pressure on capacity.

Centres acknowledged that the patient numbers included in the CtE were not necessarily an indication of the numbers of patients who would be treated if the service was commissioned in the future. One centre noted that there were many patients who may have fulfilled the criteria for SABR but were not referred on and suggested that if the service becomes routinely available, the programme would need expanding to more centres to cope with the increase in referrals. Another centre noted that in any further roll out, the issue of service quality would be very important and that there may be a snowballing of consequences beyond treatment capacity.

Future with SABR

All centres felt that emerging evidence suggests that SABR will be suitable for a wider number of indications and will increasingly become part of standard of care. Commissioning SABR may result in a potential paradigm shift from a palliative to a radical treatment pathway. Centres noted that that this shift would profoundly affect pathways both before SABR treatment and at follow up. Some centres noted that a more effective curative treatment may heighten the need for more intensive screening programmes in patient groups such as breast and lung (as opposed to diseases with established biomarkers such as prostate cancer, for example, which already has an effective screening programme).

Centres agreed that follow up may become more intense with SABR. One centre noted that if the CtE inclusion criteria were widened then some indications may be considered palliative (such as oligoprogressive disease) and some radical. The centre suggested that follow up for people with oligoprogression may be easier due to the likelihood of patients also having systemic treatment. For

patients having treatment described as radical, there may be more uncertainty about follow-up time points and more collaboration required with the referring centre.

One centre noted that with the advance of imaging technology, surveillance is likely to become more routine and intensive regardless of the commissioning policy for SABR. Anecdotally they noted that the use of PET had increased with the use of SABR: "If you're going to subject someone to a more radical ablative treatment, be it surgery or radiotherapy, then people have more confidence it is oligometastatic if you do a PET".

Some centres suggested there may be wider cost implications of not treating with SABR. If SABR is shown to be effective, then the treatment may prevent the need for further treatment such as RFA or resection and costs entailed.

9.2.5 Key learning points

- **Staffing resource:** Centres stated it was crucial to have an adequately resourced, dedicated SABR team and this included a SABR administrative coordinator. Some centres suggested an optimal MDT structure (see sections about MDT and resourcing above).
- **Quality assurance:** Centres noted that it was extremely helpful to have contouring and planning approval via a centralised RTTQA but that it was also important to have local peer review of patient eligibility and treatment plans. Centres suggested that local cancer networks could work together to set up a peer review system. This may be especially important for oligometastases at less common anatomical sites and it may not be possible to have enough clinicians available locally to peer review.
- **Communication network:** The importance of setting up or reinforcing strong lines of communication between referral and treatment centres was noted. It was also important to ensure that site specific MDTs and external referral centres were aware of the SABR service and had an informed and simple process for referral (for example with a single centralised dedicated SABR service email account, and a good quality referral proforma).
- **Radiology:** Access to radiologists was vital. Many centres noted that radiology input was critical to MDT decision making, but was often difficult to procure. SABR would also entail training for radiologists for newer processes introduced by SABR.
- **Imaging transfer:** Centres often mentioned that not having timely access to imaging results could delay treatment. A smoothly running service would have an established process of obtaining scans from referring centres.

- **Managing resource implications over time:** The change in resource requirements over the life of a service was discussed. Noting the importance of a successful start to a project, centres stated that significant resource was required upfront in the designing and setting up phase.
- **Peripheral equipment:** Some centres noted that additional equipment may be required as the SABR service develops. In particular, centres mentioned access to/funding for MRI resources especially tailored to radiotherapy and not just standard diagnostic MRI. One centre was considering introducing fluoroscopy to improve their SABR service further.
- **National SABR rollout:** Many centres felt that the SABR service should be rolled out to more centres nationally, with the strong caveat that this needed a framework for training and support, and QA. Centres also noted that treatments are increasingly complex and specialised - any national rollout would need to consider this to ensure adequate efficacy and competence.

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10 Conclusions

The available evidence from the literature and the CtE data supports the use of SABR in adult patients with metachronous extracranial oligometastases (up to 4 metastases from the literature and 3 metastases from the CtE). There is evidence of clinically and statistically significant improvement in overall survival, progression free survival, and local control. These findings, however, will need to be confirmed by an adequately powered phase III RCT. A conclusion about the safety profile of SABR in this population is less clear as the majority of the evidence, including the CtE data analysis reported low levels of severe toxicity and absence of grade 5 toxicity. The exception to this is the high incidence of grade 5 toxicity reported by the SABR-COMET RCT (4.5%) as a secondary outcome measure. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care and active surveillance, the impact of severe toxicity is clinically important and should be investigated further in future studies and using real world data.

Because of the heterogeneity in treatment doses and schedules used, the optimal dose and fractionation of SABR, and the optimal number of lesions treatable with acceptable risk, remain unknown from the current evidence.

The cost-effectiveness analysis found that for adult patients with borderline resectable liver oligometastases who may be candidates for surgery, SABR results in more QALY gains and lower cost compared to surgery. This finding assumes that SABR and surgery lead to similar overall survival and local control over the duration of the analysis. Data from the CtE cohort indicates lower overall survival and local control rates with SABR when compared to published data on resection, and application of this data in sensitivity analysis leads to the inference that resection is the most cost-effective intervention. It should be noted however, that these studies usually recruited patients with better prognosis than studies with SABR. In the case of pulmonary metastases for example there is low quality evidence that SABR achieves equivalent results to surgery when the 2 groups have comparable characteristics. Therefore, inference from the sensitivity analysis must be treated with caution as most of the SABR cohort would not have been considered candidates for surgery and hence comparison of survival with patients undergoing resection is potentially compromised. The data indicate a potential for SABR to be cost-effective, if it can achieve similar survival to that achieved with surgery. Ultimately, a randomised trial would be required to provide robust evidence on the cost-effectiveness of SABR for patients with resectable liver oligometastases.

Finally, the providers' feedback reported that according to their experience, the programme was successfully implemented in their NHS Trusts, however, the centres noted the possible future need to expand the programme in order to cover demand.

11 Appendix A: Prisma flowchart

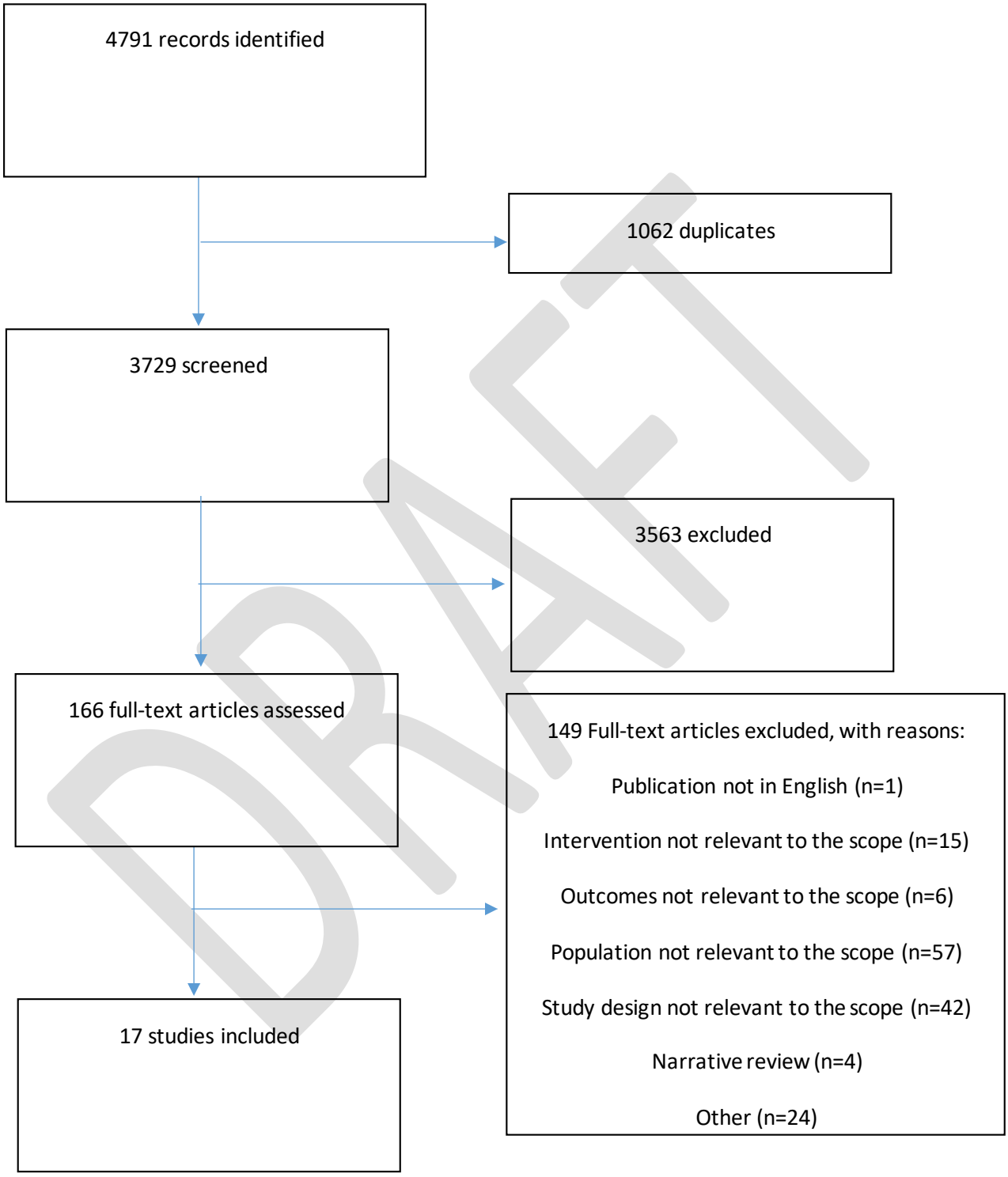


Figure 1: PRISMA table for oligometastases literature

12 Appendix B: Search strategies

12.1 Search strategy for clinical effectiveness, quality of life, and safety.

Total number of references: 4791

Total following de-duplication: 3729

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 07, 2019
- 8th March 2019

1	(((solitar* or isolate*) adj4 metasta*) or ((one or two or three or four or multi* or numerous) adj3 metastas*)).tw.	27584
2	(oligomet* or oligo-met* or oligo met*).tw.	1432
3	exp Neoplasm Metastasis/	191806
4	sc.fs.	151606
5	or/1-4	318046
6	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	11342
7	(arc therap* or vmat).tw.	2815
8	radiosurg*.tw.	11519
9	Radiosurgery/	13787
10	or/6-9	22504

11	5 and 10	4266
12	limit 11 to yr="2009 -Current"	3039
13	(editorial or letter or case report or comment or news).pt.	1880897
14	12 not 13	2920

- Embase 1974 to 2019 Week 09
- 8th March 2019

1	((solitar* or isolate*) adj4 metasta*).tw.	8954
2	(oligomet* or oligo-met* or oligo met*).tw.	2867
3	((one or two or three or four or multi* or numerous) adj3 metastas*).tw.	31647
4	or/1-3	41744
5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	20863
6	(arc therap* or vmat).tw.	7217
7	radiosurg*.tw.	17079
8	exp Radiosurgery/	61567
9	or/5-8	72601
10	4 and 9	3640

11	limit 10 to yr="2009 -Current"	3128
12	(editorial or letter or case report or comment or news or conference abstract or Conference Paper or Conference Review).pt.	5688078
13	11 not 12	1606

- Cochrane (CDSR and CENTRAL)
- 8th March 2019

ID	Search	Hits
#1	((solitar* or isolate*) NEAR/4 metasta*):ti,ab,kw	129
#2	(oligomet* or oligo-met* or oligo met*):ti,ab,kw	353
#3	((one or two or three or four or five or six or multi* or numerous) NEAR/3 metastas*):ti,ab,kw	2512
#4	[mh /SC]	3199
#5	(Pastorino et al. -#4)	5574
#6	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*):ti,ab,kw	975
#7	radiosurg*:ti,ab,kw	617
#8	[mh Radiosurgery]	196
#9	(arc therap* or vmat):ti,ab,kw	570
#10	(Franceschini et al. -#9)	1714
#11	#5 and #10 with Cochrane Library publication date from Jan 2009 to present	265

12.2 Search strategies for cost-effectiveness

- Embase 1974 to 2019 Week 16, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to April 22, 2019
- Search Date 23 April 2019

1. oligometastas?s.tw.

2. oligomet$.tw.

3. (solitary adj4 metastas?s).tw.

4. (isolated adj4 metastas?s).tw.

5. 1 or 2 or 3 or 4

6. Liver/ or Liver Diseases/

7. Liver.tw.

8. Liver Neoplasm.tw.

9. 6 or 7 or 8

10. RFA.tw.

11. radiofrequency ablation.tw.

12. surgery.tw.

13. General surgery/

14. SBRT.tw.

15. SABR.tw.

16. 10 or 11 or 12 or 13 or 14 or 15

17. 5 and 9 and 16

18. Survival Analysis/ or Survival/

19. (survival or progression-free survival or PFS or progression free survival or local control).tw.

20. (quality of life or QoL or EQ-5D or EQ5D or utilit$).tw.

21. (cost$ or economic$).tw.

22. (pain control or pain management or toxicity or patient experience).tw.

23. 18 or 19 or 20 or 21 or 22

24. 17 and 23

25. limit 24 to english language

26. limit 25 to yr="2016 -Current"

27. remove duplicates from 26

Following de-duplication : 255

13Appendix C: CtE analysis plan and data forms

13.1 Statistical Analysis Plan

As per SABR Data Analysis Protocol 17/02/2016 – Version 2.2:

Statistical Analysis

The statistical analysis will address the research questions set out in section 1.2. Descriptive statistics will be presented to characterise the patient populations. This will include demographic and clinical factors.

Estimates of the rates of overall survival and progression-free survival (local control) at 1 year and 2 years following treatment with SABR will be calculated using the Kaplan-Meier method, for each of the three included indications (oligometastatic disease, re-irradiation of pelvis/spine, and hepatocellular carcinoma). A measure of the precision of each estimate will be provided by 95% confidence intervals. Kaplan-Meier graphs will be presented for key outcomes.

Survival estimates will be compared narratively with the 'target outcomes' for each condition (i.e. not using statistical tests), since the target outcomes were informed by a mixture of relevant literature and expert opinion, and therefore there is no appropriate 'sampling error' which can be attributed to these outcomes (a requirement of statistical tests).

The number and percentage of adverse events following treatment with SABR will be presented with 95% confidence intervals, for each of the three indications.

The number and percentage of patients with a positive patient experience of SABR will be presented with 95% confidence intervals, for each of the three indications. Patient experience will be assessed using a single question: "How likely are you to recommend our SABR service to friends and family if they needed similar care or treatment?"

If numbers within subgroups suffice, the results of the above analyses for Oligometastases may be stratified by location or histology.

13.2 CtE monitoring forms- clinical data – initial

Initial clinical data set	
Patient number and initials	
Date of assessment	
Age at treatment	
Primary site	
Treatment for primary	
Date of primary treatment	
Number of metastases	
Site of metastases	
Tumour marker at baseline (if appropriate) and date	
Baseline imaging modality used	
Number of previous lines of systemic therapy (including hormone therapy)	
Current systemic therapy (may be none)	
Previous radiotherapy (date, site)	
WHO performance status at baseline	0 1 2
Relevant past medical history	
Treatment technique and method of image guidance	
Also to complete:	**CTCAE** (site-specific) **EQ-5D** **Visual analogue pain score** (if appropriate) **Radiotherapy planning details** (site-specific)

13.3 CtE monitoring forms- clinical data – follow-up

Follow-up clinical data set	
Patient number and initials	
Date of assessment	
Months after initial treatment	
Patient alive?	Y/N Date of death: Cause of death:
Performance status	
Tumour markers (if relevant)	Date: Value:
Imaging done?	Y/N Type: Date:
Local progression?	Y/N Date:
Distant progression?	Y/N Date: Site(s):
If distant progression, amenable to further SABR?	Y/N
Details of further SABR:	Date given: Site(s) treated:
Systemic therapy status (circle appropriate):	None Change/initiation (describe + date):
Also to complete:	**CTCAE** (site-specific) **EQ-5D** **Visual analogue pain score** (if appropriate)

13.4 Site-specific CTCAE toxicity scores: Toxicity A

Toxicity A: cervical spine, thorax, lung, mediastinum					
Patient number and initials:			Date:		
	1	2	3	4	5
Pericarditis	Assymptomatic clinical or ECG findings	Symptomatic pericarditis	Pericarditis with physiological consequences	Life-threatening consequences	Death
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic with altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
GI haemorrhage	Mild, intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Upper GI ulcer	Assymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-

Toxicity A: cervical spine, thorax, lung, mediastinum					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Fatigue	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

13.5 Site-specific CTCAE toxicity scores: Toxicity B

Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic region					
Patient number and initials:			Date:		
	1	2	3	4	5
Duodenal/ Gastric ulcer	Assymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic with altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
GI haemorrhage	Mild, intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Fatigue	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-

Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic region					
Fever	38.0-39.0 degrees	39.1-40.0	>40.0 degrees for <24 hours	>40.0 degrees for >24 hours	Death
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Liver enzymes: ALT	ULN- 3*ULN	3*ULN – 5*ULN	>5.0 - 20.0 x ULN; >5 x ULN for >2 weeks	>20 *ULN	Death
Bilirubin	ULN- 1.5* ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	

13.6 Site-specific CTCAE toxicity scores: Toxicity C

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
Patient number and initials:			Date:		
	1	2	3	4	5
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Haematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
			intervention indicated; limiting self care ADL		
Urinary frequency	present	Limiting instrumental ADL; medical management indicated	-	-	-
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Fatigue	Relieved by rest	Fatigue not relieved by rest;	Fatigue not relieved by rest, limiting self care ADL	-	-

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
		limiting instrumental ADL			
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

13.7 EQ-5D

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

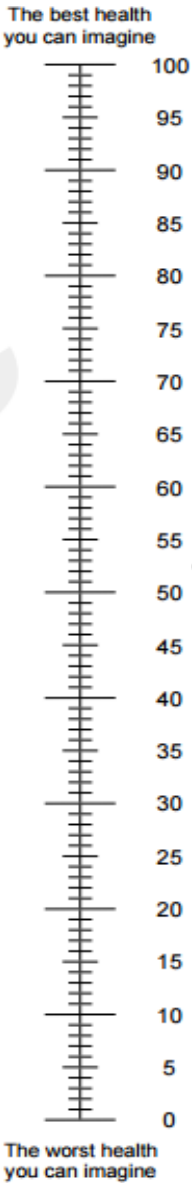
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

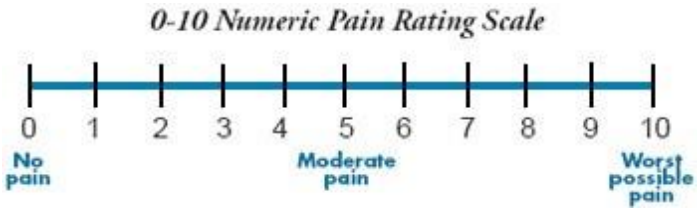
2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



13.8 Visual analogues pain score (Brief Pain Inventory)



STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

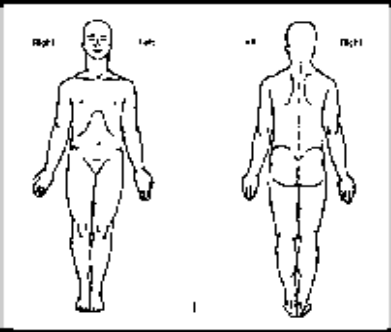
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

14 Appendix D: Data dictionary (UHB)

The following are extracts of the UHB PROPEL Data Dictionary as provided to KiTEC on the 11th January 2019 in MS-Excel spreadsheets. The spreadsheets consisted of: Time Points, Demographics, Clinical Assessment –Baseline, Clinical Assessment – Follow Up, CTCAE, CTCAE Defn, EQ-5D, Pain Score, Patient Experience, Radiotherapy Planning Details_1, Radiotherapy Planning Details_2, Radiotherapy Planning Details_3, and Death.

Please see the above methods and data quality sections for further descriptions of the UHB data dictionary.

TIME POINTS

Forms	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Demographics	√						
Clinical Assessment - Baseline	√						
Clinical Assessment - Follow Up	√	√	√	√	√	√	√
EQ-5D	√	√	√	√	√	√	√
CTCAE	√	√	√	√	√	√	√
Pain Score	√	√	√	√	√	√	√
Patient experience		√					
Radiotherapy planning details (Trt 1)	√						
Radiotherapy planning details (Trt 2)	√						
Radiotherapy planning details (Trt 3)	√						
Death		√	√	√	√	√	√

DEMOGRAPHICS

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
DEM_SITE	Site	number	drop down list of sites		√	
DEM_NN	NHS Number	text (10)			√	
DEM_INIT	Initials	text			√	
DEM_DOB	Date of birth	date			√	
DEM_GENDER	Gender	numeric	1-male 2-female		√	
DEM_ETH	Ethnicity	numeric	1-White - British 2-White-Irish 3-White-Any other white background 4-Mixed-White and Black Caribbean 5-Mixed-White and Black African 6-Mixed-White and Asian 7-Mixed-Any other mixed background 8-Asian or Asian British-Indian 9-Asian or Asian British-Pakistani 10-Asian or Asian British-Bangladeshi 11-Asian or Asian British-Any other Asian Background			Standard NHS ethnicity options

			12-Black or Black British-Caribbean 13-Black or Black British-African 14-Black or Black British-Any other Black background 15-Other Ethnic Groups-Chinese 16-Other Ethnic Groups - Any other ethnic group 17-Not stated			
DEM_CF	Consent Form	document			√	Consent form
DEM_CD	Consent Date	date		__/__/____	√	

Clinical Assessments - Baseline

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_DOA	Date of assessment	date			√	
CAB_IND	CtE Indication	numeric	1-oligomet 2-Hepatocellular carcinoma 3-re-irradiation		√	
CAB_REIR	Re-irradiation of primary or metastasis	numeric	1-primary 2-metastases	Required if CAB_IND (CtE Indication) is 3 (Re-irradiation)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_PS	Primary site	numeric	1-H&N (include thyroid) 2-lung cancer 3-breast cancer 4-prostate cancer 5-renal cancer 6-colonic cancer 7-oesophageal cancer 8-pancreatic cancer 9-gastrointestinal stromal tumour (GIST) 10-endometrial cancer 11-cervical cancer 12-melanoma 13-sarcoma 14-germ cell tumour 15-gastric cancer 16-bladder cancer 17-rectal cancer 18-anal cancer 19-upper tract (TCC)	Required if CAN_IND (CtE Indication)<>2 (Hepatocellular carcinoma)	√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			20-penile cancer 21-ovarian cancer 22-cholangio cancer 23-vulva cancer 24-urothelial cancer 25-HCC 26-lymphoma [HIDDEN] 27-other			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_OPS	Other primary site	text		Required if CAB_PS (primary site) is 27 (other)		
CAB_PSLAT	Primary site laterality	numeric	1-left 2-right 3-bilateral 4-central	Required if CAB_PS (primary site) is 1 (H&N) or 13 (sarcoma) or 2 (lung cancer) or 3 (breast cancer) or 5 (renal cancer) or 12 (melanoma) or 14 (germ cell tumour)		
CAB_REG	Primary site region	numeric	1-C-spine /Neck 2. Thorax 3-abdomen 4-pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_REIR (reirradiation...) is 1 (primary) and COB_PS (primary site) is 12 (melanoma) or 13 (sarcoma) or 14 (gem cell tumour) or 7 (oesophageal cancer) or 15 (gastric cancer) or 17 (rectal cancer) or 9 (GIST)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_CM_NO	Number of Co-morbidities	numeric	Range (0-6)		√	
	Primary treatment RFA: Radiofrequency ablation RT: Radiotherapy CRT: Chemo-radiation ADT : Androgen Deprivation Therapy Brachy: Brachytherapy HIFU: High intensity	numeric	1-surgery only 2-surgery+ systemic treatment 3-surgery+ radiotherapy 4-surgery + systemic treatment + radiotherapy 5-systemic treatment only 6-Radiotherapy only 7- Systemic Tx + Radiotherapy 8-primary RT [HIDDEN] 9-brachy 10-chemo only 11-RFA 12-ADT 13-ADT+RT 14-ADT+RT+brachy 15-active surveillance [HIDDEN] 16-cryoabalation 17-HIFU	Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	focused ultrasound Chemo: Chemotherapy		18-CRT: Chemoradiation			
CAB_DOPT	Date of primary treatment	date	date	Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		
CAB_NOM	Number of metastases	numeric		Range (1,2,3) Required if CAB_IND (CtE Indication) is 1 (oligomet) or CAB_REIR		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
				(reirradiation…) is 2 (metastases)		
CAB_TOM	Type of metastases	numeric	1-Synchronous 2-Metachronous			
CAB_TTM	Time to metastases (years)	numeric				Time from initial treatment to development of metastases
CAB_SOM_1	Site of 1st metastases	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [HIDDEN] 6-pelvic 7-liver 8-brain [HIDDEN] 9-nodes	Required if CAB_IND (CtE Indication) is 1 (oligomet) or CAB_REIR (reirradiation…) is 2 (metastases)		
CAB_SOM_1_LTYP	Type of 1st metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_SOM_1 (site of 1st metastases) is 1 (lung)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_ROM_1	Region of 1st metastases	numeric	1-C-spine/neck 2.-Thorax 3-abdomen 4-pelvis 5.-Upper limbs 6-Lower limbs	Required if CAB_SOM_1 (site of 1st metastases) is 2 (spine) or 3 (bone) or 9 (nodes)		
CAB_SOM_2	Site of 2nd metastases	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [HIDDEN] 6-pelvic 7-liver 8-brain [HIDDEN] 9-nodes	Required if CAB_NOM(Number of metastases) is two or three		
CAB_SOM_2_LTYP	Type of 2nd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_SOM_2 (site of 1st metastases) is 1 (lung)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_ROM_2	Region of 2nd metastases	numeric	1-C-spine/neck 2.-Thorax 3-abdomen 4-pelvis 5- Upper limbs 6-Lower limbs	Required if CAB_SOM_2 (site of 2nd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)		
CAB_SOM_3	Site of 3rd metastases	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [HIDDEN] 6-pelvic 7-liver 8-brain [HIDDEN] 9-nodes	Required if CAB_NOM (Number of metastases) is thr		
CAB_SOM_3_LTYP	Type of 2nd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_SOM_3 (site of 1st metastases) is 1 (lung)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_ROM_3	Region of 3rd metastases	numeric	1-C-spine/Neck 2.Thorax 3-abdomen 4-pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_SOM_3 (site of 3rd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)		
CAB_BPML	Biopsy proven [metastatic lesion(s)]	numeric	1-yes 2-no	Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		
CAB_LSIZE	Size of largest lesion (cm)	numeric		Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		
CAB_DSTG	Disease stage	numeric	1-Ia 2-Ib 3-Ic 4-IIa 5-IIb 6-IIc 7-IIIa			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			8-IIIb 9-IIIc 10-IVa 11-IVb 12-IVc			
CAB_HOPT	Histology of primary tumour	numeric	1-HPV P16 +ve 2-HPV P16 -ve 3-EGFR+, ALK- 4-EGFR+, ALK+ 5-EGFR-, ALK+	Required if CAB_PS (Primary site) is 1 (H&N) Required if CAB_PS (Primary site) is 1 (H&N) Required if CAB_PS(Primary site) is 2 (lung cancer) Required if CAB_PS(Primary site) is 2 (lung cancer) Required if CAB_PS(Primary site) is 2 (lung cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			6-EGFR-, ALK-	Required if CAB_PS(Primary site) is 2 (lung cancer)		
			7-ER+, PR+, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			8-ER+, PR-, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			9-ER-, PR+, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			10-ER-, PR-, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			11-ER-, PR-, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			12-ER+, PR+, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		
			13-Gleason Score 6 (3+3)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			14-Gleason Score 7 (3+4)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			15-Gleason Score 7 (4+3)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			16-Gleason Score 8 (4+4)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			17-Gleason Score 9 (5+4)	Required if CAB_PS (primary site) is 4 (prostate cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			18-Gleason Score 10 (5+5)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			19-AdenoCa (Her 2+ve)	Required if CAB_PS (primary site) is 15 (gastric cancer) or 17 (rectal cancer)		
			20-AdenoCa (Her 2 -ve)	Required if CAB_PS (primary site) is 15 (gastric cancer) or 17 (rectal cancer)		
			21-BRAF +ve	Required if CAB_PS (primary site) is 12 (melanoma)		
			22-BRAF -ve	Required if CAB_PS (primary site) is 12 (melanoma)		
			23-NSGCT	Required if CAB_PS (primary site) is 14 (germ cell tumour)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			24- Seminoma	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			25-C-Kit+ve	Required if CAB_PS (primary site) is 9 (GIST)		
			26-C-Kit-ve	Required if CAB_PS (primary site) is 9 (GIST)		
			27-DOG1	Required if CAB_PS (primary site) is 9 (GIST)		
			28-ER+, PR-, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		
			29-ER-, PR+, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		
			30-Gleason Score 9 (4+5)	Required if CAB_PS (primary site) is 4 (prostate cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			31-KRAS +ve 32-KRAS -ve	Required if CAB_PS (primary site) is 6 (colonic cancer) Required if CAB_PS (primary site) is 6 (colonic cancer)		
CAB_HOPT_TNM	Prostate Cancer TNM staging	numeric	1-1 2-2 3-3a 4-3b 5-4	Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TM_1	Tumour marker_1	numeric	1-CEA 2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) or 17 (rectal cancer) Required if CAB_PS (primary site) is 3 (breast cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			3-CA199 4-bHCG 5-AFP 6-LDH 7-PSA 8-None performed	Required if CAB_PS (primary site) is 8 (pancreas cancer) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TMV_1	Tumour marker_1 value			Required if CAB_TM_1 (Tumour marker) is completed		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_TMU_1	Tumour marker_1 unit			Required if CAB_TM_1 (Tumour marker) is completed		
CAB_DOTM_1	Tumour marker_1 date	date		Required if CAB_TM_1 (Tumour marker) is completed		
CAB_TM_2	Tumour marker_2	numeric	1-CEA 2-CA153 3-CA199 4-bHCG	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) or 17 (rectal cancer) Required if CAB_PS (primary site) is 3 (breast cancer) Required if CAB_PS (primary site) is 8 (pancreas cancer) Required if CAB_PS (primary site) is 14 (germ cell tumour)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			5-AFP 6-LDH 7-PSA 8-None performed	Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TMV_2	Tumour marker_2 value			Required if CAB_TM_2 (Tumour marker) is completed		
CAB_TMU_2	Tumour marker_2 unit			Required if CAB_TM_2 (Tumour marker) is completed		
CAB_DOTM_2	Tumour marker_2 date	date		Required if CAB_TM_2 (Tumour marker) is completed		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_TM_3	Tumour marker_3	numeric	1-CEA	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) or 17 (rectal cancer)		
			2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer)		
			3-CA199	Required if CAB_PS (primary site) is 8 (pancreas cancer)		
			4-bHCG	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			6-LDH	Required if CAB_PS (primary site) is 14 (germ cell tumour)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			7-PSA 8-None performed	Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TMV_3	Tumour marker_3 value			Required if CAB_TM_3 (Tumour marker) is completed		
CAB_TMU_3	Tumour marker_3 unit			Required if CAB_TM_3 (Tumour marker) is completed		
CAB_DOTM_3	Tumour marker date_3	date		Required if CAB_TM_3 (Tumour marker) is completed		
CAB_IM	Imaging modality	numeric	1-CT CAP 2-CT 3-Bone Scan 4-CT/FDG-PET 5-CT/Choline-PET 6-MRI 12-CT CAP and Bone Scan		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_PSR	Prior systemic therapy INT	numeric	1-yes 2-no		√	
CAB_NOLPSR	Number of lines of prior systemic review	numeric		Range (0,1,2,3,4,5,6)		
CAB_TOPSR	Type of prior systemic treatment	numeric	1-hormonal treatment 2-chemotherapy 3-targeted treatment 4-hormonal and chemotherapy treatment	Required if CAB_NOLPSR (Number of lines of prior systemic review) between 1 and 6 inclusive (yes)		
CAB_CST	Current systemic therapy	numeric	1-yes 2-no		√	
CAB_TOCSTT_2	Type(s) of current systemic therapy	numeric	**prostate cancer(CAB_PS=4)** 1-ADT 2-MAB 3-Arbiraterone	Required if CAB_CST (Current systemic therapy) is 1 (yes); Options		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			4-Enzalutamide 5-Docetaxel **breast cancer(CAB_PS=3)** 6-Tamoxifen 7-Ai-LHRH 8-Ais 9-FEC-T-heceptin 10-FEC only 11-Docetaxel-hecptin 12-Heceptin 13-Docetaxel 14-Capecitabine 15-Vinorelbine 16-Eribulin **lung cancer(CAB_PS=2)** 17-erlotinib 18-gefitinib 19-crizotinib 20-Gem/carbo 21-Cis/pem	restricted by values CAB_PS (Primary Site).		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			22-Carbo/pem 23-Doxetaxel 24-Cis/Vinorelbine 25-Cis/Etope 26-Carbo/Etope **bladder cancer(CAB_PS=16)** 27-Gem/Cis 28-Gem/Carbo 29-Vinflunine 30-Cis/5FU 31-gemcitabine 32-mitomycin/5FU **gem cell tumour(CAB_PS=14)** 33-BEP 34-EP 35-TIP 36-C/BOP/BEP 37-Transplant **H+N(CAB_PS=1)**			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			38-Cis/5FU 39-carbo/5FU 40-Cetuximab 41-Paclitaxel 87-Radio-iodine 42-Cisplatin 43-Carboplatin 44-Cetuximab **HCC(CAB_PS=25)** 45-Sorafenib **Lymphoma(CAB_PS=26)** 46-R-CHOP **Colorectal(CAB_PS=6)** 47-FOLFOX 48-FOIFIRI 49-XELOXA 50-CapOX 51-Cetuximab-FOLFOX 52-Bavacizumab 53-capcitabine			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			Kidney(CAB_PS=5) 54-sunitinib 55-pazopanib 56-sorafenib **Oesophagus(CAB_PS=7)/Gastric(CAB_PS=15)** 57-Cis/5FU 58-ECF/ECX/EOX/EOF 59-TC 60-Cis/5FU 61-Capecitabine/Cetuximab **Pancreas(CAB_PS=8)** 62-Gem 63-FOLFIRINOX 64-Gem/CAP 65-Capecitabine 66-Gemcitabine **endometrial(CAB_PS=10)** 67-megase			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			68-tamoxifen 69-Pac/carbo 70-Carbo 71-Cisplatin 72-Carboplatin **Cervix(CAB_PS=11)** 73-Cis/5FU 74-Pac/Carbo 75-Cisplatin **Sarcoma(CAB_PS=13)** 76-Antracycline based chemo 77-Trabectedin 78-Imatinib **Melanoma(CAB_PS=12)** 79-venumafenib 80-dabrafenib 81-Ipilimumab 82-Ipilimimab Combi 83-Nivolumab **GIST(CAB_PS=9)**			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			84-Imatinib 85-Sunitinib 86-regorafeni **Vulva (CAB_PS=23)** 88-Cis/5FU **Penile (CAB_PS=20)** 89-Cis/5FU 90-Cis **Ovarian (CAB_PS=21)** 91-Carboplatin 92-Pac/Carbo **Cholangio (CAB_PS=22)** 93-Gem/Cis **Anal (CAB_PS=18)** 94-Mitomycin/5FU 95-Cis/5FU **Urothelial (CAB_PS=24)** 96-Gem/Cis 97-Gem/Carbo 98-Vinflunine			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			99-Cis/5FU 100- Gemcitabine 101-Mitomycin/5FU **Rectal Cancer (CAB_PS=17)** 102-5FU 103-Irinotecan 104-Oxaliplatin 105-Capecitabine 106-Leucovorin 107-5FU/Leucovorin/Oxaliplatin 108-Capecitabine/Oxaliplatin 109-5FU/Leucovorin 110-Capecitabine monotherapy			
CAB_CTT	Therapy to continue through treatment	numeric	1-yes 2-no	Required if CAB_CST(Current systemic therapy) is 1 (yes)		
CAB_LDA	Last date of administration	date		Required if CAB_CTT (Therapy to continue		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
				through treatment) is 1 (no)		
CAB_PR	Previous radiotherapy	numeric	1-yes 2-no		√	
CAB_SOPR	Site of previous radiotherapy	numeric	1-H&N (include thyroid) 2-lung cancer 3-breast cancer 4-prostate cancer 5-renal cancer 6-colonic cancer 7-oesophageal cancer 8-pancreatic cancer 9-gastrointestinal stromal tumour (GIST) 10-endometrial cancer 11-cervical cancer 12-melanoma 13-sarcoma	Required if CAB_PR (Previous radiotherapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			14-germ cell tumour 15-gastric cancer 16-bladder cancer 17-rectal cancer 18-anal cancer 19-upper tract (TCC) 20-penile cancer 21-ovarian cancer 22-cholangio cancer 23-vulva cancer 24-urothelial cancer 25-HCC 26-lymphoma [HIDDEN] 27-other			
CAB_OSPR	Other site of previous radiotherapy	text		Required if CAB_SOPR (site of previous radiotherapy) is 27 (other) and CAB_PR (previous radiotherapy) is 1		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_PR_LAT	Previous radiotherapy laterality	numeric	1-left 2-right 3-bilateral 4-central	Required if CAB_SOPR (Previous radiotherapy) is 1 (H&N (include thyroid)) or 13 (sarcoma) or 12 (melanoma) or 14 (germ cell tumour) or 5 (renal cancer) or 2 (lung cancer) or 3 (breast cancer) and CAB_PR (Previous radiotherapy) is 1 (yes)		
CAB_PR_LATDET	Previous radiotherapy laterality detail	text		Required if CAB_SOPR (Previous radiotherapy) is 1 (H&N (include thyroid)) or 13 (sarcoma) or 12 (melanoma) or 14 (germ cell tumour) or 5 (renal cancer) or 2 (lung cancer) or 3 (breast cancer) and CAB_PR (Previous radiotherapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_FOPTF	Fractionation of previous RT: Fractions	numeric		Required if CAB_PR (Previous radiotherapy) is 1 (yes); Range (1-100)		
CAB_FOPTD	Fractionation of previous RT: Dose	numeric		Required if CAB_PR (Previous radiotherapy) is 1 (yes); Range (1-100)		
CAB_DOCPR	Date of completion of previous radiotherapy	date		Required if CAB_PR (Previous radiotherapy) is 1 (yes)		
CAB_WHO_PST	WHO performance status	numeric	0-Fully active, able to carry on all pre-disease performance without restriction 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 2-Ambulatory and capable of all selfcare but unable to carry out		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			any work activities. Up and about more than 50% of waking hours			
CAB_SABR_TRTS	How many SABR treatments were done	numeric	Range (1-3)		√	
CAB_TRTDTE_1	Start date of first SABR treatment	date			√	
CAB_COMPDTE_1	Completion date of first SABR treatment	date			√	
CAF_TRTAREA_1	First SABR treatment area	date			√	
CAB_TRT_1	Platform for first SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			4-Tomotherapy			
CAB_IGRT_TECH_1	IGRT technique for first SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial) 4-kV planar (spine) 5-kV planar (cranial) 6-kV planar (lung)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife)	√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			7-MVCT	Required if CAB_TRT (Treatment option) is 4 (Tomotherapy)		
CAB_IDF_SBRT_1	Intended dose fractionation for first SBRT treatment	text			√	
CAB_PDOSE_1	Prescribed dose for first SABR treatment	numeric			√	
CAB_NFRAC_1	Number of fractions for first SABR treatment	numeric			√	
CAB_RSENSI_1	Radiosensitivity (a/b) for first SABR treatment			User to add 0 if the input in N/A	√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_BED_1	Biological effective dose (100Gy as cutoff) for first SABR treatment	numeric		User to add 0 if the input in N/A	√	BED=nd[1+(d/(a/b))] where n is CAB_PDOSE (Prescribed dose) and d is CAB_NFRAC (Number of fractions)
CAB_TRTDTE_2	Start date of second SABR treatment	text				
CAB_COMPDTE_2	Completion date of second SABR treatment	date				
CAB_TRTAREA_2	Second SABR treatment area	date				
CAB_TRT_2	Platform for second SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_IGRT_TECH_2	IGRT technique for second SABR treatment	numeric	1-CBCT (soft tissue)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian)		
			2-CBCT (fiducial)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian)		
			3-kV planar (fiducial)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			4-kV planar (spine)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			5-kV planar (cranial)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			6-kV planar (lung)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			7-MVCT	Required if CAB_TRT (Treatment option) is 4 (Tomotherapy)		
CAB_IDF_SBRT_2	Intended dose fractionation for second SBRT treatment	text				
CAB_PDOSE_2	Prescribed dose for second SABR treatment	numeric				
CAB_NFRAC_2	Number of fractions for second SABR treatment	numeric				
CAB_RSENSI_2	Radiosensitivity (a/b) for second SABR treatment					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_BED_2	Biological effective dose (100Gy as cutoff) for second SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAB_PDOSE (Prescribed dose) and d is CAB_NFRAC (Number of fractions)
CAB_TRTDTE_3	Start date of third SABR treatment	text				
CAB_COMPDTE_3	Completion date of third SABR treatment	date				
CAB_TRTAREA_3	Third SABR treatment area	date				
CAB_TRT_3	Platform for third SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			4-Tomotherapy			
CAB_IGRT_TECH_3	IGRT technique for third SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial) 4-kV planar (spine) 5-kV planar (cranial) 6-kV planar (lung)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			7-MVCT	Required if CAB_TRT (Treatment option) is 4 (Tomotherapy)		
CAB_IDF_SBRT_3	Intended dose fractionation for third SBRT treatment	text				
CAB_PDOSE_3	Prescribed dose for third SABR treatment	numeric				
CAB_NFRAC_3	Number of fractions for third SABR treatment	numeric				
CAB_RSENSI_3	Radiosensitivity (a/b) for third SABR treatment					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_BED_3	Biological effective dose (100Gy as cutoff) for third SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAB_PDOSE (Prescribed dose) and d is CAB_NFRAC (Number of fractions)

Clinical Assessments – Follow-Up

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_DOA	Date of assessment	date			√		
CAF_WHO_ST	WHO performance status	numeric	1-Fully active, able to carry on all pre-disease performance without restriction 2-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 3-Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours 4-Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours		√		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			5-Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair				
CAF_TM_1	Tumour marker_1	numeric	1-CEA	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer)			
			2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer)			
			3-CA199	Required if CAB_PS (primary site) is 8 (pancreas cancer)			
			4-bHCG	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			6-LDH 7-PSA	Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 4 (prostate cancer)			
CAF_TMV_1	Tumour marker_1 value			Required if CAF_TM_1 (Tumour marker) is completed			
CAF_TMU_1	Tumour marker_1 unit			Required if CAF_TM_1 (Tumour marker) is completed			
CAF_DOTM_1	Tumour marker_1 date	date		Required if CAF_TM_1 (Tumour marker) is completed			
CAF_TM_2	Tumour marker_2	numeric	1-CEA	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			2-CA153 3-CA199 4-bHCG 5-AFP 6-LDH 7-PSA	Required if CAB_PS (primary site) is 3 (breast cancer) Required if CAB_PS (primary site) is 8 (pancreas cancer) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 4 (prostate cancer)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_DOTM_2	Tumour marker_2 date	date		Required if CAF_TM_2 (Tumour marker) is completed			
CAF_TMV_2	Tumour marker_2 value			Required if CAF_TM_2 (Tumour marker) is completed			
CAG_TMU_2	Tumour marker_2 unit			Required if CAF_TM_2 (Tumour marker) is completed			
CAF_TM_3	Tumour marker_3	numeric	1-CEA 2-CA153 3-CA199	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) Required if CAB_PS (primary site) is 3 (breast cancer) Required if CAB_PS (primary site) is 8 (pancreas cancer)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			4-bHCG	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			6-LDH	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			7-PSA	Required if CAB_PS (primary site) is 4 (prostate cancer)			
CAF_TMV_3	Tumour marker_3 value			Required if CAF_TM_3 (Tumour marker) is completed			
CAG_TMU_3	Tumour marker_3 unit			Required if CAF_TM_3 (Tumour marker) is completed			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_DOTM_3	Tumour marker_3 date	date		Required if CAF_TM_3 (Tumour marker) is completed			
CAF_ITR	Is there imaging to interpret	numeric	1-yes 2-no		√		
CAF_NOI	How many imaging modality	numeric		Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_TOIR	Type of imaging to report	numeric	1-CT CAP 2-CT 3-Bone Scan 4-CT/FDG-PET 5-CT/Choline-PET 6-MRI Pelvis 7-Whole Body MRI 8-Whole Body fMRI 9-MRI spine	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			10-MRI liver 11-MRI soft tissue 12-other				
CAF_OTIR	Other type of imaging to report	text		Required if CAF_TOIR (Type of imaging to report) is 12 (Other) and CAF_ITR(Imaging to report) is 1 (yes)			
CAF_DOI	Date of image (s)	date		Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR (Line40)
CAF_ADIMG	Additional imaging to be done	numeric	1-yes 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_ADTOIR	Type of additional imaging to report	numeric	1-CT CAP 2-CT 3-Bone Scan 4-CT/FDG-PET 5-CT/Choline-PET 6-MRI Pelvis 7-Whole Body MRI 8-Whole Body fMRI 9-MRI spine 10-MRI liver 11-MRI soft tissue 12-other	Required if CAF_ADIMG(Imaging to report) is 1 (yes)			
CAF_ADOTIR	Other type of imaging to report	text		Required if CAF_ADTOIR (Type of imaging to report) is 12 (Other) and CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_LP_TRTDTE_1	Start date of first treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_COMPDTE_1	Completion date of first treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_TRTAREA_1	First treated area at baseline	text				Cannot be modified. This is read from the baseline form.	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_LP_STATUS_1	Is the first treated area at baseline stable/reduced in size/disappeared	numeric	1-yes (local control) 2-uncertain/equivocal (either discuss at MDT and consider requesting complementary imaging - e.g. PET to clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR(Line)
CAF_LP_MS_1	Is there any evidence of metastatic disease in the first organ treated at baseline or next	numeric	1-yes (loco-regional progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR(Line)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	echelon lymph nodes		2-no				
CAF_LP_TRTDTE_2	Start date of second treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_COMPDTE_2	Completion date of second treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_TRTAREA_2	Second treated area at baseline	text				Cannot be modified. This is read from the	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
						baseline form.	
CAF_LP_STATUS_2	Is the second treated area at baseline stable/reduced in size/disappeared	numeric	1-yes (local control) 2-uncertain/equivocal (either discuss at MDT and consider requesting complementary imaging - e.g. PET to clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_LP_MS_2	Is there any evidence of metastatic disease in the second organ treated at	numeric	1-yes (loco-regional progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	baseline or next echelon lymph nodes		2-no				
CAF_LP_TRTDTE_3	Start date of third treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_COMPDTE_3	Completion date of third treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_TRTAREA_3	Third treated area	text				Cannot be modified. This is read from the	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
						baseline form.	
CAF_LP_STATUS_3	Is the third treated area stable/reduced in size/disappeared	numeric	1-yes (local control) 2-uncertain/equivocal (either discuss at MDT and consider requesting complementary imaging - e.g. PET to clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_LP_MS_3	Is there any evidence of metastatic disease in the third organ treated or next	numeric	1-yes (loco-regional progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	echelon lymph nodes		2-no				
CAF_DP_STATUS	Is there any evidence of metastatic disease in other organs	numeric	1-yes (distant progression - metastatic disease) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR(Line40)
CAF_DP_OP	Are there less than 3 areas of new disease	numeric	1-yes (oligometastatic progression) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_PROG_SABR	Progression amenable to further SABR	numeric	1-yes	Required if CAF_LP_STATUS_(1,2,3), CAF_LP_MS_(1,2,3) (Local progression) , CAF_DP_STATUS or			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			2-no	CAF_DP_OP (Distant progression) is 1 (yes)			
CAF_FUTH_SABR	Number of sites for further SABR treatment	numeric	Range(0,1,2,3)		√		
CAF_ST_1	Site of 1st metastases treated	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [Hidden] 6-pelvic 7-liver 8-brain [Hidden] 9-nodes	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 1			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_TYP_1	Type of 1st metastases	numeric	1-Unilateral 2-Bilateral	Required if CAF_ST_1 (site of 1st metastases) is 1 (lung)			
CAF_ROM_1	Region of 1st metastases	numeric	1-C spine/Neck 2-Thorax 3-Abdomen 4-Pelvis 5-Upper limbs 6-Lower limbs	Required if CAF_ST_1 (site of 1st metastases) is 2 (spine) or 3 (bone) or 9 (nodes)			
CAF_ST_2	Site of 2nd metastases treated	numeric	1-lung 2-spine 3-bone 4-adrenal	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 2			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			5-renal 6-pelvic 7-liver 8-brain 9-nodes				
CAF_TYP_2	Type of 2nd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_ST_2 (site of 2nd metastases) is 1 (lung)			
CAF_ROM_2	Region of 2nd metastases	numeric	1-C spine/Neck 2-Thorax 3-Abdomen 4-Pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_ST_2 (site of 2nd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_ST_3	Site of 3rd metastases treated	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal 6-pelvic 7-liver 8-brain 9-nodes	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 3			
CAF_TYP_3	Type of 3rd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_ST_3 (site of 3rd metastases) is 1 (lung)			
CAF_ROM_3	Region of 3rd metastases	numeric	1-C spine/Neck 2-Thorax 3-Abdomen 4-Pelvis	Required if CAB_ST_3 (site of 3rd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			5-Upper limbs 6-Lower limbs				
CAF_FSABR_TRTS	Number of further SABR treatments	numeric		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTDTE_1	Start date of first further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_COMPDTE_1	Completion date of first further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTAREA_1	Treatment area for first further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
				treatment) is larger than 0			
CAF_TRT_1	Platform for first further SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy	Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_IGRT_TECH_1	IGRT technique for first further SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial)	Required if CAF_TRT_1 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_1 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			4-kV planar (spine)	Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife)			
			5-kV planar (cranial)	Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife)			
			6-kV planar (lung)	Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife)			
			7-MVCT	Required if CAF_TRT_1 (Treatment option) is 4 (Tomotherapy)			
CAF_IDF_SBRT_1	Intended dose fractionation for first further SBRT treatment	text		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_PDOSE_1	Prescribed dose for first further SABR treatment	numeric		Required if CAF_FUTH_SABR(Details of further SABR			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
				treatment) is larger than 0			
CAF_NFRAC_1	Number of fractions for first further SABR treatment	numeric		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_RSENSI_1	Radiosensitivity (a/b) for first further SABR treatment			Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_BED_1	Biological effective dose (100Gy as cutoff) for first further SABR treatment	numeric		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0		BED=nd[1+(d/(a/b))] where n is CAF_PDOSE_1 (Prescribed dose) and d is	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
						CAF_NFRAC_1 (Number of fractions)	
CAF_TRTDTE_2	Start date of second further SABR treatment	date					
CAF_COMPDTE_2	Completion date of second further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTAREA_2	Treatment area for second further SABR treatment	text					
CAF_TRT_2	Platform for second further SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_IGRT_TECH_2	IGRT technique for second further SABR treatment	numeric	1-CBCT (soft tissue)	Required if CAF_TRT_2 (Treatment option) is 1 (Elekta) or 2 (Varian)			
			2-CBCT (fiducial)	Required if CAF_TRT_2 (Treatment option) is 1 (Elekta) or 2 (Varian)			
			3-kV planar (fiducial)	Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife)			
			4-kV planar (spine)	Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife)			
			5-kV planar (cranial)	Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife)			
			6-kV planar (lung)	Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			7-MVCT	Required if CAF_TRT_2 (Treatment option) is 4 (Tomotherapy)			
CAF_IDF_SBRT_2	Intended dose fractionation for second further SBRT treatment	text					
CAF_PDOSE_2	Prescribed dose for second further SABR treatment	numeric					
CAF_NFRAC_2	Number of fractions for second further SABR treatment	numeric					
CAF_RSENSI_2	Radiosensitivity (a/b) for second further SABR treatment						

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_BED_2	Biological effective dose (100Gy as cutoff) for second further SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAF_PDOSE_2 (Prescribed dose) and d is CAF_NFRAC_2 (Number of fractions)	
CAF_TRTDTE_3	Start date of third further SABR treatment	date					
CAF_COMPDTE_3	Completion date of third further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_TRTAREA_3	Treatment area for third further SABR treatment	text					
CAF_TRT_3	Platform for third further SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy				
CAF_IGRT_TECH_3	IGRT technique for third further SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial)	Required if CAF_TRT_3 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_3 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			4-kV planar (spine) 5-kV planar (cranial) 6-kV planar (lung) 7-MVCT	Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_3 (Treatment option) is 4 (Tomotherapy)			
CAF_IDF_SBRT_3	Intended dose fractionation for third further SBRT treatment	text					
CAF_PDOSE_3	Prescribed dose for third further SABR treatment	numeric					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_NFRAC_3	Number of fractions for third further SABR treatment	numeric					
CAF_RSENSI_3	Radiosensitivity (a/b) for third further SABR treatment						
CAF_BED_3	Biological effective dose (100Gy as cutoff) for third further SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAF_PDOSE_3 (Prescribed dose) and d is CAF_NFRAC_3 (Number of fractions)	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_CST	Has there been a change in systemic therapy since last assessment	numeric	1-yes 2-no		√		
CAF_CST_WHT	What change has there been	numeric	1-re-start 2-stop 3-change	Required if CAF_CST (Has there been a change in...) is 1 (yes)			
CAF_TCSTT	Type(s) of current systemic therapy	numeric	**prostate cancer(CAB_PS=4)** 1-ADT 2-MAB 3-Arbiraterone 4-Enzalutamide 5-Docetaxel **breast cancer(CAB_PS=3)**	Required if CAF_CST_WHT (What change...) is 1 (start) or 3 (change); Options restricted by values in CAB_PS (Primary Site)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			6-Tamoxifen 7-Ai-LHRH 8-Ais 9-FEC-T-heceptin 10-FEC only 11-Docetaxel-hecptin 12-Heceptin 13-Docetaxel 14-Capecitabine 15-Vinorelbine 16-Eribulin **lung cancer(CAB_PS=2)** 17-erlotinib 18-gefitinib 19-crizotinib 20-Gem/carbo 21-Cis/pem 22-Carbo/pem 23-Doxetaxel 24-Cis/Vinorelbine				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			25-Cis/Etope 26-Carbo/Etope **bladder cancer(CAB_PS=16)** 27-Gem/Cis 28-Gem/Carbo 29-Vinflunine 30-Cis/5FU 31-gemcitabine 32-mitomycin/5FU **gem cell tumour(CAB_PS=14)** 33-BEP 34-EP 35-TIP 36-C/BOP/BEP 37-Transplant **H+N(CAB_PS=1)** 38-Cis/5FU 39-carbo/5FU 40-Cetuximab 41-Paclitaxel				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			87-Radio-iodine 42-Cisplatin 43-Carboplatin 44-Cetuximab **HCC(CAB_PS=25)** 45-Sorafenib **Lymphoma(CAB_PS=26)** 46-R-CHOP **Colorectal(CAB_PS=6)** 47-FOLFOX 48-FOIFIRI 49-XELOXA 50-CapOX 51-Cetuximab-FOLFOX 52-Bavacizumab 53-capcitabine **Kidney(CAB_PS=5)** 54-sunitinib 55-pazopanib 56-sorafenib				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			Oesophagus(CAB_PS=7)/Gastric(CAB_PS=15) 57-Cis/5FU 58-ECF/ECX/EOX/EOF 59-TC 60-Cis/5FU 61-Capecitabine/Cetuximab **Pancreas(CAB_PS=8)** 62-Gem 63-FOLFIRINOX 64-Gem/CAP 65-Capecitabine 66-Gemcitabine **endometrial(CAB_PS=10)** 67-megase 68-tamoxifen **endometrial(CAB_PS=10)** 69-Pac/carbo 70-Carbo 71-Cisplatin				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			72-Carboplatin **Cervix(CAB_PS=11)** 73-Cis/5FU 74-Pac/Carbo 75-Cisplatin **Sarcoma(CAB_PS=13)** 76-Antracycline based chemo 77-Trabectedin 78-Imatinib **Melanoma(CAB_PS=12)** 79-venumafenib 80-dabrafenib 81-Ipilimumab 82-Ipilimimab Combi 83-Nivolumab **GIST(CAB_PS=9)** 84-Imatinib 85-Sunitinib 86-regorafeni **Vulva (CAB_PS=23)**				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			88-Cis/5FU **Penile (CAB_PS=20)** 89-Cis/5FU 90-Cis **Ovarian (21)** 91-Carboplatin 92-Pac/Carbo **Cholangio (22)** 93-Gem/Cis **Anal (18)** 94-Mitomycin/5FU 95-Cis/5FU **Urothelial (CAB_PS=24)** 96-Gem/Cis 97-Gem/Carbo 98-Vinflunine 99-Cis/5FU 100-Gemcitabine 101-Mitomycin/5FU **Rectal Cancer (CAB_PS=17)**				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			102-5FU 103-Irinotecan 104-Oxaliplatin 105-Capecitabine 106-Leucovorin 107-5FU/Leucovorin/Oxaliplatin 108-Capecitabine/Oxaliplatin 109-5FU/Leucovorin 110-Capecitabine monotherapy				
CAF_DOCIST	Date of change/initiation of new therapy	date		Required if CAF_CST (Current systemic therapy) is 1 'yes'			

CTCAE

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_ANY	Any toxicities?	numeric	1 - Yes 2-No		√	
CTCAE_TD	Toxicity date	date		Required if CTCAE_ANY (Any toxicities)=1 (yes)		
CTCAE_TS_1	Toxicity site 1	numeric	1-Toxicity A: cervical spine, thorax, lung, mediastinum 2-Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic 3-Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall	Required if CTCAE_ANY (Any toxicities)=1 (yes)		
CTCAE_TS_2	Toxicity site 2	numeric	1-Toxicity A: cervical spine, thorax, lung, mediastinum 2-Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic 3-Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall	Required if CTCAE_ANY (Any toxicities)=1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_TS_3	Toxicity site 3	numeric	1-Toxicity A: cervical spine, thorax, lung, mediastinum 2-Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic 3-Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall	Required if CTCAE_ANY (Any toxicities)=1 (yes)		
CTCAE_PERI	Pericarditis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		Grades definitions are on CTCAE-Defn tab
CTCAE_DYSP	Dysphagia	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_GIHA	GI haemorrhage	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_GAST	Gastritis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_UGIU	Upper GI Ulcer	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
CTCAE_NAUS	Nausea	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_VOMI	Vomiting	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
CTCAE_FATI	Fatigue	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2 or 3		
CTCAE_SFRA	Spinal fracture	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2 or 3		
CTCAE_MYEL	Myelitis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 3		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_COUG	Cough	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
CTCAE_PNEU	Pneumonitis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
CTCAE_DGUL	Duodenal/Gastric ulcer	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_FEVE	Fever	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_LALT	Liver enzymes : ALT	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_BILI	Bilirubin	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_DIAR	Diarrhoea	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_PROC	Proctitis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_RHAE	Rectal Haemorrhage	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_HAEM	Haematuria	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_UFRE	Urinary frequency	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_UINC	Urinary incontinence	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_URET	Urinary retention	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_UURG	Urinary urgency	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_ULCE	Ulcer	numeric	Grade (1-6)			CTCAE grade definition depends on type of Ulcer
CTCAE_ULCE_LOC	Ulcer location	text		Required if CTCAE_ULCE_LOC (Ulcer) is larger than 0		
CTCAE_FIST	Fistula	numeric	Grade (1-6)			CTCAE grade definition depends on type of Fistula
CTCAE_FIST_LOC	Fistula location	text		Required if CTCAE_FIST_LOC (Fistula) is larger than 0		
CTCAE_PERF	Perforation	numeric	Grade (1-6)			CTCAE grade definition depends on type of Perforation
CTCAE_PERF_LOC	Perforation location	text		Required if CTCAE_PERF_LOC (Perforation) is larger than 0		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_BPAI	Bone pain	numeric	Grade (1-6)			
CTCAE_BPAI_LOC	Bone pain location	text		Required if CTCAE_BPAI_LOC (Bone pain) is larger than 0		
CTCAE_FRAC	Fracture	numeric	Grade (1-6)			
CTCAE_FRAC_LOC	Fracture location	text		Required if CTCAE_FRAC_LOC (Fracture) is larger than 0		

CTCAE Definitions

Note: Grade 0 not applicable.

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
1	PERI	**Pericarditis**	Asymptomatic clinical or ECG findings	Symptomatic pericarditis	Pericarditis with physiological consequences	Life-threatening consequences	Death	No Toxicities
1,2	DYSP	**Dysphagia**	Symptomatic, able to eat regular diet	Symptomatic with altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
1,2	GIHA	**GI haemorrhage**	Mild, intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
1,2	GAST	**Gastritis**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death	No Toxicities
1	UGIU	**Upper GI ulcer**	Asymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	No Toxicities
1,2	NAUS	**Nausea**		Oral intake decreased without	Inadequate oral caloric or fluid	-	-	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			Loss of appetite without alteration in eating habits	significant weight loss, dehydration or malnutrition	intake; tube feeding, TPN, or hospitalization indicated			
1	VOMI	**Vomiting**	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
1,2,3	FATI	**Fatigue**	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-	No Toxicities
1,2,3	SFRA	**Spinal fracture**	Mild back pain; nonprescription analgesics	Moderate back pain; prescription analgesics	Severe back pain; hospitalization or intervention	Life-threatening consequences; symptoms	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			indicated	indicated; limiting instrumental ADL	indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	associated with neurovascular compromise		
1,3	MYEL	**Myelitis**	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
1	COUG	**Cough**	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	No Toxicities
1	PNEU	**Pneumonitis**	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; medical intervention indicated; limiting	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			intervention not indicated	instrumental ADL		intervention indicated (e.g., tracheotomy or intubation)		
2	DGUL	**Duodenal/ Gastric ulcer**	Asymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention	Life-threatening consequences; urgent operative intervention	Death	No Toxicities
					intervention indicated; limiting self care ADL; disabling	indicated		
2	FEVE	**Fever**	38.0-39.0 degrees	39.1-40.0	>40.0 degrees for <24 hours	>40.0 degrees for >24 hours	Death	No Toxicities
2	LALT	**Liver enzymes: ALT**	ULN- 3*ULN	3*ULN – 5*ULN	>5.0 - 20.0 x ULN; >5 x ULN for >2 weeks	>20 *ULN	Death	No Toxicities
2	BILI	**Bilirubin**	ULN- 1.5* ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN		No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
3	DIAR	**Diarrhoea**	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
3	PROC	**Proctitis**	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; faecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
3	RHAE	**Rectal haemorrhage**	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
3	HAEM	**Haematuria**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
3	UFRE	**Urinary frequency**	present	Limiting instrumental ADL; medical management indicated	-	-	-	No Toxicities
3	UINC	**Urinary incontinence**	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention	-	-	No Toxicities
					indicated; limiting self care ADL			
3	URET	**Urinary retention**	Urinary, suprapubic or intermittent catheter placement not indicated; able	Placement of urinary, suprapubic or intermittent catheter placement indicated;	Elective operative or radiologic intervention indicated; substantial loss of	Life-threatening consequences; organ failure; urgent operative intervention	Death	No Toxicities

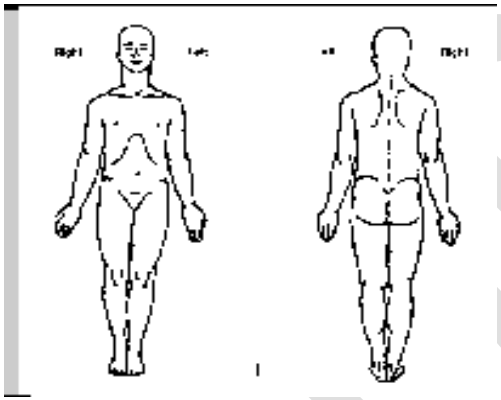
CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			to void with some residual	medication indicated	affected kidney function or mass	indicated		
3	UURG	**Urinary urgency**	Present	Limiting instrumental ADL; medical management indicated	-	-	-	No Toxicities
	BPAI	**Bone pain**	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	No Toxicities
	FRAC	**Fracture**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

EQ-5D

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
EQ5D_0	Mobility	numeric	1-I have no problems in walking about 2-I have some problems in walking about 3-I am confirmed to bed	Range (1-3)	√	
EQ5D_1	Self-care	numeric	1-I have no problems with self-care 2-I have some problems washing or dressing myself 3-I am unable to wash or dress myself	Range (1-3)	√	
EQ5D_2	Usual activities	numeric	1-I have no problem with performing my usual activities 2-I have some problems performing my usual activities 3-I am unable to perform my usual activities	Range (1-3)	√	
EQ5D_3	Pain/discomfort	numeric	1-I have no pain or discomfort 2-I have moderate pain or discomfort 3-I have extreme pain or discomfort	Range (1-3)	√	
EQ5D_4	Anxiety/depressio n	numeric	1-I am not anxious or depressed 2-I am moderately anxious or depressed 3-I am extremely anxious or depressed	Range (1-3)	√	
EQ5D_5	Your health today	numeric		Range (1-100)	√	

Pain Score (Brief Pain Inventory)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
BPI_NPRS	Numeric pain rating scale	numeric		Range (0-10)	√	0 - no pain; 5 - moderate pain; 10-worst possible pain
BPI_Related	Is this pain related to current diagnosis (oligomets, recurrence, mets for re-treatment) or related to recent SABR treatment?	numeric	1-Yes 2-No		Required if BPI_NPRS (Numeric pain rating scale)>0	
BPI_1	1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?				Required if BPI_NPRS (Numeric pain rating scale)>0	
BPI_2	2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.	1-Thorax front 2-Thorax back 3-Abdomen front 4-Abdomen back 5-Left arm 6-Right arm 7-Left leg 8-Right leg			Required if BPI_NPRS (Numeric pain rating scale)>0	This will have to be digitized. Such that if there is an X on the right side of the head it will be 1, etc..

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
		9-Right leg 10-Head				
BPI_3	3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
BPI_4	4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)
BPI_5	5. Please rate your pain by circling the one number that best describes your pain on average.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)
BPI_6	6. Please rate your pain by circling the one number that tells how much pain you have right now.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)

Patient Experience

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CONSENT						
PE_1	How likely are you to recommend our SABR service to friends and family if they needed similar care or treatment?	Numeric	1-Extremely likely 2-Likely 3-Neither likely or unlikely 4-Extremely likely 5-Don't know		√	

Radiotherapy Planning Details_1

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_TRTAREA_1	First treatment area at baseline	text				Cannot be modified. This is read from the baseline form.
RPD_STDTE_1	Start date of first SABR treatment at baseline	date			√	
RPD_SPDTE_1	Completion date of first SABR treatment at baseline	date			√	
RPD_PCON_1	Were all planning constraints met?	numeric	1-yes 2-no		√	At least one site to be chosen
RPD_PTVC_1	Was PTV coverage >95% achieved?	numeric	1-yes 2-no		√	
RPD_SITE_THO_1	Thorax treated for first SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_UABM_1	Upper Abdomen treated for first SABR treatment	numeric	-1-yes			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			0-no			
RPD_SITE_LABM_1	Lower Abdomen treated for first SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_ULMB_1	Upper Limb treated for first SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LLMB_1	Lower Limb treated for first SABR treatment	numeric	-1-yes 0-no			
THORAX (C SPINE, T SPINE, LUNG, MEDIASTINUM)						
RPD_THO_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_THO_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_THO_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_PISO_1	Prescription isodose	numeric				
RPD_THO_SC_DM01_1	Spinal Canal: DMax (0.1cc)	numeric				
RPD_THO_SC_D12_1	Spinal canal: D1.2cc	numeric				
RPD_THO_OG_DM05_1	Oesophagus: DMax (0.5cc)	numeric				
RPD_THO_LG_V20_1	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_THO_LG_V125_1	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_THO_HR_DM05_1	Heart: DMax (0.5cc)	numeric				
RPD_THO_SK_DM05_1	Skin: DMax (0.5cc)	numeric				
RPD_THO_SK_D10_1	Skin: D10cc	numeric				
RPD_THO_ST_DM05_1	Stomach: DMax (0.5cc)	numeric				
RPD_THO_ST_D55_1	Stomach: D5cc	numeric				
RPD_THO_ST_D10_1	Stomach: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_ST_D50_1	Stomach: D50cc	numeric				
RPD_THO_LV_V10_1	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_THO_LV_MLD_1	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_THO_LV_D50PT_1	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_THO_LV_D700_1	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_THO_CW_DM05_1	Chest Wall: DMax (0.5cc)	numeric				
RPD_THO_CW_D30_1	Chest Wall: D30cc	numeric				
RPD_THO_GV_DM05_1	Great Vessels: DMax (0.5cc)	numeric				
RPD_THO_BP_D05_1	Brachial Plexus: Dmax (0.5cc)	numeric				
RPD_THO_TB_D05_1	Trachea and bronchus: Dmax (0.5cc)	numeric				
RPD_THO_TTMIN_1	Treatment time (mins)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_PPMIN_1	Physics time to plan (mins)	numeric				
UPPER ABDOMEN						
RPD_UA_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_UA_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UA_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UA_PISO_1	Prescription isodose	numeric				
RPD_UA_SC_D01_1	Spinal Canal : DMax (0.1cc)	numeric				
RPD_UA_SC_D12_1	Spinal Canal: D1.2cc	numeric				
RPD_UA_OG_D05_1	Oesophagus: DMax (0.5cc)	numeric				
RPD_UA_CE_D01_1	Cauda Equina: DMax (0.1cc)	numeric				
RPD_UA_CE_D5_1	Cauda Equina: D5cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_LG_V20_1	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UA_LG_V125_1	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_UA_HR_D05_1	Heart: DMax (0.5cc)	numeric				
RPD_UA_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_UA_SK_D10_1	Skin: D10cc	numeric				
RPD_UA_ST_D05_1	Stomach: DMax (0.5cc)	numeric				
RPD_UA_ST_D5_1	Stomach: D5cc	numeric				
RPD_UA_ST_D10_1	Stomach: D10cc	numeric				
RPD_UA_ST_D50_1	Stomach: D50cc	numeric				
RPD_UA_DD_D05_1	Duodenum: DMax (0.5cc)	numeric				
RPD_UA_DD_D1_1	Duodenum: D1cc	numeric				
RPD_UA_DD_D5_1	Duodenum: D5cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_DD_D9_1	Duodenum: D9cc	numeric				
RPD_UA_DD_D10_1	Duodenum: D10cc	numeric				
RPD_UA_SB_D05_1	Small bowel: DMax (0.5cc)	numeric				
RPD_UA_SB_D5_1	Small bowel: D5cc	numeric				
RPD_UA_SB_D10_1	Small bowel: D10cc	numeric				
RPD_UA_LB_D05_1	Large bowel: DMax (0.5cc)	numeric				
RPD_UA_KD_MKD_1	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_UA_KD_D700_1	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_UA_SKD_D10_1	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_UA_LV_V10_1	Normal Liver (Liver minus GTV): V10Gy	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_LV_MLD_1	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_UA_LV_D50_1	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_UA_LV_D700_1	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_UA_TTMIN_1	Treatment time (mins)	numeric				
RPD_UA_PPMIN_1	Physics time to plan (mins)	numeric				
LOWER ABDOMEN						
RPD_LA_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_LA_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LA_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LA_PISO_1	Prescription isodose	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_SC_D01_1	Spinal Canal: DMax (0.1cc)	numeric				
RPD_LA_SC_D12_1	Spinal Canal: D1.2cc	numeric				
RPD_LA_CE_D01_1	Cauda Equina: Dmax (0.1cc)	numeric				
RPD_LA_CE_D5_1	Cauda Equina: D5cc	numeric				
RPD_LA_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_LA_SK_D10_1	Skin: D10cc	numeric				
RPD_LA_DD_D05_1	Duodenum: DMax (0.5cc)	numeric				
RPD_LA_DD_D1_1	Duodenum: D1cc	numeric				
RPD_LA_DD_D5_1	Duodenum: D5cc	numeric				
RPD_LA_DD_D9_1	Duodenum: D9cc	numeric				
RPD_LA_DD_D10_1	Duodenum: D10cc	numeric				
RPD_LA_SB_D05_1	Small bowel: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_SB_D5_1	Small bowel: D5cc	numeric				
RPD_LA_SB_D10_1	Small bowel: D10cc	numeric				
RPD_LA_LB_D05_1	Large bowel: DMax (0.5cc)	numeric				
RPD_LA_LB_D20_1	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_1	Bladder: D15cc	numeric				
RPD_LA_BL_D05_1	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_1	Femoral heads - Left: D10cc	numeric				
RPD_LA_FHR_D10_1	Femoral heads - Right: D10cc	numeric				
RPD_LA_KD_MKD_1	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_LA_KD_D700_1	Kidneys (individual and combined): Dose to >=700	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_SKD_D10_1	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_LA_LV_V10_1	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_LA_LV_MLD_1	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_LA_LV_D50_1	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_LA_LV_D700_1	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_LA_S_D01_1	Sacral plexus: DMax (0.1cc)	numeric				
RPD_LA_S_D5_1	Sacral plexus: D5cc	numeric				
RPD_LA_PB_D3_1	Penile Bulb: D3cc	numeric				
RPD_LA_PB_D05_1	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LA_UR_D05_1	Ureter: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_TTMIN_1	Treatment time (mins)	numeric				
RPD_LA_PPMIN_1	Physics time to plan (mins)	numeric				
UPPER LIMBS						
RPD_UL_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_UL_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UL_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UL_PISO_1	Prescription isodose	numeric				
RPD_UL_LG_V20_1	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UL_LG_V125_1	Normal Lungs (Lungs-GTV):V12.5Gy	numeric				
RPD_UL_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_UL_SK_D10_1	Skin: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UL_HR_D05_1	Heart: DMax (0.5cc)	numeric				
RPD_UL_TTMIN_1	Treatment time (mins)	numeric				
RPD_UL_PPMIN_1	Physics time to plan (mins)	numeric				
LOWER LIMBS						
RPD_LL_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_LL_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LL_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_1	Prescription isodose	numeric				
RPD_LL_BL_D15_1	Bladder: D15cc	numeric				
RPD_LL_BL_D05_1	Bladder: DMax (0.5cc)	numeric				
RPD_LL_PB_D3_1	Penile Bulb: D3cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LL_PB_D05_1	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LL_UR_D05_1	Ureter: DMax (0.5cc)	numeric				
RPD_LL_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_LL_SK_D10_1	Skin: D10cc	numeric				
RPD_LL_TTMIN_1	Treatment time (mins)	numeric				
RPD_LL_PPMIN_1	Physics time to plan (mins)	numeric				

Radiotherapy Planning Details_2

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_TRTAREA_2	Second treatment area at baseline	text				Cannot be modified. This is read from the baseline form.
RPD_STDTE_2	Start date of second SABR treatment at baseline	date			√	
RPD_SPDTE_2	Completion date of second SABR treatment at baseline	date			√	
RPD_PCON_2	Were all planning constraints met?	numeric	1-yes 2-no		√	At least one site to be chosen
RPD_PTVC_2	Was PTV coverage >95% achieved?	numeric	1-yes 2-no		√	
RPD_SITE_THO_2	Thorax treated for second SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_UABM_2	Upper Abdomen treated for second SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LABM_2	Lower Abdomen treated for second SABR treatment	numeric	-1-yes			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			0-no			
RPD_SITE_ULMB_2	Upper Limb treated for second SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LLMB_2	Lower Limb treated for second SABR treatment	numeric	-1-yes 0-no			
THORAX (C SPINE, T SPINE, LUNG, MEDIASTINUM)						
RPD_THO_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_THO_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_THO_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_THO_PISO_2	Prescription isodose	numeric				
RPD_THO_SC_DM01_2	Spinal Canal: DMax (0.1cc)	numeric				
RPD_THO_SC_D12_2	Spinal canal: D1.2cc	numeric				
RPD_THO_OG_DM05_2	Oesophagus: DMax (0.5cc)	numeric				
RPD_THO_LG_V20_2	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_THO_LG_V125_2	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_THO_HR_DM05_2	Heart: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_SK_DM05_2	Skin: DMax (0.5cc)	numeric				
RPD_THO_SK_D10_2	Skin: D10cc	numeric				
RPD_THO_ST_DM05_2	Stomach: DMax (0.5cc)	numeric				
RPD_THO_ST_D55_2	Stomach: D5cc	numeric				
RPD_THO_ST_D10_2	Stomach: D10cc	numeric				
RPD_THO_ST_D50_2	Stomach: D50cc	numeric				
RPD_THO_LV_V10_2	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_THO_LV_MLD_2	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_THO_LV_D50PT_2	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_THO_LV_D700_2	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_THO_CW_DM05_2	Chest Wall: DMax (0.5cc)	numeric				
RPD_THO_CW_D30_2	Chest Wall: D30cc	numeric				
RPD_THO_GV_DM05_2	Great Vessels: DMax (0.5cc)	numeric				
RPD_THO_BP_D05_2	Brachial Plexus: Dmax (0.5cc)	numeric				
RPD_THO_TB_D05_2	Trachea and bronchus: Dmax (0.5cc)	numeric				
RPD_THO_TTMIN_2	Treatment time (mins)	numeric				
RPD_THO_PPMIN_2	Physics time to plan (mins)	numeric				
UPPER ABDOMEN						

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_UA_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UA_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UA_PISO_2	Prescription isodose	numeric				
RPD_UA_SC_D01_2	Spinal Canal : DMax (0.1cc)	numeric				
RPD_UA_SC_D12_2	Spinal Canal: D1.2cc	numeric				
RPD_UA_OG_D05_2	Oesophagus: DMax (0.5cc)	numeric				
RPD_UA_CE_D01_2	Cauda Equina: DMax (0.1cc)	numeric				
RPD_UA_CE_D5_2	Cauda Equina: D5cc	numeric				
RPD_UA_LG_V20_2	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UA_LG_V125_2	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_UA_HR_D05_2	Heart: DMax (0.5cc)	numeric				
RPD_UA_SK_D05_2	Skin: DMax (0.5cc)	numeric				
RPD_UA_SK_D10_2	Skin: D10cc	numeric				
RPD_UA_ST_D05_2	Stomach: DMax (0.5cc)	numeric				
RPD_UA_ST_D5_2	Stomach: D5cc	numeric				
RPD_UA_ST_D10_2	Stomach: D10cc	numeric				
RPD_UA_ST_D50_2	Stomach: D50cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_DD_D05_2	Duodenum: DMax (0.5cc)	numeric				
RPD_UA_DD_D1_2	Duodenum: D1cc	numeric				
RPD_UA_DD_D5_2	Duodenum: D5cc	numeric				
RPD_UA_DD_D9_2	Duodenum: D9cc	numeric				
RPD_UA_DD_D10_2	Duodenum: D10cc	numeric				
RPD_UA_SB_D05_2	Small bowel: DMax (0.5cc)	numeric				
RPD_UA_SB_D5_2	Small bowel: D5cc	numeric				
RPD_UA_SB_D10_2	Small bowel: D10cc	numeric				
RPD_UA_LB_D05_2	Large bowel: DMax (0.5cc)	numeric				
RPD_UA_KD_MKD_2	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_UA_KD_D700_2	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_UA_SKD_D10_2	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_UA_LV_V10_2	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_UA_LV_MLD_2	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_UA_LV_D50_2	Normal Liver (Liver minus GTV): D50%	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_LV_D700_2	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_UA_TTMIN_2	Treatment time (mins)	numeric				
RPD_UA_PPMIN_2	Physics time to plan (mins)	numeric				
LOWER ABDOMEN						
RPD_LA_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_LA_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LA_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LA_PISO_2	Prescription isodose	numeric				
RPD_LA_SC_D01_2	Spinal Canal: DMax (0.1cc)	numeric				
RPD_LA_SC_D12_2	Spinal Canal: D1.2cc	numeric				
RPD_LA_CE_D01_2	Cauda Equina: Dmax (0.1cc)	numeric				
RPD_LA_CE_D5_2	Cauda Equina: D5cc	numeric				
RPD_LA_SK_D05_2	Skin: DMax (0.5cc)	numeric				
RPD_LA_SK_D10_2	Skin: D10cc	numeric				
RPD_LA_DD_D05_2	Duodenum: DMax (0.5cc)	numeric				
RPD_LA_DD_D1_2	Duodenum: D1cc	numeric				
RPD_LA_DD_D5_2	Duodenum: D5cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_DD_D9_2	Duodenum: D9cc	numeric				
RPD_LA_DD_D10_2	Duodenum: D10cc	numeric				
RPD_LA_SB_D05_2	Small bowel: DMax (0.5cc)	numeric				
RPD_LA_SB_D5_2	Small bowel: D5cc	numeric				
RPD_LA_SB_D10_2	Small bowel: D10cc	numeric				
RPD_LA_LB_D05_2	Large bowel: DMax (0.5cc)	numeric				
RPD_LA_LB_D20_2	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_2	Bladder: D15cc	numeric				
RPD_LA_BL_D05_2	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_2	Femoral heads - Left: D10cc	numeric				
RPD_LA_FHR_D10_2	Femoral heads - Right: D10cc	numeric				
RPD_LA_KD_MKD_2	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_LA_KD_D700_2	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_LA_SKD_D10_2	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_LA_LV_V10_2	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_LA_LV_MLD_2	Normal Liver (Liver minus GTV): mean liver dose	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_LV_D50_2	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_LA_LV_D700_2	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_LA_S_D01_2	Sacral plexus: DMax (0.1cc)	numeric				
RPD_LA_S_D5_2	Sacral plexus: D5cc	numeric				
RPD_LA_PB_D3_2	Penile Bulb: D3cc	numeric				
RPD_LA_PB_D05_2	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LA_UR_D05_2	Ureter: DMax (0.5cc)	numeric				
RPD_LA_TTMIN_2	Treatment time (mins)	numeric				
RPD_LA_PPMIN_2	Physics time to plan (mins)	numeric				
UPPER LIMBS						
RPD_UL_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_UL_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UL_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UL_PISO_2	Prescription isodose	numeric				
RPD_UL_LG_V20_2	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UL_LG_V125_2	Normal Lungs (Lungs-GTV):V12.5Gy	numeric				
RPD_UL_SK_D05_2	Skin: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UL_SK_D10_2	Skin: D10cc	numeric				
RPD_UL_HR_D05_2	Heart: DMax (0.5cc)	numeric				
RPD_UL_TTMIN_2	Treatment time (mins)	numeric				
RPD_UL_PPMIN_2	Physics time to plan (mins)	numeric				
LOWER LIMBS						
RPD_LL_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_LL_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LL_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_2	Prescription isodose	numeric				
RPD_LL_BL_D15_2	Bladder: D15cc	numeric				
RPD_LL_BL_D05_2	Bladder: DMax (0.5cc)	numeric				
RPD_LL_PB_D3_2	Penile Bulb: D3cc	numeric				
RPD_LL_PB_D05_2	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LL_UR_D05_2	Ureter: DMax (0.5cc)	numeric				
RPD_LL_SK_D05_2	Skin: DMax (0.5cc)	numeric				
RPD_LL_SK_D10_2	Skin: D10cc	numeric				
RPD_LL_TTMIN_2	Treatment time (mins)	numeric				
RPD_LL_PPMIN_2	Physics time to plan (mins)	numeric				

Radiotherapy Planning Details_3

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_TRTAREA_3	Third treatment area at baseline	text				Cannot be modified. This is read from the baseline form.
RPD_STDTE_3	Start date of third SABR treatment at baseline	date			√	
RPD_SPDTE_3	Completion date of third SABR treatment at baseline	date			√	
RPD_PCON_3	Were all planning constraints met?	numeric	1-yes 2-no		√	At least one site to be chosen
RPD_PTVC_3	Was PTV coverage >95% achieved?	numeric	1-yes 2-no		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_SITE_THO_3	Thorax treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_UABM_3	Upper Abdomen treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LABM_3	Lower Abdomen treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_ULMB_3	Upper Limb treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LLMB_3	Lower Limb treated for third SABR treatment	numeric	-1-yes 0-no			
THORAX (C SPINE, T SPINE, LUNG, MEDIASTINUM)						
RPD_THO_TDOS_3	Total dose of radiotherapy administered	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_THO_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_THO_PISO_3	Prescription isodose	numeric				
RPD_THO_SC_DM01_3	Spinal Canal: DMax (0.1cc)	numeric				
RPD_THO_SC_D12_3	Spinal canal: D1.2cc	numeric				
RPD_THO_OG_DM05_3	Oesophagus: DMax (0.5cc)	numeric				
RPD_THO_LG_V20_3	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_THO_LG_V125_3	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_THO_HR_DM05_3	Heart: DMax (0.5cc)	numeric				
RPD_THO_SK_DM05_3	Skin: DMax (0.5cc)	numeric				
RPD_THO_SK_D10_3	Skin: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_ST_DM05_3	Stomach: DMax (0.5cc)	numeric				
RPD_THO_ST_D55_3	Stomach: D5cc	numeric				
RPD_THO_ST_D10_3	Stomach: D10cc	numeric				
RPD_THO_ST_D50_3	Stomach: D50cc	numeric				
RPD_THO_LV_V10_3	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_THO_LV_MLD_3	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_THO_LV_D50PT_3	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_THO_LV_D700_3	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_THO_CW_DM05_3	Chest Wall: DMax (0.5cc)	numeric				
RPD_THO_CW_D30_3	Chest Wall: D30cc	numeric				
RPD_THO_GV_DM05_3	Great Vessels: DMax (0.5cc)	numeric				
RPD_THO_BP_D05_3	Brachial Plexus: Dmax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_TB_D05_3	Trachea and bronchus: Dmax (0.5cc)	numeric				
RPD_THO_TTMIN_3	Treatment time (mins)	numeric				
RPD_THO_PPMIN_3	Physics time to plan (mins)	numeric				
UPPER ABDOMEN						
RPD_UA_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_UA_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UA_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UA_PISO_3	Prescription isodose	numeric				
RPD_UA_SC_D01_3	Spinal Canal : DMax (0.1cc)	numeric				
RPD_UA_SC_D12_3	Spinal Canal: D1.2cc	numeric				
RPD_UA_OG_D05_3	Oesophagus: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_CE_D01_3	Cauda Equina: DMax (0.1cc)	numeric				
RPD_UA_CE_D5_3	Cauda Equina: D5cc	numeric				
RPD_UA_LG_V20_3	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UA_LG_V125_3	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_UA_HR_D05_3	Heart: DMax (0.5cc)	numeric				
RPD_UA_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_UA_SK_D10_3	Skin: D10cc	numeric				
RPD_UA_ST_D05_3	Stomach: DMax (0.5cc)	numeric				
RPD_UA_ST_D5_3	Stomach: D5cc	numeric				
RPD_UA_ST_D10_3	Stomach: D10cc	numeric				
RPD_UA_ST_D50_3	Stomach: D50cc	numeric				
RPD_UA_DD_D05_3	Duodenum: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_DD_D1_3	Duodenum: D1cc	numeric				
RPD_UA_DD_D5_3	Duodenum: D5cc	numeric				
RPD_UA_DD_D9_3	Duodenum: D9cc	numeric				
RPD_UA_DD_D10_3	Duodenum: D10cc	numeric				
RPD_UA_SB_D05_3	Small bowel: DMax (0.5cc)	numeric				
RPD_UA_SB_D5_3	Small bowel: D5cc	numeric				
RPD_UA_SB_D10_3	Small bowel: D10cc	numeric				
RPD_UA_LB_D05_3	Large bowel: DMax (0.5cc)	numeric				
RPD_UA_KD_MKD_3	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_UA_KD_D700_3	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_UA_SKD_D10_3	If solitary kidney or if one kidney mean dose >10Gy	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_LV_V10_3	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_UA_LV_MLD_3	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_UA_LV_D50_3	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_UA_LV_D700_3	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_UA_TTMIN_3	Treatment time (mins)	numeric				
RPD_UA_PPMIN_3	Physics time to plan (mins)	numeric				
LOWER ABDOMEN						
RPD_LA_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_LA_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LA_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LA_PISO_3	Prescription isodose	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_SC_D01_3	Spinal Canal: DMax (0.1cc)	numeric				
RPD_LA_SC_D12_3	Spinal Canal: D1.2cc	numeric				
RPD_LA_CE_D01_3	Cauda Equina: Dmax (0.1cc)	numeric				
RPD_LA_CE_D5_3	Cauda Equina: D5cc	numeric				
RPD_LA_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_LA_SK_D10_3	Skin: D10cc	numeric				
RPD_LA_DD_D05_3	Duodenum: DMax (0.5cc)	numeric				
RPD_LA_DD_D1_3	Duodenum: D1cc	numeric				
RPD_LA_DD_D5_3	Duodenum: D5cc	numeric				
RPD_LA_DD_D9_3	Duodenum: D9cc	numeric				
RPD_LA_DD_D10_3	Duodenum: D10cc	numeric				
RPD_LA_SB_D05_3	Small bowel: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_SB_D5_3	Small bowel: D5cc	numeric				
RPD_LA_SB_D10_3	Small bowel: D10cc	numeric				
RPD_LA_LB_D05_3	Large bowel: DMax (0.5cc)	numeric				
RPD_LA_LB_D20_3	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_3	Bladder: D15cc	numeric				
RPD_LA_BL_D05_3	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_3	Femoral heads - Left: D10cc	numeric				
RPD_LA_FHR_D10_3	Femoral heads - Right: D10cc	numeric				
RPD_LA_KD_MKD_3	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_LA_KD_D700_3	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_LA_SKD_D10_3	If solitary kidney or if one kidney mean dose >10Gy	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_LV_V10_3	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_LA_LV_MLD_3	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_LA_LV_D50_3	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_LA_LV_D700_3	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_LA_S_D01_3	Sacral plexus: DMax (0.1cc)	numeric				
RPD_LA_S_D5_3	Sacral plexus: D5cc	numeric				
RPD_LA_PB_D3_3	Penile Bulb: D3cc	numeric				
RPD_LA_PB_D05_3	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LA_UR_D05_3	Ureter: DMax (0.5cc)	numeric				
RPD_LA_TTMIN_3	Treatment time (mins)	numeric				
RPD_LA_PPMIN_3	Physics time to plan (mins)	numeric				
UPPER LIMBS						

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UL_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_UL_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UL_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UL_PISO_3	Prescription isodose	numeric				
RPD_UL_LG_V20_3	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UL_LG_V125_3	Normal Lungs (Lungs-GTV):V12.5Gy	numeric				
RPD_UL_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_UL_SK_D10_3	Skin: D10cc	numeric				
RPD_UL_HR_D05_3	Heart: DMax (0.5cc)	numeric				
RPD_UL_TTMIN_3	Treatment time (mins)	numeric				
RPD_UL_PPMIN_3	Physics time to plan (mins)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
LOWER LIMBS						
RPD_LL_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_LL_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LL_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_3	Prescription isodose	numeric				
RPD_LL_BL_D15_3	Bladder: D15cc	numeric				
RPD_LL_BL_D05_3	Bladder: DMax (0.5cc)	numeric				
RPD_LL_PB_D3_3	Penile Bulb: D3cc	numeric				
RPD_LL_PB_D05_3	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LL_UR_D05_3	Ureter: DMax (0.5cc)	numeric				
RPD_LL_SK_D05_3	Skin: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LL_SK_D10_3	Skin: D10cc	numeric				
RPD_LL_TTMIN_3	Treatment time (mins)	numeric				
RPD_LL_PPMIN_3	Physics time to plan (mins)	numeric				

Death

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
DT_DEAD	Patient deceased	numeric	1-yes 2-no		√	
DT_DOD	Date of death	date		Required if DT_DEAD (Patient deceased) is 1 (yes)	√	
DT_COD	Cause of death	text?		Required if DT_DEAD (Patient deceased) is 1 (yes)		
DT_CRD	Cancer related death	numeric	1-yes 2-no	Required if DT_DEAD (Patient deceased) is 1 (yes)		

15 Appendix E: Health economics appendices

15.1 Summary of parameters used in model:

Baseline deterministic values, range used in one-way and multi-way sensitivity analysis, distribution used in probabilistic sensitivity analyses, and references.

Interventions	Base-line value	Standard error	Range	Distribution	Source
Progression rate for treated patients (monthly)					
No progression to local progression	2.10%	Not reported	1-5%	Beta (α=16.93, β=789.07)	Calibrated from de Haas et al (de Haas et al., 2010)
No progression to regional/distant progression	0.93%	Not reported	0.5-2%	Beta (α=7.50, β=798.50)	As above
Local progression to regional/distant progression	3.58%	Not reported	1-5%	Beta (α=13.96, β=376.04)	As above
Progression rate for recurrent patients without retreatment (monthly)					
Local progression to regional/distant progression	12.49%	Not reported	10-15%	Beta (α=2.12, β=14.88)	Calibrated from mortality data for untreated patients with different cancer progression status
Mortality rate for treated patients (monthly)					
Patients with no progression	0.13%	Not reported	0.1-0.20%	Beta (α=0.32, β=242.68)	Calibrated from de Haas et al (de Haas et al., 2010)
Patients with local progression	1.55%	Not reported	1-3%	Beta (α=6.05, β=383.96)	Calibrated from de Haas et al (de Haas et al., 2010) and mortality rate for patients with no progression or

Interventions	Base-line value	Standard error	Range	Distribution	Source
Patients with regional/distant progression	3.06%	Not reported	1-5%	Beta (α=11.60, β=367.40)	regional/distant progression Rees et al (Rees et al., 2008)
Mortality for recurrent patients without retreatment (monthly)					
Patients with local progression	8.67%	Not reported	5-15%	Beta (α=1.47, β=15.53)	Calibrated from Görög et al (Gorog et al., 1997)
Probability of retreatment (monthly)					
Probability of retreatment for patients receiving surgery	30.74%	Not reported	30.74-54.00%	Beta (α=71, β=160)	(Lee et al., 2015, Neal et al., 2017, Imai et al., 2018)
Probability of retreatment for patients receiving RFA	34.78%	Not reported	18.18-66.67%	Beta (α=8, β=15)	(Wood et al., 2000, Aloia et al., 2006, van Duijnhoven et al., 2006, Berber & Siperstein, 2008, Sgouros et al., 2011, Shady et al., 2016)
Probability of retreatment for patients receiving SABR	As above	Not reported	18.18-80.00%	As above	As above
SAEs (monthly)					
Probability of SAEs after surgery	16.55%	Not reported	5-20%	Beta (α=46, β=232)	Calculated from Kim et al (Kim et al., 2011)

Interventions	Base-line value	Standard error	Range	Distribution	Source
Probability of SAEs after RFA	5.08%	Not reported	2-10%	Beta (α=9, β=168)	As above
Probability of SAEs after SABR	2.97%	Not reported	2-10%	Beta (α=3, β=98)	CtE programme
Cost of interventions					
Cost of surgery	£6,938.15	Assumed 30% of mean value	£5,000-£8,000	Gamma	NHS reference cost 2015-16 (Department of Health, 2016)
Cost of retreatment with surgery	As above	As above	As above	As above	As above
Cost of RFA	£4,961.46	Assumed 30% of mean value	£3,000-£6,000	Gamma	Uplifted from Loveman et al (Loveman et al., 2014) and adjusted for days of additional hospital stay (Kim et al., 2011)
Cost of retreatment with RFA	As above	As above	As above	As above	As above
Cost for SABR	4,433.00	Assumed 30% of mean value	£3,000-£6,000	Gamma	(NHS England, 2015)
Cost of retreatment with SABR	As above	As above	As above	As above	As above
Cost of treating SAEs					

Interventions	Base-line value	Standard error	Range	Distribution	Source
Cost of treating SAEs	£557.49	Assumed 30% of mean value	£200-£2,000	Gamma	Uplifted from Loveman et al (Loveman et al., 2014)
Other cost data					
Outpatient follow-up	£296.84	Assumed 30% of mean value	Assumed fixed	Gamma	(Department of Health, 2016)
Palliative care (per month)	£775.44	As above	Assumed fixed	Gamma	Uplifted from Tappenden et al (Tappenden et al., 2007)
Utility					
Progression free without SAEs	0.86	0.21	0.65-0.90	Beta	CtE programme and other published data (Krabbe et al., 2004, Mendez Romero et al., 2008, Wiering et al., 2010)
Progression free with SAEs	0.40	As above	0.26-0.56	Beta	(Mendez Romero et al., 2008, Wiering et al., 2011, Roberts et al., 2015)
Local progression	0.65	As above	0.60-0.70	Beta	(Mendez Romero et al., 2008,

Interventions	Base-line value	Standard error	Range	Distribution	Source
Regional/ distant progression	0.19	As above	0.15-0.40	Beta	Wiering et al., 2011, Roberts et al., 2015) (Mendez Romero et al., 2008, Wiering et al., 2011, Roberts et al., 2015)

15.2 One-way sensitivity analysis results

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Base case analysis results							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set transition rate from no progression to local progression to 1% *(base case value: 2.1%)*							
SABR	15,948	2.7980	–	–	Dominating	1	1
RFA	16,542	2.7975	–	–	Dominated	2	2
Surgery	18,718	2.7830	–	–	Dominated	3	3
Set transition rate from no progression to local progression to 5% *(base case value: 2.1%)*							
SABR	18,249	2.1282	–	–	Dominating	1	1
RFA	18,926	2.1276	–	–	Dominated	2	2
Surgery	21,305	2.1047	–	–	Dominated	3	3
Set transition rate from no progression to regional/distant progression to 0.5% *(base case value: 0.93%)*							
SABR	15,477	2.7704	–	–	Dominating	1	1
RFA	16,119	2.7699	–	–	Dominated	2	2
Surgery	18,442	2.7454	–	–	Dominated	3	3
Set transition rate from no progression to regional/distant progression to 2% *(base case value: 0.93%)*							
SABR	19,468	2.1462	–	–	Dominating	1	1
RFA	20,082	2.1457	–	–	Dominated	2	2
Surgery	22,281	2.1315	–	–	Dominated	3	3
Set transition rate from local progression to regional/distant progression to 1% *(base case value: 3.58%)*							
SABR	15,105	2.6812	–	–	Dominating	1	1
RFA	15,737	2.6806	–	–	Dominated	2	2
Surgery	17,950	2.6646	–	–	Dominated	3	3

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Set transition rate from local progression to regional/distant progression to 5% *(base case value: 3.58%)*							
SABR	17,456	2.5181	–	–	Dominating	1	1
RFA	18,089	2.5175	–	–	Dominated	2	2
Surgery	20,389	2.4951	–	–	Dominated	3	3
Set transition rate from local progression to regional/distant progression for untreated patients to 10% *(base case value: 12.49%)*							
SABR	15,105	2.6812	–	–	Dominating	1	1
RFA	15,737	2.6806	–	–	Dominated	2	2
Surgery	17,950	2.6646	–	–	Dominated	3	3
Set transition rate from local progression to regional/distant progression for untreated patients to 15% *(base case value: 12.49%)*							
SABR	17,456	2.5181	–	–	Dominating	1	1
RFA	18,089	2.5175	–	–	Dominated	2	2
Surgery	20,389	2.4951	–	–	Dominated	3	3
Set mortality rate for patients with no progression to 0.10% *(base case value: 0.13%)*							
SABR	16,931	2.5764	–	–	Dominating	1	1
RFA	17,564	2.5758	–	–	Dominated	2	2
Surgery	19,845	2.5547	–	–	Dominated	3	3
Set mortality rate for patients with no progression to 0.20% *(base case value: 0.13%)*							
SABR	16,707	2.5228	–	–	Dominating	1	1
RFA	17,338	2.5223	–	–	Dominated	2	2
Surgery	19,615	2.5020	–	–	Dominated	3	3
Set mortality rate for patients with local progression to 1% *(base case value: 1.55%)*							
SABR	17,141	2.5915	–	–	Dominating	1	1
RFA	17,774	2.5909	–	–	Dominated	2	2
Surgery	20,065	2.5710	–	–	Dominated	3	3
Set mortality rate for patients with local progression to 3% *(base case value: 1.55%)*							
SABR	16,249	2.4921	–	–	Dominating	1	1
RFA	16,881	2.4915	–	–	Dominated	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Surgery	19,135	2.4688	–	–	Dominated	3	3
Set mortality rate for patients with regional/distant progression to 1% *(base case value: 3.06%)*							
SABR	20,131	2.6193	–	–	Dominating	1	1
RFA	20,763	2.6187	–	–	Dominated	2	2
Surgery	23,073	2.5985	–	–	Dominated	3	3
Set mortality rate for patients with regional/distant progression to 5% *(base case value: 3.06%)*							
SABR	14,978	2.5260	–	–	Dominating	1	1
RFA	15,611	2.5254	–	–	Dominated	2	2
Surgery	17,873	2.5043	–	–	Dominated	3	3
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of surgery to 54.00% *(base case value: 30.74%)*							
SABR	16,863	2.5601	–	–	–	1	2
RFA	17,496	2.5596	–	–	Dominated	2	3
Surgery	20,352	2.6416				3	1
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of RFA or SABR to 18.18% *(base case value: 34.78%)*							
SABR	16,675	2.4863	–	–	–	1	2
RFA	17,261	2.4858	–	–	Dominated	2	3
Surgery	19,775	2.5387	3,100	0.0524	59,107	3	1
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of RFA or SABR to 66.67% *(base case value: 34.78%)*							
SABR	17,224	2.7019	–	–	Dominating	1	1
RFA	17,947	2.7013	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of SABR to 80.00% *(base case value: 34.78%)*							
SABR	17,375	2.7612	–	–	Dominating	1	1

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set probability of developed SAEs after surgery to 5% *(base case value: 16.55%)*							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,733	2.5416	–	–	Dominated	3	3
Set probability of developed SAEs after surgery to 20% *(base case value: 16.55%)*							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,788	2.5379	–	–	Dominated	3	3
Set probability of developed SAEs after RFA to 2% *(base case value: 5.08%)*							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,484	2.5604	621	0.0003	2,472,232	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set probability of developed SAEs after RFA to 10% *(base case value: 5.08%)*							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,514	2.5583	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set probability of developed SAEs after SABR to 2% *(base case value: 2.97%)*							
SABR	16,860	2.5604	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set probability of developed SAEs after SABR to 10% *(base case value: 2.97%)*							
SABR	16,890	2.5583	–	–	–	1	1
RFA	17,496	2.5596	606	0.0013	475,736	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set cost of surgery to £5,000 *(base case value: £6,938.15)*							

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	17,525	2.5387	–	–	Dominated	3	3
Set cost of surgery to £8,000 *(base case value: £6,938.15)*							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	21,008	2.5387	–	–	Dominated	3	3
Set cost of RFA to £3,000 *(base case value: £4,961.46)*							
SABR	16,863	2.5601	1,686	0.0005	3,085,443	2	2
RFA	15,177	2.5596	–	–	–	1	1
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set cost of RFA to £6,000 *(base case value: £4,961.46)*							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	18,723	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set cost of SABR to £3,000 *(base case value: £4,433.00)*							
SABR	15,169	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set cost of SABR to £6,000 *(base case value: £4,433.00)*							
SABR	18,715	2.5601	1,220	0.0005	2,232,114	2	2
RFA	17,496	2.5596	–	–	–	1	1
Surgery	19,775	2.5387	–	–	Dominated	3	3
Set cost of treating SAEs to £200 *(base case value: £557.49)*							
SABR	16,856	2.5601	–	–	Dominating	1	1
RFA	17,484	2.5596	–	–	Dominated	2	2
Surgery	19,736	2.5387	–	–	Dominated	3	3

Intervention	Cost (£)	QALY	Incremental cost	ncremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Set cost of treating SAEs to £2,000 *(base case value: £557.49)*							
SABR	16,892	2.5601	–	–	Dominating	1	1
RFA	17,545	2.5596	–	–	Dominated	2	2
Surgery	19,932	2.5387	–	–	Dominated	3	3
Set utility for 'progression free without SAEs' = 0.65 *(base case value: 0.86)*							
SABR	16,863	2.0584	–	–	Dominating	1	1
RFA	17,496	2.0581	–	–	Dominated	2	2
Surgery	19,775	2.0458	–	–	Dominated	3	3
Set utility for 'progression free without SAEs' = 0.90 *(base case value: 0.86)*							
SABR	16,863	2.6557	–	–	Dominating	1	1
RFA	17,496	2.6551	–	–	Dominated	2	2
Surgery	19,775	2.6326	–	–	Dominated	3	3
Set utility for 'Progression free with SAEs' = 0.26 *(base case value: 0.40)*							
SABR	16,863	2.5599	–	–	Dominating	1	1
RFA	17,496	2.5592	–	–	Dominated	2	2
Surgery	19,775	2.5375	–	–	Dominated	3	3
Set utility for 'Progression free with SAEs' = 0.56 *(base case value: 0.40)*							
SABR	16,863	2.5604	–	–	Dominating	1	1
RFA	17,496	2.5600	–	–	Dominated	2	2
Surgery	19,775	2.5402	–	–	Dominated	3	3
Set utility for 'Local progression' = 0.60 *(base case value: 0.65)*							
SABR	16,863	2.5326	–	–	Dominating	1	1
RFA	17,496	2.5321	–	–	Dominated	2	2
Surgery	19,775	2.5104	–	–	Dominated	3	3
Set utility for 'Local progression' = 0.70 *(base case value: 0.65)*							
SABR	16,863	2.5876	–	–	Dominating	1	1
RFA	17,496	2.5871	–	–	Dominated	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Surgery	19,775	2.5671	–	–	Dominated	3	3
Set utility for 'Regional/ distant progression' = 0.15 *(base case value: 0.19)*							
SABR	16,863	2.5292	–	–	Dominating	1	1
RFA	17,496	2.5286	–	–	Dominated	2	2
Surgery	19,775	2.5075	–	–	Dominated	3	3
Set utility for 'Regional/distant progression' = 0.40 *(base case value: 0.19)*							
SABR	16,863	2.7226	–	–	Dominating	1	1
RFA	17,496	2.7221	–	–	Dominated	2	2
Surgery	19,775	2.7027	–	–	Dominated	3	3

16 Appendix F: Adverse events data quality checks

KiTEC note that there were n=17 CTCAE grade 5 adverse events amongst n=17 patients (corresponding to death) across all three CtE indications. Of these, three patients were also recorded as having died as defined by the date of death (variable DT_DOD). One of these patients had a CTCAE grade 5 '*Urinary Retention*' death adverse event occurring (according to the Adverse Event form) five months before the DT_DOD reported date of death. One of these patients had a CTCAE grade 5 '*Spinal Fracture*' death adverse event occurring (according to the Adverse Event form) almost two years before the DT_DOD and HES/ONS reported date of death. KiTEC have used the DT_DOD date of death in the analysis in this report in these two instances. One of these patients had a CTCAE grade 5 '*Pneumonitis*' death adverse event (according to the Adverse Event form) with no recorded adverse event date, therefore KiTEC have used the DT_DOD variable as date of death.

KiTEC note that the remaining n=14 adverse events amongst 14 patients recorded as a CTCAE grade 5 (i.e. death) did not have death recorded as an outcome in either the PROPEL database designated field or in the HES/ONS national registries. These adverse event/deaths were therefore, considered errors, and were not included as events in the survival analyses.

As part of data quality checks, KiTEC requested the database provider to contact all centres and verify the presence or not of grade 5 events. All centres verified that no grade 5 events occurred in these 17 patients and that the recording of those events in PROPEL was due to wrong data entries.

17Appendix G: Data working group membership

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