Clinical Commissioning Policy
Stereotactic ablative radiotherapy (SABR) for patients with metachronous extracranial oligometastatic cancer (all ages) (URN: 1908) [200205P]

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Commissioning position

Summary
SABR will be available as a treatment option through routine commissioning for patients (all ages) with controlled primary cancer presenting with up to three extracranial metachronous oligometastases which manifest after a disease-free interval following primary treatment of at least 6 months, in line with the criteria set out in this document.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

About metachronous oligometastatic cancer

Oligometastatic cancer is a form of metastatic cancer. Metastatic cancer is a cancer that has spread from the part of the body where it started (the primary site) to other parts of the body. When cancer spreads, the most common sites it spreads to are the lymph nodes, lung, bones, spine and liver. Metastatic cancer is diagnosed in approximately 140,000 patients in England per year (Cancer Research UK (CRUK)), 2018.

There is no consensus on the definition of oligometastatic cancer, however, the disease is usually confined to a small number of sites in the body (between one to five sites), as opposed to being widespread across the body (European Society for Medical Oncology, 2018).

Metastatic cancer can occur at diagnosis or the cancer can come back after previous treatment. If the metastasis develops more than six months after the original (primary) cancer is treated this is called a metachronous metastasis.

This policy is specifically for people with metachronous oligometastatic disease who present with up to three sites of metastases, confined to the following organs: (i) bone; (ii) spine; (iii) lymph nodes; (iv) liver; (v) adrenal gland; and/or (vi) lung.

About the new treatment

SABR is a highly targeted form of radiotherapy which targets a tumour with radiation beams from different angles at the same time. The treatment is delivered in a fewer number of treatments (hypofractionation) than conventional radiotherapy using one, three, five or eight

fractions. The aim of treatment with SABR is to ensure that the tumour receives a high dose of radiation whilst the tissues close to the tumour receive a lower dose of radiation sparing the surrounding healthy normal tissues.

SABR, limited to up to three sites of oligometastatic disease, may prolong disease-free survival and overall survival, delaying the use of systemic treatment in people with metachronous oligometastatic disease.

What we have decided

NHS England has carefully reviewed the evidence to treat metachronous extracranial oligometastatic cancer with SABR within the criteria set out in this document. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This document replaces and updates:
NHS England (2016). *Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of Oligometastatic disease.* Available at: https://www.england.nhs.uk/wp-content/uploads/2018/07/Stereotactic-ablative -radiotherapy-as-a-treatment-option-for-patients-with-oligometastatic-disease.pdf [Accessed 25 Apr. 2019].

Committee discussion

The Clinical Panel noted that the evidence base suggested that there was a significant benefit with respect to survival demonstrated with the use of SABR, doubling overall survival to around 13-14 months. Although some toxicity was demonstrated, this was likely to be considered tolerable by patients. In addition, there was some additional benefit demonstrated in terms of local control with respect to the newer technology and some studies reporting an increase in quality of life using disease specific questionnaires.

The Clinical Panel noted that the evidence base provided support the clinical effectiveness of SABR was further supported by the CtE report. They agreed that it was appropriate for the policy to include all types of metastases as there was no evidence to suggest this was not appropriate and the evidence presented for breast and bowel cancer was considered translatable to other tumour sites.

See the committee papers (link) for full details of the evidence.

The condition

Oligometastatic disease is defined by the presence of a limited number of clinically detectable lesions, usually between one to five metastases across the body (European Society for Medical Oncology, 2018). It is thought that treatment of oligometastatic disease can result in local control and can prevent the spread of widespread metastases (Hellman and Weichselbaum, 1995).

The time lag between primary and secondary tumours (metastases) can vary. If metastases develop at the time of diagnosis of the primary tumour, this is referred to as synchronous disease. However, this policy is specifically for the treatment of people with oligometastatic disease that develops at least six months after treatment of the primary tumour, known as metachronous disease.

Current treatments

Treatments for metachronous oligometastatic disease depend on location of the metastases but can include: (i) surgical excision; (ii) RFA; (iii) systemic treatment; and (iv) radiotherapy. The aim of treatment is usually to control symptoms and extend life expectancy.

Proposed treatments

SABR, a form of hypofractionated radiotherapy, should be routinely offered for the treatment of metachronous extracranial oligometastatic cancer. The use of SABR in this indication is thought to: (i) prolong disease free survival; (ii) delay the use of systemic treatment; (iii) improve quality of life; and (iv) improve overall survival in this indication.

Epidemiology and needs assessment

Metastatic cancer is diagnosed in approximately 140,000 patients in England per year (Cancer Research UK (CRUK), 2018). All patients presenting with maximum of three sites of extracranial, metachronous oligometastatic disease from any primary site and confined to the bone, spine, lymph nodes, liver, adrenal gland and/or lung would be eligible for treatment with SABR.

The SABR Commissioning through Evaluation (CtE) programme treated 1,500 patients over a three-year period. As a result, the Policy Working Group estimate that approximately 2,200 patients per year would be suitable for SABR treatment in line with the criteria set out in this policy.

Cranial Central Nervous System (CNS) metastases are covered by a separate clinical commissioning policy (NHS England Reference: NHSCB/ D05/P/d).

Evidence review

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication. NHS England has carried out an evidence review (KiTEC, 2019) and an evaluation report of the SABR Commissioning through Evaluation (CtE) programme (KiTEC, 2019).

Sixteen studies met the inclusion criteria for clinical effectiveness and safety (Kunos et al. 2012, Stintzing et al. 2013, Comito et al. 2014, Navarria et al. 2014, Filippi et al. 2016, Lodeweges et al. 2017, Ricco et al. 2017, Warren et al. 2017, Andratschke et al. 2018, Klement et al. 2018, Lee et al. 2018, Mahadevan et al. 2018, Ost et al. 2018, Siva et al. 2018, Palma et al. 2019, Sutera et al. 2019).

Two studies reported results of a randomised controlled trial (RCT) (Ost et al. 2018, Palma et al. 2019).

There were four non randomised comparative studies (Stintzing et al. 2013, Filippi et al. 2016, Lodeweges et al. 2017, Lee et al. 2018). Three of them compared SABR with surgery (Filippi et al., 2016, Lee et al., 2018, Lodeweges et al., 2017) for treating patients with pulmonary metastases and one (Stintzing et al. 2013) compared SABR with RFA for treating patients with liver oligometastases. Six studies were prospective non-comparative cohort studies (Kunos et al. 2012, Comito et al. 2014, Navarria et al. 2014, Warren et al. 2017, Siva et al. 2018, Sutera et al. 2019).

Finally, four studies were large registries mainly of retrospectively collected data (Ricco et al. 2017, Andratschke et al. 2018, Klement et al. 2018, Mahadevan et al. 2018).

SABR effect on overall survival

Twelve studies reported the impact of SABR treatment on overall survival. All of the studies reported actuarial survival and 9 of the studies additionally reported median overall survival. The strongest evidence is provided by a phase II RCT by Palma et al. (2019)[1] that analysed patients with oligometastases from various primary tumours and in various locations. The authors reported a median overall survival of 41 months (95% CI 26-not reached) with SABR and 28 months (95% CI 19-33, HR: 0.57, p=0.09) with standard care (comprising of palliative radiotherapy and/or chemotherapy). 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%) compared to standard care. 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 findings of SABR-COMET, is corroborated by a prospective cohort study (Sutera et al. 2019) with a median overall survival of 42.3 months (95%CI 27.4-not reached). Both studies recruited a contemporary cohort, and had comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various metastases locations.

Although some studies reported smaller median survival with SABR, for example Kunos et al. 2012 reported only 20.2 months median overall survival (95% CI 10.9-29.5), they were characterised by potential sources of bias such as short follow-up duration, recruiting only patients from a single primary diagnosis, treated with palliative intent, and in some cases recruiting patients for almost two decades, making the population, intervention and other aspects of the patient treatment and follow-up less comparable to a contemporary cohort. There is good evidence to confirm the superiority of SABR against standard care (RCT by Palma et al. 2019), albeit to the expense of a higher rate of toxicity with the intervention, and more importantly grade 5 (G5) adverse events (i.e. deaths).

Four other comparative studies, provided weak evidence that SABR is non-inferior to surgery in the case of pulmonary metastases, and to radiofrequency ablation (RFA) for liver metastases. However, the evidence provided should be interpreted with caution given that these were retrospective and underpowered studies.

SABR effect on progression free survival

Ten of the included studies reported progression-free survival (PFS) with SABR as a secondary outcome. The strongest evidence for this outcome is provided by SABR-COMET. The authors concluded that use of SABR doubles the PFS from 6 months with standard care to 12 months (HR: 0.47, 95% CI 0.3-0.6, p=0.0012).

SABR effect on local control

Ten studies reported the impact of SABR treatment on local control (LC). The majority of the evidence comes from non-comparative cohort studies, with three case -control series. The studies report local control rates of 83-97% at 1 year and 71-95% at 2 years. Lower lesion size and higher overall dose received improved LC. However, primary tumour histology did not affect the outcome in most studies. The study reported 91% and 80% local control rates at 1- and 2-years, respectively. In all three comparative studies LC with SABR was not statistically significant to either surgery or RFA. However, the evidence provided should be interpreted with caution given the retrospective nature and small sample sizes of these studies.

[1]Throughout the document the references Palma et al. (2019) and SABR-COMET are used interchangeably.

SABR effect on toxicity

Fourteen of the included studies provided results on toxicity. The strongest evidence comes from two RCTs, one investigating patients with oligometastases from different primary cancers with various lesion locations. The second RCT investigated only patients with prostate -related oligometastatic disease. Almost all studies used the Common Terminology Criteria for Adverse Events (CTCAE) criteria to record toxicity information; however, often the reporting was poor, failing to distinguish between acute and chronic toxicity.

With the exception of the RCT by 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 absence of grade 4 and grade 5 acute and chronic toxicity and very low rates of grade 3 events. In the case of the second RCT (Ost et al., 2018), there was only a low incidence of grade 1 toxicity reported with SABR. It should be noted, however, that (Ost et al. 2018) only included patients with prostate cancer.

Limitations of the evidence

Unlike the scope of the review, that includes patients with extracranial oligometastatic disease independent of the primary tumour histology and location of metastases, most existing evidence is focused either on a single histology (for example prostate or colorectal cancer) or location (pulmonary or liver metastases) and it is therefore difficult to generalise their findings. With the exception of the two RCTs, none of the other studies was adequately powered to detect a difference between the intervention and the comparator. Among other potential sources of bias we note the short follow-up duration in some studies, patients treated with palliative intent, and in some cases recruiting patients for almost two decades, making the population, intervention, and other aspects of the patient treatment and follow-up less comparable to a contemporary cohort. None of the studies included children.

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.

Finally, although the RCT by Palma et al. 2019 was powered to detect a difference in overall survival, this was calculated on the basis of a phase 2 study design (with an alpha of 0.20). A phase 3 trial adequately powered for survival and toxicity will be required to provide definitive evidence of the overall benefit.

CtE evaluation report

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 overall survival (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.

Implementation

All patients with cancer should have their care managed by a variety of different specialists working together as part of a tumour specific cancer multi-disciplinary team (MDT). The tumour specific MDT is responsible for radiotherapy case selection and should take into consideration patient comorbidities, potential adverse events and likely outcomes of treatment.

Inclusion Criteria

Patients meeting **all** of the following criteria will be eligible for treatment with SABR:

- Confirmed histological diagnosis of metastatic cancer originating from any primary cancer in the body, including carcinoma, sarcoma and melanoma.
- A disease-free interval between primary treatment and manifestation of metastases of at least six months.
- One to three sites of extracranial, metastatic disease only at the time of disease presentation, confined to one to two organs (defined after appropriate imaging) in the following:
- Bone;
- Spine
- Lymph node;
- Liver
- Adrenal gland; and/or
- Lung.
- Maximum size of 5 cm for any single metastasis.

In addition, patients eligible for SABR must have:

- A life expectancy of at least 6 months AND
- World Health Organisation (WHO) performance status ≤ 2.

Patients may only receive treatment with SABR for a maximum of three sites of metastases in line with the criteria described above. Should further metastases develop, alternative treatment options should be sought.

For patients being treated for spinal metastases, a maximum of 2 sites in the spine can be treated with SABR.

Exclusion Criteria

Treatment with SABR is unsuitable in people with:

- Haematological malignancies (e.g. lymphoma, myeloma);
- Evidence of intracranial disease;
- Evidence of spinal cord compression or spinal instability;
- Evidence of severe interstitial lung disease (for lung metastases);
- Poor liver function and a Child-Pugh score B (for liver metastases);
- More than three sites of metastatic disease or development of new metastases post treatment of a maximum of three lesions;
- A disease-free interval between primary treatment and manifestation of metastases of less than six months;
- A life expectancy of less than six months;
- Severe co-morbidities; or
- WHO performance status > 2.

In addition, SABR is not suitable in people who:

- Require irradiation of whole nodal field (e.g. supra-clavicular recurrence for breast cancer); or
- Have had previous treatment with SABR to the same site of the metastases in line with the criteria set out in this policy.

Dose and fractionation

It is expected that either one, three, five or eight fractions of SABR are used in the treatment of oligometastases. The dose and fractionation are dependent on the site of the oligometastatic disease and clinical scenario.

Patient pathway

Radiotherapy is part of an overall cancer management and treatment pathway. Decisions on the overall treatment plan should relate back to an MDT discussion and decision. Patients requiring radiotherapy are referred to a clinical oncologist for assessment, treatment planning and delivery of radiation fractions. Each fraction of radiation is delivered on one visit, usually as an outpatient basis.

Governance arrangements

The Service Specification for External Beam Radiotherapy (NHS England Reference: 170091S) describes the governance arrangements for this service. It is imperative that the radiotherapy service is fully compliant with this Service Specification and in particular, with the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) 2017.

Clinical governance systems and policies should be in place and integrated into the organisational governance with clear lines of accountability and responsibility for all clinical

governance functions. Providers should produce annual clinical governance reports as part of the NHS clinical governance reporting system. Providers must have an externally accredited quality management system (e.g. BSI) in place.

All providers must be compliant with radiotherapy quality assurance (RTQA) for contouring and outlining. A national approach to regular peer review of patient eligibility and treatment plans will be required.

In addition, all providers of treatment with SABR must:

- be compliant with the Improving Outcomes Guidance (IOG) for the range of primary tumours and have the relevant site-specific MDTs in place
- ensure all patients treated are subject to an MDT approach to patient selection and treatment including discussion at the site-specific MDT and SABR planning group
- have an adequate technical multi-professional radiotherapy SABR team present and able to deliver SABR radiotherapy and
- have minimum of two subspecialist clinical oncologists with experience in treating SABR patients.

Mechanism for funding

Radiotherapy planning and delivery is reimbursed through national prices included within the National Tariff Payment System.

Audit requirements

Radiotherapy providers must submit their activity to the national Radiotherapy Dataset (RTDS) on a monthly basis. Providers will collect the audit clinical outcome data through their own collection process for all SABR in line with the requirements set out in the Service Specification for External Beam Radiotherapy (NHS England Reference: 170091S).

Radiotherapy services are subject to regular self -assessment by the national Specialised Commissioning Quality Surveillance. The quality system and its treatment protocols will be subject to regular clinical management and audit as part of the development of radiotherapy networks in England.

The SABR Consortium Guidelines 2019 provide detailed information on each indication contained within this policy and can be found online here.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Best supportive care	Care which aims to prevent or treat as early as possible the symptoms of a disease and the side effects caused by treatment of a disease. It also aims to maintain psychological and emotional wellbeing. It is sometime also called palliative treatment.
Chemotherapy	The use of a drug to kill or damage cells, most commonly used in cancer treatment.
Child-Pugh score	A scoring system used to assess liver disease.
External beam radiotherapy (EBRT)	A form of radiotherapy delivered by a linear accelerator, which focuses high-energy radiation beams onto the area requiring treatment.
Extracranial	This means the disease is outside of the cranium, the bony dome that houses and protects the brain.
Fractionation	The term that describing how the full dose of radiation is divided into a number of smaller doses called fractions. The fractions are given as a series of treatment sessions which make up a radiotherapy course.
Hypofractionation	Describes a treatment regimen that delivers high doses of radiation using a shorter number of treatments as compared to conventional treatment regimens.
Metastatic cancer/metastases	Metastatic cancer is a cancer that has spread from the part of the body where it started (the primary site) to other parts of the body. Metastases is the plural form of metastasis and indicates that the cancer spread to more than one other site in the body.
Metachronous disease	Refers to development of metastases at least six months after treatment of the primary cancer.
Oligometastatic disease	A type of metastatic cancer, defined by the presence of a limited number of clinically detectable lesions, usually between one to five metastases across the body.
Overall Survival (OS)	The length of time from either diagnosis or start of treatment that the patient is still alive.
Performance Status	A recognised system developed by the World Health Organisation and other bodies to describe the general health and daily activity of patients.
Primary cancer or tumour	The term used for where in the body that a cancer starts.
Progression free survival (PFS)	The length of time from start of treatment to when the disease gets worse or death.
Radiofrequency ablation (RFA)	A cancer treatment that uses heat to destroy cancer cells.
Radiotherapy	The safe use of ionising radiation to destroy cancer cells with the aim of cure or effective palliation.
Stereotactic Ablative Radiotherapy (SABR)	Refers to the irradiation of an image defined extra cranial lesion and is associated with the use of high radiation dose delivered in a small number of fractions. The technique requires specialist positioning equipment and imaging to confirm correct targeting. It allows sparing of healthy normal tissues.
Synchronous disease	Development of metastases at the time of diagnosis of the primary tumour.
Systemic treatment	Treatment, usually involving chemotherapy or hormone treatment, which aims to treat the whole body.

References

Cancer Research UK. (2019). *Cancer incidence statistics*. [online] Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-Zero [Accessed 29 Apr. 2019].

European Society of Medical Oncology (ESMO). (2018). Oligometastatic Disease - A true clinical entity in Oncology? *European Society of Medical Oncology.*

Hellman S & Weichselbaum R.R. (1995). Oligometastases. *Journal of Clinical Oncology*; 13(1):8-10.

KiTEC. (2019). *Commissioning through Evaluation: Stereotactic ablative radiotherapy (SABR).* King's College Technology Evaluation Centre, London.

KiTEC. (2019). *Evidence Review: Efficacy, toxicity and cost-effectiveness of stereotactic ablative radiotherapy (SABR) in patients with metachronous extracranial oligometastatic cancer.* King's College Technology Evaluation Centre, London.

Palma D.A., Olson R.A., Harrow S., Gaede S., Louie A.V., Haasbeek C. et al. (2019). Stereotactic ablative radiotherapy versus standard-of-care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomized, phase II, open-label trial. *The Lancet*; in press.

Palma D.A., Olson R.A., Harrow S., Gaede S., Louie A.V., Haasbeek C., et al. (2018) Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): Results of a Randomized Trial. *International Journal of Radiation Oncology • Biology • Physics;* 102(3):S3-S4.