NHS England

Clinical Commissioning Policy Proposition:

Stereotactic ablative radiotherapy for small cell lung cancer and stage I-III non small cell primary lung cancer (excluding early stage non small cell lung cancer unsuitable for surgery) [All ages]

Reference: NHS England 1674

Prepared by NHS England Specialised Services Clinical Reference Group for Radiotherapy

Published by NHS England, in electronic format only.

Contents

1 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

Plain Language Summary

About lung cancer

Primary lung cancer, which means the cancer first developed in the lungs, is one of four most common cancers affecting people in the United Kingdom (UK) and each year over 41,000 people are diagnosed. The condition mainly affects older adults, most commonly people aged over 70 years. Although people who have never smoked can develop lung cancer, smoking remains a significant risk factor and is thought to account for approximately 90% of cases (NHS Choices, 2017).

Primary lung cancer can be grouped into two main types:

- Non-small cell lung cancer - the most common type, accounting for more than 80% of cases; and
- Small cell lung cancer - a less common type that usually spreads faster than non small cell lung cancer and is therefore usually diagnosed at an advanced stage.

The scope of this policy includes all small cell lung cancer and non small cell lung cancer (stage I-III). It is important to note that this document does not include the

subset of early stage non small cell lung cancers that are not suitable for surgical intervention.

About current treatments

There are a range of different treatments currently available in the treatment of lung cancer, including surgery, radiotherapy, chemotherapy, or a combination of all three. These treatments can be given either to cure the cancer or to manage symptoms and pain which is called palliation. The appropriate treatment for lung cancer depends on a range of factors, including its type, how far it has spread (determined by the stage) and the overall health and fitness of each individual patient.

Where lung cancer is diagnosed at an early stage and the overall health and fitness of an individual is good, surgery is the preferred first treatment, sometimes followed by chemotherapy. Where surgery isn't possible and the cancer has spread too far, radiotherapy is usually the preferred treatment. Chemotherapy is usually only given as a first treatment for lung cancer in cases that are diagnosed at an advanced stage and where surgery and radiotherapy are not considered to be effective.

About the new treatment

Stereotactic ablative radiotherapy (SABR) is a radiotherapy technique that usually involves the delivery of a high radiation dose spread over a smaller number of treatment sessions, or 'fractions', than would normally be the case. It is associated with lower rates of acute and late morbidity. The technique requires specialist positioning equipment and imaging and is sometimes referred to as stereotactic body radiotherapy (SBRT).

SABR is currently commissioned to treat early stage primary non small cell lung cancer that is unsuitable for surgery, either because medical co-morbidity would prevent surgery or because the cancer is surgically inoperable (NHS England clinical commissioning policy, reference: NHSCB/B01/P/a).

What we have decided

NHS England has carefully reviewed the evidence for the treatment of small cell primary lung cancer and stage I-III non small cell primary lung cancer (excluding early stage non small cell lung cancer that is unsuitable for surgery) with SABR. We have concluded that there is not enough evidence to make the treatment available as an alternative to conventional treatment.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission stereotactic ablative radiotherapy (SABR) for the treatment of small cell primary lung cancer (SCLC) and stage I-III non small cell primary lung cancer (NSCLC). This document does not cover SABR in the treatment of early stage primary NSCLC that is unsuitable for surgery, as this is subject to a separate published clinical commissioning policy (reference: NHSCB/B01/P/a) that is unaffected by this document.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether SABR for the treatment of both primary SCLC and stage I-III primary NSCLC (excluding early stage NSCLC unsuitable for surgery) will be not routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Clinical Indication

Primary lung cancer, which means that the cancer first developed in the lungs, is one of the most common and serious types of cancer affecting people in the United Kingdom (UK). Although people who have never smoked can develop lung cancer, smoking is the main cause (about 90% of the cases).

Many people with primary lung cancer develop symptoms as the disease progresses but in the early stages there are usually none. Common symptoms include:

- a cough that doesn't go away after two or three weeks or a long-standing

cough that gets worse;

- persistent chest infections;
- coughing up blood;
- an ache or pain when breathing or coughing;
- persistent breathlessness;
- persistent tiredness or lack of energy; and
- loss of appetite or unexplained weight loss.

Primary lung cancer can be grouped in to two main types, which is determined by the cells affected (histology):

- NSCLC – the most common type, accounting for more than 80% of cases; these can be either squamous cell carcinoma, adenocarcinoma or large-cell carcinoma depending on the cell type involved; and
- SCLC – a less common type that usually spreads faster than non-small cell lung cancer.

The appropriate treatment for lung cancer depends on the type of cancer, how far it has spread (determined by the stage) and general health status. There are a range of different interventions available, including surgery, radiotherapy and chemotherapy. Treatment may be curative or palliative. Current treatment options include the following:

- NSCLC –
    - If the cancer is confined to one lung and the patient is in good general health, surgery is done to remove the cancerous cells. This may be followed by a course of chemotherapy to destroy any cancer cells that may have remained in the body.
    - If surgery isn't possible, and the cancer hasn't spread too far, then radiotherapy is usually used.
    - If the cancer has spread too far for surgery or radiotherapy to be effective, systemic therapy is usually recommended.
- SCLC –
    - Surgery may be used if the cancer is found very early (this is called limited disease) but this is rare as the cancer has often spread by the

time it is diagnosed (this is called extensive disease). Chemotherapy or radiotherapy may be given as an alternative to surgery or given after surgery to help reduce the risk of the cancer returning.

- SCLC is usually treated with chemotherapy, either on its own or, more commonly, in combination with radiotherapy.

Proposed intervention

SABR is a type of external beam radiotherapy and is a method of delivering doses of precisely targeted radiotherapy treatment to extracranial organs. It is a highly conformal hypo-fractionated radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. The tumour therefore receives a high dose of radiation whilst surrounding, healthy, tissues receive a much reduced dose. This lowers the risk of side effects. Patients having lung SABR only need 3, 5 or 8 treatments, or fractions, which is fewer than required by other types of external beam radiotherapy.

The technique is already used in the treatment of early stage primary NSCLC cases that are unsuitable for surgery, either because medical co-morbidity would prevent surgery or because the cancer is surgically inoperable (NHSCB/B01/P/a).

4 Definitions

Cancer – are abnormal cells that divide in an uncontrolled way and can spread elsewhere in the body

Chemotherapy – is a cancer treatment where medication is used to kill the cancer cells and is a type of systemic therapy. There are many different types of chemotherapy medication. They all work in a similar way by stopping cancer cells reproducing, which prevents them from growing and spreading in the body. Chemotherapy also affects healthy cells and this can cause side-effects, which will vary depending on the type of cell affected.

Dose – is the amount of radiation that a tissue receives.

External beam radiotherapy – is a type of radiotherapy, the most common types of external beam radiotherapy use high energy x-ray beams, such as photon beams but other types of radiotherapy include particle beams, such as protons or electrons.

Fraction – is a term used to describe each episode of radiotherapy a patient receives. A patient having radiotherapy treatment can have one or more fractions.

Immunotherapy – is a type of systemic therapy that uses substances to stimulate or suppress the patient's immune system to fight cancer.

Metastasis (or secondary tumour) – is the term used if the cancer has spread to other parts of the body.

Primary lung cancer – is a cancer that first develops in the lungs.

Primary tumour - is the term used for where in the body that a cancer starts.

Radiotherapy – is a treatment where radiation is used to kill cancer cells. There are many different ways radiotherapy can be given, but they all work in a similar way. They damage cancer cells and stop them from growing or spreading in the body. Side-effects may occur and are caused by radiation affecting the surrounding healthy tissues. These will vary depending on the healthy tissue affected and amount of radiation received.

Staging for lung cancer – this describes the size of the cancer, where it is and whether it has spread. It is used to help guide treatment. Scans and other tests, such as biopsies, will give information about the staging. In some instances it may not be possible to accurately determine the stage until after surgery. All lung cancers should be staged using the Tumour, Node, Metastases (TNM) staging system, version 8.0.

Stereotactic ablative radiotherapy (SABR) – is also sometimes called stereotactic

body radiotherapy (SBRT). SABR is a highly conformal hypo-fractionated radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. It is a way of giving external beam radiotherapy. The tumour receives a high dose of radiation but the risk of side effects are reduced because the surrounding tissues receive a lower dose. Usually only 3, 5 or 8 treatments or fractions, are given.

Systemic therapy – are treatments for cancer using substances that travel through the blood stream to reach and affect cells all over the body. Chemotherapy, immunotherapy and targeted agents are types of systemic therapy.

Targeted agents – are a type of systemic therapy that uses substances to identify and attack specific types of cancer cell. This cause less harm to normal cells and may have fewer side effects.

Tumour, Node and Metastases (TNM) staging system – the TNM staging is a common classification system used to describe the stage of a cancer, measuring the size of the tumour and how far it has spread in the body including the lymph nodes and other parts of the body.

5 Aims and Objectives

This policy proposition considered: stereotactic ablative radiotherapy (SABR) as part of the treatment pathway for primary lung cancer as compared to any treatment, specifically:

- Adults with limited stage SCLC; limited stage being defined as T1-T2bN0M0 using the TNM staging system (8th edition); and
- Adults with stage I to III NSCLC.

The objectives were to: determine the clinical effectiveness, cost effectiveness and efficacy of using

- SABR for the treatment of SCLC as compared with conventional treatments for patients with SCLC; and

- SABR for the treatment of NSCLC as compared with conventional treatments for patients with NSCLC.

6 Epidemiology and Needs Assessment

In 2014, there were over 41,000 people diagnosed with lung cancer in the UK. It is the third most common type of cancer and accounts for over 10% of all new cancer cases. Incidence rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.

Lung cancer is more common in men but rates are rising in women. It is more likely to occur in older people with over 40% of new cancers being diagnosed in people over 75. Lung cancer is more common in White people than in Black or Asian people. It is also more common in people living in deprived areas.

Over 85% of all lung cancers are NSCLC and approximately three-quarters are diagnosed at a late stage. In England, during 2013-2014, 42% of patients diagnosed with SCLC and 28% of patients diagnosed with NSCLC had curative or palliative radiotherapy, as part of their primary cancer treatment. This includes patients who had radiotherapy alone, and those who also had other treatments such as surgery to remove the tumour, or chemotherapy.

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Evidence review results

The evidence on the use of SABR in the treatment of primary lung cancer was reviewed for the following scenarios:

- The use of SABR for the treatment of patients who have NSCLC cancer, stages I-III (and including central and / or peripheral disease) compared with

any treatment; and

- The use of SABR for the treatment of patients who have limited stage (T1-T2bN0M, TNM 8th edition) SCLC compared with any treatment.

1. **The use of SABR for the treatment of patients who have non-small cell lung cancer, stages I-III (and including central and / or peripheral disease) compared with any treatment, outside of the then existing commissioning policy (NHSCB/B01/P/a)**

The evidence review identified three systematic reviews of the use of SABR for NSCLC: one of SABR versus open surgery, one of SABR vs video-assisted thoracic surgery and one of the incidence of lung toxicity after SABR. It also identified two controlled studies of SABR versus open surgery (one a randomised trial which also reported economic results and one an unrandomised comparison), two controlled studies of SABR versus video-assisted thoracic surgery and three studies reporting health economic results. The evidence review did not find sufficient evidence to support the use of SABR in stage II and III NSCLC.

Six studies reported overall survival:

- *SABR with video-assisted thoracic surgery*: An unrandomised controlled comparison of SABR with video-assisted thoracic surgery by Paul et al (2016) reported better survival after surgery (hazard ratio (HR) 1.80, 95% confidence interval (CI) 1.33 to 2.43; $p < 0.001$). Hamaji et al (2015) published a similar study with similar results (HR 0.39 (surgery better), 95% CI 0.20 to 0.76, $p = 0.0051$). In this study, the three-year, five-year, and ten-year survival rates in VATS lobectomy patients were 80.1%, 68.5%, and 61.6%, respectively, compared with 52.7%, 37.3%, and 20.7% in SABR patients respectively ($p = 0.0016$). However, the meta-analysis by Ma et al (2016) reported no significant survival differences between SABR and video-assisted thoracic surgery (HR 2.02, 95% CI 1.45 to 3.07, $p = 0.47$; the authors state this result is non-significant, although the 95% CI excludes an HR of 1).

- *SABR versus open surgery*: Li et al (2017) reported a meta-analysis of SABR versus open surgery. Surgery was associated with better overall survival (HR 1.40, 95% CI 1.21 to 1.61, p < 0.001). This was corroborated by an unrandomised comparison of SABR and wedge resection, in which five-year survival was 31.0% after SABR (95% CI 26.1% to 36.0%), and 49.9% after wedge resection (95% CI 45.1% to 54.6%) (p < 0.0001) (Yerukan et al 2017). Smith et al (2015) reported an unrandomised comparison of SABR, sub-lobar resection and lobectomy, with no significant differences in survival between SABR and sublobar resection (p = 0.81).

Recurrence-free survival[1] was reported as better after surgery in Li et al (2017)'s meta-analysis (HR 1.84, 95% CI 1.26 to 2.68, p = 0.02). Hamaji et al (2015) also reported better recurrence-free survival after surgery (HR 0.32, 95% CI 0.17 to 0.58. p = 0.0002). However, Ma et al (2016) reported no significant differences in recurrence-free survival after SABR and video-assisted thoracoscopic surgery (HR 0.42, 95% CI 0.21 to 1.12, p = 0.52).

There was no significant difference in loco-regional recurrence[2] after surgery and SABR reported in Li et al (2017)'s meta-analysis (HR 1.17, 95% CI 0.68 to 1.98, p = 0.57), nor in distant recurrence (HR 1.36, 95% CI 0.77 to 2.39, p = 0.29).

Global health status was reported as better after SABR than after surgery in Louie et al (2015)'s randomised trial (HR 0.19, p = 0.038). However, the apparent statistical significance of this result may well be because of multiple comparisons and it should be regarded as arising from chance.

No significant difference in cancer-specific survival[3] after surgery and SABR was reported by Paul et al (2016), while Hamaji et al (2015) reported longer survival after surgery (respectively HR 1.32, 95% CI 0.77 to 2.26, p = 0.32, and HR 0.228, 95% CI

[1] Recurrence-free survival is the proportion of participants alive with no apparent recurrent tumour at specified intervals after completion of SABR.
[2] Loco-regional recurrence is the appearance of new tumour at the site of the primary or elsewhere in the lung, after initial treatment is complete.
[3] Cancer-specific survival is survival without death from SCLC. All other causes of death are censored (i.e. disregarded in the analysis).

0.09 to 0.62, p = 0.0035).

Local[4] and distant[5] control was reportedly better after surgery (respectively HR 0.13, 95% CI 0.029 to 0.59, p = 0.0077 and HR 0.17, 95% CI 0.069 to 0.43, p = 0.0002) (Hamaji et al 2015). These authors reported no significant differences in regional lymph node control[6] after surgery and after SABR (HR 0.33, 95% CI 0.082 to 1.33, p = 0.12).

The incidence of radiation-induced lung toxicity was reported as 10.4% (95% CI 9.8% to 15.2%) (Zhao et al 2016).

Four health economic analyses were identified:

- Louie et al (2015)'s randomised trial reported higher productivity costs after open surgery than after SABR (SABR: €95 (£86.80), surgery €3513 (£3210), p = 0.044). The productivity cost is calculated from the perspective of the participant's employer and is of limited relevance to NHS decision-making.
- Smith et al (2015)'s uncontrolled comparison reported the following incremental costs per life-year gained: SABR vs sublobar resection $45,683 (£35,100), 95% CI -US$325,572 to $269,807 (-£250,400 to £207,500); SABR vs lobectomy $28,645 (£22,000), 95% CI -$119,828 to $207,822 (-£92,200 to £159,900).
- Shah et al (2013)'s modelling paper reported an incremental cost per QALY for lobectomy compared with SABR of US$13,215 (£10,200).
- Finally, Grutters et al (2010)'s modelling paper reported that SABR dominated carbon ion treatment, being both more effective and less expensive (SABR: €8,485 (£7,800), 3.20 QALYs; carbon ions: €14,620 (£13,400), 3.16 QALYs).

The evidence found indicates that open or video-assisted thoracoscopic surgery is

[4] Local control is the absence of radiological evidence of further growth of the cancer at its site of origin.
[5] Distant control is the absence of radiological evidence of new metastases from the primary tumour.
[6] Regional lymph node control is the absence of radiological evidence of further growth of the cancer in regional lymph nodes which drain the primary tumour.

probably more effective than SABR in the treatment of early stage NSCLC. It appears to be associated with longer survival, and better tumour control on some metrics.

The health economic analyses suggest that surgery is also more cost effective than SABR.

SABR has adverse effects but they do not appear to be common or serious enough to cast doubt on its suitability for use.

2. **The use of SABR for the treatment of patients who have limited stage (T1-T2bN0M, 8th edition) small cell lung cancer compared with any treatment.**

One systematic review and two other studies were identified. The studies were small, including in total 190 participants, with some duplication between two studies in the systematic review. All the studies were uncontrolled, apart from one reported comparison of SABR versus SABR plus chemotherapy.

The systematic review by Alongi et al (2017) was descriptive and included no comparisons. It summarised four uncontrolled studies, with a total of 108 participants with stage I to III SCLC; a fifth study, a case report, was included without further description. There was some duplication between two of the studies included. The studies reported local control of between 82% (crude rate) and 100% at 36 months, overall survival of between 48% at 24 months and 76% at 24 months, and disease-specific survival of between 75% at 12 months and 86% at 36 months.

Progression-free survival at 24 months was 22% after SABR and 67% after SABR plus chemotherapy, the latter results being described as “significantly higher”.

Verma et al (2017) reported an uncontrolled study of 74 people with stage 1 SCLC treated with SABR. A complete radiological response was reported in 19/76 lesions (25%), a partial response in 29/76 (38%), stable disease in 13/76 (17%) and progression in 3/76 (4%). Local control at one year was 97%, and at three 3 years was 96%. Local failure-free survival at one year was 97% and at three years was 97%. Distant metastasis-free survival at one year was 73%, and at three years was 63%. Disease-free survival at one year was 59% and at three years was 54%, with

a median disease-free survival of 49.7 months. Disease-specific survival at one year was 84% and at three years was 64%, with a median disease-specific survival of 52.3 months. Overall survival at one year was 71% and at three years was 35%, with a median overall survival of 17.8 months.

Ly et al 2013 reported an uncontrolled study of 8 people with stage 1 SCLC treated with SABR. Overall survival at one year was 88% and at three years was 37%, with a median overall survival of 22 months. Recurrence-free survival at one year was 50% and at three years was 38%, with a median recurrence-free survival of 8.4 months.

Alongi et al 2017 reported one grade 2 adverse reaction (chest wall toxicity) and five grade 3 adverse reactions (4 oesophagitis, 1 neutropenia) (n=29). Verma et al (2017) reported pneumonitis after treatment of 15 lesions (grade 1 adverse reaction: 9/76 lesions (12%), grade 2: 3/76 lesions (4%), grade 3: 1/76 lesions (1%)), grade 1 dermatitis after treatment of 1/76 lesions (1%), grade 2 fatigue after treatment of 1/76 lesions (1%) and grade 2 chest wall pain after treatment of 3/76 lesions (4%).

No relevant cost utility studies were identified nor studies which evaluated the clinical and cost-effectiveness of SABR in subgroups of patients.

The evidence does not indicate any benefits from SABR in the treatment of early stage SCLC compared to standard care (surgery, chemotherapy with or without conventional radiotherapy). All the studies were uncontrolled; none compared SABR to an alternative treatment. This means that conclusions cannot be drawn about whether SABR increases the quality or duration of life compared with alternatives, nor whether any potential benefits are justified by its costs.

SABR has adverse effects but they do not appear to be common or serious enough to cast doubt on its suitability for use.

8 Documents That Have Informed This Policy Proposition

- Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (reference NHSCB/B01/P/a); and

- Radiotherapy (all ages) service specification (reference B01/S/a).
- Clinical Commissioning policy: SABR in the treatment of Oligometastatic disease (reference NHS England B01X28)

9 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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