Clinical Commissioning Policy: Stereotactic radiosurgery/ radiotherapy for the treatment of pituitary adenomas (all ages)

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Clinical Commissioning Policy: Stereotactic radiosurgery/ radiotherapy for the treatment of pituitary adenomas (all ages)

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Policy Statement

NHS England will commission stereotactic radiosurgery/radiotherapy for the treatment of pituitary adenomas in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

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 pituitary adenomas

The pituitary is a gland about the size of a pea that lies beneath the base of the brain. It releases hormones which affect growth, sexual development, reproduction

and metabolism. A pituitary adenoma is a benign (non-cancerous) slow growing tumour that arises within the pituitary gland. Most pituitary adenomas occur in the front of the pituitary gland which regulates hormones. There are two main types of pituitary adenoma:

- Functioning pituitary adenomas which are non-cancerous tumours in the pituitary gland that secrete hormones which cause symptoms.
- Non-functioning pituitary adenomas which are non-cancerous tumours in the pituitary gland that do not secrete hormones but cause effects as they grow and press onto nearby structures in the brain.

The majority of pituitary adenomas will be first treated with surgery. However, sometimes it is not possible to remove the whole tumour with surgery, this means that some of the tumour cells are left behind which is called ‘residual tumour’. In addition, sometimes the tumour can return following surgical treatment, this is called ‘recurrent tumour’. Both residual and recurrent tumours can grow and continue to cause harmful effects and may require further treatment.

This policy relates to the treatment of residual and recurrent pituitary adenomas following first (or ‘primary’) treatment with surgery and where primary treatment with surgery is not medically possible.

About current treatments

There are currently three treatment options for patients with residual and recurrent pituitary adenomas:

- further surgery;
- conventional radiotherapy for larger or diffuse lesions; and
- SRS/SRT.

In addition, there are medical treatments available for functioning pituitary adenomas. SRS/SRT is a current treatment option for some recurrent or residual pituitary adenomas. It can be used in certain highly selected relatively small tumours where primary surgery is not an option.

About the new treatment

SRS/SRT are highly targeted radiation therapies that can be used to treat a wide range of conditions, including pituitary tumours. The benefit of this treatment over further surgery or conventional radiotherapy is that it is possible to give the tumour cells a high dose of radiation while better protecting the surrounding healthy tissue. Treatment with SRS/SRT can also be given in fewer visits to the hospital.

What we have decided

NHS England has carefully reviewed the evidence to treat pituitary tumours with SRS/SRT. We have concluded that there is enough evidence to make this treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in deciding to routinely commission stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS) as a treatment option, for adults and children and young people presenting with an adult type tumour, with recurrent or residual pituitary adenomas following primary treatment with surgery and for the primary treatment of pituitary adenomas in cases where surgery is not medically possible.

This document also describes the criteria for commissioning, governance arrangements and funding mechanisms.

Clinical indication

Pituitary adenomas tend to be benign and have a slow growth rate. There are two main types of pituitary adenomas, those that secrete hormones (functioning) causing clinical syndromes of hormone excess such as Cushing's disease, and those that do not secrete hormones (non-functioning).

Surgery is the primary treatment for pituitary adenomas, except for prolactinomas, which are functioning pituitary adenomas and which are treated medically. However, residual tumour is common after surgery (Reddy et al 2011). Residual non-functioning tumours can start to grow, or grow and continue to secrete hormones in the case of functioning tumours. This may necessitate additional treatment. For patients with confirmed symptomatic residual disease further surgery is possible, but it has increased risk of complications and less favourable clinical outcomes than primary surgery alone.

Intervention

SRS and SRT will be commissioned by NHS England as a treatment option for the management of residual and recurrent pituitary adenomas (for adults and children presenting with an adult type tumour) following primary treatment with surgery and for those patients that are not able to have surgery as a primary treatment.

Both SRS/SRT are methods of delivering doses of precisely targeted cranial radiotherapy treatment. The basic principle of the treatment is the targeted elimination of tumour viability to improve local control. As the radiation is precisely focused on the target area this reduces potential toxicity in the surrounding tissues e.g. the optic apparatus.

The use of SRS or SRT in the treatment of pituitary adenomas has demonstrated evidence of clinical effectiveness in both tumour and hormonal control. This effectiveness is demonstrated in patients who have had prior therapy as well as those that are treatment naïve. There is also potential to improve patient experience and overall service delivery, in that treatments are accomplished in a single setting or in fewer episodes than conventionally fractioned treatments.

For the purposes of this policy, both SRS and SRT are defined as highly conformal radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. SRS treatment is delivered in a single fraction and SRT must be delivered in two to five fractions. SRT is sometimes referred to as ‘intracranial hypofractionated SRT’.

2 Definitions

Functioning adenoma – is a pituitary tumour that secretes a hormone in excess to cause a recognisable clinical condition (such as Cushing’s disease, acromegaly, prolactinomas).

Non-functioning adenoma – is a pituitary tumour that does not secrete hormones. These pituitary adenomas create clinical symptoms by growing and putting pressure on adjacent structures such as the normal pituitary gland and the optic nerves.

Hypofractionated radiation – is a treatment in which the total dose of radiation is divided into relatively large doses and intracranial treatments are given in up to 5 fractions over 5 days or less (typically 3-5 fractions over 3-5 days).

Conventional fractionated radiotherapy - is a treatment in which the total dose of radiation is divided into relatively small doses and treatments are given in 20-30 fractions daily (usually Monday to Friday).

Intracranial - means within the cranial cavity (skull).

Prolactinoma – is a prolactin producing tumour of the pituitary gland
Cushing's disease: a clinical syndrome caused by increased secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland (of which a pituitary adenoma is the most common cause) leading to over production of cortisol by the adrenal glands and resulting in Cushing's syndrome.

Acromegaly – is a disorder caused by excessive production of growth hormone (GH) by the pituitary gland and marked by progressive enlargement of hands, feet, and face. There is also increased risk of cancer.

3 Aims and Objectives

This policy considers SRS/SRT as a treatment option for the management of patients with residual and recurrent pituitary adenomas, together with those who are medically unable to have surgery.

The objectives were to establish, via an evidence review, the following information:

- Efficacy, safety and toxicity of the treatment;
- Identification of patient sub-groups (i.e., functioning and non-functioning tumours) and appropriate clinical criteria; and
- Cost effectiveness of the treatment.

4 Epidemiology and Needs Assessment

Epidemiology

Pituitary adenomas are usually benign and grow slowly to exert their harmful effects by pressure on surrounding structures or through hormone secretion. Autopsy studies suggest pituitary tumours are found in 10% of the population, but the clinically relevant incidence is much lower (Kontogeorgos, 1991).

Non-functioning pituitary adenomas have a prevalence rate of 22.2 per 100,000 (Fernandez, 2010) and are the second largest group of pituitary adenomas after prolactinomas, accounting for 70% of the relevant neurosurgical operations performed each year in the UK. Most non-functioning pituitary adenomas will require primary surgery and, potentially, may also need adjuvant treatment.

There are three types of functioning pituitary adenomas;

- Prolactinomas, which have a prevalence rate of 44.4 per 100,000 (Fernandez, 2010) and secrete prolactin. These are usually small microadenomas, 80% of which are less than 1 cm in diameter;
- Growth hormone (GH) secreting pituitary adenomas, which cause a condition called Acromegaly and have a prevalence rate of 8.6 per 100,000 (Fernandez, 2010); and
- Adrenocorticotrophic hormone (ACTH) secreting pituitary adenomas, which cause a condition called Cushing's disease and have a prevalence rate of 1.2 per 100,000 (Fernandez, 2010).

Both Cushing's Disease and Acromegaly are rarer conditions associated with higher morbidity and mortality.

Needs Assessment

Based on the epidemiology, it is estimated that approximately 400 patients per year may be suitable for SRS or SRT.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication.

Study design

Fifty-six published studies were identified evaluating the effectiveness and safety of SRS or SRT for recurring and residual tumours. However they tended to be of low to moderate quality. The majority of the papers were retrospective case series ranging in size, baseline characteristics and treatment dosage. There were also a number of

retrospective non-controlled cohort studies comparing different interventions. There was no randomisation or blinding in any study including the comparison studies. One study evaluated health related quality of life. There were no cost effectiveness studies. Approximately a quarter of studies had more than 100 patients but over half included only 9-40 patients.

Baseline characteristics

The baseline characteristics of patients differed significantly in terms of tumour volume, tumour functional status and previous treatment. This an important limitation for the comparator studies as these characteristics have been shown to have an effect on both efficacy and safety outcomes.

The majority of patients had recurrent or residual pituitary adenoma despite ≥1 prior treatment. Around 15% of patients were treatment naïve. The majority of these patients were inappropriate for surgery due to medical reasons or the site and size of their tumour. As the results of the studies were presented as whole patient cohorts their outcomes could not be analysed separately. Patients underwent SRS or fractionated SRT.

The main outcomes measured were tumour growth/recurrence, control or remission of hormone secretion, progression- free survival and safety. As there are no internationally recognised standards of outcome reporting for pituitary adenomas, studies used different measures of effectiveness.

While there are studies that have compared different radiation modalities, none directly compared SRS or SRT with repeat surgery and so judgements on efficacy and safety will be limited. The picture is further complicated by the fact that patients in most of the studies had a varied clinical history ranging from those with a primary presentation to those who have had multiple surgical interventions and previous fractionated radiotherapy. Most studies analysed these patients together and thus outcomes could not be split by baseline characteristics.

Clinical effectiveness

In non-functioning tumours tumour control (a composite of complete response, tumour shrinkage and stable tumour) was reported as 93.4% at median 36 months in the largest case series (Sheehan et al 2013). Van den Burgh et al (2007) also demonstrated statistically significant ($p<0.001$) improved tumour control in 76 patients who had previously had surgery who were then treated with SRS. The comparator group (n=28) received no intervention. Tumour control ranged from 75 to 100% in all other reporting studies.

In functioning tumours hormonal control (normalisation of hormone levels with or without medication) was reported as 67% in the largest (Lee et al 2014) study and ranged from 0 to 100% in all other reporting studies.

An analysis of efficacy and safety by tumour type was undertaken but was limited by studies often pooling outcomes rather than reporting them by specific tumour type. Additionally sub-groups by tumour type were often small so led to a wide range of outcomes when comparing all case series.

SRS appears to be effective in controlling the growth of recurrent/residual pituitary tumours and has a role in hormonal remission in the short to medium term. There is evidence that SRS is more effective in achieving desired outcomes in non-functioning than functioning tumours. This is mostly due to the need to control hormonal secretion as well as tumour size in functioning tumours. SRS also appears to have variable effectiveness depending on the functioning tumour type – ACTH-secreting tumours had the best response followed by GH-secreting and PRL-secreting tumours. There were too few Nelson's and LH/FSH-secreting tumours reviewed to make a judgement on efficacy.

Follow up

The length of follow up also varied and ranged between 33 and 152 months. The studies with the shorter follow up may not have had sufficient time to record tumour response/recurrence, hormonal response/relapse or radiation-induced adverse events.

Adverse events

The main adverse events identified were hypopituitarism (ranging between 0 to 39% in functional tumours and 0 to 38% in functioning tumours) and new/deteriorating visual dysfunction (ranging from 0% to 21% for non-functioning tumours and from 0% to 9% for functioning tumours). Other adverse events such as stroke, transient ischaemic attack (TIA), and hypothyroidism were infrequently reported.

The data from the comparative studies is too limited to make any firm conclusions about efficacy relative to other treatment but suggests a reduced rate of adverse events in SRS/SRT compared to conventional fractionated radiotherapy. Additionally while SRS and SRT seem to have comparable efficacy, hypopituitarism may be higher in SRT as compared to SRS. However given the low numbers of patients, limited quality of these studies and lack of statistical testing this may not be a true difference.

It is difficult to discern whether some of the adverse events reported are attributable to the disease or to SRS/SRT, or whether both contributed to some degree. For example both SRS/SRT (radiation-induced toxicity) and disease progression (pressure effects of tumour) can lead to new visual deficit.

Conclusion

The published evidence on SRS and SRT for treatment of residual/recurrent pituitary adenoma consists of retrospective case series, prospective cohort studies and non-randomised/controlled comparative studies. The major drawback of these types of study is the difficulty in understanding the true efficacy of an intervention due to a lack of control over factors that influence the outcomes being measured.
The evidence suggests a role for SRS in effective tumour control (non-functioning pituitary adenomas) and to a lesser degree, hormonal control (functioning pituitary adenomas). The evidence for SRT suggests that it only has a role in the management of non-functioning tumours.

A lack of randomised control trials mean it is difficult to make direct comparisons with standard care. The evidence suggests lower rates of adverse events in SRS/SRT compared to conventional fractionated radiotherapy but a lack of randomised control trials mean it is difficult to make direct comparisons with standard care.

6 Criteria for Commissioning

All patients being considered for SRS or SRT must undergo prior assessment by the local multidisciplinary pituitary multi-disciplinary team (MDT) (with a core membership as defined in the NICE Improving Outcomes Guidance and described within the SRS/SRT service specification) and the SRS/SRT MDT, sometimes these may be combined. In addition, where appropriate, patients should be discussed in Teenage and Young Adult (TYA) MDTs, as well as the SRS/SRT and pituitary MDTs.

Inclusion criteria

Treatment with SRS (a single fraction of stereotactic treatment) should be considered as a treatment option for the following groups:

- People with residual or recurrent non-functioning pituitary adenomas that continue to grow following surgical intervention and require further treatment;
- People with residual pituitary adenomas who are unsuitable for further surgery who have only a small gap to the optic apparatus where future growth would preclude use of SRS;
- People with functioning pituitary adenomas with raised hormone levels that have not adequately responded to medical and/or surgical treatment and where further treatment is indicated;
- People with non-functioning pituitary adenomas or functioning pituitary adenomas who are medically unable to undergo surgery and where medical treatment is not sufficiently effective and further treatment is indicated.

Treatment with SRT (using 2-5 stereotactic radiotherapy treatments) should be considered as a treatment option in people with:

- Residual or recurrent non-functioning pituitary adenomas that continue to grow following surgical intervention; and
- Non-functioning pituitary adenomas who are medically unable to undergo surgery and treatment is indicated.

Exclusion criteria for treatment with SRS or SRT

- Non-functioning pituitary adenomas that haven't shown growth on serial imaging;
- Larger or diffuse lesions more effectively treated with conventional fractionated external beam radiotherapy;
- Lesions not sufficiently separated from the optic apparatus and brainstem to allow organ at risk preservation doses to be achieved using SRS or SRT.

Exclusion criteria specifically for the use of SRT

- Functioning pituitary adenomas must not be treated with SRT.

7 Patient Pathway

The Intracranial SRS/SRT service specification (NHS England, D05/S/a) describes the detail of the care pathways of SRS/SRT services.

The service specification states that patients with pituitary adenomas should be referred to designated Tier 1/2 SRS/SRT service providers by local brain and CNS tumour MDTs (pituitary). The decision to accept referrals will be taken by the SRS/SRT MDT, in line with clinical eligibility and referral guidelines. Clinically complex cases, such as those where the adenoma is close to the optic chiasm, may need to be treated in designated services with particular expertise.

8 Governance Arrangements

The Intracranial SRS/SRT service specification (NHS England, D05/S/a) describes the governance arrangements for this service. In particular, it is imperative that the radiotherapy service is compliant with the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) 2000.

9 Mechanism for Funding

The clinical indication forms part of the scope of the intracranial SRS/SRT services which are commissioned from a small number of designated providers with agreed local prices.

10 Audit Requirements

Audit requirements include the following data items for each patient:

- Karnofsky or World Health Organisation (WHO) Performance Status
- Functioning versus non-functioning
- Whether the tumour is primary, residual or recurrent
- Tumour volume (cc)
- Prescription isodose and dose prescription
- Fractionation
- Treatment outcome (tumour control, progression free survival and where relevant hormonal control 1,3 and 5 years)
- Side effects (including but not limited to hypopituitarism, visual defects, stroke or new malignancy)
- Visual acuity
- Quality of life and patient experience

NHS England sub-regions will have access to this data for audit purposes, as required.

11 Documents which have informed this Policy

The documents that have informed this policy are:

- NHS England Intracranial SRS/SRT service specification (D05/s/a).
- National Institute for Health and Care Excellence Clinical Guideline 10: Improving outcomes for people with brain and other CNS tumours. London NICE, 2006.
- NHS England Clinical Commissioning Policy Statement: Stereotactic Radiosurgery / Radiotherapy for Ocular Melanoma and Pituitary Adenoma (D05/PS/a), 2013.

NHS England Clinical Commissioning policies for the use of Intracranial Stereotactic Radiosurgery/ Stereotactic Radiotherapy (D05/P/e; D05/P/f).

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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