Clinical Commissioning Policy Proposition: Ablative surgery, moulage technique brachytherapy and surgical reconstruction (AMORE) for head and neck soft tissue sarcoma in children and young people.

Reference: NHS England 1827

Prepared by NHS England Specialised Services Clinical Reference Group for Children and Young People's Cancer CRG

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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 head and neck soft tissue sarcoma

Soft tissue sarcomas are rare cancers that develop in the supporting or connective tissues in the body such as the muscle, nerves, tendons, blood vessels and fatty and fibrous tissues. The condition can occur anywhere in the body and as a result, there are many different types of soft tissue sarcoma. The most common type of soft tissue sarcoma in children and young people is rhabdomyosarcoma. The condition develops first in muscle and the most commonly affected area is the head and neck region (Macmillan Cancer Support, 2016). It affects 60 children each year in the United Kingdom (UK) and is more common in males than females (Children's Cancer and Leukaemia Group, 2016). It is estimated that two thirds of cases in children occur before 6 years of age (Macmillan Cancer Support, 2016).

About current treatments

Most children and young people with head and neck sarcoma will receive a combination of chemotherapy, radiotherapy and surgery. This means that the duration of treatment can be very prolonged.

Chemotherapy is usually given first, using a combination of different drugs with the aim of treating the whole body. This is then followed by more targeted treatment to the tumour site itself, called local therapy. Local therapy usually involves a period of radiotherapy, which is sometimes accompanied by surgery to remove the tumour (ablative surgery). Traditionally radiotherapy has been delivered through conventional methods but over the last few years, the use of proton beam therapy (PBT) has been increasing. The different components of local therapy are delivered separately and treatment can take up to 12 weeks to complete.

Although current treatments achieve high cure rates (over 80%), they can also cause significant long term effects including cosmetic effects (such as musculoskeletal deformity of the face) and functional effects (such as hearing loss, cataracts, slurred speech and difficulty swallowing). In order to overcome the cosmetic and sometimes functional effects of radiotherapy, some children and young people require reconstructive surgery several years after completing cancer treatment.

Although uncommon, the cancer can return following initial treatment. This is called disease relapse and is usually treated in a similar way to newly diagnosed cases, i.e., chemotherapy followed by local therapy.

About the new treatment

The new treatment is an alternative local therapy option which combines both surgery and radiotherapy treatments into a single episode of care. The combined interventions are ablative surgery, moulage technique brachytherapy and surgical reconstruction, collectively known as AMORE. Because treatment is combined into a single episode of care, it is delivered over much shorter timescale, usually between 3-4 weeks.

It is thought that the AMORE technique offers the same cure rates for children with head and neck rhabdomyosarcoma, as compared to current treatment options, but may reduce the long term effects of treatment.

AMORE is considered to be a treatment option for both children with newly diagnosed head and neck rhabdomyosarcoma and where the disease has relapsed.

What we have decided

NHS England has carefully reviewed the evidence to treat head and neck rhabdomyosarcoma in children and young people with AMORE. We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission ablative surgery, moulage technique brachytherapy and surgical reconstruction (AMORE) for head and neck rhabdomyosarcoma in children.

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 AMORE will be not routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Clinical Indication

Soft tissue sarcomas are rare cancers that develop in the supporting or connective tissues anywhere in the body and as a result there are lots of different types of soft tissue sarcoma.

In children and young people, the most common type of soft tissue sarcoma is rhabdomyosarcoma, accounting for almost two thirds of all soft tissue sarcomas. Rhabdomyosarcomas start in the muscle cells in the body and it is estimated that 40% of these cancers occur in the head and neck region (Radzikowska et al, 2015).

Treatment of children and young people with head and neck soft tissue sarcoma is complex and usually involves different treatment modalities including chemotherapy, radiotherapy and surgery in order to optimise the chance of cure. Chemotherapy, usually involving multiple drugs, is given first and aims to treat the whole body (systemic treatment). Following chemotherapy, children and young

people will undergo more targeted treatment to the tumour site itself, called local therapy.

Local therapy may involve both surgical resection and radiotherapy, but radiotherapy can be given alone. Radiotherapy is typically delivered as conventional external beam radiotherapy, however over recent years the use of proton beam therapy radiotherapy has been increasing. Local therapy is usually delivered separately (i.e., surgery and radiotherapy treatment are delivered as separate episodes of care) and typically takes up to 12 weeks.

Current treatments for head and neck soft tissue sarcomas achieve high cure rates, over 80%. However, they can also result in significant cosmetic and functional long term effects, including: (i) musculoskeletal deformity of the face; (ii) growth problems; (iii) hearing loss; (iv) cataracts; (v) slurred speech; (vi) swallowing difficulties; and (vii) impaired heart and kidney function. Some children and young people will require reconstructive surgery several years after completing cancer treatment to overcome these effects.

Despite the high cure rates, some children and young people will experience disease relapse. Treatment for disease relapse is individualised, however, it will usually include systemic therapy followed by local therapy.

<u>Proposed Intervention</u>

AMORE is a combination of ablative surgery, moulage technique brachytherapy and surgical reconstruction which is given as an alternative local therapy option. It combines both surgery and radiotherapy treatments into a single episode of care, which is delivered over a 3 – 4 week period.

In this technique, surgery is performed first to remove any remaining tumour following systemic chemotherapy. During surgery, a plastic mould is placed into the surgical site along with catheters to carry the radiation source. After surgery, the surgical area is treated with brachytherapy, a form of radiotherapy in which sealed radioactive substances are placed into or near the surgical bed. Brachytherapy is usually started 2-3 days after surgery and is usually administered for 3 – 4 days in total. Once brachytherapy is complete, reconstructive surgery is

carried out which involves removal of the mould and catheters, and also reconstruction of the site of resection.

The AMORE technique is thought to offer the same cure rates as current local therapy options, and may also reduce the long term effects of treatment. As AMORE involves the use of brachytherapy, it is also a treatment option for patients with disease relapse who may have been previously treated with conventional radiotherapy or proton beam therapy.

4 Definitions

Brachytherapy – a form of internal radiotherapy that works by placing a source of radiation directly in, or next to the cancerous tumour. This method allows the radiation therapy to be precisely targeted to the tumour site.

Chemotherapy – cancer treatment where drugs are used to kill cancer cells.

Cataracts - a medical condition in which the lens of the eye becomes progressively opaque, resulting in blurred vision.

External beam radiotherapy – a method of delivering radiation therapy using high energy rays from outside of the body to kill cancer cells.

Local therapy - treatment that is directed to the site of origin of the tumour.

Musculoskeletal – relating to the muscles and skeleton (including bones).

Proton beam radiotherapy - A type of external beam radiation therapy that uses tightly focussed streams of protons (tiny particles with a positive charge) to kill tumour cells.

Reconstructive surgery - surgery that aims to restore and repair function by reconstructing defective organs or parts.

Rhabdomyosarcoma – a type of soft tissue sarcoma, common in children.

Soft tissue sarcoma – rare cancers that develop in the supporting or connective tissues in the body such as the muscle, nerves, tendons, blood vessels and fatty and fibrous tissues.

Surgical resection – surgery to remove part or all of the tumour.

5 Aims and Objectives

This policy proposition considered: AMORE for head and neck soft tissue sarcoma in children and young people.

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

- Efficacy, safety and cost-effectiveness of AMORE therapy in the treatment of head and neck rhabdomyosarcoma compared with radiotherapy with or without surgery; and
- Identify any sub-groups of patients with head and neck rhabdomyosarcoma who would gain greater benefit from AMORE therapy compared with radiotherapy with or without surgery.

6 Epidemiology and Needs Assessment

Soft tissue sarcomas are extremely rare cancers in children. It is estimated that approximately 100 children develop a soft tissue sarcoma in the UK per year. The most common soft tissue sarcoma in children is rhabdomyosarcoma, accounting for almost two thirds of all soft tissue sarcomas in children of which 40% are estimated to occur in the head and neck region. This means that the estimated number of children with newly diagnosed head and neck rhabdomyosarcoma in England is 23 cases per annum.

Cure rates for head and neck rhabdomyosarcoma are high, however, it is estimated that approximately 20% of patients will suffer from disease relapse. The number of relapses per year is estimated to be between 4 – 5 cases.

Not all children with head and neck rhabdomyosarcoma would be suitable for surgery and therefore the Policy Working Group (PWG) estimate that approximately 8 patients (first line and relapse) would be eligible for AMORE treatment per year.

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.

Four papers were included in this evidence review (Schoot et al 2017; Clement et al 2016; Schoot et al 2015a; Schoot et al 2015b). These reported different outcomes from a prospective, non-randomised study of the same cohort of head and neck rhabdomyosarcoma patients who were treated either in Amsterdam, where AMORE was available as a treatment option (n=49) (hereafter referred to as the Amsterdam cohort), or in London where AMORE was not available (n=31) (hereafter referred to as the London cohort). Only patients who had survived more than two years after treatment were included in the analyses. Patients in Amsterdam were followed up for a median of 9.7 years and in London for a median of 11.0 years. Patients were children aged 0-13.6 years (median age 5.2 years) at diagnosis.

Clinical effectiveness

- Failure-free survival (one paper). There was no significant difference in five year failure-free survival between survivors in the Amsterdam cohort (53%) and those in the London cohort (64%) (p=0.37) (Schoot et al 2015a, n=80).

- Overall survival (one paper). There was no significant difference in five year overall survival between survivors in the Amsterdam cohort (77%) and survivors in the London cohort (75%) (p=0.56) (Schoot et al 2015a, n=80).
- Health-related quality of life (PedsQL questionnaire) (one paper). The authors (Schoot et al 2015a, n=80) reported no significant difference in mean health-related quality of life scores between Amsterdam and London survivors but did not report a p value. Total score and psychological health score were reported for three age groups: aged more than eight years, aged eight to 17 years and aged 18 years or more. For the Amsterdam cohort survivors total scores ranged from 81 to 82 out of 100 for the three age groups and psychological health scores ranged from 77 to 80. For the London cohort survivors total scores ranged from 74 to 83 and psychological health scores ranged from 73 to 79.
- Health-related quality of life scores were also compared to country-specific weighted norms adjusted for sex and attained age. For Amsterdam cohort survivors there was no significant difference to weighted norms in total or psychological health scores for any of the three age groups. London cohort survivors had statistically significant worse scores compared to weighted norms for:
    - Psychological health score for survivors aged more than eight years (effect size (ES) -0.55, p=0.037)
    - Total score for survivors aged 18 years or more (ES -0.25, p=0.030)
    - Psychological health score for survivors aged 18 years or more (ES -0.35, p=0.022).

  There was no significant difference to weighted norms for London cohort survivors aged eight to 17 years or for survivors aged more than eight years for the total score.

Safety

- Number, severity and type of adverse events (one paper) (Schoot et al 2015a, n=80):

- Significantly fewer survivors in the Amsterdam cohort experienced a grade 3 or 4 adverse event (53%) than survivors in the London cohort (77%) (p=0.028). This statistically significant difference was retained in multivariate analysis after adjustment for primary tumour site, age at diagnosis and follow-up duration (odds ratio (OR) 0.29 95%CI 0.10 to 0.90, p=0.032).
- Amsterdam cohort survivors were significantly less likely to develop ten or more adverse events of any grade than London cohort survivors (18% vs 48%) (p=0.04). In multivariate analysis, adjusted for primary tumour site, age at diagnosis and follow-up duration, Amsterdam cohort survivors were significantly less likely to have five or more adverse events of any grade (OR 0.11 95%CI 0.02 to 0.60, p=0.01). Parameningeal tumour site was an independent risk factor for the development of five or more adverse events of any grade (OR 13.34 95%CI 2.52 to 70.60, p=0.002).
- Survivors treated in Amsterdam had a significantly lower burden of adverse events than those treated in London (p=0.04). The number of survivors with a burden score of severe or high was similar between the treatment centres (Amsterdam n=15; London n=12) but more Amsterdam cohort survivors had a burden score of low or none (11 vs 4).
- The following adverse events (of any grade) were significantly less common in survivors in the Amsterdam cohort than survivors in the London cohort (p values not reported): dry eye (25% vs 55% OR 4.20 95%CI 1.55 to 11.40); alopecia (21% vs 42% OR 2.99 95%CI 1.10 to 8.15); cataract (19% vs 39% OR 2.95 95%CI 1.05 to 8.28); growth hormone deficiency (12% vs 48% OR 7.56 95%CI 2.42 to 23.58) and dysarthria (10% vs 32% OR 4.63 95%CI 1.39 to 15.40).
- Facial asymmetry (one paper). Clinician assessed facial asymmetry was significantly less severe for survivors in the Amsterdam cohort (median 1, interquartile range (IQR) 0 to 2) compared to survivors in the London cohort (median 1.5, IQR 0 to 3) (p=0.039) (Schoot et al 2017, n=75).
- Pituitary dysfunction (one paper). Seven survivors in the Amsterdam cohort (n=49) and 17 survivors in the London cohort (n=31) developed pituitary dysfunction. In multivariate analysis, the risk of pituitary dysfunction was

significantly lower among patients in the Amsterdam cohort compared to patients in the London cohort (OR 2.06 95%CI 1.79 to 2.46, p<0.05). The authors reported that adjustment for follow-up time produced similar results (precise figures not reported) (Clement et al 2016, n=80).

- Hearing threshold (one paper). Survivors in the Amsterdam cohort had a significantly better median hearing threshold at a pure-tone average of 0.5 to 1-2kHz air conduction (AC) (speech frequency) (5dB, range 0 to 118) compared to survivors in the London cohort (10dB, range 0 to 75) (p=0.002). Amsterdam cohort survivors also had a significantly better median hearing threshold at a pure-tone average of 4kHz AC (5dB, range 0 to 115) compared to London cohort survivors (10dB, range 0 to 85) (p=0.0007). The difference between treatment centres remained statistically significant in multivariate analysis adjusted for tumour location (difference in expected hearing threshold 5.4dB, p=0.001). For all survivors, hearing threshold was worse than age-corrected normal hearing levels. Hearing threshold was worse in survivors with parameningeal tumours compared to non-parameningeal tumours after adjustment for treatment centre (difference in expected hearing threshold 6.6dB, p=0.008) (Schoot et al 2015b, n=73).
- Hearing loss (one paper). There was no significant difference in any grade hearing loss between the Amsterdam and London cohort survivors using the Common Terminology for Adverse Events (41% vs 44%, p=0.55) or Boston criteria (52% vs. 59%, p=0.67). There was no significant difference between the Amsterdam cohort survivors and the London cohort survivors in clinically significant hearing loss at 0.5 to 1-2kHz AC (15% vs 26%, p=0.26) or 4kHz AC (20% vs 33%, p=0.19) (Schoot et al 2015b, n=73).

Cost-effectiveness

No studies were identified that reported the cost-effectiveness of having AMORE therapy available as a treatment option for patients with head and neck rhabdomyosarcoma.

8 Documents That Have Informed This Policy Proposition

The documents that have informed this policy proposition are:

- NHS England Evidence Review Policy 1827. (2018) Local therapy (surgery/ radiotherapy) in the form of AMORE treatment for non-metastatic rhabdomyosarcoma of the head and neck.
- NHS England Service Specification. (2013) Paediatric Oncology. (NHS England Reference: E04/S/a)

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 not for routine commissioning.

10 References

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Radzikowska J, Kukwa W, Kukwa A, Czarnecka, Krzeski A. 2015. Rhabdomyosarcoma of the head and neck in children. *Contemporary Oncology.* 19(2): 98 - 107