NHS England

Evidence review: Local therapy (surgery/ radiotherapy) in the form of AMORE treatment for non-metastatic rhabdomyosarcoma of the head and neck

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First published: September 2018

Updated: Not applicable

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Contents

1 Introduction

Introduction

- Soft tissue sarcomas are rare and aggressive cancers that can occur at all ages (NHS England 2018). Rhabdomyosarcoma is the most common soft tissue sarcoma in children (Schoot et al 2015b). The peak age for rhabdomyosarcoma is two to five years old and two thirds of cases occur in children who are less than 10 years old (NHS England 2018).
- Rhabdomyosarcomas occur in the head and neck area in 40% of cases (NHS England 2018). They are sub-classified as orbital, parameningeal (i.e. involving the nasopharynx, middle ear, paranasal sinuses, infratemporal fossa or skull base) or non-parameningeal (NHS England 2018).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE have not published any guidance on the use of AMORE treatment (Ablative surgery, MOuld[1] technique brachytherapy and surgical REconstruction) for non-metastatic rhabdomyosarcoma of the head and neck.

The indication and epidemiology

- Around two thirds of soft tissue sarcomas in children and young people are rhabdomyosarcomas (NHS England 2018).
- In England, there are approximately 58 cases of rhabdomyosarcoma per year in patients aged 19 years or less (NHS England 2018).

Standard treatment and pathway of care

- Complete surgical resection of rhabdomyosarcoma of the head and neck may not be possible due to the position and nature of the tumour. Radiotherapy may be required to achieve local control (Schoot et al 2015a).
- The international standard treatment is based on external beam radiotherapy (EBRT) local treatment (Schoot et al 2015a).

The intervention (and licensed indication)

- The AMORE local treatment approach was developed at the Emma Children's Hospital-Academic Centre (EKZ-AMC) in Amsterdam in 1990 (Schoot et al 2015a). This consists of Ablative surgery, MOuld technique brachytherapy (internal radiotherapy) and surgical REconstruction (Schoot et al 2015a).

Rationale for use

- In radiotherapy all tissues in the radiation field are damaged, including healthy tissue surrounding a tumour (Schoot et al 2017).
- AMORE uses brachytherapy where a higher dose of radiotherapy is delivered to the tumour bed with less exposure of the surrounding tissues. Reducing dose to surrounding tissues may reduce morbidity and improve functional and cosmetic outcomes and health related quality of life (Schoot et al 2015a).

[1] Also known as MOulage technique

2 Summary of results

- 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[2] (n=49) (hereafter referred to as the Amsterdam cohort), or in London where AMORE was not available[3] (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[4]) (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[5] (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).

[2] Patients treated in Amsterdam received AMORE if feasible i.e. if macroscopic radical resection and adequate brachytherapy mould placement seemed possible. Other patients received EBRT or no radiotherapy. Overall, 36 of the 49 Amsterdam cohort survivors received AMORE (73%) either as an initial treatment or following recurrence

[3] Overall 29 of the 31 London cohort survivors received EBRT as initial treatment or following recurrence. Two patients did not receive radiotherapy

[4] A validated, standardised, self-reported questionnaire assessing health-related quality of life in physical, emotional, social and school domains. Total score and psychosocial health score (mean of the emotional, social and school functioning scales) are reported on a scale of 0 to 100 with higher scores indicating better health-related quality of life. 100 = 'never'; 75 = 'almost never', 50 = 'sometimes', 25 = 'often' and 0 = 'almost always' https://www.corc.uk.net/outcome-experience-measures/paediatric-quality-of-life/

[5] The authors considered an effect size of 0.2 as small, 0.5 as moderate and 0.8 as large

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[6]

- 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[7] (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[8] 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[9] 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[10] (one paper). Clinician assessed facial asymmetry was significantly less severe for survivors in the Amsterdam cohort (median 1, interquartile range (IQR) 0

[6] Including complications of treatment

[7] Graded using the Common Terminology Criteria for Adverse Events where grade 1 = 'mild'; grade 2 = 'moderate', grade 3 = 'severe or medically significant but not immediately life-threatening'; grade 4 = 'life-threatening consequences' and grade 5 = 'death' (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

[8] Multivariate analysis for the proportion of survivors developing 10 or more adverse events was not reported

[9] The authors developed a burden of treatment score based on the number and severity of adverse events ranging from 'none' to 'severe'. For example a 'severe' score was given to 2 patients who experienced ≥2 grade 4 adverse events and 3 patients who experienced 1 grade 4 adverse event and ≥2 grade 3 adverse events

[10] Clinicians graded facial asymmetry using 4 grades from the Common Terminology Criteria for Adverse Events (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Grade 1 = 'cosmetically and functionally insignificant hypoplasia'; grade 2 = 'deformity, hypoplasia or asymmetry able to be covered'; grade 3 = 'significant deformity, hypoplasia or asymmetry unable to be remediated by prosthesis or covered by clothing, disabling'; grade 4 = 'orbital exenteration, which results in asymmetry which cannot be covered and in blindness of at least 1 eye'

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[11]).

- Pituitary dysfunction[12] (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[13] (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[14]).
- 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[15] (41% vs 44%, p=0.55) or Boston criteria[16] (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[17] 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[14]).

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.

[11] 80 head and neck rhabdomyosarcoma survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. Five survivors in the London cohort did not have a 3D image to assess facial asymmetry due to organisational issues

[12] This included growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocortcotropic deficiency, gonodotropin deficiency and precocious puberty

[13] Hearing threshold is the sound level below which a person is unable to detect any sound with 0dB as the reference level (http://ec.europa.eu/health/scientific_committees/opinions_layman/en/hearing-loss-personal-music-player-mp3/glossary/ghi/hearing-threshold.htm). Schoot et al (2015b) defined clinically relevant hearing loss as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC

[14] 80 head and neck rhabdomyosarcoma survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. Audiological assessment was not performed in 7 patients (1 was too young and in 6 cases this was due to logistical reasons (not further specified))

[15] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

[16] https://www.researchgate.net/figure/SIOP-Boston-Ototoxicity-Scale_tbl2_224871212

[17] Clinically relevant hearing loss was defined as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2003 and 10th July 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Comparative evidence matching the PICO was identified. This was therefore selected for inclusion in this review using established hierarchy of evidence criteria[18].
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

This evidence review identified four papers reporting 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) (Schoot et al 2017; Clement et al 2016; Schoot et al 2015a; Schoot et al 2015b). Patients treated in Amsterdam received AMORE if feasible i.e. if macroscopic radical resection and adequate brachytherapy mould placement seemed possible. Other patients received EBRT or no radiotherapy. Overall, 36 of the 49 included patients in Amsterdam received AMORE (73%) either as an initial treatment or following recurrence. Twenty-nine of the 31 patients treated in London received EBRT as initial treatment or after recurrence (94%) and two patients received no radiotherapy (Appendix 1). Only patients who had survived more than two years after treatment were included in the analysis. All patients were children (age range 0-13.6 years, median age 5.2 years) at diagnosis. Each paper reported different outcomes for the same cohort of patients, and full details of study design and outcomes are summarised in the evidence tables in section 7.

1. **What is the evidence for the clinical effectiveness of Ablative surgery, MOulage technique brachytherapy and surgical REconstruction (AMORE) therapy being available as a treatment option for patients with head and neck rhabdomyosarcoma compared with radiotherapy with or without surgery?**

Clinical outcomes reported included failure-free survival, overall survival and health-related quality of life. The analysis compared head and neck rhabdomyosarcoma survivors treated in Amsterdam

[18] https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

(where AMORE was available as a treatment option) to survivors treated in London (where AMORE was not available). Patients in Amsterdam were followed up for a median of 9.7 years and in London for a median of 11.0 years.

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

Overall survival
Overall survival was reported in one paper (Schoot et al 2015a, n=80). There was no significant difference in five year overall survival between the Amsterdam cohort survivors (77%) and the London cohort survivors (75%) (p=0.56).

Health-related quality of life
Health-related quality of life was reported in one paper (Schoot et al 2015a, n=80) using the self-reported PedsQL questionnaire[19]. Health-related quality of life scores were also compared to country-specific weighted norms adjusted for sex and attained age. Results were reported for three age groups: aged more than eight years, aged eight to 17 years and aged 18 years or more. The authors reported no significant difference in mean health-related quality of life scores between the Amsterdam cohort survivors and the London cohort survivors but did not report a p value. 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.

For the Amsterdam cohort survivors there was no significant difference to weighted norms in total or psychological health scores for any of the three age groups. For the London cohort survivors there was a statistically significant difference to weighted norms in the psychological health score for survivors aged more than eight years (effect size (ES) -0.55, p=0.037) and for survivors aged 18 years or more in the total (ES -0.25, p=0.030) and psychological health (ES -0.35, p=0.022) scores. There was no significant difference to weighted norms for London cohort survivors aged eight to 17 or for survivors aged more than eight years for the total score.

2. **What is the evidence relating to the incidence and severity of adverse events/ complications in patients with head and neck rhabdomyosarcoma where AMORE is available as a treatment option compared with radiotherapy with or without surgery:**
    a) **Short term?**
    b) **Long term?**

Adverse events/ complications reported included number, severity and type of adverse events, facial asymmetry, pituitary dysfunction, hearing threshold and hearing loss. The analyses compared outcomes between head and neck rhabdomyosarcoma survivors treated in Amsterdam (where AMORE was available as a treatment option) and survivors treated in London (where AMORE was not available). All outcomes were reported for a median follow-up of at least nine years. No papers distinguished between short-term and long-term adverse events or complications.

[19] A validated standardised questionnaire assessing health-related quality of life in physical, emotional, social and school domains. Total score and psychosocial health score (mean of the emotional, social and school functioning scales) are reported on a scale of 0 to 100 with higher scores indicating better health-related quality of life. 100 = 'never'; 75 = 'almost never', 50 = 'sometimes', 25 = 'often' and 0 = 'almost always' https://www.corc.uk.net/outcome-experience-measures/paediatric-quality-of-life/

Number, severity and type of adverse events

One paper (Schoot et al 2015a, n=80) reported the number, severity and type of adverse events graded using the Common Terminology Criteria for Adverse Events[20]. The authors also developed a burden of treatment score ranging from 'none' to 'severe'[21], based on the number and severity of adverse events. Patients were followed-up for a median of 10.5 years.

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 also less likely to develop ten or more adverse events of any grade (18% vs 48%) (p=0.04). Multivariate analysis, adjusted for primary tumour site, age at diagnosis and follow-up duration, found that Amsterdam cohort survivors were also significantly less likely to have five[22] 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).

The Amsterdam cohort had a significantly lower burden of adverse events than the London cohort (p=0.04). The number of patients with a burden of treatment 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).

Adverse events (of any grade) that were significantly less common in Amsterdam cohort survivors than London cohort survivors were 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) (p values not reported).

Facial asymmetry

One paper reported clinician assessed facial asymmetry (Schoot et al 2017, n=75[23]). Clinicians graded facial asymmetry using four grades from the Common Terminology Criteria for Adverse Events[24] with higher grades indicating more severity. Facial asymmetry was judged significantly less severe for Amsterdam cohort survivors (median 1, IQR 0 to 2) compared to London cohort survivors (median 1.5, IQR 0 to 3) (p=0.039). Median follow-up was 9.7 years for Amsterdam cohort survivors and 11.0 years for London cohort survivors.

[20] There are 5 severity grades: grade 1 = 'mild'; grade 2 = 'moderate', grade 3 = 'severe or medically significant but not immediately life-threatening'; grade 4 = 'life-threatening consequences'; grade 5 = 'death' (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

[21] For example a 'severe' score was given to 2 survivors who experienced ≥2 grade 4 adverse events and 3 survivors who experienced 1 grade 4 adverse event and ≥2 grade 3 adverse events

[22] Multivariate analysis for the proportion of survivors developing 10 or more adverse events was not reported

[23] 80 head and neck rhabdomyosarcoma survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. Five London cohort survivors did not have a 3D image to assess facial asymmetry due to organisational issues

[24] There were 4 grades, where grade 1 = 'cosmetically and functionally insignificant hypoplasia'; grade 2 = 'deformity, hypoplasia or asymmetry able to be covered'; grade 3 = 'significant deformity, hypoplasia or asymmetry unable to be remediated by prosthesis or covered by clothing, disabling'; grade 4 = 'orbital exenteration, which results in asymmetry which cannot be covered and in blindness of at least 1 eye' (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

Pituitary dysfunction

Pituitary dysfunction can develop as an adverse effect of radiotherapy to the pituitary area. One paper (Clement et al 2016, n=80) reported pituitary dysfunction which included growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocorticotropic deficiency, gonodotropin deficiency and precocious puberty. Seven (of 49) survivors in the Amsterdam cohort and 17 (of 31) survivors in the London cohort developed pituitary dysfunction at a median follow-up of 11.8 years. 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).

Hearing threshold

Median hearing threshold[25] was reported in one paper (Schoot et al 2015b, n=73[26]). Median follow-up was 11 years. Amsterdam cohort survivors had a significantly better median hearing threshold at a pure-tone average of 0.5 to 1-2kHz AC (speech frequency) (5dB, range 0 to 118) compared to London cohort survivors (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 patients with parameningeal tumours compared to non-parameningeal tumours after adjustment for treatment centre (difference in expected hearing threshold 6.6dB, p=0.008).

Hearing loss

Hearing loss was reported in one paper (Schoot et al 2015b, n=73[27]) with median follow-up of 11 years. This was assessed using the Common Terminology Criteria for Adverse Events[28] (CTCAE) and the Boston criteria[29], both of which have four severity grades with higher grades indicating more severe impairment. There was no significant difference in any grade hearing loss between the Amsterdam cohort and London cohort survivors. For CTCAE this was 41% and 44% respectively (p=0.55) and for the Boston criteria this was 52% and 59% (p=0.67). There was no significant difference between treatment centres in the proportion of survivors experiencing clinically significant hearing loss. The proportion of survivors in the Amsterdam and London cohorts who had clinically significant hearing loss[30] at 0.5 to 1-2kHz AC was 15% and 26% (p=0.26), and at 4kHz AC was 20% and 33% (p=0.19).

[25] Hearing threshold is the sound level below which a person is unable to detect any sound with 0dB as the reference level (http://ec.europa.eu/health/scientific_committees/opinions_layman/en/hearing-loss-personal-music-player-mp3/glossary/ghi/hearing-threshold.htm). Schoot et al (2015b) defined clinically relevant hearing loss as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC

[26] 80 head and neck rhabdomyosarcoma survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. Audiological assessment was not performed in 7 patients (1 was too young and in 6 cases this was due to logistical reasons (not further specified))

[27] 80 head and neck rhabdomyosarcoma survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. Audiological assessment was not performed in 7 patients (1 was too young and in 6 cases this was due to logistical reasons (not further specified))

[28] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

[29] https://www.researchgate.net/figure/SIOP-Boston-Ototoxicity-Scale_tbl2_224871212

[30] Clinically relevant hearing loss was defined as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC

3. **What is the cost-effectiveness when AMORE therapy is available as a treatment option for patients with head and neck rhabdomyosarcoma, compared with radiotherapy with or without surgery?**

No studies were identified reporting the cost-effectiveness of having AMORE therapy available as a treatment option for patients with head and neck rhabdomyosarcoma compared with radiotherapy with or without surgery.

4. **Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with head and neck rhabdomyosarcoma who would gain greater benefit from AMORE therapy compared with radiotherapy with or without surgery:**
    a) **Age?**
    b) **Tumour site sub-classification (parameningeal, non-parameningeal, orbital)?**

No papers reported subgroups of patients with head and neck rhabdomyosarcoma who would gain greater benefit from AMORE therapy compared to radiotherapy with or without surgery. The selection of patients for AMORE therapy was based on feasibility. Two papers (Schoot et al 2015a; Schoot et al 2015b) reported outcomes by tumour-site sub-classification but this was performed across the treatment centres (as presented in question two above). No papers reported outcomes by age.

5 Discussion

Four papers reported different clinical and safety outcomes for the same cohort of patients with head and neck rhabdomyosarcoma included in a prospective, non-randomised study. These patients were either treated in Amsterdam where AMORE was available as a treatment option, or in London where AMORE was not available. The same International or European assessment and treatment protocols were applied in Amsterdam and London. The selection of patients for AMORE (in Amsterdam) was based on feasibility, and it is not clear how many of the patients treated in London would have been judged suitable for AMORE treatment if it had been available.

In total 153 head and neck rhabdomyosarcoma patients received treatment in Amsterdam or London between 1990 and 2010. The papers included in this review reported outcomes for up to 80 patients who had survived more than two years after treatment. The 73 patients who were not included in any of the papers consist of 40 patients who died within two years of treatment and 33 who were not available or declined to participate. The proportion of patients who died within two years of treatment was similar (25% and 27%) in Amsterdam and London.

Overall, clinical outcomes, including failure-free survival, overall survival and health-related quality of life, were similar for patients treated in Amsterdam, where AMORE was available as a treatment option, and those treated in London, where AMORE was not available. However, Amsterdam survivors had significantly better results than London survivors on a range of safety outcomes and other complications, including the number of grade 3 and 4 adverse events, the number of any type of adverse event, the severity of facial asymmetry, the presence of pituitary dysfunction, and hearing threshold. Patients were assessed at multi-disciplinary follow-up clinics, one held in Amsterdam and the other in London and adverse events were scored by the two multidisciplinary teams. One clinician attended clinics in Amsterdam and London to ensure consistency of adverse event scoring and common criteria were used to assess adverse events. However, the clinical meaningfulness of the statistically significant differences observed was unclear. Effect sizes, where reported, were small to moderate and the confidence intervals around the odds ratios reported were generally wide, reducing confidence in the results.

The authors reported that all surviving patients treated in Amsterdam (including patients ineligible for AMORE who received alternative treatments) were compared to all surviving patients treated in London to reduce bias due to potential selection of the most favourable patients for AMORE treatment. However, it is impossible to eliminate bias due to the study design in which two patient groups recruited separately in different countries were compared. The authors of one paper reported that a significantly higher proportion of survivors treated in London were of non-Caucasian ethnicity compared to those treated in Amsterdam, but no other significant differences in patient characteristics were reported between treatment centres. In addition, there were significant differences between the Amsterdam and London patient groups in the number of radiotherapy treatments received and the proportion of patients who had major surgery. The authors noted that the adverse events were reduced in patients treated in Amsterdam despite the fact that a higher proportion had major surgery and additional radiotherapy treatments which may themselves be associated with adverse events.

The patients were treated over a twenty year period (1990 to 2010). Treatment techniques as well as treatment protocols changed over that period and may not reflect current practice.

6 Conclusion

The best evidence considering the effectiveness of AMORE compared to radiotherapy with or without surgery in patients with head and neck rhabdomyosarcoma comes from four papers reporting outcomes for patients treated in Amsterdam where AMORE was available as a treatment option compared to patients treated in London where AMORE was not available. These papers report different outcomes for the same 80 patients who had survived at least two years after treatment.

Treatment in the Amsterdam patient group was associated with fewer serious adverse events with no difference in failure-free survival, overall survival or health-related quality of life compared to treatment in the London patient group. These results should be treated with caution because they come from a small number of surviving patients that form a subset of all the patients treated. While the type of safety outcomes reported include many that will be important to patients, their families and clinicians, the clinical significance of the statistical differences in the results reported was not always clear. The extent to which the better safety outcomes observed can be attributed to the availability of AMORE as a treatment option is unclear given that there are inherent biases related to study design and the two patient groups were treated at different centres.

7 Evidence Summary Table

For abbreviations see list after each table

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Schoot et al 2017	P1 The aim was to develop methodologies for visualising and quantifying facial asymmetry in head and neck RMS and to use these in an, analysis of 2 treatment cohorts in Amsterdam and London	n=75[31] Children (0-18 years at diagnosis) presenting between 1990 and 2010 with newly diagnosed head and neck RMS and surviving ≥2 years post-treatment **Amsterdam cohort** (EKZ-AMC): n=49 Tumour site: Orbit: 20 (41%) Parameningeal: 23(47%) Non-parameningeal: 6 (12%) Median age at	All patients received 2 or 3 courses of induction chemotherapy After chemotherapy all patients in Amsterdam and London were staged and treated according to the same protocols[32] Patients requiring local treatment received: **Amsterdam cohort** AMORE if feasible[33] or EBRT/other treatment if not. n=49, of which initial treatment	Primary Safety	Clinical assessment of facial asymmetry Graded using the Common Terminology Criteria for Adverse Events (CTCAE v4)[35]	Median follow-up Amsterdam cohort (n=49): 9.7 years London cohort (n=26): 10.5 years Median (IQR) grade facial asymmetry Amsterdam cohort: 1 (0 to 2) London cohort: 1.5 (0 to 3) The severity of clinically-assessed facial asymmetry was significantly lower for Amsterdam cohort survivors (where AMORE was available as a treatment option) compared to London cohort survivors (where AMORE was not available) (p=0.039)	7	Direct	Patients in the Amsterdam cohort received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of the mould for the internal radiotherapy. AMORE was not available as a treatment option in London The authors reported that the complete Amsterdam cohort of 49 surviving patients (including patients ineligible for AMORE who received alternative treatments) was compared to the complete London cohort of 26 surviving patients to reduce bias due to potential selection of the most favourable patients for AMORE treatment. However, it is impossible to eliminate bias due to the study design in which 2 separate cohorts were compared There were significant differences between the Amsterdam and London cohorts in the proportion of patients who were of non-Caucasian ethnicity and the number of radiotherapy treatments received. Other papers

[31] 80 head and neck RMS survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. 5 London cohort survivors did not have a 3D image due to organisational issues

[32] Protocols during the study period included the International Society of Paediatric Oncology-Malignant Mesenchymal Tumour Group (SIOP-MMT) protocols for 1989, 1995 and 1998 and the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) protocols for 2005

[33] AMORE was considered feasible if macroscopic radical resection and adequate brachytherapy mould placement seemed possible

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		diagnosis: 5.9 years (IQR 3.2 to 9.3) Median attained age: 16.6 years (IQR 11.3 to 22.4) Median follow-up: 9.7 years (IQR 6.3 to 15.8) **London cohort** (GOSH; RMH): n=26 Tumour site: Orbit: 8 (31%) Parameningeal: 15(58%) Non-parameningeal: 3 (12%) Median age at diagnosis: 5.1 years (IQR 2.2 to 6.3) Median attained age:	was AMORE: 25 (51%) EBRT: 10 (20%) Proton RT[34]: 2 (4%) No RT: 12 (24%) Only details of initial treatment were reported **London cohort** n=26, of which initial treatment was EBRT: 25 (96%) No RT: 1 (4%) Significantly more Amsterdam cohort survivors were treated with >1 radiotherapy treatment (n=10/49) compared to London cohort survivors (n=0/26) (p=0.02)						based on the same patient cohort also reported a significant difference in the proportion of patients who had major surgery Details of subsequent treatment after recurrence were not reported in this paper but were reported for the same patient cohort in other papers (see appendix 1). The proportion of Amsterdam cohort patients who received AMORE treatment at some point is higher than the 51% who received AMORE as initial treatment The authors also attempted to visualise and quantify facial asymmetry and collected data on facial asymmetry in British and Dutch healthy controls. However, they found statistically significant differences in facial asymmetry between the British and Dutch controls Only the details of the clinical assessment of facial asymmetry are reported here. However, these results should be treated with caution due to the differences found in healthy controls in the 2 countries The patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not

[35] Grade 1 – cosmetically and functionally insignificant hypoplasia; grade 2 – deformity, hypoplasia or asymmetry able to be covered; grade 3 – significant deformity, hypoplasia or asymmetry unable to be remediated by prosthesis or covered by clothing, disabling; grade 4 – orbital exenteration, which results in asymmetry which cannot be covered and in blindness of at least 1 eye (scored as grade 4 because there was no associated grading in CTCAE)

[34] Proton radiotherapy is a type of external beam radiotherapy

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Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		13.4 years (IQR 11.6 to 22.8) Median follow-up: 10.5 years (IQR 6.1 to 18.2) Significantly fewer Amsterdam cohort survivors were of non-Caucasian ethnicity (16%) compared to London cohort survivors (42%) (p=0.02)	All eligible patients were invited to have a 3D photograph taken at a multi-disciplinary follow-up clinic held as part of the wider assessment of survival and adverse events (see Schoot et al 2015a)						reflect current practice. The authors reported no significant trend in the severity, number or burden of adverse events over the treatment period but did not provide details
Clement et al 2016	P1 Assessing the risk of pituitary dysfunction in survivors of head and neck RMS. Including a comparison of 2 treatment cohorts in Amsterdam and London	n=80 Children (0-18 years at diagnosis) presenting between 1990 and 2010 with newly diagnosed head and neck RMS and surviving ≥2 years post-treatment	All patients received 2 or 3 courses of induction chemotherapy After chemotherapy all patients in Amsterdam and London were staged and treated according to the same protocols[36]	Primary Safety	Pituitary dysfunction[39]	At median 11.8 years follow-up, 24/ 80 (30%) of all patients developed pituitary dysfunction. Of these 7 (29%) were from the Amsterdam cohort (where AMORE was available as a treatment option) and 17 (71%) were from the London cohort (where AMORE was not available) In multivariate analysis, there was a significantly lower risk of pituitary dysfunction among survivors in the Amsterdam cohort, compared to survivors in the London cohort (OR 2.06 95%CI 1.79 to 2.46, p<0.05)	7	Direct	Patients in the Amsterdam cohort received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of the mould for the internal radiotherapy. AMORE was not available as a treatment option in London The authors reported that the complete Amsterdam cohort of surviving patients (including patients ineligible for AMORE who received alternative treatments) was compared to the complete London cohort of surviving

[36] Protocols during the study period included the International Society of Paediatric Oncology-Malignant Mesenchymal Tumour Group (SIOP-MMT) protocols for 1989, 1995 and 1998 and the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) protocols for 2005

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Tumour site: Orbit: 28 (35%) Parameningeal: 38(48%) Orbit & parameningeal: 4 (5%) Non-parameningeal: 10 (13%) Median age at diagnosis: 5.2 years (range 0.0 to 13.6) Median attained age: 16.8 years (range 6.3 to 35.6) Median follow-up: 11.8 years (range 2.4 to 22.9) **Amsterdam cohort** (EKZ-AMC): n=49 **London cohort** (GOSH; RMH): n=31	Patients requiring local treatment received: No RT 15 (19%) AMORE 25 (31%) EBRT 38 (48%) Proton RT[37] 2 (3%) Patients in the Amsterdam cohort received AMORE if feasible[38] or EBRT/other treatment if not. Patients in the London cohort received EBRT or other treatment In this paper, treatment received was reported for the whole cohort All eligible patients were assessed once at a multi-			The authors reported that the results were similar when adjusted for follow-up time (figures not reported)			patients to reduce bias due to potential selection of the most favourable patients for AMORE treatment. However, it is impossible to eliminate bias due to the design in which 2 separate cohorts were compared Differences between the Amsterdam and London cohorts were not reported in this paper, but other reports of the same patient cohort noted significant differences in the number of radiotherapy treatments received and the proportion of patients who had major surgery In this paper some outcomes, including the main outcome, were reported for the whole patient cohort i.e. without separate results for treatment centres. A multivariate analysis which included comparison by treatment centre is reported here. Limited details about treatment received were reported in this paper The patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice. The authors reported no significant trend in the severity, number or burden of adverse events over the treatment period but did not provide details

[39] Pituitary dysfunction encompassed growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocorticotropic deficiency, gonodotropin deficiency and precocious puberty (pubertal stage was assessed using the Tanner criteria https://patient.info/doctor/normal-and-abnormal-puberty)
[37] Proton radiotherapy is a type of external beam radiotherapy
[38] AMORE was considered feasible if macroscopic radical resection and adequate brachytherapy mould placement seemed possible

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		In this paper baseline characteristic were reported for the whole patient cohort with no comparison by treatment centre	disciplinary clinic (1 in Amsterdam and 1 in London) using the same protocol. Additional clinical data was retrieved from patient charts						
Schoot et al 2015a	P1 Analysis comparing 2 treatment cohorts in Amsterdam and London	n=80 Children (0-18 years at diagnosis) presenting between 1990 and 2010 with newly diagnosed head and neck RMS and surviving ≥2 years post-treatment **Amsterdam cohort** (EKZ-AMC): n=49 Tumour site: Orbit: 19 (39%) Parameningeal: 21(43%)	All patients received 2 or 3 courses of induction chemotherapy After chemotherapy all patients in Amsterdam and London were staged and treated according to the same protocols[40] Patients requiring local treatment received: **Amsterdam cohort** AMORE if	Primary Clinical effectiveness	Failure-free survival[43]	Median follow-up Amsterdam cohort (where AMORE was available as a treatment option): 9.7 years London cohort (where AMORE was not available): 11.0 years 5 year failure-free survival Amsterdam cohort: 53.2% London cohort: 63.8% 95%CI not reported There was no significant difference between the treatment centres (p=0.37)	9	Direct	Patients in the Amsterdam cohort received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of the mould for the internal radiotherapy. AMORE was not available as a treatment option in London The authors reported that the complete Amsterdam cohort of surviving patients (including patients ineligible for AMORE who received alternative treatments) was compared to the complete London cohort of surviving patients to reduce bias due to potential selection of the most favourable patients for AMORE treatment. However, it is impossible to eliminate bias due to the design in which 2 separate cohorts were compared There were no significant differences in the reported patient characteristics
				Primary Clinical effectiveness	Overall survival	Median follow-up Amsterdam cohort (where AMORE was available as a treatment option): 9.7 years London cohort (where AMORE was not available): 11.0 years 5 year overall survival Amsterdam cohort: 76.9% London cohort: 75.0%			

[40] Protocols during the study period included the International Society of Paediatric Oncology-Malignant Mesenchymal Tumour Group (SIOP-MMT) protocols for 1989, 1995 and 1998 and the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) protocols for 2005
[43] Not further defined

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Orbit & parameningeal: 2 (4%) Non-parameningeal: 7 (14%) Median age at diagnosis: 5.9 years (range 0.0 to 13.6) Median attained age: 16.6 years (range 5.0 to 34.9) Median follow-up: 9.7 years (IQR 6.3 to 15.8) **London cohort** (GOSH; RMH): n=31	feasible[41] or EBRT/ other treatment if not). n=49, of which initial treatment was AMORE: 25 (51%) EBRT: 10 (20%) Proton RT[42]: 2 (4%) No RT: 12 (24%) 7/12 survivors who had no RT as initial treatment, had AMORE after a 1st recurrence and 1/12 had EBRT. 4/10 survivors who had EBRT as initial treatment had AMORE after a 1st			95%CI not reported There was no significant difference between the treatment centres (p=0.56)			between treatment centres. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery A selection of predefined adverse events were graded using the Common Terminology Criteria for Adverse Events (v4)[44]. This included all potential adverse events following local treatment in the head and neck area plus adverse events identified from a pilot study of 14 survivors of rhabdomyosarcoma of the head and neck. Adverse events were scored by 2 separate multidisciplinary teams. One clinician attended clinics in Amsterdam and London to ensure consistency of adverse event scoring The patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice. The authors reported no significant trend in the
				Primary Clinical effectiveness	Health-related quality of life Assessed using PedsQL[45] compared to weighted norms[46]	Completed by 36/49 (73%) Amsterdam cohort survivors (where AMORE was available as a treatment option) and 29/31 (94%) London cohort survivors (where AMORE was not available) There were no significant differences in a comparison of these mean scores between treatment centres (p value not reported) **Amsterdam cohort survivors (median follow-up 9.7 years)** All ages (>8): • No significant difference in total score (81.4) compared to weighted norm (83.6) (ES -0.19, p=0.30) • No significant difference in psychological health score (78.2) compared to weighted norm (81.8) (ES -0.25, p=0.11) 8-17 years:			

[41] AMORE was considered feasible if macroscopic radical resection and adequate brachytherapy mould placement seemed possible
[42] Proton radiotherapy is a type of external beam radiotherapy
[44] https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
[45] A validated standardised questionnaire assessing health-related quality of life in physical, emotional, social and school domains. Total score (0-100) and psychosocial health score (0-100) (mean of the emotional, social and school functioning scales) were reported. Higher scores indicate better self-reported health-related quality of life with 100 meaning 'never'; 75 'almost never', 50 'sometimes', 25 'often' and 0 'almost always' (https://www.corc.uk.net/outcome-experience-measures/paediatric-quality-of-life/)
[46] Country-specific weighted norms adjusted for sex and attained age for patients aged <18 years at follow-up. Dutch norm values used for all patients aged ≥18 years at follow-up, adjusted for sex and age (the authors used Dutch norm values for patients ≥18 years because norm values for patients <18 years were comparable for the Netherlands and United Kingdom)

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Tumour site: Orbit: 9 (29%) Parameningeal: 17(55%) Orbit & parameningeal: 2 (7%) Non-parameningeal: 3 (10%) Median age at diagnosis: 5.1 years (range 1.0 to 11.9) Median attained age: 15.8 years (range 8.4 to 27.5) Median follow-up: 11.0 years (IQR 6.0 to 18.1) There were no statistically significant differences in the reported patient characteristics between treatment centres	recurrence. Overall 36/49 Amsterdam cohort survivors had AMORE at some stage (73%) (see appendix 1) **London cohort** n=31, of which initial treatment was EBRT: 28 (90%) No RT: 3 (10%) 1/3 survivors who had no RT as initial treatment, had EBRT after a 1st recurrence. Overall 29/31 London cohort survivors had EBRT at some stage (94%) (see appendix 1) There were significant differences between the treatment centres in number of radiotherapy treatments			• No significant difference in total score (81.0) compared to weighted norm (82.2) (ES -0.19, p=0.60) • No significant difference in psychological health score (76.8) compared to weighted norm (80.4) (ES -0.35, p=0.27) ≥18 years: • No significant difference in total score (82.3) compared to weighted norm (84.1) (ES -0.20, p=0.20) • No significant difference in psychological health score (80.0) compared to weighted norm (83.0) (ES -0.21, p=0.05) **London cohort survivors (median follow-up 11.0 years)** All ages (>8): • No significant difference in total score (76.8) compared to weighted norm (83.9) (ES[47] -0.54, p=0.063) • Significantly lower psychological health score (74.3) than the weighted norm (82.0) (ES -0.55, p=0.037) 8-17 years: • No significant difference in total score (74.3) compared to weighted norm (82.7) (ES -0.64, p=0.091) • No significant difference in psychological health score (72.6) compared to weighted norm (80.3) (ES -0.55, p=0.084) ≥18 years: • Significantly lower total score (82.5) than the weighted norm (85.7) (ES -			severity, number or burden of adverse events over the treatment period but did not provide details 153 patients were treated between 1990 and 2010, 80 in Amsterdam, 73 in London. 113 were alive ≥2 years after treatment (of the 40 children that died, 20/80 were treated in Amsterdam and 20/73 in London) 80 of the 113 eligible patients participated. Reasons for non-participation were moved abroad (n=4),could not be reached (n=14), declined to participate (n=14) and died of 3rd primary tumour (n=1) The confidence intervals around the odds ratios for adverse events are wide reducing confidence in the result

[47] The authors considered an effect size of 0.2 as small, 0.5 as moderate and 0.8 as large

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Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
			(p=0.008) e.g. 10/49 (20%) Amsterdam cohort patients received >1 radiotherapy compared to 0/31 (0%) London cohort patients Significantly more of the Amsterdam cohort had major surgery (74%) compared to the London cohort (36%) (p=0.001) All eligible patients were assessed once at a multi-disciplinary clinic (1 in Amsterdam and 1 in London) using the same protocol and completed a questionnaire to assess self-reported health-related quality			0.25, p=0.030) • Significantly lower psychological health score (78.9) than the weighted norm (83.7) (ES -0.35, p=0.022)			
				Primary Safety	Number, severity and type of adverse events	At median 10.5 years follow-up **Number of survivors experiencing ≥1 grade 3 or 4 adverse event[48]:** Amsterdam cohort (where AMORE was available as a treatment option): 26/49 (53%) London cohort (where AMORE was not available): 24/31 (77%) Amsterdam cohort survivors were significantly less likely to experience grade 3 or 4 adverse events (p=0.028) than London cohort survivors In multivariate analysis (adjusted for primary tumour site, age at diagnosis and follow-up duration), Amsterdam cohort survivors were at decreased risk of grade 3 or 4 adverse events (OR 0.29 95%CI 0.10 to 0.90, p=0.032) **Number of survivors developing ≥10 adverse events (any grade):** Amsterdam cohort: 9/49 (18%) London cohort: 15/31 (48%) Amsterdam cohort survivors were significantly less likely to experience ≥10 adverse events (p=0.04) Multivariate analysis (adjusted for primary tumour site, age at diagnosis			

[48] Using the Common Terminology Criteria for Adverse Events (v4). There are 5 severity grades: grade 1 = 'mild'; grade 2 = 'moderate', grade 3 = 'severe or medically significant but not immediately life-threatening'; grade 4 = 'life-threatening consequences'; grade 5 = 'death' (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

<table>
<tr><th colspan="9">Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome measure type</th><th>Outcome measures</th><th>Results</th><th>Quality of Evidence Score</th><th>Applicability</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td></td><td></td><td>of life</td><td></td><td></td><td>and follow-up duration), explored the risk of developing ≥5 adverse events of any grade. Amsterdam cohort survivors were at decreased risk of developing ≥5 adverse events (OR 0.11 95%CI 0.02 to 0.60, p=0.01)

Parameningeal tumour site was also an independent risk factor for the development of ≥5 adverse events (OR 13.34 95%CI 2.52 to 70.60, p=0.002)

Burden of treatment[49]
<table>
<tr><th></th><th>Amsterdam cohort survivors</th><th>London cohort survivors</th></tr>
<tr><td>Severe</td><td>0</td><td>5</td></tr>
<tr><td>High</td><td>15</td><td>7</td></tr>
<tr><td>Medium</td><td>23</td><td>15</td></tr>
<tr><td>Low</td><td>9</td><td>4</td></tr>
<tr><td>None</td><td>2</td><td>0</td></tr>
</table>
Amsterdam cohort survivors had a statistically significantly lower burden of adverse events than London cohort survivors (p=0.04)

Most common adverse events (any grade)
The following adverse events were significantly less common in Amsterdam cohort survivors than in London cohort survivors
• 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</td><td></td><td></td><td></td></tr>
</table>

[49] The authors combined the number and severity of adverse events to create a burden score, classed as none; low; medium; high or severe. For example, the 5 survivors classed as severe included 2 survivors who experienced ≥2 grade 4 adverse events and 3 survivors who experienced 1 grade 4 adverse event and ≥2 grade 3 adverse events

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• 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) • Dysarthria 10% vs 32% (OR 4.63 95%CI 1.39 to 15.40)			
Schoot et al 2015b	P1 Analysis comparing 2 treatment cohorts in Amsterdam and London	n=73[50] Children (0-18 years at diagnosis) presenting between 1990 and 2010 with head and neck RMS and surviving ≥2 years post-treatment **Amsterdam cohort** (EKZ-AMC): n=46 Tumour site: Orbit: 16 (35%) Parameningeal: 23(50%) Non-parameningeal:	All patients received 2 or 3 courses of induction chemotherapy After chemotherapy all patients in Amsterdam and London were staged and treated according to the same protocols[51] Patients requiring local treatment received: **Amsterdam cohort** AMORE if	Primary Safety	Hearing threshold Pure tone hearing threshold assessed at 0.5 to 1-2kHz AC and at 4kHz AC	Median follow-up Amsterdam cohort (where AMORE was available as a treatment option): 11.0 years London cohort (where AMORE was not available): 11.0 years **Median hearing threshold[56]** • Pure-tone average 0.5 to 1-2kHz AC[57]: significantly better in Amsterdam cohort survivors (5.0dB, range 0 to 118) compared to London cohort survivors (10.0dB, range 0 to 75) (p=0.002) • Pure-tone average 4kHz AC: significantly better in Amsterdam cohort survivors (5.0dB, range 0 to 115) compared to London cohort survivors (10.0dB, range 0 to 85) (p=0.0007) In multivariate analysis the difference between the treatment centres remained significant after adjustment for tumour localisation (5.4dB, p=0.001)	8	Direct	Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of the mould for the internal radiotherapy. AMORE was not available as a treatment option in London The authors reported that the complete Amsterdam cohort of surviving patients (including patients ineligible for AMORE who received alternative treatments) was compared to the complete London cohort of surviving patients to reduce bias due to potential selection of the most favourable patients for AMORE treatment. However, it is impossible to eliminate bias due to the design in which 2 separate cohorts were compared There were no significant differences in the reported patient characteristics between treatment cohorts. No

[50] 80 head and neck RMS survivors were assessed for adverse events at multi-disciplinary clinics in Amsterdam and London. Audiological assessment was not performed in 7 patients (1 was too young and in 6 cases this was due to logistical reasons (not further specified))

[51] Protocols during the study period included the International Society of Paediatric Oncology-Malignant Mesenchymal Tumour Group (SIOP-MMT) protocols for 1989 and 1995 and the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) protocols for 2005. 2 patients were treated with other protocols (not specified)

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Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		7 (15%) Median age at diagnosis: 5.7 years (range 0.0 to 13.7) Median attained age: 17.6 years (range 5.9 to 33.6) Median follow-up: 11.0 years (range 2.6 to 21.0) **London cohort** (GOSH; RMH; UCLH): n=27 Tumour site: Orbit: 8 (30%) Parameningeal: 17(63%) Non-	feasible[52] or EBRT/ other treatment if not) (as initial treatment or after relapse). n=46, of which AMORE: 24 (52%) EBRT: 7 (15%) Proton RT[53]: 2 (4%) Combination of AMORE and EBRT[54]: 9 (20%) No RT: 4 (9%) Overall 33/46 Amsterdam cohort survivors had AMORE at some stage (72%) **London cohort** n=27, of which EBRT: 26[55] (96%)			In multivariate analysis the hearing threshold was worse in survivors with parameningeal tumours compared to non-parameningeal tumours after adjustment for treatment centre (6.6dB, p=0.008) For all survivors, hearing threshold was higher (worse) compared to age-corrected normal hearing levels[58] (p<0.0001) (figures only reported graphically)			comparison of treatment characteristics (e.g. number of radiotherapy treatments) was reported in this paper Baseline audiometry was not available. The authors assumed that children had normal hearing at the start of treatment The patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice
				Primary Safety	Hearing loss Proportion of patients with any hearing loss, assessed using the Common Terminology Criteria for Adverse Events (CTCAEv4.0)[59] and the Boston Criteria[60] Clinically	Median follow-up Amsterdam cohort (where AMORE was available as a treatment option): 11.0 years London cohort (where AMORE was not available): 11.0 years **Any hearing loss** CTCAE grade 1 to 4 impairment: • Amsterdam cohort: 19/46 (41%) • London cohort: 12/27 (44%) Boston grade 1 to 4 impairment: • Amsterdam cohort: 24/46 (52%) • London cohort: 16/27 (59%)			

[56] Hearing threshold is the sound level below which a person is unable to detect any sound with 0dB as the reference level (http://ec.europa.eu/health/scientific_committees/opinions_layman/en/hearing-loss-personal-music-player-mp3/glossary/ghi/hearing-threshold.htm)
[57] Pure-tone average 0.5 to 1-2kHz represents speech frequency
[52] AMORE was considered feasible if macroscopic radical resection and adequate brachytherapy mould placement seemed possible
[53] Proton radiotherapy is a type of external beam radiotherapy
[54] AMORE salvaged by EBRT at relapse (n=5); EBRT salvaged by AMORE at relapse (n=4)
[55] Initial treatment (n=25); after relapse (n=1)
[58] Determined by the International Organisation for Standardisation

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		parameningeal: 2 (7%) Median age at diagnosis: 5.2 years (range 1.0 to 12.7) Median attained age: 16.7 years (range 8.5 to 27.9) Median follow-up: 11.0 years (range 2.8 to 21.7) There were no statistically significant differences in the reported patient characteristics between treatment cohorts	No RT: 1 (4%) No further treatment characteristics were reported Tympanometry and audiology were performed at the same visit. Otoscopy was performed by a head and neck surgeon attending the multidisciplinary clinic		relevant hearing loss defined as a deterioration of ≥20 decibels at pure-tone average threshold of 0.5 to 1-2kHz AC or 4kHz AC	No significant differences between Amsterdam cohort survivors and London cohort survivors on the CTCAE (p=0.55) or Boston (p=0.67) scales **Clinically relevant hearing loss** At 0.5 to 1-2kHz AC: No significant difference between Amsterdam cohort survivors (15%) and London cohort survivors (26%) (p=0.26) At 4kHz AC: No significant difference between Amsterdam cohort survivors (20%) and London cohort survivors (33%) (p=0.19)			

3D – 3-dimensional; AC – air conduction; AMORE – Ablative surgery, MOuld technique brachytherapy and surgical REconstruction; CI – confidence intervals; dB – decibel; EBRT – external beam radiotherapy; ES – effect size; EKZ-AMC – Emma Children's Hospital-Academic Medical Centre; GOSH – Great Ormond Street Hospital for Children NHS Foundation Trust; IQR – Inter-quartile range; kHz –kilohertz; OR – odds ratio; RMH – The Royal Marsden NHS Foundation Trust; RMS – rhabdomyosarcoma; RT – radiotherapy; UCLH – University College London Hospitals

[59] 4 severity grades defined with different thresholds for adults and children. Higher grades imply more severe impairment (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

[60] 4 severity grades defined with higher grades implying more severe impairment (https://www.researchgate.net/figure/SIOP-Boston-Ototoxicity-Scale_tbl2_224871212)

8 Grade of Evidence Table

For abbreviations see list after each table

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Failure-free survival	Schoot et al (2015a)	9	Direct	B	Failure-free survival was not defined, but this is generally the proportion of patients who have not experienced disease recurrence at specified intervals after completion of treatment. Schoot et al (2015a) reported 5 year failure-free survival. There was no significant difference in 5 year failure-free survival between Amsterdam cohort survivors (where AMORE was available as a treatment option) (53.2%) and London cohort survivors (where AMORE was not available) (63.8%) (p=0.37). Median follow-up was 9.7 years for the Amsterdam cohort and 11.0 years for the London cohort. There was no difference in 5 year failure-free survival between the different treatment centres. Failure-free survival is an important outcome for clinicians, patients and their families. These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible.73% of the Amsterdam cohort had AMORE treatment at some stage, either as initial treatment or after recurrence. 94% of the London cohort had EBRT as initial treatment or after recurrence. There were no significant differences in the reported patient characteristics between the treatment cohorts. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
Overall survival	Schoot et al (2015a)	9	Direct	B	Overall survival is the proportion of patients alive at specified intervals. Schoot et al (2015a) reported 5 year overall survival. There was no significant difference in 5 year overall survival between Amsterdam cohort survivors (where AMORE was available as a treatment option) (76.9%) and London cohort survivors (where AMORE was not available) (75.0%) (p=0.56). Median follow-up was

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					9.7 years for the Amsterdam cohort and 11.0 years for the London cohort. There was no difference in 5 year overall survival between the different treatment centres. Overall survival is important to clinicians, patients and their families. These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 73% of the Amsterdam cohort had AMORE treatment at some stage, either as initial treatment or after recurrence. 94% of the London cohort had EBRT as initial treatment or after recurrence. There were no significant differences in the reported patient characteristics between the treatment centres. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
Health-related quality of life	Schoot et al (2015a)	9	Direct	B	Health-related quality of life was assessed using the self-reported Peds QL, a validated standardised questionnaire assessing health-related quality of life in physical, emotional, social and school domains. Schoot et al (2015a) reported the total score (0-100) and psychosocial health score (mean of the emotional, social and school functioning scales) (0-100) for 3 groups (all patients aged >8 years; patients aged 8 to 17 and patients aged ≥18). Higher scores indicate better health-related quality of life with 100 meaning 'never'; 75 'almost never', 50 'sometimes', 25 'often' and 0 'almost always'[61]. Health-related quality of life scores were also compared to country-specific weighted norms adjusted for sex and attained age. The authors considered an effect size of 0.2 as small, 0.5 as moderate and 0.8 as large. For Amsterdam cohort survivors (where AMORE was available as a treatment option) PedsQL total scores ranged from 81.0 to 82.3 for the 3 age groups. Psychological health scores ranged from 76.8 to 80.0. For London cohort survivors (where AMORE was not available)

[61] https://www.corc.uk.net/outcome-experience-measures/paediatric-quality-of-life/

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					total scores ranged from 74.3 to 82.5 for the 3 age groups. Psychological health scores ranged from 72.6 to 78.9. The authors reported no difference in mean health-related quality of life scores between the treatment centres (p value not reported). There was no significant difference in total score or psychological health score between the Amsterdam cohort survivors and weighted norms for any of the 3 age groups. For London cohort survivors there was no significant difference with weighted norms for patients aged 8 to 17 on the total or psychological scores, or on the total score for all patients aged >8 years. There was a statistically significant difference between London cohort survivors and weighted norms for psychological health score for patients all aged >8 years (ES -0.55, p=0.037) for patients aged ≥18 years on total (ES -0.25, p=0.030) and psychological health (ES -0.35, p=0.022) scores. There was no reported difference between the treatment centres in health-related quality of life scores. Some statistically significant differences were found between London survivors and weighted norms, with effect sizes that were considered to be between small and moderate. The health-related quality of life scores reported were all between 72 and 82 out of 100. On the Peds QL scale, higher scores indicate better health-related quality of life and a score of 75 represents 'almost never'. These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible.73% of the Amsterdam cohort had AMORE treatment at some stage, either as initial treatment or after recurrence. 94% of the London cohort had EBRT as initial treatment or after recurrence. There were no significant differences in the reported patient characteristics between the treatment cohorts. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Number, severity and type of adverse events	Schoot et al (2015a)	9	Direct	B	Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAEv4[62]). The 5 severity grades were grade 1 'mild'; grade 2 'moderate', grade 3 'severe or medically significant but not immediately life-threatening'; grade 4 'life-threatening consequences'; grade 5 'death'. Schoot et al (2015a) also developed a burden of treatment score ranging from 'none' to 'severe', based on the number and severity of adverse events. For example a 'severe' score was given to 2 patients who experienced ≥2 grade 4 adverse events and 3 patients who experienced 1 grade 4 adverse event and ≥2 grade 3 adverse events. Patients were followed-up for a median of 10.5 years. Amsterdam cohort survivors (where AMORE was available as a treatment option) were significantly less likely to experience a grade 3 or 4 adverse event (53%) compared to London cohort survivors (where AMORE was not available) (77%) (p=0.028). This significant difference was retained in multivariate analysis adjusted for primary tumour site, age at diagnosis and follow-up duration (OR 0.29 95%CI 0.10 to 0.90, p=0.032). Amsterdam cohort survivors were less likely to develop ≥10 adverse events of any grade (18% vs 48%) (p=0.04). In multivariate analysis Amsterdam cohort survivors were also significantly less likely to have ≥5 adverse events of any grade, after adjustment for primary tumour site, age at diagnosis and follow-up duration (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 ≥5 adverse events of any grade (OR 13.34 95%CI 2.52 to 70.60, p=0.002). Availability of AMORE treatment (in Amsterdam) was associated with a significantly lower burden of adverse events than no availability of AMORE (in London) (p=0.04). The number of patients scoring 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). Five types of adverse event (any grade) were significantly less common in Amsterdam cohort survivors than London cohort survivors. These were 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). The effect size represented by the odds ratios reported varied from small to moderate and the confidence intervals are wide reducing confidence in the results. Number and severity of adverse events is an important outcome for patients, families and clinicians.

[62] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 73% of the Amsterdam cohort had AMORE treatment at some stage, either as initial treatment or after recurrence. 94% of the London cohort had EBRT as initial treatment or after recurrence. There were no significant differences in reported patient characteristics between the treatment centres. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were assessed for adverse events at multi-disciplinary clinics in London and Amsterdam using the same protocol. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
Clinical assessment of facial asymmetry	Schoot et al (2017)	7	Direct	B	In Schoot et al (2017) clinicians graded facial asymmetry using the Common Terminology Criteria for Adverse Events (CTCAEv4[63]). There were 4 grades, where grade 1 = 'cosmetically and functionally insignificant hypoplasia'; grade 2 = 'deformity, hypoplasia or asymmetry able to be covered'; grade 3 = 'significant deformity, hypoplasia or asymmetry unable to be remediated by prosthesis or covered by clothing, disabling'; grade 4 = 'orbital exenteration, which results in asymmetry which cannot be covered and in blindness of at least 1 eye'. The severity of clinically assessed facial asymmetry was significantly lower for Amsterdam cohort survivors (where AMORE was available as a treatment option) (median 1, IQR 0 to 2) compared to London cohort survivors (where AMORE was not available) (median 1.5, IQR 0 to 3) (p=0.039). Median follow-up was 9.7 years for the Amsterdam cohort survivors and 11.0 years for the London cohort survivors. The median severity scores are associated with facial asymmetry that is either 'insignificant' or between 'insignificant' and 'able to be covered'. The importance of this degree of facial asymmetry to patients, families and clinicians is not clear. These results should be treated with caution. Patients were treated

[63] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					in 2 countries (The Netherlands and England). The authors reported significant differences in facial asymmetry between a cohort of British and Dutch healthy controls raising uncertainty about the direct comparison of patients from the different treatment centres. The results are from a small, non-randomised study including 49 patients who received treatment in Amsterdam and 26 patients who received treatment in London and had a 3D photograph taken. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 51% of the Amsterdam cohort received AMORE as an initial treatment. The proportion of patients who had AMORE or EBRT treatment at some stage (as initial treatment or after recurrence) was not reported in this paper, but other papers about the same patient cohort reported that 73% of the Amsterdam cohort had AMORE treatment at some stage and 94% of the London cohort had EBRT treatment at some stage. Significantly more of the London cohort were of non-Caucasian ethnicity. The Amsterdam cohort received a significantly higher number of radiotherapy treatments than the London cohort. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
Pituitary dysfunction	Clement et al (2016)	7	Direct	B	Pituitary dysfunction encompassed growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocortcotropic deficiency, gonodotropin deficiency and precocious puberty[64]. No further definition of pituitary dysfunction was provided by Clement et al (2016). 24 (of 80) patients developed pituitary dysfunction at median follow-up of 11.8 years, consisting of 7 of the 49 Amsterdam cohort survivors and 17 of the 31 London cohort survivors. In multivariate analysis, there was a significantly lower risk of pituitary dysfunction among survivors treated in Amsterdam (where AMORE was available as a treatment option), compared to those treated in London (where AMORE was not available) (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). Pituitary dysfunction can develop as an adverse effect of radiotherapy to the pituitary area. The clinical significance of the pituitary dysfunction observed, and its importance to patients, families and clinicians, is unclear.

[64] Pubertal stage was assessed using the Tanner criteria (https://patient.info/doctor/normal-and-abnormal-puberty)

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. The proportion of patients who had AMORE or EBRT treatment at some stage (as initial treatment or after recurrence) was not reported in this paper, but other papers about the same patient cohort reported that 73% of the Amsterdam cohort had AMORE treatment at some stage and 94% of the London cohort had EBRT treatment at some stage. Other papers also reported significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were assessed for adverse events at multi-disciplinary clinics in London and Amsterdam using the same protocol. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
Hearing threshold	Schoot et al (2015b)	8	Direct	B	Hearing threshold is the sound level below which a person is unable to detect any sound with 0dB as the reference level[65]. Median hearing threshold was assessed at 0.5 to 1-2kHz AC (speech frequency) and 4kHz.AC. Schoot et al (2015b) defined clinically relevant hearing loss as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC. Median follow-up was 11.0 years for survivors at both treatment centres. Median hearing threshold at pure-tone average 0.5 to 1-2kHz AC was significantly better in Amsterdam cohort survivors (where AMORE was available as a treatment option) (5dB, range 0 to 118) compared to London cohort survivors (where AMORE was not available) (10dB, range 0 to 75) (p=0.002). Median hearing threshold at pure-tone average 4kHz AC was significantly better in Amsterdam cohort survivors (5dB, range 0 to 115) compared to London cohort survivors (10dB, range 0 to 85) (p=0.0007). For all survivors, hearing threshold was worse than age-corrected normal hearing levels. In multivariate analysis the difference between treatment centres remained significant after adjustment for tumour localisation (difference in expected hearing threshold.5.4dB, p=0.001). In multivariate analysis, hearing threshold was worse in

[65] http://ec.europa.eu/health/scientific_committees/opinions_layman/en/hearing-loss-personal-music-player-mp3/glossary/ghi/hearing-threshold.htm)

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					patients with parameningeal tumours compared to non-parameningeal tumours after adjustment for treatment centre (difference in expected hearing threshold 6.6dB, p=0.008). Hearing thresholds were worse than normal hearing levels for head and neck RMS patients, with worse outcomes for London cohort survivors (where AMORE was not available). It is not clear how important the hearing threshold observed would be for patients and families. These results should be treated with caution as they are from a small, non-randomised study which included 46 patients who received treatment in Amsterdam and 27 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Baseline audiometry was not available. The authors assumed that children had normal hearing at the start of treatment. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 72% (33/46) of the Amsterdam cohort survivors had AMORE treatment at some stage, either as initial treatment or after recurrence. 96% (26/27) of London cohort survivors had EBRT. There were no significant differences in the reported patient characteristics between the treatment cohorts. Differences in treatment characteristics were not reported, but other papers on the same patient cohort reported significant differences in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
Hearing loss	Schoot et al (2015b)	8	Direct	B	Hearing loss was assessed using the Common Terminology Criteria for Adverse Events[66] (CTCAE) and the Boston criteria[67], both of which have 4 severity grades with higher grades indicating more severe impairment. Schoot et al (2015b) defined clinically relevant hearing loss as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC. There was no significant difference in the proportion of patients with any grade (1 to 4) of hearing loss between Amsterdam cohort survivors (where AMORE was available as a treatment option) and London cohort survivors (where AMORE was not available). For CTCAE this was 41% and 44% respectively (p=0.55) and for the

[66] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
[67] https://www.researchgate.net/figure/SIOP-Boston-Ototoxicity-Scale_tbl2_224871212

Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Boston criteria this was 52% and 59% respectively (p=0.67). There was no significant difference between Amsterdam cohort survivors (15%) and London cohort survivors (26%) in the proportion of patients with clinically significant hearing loss at 0.5 to 1-2kHz AC (p=0.26). There was no significant difference between Amsterdam cohort survivors (20%) and London cohort survivors (33%) in the proportion of patients with clinically significant hearing loss at 4kHz AC (p=0.19). Median follow-up was 11.0 years for survivors at both treatment centres. Clinically significant hearing loss is an important outcome. Whilst up to a third of survivors experienced clinically significant hearing loss, the proportion who did so did not differ significantly between the treatment centres. These results should be treated with caution as they are from a small, non-randomised study which included 46 patients who received treatment in Amsterdam and 27 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Baseline audiometry was not available. The authors assumed that children had normal hearing at the start of treatment. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 72% (33/46) of the Amsterdam cohort survivors had AMORE treatment at some stage, either as initial treatment or after recurrence. 96% (26/27) of London cohort survivors had EBRT. There were no significant differences in reported patient characteristics between the treatment cohorts. Differences in treatment characteristics were not reported, but other papers on the same patient cohort reported significant differences in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.

3D – 3-dimensional; AC – air conduction; AMORE – Ablative surgery, MOuld technique brachytherapy and surgical REconstruction; CI – confidence intervals; dB – decibel; EBRT – external beam radiotherapy; ES – effect size; IQR – Inter-quartile range; kHz –kilohertz; OR – odds ratio; RT – radiotherapy; UCLH – University College London Hospitals

9 Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with primary or relapsed non-metastatic rhabdomyosarcoma of the head and neck (parameningeal, non-parameningeal or orbital) who have been treated with induction chemotherapy
I – Intervention Which intervention, treatment or approach should be used?	AMORE treatment (Ablative surgery, MOulage technique brachytherapy and surgical REconstruction) This treatment has 3 components which are delivered as a single package of care • Ablative surgery • Moulage technique brachytherapy (internal radiotherapy) • Surgical reconstruction
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	External beam radiotherapy (e.g. photons or proton beam) with or without surgery Internal radiotherapy (e.g. brachytherapy) with or without surgery
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Critical to decision making: 1. Failure free survival 2. Overall survival 3. Short term adverse events/ complications of treatment 4. Long term adverse events/ complications of treatment 5. Cost effectiveness of treatment 6. Quality of life
Assumptions / limits applied to search	
Inclusion criteria: • Peer reviewed publications • English language Exclusion criteria: • Abstracts • Letters • Commentaries • Conference papers • Case reports • Papers published before 2003	

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in England from January 1st 2003 to 10th July 2018. We excluded conference abstracts, commentaries and editorials.

Search date: 10th July 2018
Embase search:

#	Searches
1	exp Rhabdomyosarcoma/
2	"head and neck tumor"/ or "head and neck cancer"/
3	(rhabdomyosarcoma? or rhabdo-myosarcoma? or rhabdomyo-sarcoma? or rhabdo-myo-sarcoma?).ti,ab.
4	((head or neck) and (cancer? or neoplas* or sarcoma? or tumour? or tumor? or malignan*)).ti.
5	1 or 2 or 3 or 4
6	amore.ti,ab,kw.
7	ablation therapy/
8	ablat*.ti,ab,kw.
9	7 or 8
10	Brachytherapy/
11	(brachytherap* or moulage).ti,ab,kw.
12	10 or 11
13	reconstructive surgery/
14	(surg* or reconstruct*).ti,ab,kw.
15	13 or 14
16	9 and 12 and 15
17	6 or 16
18	limit 17 to "reviews (maximizes specificity)"
19	5 and 17
20	18 or 19

11 Evidence Selection

- Total number of publications reviewed: 10
- Total number of publications considered potentially relevant: 5
- Total number of publications selected for inclusion in this briefing: 4

12 References

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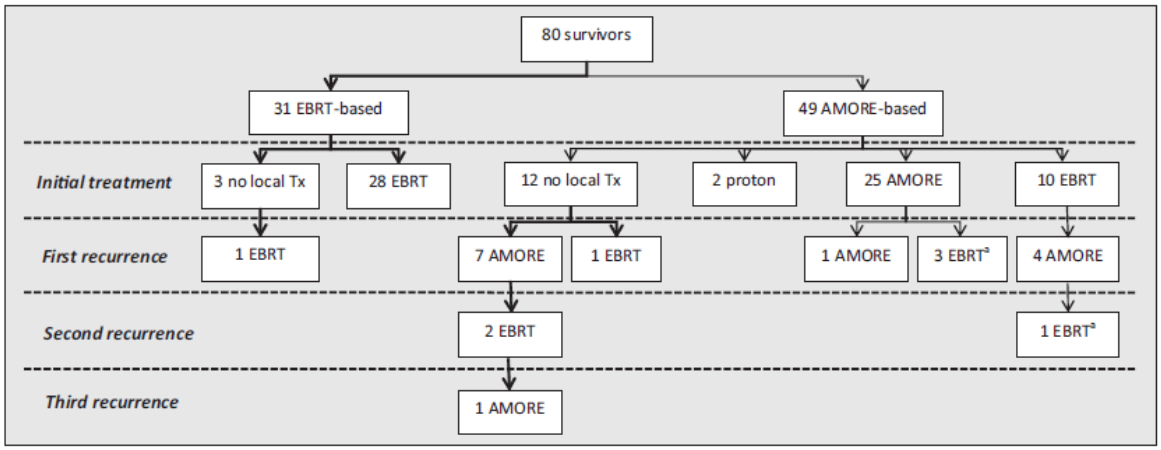
13 Appendix 1

Figure 1: Flow chart showing treatment received by 49 survivors in the Amsterdam cohort ('AMORE-based') and 31 survivors in the London cohort ('EBRT-based') (Schoot et al 2015a)



AMORE - Ablative surgery, MOuld technique brachytherapy and surgical REconstruction; EBRT – external beam radiotherapy; Tx - treatment