Pre-Registration: EARAD: Discovery Phase

Study Information

1. Title: The Effects on Auditory Function of Radiotherapy and Chemotherapy Treatments for Head and Neck Tumours (EARAD)

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3. Description: This study is designed to measure and locate damage caused by radiotherapy only and chemoradiotherapy regimens, specific to the auditory system. This will be tested using a robust battery of hearing threshold tests. The participants will have been diagnosed with oropharyngeal, nasopharyngeal, parotid gland or brain cancers. The test battery will be performed on the participants prior to the start of treatment, and at 3 months post-treatment. Additionally, blood tests will be used to identify and monitor serum levels of the protein 'Prestin', a biomarker for outer hair cells. These will be drawn during regular blood draws throughout treatment.

4. Hypotheses:

   For each *ear-specific* outcome measure:

   H1. The RT group will show a deficit in the treatment ear, post vs. pre treatment
   H2. The effect of treatment for the RT group will be greater in the treatment compared to the control ear
   H3. The CRT group will show a deficit in the treatment ear, post vs. pre treatment
   H4. The CRT group will show a deficit in the control ear, post vs. pre treatment
   H5. The effect of treatment for the CRT group will be greater in the treatment compared to the control ear
   H6. Effects of CRT will be greater than RT in the treatment ear

   For each *non-ear-specific* outcome measure:

   H7. The RT group will show a deficit post vs. pre treatment
   H8. The CRT group will show a deficit post vs. pre treatment
   H9. CRT group will show greater deficits than RT group

   H10. For each basic auditory measure, the effects of RT treatment will vary depending on the dose to each substructure associated with the measure

H11. Effects on DTT will vary depending on the RT dose to different substructures

Design Plan

5. Study type: Observational Study

6. Blinding: No blinding is involved in this study.

7. Study design: We have a two-group, repeated measures study design. Each participant is given the battery of hearing tests twice (before and after treatment), and repeated serum levels of Prestin checked. Each participant is compared to their earlier measurements. There are two groups, one for participants receiving Radiotherapy only treatment, and one for those receiving Chemoradiotherapy treatment. Once each individual is assessed and the group's results amalgamated in accordance with a variety of variables, like variables, for example those of a certain age or gender, will be compared across groups.

Sampling Plan

8. Existing data: Registration prior to creation of data: As of the date of submission of this research plan for preregistration, the data have not yet been collected, created, or realized.

9. Data collection procedures: Participants will be recruited by research nurses at the Christie Hospital, having been recently diagnosed with oropharyngeal, nasopharyngeal, parotid gland or brain cancers. Those who want to take part will be consented by the nurses. Criteria for inclusion include diagnosis with one of these cancers, being over the age of 18, and no significant prior hearing loss. Hearing will be screened at the hearing lab. For those with occluding wax which would contraindicate continuing with testing, procedures are being put into place to allow wax removal on site by a trained professional. High levels of wax will be identified by the research nurses at the time of consenting, and forwarded onto the researchers, so that wax removal can be arranged ahead of time. Participants will be paid at a rate of £10 per hour, with travel via public transport or personal vehicle refunded. Taxis will be provided where necessary. Testing is expected to take 2.5 hrs on each of two testing sessions, 5 hrs total. These sessions will take place prior to the start of treatment, and 3 months post treatment. Blood will be taken at the Christie hospital, stored, frozen and processed at a later date.

10. Sample size: Our target sample size is 50 participants, with 25 undergoing radiotherapy only treatment, and 25 undergoing Chemoradiotherapy treatment.

11. Sample size rationale:

    For the power calculation, we used the effect size from Herrmann et al. (2006), who reported an effect of 0.1-0.2 dB/Gy. We wrote a small simulation programme that draws dose values from the observed distribution with mean and SD of ~16 Gy, draws a random effect size of mean 0.15 dB/Gy with SD of 0.03 dB/Gy. Assuming a measurement uncertainty of 2.5 dB, the expected correlation between dose and hearing loss is 0.628. With 40 patients and assuming a lower actual correlation of 0.37, there is a 99% power to detect true correlation. Because we will use multiple testing, the actual power will be somewhat lower, but it is extremely likely that the most sensitive substructure will be detected.

Variables

12. Measured variables:
    - 12.1. Pure tone audiometry average thresholds measured at 0.5, 1, 2, 4, 8, 10, 12.5, 14 (kHz), L & R ears
      Grouped (averaged) as: 0.5 kHz – 1 kHz (Low)
      2 kHz – 4 kHz (Medium)
      8 kHz – 14 kHz (High)
    - 12.2. DPOAE at 0.5-10kHz, L & R ears
    - 12.3. ABR at 11 clicks/sec at 75 dB peSPL for 6000 repetitions, L& R ears
    - 12.4. Digit Triplet Test threshold, L & R ears
    - 12.5. Coordinate Response Measure
    - 12.6. Tinnitus functional index
    - 12.7. Quality of life form EQ-5D Extended
    - 12.8. Speech, Spatial and Qualities of Hearing
    - 12.9. Prestin levels
    - 12.10. Qualitative interview

Data Mining Procedure

13. The radiotherapy plans (CT scan, structure set and dose distribution) from all participants will be collected from the clinical database at the Christie. The dose distributions from all patients will be spatially normalized using deformable image registration to a common frame of reference (i.e. one “reference patient”).

Analysis Plan

14. For H1, H3, H4, t-test or non-parametric equivalent: pre vs. post

For H2, H5, ANOVA with factors: Ear (treatment, control), Time (pre, post)
For H6. ANOVA with factors: Time (pre, post), Group (RT, CRT)

For H7, H8, t-test or non-parametric equivalent: pre vs. post
For H9. ANOVA with factors: Time (pre, post), Group (RT, CRT)

H10, H11. A Cox regression will be performed on a per-voxel basis in order to identify dose-sensitive substructures associated with the hearing outcome measures. Statistical significance will be investigated using permutation testing.

Pre-Registration EARAD: Validation Phase

Study Information

1. Description: This phase is designed to identify and validate the hearing test most predictive of damage to the auditory substructure most associated with speech in noise deficit, as identified in the discovery phase via data mining. As in the discovery phase, it will involve testing patients undergoing RT only and combined CRT for oropharyngeal, nasopharyngeal parotid gland and brain tumours. This cohort will be independent of those for the discovery phase.

2. Hypotheses:

    H1: RT dosage to the substructure identified in the Discovery phase as being most associated with speech in noise deficit will be associated with speech in noise deficits in the validation phase

    H2: The test identified in the Discovery phase as most predictive of damage to that substructure will be associated with damage to that substructure

    H3. The test identified in the Discovery phase as most predictive of damage to that substructure will be associated with speech-in-noise deficits

Sampling Plan

3. Data collection procedures: Participants will be recruited by research nurses at the Christie Hospital, having been recently diagnosed with oropharyngeal, nasopharyngeal or parotid

gland cancers. Those who want to take part will be consented by the nurses. Criteria for inclusion include diagnosis with one of these cancers, being over the age of 18, and no significant prior hearing loss. Hearing will be screened at the hearing lab. For those with occluding wax which would contraindicate continuing with testing, procedures are being put into place to allow wax removal on site by a trained professional. High levels of wax will be identified by the research nurses at the time of consenting, and forwarded onto the researchers, so that wax removal can be arranged ahead of time. Participants will be paid at a rate of £10 per hour, with travel via public transport or personal vehicle refunded. Testing is expected to take 2 hrs on each of two testing sessions,4 hrs total. These sessions will take place prior to the start of treatment, and 3 months post treatment. Blood will be taken at the Christie hospital, stored, frozen and processed at a later date.

4. Sample size: Our target sample size is 50 participants, with 25 undergoing radiotherapy only treatment, and 25 undergoing Chemoradiotherapy treatment.

5. Sample size rationale:

   The Validation phase will again use a cohort of 40 patients in the same two groups (50 to be recruited to allow for 80% compliance) as for the Discovery phase. Since multiple testing is avoided, the statistical power of the Validation phase (around 99%) will be much greater than in the Discovery phase.

Variables

6. Measured variables

   6.1. Test most sensitive to dose to identified substructure in Discovery phase
   6.2. Audiometry
   6.3. DTT
   6.4. Prestin levels
   6.5. Qualitative interview

Analysis Plan

Pearson's correlations or non-parametric equivalents to test for associations between variables.

Pre-Registration: EARAD: Retrospective Study

Study Information

1. Description: This study is designed to measure and locate damage caused by RT regimens, specific to the auditory system. This will be tested using a robust battery of hearing threshold tests. The participants will have previously been diagnosed and treated with RT for unilateral oropharyngeal, nasopharyngeal or parotid gland cancers. The test battery will be performed on the participants post-treatment, up to a limit of 5 years post-treatment. There will be two age-matched control groups, those with hearing impairment and those without. Additionally, blood tests will be used to identify serum levels of the protein 'Prestin', a biomarker for outer hair cells. These will be drawn during the testing session.

2. Hypotheses:

   For each *ear-specific* outcome measure:

   H1. The RT group will show a deficit in the treatment ear compared to the control ear

   For all outcome measures:

   H2. The RT group will show a deficit as compared to the normal hearing controls

   For the Prestin measure:

   H3. The RT group will show lower levels of serum Prestin compared to normal hearing controls
   H4. The age matched normal hearing control group will have higher serum Prestin levels compared to hearing impaired control group
   H5. The age matched hearing impaired control group will have higher serum Prestin levels compared to the RT group

   Relation to substructures:

   H6. For each basic auditory measure, the effects of RT treatment will vary depending on the dose to each substructure associated with the measure
   H7. Effects on DTT will vary depending on the RT dose to different substructures

Design Plan

3. Study type: Observational Study

4. Blinding: No blinding is involved in this study.

5. Study design: We have a three-group, single measures study design. Each participant is given the battery of hearing tests once, and serum levels of Prestin checked during this session. There are three groups, one for participants receiving unilateral RT treatment, and two age-matched control groups, those with hearing impairment and those without. If the RT group have a significant hearing loss overall, the hearing-impaired control group will be group matched in terms of average audiogram from 1-8 kHz with the RT group. Once each individual is assessed and the group's results amalgamated in accordance with a variety of variables, they will be compared across groups.

Sampling Plan

6. Existing data: Registration prior to creation of data: As of the date of submission of this research plan for preregistration, the data have not yet been collected, created, or realized.

7. Data collection procedures: Participants will be identified by research nurses at the Christie Hospital, having previously received treatment for oropharyngeal, nasopharyngeal or parotid gland cancers, up to a period of five years post treatment. Those who want to take part will be by the PhD student. Criteria for inclusion include diagnosis with one of these cancers, being over the age of 18, and no significant prior hearing loss. Hearing will be screened at the hearing lab. For those with occluding wax which would contraindicate continuing with testing, procedures are being put into place to allow wax removal on site by a trained professional. Participants will be paid at a rate of £10 per hour, with travel via public transport or personal vehicle refunded. Testing is expected to take 2.5 hrs. Blood will be taken at a site to be determined, stored, frozen and processed at a later date.

8. Sample size: Our target sample size is 50 for each group.

9. Sample size rationale:

   For the power calculation, we used the effect size from Herrmann et al. (2006), who reported an effect of 0.1-0.2 dB/Gy. We wrote a small simulation programme that draws dose values from the observed distribution with mean and SD of ~16 Gy, draws a

random effect size of mean 0.15 dB/Gy with SD of 0.03 dB/Gy. Assuming a measurement uncertainty of 2.5 dB, the expected correlation between dose and hearing loss is 0.628. With 40 patients and assuming a lower actual correlation of 0.37, there is a 99% power to detect true correlation. Because we will use multiple testing, the actual power will be somewhat lower, but it is extremely likely that the most sensitive substructure will be detected.

Variables

10. Measured variables:
    - 12.1. Pure tone audiometry average thresholds measured at 0.5, 1, 2, 4, 8, 10, 12.5, 14 (kHz), L & R ears
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    - 12.3. ABR at 11 clicks/sec at 75 dB peSPL for 6000 repetitions, L& R ears
    - 12.4. Digit Triplet Test threshold, L & R ears
    - 12.5. Coordinate Response Measure
    - 12.6. Tinnitus functional index
    - 12.7. Quality of life form EQ-5D Extended
    - 12.8. Speech, Spatial and Qualities of Hearing
    - 12.9. Prestin levels
    - 12.10. Qualitative interview

Data Mining Procedure

11. The radiotherapy plans (CT scan, structure set and dose distribution) from all participants will be collected from the clinical database at the Christie. The dose distributions from all patients will be spatially normalized using deformable image registration to a common frame of reference (i.e. one “reference patient”).

Analysis Plan

14. For H1, t-test or non-parametric equivalent: Treatment ear vs control ear

    For H2, t-test or non-parametric equivalent: Group (RT, Normal Hearing Controls)

    For H3, H4, H5. t-test or non-parametric equivalent: Group (RT, Hearing Impaired Controls, Normal Hearing Controls)

    H6, H7. A Cox regression will be performed on a per-voxel basis in order to identify dose-sensitive substructures associated with the hearing outcome measures. Statistical

significance will be investigated using permutation testing.