Version date: October 19, 2019

PAEDIATRIC AND ADOLESCENT RADIOTHERAPY WITHOUT ANAESTHESIA USING AUDIO-VISUAL DISTRACTION – ARE THE PATIENTS MOVING?

Short title: Motion of Kids on RT

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Background
Although generally safe [1], use of anaesthesia in paediatric radiation oncology can be costly [2] and cumbersome, and adds to the burden of cancer treatment in children and adolescents.[3, 4] In many institutions, a majority of young children and some adolescents undergo general anaesthesia for radiation treatments.[2, 5] At our institution, a multi-faceted approach has been used to reduce anaesthesia utilization as a standard-of-care treatment: presence of a dedicated paediatric nurse for procedural preparation, comfort objects (stuffed animal), and most importantly, audio-visual distraction (television). However, this approach has not been systematically evaluated to determine its effectiveness at immobilizing children receiving RT.

Cone beam CT (CBCT) is a technology available at Princess Margaret Cancer Centre that is used routinely to deliver image-guided radiotherapy (IGRT).[6] Patients routinely receive at least one CBCT scan before each daily radiation treatment to ensure correct and accurate treatment positioning. CBCT has allowed our institution to reduce the irradiated treatment volume; for example, in brain tumours, the RT planning target volume (PTV) margin has decreased from 5 mm to 3 mm due to more accurate positioning before treatment. In this study, we propose to use a post-radiation CBCT acquisition to assess patient motion. Cone beam CT (CBCT) has been successfully used by other investigators in the past to evaluate intra-fraction motion in a small number of patients with Wilms' tumour (n = 15), but their results are not generalizable to paediatric tumours located in other body sites.[7] Pre- and post-irradiation CBCT has also been used in adult patients with lung cancer to evaluate patient motion.[8, 9] CBCT is a standard investigation to assess patient position for radiation therapy.

Goal of study
To evaluate the intra-fraction motion of paediatric patients receiving an existing multi-faceted approach to reduce anaesthesia use in paediatric and adolescent radiotherapy (RT), including audio-visual distraction.

Rationale
If deemed effective, this study will validate our method of reducing anaesthesia use, thus continuing to reduce the burden of therapy and cost of care for this population. It will also allow other institutions to learn from these techniques.

The method of non-invasive immobilization will be deemed effective if 90% of CBCT acquisitions report movement <3 mm (head-and-neck targets) and <5 mm (non-head-and-neck targets).

Primary objective
To determine the proportion of patients with adequate immobilization by measuring motion between pre- and post-RT CBCT acquisitions for patients treated without anaesthesia

Secondary objectives
1. To quantitatively determine intra-fraction motion of patients treated with RT without anaesthesia
2. To evaluate factors associated with intra-fraction patient motion, thus facilitating creation of individualized, patient-specific planning target volumes (PTV)

3. To calculate perturbations in delivered treatment dose using dose-accumulation upon on-treatment CBCT images

Primary endpoint
1. The portion of patients achieving adequate immobilization before and after RT (<3 mm for head-and-neck targets, <5 mm for non-head-and-neck targets)

Secondary endpoints
1. The magnitude of vector change in patient position between pre-RT CBCT and post-RT CBCT
2. Factors associated with intra-fraction motion, as a continuous variable, that will be evaluated include: fraction number, age, site of treatment, use of immobilization, and treatment/fraction length
3. Dose-volume distributions to the PTV and organs-at-risk will be compared using descriptive statistics and coverage parameters (V95, V100, Dmax, D100, D95)

Patient population
Inclusion criteria
Patient (paediatric or adolescent) age 18 or under receiving RT without anaesthetic or procedural sedation (anaesthetic gas or intravenous sedative medication).

Exclusion criteria
Patients receiving oral midazolam or ketamine are ineligible.
Patient is receiving total body irradiation without CBCT.

Methods and analysis
Patients will be approached for informed consent at Princess Margaret Cancer Centre either at the time of radiation consultation, radiation planning, or during the first two weeks of radiation therapy.

Standard of Care: Paediatric patients treated with RT routinely receive one or two pre-irradiation daily CBCT acquisitions as part of image-guided RT (IGRT). Patients who receive audio-visual distraction will undergo their routine RT procedures, including clinical setup to body anatomy, pre-RT CBCT, and treatment.

Study Procedures: After the patients are done with their standard of care RT/routine RT, a post-treatment, low-dose CBCT, will be followed at the end of each treatment session. The additional study procedure of post-treatment CBCT will be applied at the first RT session after study enrollment, and then applied again on a weekly basis at each RT session, and at the last RT session, per isocenter treated. This will allow for intra-fraction motion to be calculated.

By comparing the pre-RT CBCT and post-RT CBCT, an estimate of the intrafraction motion of the patient can be obtained. The primary endpoint is the magnitude of vector change between the two scans, which is calculated using shifts in craniocaudal (CC), mediolateral (ML) and anteroposterior (AP) directions.

Descriptive statistics (mean, median, 95% confidence intervals) will be used to describe the proportion of patients with adequate immobilization (<3 mm for head-and-neck targets, <5 mm for non-head-and-neck targets), as well as the magnitudes of vector change at the patient level. Vector change over time will be plotted for each patient, and analyzed using a linear mixed effects model to determine if movement changes over fraction number, age, site of treatment, use of immobilization, and treatment/fraction length.

Using the dose-accumulation application in the radiation treatment planning system (TPS), the post-treatment CBCT will be used to calculate and summate delivered dose in the patient over each fraction. Planned and accumulated doses will be compared. Intracranial tumours will be analyzed using rigid registration, while torso/body tumours will be analyzed using deformable registration. Dose-volume distributions to the PTV and organs-at-risk will be compared using descriptive statistics and coverage parameters (V95, V100, Dmax, D100, D95).

Sample size

The primary endpoint is determined using the patient's motion between pre-RT and post-RT CBCT, which is expressed as two mean values. Assuming that true motion is 1 mm for head-and-neck (HN) treatments and 3 mm for non-head-and-neck treatments, the study will deem it acceptable to have motion of <3 mm for HN and <5 mm for non-HN treatments.

Thus, we will compare the average movement of the HN group with 1 mm; therefore, a difference of 2 mm or less (3 mm – 1 mm = 2 mm) is considered acceptable. In the similar way, we will compare the average movement of the non-HN group to 3 mm, for a difference of 2 mm or less (5 mm – 3 mm = 2 mm).

In an equivalence test of means using two one-sided tests on data from a paired design, a sample size of 58 achieves 80% power at a 0.05 significance level when the true difference between the means is 2 mm (for both head-and-neck target / non-head-and-neck targets). This assumes that the standard deviation of the paired differences is 3 mm, and the equivalence limits are 0 mm and 3 mm. In this design, if the average difference between pre-RT CBCT and post-RT CBCT is between these two equivalence limits (i.e. <3 mm), the two means are said to be equivalent (which means no motion was observed).

We will plan to enroll and consent a total of 65 patients to account for study attrition, over a 12 month period.

Informed consent

Written, informed consent will be obtained from the child or patient's substitute decision maker (usually a parent) prior to enrollment. If the child does not wish to provide consent, but is willing to provide written assent, then this will be documented as part of the consent form. The consent will be obtained and documented by a specialized clinical research coordinator with experience in research consent for paediatric research subjects.

Ethical considerations

This is a study to determine the effectiveness of an existing approach to reduce anaesthesia use in children receiving RT. This approach has been in use for years at University Health Network as standard-of-care. The study procedures of:

a) presence of a dedicated paediatric nurse for procedural preparation
b) comfort objects (stuffed animal)
c) audio-visual distraction (television)

involve minimal risk to patients. In addition, as part of this study, the following additional procedures will be applied to patients:

d) post-treatment, low-dose CBCT (60 seconds or less)

Radiation dose

The low-dose CBCT applies a dose of 2 mGy to the patient (XVI Memo, XVI Presets, Radiation Medicine Program, version 12/2016). This is in addition to the following radiation applied to the patient as part of standard of care:

Source of radiation dose	**Dose**	**Daily dose (mGy)**
Pre-RT CBCT (average of 1.1 scans per day)	2.2 mGy	2.2
Daily radiation treatment (with ±1% annual QA tolerance)	180 ± 3.6 cGy	1 800 ± 18
TOTAL (standard of care)		1 802.2

To further reduce the dose to the patient according to the principles of ALARA (as low as reasonably achievable):
a) a special CBCT setting to visualize bony structures will be used for the post-RT CBCT, which will halve the CBCT dose to 1 mGy (from 2 mGy)
b) post-RT CBCT will be applied weekly and with first/last treatments, rather than daily.

The daily incremental isocentre radiation dose from a post-RT, low-dose CBCT is 0.06% (1 mGy / 1 802 mGy = 0.0006). The annual QA tolerance of a commissioned linear accelerator is 1%. Thus, the incremental dose from a low-dose CBCT is 18-fold smaller than the QA tolerance margin of RT dose variation delivered to the patient (18 mGy vs 1 mGy).

Therefore, over a 30-fraction treatment course:

Source of radiation dose	**Average daily dose**	**Total dose over 30 fractions (mGy)**	**Proportion of total dose (%)**
Pre-RT CBCT (average of 1.1 scans per day)	2.2 mGy	72.6	0.13%
Radiation treatment	180 ± 3.6 cGy	54 000	99.85%
Post-RT CBCT (7 scans over 6 weeks)	0.23 mGy	7	0.013%
TOTAL		54 079.6	100%

By way of comparison, the following are estimated exposures for other sources of ionizing radiation [10, 11]:

Source	**Exposure (1 mSv = 1 mGy)**[10]
Background radiation in Winnipeg, Canada	4.1 mSv/year
Background radiation in Yangjiang, China	6.3 mSv/year
Total proposed CBCT exposure related to study	**7 mGy**
Background radiation in Guarapari, Brazil	35 mSv/year
Dose limit for radiation workers	100 mSv/5 years
Abdominal CT	22-60 mGy/scan
Background radiation in Ramsar, Iran	200 mSv/year
Palliative course of radiation	8,000 mGy (8 Gy)
Curative course of radiation for a brain tumour	54,000 mGy (54 Gy)

Time commitment

The total scheduled treatment time for a routine paediatric treatment is 20-30 minutes. The additional study procedure of having a post-RT CBCT requires 60 seconds or less to perform; Thus, the incremental relative increase in time commitment for study procedures is up to 5% on days with a post-RT CBCT and 0% on days without a post-RT CBCT.

Justification

A post-RT CBCT is essential to compare the motion of a patient between the beginning and end of a radiation fraction. Benefits of this approach include the use of existing infrastructure and minimal additional time commitment to the patient. Disadvantages of this approach include the use of a modality that provides a very, very small increase in imaging dose to the patient, and the inability to measure motion in between CBCT acquisitions.

We considered use of a real-time, non-RT tracking modality using optical reflectors and a camera system, but prior use of this system in the Radiation Medicine Program has shown low reliability. Furthermore, use of an optical tracking system requires line of sight visibility to the patient, which is not possible with concomitant audio-visual distraction (television) and warming blanket for paediatric patients. Finally, we considered applying post-RT CBCT to a group of children treated with general anaesthetic; however, this would apply unnecessary radiation to patients who would not benefit and was felt to not be ethical.

Potential benefits to the patient

Radiation therapists on the treatment unit will rapidly evaluate post-RT CBCT to determine if a patient has moved between the pre-RT and post-RT CBCT. We expect that most patients will have minimal or no motion. However, selected patients may have motion detected on the post-RT CBCT. Patients with detected motion beyond planning target volume margins (>3 mm) will be informed and counselled to avoid moving during RT. If motion persists, then the following modifications to their daily RT may be considered, as part of standard-of-care, to improve the quality of RT treatment:

a) re-plan RT with increased PTV margins (e.g. from 3 mm to 5 mm)
b) initiate daily anaesthesia for definite patient immobilization

The benefit to the patient is that intra-fraction motion is assessed on a regular basis. This will reduce the chance of a geographical miss by the RT, and increase the quality of RT delivery.

Privacy considerations

Personal health information (PHI) will be collected for study purposes in a de-identified manner without identifying details, minimizing the chance of disclosure of PHI that could identify a patient. Extracted PHI will be stored in password-protected files located on encrypted hospital network drives and encrypted USB drives. PHI will also be de-identified and coded with a study-specific numerical patient identifier. The key that links the study-specific numerical patient identifier to patient-specific information (such as a hospital record number) will be stored separately from the remainder of study information and not be transported or transmitted outside the institution. Finally, access to study data will be limited to the investigators or delegates (summer students and/or research assistants) involved in this study, all of whom will have completed UHN privacy training.

Data will be reported in presentations and/or publications in aggregate format without identifying details. In the event of inappropriate release of personal health information, the following will be done: further release of information must be stopped, any information that could be retrieved should be retrieved, the UHN Privacy Office must be notified, and then further actions might be taken according to recommendations from the UHN Privacy Office.

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