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Pencil beam scanning proton therapy for pregnant patients with brain and head and neck cancers

PRT for pregnant patients

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Purpose:

When radiotherapy is medically necessary for pregnant patients, photon-based treatments (XRT) have traditionally been used, while proton radiotherapy (PRT) is avoided due to concerns about neutron dose. This retrospective study analyzes pregnant patients treated with XRT and models the equivalent dose that would have been delivered to the fetus with proton radiation compared to XRT. The purpose of this work is to provide a comprehensive analysis of pencil beam scanning proton therapy (PBS-PRT) for pregnant patients and to evaluate whether PBS-PRT should be the new standard of practice for treating pregnant patients with brain and head and neck cancers.

Materials and Methods:

PBS-PRT plans were made for seven pregnant patients who received XRT: four treated for brain tumors and three for head and neck tumors. Measurements were performed with the patient plans using an anthropomorphic phantom and Wendi-2 meter placed at the phantom's abdomen. Patient specific measurements were used to determine the total fetal equivalent dose from PBS-PRT compared to XRT. Imaging dose was also evaluated with a Fluke 451 dose meter.

Results:

The average measured fetal equivalent dose, accounting for photons and neutrons, for the brain plans was 0.4 mSv for PBS-PRT and 7 mSv for XRT. For the head and neck plans, it was 6 mSv and 90 mSv for PBS-PRT and XRT respectively. The PBS-PRT plans were preferred by the physicians for both tumor coverage and normal tissue sparing. Daily imaging added between 0.05 and 1.5 mSv to the total dose.

Conclusions:

This retrospective study showed that when treating brain or head and neck cancers in pregnant patients, fetal equivalent dose is reduced by approximately a factor of 10 with PBS-PRT than with XRT

without making any compromises in treatment planning objectives. These results support a change of practice to utilize PBS-PRT as the new standard for treating pregnant patients with brain or head and neck tumors compared to XRT.

Keywords: Pencil beam scanning proton therapy; brain cancer; head and neck cancer; fetal dose; neutron dose

Introduction

Approximately 4,000 pregnant women per year in the United States require radiation therapy.[1] Delaying treatment may not be safe for the mother in the case of aggressive malignancies or when chemotherapy or surgical resection alone would be insufficient to ensure survival. Radiation therapy during pregnancy is commonly used for anatomic sites far from the fetus such as brain or head and neck cancers. Even with the fetus far outside the primary radiation field, scattered or secondary radiation will contribute dose to the fetus. The potential effect of radiation to the fetus includes lethality, organ malformations, growth retardation, intellectual disability, sterility, cataracts, other neuropathology, and carcinogenesis though these risks are dose and time of gestation dependent.[2] TG-36 suggests there is little risk of damage to the fetus for doses below 5 cGy and a significant risk in the first trimester for doses above 10 cGy.[3]

The current standard of practice is to treat pregnant patients with x-ray therapy (XRT). A lead fetal shield, as recommended by TG-36, is effective for shielding the collimator scatter and leakage from the treatment head and can often reduce the fetal dose by about 50%.[3] However, the shield can also limit the gantry rotation to partial anterior arcs when Volumetric Modulated Arc Therapy (VMAT) is utilized, and limits beam directions for static Intensity Modulated Radiation Therapy (IMRT) or 3D conformal treatment. Additionally, the isocenter is commonly shifted to the superior edge of the field and anteriorly to achieve clearance between the gantry and shield. The resulting modified planning techniques to accommodate the shield may compromise plan quality for pregnant patients.

While proton radiation typically provides less integrated dose to surrounding tissue, it has historically been avoided in pregnant patients due to uncertainty in the dose from internal neutron scatter.[4,5] Neutrons tend to transfer energy to protons and heavier ions leading to high LET deposition of dose.[6] As a result, the biological effectiveness of neutrons can vary from as low as 2 to as high as 20 depending on the energy of the neutrons, the dose fractionation, and the particular type of cells involved.[7,8] Estimating this particular uncertainty is challenging. Literature suggests a broad range in the relative biological equivalent (RBE) dose for fetal dosimetry of between 2 and 10.[9,10]

A Wendi-2 meter is a neutron rem meter with a response function specifically designed to match a fluence-to-ambient dose conversion function, providing accurate measurements of ambient dose equivalent.[11-13] It also has a higher sensitivity and a wider energy response range compared to other neutron detectors.[14]

Previous studies have indicated lower equivalent doses for PBS-PRT compared to XRT. Heimovaara et al treated a nasopharyngeal carcinoma in a pregnant patient using PBS-PRT to 70 Gy in 35 fractions.[15] A total fetal dose of 5.5 mSv was measured with a Wendi-2 meter compared to 185 mSv from XRT using lead shielding. Wang et al reported a pregnant patient with a chordoma of the base of skull treated with PBS-PRT to 70 Gy in 35 fractions.[16] A total neutron dose equivalent of 0.35 mSv was measured with a REM500 meter compared to 70 mSv for the x-ray plan. In addition, Kalbasi et al treated a pregnant patient with craniospinal irradiation (CSI). The total dose to the fetus was 65 mGy from imaging and 72 mSv from neutrons.[17] Monte Carlo calculations have also been performed to measure neutron dose equivalent to the fetus. Geng et al calculated 0.13 mSv from PBS-PRT compared to 1.57 mSv from XRT to the fetus when treating a brain tumor to 52.2 Gy.[18]

An analytical model was used to estimate dose equivalent from internal neutrons in PRT of children with brain tumors and calculated a dose equivalent of 0.13-1.28 mSv/Gy for 3-10 cm from the field edge and <0.03 mSv/Gy at >20 cm.[19] Another study created personalized 3D-printed anthropomorphic whole-

body phantoms compatible with dosimeters and measured the out-of-field dose from PBS-PRT intracranial treatment beams from the cranium to the pelvis.[20] For locations beyond the thyroid, out-of-field measurements were not reported because they could not be distinguished from background and noise. Neutron dose was found to be insignificant beyond 20 cm from the field edge.

Previous studies suggest PBS-PRT for brain or head and neck cancers would reduce the fetal dose by at least a factor of 10 compared to XRT. However, each report presents data from only a single case study – and in at least some of the cases, using simplified beam arrangements not representative of true treatment plans. This work aims to provide a more comprehensive analysis of fetal equivalent dose from PBS-PRT compared to standard of practice XRT by performing a retrospective study on several pregnant patients previously treated at our institution with XRT. The equivalent dose that would be delivered to the fetus with PBS-PRT was measured with plans that were reviewed by radiation oncologists and deemed to be acceptable for treatment.

Methods

Treatment Planning

This retrospective analysis included seven pregnant patients who were treated at our institution with XRT. Four of the patients were treated for brain tumors and three for head and neck tumors. During simulation, measurements were acquired of the anterior to posterior patient thickness at the fundus and distance from the patient's bottom of chin to fundus, umbilicus, and pubis. In order to ensure enough clearance to position the fetal shielding between the fetus and linear accelerator's gantry for XRT, it was sometimes necessary to offset the treatment isocenter a large distance anterior and superior to the center of the target. This offset reduces dose conformality for the inferior portion of the target. All patients received VMAT treatment, restricted to anterior half-arcs to accommodate the

fetal shield, using either 6 MV or 6 MV FFF, with small planning margins added to the standard clinical target volume (CTV). Most of the patients were treated to 60 Gy in 30 fractions except for Patient 3, 54 Gy in 30 fractions, and Patient 5, 70 Gy in 35 fractions. The plans were calculated in Eclipse (Varian) using the AAA dose calculation algorithm.

The position of the fundus was marked each week of the patient's treatment using ultrasound. The distance was measured from this mark to the isocenter to accurately provide dose estimates accounting for varying fetal positions. Due to the growth of the fetus during the course of treatment, it was often necessary to adapt the treatment plan for head and neck patients to shift the isocenter further superiorly to ensure clearance of the treatment beams with the fetal shield in place. These additional shifts had potential to compromise plan quality.

A proton plan was retrospectively generated for each patient using their simulation CT, contours, and prescription from the x-ray plan using standard beam arrangements and treatment planning approaches; the plans were equivalent to what would have been created for a patient who was not pregnant. An extended range shifter was used as indicated to treat more superficial tumors. The treatment plan dose calculations were performed with both Eclipse Proton Convolution Superposition (Varian) and an in-house Monte Carlo system, as is standard practice for all PBS-PRT patients at our institution.[21] The proton plans were evaluated by a dosimetrist and a radiation oncologist with both clinical PBS-PRT and XRT experience and deemed clinically acceptable. The radiation oncologist was also asked to specify their preference between the retrospective PBS-PRT treatment plan and the clinically delivered XRT plan.

Measurements

An anthropomorphic Alderson Rando phantom (Radiology Support Devices, Long Beach, CA) was treated with the x-ray plans using a Varian TrueBeam with a solid water block at a height of 30 cm placed at the phantom's abdomen, Figure A1 Supplemental. A Farmer chamber was placed at a 5 cm

depth from the surface of the block, oriented crossline, to measure the fetal dose from XRT. The phantom was aligned to isocenter using the same anterior posterior distance from the couch to isocenter as the patient plan to accurately set the height of the shield. The fetal shield was positioned between the detector and gantry and at a height of about 1 cm above the solid water block simulating a patient setup that allows for breathing room. The shield was positioned in close proximity to the gantry to maximize its efficacy while adhering to the gantry's clearance limits, as is done for the clinical setup. Slices of the anthropomorphic phantom were added to measure at several distances from isocenter to detector to account for the varying position of the apex of the fetal fundus. The imaging dose was measured with this setup using a Fluke 451 dose meter to determine the dose from the setup kV x-rays. A cone-beam CT cannot be acquired for pregnant patients using the linear accelerator's on-board imaging due to the limited gantry rotation with the shield in place. Changes in imaging dose due to the shield placement for XRT were considered as well.

The proton plans were delivered using a Hitachi Probeat V Pencil-Beam-Scanning system. The Probeat V nozzle has a vacuum beam line all the way through the steering magnets, minimizing material in the beam. By reducing the total amount of material the beam interacts with on the way to the patient, this design reduces spot size and, by extension, neutron production. The plans were delivered to an anthropomorphic phantom with a Wendi-2 meter placed at the phantom's abdomen, Figure A2 Supplemental. The dose was measured at varying distances from isocenter to the center of the detector by altering the amount of acrylic between the phantom and detector. The neutron dose equivalent and the total dose equivalent from all particles were both recorded for each field.

Imaging for PBS-PRT patients is typically performed using an orthogonal pair of oblique planar kV x-rays. The standard 2D imaging protocols for brain and head-and-neck patients use the same settings of 85 kV, 800 mA, and 63 ms. Because of the potential for dose variation in proton treatments with anatomical changes in the patients, verification CT scans are a standard part of many treatments.

For head and neck patients, weekly verification CTs are typically performed using the in-room CT-on-rails (CToR, Siemens). For brain patients, CToR verifications may be used as requested by the physician. The $CTDI_{vol}$ averages 48 mGy for the head and neck scans and 22 mGy for the brain scans. The imaging dose was measured both for the 2D oblique x-ray pair and for a CToR scan system using the same setup described above but with a Fluke 451 meter centered at 25 cm above the tabletop. A head and neck protocol was used for CToR with 120 kV, 180 mAs, 2 mm slice thickness, and 35 cm scan range from the top of head. The 2D imaging dose was evaluated at the cardinal couch angles, and the sensitivity of positional changes to the detector was also investigated by placing the detector at different heights and orientations.

Neutron shielding was also evaluated with a generic plan using slabs of 1-inch borated polyethylene and the results are presented in Table A Supplemental. A Wendi-2 meter was placed at the abdomen of an anthropomorphic phantom at 40-50 cm from the isocenter. Measurements were recorded with shielding externally surrounding the Wendi-2 meter. Additional measurements were acquired with the Wendi-2 meter at 45 cm from isocenter with 0-4 axial slices of the phantom replaced with borated polyethylene.

Analysis

Data is reported based on the distance from the inferior edge of CTV to fundus. The measured dose equivalent was plotted for each plan in mSv, normalized to the prescription dose, as a function of distance from inferior CTV edge to fundus. To estimate the total delivered fetal dose from each plan using the weekly CTV-to-fundus distance measurements, the measured dose data for each treatment plan was fit using a third order polynomial function.

Results

The simulation CT scans of seven pregnant patients were used to create proton plans as seen in Figure B Supplemental using the dose prescriptions and beam configurations listed in Table 1. The measured dose equivalent at various CTV-to-fundus distances for the XRT and PBS-PRT plans is presented in Figure 1. The total dose equivalent, accounting for photons and neutrons, was measured for each patient using their specific measurements. For the brain plans, the average was 0.007 mSv/Gy (0.4 mSv) for PBS-PRT and 0.23 mSv/Gy (7 mSv) for XRT. For the head and neck plans, it was 0.19 mSv/Gy (6 mSv) for PBS-PRT and 2.84 mSv/Gy (90 mSv) for XRT. The PBS-PRT dose reductions compared to XRT were 81-98% across all plans, averaging 91%.

2D imaging doses at all treatment angles for PBS-PRT were measured to fall within the range of 0.0005-0.005 mSv per image (from out of field to isocenter). The dose from CToR is highly dependent on the imaging parameters used such as scan range, beam current, and voltage. Based on patient specific measurements, the dose from weekly CToR verification scans for a course of treatment would be about 1.4 mSv. Thus 2 mSv is a good upper-limit approximation for imaging dose for the entire treatment course of a head and neck plan.

The uncertainties in the XRT dose estimates due to variations in the shield positioning are generally 15% but changes of up to 30% can be seen in Figure 1. The dosimetry of the x-ray plans was poorer due to the limited arc rotation to accommodate the fetal shield whereas no compromises to the proton plan quality were made. Physicians reported a preference for the proton plans in every case when considering tumor coverage and other normal tissue sparing.

Proton posterior and vertex fields contributed up to twice as much neutron dose per monitor unit compared to lateral or anterior beams. In addition, plans with the range shifter averaged about 30% more neutron dose compared to proton plans without the range shifter. Therefore, further dose reductions could be achieved with the proton plans by considering these factors. In all cases, the dose equivalent was significantly less in PBS-PRT plans than in XRT plans.

The borated-polyethylene neutron shielding resulted in minimal dose reductions when used as an external and internal shield.

Discussion

The analysis of seven patients treated with radiotherapy demonstrated significant reduced dose equivalent to the fetus with PBS-PRT compared to XRT. A factor of 10 difference was observed for every case. These results are consistent with previous case studies. The average fetal dose equivalent from the PBS-PRT brain plans in this work was 0.4 mSv compared to 0.35 mSv by Weng et al and 0.13 mSv by Geng et al. For head and neck, 6 mSv was measured in this work for PBS-PRT and 5.5 mSv was measured by Heimovaara et al.

The dose from XRT was much more sensitive to changes in setup related to the shield positioning as the fetus grows and moves closer to the shield. Therefore, variations in setup seem to be more of a concern for XRT treatments.

Not all practices use shielding for pregnant patients receiving XRT. Techniques without a fetal shield would allow for full treatment arcs, resulting in better dosimetry; however, the fetal dose could increase by approximately two-fold. Imaging dose for XRT was not reported because the fetal shield effectively attenuates the 2D x-ray imaging dose below detectable levels for the Fluke 451 dose meter.

Unlike the XRT measurements, fetal dose measurements with PBS-PRT were not sensitive to setup variations. The main source of uncertainty is systematic uncertainty related to the calibration of the measurement device and the global uncertainty in the applicable RBE of neutrons for fetal toxicities. The tolerances on neutron detector calibrations are much wider than for ion chamber calibrations used to measure x-rays. Thus, the meter reading should only be considered accurate to within approximately a factor of 2 in either direction. Secondly, the biological effectiveness of the neutron dose to the fetus is subject to greater uncertainty than with x-rays. Reasonably conservative estimate suggests the RBE,

including neutrons, for fetal dose effects could be as high as 10.[9,22] The quality factor implicitly applied by the Wendi-2 meter is about 4-5.[11] Therefore, the uncertainty associated with the estimate of the equivalent dose might be as high as 2.5. Taken along with the additional factor of 2 for the uncertainty of the detector calibration, this suggests that the true equivalent dose should not be more than a factor of 5 different from the measurement.

Even taking the maximally conservative assumption (that is, our estimates are a factor of 5 lower than the true equivalent dose), the fetal dose would be substantially lower with PBS-PRT (by 70% on average for brain and head and neck). In addition, the treatment plan dose distributions for PBS-PRT were clinically preferred over XRT for all cases studied. Given their age and the reduced dose to normal tissues from proton plans, pregnant patients with CNS or head and neck cancers can benefit significantly from proton therapy.[23,24] For head and neck patients in particular, proton plans may result in reduced hospitalizations and other complications from RT.[25] Thus, proton therapy appears to be the preferred treatment both for the benefit of the mother and for the fetus.

The XRT treatment process for pregnant patients at our institution involves weekly ultrasounds to mark the position of the fundus to accurately position the shield and acquire new distance measurements. The fundus is also palpated each treatment to ensure the shield is placed properly. The shield can be difficult to move because it is very large and heavy. The shield may also limit gantry angles, and additional effort is required in XRT planning and setup to assure proper clearances. For XRT, these limitations are generally accepted because unshielded plans often result in fetal dose greater than the limits recommended by TG-36. PBS-PRT does not have these challenges because no shielding is necessary to reduce the dose well below that of shielded XRT.

Considering the factors listed above, we recommend PBS-PRT as the preferred treatment for pregnant patients with brain and head and neck cancers. Importantly, passive scattering (PS) PRT was not considered in this study and is not recommended due to the higher neutron doses. Notably, not all

PBS-PRT systems are the same. Since the neutron dose may be different for other facilities, each facility should make phantom measurements for representative plans before treating pregnant patients with PBS-PRT.

Measurements with the borated polyethylene shielding suggest it provides minimal benefit. This is not entirely surprising as the neutrons delivering the dose to the fetus are likely fast neutrons and thus difficult to shield. The size of the material required for an effective shield (lead and/or steel and/or borated polyethylene) would significantly complicate setup for a small fraction of the gain provided by an XRT shield. Thus, the complexities of working with a neutron shield seem to outweigh the minimal benefit, and so shielding is not recommended.

In PBS-PRT, standard of practice weekly CToR scans can increase the estimated dose to the fetus in head and neck patients by over 30%. Even with this increase, the combined treatment and imaging dose is still less than 10% of the fetal dose during an XRT course of treatment with a shield. CToR verification scans for pregnant head and neck patients are still recommended but with considerations to limit the number of scans and keep scan range to the minimum required. The 2D alignment imaging should also be carefully evaluated. The measurements here suggest that a 30-fraction treatment with two images taken each day would result in less than 0.3 mSv per treatment course. Given the low dose of 2D imaging and the importance of an accurate setup in PBS-PRT, the standard of practice for 2D patient alignment is recommended.

This study was retrospective therefore it lacks clinical outcomes, and it comprises a small total number of patients. A larger, prospective study would further supplement the data on a broader scope. Measurements were performed using a phantom and there are small discrepancies in electron density between phantom and tissue. The International Network of Cancer, Infertility, and Pregnancy reports breast cancer and lymphoma as the most common cancers during pregnancy along with the occurrence of melanoma, brain cancer, and thyroid cancer.[26] Only brain and head and neck cancers were examined

in this work. It is possible PBS-PRT may be appropriate for other sites but would involve further investigation. The neutron measurements in this study were limited to a Wendi-2 meter. A second detector would provide a better understanding of the sensitivity of measured dose equivalent to the detector being used.

Conclusions

The measurements presented in this retrospective study support using PBS-PRT over photon-based treatment (IMRT) for treating pregnant patients with brain or head and neck cancers. The measurements indicate the fetal dose for PBS-PRT is approximately 10 times less than in IMRT plans utilizing photons. Even when considering extra dose from verification CTs and very conservative assumptions about the uncertainty in RBE, the preference for PBS-PRT over XRT still holds. Given these results, PBS-PRT should be considered as preferrable over XRT for pregnant patients for both treatments in the brain and head and neck disease sites.

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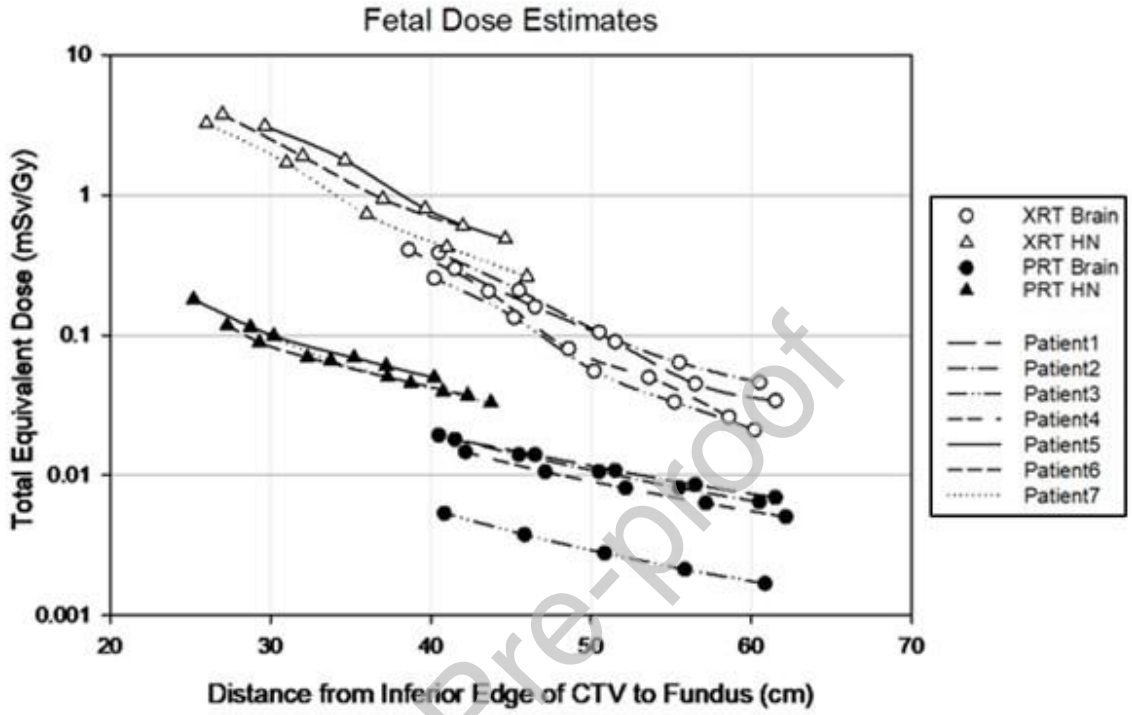

Figure 1: Total dose equivalent estimates for the fetus from the brain and head-and-neck XRT and PRT plans as a function of distance from the inferior edge of the CTV to the fundus (detector).

Table 1: Dose prescription, beam arrangements, and accessories for each proton plan (HN = head and neck, RS = range shifter, G = gantry angle, T = table angle).

Patient	Site	Prescription	Field 1	Field 2	Field 3	Field 4	Accessory
Patient 1	Brain	200 cGy x 30 fx	G160T0	G115T250	G70T180	-	RS
Patient 2	Brain	200 cGy x 30 fx	G50T240	G30T180	G100T0	-	RS
Patient 3	Brain	180 cGy x 30 fx	G65T0	G65T180	G180T180	-	-
Patient 4	Brain	200 cGy x 30 fx	G30T180	G50T270	G100T0	-	RS
Patient 5	HN	200 cGy x 35 fx	G0T270	G85T0	G85T180	G180T180	RS
Patient 6	HN	200 cGy x 30 fx	G70T0	G70T180	G0T0	G180T180	RS

Patient 7	HN	200 cGy x 30 fx	G45T180	G100T180	G160T350	-	RS