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CARDIAC-SPARING WHOLE LUNG IMRT IN PATIENTS WITH PEDIATRIC TUMORS AND LUNG METASTASIS: FINAL REPORT OF A PROSPECTIVE MULTICENTER CLINICAL TRIAL

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Abstract

PURPOSE—A prospective clinical trial was conducted for patients undergoing cardiac sparing (CS) whole lung irradiation (WLI) using IMRT. The 3 trial aims were: 1) To demonstrate the feasibility of CS IMRT with real time central quality control; 2) To determine the dosimetric advantages of WLI using IMRT compared to standard antero-posterior (AP) techniques; and 3) To determine acute tolerance and short-term efficacy after a protocol mandated minimum 2 year follow up for all patients.

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Conflicts of Interest statement for all authors: None

METHODS—All patients underwent a 3D chest CT scan and a contrast-enhanced 4D gated chest CT scan using a standard gating device. The CTV was the entire bilateral 3D lung volume and the ITV was the 4D minimum intensity projection of both lungs. The ITV was expanded by 1cm to get the PTV. All target volumes, cardiac contours and treatment plans were centrally reviewed before treatment. The different cardiac volumes (V) receiving percentages (%) of prescribed RT doses on AP and IMRT WLI plans were estimated and compared.

RESULTS—The target 20 patients were accrued in 2 years. Median RT dose was 15Gy. Real time central Quality Assurance review and plan pre-approval was obtained for all patients. WLI using IMRT was feasible in all patients. Compared to standard AP WLI, CS IMRT resulted in statistically significant reduction in radiation doses to the whole heart, atria, ventricles and coronaries. One child developed cardiac dysfunction and pulmonary restrictive disease 5.5 years after CS IMRT (15Gy) and doxorubicin (375mg/m²). The 2 and 3 year lung metastasis progression free survival was 65% and 52% respectively.

CONCLUSIONS—We have demonstrated the feasibility of WLI using CS IMRT and confirmed the previously reported advantages of IMRT including superior cardiac protection and superior dose coverage of 4D lung volumes. Further studies are required to establish the efficacy and safety of this irradiation technique.

Abstract

A prospective clinical trial was conducted to demonstrate the feasibility of whole lung IMRT, study its dosimetric advantages and assess the short term clinical outcomes in children with lung metastasis. Real time central QA review and pre-approval was obtained. Cardiac sparing IMRT was feasible in all patients and showed improved 4D lung dose coverage and significant reduction in cardiac doses compared to standard techniques. One patient developed cardiac and pulmonary toxicity 5 years after treatment.

Whole lung Irradiation (WLI) is widely used in the management of lung metastases from Wilms tumor, Ewing Sarcoma and rhabdomyosarcoma (1-10). Cardiac failure is an important late effect observed in childhood cancer survivors after WLI and doxorubicin (11-21). A dosimetry study has shown that WLI using IMRT has the potential to reduce radiation exposure to the heart while improving coverage to 4D lung volumes compared to standard antero-posterior (AP) techniques (22). This dosimetry report formed the basis of this novel NIH funded prospective multicenter clinical trial using cardiac sparing (CS) IMRT for WLI in children and young adults with lung metastasis. The 3 aims of this study were: 1) to demonstrate the feasibility of delivering cardiac-sparing WLI using IMRT with central quality control; 2) to prospectively determine the dosimetric advantages of WLI using IMRT over standard AP WLI and 3) to determine the acute tolerance of CS IMRT and short-term efficacy after a mandated minimum follow up of 2 years for all patients.

METHODS

Credentialing Requirements

All centers were required to complete a questionnaire and irradiation of the IMRT benchmark body radiosurgery (lung) phantom under the supervision of the Imaging and Radiation Oncology Core (Houston, TX). The phantom gross tumor volume (GTV) was the

entire lung volume that was expanded by 1cm for the planning target volume (PTV). The prescription guidelines were: a) prescribed dose of 6Gy to at least 95% of the PTV; b) minimum dose of 5.4Gy to at least 99% of the PTV; c) hotspots should be within the PTV; d) the critical normal structure was the heart. All centers met these dose planning and delivery requirements and were credentialed prior to patient enrollment.

Patient Eligibility

This prospective clinical protocol was registered on [Clinical trials.gov](https://clinicaltrials.gov) and was conducted in five institutions in the U.S. All centers obtained local IRB approval prior to patient enrollment. All records including patient registration, consent, treatment details and follow up information were kept at the Imaging and Radiation Oncology Core, Rhode Island (IROC RI). Patient eligibility requirements were: age > 12 months and < 30 years; pulmonary metastasis (single or multiple) from any pediatric malignancy that may include Wilms tumor, Ewing Sarcoma, Rhabdomyosarcoma or other sarcomas; pulmonary metastases may have occurred at diagnosis or at relapse; Karnofsky performance status >50 or Lansky performance status >50; pulmonary metastasis was defined as one pulmonary nodule 1cm or more than one pulmonary nodule 0.5cm; patients should have adequate cardiac function (shortening fraction 27% or ejection fraction 50%). The exclusion criteria included prior history of WLI, Hodgkin's Lymphoma and presence of mediastinal disease that required additional RT.

Chemotherapy

Patients received chemotherapy according to standard Children's Oncology Group (COG) or institutional protocols for their respective tumors. Doxorubicin dose was reduced by 50% if administered during or within 6 weeks after WLI. The first dose of dactinomycin after WLI was reduced by 50%. The timing or doses of other drugs like irinotecan or topotecan during WLI was not modified. Standard chemotherapy dose modifying guidelines for hematologic, cardiac, pulmonary and hepatic toxicity were followed.

CT-simulation and normal tissue and target volume definitions

All patients were immobilized using a Vac-LokTM with a neck rest or aquaplast mask to keep the neck extended. The arms were placed on the side away from the body or alternatively above the head using a wing board. Appropriate sedation or anesthesia was to be used as indicated.

At simulation, CT slices 2-3 mm in thickness were obtained from the mandible to the pelvic brim. The first CT scan was a non-contrast scan for IMRT planning with heterogeneity corrections applied and no gating devices. The lung CTV was the entire 3D bilateral lung volume. The second CT scan was a contrast-enhanced 4-D gated scan using a standard gating device. This 4-D scan was analyzed for maximum expansion of the lungs in the superior-inferior, anterior-posterior, and mediolateral dimensions. The lung internal target volume (ITV) was the maximum lung expansion volume defined as the minimum intensity projection (MinIP) bilateral lung volume on 4D CT simulation scans (including lung expansions into the anterior and posterior costophrenic recesses and bilateral hila). The lung Planning target volume (PTV) was obtained by a 1cm expansion of this ITV in all

dimensions but not outside the patient. The PTV was then expanded to include the entire vertebrae and mediastinum (to include lymph nodes from the sternal manubrium up to 1.5cm inferior to the carina) (Fig. 1). An atlas for contouring cardiac anatomy (heart chambers, myocardium and coronary arteries) was developed by our cardiac radiologist (CKR) and was uploaded on the IROC RI website to facilitate investigator compliance with protocol guidelines. For dosimetry comparison between IMRT and AP WLI the different cardiac volumes (V) receiving percentage (%) of prescribed RT doses (V95, V83, V67, V50) were estimated.

Target Dose

The daily fraction dose was 1.5Gy. The total prescription dose was 12Gy for Wilms tumor and 15Gy for other tumors. No additional boost doses were allowed.

Treatment planning and Prescription guidelines

X-rays with a nominal energy between 4 and 6MV were to be used. Lung heterogeneity corrections were applied for all patients. The target dose was prescribed to an isodose surface that satisfied the dose uniformity requirements. At least 95% of the PTV should receive at least 95% of the prescribed dose, no more than 2% of the PTV should receive more than 105% of the prescribed dose, and no more than 1% should receive more than 110% of the prescribed dose.

Heart dose-volume constraints for IMRT planning were derived from the Northwestern dosimetry study (22). For organs at risk dose (OARs), the maximum dose to the spinal cord, heart and liver should be <107%, <110% and <110% respectively of the prescribed dose.

In order to limit the dose uncertainty during delivery of small IMRT segments to moving targets like the lungs, the following measures were recommended: 1) limit the total number of IMRT segments to about 70-80 for the 9 beams 2) use a minimum field size of 5cm and 5 MUs per segment and 3) use lower dose-rates (< 400MU/Min) and 4) provide an approximately 1cm dosimetric margin to the 4D lung volumes. Further, in this feasibility trial only “step and shoot” and “sliding window” IMRT techniques were allowed due to the lack of experience at the time of initiation of this study with current techniques like volumetric modulated arc radiotherapy (VMAT).

Dosimetry study comparing WLI using AP vs. IMRT techniques (Aim 2)

Historically, heterogeneity corrections have not been applied on standard AP WLI plans. However, all IMRT plans are performed with heterogeneity corrections. In order to perform this dosimetry comparison study two steps were required: 1). The first treatment plan was done using standard AP WLI fields with a 1cm-field edge margin beyond the 3D whole lung volume without using heterogeneity corrections. The dose was prescribed to the mid-plane with a dose variation not to exceed -5 to +7%; 2). A second treatment plan was performed for the same fields, but with heterogeneity corrections turned on. To perform a dosimetry comparison of lung doses between AP and IMRT WLI techniques, this second plan was recalculated with the same monitor units used in the homogeneous plan as in #1 above. Using the AP WLI plan and IMRT plans the following dose-volume histograms (DVHs)

were calculated: V100, 105, V110 for lungs; V95, V83, V67, V50 for the atria and ventricles, myocardium, coronary arteries, stomach, liver, kidneys and thyroid; and V5, V10 isodose lines.

Real time Central Multidisciplinary Quality Assurance (QA) Review and Preapproval

An important aspect of this feasibility study was the requirement for real time QA and pre-approval for all patients. CT simulation and treatment planning data for each patient was submitted to IROC RI in digital format. These data were reviewed in real time by the principal investigator (JAK), IROC (TJF), study physicist (MGK) and study diagnostic radiologist (CKR) to ensure that protocol requirements for target and normal tissue contouring, IMRT planning and delivery were complied with in all patients. Post-QA review feedback regarding compliance was provided promptly within 1-2 days with suggestions for corrective implementation and re-verification prior to treatment.

Definition of Protocol Performance

A minor deviation was defined as when 95% of the PTV was not encompassed within the isodose surface representing 95% of the prescription dose, or more than 5% of the PTV received more than 105% of the prescription dose. Planning target margins was less than specified or fields were excessively large. A major deviation was defined as when 95% of the PTV was not encompassed within the isodose surface representing 90% of the prescription dose, or more than >5% of the PTV received more than 105% of the prescription dose or a portion of the tumor (GTV) or potentially tumor bearing area (CTV) was not included in the treated volume.

Follow Up

All patients were followed every 4 months for 2 years. At each follow up, a detailed history and physical examination, complete blood counts and liver enzymes were obtained. CT scans of the chest, EKG and echocardiograms were obtained at a minimum of every 6 months for 2 years. All patients were closely monitored for any treatment-related toxicity during follow up. Tumor response was assessed using RECIST criteria every six months. IROC RI provided the Northwestern University Data and Safety Monitoring Committee and all institutional IRBs detailed reports regarding all aspects of the trial every 3-4 months.

Statistics

This was a one sample pilot study to evaluate the feasibility of WLI using CS IMRT in a multi-institutional setting. Feasibility was defined as an enrolled patient receiving the IMRT treatment as planned. It was expected that the treatment would be feasible in at least 90% of patients. Due to the pilot characteristics of this study and the primary objective being the evaluation of feasibility of IMRT, a preliminary power analysis was done to compare the heart and cardiac sub-region DVHs from IMRT and standard AP WLI (Aim 2). Based on preliminary data from a dosimetry study (22), compared to cardiac DVH values from standard AP-WLI (V95, V83, V67 and V50 of 100%), the IMRT values ranged from 45% to 81% for the whole heart (standard deviation sd=8), 43% to 84% for the left ventricle (sd=10), 23% to 77% for the right ventricle (sd=18) and 47% to 85% for the atria (sd=17).

Assuming that for each structure, four statistical tests would be done, one each at V95, V83, V67 and V50 with 20 patients, there would be an 80% power to detect a difference of 100% with Standard AP WLI versus 93% with IMRT assuming a standard deviation of 8 (as seen for the whole heart), a one-tailed test and a Bonferroni correction for 4 statistical tests so that each test was done at $p < 0.0125$. This calculation assumed that a nonparametric test would be done, and that such a test was 91% efficient if the data were truly normally distributed. Assuming a standard deviation of 10 (as seen for the left ventricle), the effect size was 100% versus 92%. Assuming a standard deviation of 17 as seen for other structures, the effect size was 100% versus 86%. These detectable effect sizes were smaller than the effect sizes observed in the pilot data, indicating sufficient power to detect expected differences between IMRT and Standard WLI. A total of 20 patients would be recruited within 2-3 years and this sample would also allow the assessment of feasibility of recruitment at multiple centers. In addition to the heart, the other organ-doses to be studied in this protocol (IMRT vs Standard WLI) include the thyroid gland, whole lungs, right and left lungs, liver and stomach. Lung-metastases-free survival and overall survival would be estimated using Kaplan-Meier survival curves (minimum period of six months).

RESULTS

Patient and treatment characteristics

The target 20 patients (mean and median age was 10 years, range (2 – 25 years) were accrued from 5 centers in 2 years. Eleven patients were males. Patients were classified into two groups: Group 1 (n=14) had lung metastasis at the time of primary diagnosis (Wilms tumor 3, Ewing Sarcoma 9, Rhabdomyosarcoma 1, Undifferentiated sarcoma 1); and Group 2 (n=6) had lung metastasis at first or subsequent relapse, and had progressive disease after prior multimodality treatment (Wilms tumor 2, Ewing Sarcoma 2, hepatoblastoma 1, Rhabdomyosarcoma 1).

The WL IMRT dose was 15Gy in 10 fractions (14 patients) and 12Gy in 8 fractions (6 patients).

The chemotherapy regimens were: vincristine/dactinomycin/doxorubicin per the National Wilms Tumor Study (NWTs) DD4A regimen (Wilms tumor); vincristine/doxorubicin/cyclophosphamide (VDC) and ifosfamide/etoposide (IE) per COG AEWS0031 or Memorial SloanKettering Ewing Family Tumor protocol (primary Ewing Sarcoma); irinotecan/temozolamide (recurrent Ewing sarcoma); vincristine/irinotecan, vincristine/doxorubicin/cyclophosphamide (VDC), ifosfamide/etoposide (IE) and vincristine/dactinomycin/cyclophosphamide per COG ARST0431 (rhabdomyosarcoma); ifosfamide/doxorubicin with or without etoposide (non-rhabdomyosarcoma soft tissue sarcoma); or cisplatin/5-fluorouracil/vincristine/doxorubicin (C5VD) per COG AHEP0731 (hepatoblastoma). None of the children were enrolled on COG studies.

Feasibility of WL IMRT (Aim 1)

The cardiac sparing IMRT WLI technique was feasible and delivered per protocol in all 20 patients. Four dimensional (4D) CT simulation with a gating device was feasible in all

patients including in younger children and infants (ten patients were 10 years old and 8 children were 6 years [2-6 years]). The median RT dose was 15Gy (12-15Gy) using a mean of 9 fields. All WL IMRT treatment plans were centrally reviewed within 1-2 days. Pre-treatment real time central review resulted in target contour changes in 7 (35%) patients, re-planning in 3 (15%) and minor deviations in 2 (10%) patients. There were no major deviations. All recommended contouring and planning changes after pre-treatment review were made by investigators and re-reviewed centrally before the actual WL IMRT was delivered.

During this study, no guidelines were provided for thyroid gland and breast tissue protection. However, several investigators did attempt to reduce radiation exposure to the thyroid gland and breast tissues. In order to ensure adequate dose coverage of the lungs, a new treatment planning guideline was introduced that required the creation of a maximum lung expansion planning volume that was obtained by expanding the 4D lung internal target volume (ITV) by 5mm in all directions. It was required that in addition to following all other treatment planning guidelines, 100% of this planning volume was to be covered by 95-100% of the prescribed dose. This dose planning requirement was also met in all patients.

Dosimetry comparison between WL CS IMRT and standard AP WLI (Aim 2) (Fig. 1-5, Table 1).

The dosimetry data shown in table 1 and figures 1 and 5, show that compared to standard AP WLI, CS IMRT resulted in significantly lower radiation dose exposure to the mean whole heart, left and right ventricles and left ventricular myocardium for V95, V83, V67 and V50. For the coronary arteries, whole lung CS IMRT also resulted in significantly lower doses for V95, V83 and V67. The dose volume histograms of the whole heart, left and right ventricles shown in Figs. 2-4 demonstrate the similarity between the mean DVHs of these structures in this prospective clinical trial and the prior dosimetry study (22). The 4D lung volumes were significantly larger than 3D volumes (mean 1725cc $\pm$ 1153 vs. 1573 $\pm$ 1060 P<0.0001). The 4D lung volume dose coverage was significantly lower with standard 3D AP fields compared to CS IMRT (97.8% $\pm$ 2.6 vs. 98.4% $\pm$ 3.7 P=0.008). The V_{105%} hot spot with homogeneous WLI standard 3D AP plan was significantly higher than heterogeneous WLI plan 53.8% $\pm$ 20.7 vs. 1.5% $\pm$ 2.6 P<0.001). There was no trend towards any significant dose reduction to the thyroid gland, liver, stomach, spleen and stomach following WLI using CS IMRT compared to standard AP techniques.

Patient Tolerance and 2 year tumor control rates (Aim 3)

Whole lung IMRT was well tolerated with no acute side effects. All patients had reversible chemotherapy and RT-related reduction in blood counts. No patient reported any pulmonary symptoms suggestive of radiation pneumonitis or pulmonary toxicity at any time during the minimum 2 year follow-up after WL IMRT and chemotherapy. Post CS IMRT CT scans throughout follow up for all 20 patients revealed no evidence of RT-related lung consolidation in any patient despite the use of multiple chemotherapy regimens including high dose chemotherapy and stem cell rescue, and re-irradiation in patients who had progressive disease. Longer follow up revealed that one child, a 4 year old girl with rhabdomyosarcoma developed cardiac dysfunction and pulmonary restrictive disease 5.5

years after CS IMRT (15Gy) and a cumulative doxorubicin dose of 375mg/m². She developed markedly decreased left ventricular ejection fraction (LVEF of 37%) with mild dyspnea on exertion. Her Pulmonary Function Tests showed a moderate restrictive defect. Her cardiac DVHs following whole lung CS IMRT were reviewed and compared to standard AP WLI. Compared to standard AP WLI (V100, V95, V83, V67 and V50 for the heart was 100%), the CS IMRT-related DVHs for the heart and cardiac sub-regions were: Whole heart - V100, V95, V83, V67 and V50 was 9%, 34%, 50%, 66% and 82% respectively; Left Ventricle - V100, V95, V83, V67 and V50 was 5%, 32%, 47%, 61% and 75% respectively; Right Ventricle - V100, V95, V83, V67 and V50 was 2%, 14%, 33%, 54% and 77% respectively; Myocardium - V100, V95, V83, V67 and V50 was 0%, 13%, 32%, 50% and 70% respectively.

For all patients, the 2 and 3 year OS was 90% (66%, 97%). The 2 and 3 year lung metastasis progression free survival (PFS) was 65% (40%, 81%), and 52% (22%, 75%) respectively. At the time of CS IMRT, all 14 group 1 and 4/6 group 2 patients had complete or partial response (CR/PR) of lung metastases after chemotherapy. The pulmonary relapse rate was 4/14 (29%) in Group 1 patients (n=4 Ewing Sarcoma) compared to 4/6 (67%) in Group 2 (Wilms tumor 1, Ewing Sarcoma 2, Hepatoblastoma 1). At last follow up two patients died, both had progressive disease (Group 2) at the time of WL IMRT. The 2 year OS for Group 1 and 2 patients was 100% (100%, 100%) and 80% (20%, 97%) respectively (P 0.11). The 2 year PFS for Group 1 was 77% (44%, 91%), and for Group 2 the PFS at 1.9 years was 33% (5%, 68%) (P 0.05). As expected, the lower doses of RT (12-15Gy) and the lack of effective systemic therapy after multiple recurrences did not provide much clinical benefit for these Group 2 patients.

DISCUSSION

Whole lung Irradiation (WLI) (12-15Gy) has improved survival rates and is widely used in the management of pulmonary metastasis from common pediatric tumors like Wilms tumor, Ewing Sarcoma and rhabdomyosarcoma (1-10). In NWTS-3, children with chest x-ray positive favorable histology (FH) lung metastasis treated with WLI had an EFS and OS of 72% and 78% respectively (1). In NWTS-3 and 4, the 4-year EFS and OS in patients with CT-only lung metastasis was 89% and 91% after WLI compared to 80% and 85% with chemotherapy alone (2). A UKCCSG report showed that chest x-ray positive FH Wilms tumors had significantly improved RFS and OS (73% and 85%) after WLI compared to chemotherapy alone (53% and 79%) (3-5). The European Intergroup Ewing Sarcoma Study (EICESS-92) trial reported that WLI was associated with superior survival and quality of life outcomes (5 year OS of 61% compared to 49% with chemotherapy alone) (8, 9).

Irradiation of the heart can cause a spectrum of disorders that can affect the pericardium, myocardium, endocardium, cardiac valves, conduction system and coronary arteries. A number of risk factors have been identified including RT dose-fractionation, patient age, volume of heart irradiated, chemotherapy drugs and presence of cardiovascular risk factors (11-21).

A number of chemotherapeutic agents are known to cause cardiac injury, including anthracyclines such as doxorubicin, epirubicin, and high-dose cyclophosphamide. Many reports have documented the effects of doxorubicin on the heart such as left ventricle end-diastolic stress, reduction of ejection fraction, and congestive heart failure (CHF) (14-21). In the NWTs late effects study (LES), the 20 year cumulative frequency of CHF was 4.4% and 17.4% respectively after treatment with doxorubicin at initial diagnosis or at relapse. The relative risk (RR) of CHF was increased: in females (RR 4.5); by cumulative doxorubicin dose (RR 3.3/100mg/m²); lung irradiation (RR 1.6/10Gy) and left abdominal irradiation (RR 1.8/10Gy) (16, 17).

Data from the Childhood Cancer Survivor Study (CCSS) showed a higher incidence of CHF, myocardial infarction, pericardial disease and valvular abnormalities in childhood cancer survivors. Anthracycline doses $\geq 250\text{mg/m}^2$ and cardiac doses $\geq 15\text{Gy}$ were associated with complications (18). The Institute Gustave Roussy report showed that the 20 year incidence of CHF was 18% after heart dose $>3.7\text{Gy}$ and 9% after lower doses (20). Another study of 4122 French-British cancer survivors followed for 27 years was the first to establish a relationship between average heart RT dose and long-term cardiac mortality. The adjusted RR increased with an average heart dose $> 5\text{Gy}$ and with anthracycline dose $>360\text{mg/m}^2$ (21). The NWTs and CCSS have shown that second malignancies and cardiovascular disease was the leading cause of morbidity and mortality among long-term survivors (23, 24). In a recent review of the epidemiology and pathophysiology of cardiovascular disease in childhood Cancer survivors, the known risk factors for cardiomyopathy/congestive heart failure were anthracyclines $\geq 250\text{mg/m}^2$ when administered alone or anthracyclines $\geq 100\text{mg/m}^2$ when administered in combination with $\geq 15\text{Gy}$ chest RT. Children <5 years of age at diagnosis were also at a higher risk for these complications (29).

Based on these treatment-related risk factors for cardiac morbidity and mortality, investigators have explored the value of strategies to mitigate these risks including reducing doxorubicin doses, using newer anthracycline analogs and cardioprotective agents and reducing cardiac RT dose exposure by using novel RT techniques such as IMRT (25-28).

In this report we have successfully demonstrated that WLI using CS IMRT was feasible in a multicenter setting with real time central quality control. Pre-treatment real time central review resulted in target contour changes in 7 (35%) patients, re-planning in 3 (15%) and minor deviations in 2 (10%) patients. There were no major deviations. This study also confirmed the previously reported dosimetric advantages of IMRT over standard AP WLI techniques including superior cardiac protection, superior 4-dimensional lung planning target volume coverage and superior dose uniformity in the lungs with fewer hot spots (22). This was a feasibility study and thus the sample size and relatively short follow-up does not permit arriving at any conclusions regarding the long-term safety or efficacy of CS IMRT. The use of CS IMRT was safe with only one patient reported to have cardiac dysfunction and pulmonary restrictive disease 5.5 years after treatment. The risk factors for cardiomyopathy in this patient included younger age, cumulative doxorubicin dose of 375mg/m^2 and whole lung RT (15Gy). However, the dose-volume histograms for the heart, ventricles and myocardium revealed that these regions received significantly lower RT doses after CS IMRT compared to standard AP WLI. The impact of lower dose spillage after WLI

using IMRT on the risks for developing late effects such as second malignant neoplasms requires further study. In our previous dosimetry report, there was no significant difference in the volume of tissues receiving 5% or 10% of the prescribed dose after WLI using IMRT or standard AP techniques (22). Further studies are required to establish the true relationship between chemotherapy agents and IMRT doses to the heart, lungs and other organs in the high and low-dose regions for the development of late effects such as congestive heart failure, pulmonary disease and second malignant neoplasms. Regarding tumor control, the 2 and 3 year tumor control rates in this study were similar to previous reports after WLI (1-10). Further, given the improved dose coverage of 4D lung volumes using IMRT compared to standard AP techniques, it can be surmised that CS IMRT would at least have equivalent or superior outcomes. This CS IMRT technique with real time central multidisciplinary QA review and preapproval as performed in this study will be utilized group wide in COG for the next generation of Wilms tumor protocols. In order to improve compliance with protocol guidelines including 4D target contouring and IMRT planning, a detailed contouring atlas and sample treatment plans with IMRT planning guidelines will be made available to all investigators on the IROC RI website.

CONCLUSIONS

This clinical trial has demonstrated the feasibility and dosimetric advantages (superior cardiac protection and superior dose coverage of 4D lung volumes) of cardiac sparing whole lung IMRT given concurrently with chemotherapy in pediatric tumors with lung metastases. Further studies and longer follow-up will be required to establish the long-term efficacy and safety of this irradiation technique.

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Fig. 1. Cardiac sparing Intensity Modulated Radiation Therapy (IMRT) plan showing 95% isodose line (blue), 80% (yellow), 70% (magenta) and 50% (white) on CT images of left ventricle (red), right ventricle (teal), and whole lung planning target volume (purple). (A) Axial image (B) Sagittal and (C) Coronal image showing biventricular sparing with IMRT.

Fig. 2.
Dose Volume Histograms (DVH) of the Whole Heart following Whole Lung Intensity Modulated Radiation Therapy (IMRT) of 20 patients (brown), mean heart DVH (black) and mean heart DVH from a prior in-house dosimetry study (red).

Fig. 3.

Dose Volume Histograms (DVH) of the Left Ventricle following Whole Lung Intensity Modulated Radiation Therapy (IMRT) of 20 patients (brown), mean Left Ventricle DVH (black) and mean Left Ventricle DVH from a prior in-house dosimetry study (red).

Fig. 4. Dose Volume Histograms (DVH) of the Right Ventricle following Whole Lung Intensity Modulated Radiation Therapy (IMRT) of 20 patients (brown), mean Right Ventricle DVH (black) and mean Right Ventricle DVH from a prior in-house dosimetry study (red).

Fig. 5. Dose Volume Histograms (DVH) of the Left Ventricular (LV) Myocardium following Whole Lung Intensity Modulated Radiation Therapy (IMRT) of 20 patients (brown), mean LV Myocardium DVH (black) and mean LV Myocardium DVH after AP-PA Whole lung RT (dotted black).

Comparison of cardiac-sparing intensity modulated radiation therapy (IMRT) and Standard AP-PA whole lung RT doses to the whole heart, ventricles, atria, coronaries, myocardium, thyroid gland, kidneys, spleen, stomach and liver.

Table 1.

Normal tissue		V50			V67			V83			V95		
		IMRT	AP-PA	P-value	IMRT	AP-PA	P-value	IMRT	AP-PA	P-value	IMRT	AP-PA	P-value
Heart	Mean	96%	100%	0.0083	85%	100%	<0.001	65%	100%	<0.001	39%	97	<0.001
	SD	5.4	0.8		9.5	1.3		12.1	2.2		15.5	6.7	
LV	Mean	95%	100%	0.006	82%	100%	<0.001	61%	100%	<0.001	33%	99%	<0.001
	SD	7.8	0		13.5	0.2		15.2	0.5		15.9	2.7	
RV	Mean	91%	100%	0.002	69%	99%	<0.001	42%	99%	<0.001	18%	97%	<0.001
	SD	10.8	1.6		15.2	2.6		12.7	4		8.9	8.2	
LA	Mean	99%	100%	0.36	98%	100%	0.036	87%	100%	0.0002	55%	94	<0.001
	SD	0.4	0.2		3.8	1.1		12.3	2.5		22.3	15.4	
RA	Mean	99%	99%	0.78	97%	100%	0.009	86%	100%	<0.001	57%	97%	<0.001
	SD	0.4	0.7		3.3	1.3		10.5	2		22.5	11.1	
LCA	Mean	99%	100%	0.33	98%	100%	0.051	91%	100%	0.0008	66%	100%	<0.001
	SD	1.1	0		4.5	0		9.5	0		25.1	0	
RCA	Mean	100%	100%	NA	98%	100%	0.025	88%	99%	<0.001	53%	96	<0.001
	SD	0	0		3.5	1.3		9.9	3.1		20.9	12.8	
Myocardium	Mean	94%	100%	<0.001	83%	98%	<0.001	69%	99%	<0.001	47%	98%	<0.001
	SD	8	0		9.76	2.54		7.56	0.88		14.1	2.54	
Thyroid	Mean	44%	33%	0.27	33%	28%	0.61	20%	23%	0.72	6%	16%	0.1
	SD	32.5	33.1		31	31.3		24.4	29.8		8.5	26.2	
Kidneys	Mean	5%	6%	0.44	4%	4%	0.55	3%	3%	0.82	1%	1%	0.31
	SD	7.6	6.8		5.9	5.6		4.1	4.5		2.1	2.3	
Spleen	Mean	66%	63%	0.85	61%	59%	0.83	54%	56%	0.83	43%	46%	0.85
	SD	16.6	20.3		16.9	20.9		17.3	21.3		16.6	21.9	
Stomach	Mean	62%	62%	0.88	53%	59%	0.35	43%	56%	0.09	29%	43%	0.05
	SD	21.7	24.5		20.4	24.6		19.6	24.4		16.6	23.2	
Liver	Mean	55%	54%	0.95	48%	51%	0.52	39%	48%	0.04	27%	37	0.03
	SD	11.4	14		11	14		10.5	14		9.7	13.6	