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Original article

Coronary stenosis risk analysis following Hodgkin lymphoma radiotherapy: A study based on patient specific artery segments dose calculation

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ABSTRACT

Background and purpose: The dose effect-effect relationship for cardiac diseases following radiotherapy suffers from uncertainties. Three dimensional coronary artery (CA) dose calculation after mediastinal Hodgkin lymphoma radiotherapy was performed, using the patient's coronary CT angiography (CCTA), and the relationship between the coronary arteries' radiation doses and the risk of stenosis was estimated.

Materials and methods: Radiotherapy simulation CT scans and CCTAs of patients treated for a mediastinal Hodgkin lymphoma were used to merge thoracic and detailed cardiovascular anatomies. Radiation treatment parameters were used to estimate CA radiation doses. Twenty-one patients without coronary stenosis (controls) were matched with twelve patients with stenosis (cases). CA segments were considered as sub-volumes of interest. Radiation doses to stenotic segments were compared with those received by normal segments (from cases and controls) using a logistic regression.

Results: In eleven cases out of twelve, the highest of the coronary dose distribution was on a damaged segment. Logistic regression with CA segments yielded an odds ratio associated with the risk of coronary stenosis of 1.049 per additional gray with the CA segment median dose (95% confidence interval, 1.004–1.095; p-value <0.05).

Conclusion: The CA segment dose significantly increased the risk of stenosis on the segment. Such personalized CA dose calculations on larger cohorts are expected to improve the understanding of the cardiovascular radiation dose–effect relationship.

Cardiovascular toxicity of radiation therapy (RT) is a major concern following chest radiotherapy [1–3]. Late mortality due to radiation-induced heart diseases following Hodgkin lymphoma RT has been thoroughly evidenced in the literature [4–12]. But, knowledge of the dose–effect relationship suffers from uncertainties mainly related to patient anatomy and confounding factors, which currently limits the scoring of the cardiovascular diseases. The relationship between radiation dose and late cardiovascular effects has been generally studied in regard to heart doses [13,14], and sometimes coronary doses using anatomical prior knowledge [15–17].

One of the most informative studies concerning the ischemia risk after RT is based on a wide cohort of breast cancer patients [18]. The rate of major coronary events was found to be increased by 7.4% (95% confidence interval: 2.9–14.5%) per gray with the mean heart dose. In that study, the simulation CT scan of a single representative patient was used and the left anterior descending (LAD) coronary artery delineation based on prior anatomical knowledge. Although the study encouraged dose assessment to heart sub-volumes, the mean heart dose was found to be a better ischemia risk predictor than the CA mean dose. The finding did not discard the interest of CA dose assessment, as important morphological approximations were made.

A prospective coronary heart disease screening using CCTA for asymptomatic Hodgkin lymphoma patients treated by radiotherapy has been recently published [19]. Patients have been proposed

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to enter into the study with the justification of high cardiovascular risk after chest irradiation and with information about the radiation dose due to the cardiac imaging. In this study, a multivariate analysis demonstrated that various clinical, genetic and radiation parameters were independent prognostic factors for the development of CA stenosis. The odds ratio related to the CA dose suffered from anatomical approximations as the CA origin dose was used as a surrogate for the CA dose, regardless of the stenosis location. For this cohort, we took advantage of the detailed coronary pattern provided by CCTA to calculate CA segment dose and further investigate the radiation-induced coronary stenosis risk.

Personalized 3D CA dosimetry was thus performed, following the method based on hybrid computational phantoms [20]: the thoracic anatomy from the simulation CT scan and the heart anatomy from CCTA were merged and doses calculated with a treatment planning system (TPS). Doses were then analyzed in terms of risk factor for CA stenosis.

Methods and materials

Patient selection

Cardiovascular dose reconstructions required to retrieve anatomical and treatment planning data. Only medical records using a simulation CT scan were considered, reducing the cohort from 179 to 87 patients that were treated between 2000 and 2008 for a mediastinal Hodgkin lymphoma. Among them 22 were diagnosed with coronary artery disease (CAD) versus 65 without, at the CCTA acquisition time. Considering lost archived data, only 12 of 22 patients (i.e. cases with stenosis) had the required anatomical and RT-planning information.

For each case, patients without CAD diagnosis, i.e. controls, were matched according to relevant CAD risk factors evidenced in [19]: hypertension (with or without), the age at treatment time (±5 years) and the time interval between the RT and the CCTA (±2 years). Hypercholesterolemia and gender were discarded as matching criteria to limit over-matching and increase the number of potential controls. In large cohort (around 1000 cases), the number of controls is usually limited since the precision increase is small above a controls-to-cases ratio of four [21]. Here, given the small sample, all matching controls were considered: 21 controls of 65 were selected.

For cases and controls, the following data were retrieved: the simulation CT scan, the CCTA, the RT plan and RT structure files in DICOM format and the number of monitor units (MUs) for each beam (paper records).

Merging anatomical information from the simulation CT scan and the CCTA

Hybrid computational phantoms of each patient were built as described in [20]. The thoracic anatomy from the simulation CT and the hearts and CAs from CCTAs were combined into a computational phantom and then imported into the TPS. The main steps of the process were: creation of volumes from anatomical contours; merging of volumes into a single computational phantom; voxelization of volumes to create DICOM images.

The thorax included the external contours, the lungs, the spine, the sternum, the aorta and the heart (cf. Supplementary data, Fig. S1). The detailed heart representation required the manual segmentation on the CCTA of the heart, the aorta and the main CAs: the LAD, the left main (LM), the circumflex and right CAs (CX and RCA), validated by an experienced radiologist (JFP).

The detailed heart model was adjusted to the heart model from the simulation CT scan with the computer-aided design software, Rhinoceros3D (McNeel, North America, Seattle, WA; http://www.rhino3d.com/). The CCTA provided an optimal coronary visualization but at a given moment of the cardiac cycle, generally the diastole. On the contrary, the simulation CT scan provided images integrating the breathing and heart beating motion. Consequently, a slight rotation of the heart around the cranio-caudal axis, a homothetic deformation along the three dimensions and a translation to match the coronary arteries origins were carried out for the adjustment. The resulting numerical model corresponded to the patient thorax with the patient heart and coronary artery tree.

Each hybrid computational phantom was inserted into the ISO gray TPS (version 4.2, Dosisoft, Cachan, France; http://www.dosisoft.com/en/radiotherapy/planning-products.html), in DICOM format [20]. Manual delineation was again performed for the above cited structures; particularly the coronary artery tree was divided into nine segments as defined in [22]: LM, LAD1-3, CX1-2, RCA1-3 (cf. Supplementary data, Fig. S1). The number assignment for LAD and RCA parts is as follows: proximal (1), mid (2) and distal (3); for the CX "1"and "2" refer to the proximal and distal parts, respectively.

The experienced radiologist indicated the damaged coronary portions on a schematic drawing of the coronary segments. Both segmentation and stenosis extension diagnostic were made in blind regarding the dose calculation and were performed by independent investigators to ensure an unbiased method. At the end, two groups of CA segments were considered: the damaged segments group from cases and the normal segments group from cases and controls.

Retrospective dose reconstruction

For each patient, the RT plan was imported and checked with the RT charts. MUs were attributed taking into account the change of the calibration factor in the TPS beam library between the RT and the dose reconstruction dates. For 2 cases of 12, the original beam library was unavailable. A beam library with close energy or beam quality index (QI) [23] to the original beam was used for substitution. A 25 MV beam (QI = 0.785) was substituted by 20 MV (QI = 0.792); 6 MV was substituted by 4 MV. The retrospective dose calculation was carried out after designing the collimator shape from drawing on radiographs.

The doses were calculated with the Clarkson algorithm, using a double decomposition and heterogeneity corrections (lungs, backbone, sternum). The calculation grid resolution was $2 \times 2 \times 2$ mm^3. For each cardiovascular structure, the mean dose (D_{mean}) and the median dose (D_{med}) were taken into account in the data analysis.

Data analysis

Data analyses were performed using the R software (version 3.0, www.r-project.org). Correlations between heart and coronary D_{mean} were analyzed through a linear regression, to estimate the reliability of using the heart D_{mean} as surrogate to the coronary doses.

Although the literature usually reports CA D_{mean}, this study focused on the CA segments and reported D_{med} since it is less sensitive than D_{mean} to the extreme dose values, more subject to uncertainties. CA segment volumes were compared and boxplots of D_{med} were created for both coronary segment groups considering the CA segments as comparable CA sub-volumes. A Wilcoxon rank-sum was performed to provide a p-value assessing the significance of the group difference (damaged versus normal segments) disregarding the case-control matching.

Only a regression analysis taking into account the case-control matching along with a statistical estimation can identify the relationship between the dose and the stenosis occurrence, and its

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