**AAPM 2022 – John R. Cameron Early-Career Investigator**

**Title:** Development and validation of a population-based anatomical colorectal model for radiation dosimetry in late effects studies of childhood cancer survivors

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**Purpose:**
Study purposes were to develop and integrate a colorectal model that incorporates anatomical variations of pediatric patients into an age-scalable computational phantom, and to validate the model for pediatric radiation therapy (RT) dose reconstructions.

**Methods:**
Colorectal contours were manually derived by two physicians from whole-body non-contrast CT scans of 114 pediatric patients (age range: 2.1-21.6years, 74males, 40females). One contour was used for an anatomical template, 103 for training and 10 for testing. Training contours were used to create a colorectal principal component analysis (PCA)-based statistical shape model (SSM) to extract the population's dominant deformations. The SSM was integrated into our in-house age-scalable phantom. Geometric accuracy was assessed between patient-specific and SSM reconstructed contours. Two alternative colorectal shapes (hereafter alternative #1, #2) were generated using the first 17 dominant SSM modes. Dosimetric accuracy was assessed by comparing colorectal doses from 10 test patients' CT-based RT plans (ground-truth) with reconstructed doses for the mean, alternative #1 and #2 colorectal models in age-matched phantoms. Lastly, a proof-of-concept study was conducted to demonstrate that our colorectal models can be integrated into any computational phantom.

**Results:**
Using all 103 PCA modes, mean(min-max) Dice similarity coefficient, distance-to-agreement and Hausdorff distance between patient-specific and reconstructed contours were 0.89(0.85-0.91), 2.1mm(1.7-3.0), and 8.6mm(5.7-14.3), respectively. Average absolute difference between ground-truth and reconstructed mean and maximum colorectal doses (normalized to 20Gy prescription dose) for the mean colorectal model (alternative #1, alternative #2) were 6.33%(8.08%, 6.13%) and 4.38%(4.28%, 4.65%), respectively. Similar agreement was observed when colorectal models were integrated into a collaborator's 5-year-old phantom; 6.28%(11.73%, 0.34%) and 0.47%(0.19%, 0.90%), respectively.

**Conclusion:**
We developed and validated a population-based colorectal SSM and demonstrated its use for pediatric RT dose reconstruction in two phantoms. We will use this SSM to reconstruct pre-CT era colorectal doses for irradiated individuals in the Childhood Cancer Survivor Study.

## BACKGROUND:

- For colorectal subsequent malignant neoplasms (SMN) in childhood cancer survivors, the risk factor known to confer the highest risk is exposure to radiation therapy (RT).
- Childhood cancer survivor cohorts with long-term follow-up and colorectal outcome data include individuals treated in the pre-Computed Tomography (CT) era of RT for which colorectal doses must be reconstructed.
- Computational phantoms used for RT dose reconstruction in radiation late-effects studies of childhood cancer survivors, to date, have organ models based on anatomy of a single patient.
- Since the colorectum is highly variable in shape between patients, we developed an "average" colorectal model that incorporates anatomical variations from a population of pediatric patients.

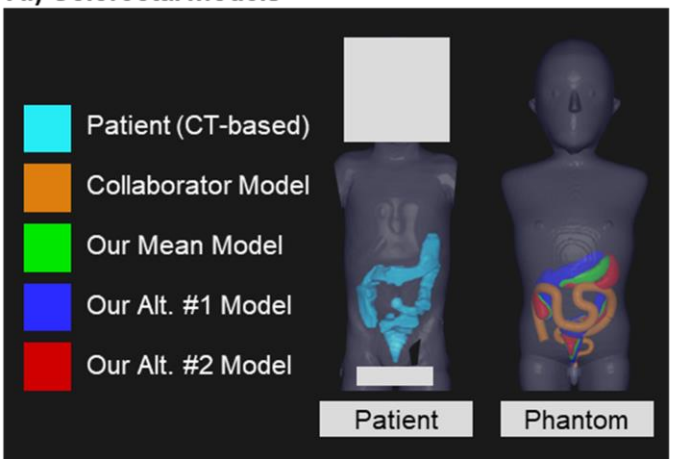
## INNOVATION/IMPACT:

- Unlike in other late effects computational phantoms, our colorectal statistical shape model (SSM):
  - Can be integrated into any computational phantom for RT dose reconstruction (**Fig. 1A**)
  - Incorporates anatomical variations of 114 unique pediatric patients (**Fig. 2**); typically, organ models are based on a single patient's organ typology
  - Can be scaled to any age at RT (**Fig. 2F**); other approaches are confined to a specific set of ages
  - Can generate alternative colorectal models to simulate different possible colorectal shapes (**Fig. 2G**)
- This is the first study to report inter-patient alignment of the colon-sigmoid-rectum (**Fig. 2C**)
- Our PCA-based SSM (**Fig. 2D**) reconstructed 10 test contours with mean Dice coefficient and distance-to-agreement of 0.89 and 2.1mm. Considering the complexity of the colon, these are great results.
- In the field of retrospective RT dosimetry (where higher dose uncertainties are observed):
  - Our results (**Fig. 3A and 3D**) are comparable to what is observed in retrospective cardiac RT dosimetry (Ntentas et al. Radiother. Oncol. 2020).
- Our colorectal model will enable:
  - Colorectal dosimetry for 12,000+ childhood cancer survivors who were treated in the pre-CT era of RT
  - Investigation of the relationship between colorectal RT dose metrics (e.g., RT mean colorectal dose) and colorectal SMN risk to develop dose-response models; current studies are limited to prescribed dose or body region dosimetry which have more uncertainties than organ-specific doses (**Fig. 3D**)
  - Alternative colorectal models (**Fig. 2G**) will be used for sensitivity analysis to see how different colorectal shapes effect dose-response models

## CLINICAL IMPACT:

- Incorporation of colon-specific RT dosimetry will establish meaningful dose-response models to [1] better inform survivorship care plans and [2] define colon/substructure RT dose constraints for RT planning
- These post-treatment and a priori planning strategies could reduce morbidity and mortality from colorectal subsequent malignant neoplasms (SMNs) in childhood cancer survivors (Daniel et al. Cancer. 2015).

**A.) Colorectal models**




**B.) Left-sided flank field**

| Dose Metric | Patient | Collab-orator | Our Mean | Our Alt. #1 | Our Alt. #2 |
|---|---|---|---|---|---|
| Mean (Gy) | 7.73 | 4.87 | 6.48* | 5.39 | 7.67* |
| Max (Gy) | 21.49 | 21.75 | 21.40 | 21.46 | 21.68 |
| V5 (%) | 37.63 | 23.35 | 31.08* | 26.10 | 36.46* |
| V10 (%) | 36.23 | 21.25 | 29.68* | 24.38 | 35.29* |
| V15 (%) | 35.53 | 20.46 | 29.39* | 23.92 | 34.97* |
| V20 (%) | 28.57 | 17.24 | 24.61 | 18.01 | 31.05 |
| D1 (Gy) | 21.07 | 21.43 | 21.02 | 21.07 | 21.26* |
| D50 (Gy) | 0.80 | 0.57 | 0.66 | 0.56 | 0.79* |
| D95 (Gy) | 0.15 | 0.12 | 0.16 | 0.13 | 0.20 |

* The median absolute difference was significantly smaller with $p<0.05$ (i.e., closer to patient data) for the respective model (Mean, Alt. #1, Alt. #2) compared to the collaborator model.

**Fig 1.** Proof-of-concept experiment. **(A)** Our in-house colorectal models were age-scaled to 5 years. The scaled models were registered with the collaborator's 5-year-old male phantom. Left- and right-sided Wilms' tumor radiation therapy (RT) plans were simulated on the CT scan of a 5-year-old male and on the collaborator's phantom. **(B)** Several RT dose metrics are reported in the table for left-sided RT plans. We repeated step (A) for 10 test patients and calculated the absolute difference between the patient (ground-truth) value and each model's value for each RT dose metric. A Wilcoxon signed-rank test was performed to compare the absolute difference in RT dose values from each of our colorectal models with the values from the collaborator's colorectal model; asterisks in table indicate statistical significance ($p<0.05$).

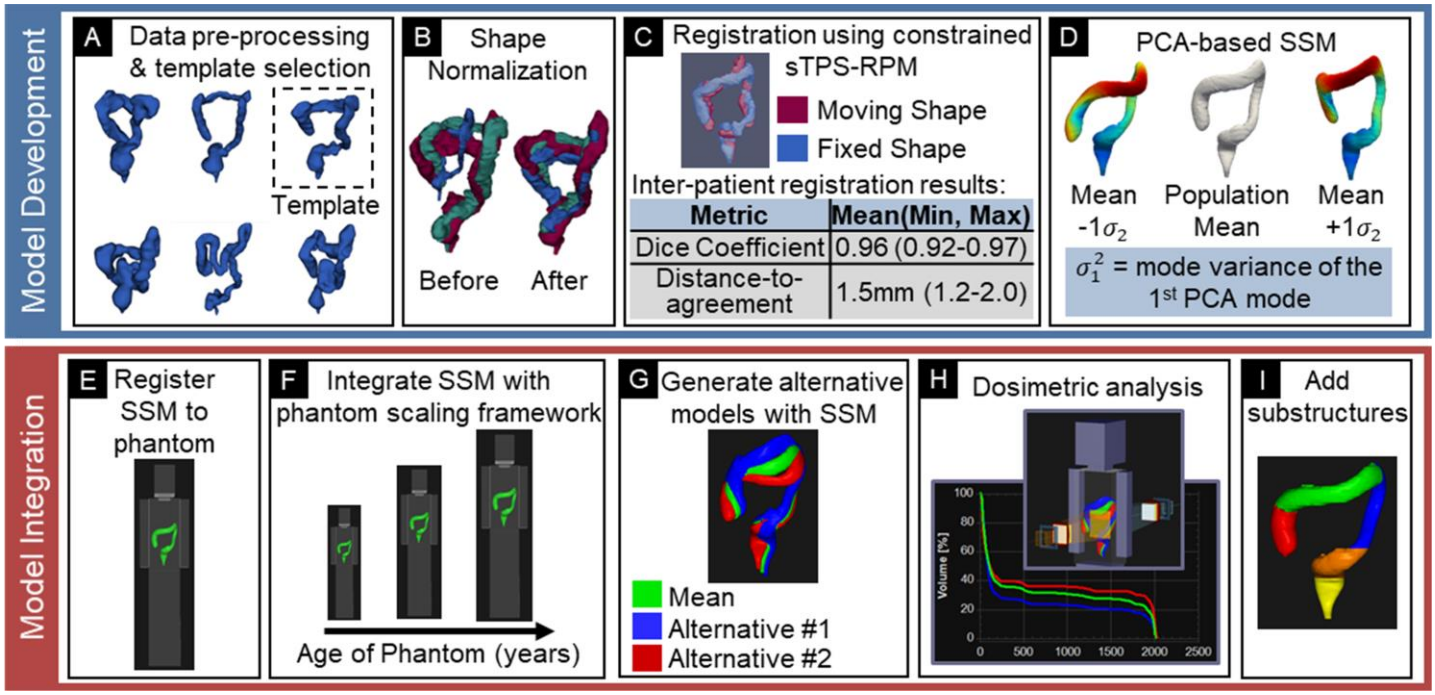
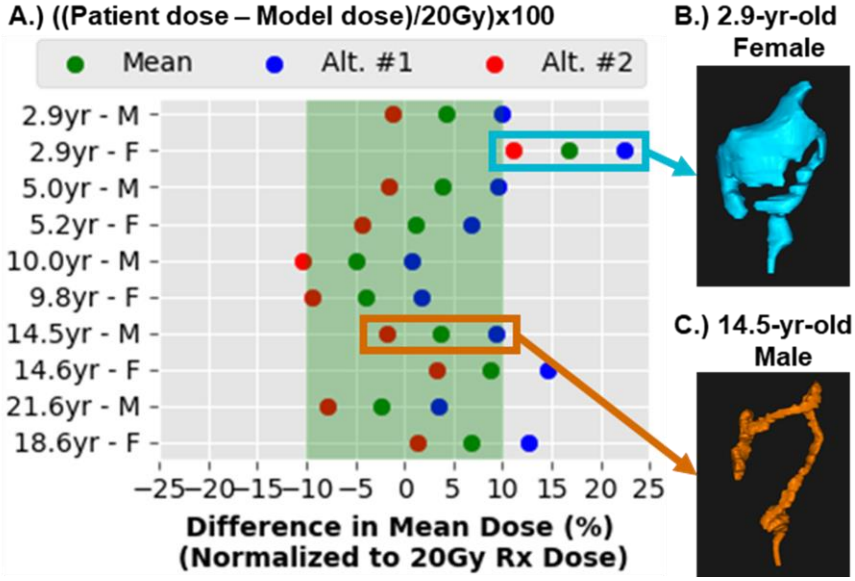



**Fig 2.** Workflow of colorectal model **(A-D)** development and **(E-I)** integration. **(A)** Each contour was pre-processed, and an anatomical template was selected. **(B)** Contours were spatially normalized. **(C)** Next, contours were registered to the anatomical template, selected in step A, using a deformable registration method, specifically the constrained symmetric thin-plate spline robust point matching (sTPS-RPM) method. **(D)** Deformed contours were used to create a principal component analysis (PCA)-based colorectal statistical shape model (SSM) to extract the dominant deformation modes of the population; shown is the 1st PCA mode. **(E)** The SSM was registered to an in-house phantom and **(F)** was integrated with the phantom's age-based scaling functions. **(G)** Next, two alternative colorectal models (alternative #1 and #2) were generated using the SSM. **(H)** The three colorectal models from step G were analyzed dosimetrically and compared with patient-specific CT-based dosimetric data. **(I)** Future work includes delineating colorectal substructures.




**D.) Mean dose (Left-sided flank field)**

| Age (yrs) | Sex | Rx | Mean Dose (Gy) Patient | Mean Model | Alt #1 Model | Alt #2 Model |
|---|---|---|---|---|---|---|
| 2.9 | M | 20 | 7.89 | 7.03 | 5.89 | 8.13 |
| 2.9 | F | 20 | 10.29 | 6.94 | 5.79 | 8.05 |
| 5.0 | M | 20 | 7.73 | 6.96 | 5.84 | 8.04 |
| 5.2 | F | 20 | 7.18 | 6.96 | 5.83 | 8.05 |
| 10.0 | M | 20 | 5.86 | 6.84 | 5.72 | 7.92 |
| 9.8 | F | 20 | 6.01 | 6.80 | 5.68 | 7.88 |
| 14.5 | M | 20 | 7.61 | 6.89 | 5.75 | 7.98 |
| 14.6 | F | 20 | 8.52 | 6.78 | 5.59 | 7.87 |
| 21.6 | M | 20 | 6.54 | 7.04 | 5.85 | 8.13 |
| 18.6 | F | 20 | 8.19 | 6.83 | 5.65 | 7.92 |

Rx = Prescription; Patient = CT-based dose; Mean, Alt #1, Alt #2 = dose from colorectal models within age-matched phantoms

**Fig 3.** **(A)** The difference in mean dose (prescription normalized) is within 10% for most test patients for left-sided flank field RT plans. **(B)** Colorectum contour for a patient (2.9-year-old female) for whom the dose difference was greater than 10% due to atypically enlarged transverse colon due to gas/constipation. **(C)** Colorectum contour for a patient (14.5-year-old male) with a more typical shaped colorectum for whom dose differences for all models were within ± 10%. **(D)** The table compares prescription dose (a commonly used RT dose surrogate in late effects studies) with the patient CT-based dose and the colorectal model-derived doses. Colorectal mean doses for the test cases ranged from of 5.86 to 10.29Gy; If prescription doses were used for dose-response modeling, doses would be overestimated by 200% to 400%, which is much greater than the dose reconstruction uncertainty observed with our colorectal models.