

Author list: * co-senior authors

Name	Degree/ Credentials	Institution, Department, City, State/Province, Country
Constance A. Owens	<i>PhD</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA
Ethan B. Ludmir	<i>MD</i>	The University of Texas MD Anderson Cancer Center, Department of Gastrointestinal Radiation Oncology, Houston, TX, USA The University of Texas MD Anderson Cancer Center, Department of Biostatistics, Houston, TX, USA
Qi Liu	<i>MSc</i>	Department of Public Health Sciences, University of Alberta, Edmonton, AB
Weiyu Qiu	<i>MS</i>	Department of Public Health Sciences, University of Alberta, Edmonton, AB
Bastien Rigaud	<i>PhD</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA
Susan A. Smith	<i>MPH</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA
Aashish C. Gupta	<i>MS</i>	The University of Texas MD Anderson Cancer Center, Department of Imaging Physics, Houston, TX, USA
Kristy K. Brock	<i>PhD</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA The University of Texas MD Anderson Cancer Center, Department of Imaging Physics, Houston, TX, USA
James E. Bates	<i>MD</i>	Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA
Taylor G. Meyers	<i>MS</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA
Arnold C. Paulino	<i>MD</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX, USA
Christine B. Peterson	<i>PhD</i>	The University of Texas MD Anderson Cancer Center, Department of Biostatistics, Houston, TX, USA
Stephen F. Kry	<i>PhD</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA
Joseph P. Neglia	MD, MPH	University of Minnesota, Department of Pediatrics, Minneapolis, MN, USA
Wendy M. Leisenring	MS, Sc.D.	Fred Hutchinson Cancer Center, Clinical and Public Health Sciences Divisions, Seattle, WA, USA
Kevin C. Oeffinger	MD	Duke University, Department of Medicine, Durham, NC, USA
Paul C. Nathan	MD, M.Sc.	The Hospital for Sick Children, Division of Paediatric Hematology/Oncology, Toronto, ON, CA
Lucie M. Turcotte	MD, MPH, MS	University of Minnesota, Department of Pediatrics, Minneapolis, MN, USA
David Hodgson	MD, MPH	University of Toronto, Department of Radiation Oncology, Toronto, ON, CA
Melissa M. Hudson	MD	St. Jude Children's Research Hospital, Department of Oncology, Memphis, TN, USA
Leslie L. Robison	PhD	St. Jude Children's Research Hospital, Department of Epidemiology and Cancer Control, Memphis, TN, USA
Chaya Moskowitz	<i>PhD</i>	Memorial Sloan Kettering Cancer Center, Department of Epidemiology and Biostatistics, New York, NY, USA
Gregory T. Armstrong	<i>MD, MSCE</i>	St. Jude Children's Research Hospital, Department of Epidemiology and Cancer Control, Memphis, TN, USA
Yutaka Yasui*	<i>PhD</i>	Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, USA
Tara O. Henderson*	<i>MD, MPH</i>	The University of Chicago, Comer Children's Hospital, Chicago, IL, USA
Rebecca M. Howell*	<i>PhD</i>	The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, USA

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Subsequent colorectal cancer risk in the Childhood Cancer Survivor Study: Colorectal-specific RT dose-volume and chemotherapy effects

Abstract (299/300 words)

Background/Purpose: Previous colorectal subsequent malignant neoplasm (SMN) risk studies have been limited to broad radiation therapy (RT) metrics to the abdominal and/or pelvic region. Using novel colorectum- and substructure-specific RT dose metrics, we evaluated colorectal SMN risk from RT and chemotherapy.

Methods: Among 25,723 five-year cancer survivors diagnosed <21 years of age in the Childhood Cancer Survivor Study (CCSS) with median follow-up of 29.9 years (range=5.0-48.9), 104 pathology-confirmed colorectal SMNs were identified. We estimated mean RT dose to the whole colorectum and its substructures. We also calculated the percent volume receiving 5(V_5), 10(V_{10}), 20(V_{20}), 30(V_{30}) and 40(V_{40}) Gy and maximum RT dose to the whole colorectum. Chemotherapy cumulative dose exposures included cyclophosphamide-equivalent dose (CED) for alkylating agents and procarbazine. Multivariable piecewise exponential models evaluated the incident rate ratio (IRR) of colorectal SMN in association with RT and chemotherapy.

Results: A dose-response relationship was observed for mean RT dose ≥ 10 Gy to the colorectum or any substructure (all $p < 0.05$, except sigmoid). For mean RT dose 10- < 20 Gy and ≥ 20 Gy to the whole colorectum vs. no exposure, the IRRs were 3.6(95%CI=1.9-6.9) and 8.3(95%CI=3.9-17.8), respectively. For each dose-volume metric, risk increased with increasing irradiated colorectal volume for $\geq 20\%$ volume; e.g., for V_{20} the IRR was 3.8(95%CI=1.9-7.6), 4.9(95%CI=2.0-12.0) and 8.7(95%CI=3.5-21.6) for irradiated volumes of 20- $< 40\%$, 40- $< 80\%$ and $\geq 80\%$, respectively. The IRR was 3.7(95%CI=2.2-6.4) for alkylating CED ≥ 6000 mg/m² vs. no exposure. For procarbazine CED, the IRR was 6.3(95%CI=3.0-13.2) for 4200- < 7036 mg/m² and 9.0(95% CI 4.3-18.9) for ≥ 7036 mg/m² vs. no exposure. High risk (IRR=22.7, 95%CI=10.6-48.8) was observed for survivors who received whole colorectal mean RT doses ≥ 10 Gy and procarbazine CED ≥ 4200 mg/m² vs. those with < 10 Gy and < 4200 mg/m².

Conclusion: These RT and chemotherapy effects can be used to better inform contemporary RT planning for newly diagnosed children and guide stratification of screening guidelines for those at high risk of colorectal cancer.