Stomach cancer risk after treatment for Hodgkin lymphoma

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SUPPLEMENTARY APPENDIX

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Supplementary Methods

Study Population

Cohort of 17,447 HL patients derived from six population-based cancer registries. Patients who survived ≥5 years following first primary, histologically confirmed Hodgkin lymphoma (HL) as reported to population-based cancer registries in Denmark (1943-1999), Finland (1953-2002), Norway (1953-2000), Sweden (1958-2002), Iowa (United States, 1973-2001), or Ontario (Canada, 1964-2003) were potentially eligible (N=17,447). Registry reports identified 81 cases with second primary invasive stomach cancer occurring ≥5 years after HL, without other intervening invasive cancer (except non-melanoma skin cancer) or bladder carcinoma *in situ*. Medical records were available for 72 (89%) cases. Records were more frequently available for cases diagnosed in 1975 or later (30/30, 100%) than for cases diagnosed before 1975 (42/51, 82%) because medical records from earlier years were more likely to have been destroyed or lost.

For cases with available medical records, two controls per case were identified by stratified random sampling from the cohort, individually matching by registry, race (Iowa only; study population was 99% Caucasian), birth date (±5 years), HL diagnosis date (±5 years), and survival without subsequent cancer at least as long as the matched case's interval from HL to stomach cancer. Patients from Norway also were matched on hospital of HL diagnosis (Radium Hospital versus all others). Medical records were obtained for 96% of initially eligible controls. The record availability was slightly higher for controls than for cases because we only sought controls for those cases with available medical records. One case was excluded because no appropriate controls were found, resulting in 71 cases and 142 matched controls from these six registries.

Dutch hospital-based cohort of 2,435 HL patients. Individual-level patient data were obtained from a previous Dutch hospital-based case-control study of second primary stomach cancer among ≥5-year survivors of HL and testicular cancer diagnosed during 1966-2005 (42 cases, 126 matched

controls).[1] In that study, up to 4 controls were individually matched to each case by sex, age at first primary cancer diagnosis, year of first primary cancer diagnosis, and survival without subsequent cancer at least as long as the matched case's interval from first primary cancer to stomach cancer. For this analysis, we restricted patients to those with first primary HL (18 cases, 48 matched controls). Radiotherapy records were obtained for the completion of uniform radiation dosimetry (described below). Combining the Dutch patients with the international, multi-center nested case-control study yielded a final analytic population of 89 cases and 190 individually-matched controls.

Chemotherapy Data

Detailed data from all available records (hospital, clinic, pathology, radiology, surgery, radiotherapy, registry) were abstracted onto standardized forms. Abstracted data on chemotherapy included dates and route of administration, reason for treatment (primary or recurrence), and specific regimens or drugs. For alkylating agents (AAs) and topoisomerase II inhibitors, dose and duration also were recorded. Analyses considered the cumulative drug dose (mg), including all treatments given prior to the date of stomach cancer diagnosis or comparable date for controls, according to patients' body surface area (BSA) as recorded in the medical record or computed from height and weight [BSA (m^2)=(71.84 $\times$ weight (kg)$^{0.425}$ $\times$ height (cm)$^{0.725}$)/10,000 according to Du Bois].[2] For patients with missing data on dose for a specific drug, the dose was imputed based on other cycles with known dose for the individual, or based on typical HL regimens used during the specified calendar period for each registry. For example, for procarbazine, the dose for at least one cycle (or one month for continuous chemotherapy) was imputed for 12 cases and 19 controls, representing 12% and 14%, respectively, of the total procarbazine doses. Data on BSA (or height/weight) were missing for 8 cases and 21 controls, for whom BSA was imputed based on sex, age, and administered dose of drugs in standard chemotherapy regimens.

Initial treatment was defined from the start of treatment until the occurrence of a >3 month period without treatment. All treatments that occurred after that period were considered subsequent therapy.

Radiation Dosimetry

Abstracted radiotherapy details included dates of administration, reason for treatment, beam energy, dose delivered, and field location and configuration. Detailed radiotherapy data were available for 204/246 (83%) patients receiving radiotherapy, and the overall data obtained were sufficient for dosimetry for all patients who received radiotherapy except 2 (2%) cases and 9 (5%) controls. Radiation doses to the stomach were estimated using a custom-designed dose program, based on measurements in water and anthropomorphic phantoms constructed of tissue-equivalent material.[3]

The stomach size, shape, and location exhibit intra- and inter-individual variation depending on stomach contents, phase of respiration, abdominal muscle tone, and body build.[4] The exact stomach position was unknown for individual patients in the study and likely varied over the course of radiotherapy. Based on comprehensive literature review of stomach morphology, our primary analyses used a typical "J-shaped" stomach for a patient in the treatment (recumbent) position (Figure 1).[5] This stomach represents a typical stomach shape for a normal weight adult with no known stomach pathology. Using individual patient treatment parameters, dose was calculated to 464 points in the stomach for this typical stomach configuration, summing all radiotherapy treatments received ≥5 years preceding stomach cancer diagnosis (comparable date for controls); only 3 patients received radiotherapy exclusively within five years of stomach cancer diagnosis (comparable date for controls). Analyses of radiotherapy risks used the mean dose to the stomach tumor location (same location for matched controls), specified as the cardia, fundus, body, lesser curvature, greater curvature, antrum, or pylorus (Figure 1).

For the conduct of sensitivity analyses, we estimated radiation dose to two alternative stomach configurations that represent the typical variation expected in the population for patients in the recumbent position (Supplementary Figure 1).[6,7] The first alternative stomach configuration, which has been correlated with massive body build and higher weight, represents a higher than usual position and reduces the lateral distance between the spine and lesser curvature of the stomach. In contrast, the second alternative stomach configuration, which has been correlated with thinner body build and lower weight, represents a lower than usual position and slightly increases the lateral distance between the spine and lesser curvature of the stomach.

Radiation dose was calculated to specific points in the stomach for all three stomach configurations, summing all radiotherapy treatments received ≥5 years preceding stomach cancer diagnosis (comparable date for controls). Analyses of radiotherapy risks used the mean dose to the stomach tumor location (same location for matched controls), specified as the cardia, fundus, body, lesser curvature, greater curvature, antrum or pylorus. The estimated dose to the tumor location for the typical stomach configuration was highly correlated to the estimated dose for each alternative stomach configuration (alternate configuration #1 and #2, r=0.97 and 0.98, respectively).

We conducted sensitivity analyses assuming that all patients had each alternative stomach configuration. The elevated risk of stomach cancer associated with ≥25 Gy radiation to the site of the stomach tumor based on the typical stomach configuration (OR=5.8, 95%CI 3.0-12.0) remained significantly elevated but was slightly attenuated when the radiation dose was estimated to the two alternative stomach configurations (OR=4.5, 95%CI 2.4-8.9 and OR=4.9, 95%CI 2.6-9.9; Supplementary Table 2). Similarly, the supra-multiplicative effect of ≥25 Gy radiation and ≥5600 mg/m^2 procarbazine remained statistically significant for both alternative stomach configurations (P=0.01 and 0.004), and the risk estimates associated with ≥25 Gy radiation regardless of procarbazine dose remained significantly elevated albeit with attenuated magnitude.

References

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Supplementary Table 1. Risk of stomach cancer associated with receipt of dacarbazine-containing chemotherapy for HL.

	No dacarbazine		Any dacarbazine				
	Cases	Controls	Cases	Controls			
Patient characteristic	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**OR (95% CI) ***		**$P_{homogeneity}$ †**
Age at HL diagnosis (years)							
<30	36 (47%)	90 (50%)	6 (50%)	4 (44%)	8.0	(1.2 , 74.5)	
≥30	41 (53%)	91 (50%)	6 (50%)	5 (56%)	9.9	(1.2 , 212)	0.63
Age at stomach cancer diagnosis (years)							
<50	34 (44%)	89 (49%)	8 (67%)	4 (44%)	13.9	(2.1 , 131)	
≥50	43 (56%)	92 (51%)	4 (33%)	5 (56%)	4.7	(0.4 , 110)	0.73
Interval from HL to stomach cancer (years)							
<15	34 (44%)	75 (41%)	7 (58%)	6 (67%)	12.0	(1.5 , 261)	
≥15	43 (56%)	106 (59%)	5 (42%)	3 (33%)	5.9	(0.9 , 51.0)	0.52
Radiation dose (Gy) ‡							
<25	32 (43%)	130 (75%)	7 (58%)	8 (100%)	5.4	(1.1 , 30.2)	
≥25	43 (57%)	43 (25%)	5 (42%)	0 (0%)	∞	(2.3 , ∞)	0.19
Procarbazine dose (mg/m^2)							
<5600	43 (56%)	136 (75%)	6 (50%)	6 (67%)	9.5	(1.7 , 68.7)	
≥5600	34 (44%)	45 (25%)	6 (50%)	3 (33%)	6.0	(0.8 , 129)	0.76

* OR (95%CI) was adjusted for radiation dose [unknown (2 cases, 9 controls); <25, ≥25 Gy] and procarbazine dose (<5600, ≥5600 mg/m^2), except when these characteristics were under evaluation.

† $P_{homogeneity}$ calculated using a likelihood ratio test.

‡ Radiation dose was estimated to the specific site of the stomach tumor (matched location for controls).

Supplementary Table 2. Risk of stomach cancer after HL in relation to radiation dose to the stomach and procarbazine dose, with radiation dose estimated to the typical and alternate stomach configurations (see Supplementary Figure 1).

		Typical stomach configuration			Alternative stomach configuration #1			Alternative stomach configuration #2		
		Cases (N=89)	Controls (N=190)		Cases (N=89)	Controls (N=190)		Cases (N=89)	Controls (N=190)	
HL treatment		**N (%)**	**N (%)**	**OR (95% CI)**	**N (%)**	**N (%)**	**OR (95% CI)**	**N (%)**	**N (%)**	**OR (95% CI)**
Radiation dose (Gy) *										
<25		39 (45%)	138 (76%)	1.0 (referent)	37 (43%)	129 (71%)	1.0 (referent)	38 (44%)	135 (75%)	1.0 (referent)
≥25		48 (55%)	43 (24%)	5.8 (3.0 , 12.0)	50 (57%)	52 (29%)	4.5 (2.4 , 8.9)	49 (56%)	46 (25%)	4.9 (2.6 , 9.9)
P_{trend} †				<0.001			<0.001			<0.001
Radiation dose (Gy)	Procarbazine dose (mg/m^2) ‡									
<25	<5600	25 (29%)	94 (52%)	1.0 (referent)	23 (26%)	88 (49%)	1.0 (referent)	25 (29%)	94 (52%)	1.0 (referent)
≥25	<5600	23 (26%)	41 (23%)	2.8 (1.3 , 6.4)	25 (29%)	47 (26%)	2.6 (1.2 , 5.7)	23 (26%)	41 (23%)	2.6 (1.2 , 5.9)
<25	≥5600	14 (16%)	44 (24%)	1.2 (0.5 , 2.7)	14 (16%)	41 (23%)	1.3 (0.5 , 3.0)	13 (15%)	41 (23%)	1.1 (0.5 , 2.5)
≥25	≥5600	25 (29%)	2 (1%)	77.5 (14.7 , 1452)	25 (29%)	5 (3%)	19.1 (6.5 , 73.1)	26 (30%)	5 (3%)	24.3 (7.7 , 111)
$P_{interaction}$ §				<0.001			0.01			0.004

Abbreviations: confidence interval (CI), Gray (Gy), odds ratio (OR).

* OR (95%CI) was adjusted for procarbazine dose (<5600, ≥5600 mg/m^2), receipt of any dacarbazine, and unknown radiation dose (2 cases, 9 controls). Patients with unknown radiation dose were excluded from percentages. Radiation dose was estimated to the specific site of the stomach tumor (matched location for controls).

† P_{trend} in radiation dose was calculated using a continuous variable on a linear scale.

‡ OR (95%CI) was adjusted for receipt of any dacarbazine and unknown radiation dose (2 cases, 9 controls).

§ $P_{interaction}$ between radiation and procarbazine was calculated using a likelihood ratio test under the multiplicative model.

Supplementary Figure 1. Typical and alternate stomach configurations used for radiation dose reconstruction, as described in the Methods.