Cancer Following Radiotherapy for Peptic Ulcer

*Melvin L. Griem, Ruth A. Kleinerman, John D. Boice, Jr., Marilyn Stovall, Deborah Shefner, Jay H. Lubin**

Background: **Radiotherapy for peptic ulcer was used between 1937 and 1965 to control excessive gastric acid secretions (mean dose, 14.8 Gy). Patients with this benign condition live many years after treatment and are at risk for late effects.** ***Purpose:*** **Our purpose was to investigate the risk of death from cancer following radiotherapy for peptic ulcer.** ***Methods:*** **A mortality study was conducted of 3609 patients with peptic ulcer; 1831 were treated with radiation and 1778 were treated by other means. Extensive methods were used to trace patients. Radiation doses to specific organs were reconstructed from the original radiotherapy records.** ***Results:*** **Nearly 70% of patients were found to have died. The average period of observation was 21.5 years (maximum 51 years). Compared with the general population, patients treated with or without radiation were at significantly increased risk of dying of cancer and nonmalignant diseases of the digestive system. Risk of death due to heart disease was slightly higher following radiotherapy. Cancers of the stomach, pancreas, lung, and prostate were increased in both irradiated and nonirradiated patients. Radiotherapy was linked to significantly high relative risks (RRs) for all cancers combined (RR = 1.53; 95% confidence interval ICI] = 1.3-1.8), for cancers of the stomach (RR = 2.77; 95% CI = 1.6-4.8), pancreas (RR = 1.87; 95% CI = 1.0-3.-4), and lung (RR = 1.70; 95% CI = 1.2-2.4), and for leukemia (RR = 3.28: 95% CI = 1.0-10.6). Radiation combined with surgery, or given to treat gastric ulcer, appeared to increase the risk of stomach cancer 10-fold, which was greater than the sum of individual effects. Patients with gastric ulcers were at higher risk for stomach cancer than patients with duodenal ulcers.** ***Conclusions:*** **Patients with peptic ulcer are at increased risk of dying of cancer, related in part to lifestyle factors and treatment. Radiotherapy and surgery together appear to induce carcinogenic processes that greatly enhance the development of stomach cancer. The risk of radiation-induced stomach cancer was 0.25 extra deaths per 10 000 persons per year per Gy, somewhat lower than reported in other studies. High-dose radiation may have increased the risk of pancreatic cancer, a condition rarely found elevated in irradiated populations, but misclassified death notices may have contributed to the excess. Cancer mortality remained high for up to 50 years, indicating that radiation damage may persist to the end of life. [J Natl Cancer Inst 86:842-849, 1994]**

Ionizing radiation is known to increase the occurrence of many forms of cancer. but quantitative estimates of risk are often uncertain due to imprecise dosimetry and limited periods of observation *(1).* Radiation studies of patients with benign conditions provide valuable information on cancer effects be-

**Affiliations of authors:* M. L. Griem. D. Shefner, Department of Radiation Oncology. University of Chicago. Ill.

R. A. Kleinerman. J. D. Boice. Jr., J. H. Lubin. Epidemiology and Biostatistics Program. National Cancer Institute, Bethesda, Md.

M. Stovall, Department of Radiation Physics, University of Texas System Cancer Center, Houston.

Correspondence to: Melvin L. Griem, M.D., Department of Radiation Oncology. University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637.

See "Notes" section following "References."

cause organ doses can be estimated accurately, survival after treatment is good, and nonexposed patients are often available for comparison. Patients treated with radiation for peptic ulcer (mean dose, 14.8 Gy) present a new opportunity to evaluate the risk of cancer in organs that received more than 1 Gy of radiation, such as the stomach, lung, and pancreas. Previous studies *(2-11)* of peptic ulcer patients have linked increased cancer rates to lifestyle factors, including tobacco use, and to surgical sequelae. The purpose of this study was to evaluate these factors in concert with radiation exposure. To control for any influence that the underlying disease or lifestyle factors might have on cancer risk, a group of patients not treated with radiation was selected for comparison.

Patients and Methods

Study Population

A total of 4577 patients treated for peptic ulcer at the University of Chicago between 1937 and 1965 were identified. Radiotherapy to the gastric fundus was given to 2057 patients to reduce acid production *(12-14)*. For comparison, 2520 patients treated by other means, including surgery, were identified from hospital records. A total of 968 patients were subsequently excluded because medical records were not available (n = 219), death occurred within I year of treatment (n = 108). ulcer diagnosis was not confirmed (n = 147). there was no follow-up beyond ulcer diagnosis (n = 326), or other reasons (n = 168). The final population included 1831 exposed and 1778 nonexposed patients. All radiotherapy patients and 763 of the 1778 medically managed patients had been previously studied *(13,15)*. In the current study. we included more than double the number of nonexposed patients, conducted a more comprehensive and complete follow-up, and computed radiation doses to each organ for each individual.

Study patients were predominantly white male professionals born before 1910 (Table l). Characteristics of irradiated and nonirradiated patients were similar, although the calendar years of treatment were somewhat earlier among the nonexposed, More than one half of the patients smoked cigarettes, with irradiated patients tending to smoke more heavily. A little more than 85% of the ulcers were duodenal and almost 9% were gastric. Partial gastrectomy occurred twice as frequently among the nonexposed (16.2%) compared with the irradiated (8.6%) patients.

Patient Follow-up

A comprehensive effort was mounted to obtain information on cause of death for all patients. Follow-up methods included searching the records of vital statistics offices in the state of last known residence and accessing mortality information available from the National Death Index. Social Security Administration. Department of Veterans Affairs. Health Care Financing Administration. and death indices of several states. Other location resources included city and telephone directories. town halls, local newspapers. relatives, credit bureaus. employers. unions, churches, synagogues. and professional associations.

As of January 1, 1985. 70% of the 3609 patients had died, 17% were still alive, and 13% were lost to follow-up. Comparisons between the located and unlocated patients revealed no peculiar differences in demographic or treatment characteristics. Death certificates were obtained for 96% of those who died. All causes of death were reviewed and coded by a nosologist. using the eighth revision of the International Classification of Diseases *(16)*.

Radiation Organ Doses

Estimates of radiation dose absorbed by organs were based on experimental measurements and a review of individual radiotherapy records. Treatments were highly stylized *(13)*. Almost all treatments used 13 x 13 cm fields, parallel-opposed anterior and posterior, centered on the stomach (Fig. 1). Several machines were used: with rare exceptions, these were orthovoltage x-ray machines operated at half-value layers of 1.3-1.5 mm Cu. The average total dose to the stomach was 14.8 Gy, and the average total dose to the midpoint of the stomach was 17 Gy. The average daily dose to the stomach was approximately 1.5 Gy delivered during about a 5-minute period. Duration of treatment ranged from 6 to 14 days.

The machine used to treat one half of the patients, a General Electric Maxitron 250 kVp x-ray unit, (GE Medical Systems, Milwaukee, Wis.) was available for experimerrtsl measurements. Lithium fluoride thermoluminescent dosimeters were placed throughout the organs of interest its art adult Alderson anthropomorphic phantom. One of the radiotherapists (M. L. Griem), who had treated many of the study patients. verified the exposure conditions, including the use of a closed-end cone and lead-rubber shielding around the cone. Table 2 lists the average dose to selected organs from a typical treatment. All of the stomach, pancreas, and spleen and portions of the left kidney, colors, liver, esophagus, left lung, and rib cage were in the direct field of radiation and received greater than 10 Gy to the areas irradiated. Scatter radiation of more than 1 Gy was received by the right kidney, gallbladder, small intestine, and heart. When only part of art organ was in the direct beam of the x-ray machine during treatment, the radiation dose was not equally distributed throughout the organ. For example, parts of the colon received 12 Gy and other parts of the colon received much less-only 0.1 Gy. For dose–response analyses and risk estimation, a mean organ dose was used. Computation of the mean organ dose took into account the nonuniform distribution of dose throughout the organ [cf. *(17)*].

Statistical Methods

The risk of radiation-induced cancer was estimated by comparing the mortality experience of irradiated patients and nonexposed patients. Person-years (1 person-year = the observation time contributed by one person followed for 1 year) were computed beginning 1 year after the date of treatment. The end of follow-up was the date of death for those who died, January 1, 1985, for those located alive, and the date last known to be alive for those lost to follow-up. Standardized mortality ratios (observed/expected [O/E] numbers of deaths) were computed, with the expected numbers of deaths estimated by multiplying the age-. sex-, race-, and calendar-year-specific person-years of observation times the corresponding age-. sex-, race-, and calendar-year-specific mortality rates from the general population of the United States-available back to 1925 for most causes *(18)*. Mortality rates for the endocrine system and for lymphomas were available only after 1950. A Poisson regression procedure was used to fit the model of relative risk (RR). This model relied on internal comparisons based on the nonexposed patient group. Maximum likelihood parameter estimates, likelihood ratio tests for nested models, and likelihood-based confidence intervals were obtained using the AMFIT regression program *(19)*.

In all analyses, RRs were adjusted using the categorical variables for smoking. sex, time since diagnosis. age, and calendar year (shown in Table 1). For stomach cancer. ulcer type and surgical status were also included. Radiation risk coefficients and dose–response analyses were based on the excess relative risk model, rate *(x*, D) = $_s$(1 + β D), where D is the organ dose and $_s$ are the parameters associated with the stratification factors *(x)*. Significance refers to *P* value <.05.

Results

Patients were treated with radiation for peptic ulcer between 1937 and 1965 (mean, 1950); the average age at radiotherapy was 49 years. The nonexposed ulcer patients were treated between 1929 and 1959 (mean, 1945), and their average age at treatment was 46 years. The average period of observation was 21.5 years; it was slightly longer for the nonexposed patients. Overall, 77 757 person-years of observation were accrued, 35 815 among the irradiated and 41 942 among the nonexposed patients.

Among the 1831 patients treated with radiation, 1294 deaths were recorded, representing a 32% excess over that expected based on general population rates (Table 3). Among the 1778 nonexposed patients, 1224 deaths occurred, compared with 1191 expected. For both irradiated and nonexposed patients, significant excesses of deaths were seen for nonmalignant diseases of the digestive system, reflecting, in large part, complications associated with peptic ulcer. Compared with the general popula-

Table 1. Characteristics of patients with peptic ulcer by radiotherapy status

Characteristic	Radiotherapy: Yes, No. of patients	Yes, %	Radiotherapy: No, No. of patients	No, %
All patients	1831	100	1778	100
Year of birth				
<1890	322	17.6	388	21.8
1890-1899	502	27.4	485	27.3
1900-1909	565	30.9	529	29.8
≥1910	442	24.1	376	21.1
Year of treatment				
<1940	226	12.3	507	28.5
1940-1944	400	21.8	424	23.8
1945-1949	313	17.1	487	27.4
1950-1959	756	41.3	360	20.2
≥1960	136	7.4	0	0.0
Age at treatment, y				
<35	268	14.6	398	22.4
35-44	483	26.4	524	29.5
45-54	540	29.5	482	27.1
≥55	540	29.5	374	21.0
Sex				
Male	1479	80.8	1366	76.8
Female	352	19.2	412	23.2
Race				
White	1719	93.9	1754	98.6
Black	59	3.2	9	0.5
Other or unknown	53	2.9	15	0.8
Religion				
Protestant	647	35.3	698	39.2
Catholic	537	29.3	581	32.7
Jewish	248	13.5	180	10.1
Other	59	3.2	51	2.9
Unknown	340	18.6	268	15.1
Occupation				
Nonprofessional	605	33.0	582	32.7
Professional	1136	62.0	1135	63.8
Other or unknown	90	4.9	61	3.4
Cigarette habits*				
Never smoked	435	23.8	482	27.1
Smoked	1078	58.8	952	53.5
Unknown	318	17.4	344	19.4
Quantity of cigarettes smoked*				
≤1 pack per day	724	67.2	699	73.4
>1 pack per day	320	29.7	222	23.3
Unknown	34	3.2	31	3.3
Alcohol habits*				
Never drank	606	33.1	621	34.9
Drank	862	47.1	762	42.9
Unknown	363	19.8	395	22.2
Quantity of alcohol*				
≤5 drinks per week	423	49.1	366	48.0
6-15 drinks per week	151	17.5	119	15.6
>15 drinks per week	179	20.8	139	18.3
Unknown	109	12.6	138	18.1
Type of ulcer				
Duodenal	1567	85.6	1483	83.4
Gastric	158	8.6	165	9.3
Duodenal or gastric	24	1.3	29	1.6
Other	65	3.5	48	2.7
Unknown	17	0.9	53	3.0
Type of surgery (ever)†				
None	1386	75.7	1208	67.9
Partial gastrectomy				
Billroth I	70	3.8	76	4.3
Billroth II	63	3.4	183	10.3
Other	25	1.4	28	1.6
Total gastrectomy	7	0.4	9	0.5
Gastrostomy	41	2.2	50	2.8
Vagotomy	311	17.0	422	23.7
Vital status (1/1/85)				
Alive	292	15.9	328	18.4
Dead	1294	70.7	1224	68.8
Lost to follow-up	245	13.4	226	12.7

*At time of ulcer treatment at University of Chicago.
†Totals more than 100% because some patients had more than one type of surgery or the same surgery more than once.

tion in the United States, patients treated with radiation were at a significantly increased risk for death due to all cancers (O/E = 1.85) and diseases of the circulatory system (O/E = 1.18). Mortality among nonexposed patients was significantly increased for all cancers (O/E = 1.19) but not for diseases of the circulatory system; mortality was significantly decreased for infections and diseases of the endocrine system. The significant difference in all-cause mortality between irradiated and nonexposed patients (RR = 1.23) was mainly due to cancer (RR = 1.53) and to circulatory disease (RR = 1.20).

Table 4 shows the distribution of observed and expected cancer deaths for both treatment groups. Among the irradiated patients, significant excesses were noted for cancers of the stomach, large intestine, pancreas, lung, breast, and prostate. Among the nonexposed patients, only cancers of the lung and prostate were significantly increased in comparison with rates from the general population. Contrasting irradiated patients with nonexposed patients, significant increases were noted for cancers of the stomach (RR = 2.77), lung (RR = 1.70), and pancreas (RR = 1.87) and for leukemia (RR = 3.28). Cancers of female genital organs were significantly decreased (RR = 0.0). The risk of nonchronic lymphocytic leukemia (RR = 2.75), however, was not significantly elevated. Breast cancers occurred in three men, one among the irradiated patients (0.21 expected) and two among the nonexposed patients (0.24 expected). One of the nonexposed men with breast cancer had a prior cancer of the prostate.

For all cancers combined, the RRs following radiotherapy were 1.49, 1.42, 1.58, 1.85, and 2.08 for those followed between 1-9, 10-19, 20-29, 30-39, and 40-51 years,.respectively. No variation in RRs over time was seen for cancers of the stomach, pancreas, and lung (data not shown). No consistent patterns with time were seen for other cancers, in large part due to the small numbers involved.

Significant risks of stomach cancer were associated with radiotherapy (RR = 2.8), partial gastrectomy (RR = 2.6) com-

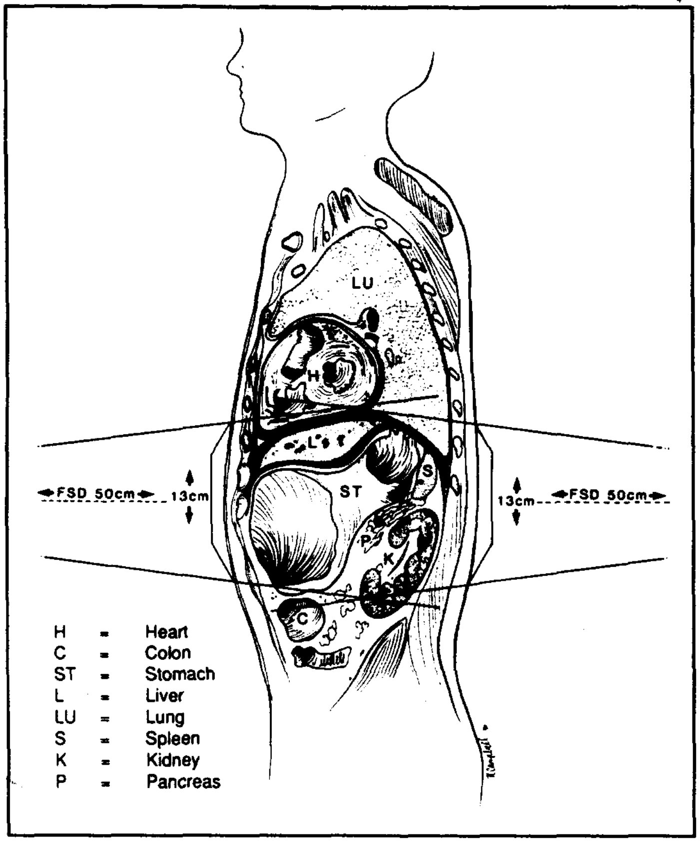

Fig. 1. Anatomical parasagittal section of the chest and abdomen 5 cm left of the midline. The diagram superimposed represents the x-ray beam geometry showing the focal skin distance (FSD) and port size in relation to the organs of the left lower chest and upper abdomen. Adaptation of the above illustration made courtesy of Rohen/Yokochi: Color Atlas of Anatomy, Igaku-Shoin Medical Publishers, 1984.

pared with no surgery. and gastric ulcer (RR = 3.7) compared with duodenal ulcer (Tables 4 and 5). The combination of radiotherapy with surgery or radiotherapy alone for gastric ulcers resulted in stomach cancer risks that exceeded 10-fold. Vagotomy was associated with a nonsignificant increased risk of stomach cancer (RR = 1.46: 95% confidence interval [CI] = 0.8-2.8). The combination of vagotomy with radiation was linked to a slightly higher risk (RR = 4.4) than radiotherapy alone (RR = 3.0).

Cancer risk was significantly higher among those treated with radiation at young ages. The RRs for all cancer deaths for patients irradiated when younger than 35 years, 35-54 years. and older than 55 years were 1.81, 1.53, and 1.11, respectively (trend *P* = .05). The most dramatic decrease in risk with increasing age at exposure was for stomach cancer, with the respective RRs of 10.0, 2.80, and 1.56 (trend *P* = .02). There were only 18p patients who received more than one course of radiation treatment, and their risk of cancer (RR = 1.67) was similar to those treated only once (RR = 1.41). For stomach cancer, however. there was evidence for a dose response with the RRs of 1.0, 2.6, and 4.4 for those not treated, treated once, or treated more than once. respectively (trend *P = .0002).* The estimated RRs at 1 Gy for cancers of the stomach. pancreas, and lung and for leukemia were 1.15, 1.08, 1.66, and 2.47, respectively. The corresponding excess absolute risk estimates were 0.25, 0.09, 2.33, and 1.40, respectively, per 10 000 persons per year per Gy.

Table 2. Estimated dose to various organs and sites following typical radiation treatment

Organ or site	Portion of organ or site in direct x-ray beam, %*	Average total dose, Gy
Stomach	100	14.8
Spleen	100	14.5
Pancreas	100	12.9
Kidney, left (right)	80 (0)	14.2 (2.07)
Liver	20	4.61
Lung, left (right)	15 (0)	1.79 (0.55)
Colon	10	0.1-12.3
Esophagus	5	2.28
Active bone marrow	5	1.55
Heart	0-5	2.10
Gallbladder	0	1.42
Small intestine	0	1.19
Ovary or uterus	0	0.35-0.44
Bladder, thyroid, rectum, breast	0	0.10-0.17
Larynx, prostate	0	0.08

*Percent of organ or site in primary x-ray field during typical radiation treatment for stomach ulcer. Note that the dose to any portion of the organs in the direct beam would be greater than 10 Gy.

Cigarette smoking was an independent risk factor for cancers of the lung (RR = 7.2; 95% CI = 3.1-15) and bladder (RR = 2.4; 95% CI=0.6-10) but not of the pancreas (RR= 1.01) or stomach (RR = 1.0). Tobacco use was also linked to a slight increase in death due to circulatory disease (RR = 1.12). All direct comparisons between irradiated and nonirradiated patients were adjusted for cigarette smoking.

Discussion

Patients with peptic ulcers are at increased risk of dying of cancer. related in part to treatment, the underlying disease, and lifestyle factors such as cigarette smoking. High-dose radiotherapy was correlated with increases in mortality from cancers of the stomach, lung, and pancreas and from leukemia. There was little evidence that radiation doses of about 1 Gy or more increased the risk of cancers of the esophagus, colon, liver, gallbladder, or kidney, although in most instances the number of deaths were small. Surgical treatment increased the risk of stomach cancer. Gastric ulcers were associated with higher stomach cancer rates than duodenal ulcers. Radiotherapy and surgery appeared to enhance the development of stomach cancer to an extent greater than expected based on the sum of their individual effects. Cancer mortality remained elevated 30 years and longer after radiotherapy, up to 50 years.

Surgery and Lifestyle

It comes as no surprise that cancer deaths were increased among both irradiated and nonexposed patients. Several large-scale studies of peptic ulcer patients *(3,5,7,10,11)* have linked stomach cancer with surgical treatment among long-term survivors. One possible mechanism is that surgery reduces acid secretions, resulting in bacterial overgrowth and subsequent production of N-nitroso carcinogens in the stomach *(20).*

Table 3. Mortality according to cause of death by treatment for peptic ulcer and relative risk (RR) due to radiotherapy

Cause of death (ICD8)*	Radiotherapy: Yes, Observed	Radiotherapy: Yes, O/E†	Radiotherapy: No, Observed	Radiotherapy: No, O/E†	RR‡	95% CI
All causes (001-998) §	1294	1.32‖	1224	1.03	1.23‖	1.1-1.3
All disease related (001-799)	1227	1.29‖	1132	1.00	1.26‖	1.2-1.4
All cancers (140-209)	341	1.85‖	256	1.19‖	1.53‖	1.3-1.8
Infections (001-139)	12	0.83	7	0.38‖	2.17	0.8-5.8
Tuberculosis (010-019)	6	0.74	6	0.57	1.26	0.4-4.2
Endocrine system (240-279)	16	0.92	11	0.47‖	1.65	0.7-3.7
Nervous system (372-389)	9	1.24	9	1.02	1.09	0.4-2.9
Circulatory system (390-458)	670	1.18‖	657	0.94	1.20‖	1.1-1.4
Respiratory system (460-519)	62	1.01	74	0.99	0.86	0.6-1.3
Digestive system (520-577)	73	1.91‖,¶	73	1.62‖,¶	1.17	0.8-1.7
Cirrhosis (571)	17	1.23	13	0.86	1.11	0.5-2.4
Genitourinary system (580-629)	26	1.35	22	0.88	1.63	0.9-2.9
All external causes (800-998)	30	0.65‖	50	0.92	0.66	0.4-1.1
Suicide (950-959)	9	0.83	17	1.40	0.60	0.3-1.4

*ICD = International Classification of Diseases; numbers in parentheses are classification numbers published by ICD (*16*).
†Observed (O) to Expected (E) ratio; expected numbers based on national rates.
‡RR due to radiotherapy, adjusted for age, calendar year, time since entry into cohort, sex, and smoking, comparing irradiated with nonirradiated patients.
§Cause of death unknown for 37 irradiated and 42 nonirradiated patients.
‖$P<.05$.
¶Thirty-one deaths (7.2 expected) and 32 deaths (8.4 expected) were ascribed to peptic ulcer (ICD 531-533) among irradiated and nonirradiated patients, respectively.

Table 4. Cancer mortality according to treatment for peptic ulcer and relative risk (RR) due to radiotherapy

Cause of death (ICD8)*	Radiotherapy: Yes, Observed	Radiotherapy: Yes, O/E	Radiotherapy: No, Observed	Radiotherapy: No, O/E	RR†	95% CI
All cancers (140-209)	341	1.85‡	256	1.19‡	1.53‡	1.3-1.8
Buccal (140-149)	1	0.20	1	0.18	0.98	0.1-16
Esophagus (150)	3	0.76	3	0.68	1.14	0.2-5.7
Stomach (151)	40	3.18‡	21	1.38	2.77‡§	1.6-4.8
Large intestine (153)	31	1.58‡	25	1.05	1.29	0.7-2.3
Rectum (154)	2	0.29	8	0.97	0.31	0.1-1.5
Liver (155-156)	9	1.83	11	1.82	0.79	0.3-2.1
Pancreas (157)	28	2.76‡	19	1.62	1.87‡	1.0-3.4
Larynx (161)	5	2.13	4	1.55	1.22	0.3-5.0
Lung (162)	99	2.22‡	63	1.31‡	1.70‡	1.2-2.4
Bone (170)	0	0.0	2	1.86	0.0	0.0-1.9
Connective tissue (171)	0	0.0	1	1.95	0.0	0.0-6.2
Breast, female (174)	11	2.01‡	5	0.64	1.82	0.5-6.3
All female genital (180-184)	0	0.0	6	0.85	0.0‡	0.0-0.4
Prostate (185)	26	1.67‡	28	1.52‡	1.39	0.8-2.4
Bladder (188)	11	1.68	4	0.51	2.66	0.8-8.8
Kidney (189)	6	1.52	2	0.45	3.40	0.7-18
Brain (191-192)	5	1.45	8	2.13	0.83	0.3-2.6
Thyroid (193)	2	4.52	1	1.88	2.70	0.2-32
Non-Hodgkin's lymphoma (200, 202)	12	NA‖	9	NA‖	1.88	0.7-5.0
Hodgkin's disease (201)	0	0.0	2	1.27	0.0	0.1-1.9
Multiple myeloma (203)	3	1.34	1	0.39	1.38	0.1-15
Leukemia & aleukemia (204-207)	11	1.58	4	0.49	3.28‡	1.0-10.6
Nonchronic lymphocytic leukemia (205-206)	8	NA‖	3	NA‖	2.75	0.7-11

*ICD = International Classification of Diseases; numbers in parentheses are classification numbers published by ICD (*16*).
†RR due to radiotherapy, adjusted for age, calendar year, time since entry into cohort, sex, and smoking, comparing irradiated with nonirradiated patients.
‡$P<.05$.
§Also adjusted for partial gastrectomy and gastric ulcer.
‖NA = mortality rates not available.

Table 5. Relative risk (RR) of stomach cancer according to type of ulcer by surgery and radiotherapy

Characteristic	Radiotherapy	No. of patients with cancer	Total No. of patients*	RR†	95% CI
Gastric ulcer‡					
No	No	17	1612	1.00	
No	Yes	33	1673	3.30	1.8-6.1
Yes	No	4	165	3.39	0.9-12
Yes	Yes	7	158	12.80	4.8-34
Partial gastrectomy§					
No	No	18	1505	1.00	
No	Yes	30	1682	2.40	1.3-4.5
Yes	No	3	272	0.95	0.3-3.4
Yes	Yes	10	149	10.62	4.6-24.8
Vagotomy‖					
No	No	16	1355	1.00	
No	Yes	27	1521	3.00	1.4-6.3
Yes	No	5	422	1.43	0.5-4.4
Yes	Yes	13	310	4.44	1.8-10.7

*One nonexposed patient had missing data on surgery and was not included in the calculations.

†RRs are adjusted for age, calendar year, time since entry into cohort, smoking, and sex. RRs for gastric ulcer were also adjusted for partial gastrectomy and vice versa.

‡RR = 3.73 (95% CI = 1.8-7.9) contrasting gastric ulcer versus duodenal ulcer, adjusted for radiotherapy.

§RR = 2.60 (95% CI = 1.4-5.0) contrasting partial gastrectomy versus no surgery, adjusted for radiotherapy.

‖RR = 1.46 (95% CI = 0.8-2.8) for vagotomy, adjusted for other surgery and radiotherapy.

Depending on the type of surgery, refluxed bile might also have a promoting role. Vagotomy and drainage also have been reported to increase the risk of gastric cancer threefold *(21).* Lung cancer excesses are also prominent features of studies of peptic ulcer *(2,4,6,11,21),* attributable, in all likelihood, to tobacco use (22). Excesses of other smoking-related cancers, such as those of the bladder *(4,6,11)* and pancreas *(2,4,6,9),* are often seen.

Increases in cancers of the colon *(2,4,6)* and bilary tract *(4,6,9)* have been reported among patients treated with surgery for peptic ulcers. whereas elevated risks for cancers of the esophagus. breast, and prostate are rarely seen. Non-Hodgkin's lymphoma and leukemia were elevated in one study *(11).* A small study of 61 patients *(23)* treated with radiation and partial gastrectomy noted increased mortality due to stomach cancer. Differences among various studies in cancer risks can be attributed to differences in lengths of follow-up. types of surgical procedures, types of ulcers. sex of patients, numbers of patients. and extent of tobacco use. Our study was consistent with previous studies, except that we were able to evaluate the additional risk conferred by radiotherapy.

Radiotherapy

Radiotherapy increased the risk of all cancers combined by approximately 50%. with the RR holding constant over time since irradiation. even among those followed for more than 30 years. This pattern of risk is consistent with studies of atomic bomb survivors *(24)* and patients treated with radiotherapy for malignant *(25)* and benign *(26)* gynecologic conditions and supports the belief that radiation damage persists for many years. Organs that received more than 1 Gy contributed to the overall excess. most notably the stomach. pancreas. and lung. As in studies of atomic bomb survivors *(24),* the RR decreased significantly by increasing age at exposure for all cancers combined and for stomach cancer in particular. It might be noted that radiotherapy is no longer used to treat peptic ulcer.

Stomach Cancer

An average total dose of 15 Gy to the stomach resulted in a nearly threefold cancer risk that persisted for more than 30 years. Our study is one of only three investigations providing quantitative risk estimates for stomach cancer *(24,27).* Radiation risk increased with increasing dose and decreased with increasing age at exposure. The estimated RR for stomach cancer at 1 Gy for patients with peptic ulcers (RR = 1.15) was similar to that for Japanese atomic bomb survivors (RR = 1. 13). The Japanese atomic bomb survivors have a very high underlying risk for stomach cancer (24). The similarity in RR estimates in these two populations suggests that radiation may interact with underlying risk factors for stomach cancer in a multiplicative rather than an additive fashion. The absolute risk (0.25 excess cancers per 10^4 person-years per Gy), however, was much lower among patients irradiated for peptic ulcers than among atomic bomb survivors (4.19 excess cancers per 10^4 person-years per Gy). This pattern in relative and absolute excess risks is the reverse of that seen for radiogenic breast cancer; where absolute excess risks are similar and RRs differ between irradiated Western populations and atomic bomb survivors, who have a very low background risk for breast cancer *(28).* These data point to the complexity in applying risk estimates from one population (such as atomic bomb survivors) to another (such as occupationally exposed populations in the United States) when the base-line rates of disease are distinctly different.

The observation that radiotherapy and surgery together greatly enhanced stomach cancer risk may be a chance finding or, possibly, indicative of a complex carcinogenic process involving radiation-damaged cells, extreme treatment-induced hypoacidity, increased bacterial growth, and associated exposure to N-nitroso compounds (or other promoting factors) of cells no longer protected by stomach mucosa.

Lung Cancer

Death due to lung cancer was significantly linked to radiotherapy, despite a nonuniform distribution of radiation dose within the lung (mean total dose, 1.79 Gy). Cancer rates were high immediately after treatment, however, suggesting some residual confounding due to cigarette smoking. Studies of underground miners exposed to radon *(1)*, patients irradiated for spondylitis *(29)*, and atomic bomb survivors *(24)* provide quantitative risk estimates of lung cancer. Our computed risk coefficient (RR = 1.66 at 1 Gy) was similar to that from the atomic bomb survivor study (RR= 1.56 at 1 Gy).

Pancreatic Cancer

Pancreatic cancer has not been linked convincingly to radiation. Studies of atomic bomb survivors *(24)* and patients irradiated for cervical cancer *(27)* and spondylitis *(29)* showed no link. Our study differs from all previous studies in that the mean total dose to the pancreas, nearly 13 Gy. was substantially larger. Other than a high-dose radiation effect, it is conceivable that inaccuracies in death certification or uncontrolled confounding by smoking may have contributed to the apparent risk of pancreatic cancer. Because the diagnoses of pancreatic cancer are notoriously inaccurate on death certificates, a portion of the excess might be related to misclassification of other radiogenic cancers, such as stomach cancer. Thus, the association with radiation must be viewed cautiously and may be noncausal.

Leukemia and Lymphoma

Radiotherapy for peptic ulcers exposed relatively small portions of the bone marrow and of the lymphatic system but might have contributed to the slight excess observed for leukemia and non-Hodgkin's lymphoma. Although similar leukemia risks have been reported in other patient populations given radiotherapy *(26,27,29)*, the small numbers in our study precluded firm conclusions. The only evidence for an association between radiation and lymphoma is from studies of patient populations treated with high-dose radiation for spondylitis, cervical cancer. and Hodgkin's disease *(30)*. Conceivably. very high therapeutic doses may be required for non-Hodgkin's lymphoma to develop. whereas lower doses would not result in detectable increases. Multiple myeloma, another malignancy of uncertain radiogenic origin, was not increased in our study.

Other Cancer Sites

Radiotherapy did not increase the risk of esophageal or colon cancer. The distribution of dose within the large intestine and esophagus was nonuniform, reaching a total mean as high as 14 Gy in some portions and less than 0.1 Gy in other portions. Possibly, for these organs, the very high doses resulted in cell killing and not transformation, and the very low doses were not sufficient to result in an expressed risk. Other organs receiving greater than 1 Gy that were not significantly increased included the liver and kidney; cancers of these organs were not convincingly related to x-ray exposure in previous studies *(1)*.

Study Strengths and Limitations

The study strengths include the exceptionally long follow-up for the expression of late effects, the accurate estimation of individual radiation dose, and a comparison group of patients with peptic ulcers who had not been treated with radiation to control for underlying risks and lifestyle factors. Limitations include the rather consistent way in which patients were treated, which restricted our ability to evaluate dose–response relationships. Further, the nonhomogeneous dose distribution within some organs was such that simple averaging of dose might not be strictly appropriate for risk assessment. The follow-up was 87% complete, and ulcer patients lost to follow-up did not differ appreciably in demographic or treatment characteristics from those successfully traced. Unadjusted confounding by cigarette smoking or other lifestyle factors may have influenced some results. Metastatic spread of primary stomach cancer might also have been misclassified on death certificates as cancer deaths for certain other sites, such as the liver or pancreas. Finally, patients treated with radiotherapy appeared to be less fit than those treated by other means, and they were less likely to be candidates for surgery. The significant excess of heart disease, for example, could be due in part to high-dose radiation damage to coronary tissue *(31)* but is more likely related to selection factors that excluded patients with serious heart conditions from surgery.

References

(1) National Academy of Sciences (NAS) Committee on the Biological Effects of Ionizing Radiations: Health Effects of Exposure to Low Levels of Ionizing Radiation (Beir V). Washington, DC: Natl Acad Press. 1990

(2) Ross AH, Smith MA, Anderson JR. et al: Late mortality after surgery for peptic ulcer. N Engl J Med 307:519-522, 1982

(3) Caygill CP, Hill, MJ, Kirkham JS. et al: Mortality from gastric cancer following gastric surgery for peptic ulcer. Lancet 1:929-931, 1986

(4) Caygill CPJ, Hill MJ, Hall CN, et al: Increased risk of cancer fit multiple sites after gastric surgery for peptic ulcer. Gut 28:924-928, 1987

(5) Viste A, Bjørnestad E, Opheim P, et al: Risk of carcinoma following gastric operations for benign disease. A historical cohort study of 3470 patients. Lancet 2:502-505, 1986

(6) Eide TJ, Viste A, Andersen A, et al: The risk of cancer at all sites following gastric operation for benign disease. A cohort study of 4,224 patients. Int J Cancer 48:333-339. 1991

(7) Lundegårdh G, Adami H-O, Helmick C. et al: Stomach cancer after partial gastrectomy for benign ulcer disease. N Engl J Med 319: 195-200, 1988

(8) Arnthorsson G. Tulinius H. Egilsson V. et al: Gastric cancer after gastrectomy. Int J Cancer 42:365-367, 1988

(9) Tersmette AC, Offerhaus GJ, Giardiello FM, et al: Occurrence of nongastric cancer in the digestive tract after remote partial gastrectomy: analysis of an Amsterdam cohort. Int J Cancer 46:792-795, 1990

(10) Tersmette AC. Goodman SN, Offerhaus GJ, et al: Multivariate analysis of the risk of stomach cancer after ulcer surgery in an Amsterdam cohort of postgastrectomy patients. Am J Epidemiol 134:14-21, 1991

(11) Møller H, Toftgaard C: Cancer occurrence in a cohort of patients surgically treated for peptic ulcer. Gut 32:740-744. 1991

(12) Palmer WL, Templeton F: The effect of radiation therapy on gastric secretion. JAMA 112:1429-1434, 1939

(13) Palmer WL: Gastric Irradiation in Peptic ulcer. Chicago: Univ of Chicago Press. 1974

(14) Carpender JWJ, Levin E, Clayman CB, et al: Radiation in the therapy of peptic ulcer. Am J Roentgenol Radiat Ther Nuc Med 75:374-379, 1956

(15) Griem ML, Justman J, Weiss L: The neoplastic potential of gastric irradiation. IV. Risk estimates. Am J Clin Oncol 7:675-677, 1984

(16) National Center for Health Statistics: International Classification of Diseases. 8th rev. DHEW Publ No. (PHS)67-1693. Washington, DC: US Govt Print Off, 1967
(17) Stovall M, Smith SA, Rosenstein M: Tissue doses from radiotherapy of cancer of the uterine cervix. Med Phys 16:726-733, 1989
(18) Monson RR: Analysis of relative survival and proportional mortality. Comput Biomed Res 7:325-332, 1974
(19) Preston DL, Lubin JH, Pierce DA: EPICURE: Generalized Regression Models for Epidemiologic Data. Seattle. Wash: Hirosoft International, 1990
(20) Correa P: A human model of gastric carcinogenesis. Cancer Res 48:3554-3560, 1988
(21) Watt PC, Patterson CC, Kennedy TL: Late mortality after vagotomy and drainage for duodenal ulcer. Br Med J (Clin Res Ed) 288: 1335-1338, 1984
(22) Friedman GD, Siegelaub AB, Seltzer CC: Cigarettes, alcohol, coffee and peptic ulcer. N Engl J Med 290:469-473, 1974
(23) Peters M, Mackay IR, Buckley JD: Occurrence of tumors and effects on longevity after limited x-irradiation in man. Am J Pathol 101:647-655, 1980
(24) Shimizu Y, Kato H, Schull WJ: Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 121: 120-141, 1990
(25) Boice JD Jr, Day NE, Andersen A, et al: Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. J Natl Cancer Inst 74:955-975, 1985
(26) Inskip PD, Monson RR, Wagoner JK, et al: Cancer mortality following radium treatment for uterine bleeding [published erratum appears in Radiat Res 128:326, 1991]. Radiat Res 123:331-344, 1990
(27) Boice JD Jr. Engholm G, Kleinerman RA, et al: Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 116:3-55, 1988
(28) Boice JD Jr, Land CE, Shore RE, et al: Risk of breast cancer following low-dose radiation exposure. Radiology 131:589-597, 1979
(29) Darby SC, Doll R, Gill SK, et al: Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 55:179-190. 1987
(30) Boice JD Jr: Radiation and non-Hodgkin's lymphoma. Cancer Res 52(19 Suppl):5489s-5491s,1992
(31) Boivin JF, Hutchison GB, Lubin JH, et al: Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 69:1241-1247, 1992

Notes

Supported in part by Public Health Service contracts N01CP41011, N01CP95614, and N01CP85604 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

We thank Ms. Florence Lowenstein, Tumor Registrar at the University of Chicago, for assistance throughout the study; Dr. George Block for a history of surgical management of peptic ulcer at the University of Chicago; Dr. W. L. Palmer for personal recollections on past treatment practices; Mr. Paul Hurwitz and Mr. Chuck Eastlack at Westat, Inc., Rockville, Md., for technical support; Ms. Sandra Coppersmith for typing support; and the many past medical students at the University of Chicago for recording such thorough medical histories. We also acknowledge the contributions of Dr. Daniel Hoffman during the early stages of this investigation.

Manuscript received July 7, 1993; revised March 1, 1994; accepted March 8, 1994.