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High-Dose Abdominal Radiotherapy and Risk of Diabetes Mellitus

Meacham et al¹ reported a significantly increased risk of diabetes mellitus (DM) following abdominal irradiation for childhood cancer, separate from the effect of total irradiation. Prompted by this finding of an increased risk of DM, we examined the risk of death from diabetes in a cohort of patients with peptic ulcers, who were treated with high-dose abdominal radiation to decrease acid secretion.

Methods. This cohort study, originally initiated to investigate the long-term cancer risk associated with radiation,^{2,3} consisted of 1832 irradiated and 1868 nonirradiated patients with peptic ulcers (treated by other means) at the University of Chicago from 1937 to 1965. Individual radiation doses were estimated to specific organs from radiotherapy records and phantom experimental measurements. Doses to the pancreas ranged from 1 to 38 Gy (to convert to rads, multiply by 100), which is the equivalent of 1000 to 38 000 mSv (1 chest radiograph=0.1 mSv). The mean age at treatment was 49 years for irradiated and 45 years for nonirradiated patients. Individuals were followed up from the time of treatment for peptic ulcer until death or censored alive as of December 31, 1997. Causes of death were obtained by linking the cohort with the National Death Index. At the end of follow-up, 84% of irradiated and 81% of nonirradiated patients had died.

Results. Thirty persons had died from DM (underlying cause), with 19 in the irradiated and 11 in the nonirra-

diated group. Using the proportional hazard method, we estimated the relative risk (hazard ratio) of death due to DM by pancreatic dose category after adjusting for age at treatment and attained age. We found a significantly increased risk, with a hazard ratio of 3.79 (95% confidence interval, 1.2-12.0) for the highest-dose category (17-38 Gy) compared with the nonirradiated group (**Table**). The increased risk at the highest-dose category was observed both within and after 15 years of radiation treatment, but the risk was statistically significant only for 15-or-more-year survivors. Because of the small number of deaths from DM, a detailed analysis of the radiation dose response was not possible, and the data were unclear about the risk at lower doses.

Comment. Although the data from Meacham et al¹ and ours differ in several respects, our results agree with the finding of an increased risk of DM following high-dose abdominal irradiation. In the study by Meacham et al,¹ the patients were irradiated during childhood, whereas the patients with peptic ulcers were irradiated much later in life, mostly at ages 30 years or older. The abdominal dose received by the patients in the study by Meacham et al¹ is assumed to be 20 to 30 Gy, whereas in our study, the increased risk of DM was found in those receiving 8 to 31 Gy to the pancreas (mean, 14.6 Gy). Doses to distant organs, such as the brain, were negligible. The association of DM following total body irradiation in children and adults has been documented,^{4,5} but less well known is the occurrence of DM following abdominal, or more specifically, pancreatic irradiation. Our previous studies³ showed radiation-related risks of pancreatic and gastric cancers in the patients with peptic ulcers. The effect of dying from these fatal cancers, if any, would have been to reduce the number of persons dying from DM in the high-radiation dose group. A small case series reported that DM occurred 6 to 20 years later in 4 of 5 adults who received abdominal radiation for either Hodgkin lymphoma or testis cancer.⁶ In the study by Meacham et al,¹ DM was considered mostly type 2 based on medication history. As we ascertained DM from death certificate information, unresolved questions in our study relate to the type of DM involved or response to insulin treatment, which reflects the degree of pancreatic cell damage from radiation at high-dose levels.

Table. Hazard Ratio (HR) for Diabetes Mortality Following Radiation Treatment for Peptic Ulcer by Time Since Treatment

Dose Category, Gy	No. of Patients	Time Since Treatment to Death From Diabetes					
		<15 Years		≥15 Years		All Years	
		Diabetes Mortality, No.	HR (95% CI)	Diabetes Mortality, No.	HR (95% CI)	Diabetes Mortality, No.	HR (95% CI)
0	1857	3	1 [Reference]	8	1 [Reference]	11	1 [Reference]
1.00-10.00	514	1	4.64 (0.2-105.4)	4	1.43 (0.4-5.1)	5	1.49 (0.5-4.3)
10.01-13.00	527	2	0.57 (0.1-4.3)	1	0.47 (0.1-3.9)	3	0.75 (0.2-2.8)
13.01-16.00	429	2	1.07 (0.1-12.3)	3	1.46 (0.2-8.0)	5	1.47 (0.4-5.4)
>16.00	362	2	2.48 (0.2-30.1)	4	4.31 (1.1-17.0)	6	3.79 (1.2-12.0)

Abbreviation: CI, confidence interval.

Conventional conversion factor: To convert grays to rads, multiply by 100.

In conclusion, our data provide additional evidence of the association between DM and high-dose pancreatic radiation but leave some questions unresolved, ie, the extent of pancreatic cell damage involved and the risk of DM at lower doses, both of which are important for both clinical practice and public health. Further research is needed to clarify these issues.

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COMMENTS AND OPINIONS

Conflicting Evidence Surrounding the Clopidogrel and Proton Pump Inhibitor Drug Interaction

In the April 26, 2010, issue of the *Archives*, Stockl et al¹ reported a clinically significant drug interaction between clopidogrel and proton pump inhibitors (PPIs) based on their retrospective cohort study of health

insurance claims. Their study concluded that concomitant clopidogrel and PPI use was associated with higher rates of hospitalization for myocardial infarction (MI) or coronary stent placement. However, there is more recent evidence that contradicts their conclusion and was not discussed in their article.

The results by Stockl et al¹ confirm a clopidogrel and PPI drug interaction that has been previously shown by other retrospective cohort studies. However, more recent and larger retrospective cohort studies contradict this purported drug interaction. Rassen et al² performed a retrospective cohort study in 18 565 patients who were prescribed clopidogrel after a recent MI and concluded that there was no increased risk of cardiac events in patients receiving concomitant clopidogrel and PPI treatments.² Ray et al³ also confirmed that there was no increased cardiac event rate with clopidogrel and PPI use in their 20 596 patient retrospective cohort study. These larger cohort studies consistently establish that there is no drug interaction between clopidogrel and PPIs.

Data from landmark, randomized controlled trials also conclude there is no drug interaction between clopidogrel and PPIs. A subgroup analysis from the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38) randomized study of 6795 post-MI patients clearly showed no increased risk of cardiovascular outcomes from clopidogrel and PPI use vs clopidogrel alone.⁴ COGENT (Clopidogrel and Optimization of Gastrointestinal Events Trial) studied clopidogrel use alone vs concomitant clopidogrel and PPI use in a prospective, randomized trial of 3627 patients. There was no difference in the rates of adverse cardiac outcomes between clopidogrel and PPI use compared with clopidogrel use alone.⁵ The results from these landmark, randomized clinical trials consistently conclude that clopidogrel and PPI use is not associated with higher cardiac event rates.

Thus, higher level evidence (larger cohort studies and data from randomized controlled trials) demonstrates that concomitant use of PPIs with clopidogrel is not associated with higher cardiac event rates, which illustrates that there is no clinically significant drug interaction. When viewed in its totality, the evidence for a clopidogrel and PPI drug interaction is conflicting, with the highest quality of evidence not supporting a clinically significant drug interaction.

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