2. Zagars GK, Ballo MT, Lee AK, et al: Mortality after cure of testicular seminoma. J Clin Oncol 22:640-647, 2004
3. Aparicio J, Germà JR, García del Muro X, et al: Risk-adapted management for patients with clinical stage I seminoma: The Second Spanish Germ Cell Cancer Cooperative Group study. J Clin Oncol 23:8717-8723, 2005
4. Tarin TV, Sonn G, Shinghal R: Estimating the risk of cancer associated with imaging related radiation during surveillance for stage I testicular cancer using computerized tomography. J Urol 181:627-632, 2009; discussion 632-633
5. Preston DL, Ron E, Tokuoka S, et al: Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res 168:1-64, 2007
6. Hall EJ, Giaccia AJ: Radiobiology for the Radiologist (ed 6). Philadelphia, PA, Lippincott Williams & Wilkins, 2006
7. Mezrich R: Are CT scans carcinogenic? J Am Coll Radiol 5:691-693, 2008
8. National Comprehensive Cancer Network (NCCN): The NCCN Clinical Practice Guidelines in Oncology, Testicular Cancer (Version 2.2011). April 13, 2011. http://www.nccn.org
9. Travis LB, Fosså SD, Schonfeld SJ, et al: Second cancers among 40,576 testicular cancer patients: Focus on long-term survivors. J Natl Cancer Inst 97:1354-1365, 2005
10. Travis LB, Curtis RE, Hankey BF: Second malignancies after testicular cancer. J Clin Oncol 13:533-534, 1995
11. Simone CB 2nd, Kramer K, O'Meara WP, et al: Predicted rates of secondary malignancies from proton versus photon radiation therapy for stage I seminoma. Int J Radiat Oncol Biol Phys [epub ahead of print on January 13, 2011]

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Reply to C.B. Simone II

We appreciate the opportunity to respond to several points made in the letter from Simone.[1] By our count, this letter makes eight points that require our response. The study by Tarin et al[2] is similar to references 22 to 32 in our article,[3] in which diagnostic radiation exposure is measured and used to estimate the expected number of excess cancers attributable to this exposure. We believe that this is a useful exercise for hypothesis generation but that studies that associate diagnostic radiation exposure with actual cancer incidence are required to determine the risk of cancers from diagnostic radiation. We agree with Simone's comments questioning the "radiobiological equivalence" of a particular radiation dose given all at one time versus that given in smaller aliquots. We hypothesized in the Discussion section of our article (third paragraph)[3] that this could explain why our study found fewer cancers than would be expected on the basis of data from atomic bomb survivors. We agree that a longer follow-up would have been ideal. We have previously discussed this issue in our response[4] to Brenner and Shuryak.[5] Observation time by second malignancy status presented in Table 1 of our article is given in years for each group (not months as stated in the letter). The difference in the median length of observation between the entire cohort and those without an abdominal-pelvic tumor was due to rounding. The median follow-up in both groups was 11.15556 years. By convention, this should be rounded up to 11.2 years. Our conclusions did not change when we included men with fewer than 5 years of observation, as shown in Appendix Table A3 (online only) in our article.[3] Unfortunately, the Ontario Cancer Registry does not categorize testicular cancers into seminomatous and nonseminomatous. We are unable to report results that apply to fewer than five people for privacy reasons, and this is why we did not analyze by testicular cancer subtype or report all types of second tumors. The suboptimal discrimination in our model, and its lack of association between chemotherapy and second malignancies, is due to the relatively few outcomes we had in our cohort. We agree that our study does not "exclude the possibility of second abdominal-pelvic tumors induced by diagnostic radiation exposure." This can be done only after combining the results from multiple studies on the topic. We are looking forward to adding the results of repeated analyses on our cohort in 10 to 15 years to data from the trial being started in Pennsylvania. Hopefully, these data will help clarify the association between diagnostic radiation and risk of additional cancers.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Simone CB II: Secondary abdominal-pelvic malignancies attributable to diagnostic radiation exposure in patients with testicular malignancies. J Clin Oncol 30:113-114, 2012
2. Tarin TV, Sonn G, Shinghal R: Estimating the risk of cancer associated with imaging related radiation during surveillance for stage I testicular cancer using computerized tomography. J Urol 181:627-632, 2009; discussion 632-633
3. van Walraven C, Fergusson D, Earle C, et al: Association of diagnostic radiation exposure and second abdominal-pelvic malignancies after testicular cancer. J Clin Oncol 29:2883-2888, 2011
4. van Walraven C, Fergusson D, Craig E, et al: Reply to D.J. Brenner et al. J Clin Oncol doi:10.1200/JCO.2011.38.0220 [epub ahead of print on September 19, 2011]
5. Brenner DJ, Shuryak I: Ten years of follow-up is not long enough to assess lifetime cancer risks caused by computed tomography scans in a young population. J Clin Oncol 10.1200/JCO.2011.37.9354 [epub ahead of print on September 19, 2011]

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FOLFIRINOX: A Great Leap Forward, but for Whom?

To the Editor: *Journal of Clinical Oncology* published an article by Ko[1] in the Comments and Controversies section. We do believe FOLFIRINOX (biweekly bolus plus infusional fluorouracil, leucovorin, irinotecan, and oxaliplatin) is a major step forward for patients with pancreatic cancer, and it must be considered the new backbone for clinical practice and also for therapy development.[2]

In his report, Ko[1] briefly discusses the influence of ethnical factors in toxicity. Several factors related to the patient as well as tumor biology can greatly interfere with the clinical outcomes of those with pancreatic cancer. A better understanding of these predictors of

efficacy and toxicity must be extensively pursued. For example, human equilibrative nucleoside transporter 1 (hENT1) is a predictor of response and survival for patients with pancreatic cancer treated with gemcitabine in different settings.[3-6] Perhaps for patients whose tumors express high levels of hENT1, the benefit of FOLFIRINOX over gemcitabine would not be clinically meaningful, therefore allowing us to continue offering such patients gemcitabine-based therapy, which has a better toxicity profile without compromising efficacy. Recently, Paproski et al[7] evaluated a new positron emission tomography tracer (ie, 30-deoxy-30-fluorothymidine), which would be a good substitute for hENT1 immunohistochemistry in pancreatic cancer. If these assumptions were real, a noninvasive procedure would be worthy for selecting patients for a certain chemotherapy regimen.

There are several other markers predicting clinical outcomes to gemcitabine, fluoropyrimidines, camptothecins, and platinum compounds in other diseases and settings, and these should be evaluated in the changing landscape of individualized care for pancreatic cancer.

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REFERENCES

1. Ko AH: FOLFIRINOX: A small step or a great leap forward? J Clin Oncol 29:3727-3729, 2011
2. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011
3. Farrell JJ, Elsaleh H, Garcia M, et al: Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. Gastroenterology 136:187-195, 2009
4. Giovannetti E, Del Tacca M, Mey V, et al: Transcription analysis of human equilibrative nucleoside transporter-1 predicts survival in pancreas cancer patients treated with gemcitabine. Cancer Res 66:3928-3935, 2006
5. Maréchal R, Mackey JR, Lai R, et al: Human equilibrative nucleoside transporter 1 and human concentrative nucleoside transporter 3 predict survival after adjuvant gemcitabine therapy in resected pancreatic adenocarcinoma. Clin Cancer Res 15:2913-2919, 2009
6. Spratlin J, Sangha R, Glubrecht D, et al: The absence of human equilibrative nucleoside transporter 1 is associated with reduced survival in patients with gemcitabine-treated pancreas adenocarcinoma. Clin Cancer Res 10:6956-6961, 2004
7. Paproski RJ, Young JD, Cass CE: Predicting gemcitabine transport and toxicity in human pancreatic cancer cell lines with the positron emission tomography tracer 3′-deoxy-3′-fluorothymidine. Biochem Pharmacol 79:587-595, 2010

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Reply to L.V. dos Santos et al

I thank dos Santos et al[1] for their insightful comments regarding my article[2] and the potential for using biomarkers to help guide the selection of treatment for patients with advanced pancreatic cancer, whether it be with FOLFIRINOX (biweekly bolus plus infusional fluorouracil, leucovorin, irinotecan, and oxaliplatin), a gemcitabine-based regimen, or other cytotoxic (or, in the future, targeted) agents. Intratumoral marker expression by immunohistochemistry (such as for human equilibrative nucleoside transporter 1, as dos Santos et al suggest) offers one straightforward approach to try and achieve this goal; global gene expression analysis may represent another.[3]

The challenge, of course, lies in procuring sufficient tumor material to be able to perform such assays of interest, because many patients are diagnosed based on relatively scant cytology from a fine-needle aspiration or endoscopic retrograde cholangiopancreatography procedure rather than via core biopsy or a previously resected surgical sample. Conroy et al[4] do not describe any central collection or planned analysis of available tumor tissues in their study, nor does the full protocol document accompanying the *New England Journal of Medicine* article include this as an exploratory aim. Thus, our ability to identify molecular subsets of study patients who did particularly well—or poorly—with either FOLFIRINOX or gemcitabine in this trial does not seem possible. Notably, other comparable multicenter phase III studies that did allow for optional participation in correlative analyses on archival tumor samples have produced a yield of only approximately one third of the total sample size,[5] thus limiting the robustness of any observations.

Some clinical trials mandate that potential study candidates undergo a pretreatment research biopsy or, at the very least, be able to produce adequate accessible archived material for trial participation so that putative predictive markers can be discovered and tested. However, aside from the ethical questions that this type of requirement raises, it also represents a particularly difficult logistic hurdle for patients with advanced pancreatic cancer, and one that may not be practically feasible in the community setting. In the end, one is left seeking surrogate indicators, such as functional bioimaging, analysis of circulating tumor cells, or serum proteomics, that are less invasive and may one day be of predictive value, but for now remain wholly exploratory.

These caveats notwithstanding, I agree wholeheartedly with dos Santos et al[1] that identification of any biomarkers in this disease that helps refine our therapeutic decision making would be immensely helpful and represent a worthy goal. If validated, getting such a test into routine clinical practice for patients with metastatic pancreatic cancer would still, undoubtedly, represent a formidable challenge, but one very much worth tackling.

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