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EDITORIAL

INDUCED SECOND CANCERS AFTER PROSTATE-CANCER RADIOTHERAPY: NO CAUSE FOR CONCERN?

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The absolute risks of a radiation-induced second cancer among long-term radiotherapy survivors are not large, typically a few percent in older patients (1–4). Hence the very real concern, expressed by Kendal *et al.* (5) in this issue, that prostate cancer patients may be unduly influenced in their treatment decision by unbalanced media reports of second-cancer risks. It is certainly the responsibility of the radiation oncologist to communicate a balanced assessment of the potential risks, be they short- or long-term, in the context of the potential benefits of the treatment.

Kendal *et al.* (5) go on to argue that there is in fact no good evidence that prostate radiotherapy produces *any* detectable increase in the risk of rectal cancer, despite the wide range of doses, from low to very high, to which the rectum is typically exposed during external-beam prostate radiotherapy (6, 7).

The article by Kendal *et al.* (5) raises two issues: (*1*) Is it true that prostate radiotherapy does not measurably increase the risk of secondary rectal cancer? (*2*) Why focus only on *rectal* cancers after prostate cancer radiotherapy?

First, is it true that prostate radiotherapy does not measurably increase the risk of secondary rectal cancer? Certainly there is evidence, from epidemiologic studies of a variety of other primary cancer sites, that radiotherapy is associated with increased rectal cancer rates; these include primary cervical cancer (8), ovarian cancer (9), testicular cancer (10), and Hodgkin's disease (11). Given that the range of doses to the rectum after prostate radiotherapy (6, 7) encompasses those from these other treatments, it would be surprising if the risks of rectal cancer after prostate radiotherapy were significantly lower or less detectable than for all these other treatments.

Kendal *et al.* (5) do not offer a mechanistic explanation for their suggestion that radiotherapy (RT) does not produce a significant increase in rectal cancer risks in long-term prostate cancer survivors. Their argument is the following: they compare rectal cancer rates taken from the SEER cancer registries (12) for prostate cancer survivors divided into three groups: RT, surgery, and conservative treatment (*i.e.,* neither RT nor surgery). They found that, for long-term survivors, whereas the rectal cancer risk after RT was indeed significantly higher than after surgery, as other analyses had found and attributed to a radiation effect (1, 2, 13), the highest rectal cancer risks were in the conservative treatment group. They concluded that the differences in rectal cancer risks between the different treatment groups, including the increase for radiotherapy relative to surgery, must be due to some unknown cause and not to radiation.

In fact there are many plausible reasons why the conservative treatment group might be expected to have high secondary rectal cancer rates. For example, the conservative treatment group (a) smoke more, (b) have a higher rate of prior heart attack, and (c) have a higher frequency of hormone therapy. As discussed below, all three of these factors are associated with increased rectal cancer rates. An understanding of the increased rectal cancer rates in the conservative treatment group allow us to return our focus back to the undisputed increase in rectal cancer rates in long-term survivors in the RT versus the surgery group, without having to speculate that some unknown effect, beyond radiation, is dominating this comparison.

Why might secondary rectal cancer rates be higher in prostate cancer patients who had conservative treatment? The first reason is smoking, which is now clearly linked to rectal cancer (14, 15). Results of a study (16) of Canadian prostate cancer patients showed that their smoking rates were about the same whether they were treated with surgery or radiotherapy (1), but that patients who had conservative treatment had significantly higher current smoking rates (conservative treatment: 26%, radiotherapy: 16%, surgery: 15%, $p = 0.046$). The second reason is prior history of heart attack. Not surprisingly, this is associated with a higher likelihood of conservative prostate cancer treatment (17), while prior coronary artery disease is also associated with colorectal cancer in men $>$ 60 years of age (18). The third reason is hormone therapy rates. In the 1980s, about 40% of

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prostate cancer patients who had conservative treatment received hormone therapy (19), whereas at that time the frequency of hormone therapy in the radiotherapy (or surgery) group was much lower (20). Thus the average levels of androgens such as testosterone would be lower in the conservative treatment group; testosterone has been shown to be an inhibitor of chemically induced rectal cancer in male rats (21), and although there are no conclusive data for rectal cancer in human beings, low androgen levels have been linked with an increased risk of colon cancer (22).

All in all, there are plausible reasons why secondary rectal cancer rates might be expected to be high in prostate cancer patients who had conservative treatment—but these reasons do not bear on the issue of the significantly higher rectal cancer rates, radiotherapy versus surgery, in long-term survivors, which is still most probably a radiation effect.

The second question is: Why focus only on *rectal* cancers after prostate cancer radiotherapy? As Kendal *et al.* (5) rightly point out, the smaller the number of individuals with a second cancer that are analyzed, the harder it is to detect meaningful associations. In the SEER database, the number of 10-year prostate cancer survivors analyzed by Kendal *et al.* (5), who developed rectal cancer, is about 100. The corresponding number in SEER with *any* second cancer is more than 1300. Given that potential radiotherapy patients are presumably concerned about the risks of any radiation-induced second cancer, to limit a study of second cancers after radiotherapy to one particular second-cancer site (5, 13) seems unnecessarily restrictive, both from a public health and a statistical point of view.

The bottom line here is that, when all second cancers are combined, there is a statistically significant increase in the risk of second cancers in long-term prostate cancer survivors who had radiotherapy compared with surgery (1, 2)—and this risk is almost certainly radiation related. The radiation-related absolute risks are not large, perhaps 1 in 70 for 10-year prostate cancer RT survivors (1), so the concern of Kendal *et al.* (5) that these risks should not be exaggerated is well taken.

However, particularly for sites such as the prostate, where the age at treatment is decreasing (23), while long-term survival rates are increasing (24), the issue of radiotherapy-related second cancers will become increasingly pertinent; and of course the issue is of overarching importance in pediatric radiotherapy (25). It is unquestionably the responsibility of the radiation oncology profession as a whole to ensure that these risks are made as low as is practical—a responsibility that is being addressed with improved understanding of the dose–risk relationship at high doses (26), with improved dose delivery technology (27–29), and with more optimized treatment planning (30–32). We have quite a way to go before radiation-induced second-cancer risks are as low as they could possibly be after external-beam radiotherapy; but stimulated by the evidence that second-cancer risks, although small, are real and reducible, we are headed in the right direction.

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