

Effect of Radiation-Associated Second Malignancies on Prostate Cancer Survival

In the prostate-specific antigen era, patients with prostate cancer are diagnosed at a younger age and earlier disease stage, and they live longer. Most patients undergo surgery or radiotherapy (RT) and are either cured or outlive their disease. In fact, among >10 000 patients treated by surgery, only 2% actually died of prostate cancer, and a 15-year nomogram predicted a 4% prostate cancer-specific mortality rate at 10 years.¹ Low mortality from prostate cancer is also observed after RT at 10 years of follow-up.² Radiotherapy, however, does not cure more patients than surgery.

Patients with prostate cancer sometimes develop a second malignancy, often in the bladder.³ Although this might be a result of detection bias, a common etiology, or other factors such as smoking, the most likely cause is RT.⁴ Patients who undergo RT to the prostate are at risk of developing second malignancies, both in the pelvis and outside the radiation field.⁵ These are highly malignant neoplasms, likely to cause death in many patients. This editorial speculates on the effect second cancers might have on the survival of patients currently diagnosed with localized prostate cancer and treated with RT. An analysis of the available data suggested that the risk of dying of a second malignancy after RT might be greater than the number of deaths from prostate cancer after curative surgery.

For this report, relevant studies were identified after searching PubMed and the ISI Web of Science databases. The literature search was restricted to the prostate-specific antigen era, from the mid-1980s to 2008. Studies were included only if they had included patients who had been followed up for >5 years and had compared the incidence of second cancers in RT vs surgically treated patients.

The risk of a second malignancy after prostate RT is still a matter of debate. Many single-institution^{6,7} and some cancer registry studies^{8,9} have concluded that no absolute increase in second cancers occurs in those who undergo RT vs those who do not. Such studies have included smaller numbers of patients, and a more accurate assessment would be that they had limited statistical power to detect a relatively small increased incidence of

second malignancies induced by treatment. Larger population-based studies have shown that RT to the prostate is associated with a statistically significant, albeit small, enhanced risk of second cancer development, particularly in long-term survivors.^{10,11}

From the Surveillance, Epidemiology, and End Results database (1973-1993), Brenner et al.¹² found significantly more second malignancies after RT than after surgery for primary prostate cancer, amounting to an increase in radiation-associated cancers of 34% for lung cancer, 29% for bladder cancer, 16% for rectal cancer, 13% for colon cancer, and 8% for sarcoma. Table 1 lists the data for the treated patients followed up for >5 years. The data presented in Table 2 show that Moon et al.¹¹ came to similar conclusions from an analysis of an updated Surveillance, Epidemiology, and End Results (1973-1999) database. A recent update from the Surveillance, Epidemiology, and End Results database has disputed that prostate RT increases the risk of second malignancies, but it has not yet been published.¹³

The risk of a second solid tumor of any type is significantly greater after RT for prostate cancer than after surgery, by about 6%. The increased relative risk becomes greater with time, reaching 34% after ≥ 10 years. The most dramatic increases were found for the bladder (77%) and the rectum (105%) at ≥ 10 years after diagnosis.¹⁴

RT to the prostate can cause cancer in adjacent organs, such as the bladder and rectum, but also at distant sites, such as the lung. This is especially true with intensity-modulated RT (IMRT). IMRT involves more fields, and, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2-3, increasing the beam-on time and total body exposure due to radiation leakage. IMRT spreads the radiation out, exposing a larger volume of tissues to lower doses, and the carcinogenic risk seems to be greatest for tissues receiving low doses (<6 Gy).¹⁵ It has been estimated that IMRT could increase the risk of a second fatal cancer by a factor of 1.2-8.¹⁶ Kry et al.¹⁶ estimated that the conservative maximal risk of a fatal second malignancy after RT to the prostate was 1.7% for conventional RT (three-dimensional conformal RT), 2.1% for IMRT using 10-MV x-rays, and 5.1% for IMRT using 18-MV x-rays.¹⁶ Others have also found an overall doubling in the risk of second

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Table 1. Second malignancies in patients with prostate cancer followed up >5 years after treatment by radiotherapy or radical prostatectomy*

Second Cancer	RT (n = 17 539)	Surgery (n = 25 394)	Increase RR [†] (%)	P Value
Bladder	210	212	55	.01
Rectum	95	86	35	.03
Colon	223	266	7	.47
Lung	381	369	42	.01
Sarcoma	34	26	36	.02
Total	943 (5.4)	947 (3.7)		.01

Abbreviations: RT = radiotherapy; RR = relative risk.

Data in parentheses are percentages.

* Data extrapolated from Brenner et al.¹⁰

[†] RR for second cancer after RT vs surgery (radical prostatectomy).

Table 2. Second malignancies in patients with prostate cancer patients followed up >5 years after radiotherapy compared with surgery or no radiotherapy*

Second Cancer	RT (n = 39 805)	Surgery/no RT (n = 94 541)	Adjusted OR (RT vs Surgery)	P Value
Bladder	665	815	1.6	<.05
Rectum	265	263	1.6	<.05
Colon	527	928	1.2	<.05
Lung	932	1534	1.3	<.05
Totals	2386 (6)	3549 (3.7)	1.37	.01

Abbreviations: RT = radiotherapy; OR = odds ratio.

Data in parentheses are percentages.

* Data extrapolated from Moon et al.¹¹

malignancies with the application of IMRT compared with conventional RT.¹⁷ Second cancers are also reportedly increased after prostate brachytherapy.¹⁸

The second cancers that develop in the bladder and rectum after prostate RT are usually of high grade and locally advanced, as are the sarcomas. More distant cancers, such as lung cancer and leukemia, usually fatal acute myelogenous leukemia, are associated with a dismal prognosis. Survival for the patients with any of these secondary malignancies is extremely poor, even with aggressive treatment, such as radical cystectomy for radiation-associated cancer in the bladder.^{19,20}

For argument's sake, let us assume that 5% of patients with prostate cancer die of their disease within 10 years after treatment. Next, let us use the raw numbers from Tables 1 and 2 and assume that another 5%-6% of patients will develop a second cancer after RT and that most, if not all, of these patients will die of it. Thus, the number of deaths after RT from a second cancer (not prostate) is equal to or greater than the number of deaths expected (5%) from prostate cancer after surgery. According to the model by Parker et al.,²¹ virtually none of the patients with a Gleason score of <7 would be expected to die of prostate cancer within a 15-year period.²¹ This means that, at least in terms of survival, a healthy patient undergoing RT would incur a risk of $\leq 5\%$ of death from a treatment-associated cancer, with no benefit to his prostate cancer. With the current shift from conventional RT to IMRT using increasingly greater doses and the survival time for patients diagnosed today with localized prostate cancer likely to exceed a decade or more, the potential adverse effect RT could have on

mortality should be considered when selecting the primary treatment modality.

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References

- Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *J Urol*. 2008;179:1889.
- D'Amico AV, Moul J, Carroll PR, et al. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol*. 2003;21:2163-2172.
- Kellen E, Zeegers MP, Dirx M, et al. Occurrence of both bladder cancer in five cancer registries in Belgium, The Netherlands and the United Kingdom. *Eur J Cancer*. 2007;43:1694-1700.
- Neugut AI, Ahsan H, Robinson E, et al. Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. *Cancer*. 1997;79:1600-1604.
- Brenner DJ. Induced second cancers after prostate-cancer radiotherapy: No cause for concern? *Int J Radiat Oncol Biol Phys*. 2006; 65:637-639.
- Bostrum PJ, Soloway MS. Secondary cancer after radiotherapy for prostate cancer: Should we be more aware of the risk? *Eur Urol*. 2007;52:973-982.
- Chrouser K, Leibovich B, Bergstralh E, et al. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol*. 2005;174:107-110.
- Movsas B, Hanlon AL, Hanks GE. Is there an increased risk of second primaries following prostate irradiation? *Int J Radiat Oncol Biol Phys*. 1998;41:251-255.
- Pickles T, Phillips N. The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984-2000. *Radiother Oncol*. 2002;65:145-151.

10. Brenner DJ, Curtis RE, Hall EJ, et al. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer*. 2000;88:398-406.
11. Moon K, Stukenborg GJ, Theodorescu D. Cancer incidence after localized therapy for prostate cancer. *Cancer*. 2006;107:991-998.
12. Brenner DJ, Hall EJ, Curtis RE, et al. Prostate radiotherapy is associated with second cancers in many organs, not just colorectum. *Gastroenterology*. 2005;129:773-774.
13. Kendal WS, Eapen L, Nicholas G. Second primary cancers after prostatic irradiation: ensuring an appropriate analysis. *Cancer*. 2007;109:164.
14. Hall EJ, Wu C-S. Radiation-induced second cancers: The impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys*. 2003;56:83-88.
15. Ruben JD, Davis S, Evans C, et al. The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. *Int J Radiat Oncol Biol Phys*. 2008;1530-1536.
16. Kry SF, Salehpour M, Follwill DS, et al. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2005;62:1195-1203.
17. Stathakis S, Li J, Ma CC. Monte Carlo determination of radiation-induced cancer risks for prostate patients undergoing intensity-modulated radiation therapy. *J Appl Clin Med Phys*. 2007;14-27.
18. Liauw SL, Sylvester JE, Morris GG, et al. Second malignancies after prostate brachytherapy: Incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. *Int J Radiat Oncol Biol Phys*. 2006;66:669-673.
19. Sandhu JS, Vickers AJ, Bochner BJ, et al. Clinical characteristics of bladder cancer in patients previously treated with radiation for prostate cancer. *BJU Int*. 2006;98:59-62.
20. Bostrum PJ, Soloway MS, Manoharan M, et al. Bladder cancer after radiotherapy for prostate cancer: Detailed analysis of pathological features and outcome after radical cystectomy. *J Urol*. 2008;179:91-95.
21. Parker C, Muston C, Mella J, et al. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. *Br J Cancer*. 2006;94:1361-1368.