Bladder Cancer After Radiotherapy for Prostate Cancer

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External beam radiotherapy (EBRT) is frequently used in the management of prostate cancer (PCa) as definitive, postoperative, or salvage local treatment. Although EBRT plays a central role in the management of PCa, complications remain a troubling by-product. Several studies have demonstrated an association between radiotherapy and elevated risk of acute and late toxicities. A secondary malignancy induced by initial therapy represents one of the most serious complications related to definitive cancer treatment. The radiation-related secondary primary malignancy risk increases with increasing survival time. Transitional cell carcinoma of the bladder is the most frequent secondary primary malignancy occurring after radiotherapy and is described as more aggressive; it may be diagnosed later because some radiation oncologists believe that the hematuria that occurs after prostate EBRT is normal. Some patients treated for localized PCa will subsequently develop invasive bladder cancer requiring surgical intervention. Patients with PCa treated with EBRT should be monitored closely for the presence of bladder cancer.

[Rev Urol. *2013;15(3):108-112 doi: 10.3909/riu0577*]

KEY WORDS

Bladder cancer • Prostate cancer • Radiotherapy • External beam radiotherapy

The phenomenon of radiation-inducing the carcinogenesis has been well described in literature for decades. The correlation between ionizing radiation and DNA damage has been discussed in several studies.[1-4] Most of these studies evaluated the growth of solid tumors in a large population exposed to moderate to heavy doses of radiation, such as factory workers, patients exposed to a large number of diagnostic radiographic studies, and survivors of atomic and nuclear explosions.[1] The casual effects of radiation exposure with subsequent mutagenesis are quite clear, shown both in vivo and in vitro.[2] Previous radiotherapy (RT) for prostate cancer (PCa) may play an important role in the development of secondary primary bladder cancer. This is a fairly uncommon event but a very real entity, of which both urologists and radiation oncologists need to be aware.

Material and Methods

A systematic review of articles published between 1997 and 2012 was been conducted via PubMed and MEDLINE using "prostate cancer", "radiotherapy", "bladder cancer", and "external beam radiotherapy" as key words. On the basis of clinical relevance and review aim, literature data were evaluated and collected. Studies on patients treated with brachytherapy were excluded from our study because there is no scientific evidence on the correlation between brachytherapy and secondary primary bladder cancer. All articles included patients with the same risk factors for age, comorbidities, race, and education. Information was evaluated from the Surveillance, Epidemiology and End Results (SEER) database, Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database, or single institutional/registry information. Selected papers were all published in urology journals with impact factors.

Epidemiology

According to American Cancer Society (ACS), approximately 69,250 new cases of bladder cancer were diagnosed in the United States in 2011 (approximately 52,020 men and 17,230 women); and approximately 14,990 patients died from bladder cancer (10,670 men and 4320 women).[5-8] In recent decades, the overall incidence of bladder cancer has increased by approximately 40% according to the National Cancer Institute's SEER Registry.[6] Previous RT for PCa may play an important role in the development of secondary primary bladder cancer. PCa is the most common malignancy in men and the second principal cause of cancer death in men. The latest ACS data estimates that 240,890 new cases of PCa were diagnosed in the United States in 2011 and resulted in 33,720 deaths.[9] Approximately one in six men will be diagnosed with PCa during their lifetimes (www.cancer.org). Treatment of localized PCa is recommended for patients with an expected life span of >10 years. Currently, RT is considered a valid alternative to surgery as treatment for PCa. Radical prostatectomy (RP) is the preferred treatment in healthier patients with a greater life expectancy and an organ-confined cancer[10]; however, RT is more frequently the first choice for patients with a lower likelihood of organ-confined disease and/or an increased risk for surgical complications.

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As the number of patients treated has increased, in addition to improved survival, delayed complications due to these therapeutic approaches have assumed increasing importance. Urinary morbidity after RT for PCa has been well documented and consists of urinary retention, intractable lower urinary tract symptoms, and hemorrhagic cystitis.[11,12] Moreover, epidemiologic studies show a relative risk of 1.5 for bladder cancer in patients treated with RT for PCa.[13]

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Second, primary cancers are a well-described complication of radiation exposure. As described by Li and colleagues, survivors of the Nagasaki atomic bomb are predisposed to develop radiosensitive solid tumors, including those of the breast, colon, lung, and urinary bladder.[14]

Diagnosis

Gross hematuria is the first sign of bladder cancer and is often due to radiation cystitis. This leads to a significantly longer latency period for the diagnosis of bladder cancer. Hemorrhagic cystitis is frequent and gross hematuria is not investigated with cystoscopy; when cystoscopy is performed, bladder cancer is often found in association with coexisting radiation cystitis.

Several researchers suggest that bladder cancer diagnosed in patients treated with RT for PCa could be more aggressive than bladder cancer without previous prostate irradiation. As Abern and colleagues suggested in their retrospective review of 275,200 cases of clinically localized PCa, RT is not only associated with increased likelihood of bladder cancer, but also with characteristic tumors and poor prognosis.[15] They observed that bladder cancer after RT was more likely to be nonurothelial compared with that after surgery. The most common nonurothelial bladder cancer was squamous cell cancer, which is largely refractory to platinum-based chemotherapy and poorer outcomes.

Transitional cell bladder cancer (TCC) remains the most common

malignancy in patients with prior RT for PCa, with greater rates of high-grade and muscle-invasive disease compared with the incidence in the general population. In 2006, Sandhu and colleagues tried to determine if TCC differs in behavior from bladder cancer diagnosed after RT for PCa.[10] A total of 100 patients diagnosed with bladder cancer following PCa were enrolled at the Memorial Sloan-Kettering Cancer Center Tumor Registry between 1992 and 2003. A total of 58 of these patients received RT for PCa. The authors concluded that bladder cancer is diagnosed later (62 vs 34 months) in irradiated patients than in those treated with other techniques for PCa. At the time of diagnosis of bladder cancer, 56 patients (97%) who had received RT had high-grade urothelial carcinoma versus 27 (64%) of those not irradiated. A total of 30 irradiated patients (52%) had muscle-invasive bladder cancer versus 17 patients (40%) who were not irradiated. Pelvic RT for PCa is also associated with an increased number of uncommon cancers, including bladder sarcomas and adenocarcinomas. The risk of developing a sarcoma within the treatment field was significantly larger after RT compared with surgery.

Shah and colleagues performed a retrospective review of patients diagnosed with bladder cancer and PCa between 1990 and 2005.[16] They observed new-onset urothelial carcinoma developed in 11 of 125 patients who had undergone external beam radiation therapy (EBRT) for PCa. Whole pelvis EBRT with a proton boost to the prostate was the radiation modality in seven patients (64%), whereas the remaining four patients received standard EBRT only. Urothelial carcinoma was detected at a mean of 3.07 years after the end of RT in the proton-beam–treated group, compared with a mean latency period of 5.75 years in the standard radiation group. All patients presented with gross hematuria and had cystoscopic findings of coexisting radiation cystitis. Of the 11 patients, five (45%) presented with Grade 3 (World Health Organization Classification 1973) carcinoma and seven (64%) required radical cystectomy. Urothelial tumors with sarcomatoid features (carcinosarcoma and spindle cell sarcomatoid) developed in two patients (18%). Of the 11 patients, 10 (91%) were nonsmokers at the time of urothelial carcinoma diagnosis. A recent study by Bostrom and associates analyzed the University of Miami cystectomy database between 1992 and 2006, and identified 34 patients with a history of RT for PCa.[17] The authors showed a significantly poorer overall survival and bladder-cancer–specific survival in patients who underwent cystectomy with a history of RT for PCa compared with that of a matched control group. They concluded that radiation-induced bladder cancers are a more aggressive form of cancer.

Risk Factors

Only EBRT has been identified as an independent risk factor for secondary primary bladder cancer. The relative risk of bladder cancer developing after EBRT, brachytherapy, and EBRT–brachytherapy has been compared with RP by Nieder and colleagues,[18] and was found to be 1.88, 1.52, and 1.85, respectively. Compared with the general US population, the standardized incidence ratio for bladder cancer developing after RP, EBRT, brachytherapy, and EBRT–brachytherapy was 0.99, 1.42, 1.10, and 1.39, respectively.

Similarly, Moon and colleagues demonstrated that men who received EBRT compared with nonirradiated patients had statistically significant increased odds of developing secondary cancers in several studies potentially related to RT, including bladder (odd ratio [OR] 1.63) and rectum (OR 1.60).[19] Moreover, they observed secondary malignancies in areas not potentially related to RT, including the cecum (OR 1.63), transverse colon (OR 1.85), and brain (OR 1.38), in addition to melanoma (OR 1.29).

Boorjian and colleagues[20] analyzed the CaPSURE disease registry for men diagnosed with PCa plus bladder cancer between 1989 and 2003 to determine the risk factors. They found that patients with bladder cancer and PCa were older than patients with PCa only. Patients treated with RP were approximately one-half as likely to have posttreatment bladder cancer as patients who underwent RT. Patients who smoked had an independent increased risk of bladder cancer, while smokers treated with RT had an almost fourfold higher risk for bladder cancer.

The risk increases as a function of the time after irradiation. The data we have analyzed show a significant increased risk after at least five years following irradiation, 15% after more than five years, and 34% after 10 years.[21] Not all studies have found an association between RT for PCa and bladder cancer. Chrouser and colleagues concluded that the natural history of bladder cancer does not seem to be altered by radiation history.[22]

Similarly, Singh and associates evaluated the risk of a second malignancy of bladder or prostate in patients with a previous diagnosis of PCa or urothelial cancer (TCC), respectively.[23] They analyzed consecutive cases of PCa and urothelial bladder cancer diagnosed at the Veterans Affairs Medical Center in Syracuse between 1996 and 2003. The authors found a correlation between PCa and bladder cancer following prior radiation treatment.

In a recent study, Huang and colleagues analyzed the incidence of secondary malignancies after different methods of RT in 2120 patients treated between 1984 and 2005 and matched them with surgical patients according to age and follow-up time.[24] They found that the overall secondary primary cancer risk was not significantly different between the matched pair (hazard ratio [HR] 4.94). Only two-dimensional RT was associated with a significantly higher risk, whereas the newer RT techniques (brachytherapy, brachytherapy boost, three-dimensional conformal RT [3 DCRT]/intensity-modulated RT [IMRT]) significantly reduced the risk.

Discussion

It is well established that higher doses of RT results in improved PCa control. The number of RT treatment modalities for PCa has increased in recent years, including different types of EBRT or brachytherapy. The risk of an induced second malignancy resulting from the mutagenic potential of ionizing radiation is well recognized.[25-27] Radiation causes its therapeutic effect by damaging DNA content of actively dividing cells. Several reports have demonstrated that PCa patients might have an inherently increased risk of bladder and rectal cancer. In our review of the literature, studies evaluated a 1-month to 10-year latency period. Boorjian and colleagues found 143 patients with secondary primary bladder cancer after RT for PCa and in 101 patients (70.6%) with bladder cancer that developed ≥ 30 days after RT. The remaining 42 patients were diagnosed with bladder cancer previous to, at the same time as, or within 30 days of receiving treatment for PCa.[20]

These analyses use SEER data or single institutional/registry information. With SEER data, a large number of patients can be studied but information is less complete with regard to treatment, radiation techniques, and/or other potential confounding factors. In comparison, single institutional reviews have more accurate data but suffer from a limited number of patients and a reliance on the use of the general population as the control. Selection, follow-up, and complete investigation bias should be considered in these studies.

Brachytherapy doesn't seem to be related to an increased risk in the development of secondary primary bladder cancer as supported by Huang and associates.[24]

We should not underestimate that a number of patients treated for localized PCa will subsequently require surgical intervention because of the development of invasive bladder cancer or radiation-related complications like refractory hemorrhagic cystitis. Although radical cystectomy with urinary diversion represents the reference standard for the treatment of muscle-invasive bladder cancer, significant morbidity may be associated with this surgery. Recently, Rao and associates proposed intravesical Bacillus Calmette-Guerin instillation for the management of nonmuscle-invasive bladder cancer in patients with prior prostate RT,[28] and observed a response in 50% of patients. The response is likely due to the chronic effects of pelvic RT on the local immune response within the bladder or possibly due to an intrinsic resistance to Bacillus Calmette-Guerin in RT-induced bladder tumors.

Conclusions

Considering the higher risk for developing bladder cancer after pelvis irradiation as highlighted in this article, it is advisable to supervise patients who undergo RT for the treatment of PCa. We propose a close follow-up with cystoscopy each year or every six months on the basis of existing comorbidities, as well as additional work-up and increased screening sampling density. ■

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MAIN POINTS

- Previous radiotherapy (RT) for prostate cancer (PCa) may play an important role in the development of secondary primary bladder cancer. This is a fairly uncommon event but a very real entity that both urologists and radiation oncologists need to be aware of.
- RT is considered a valid alternative to surgery as treatment for PCa. Radical prostatectomy is the preferred treatment in healthier patients with a greater life expectancy and an organ-confined cancer; however, RT is more frequently used for patients with a lower likelihood of organ-confined disease and/or an increased risk for surgical complications.
- Gross hematuria is the first sign of bladder cancer and is often due to radiation cystitis. This leads to a significantly longer latency period for the diagnosis of bladder cancer.
- Several researchers suggest that bladder cancer diagnosed in patients treated with RT for PCa may be more aggressive than bladder cancer without previous prostate irradiation.
- Due to the increased risk for developing bladder cancer after pelvis irradiation, it is advisable to supervise patients who undergo RT for the treatment of PCa. We propose a close follow-up with cystoscopy each year or every 6 months on the basis of existing comorbidities, as well as additional work-up and increased screening sampling density.