Review Article

Risk factors for secondary bladder cancer following prostate cancer radiotherapy

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Abstract: This review investigates the complex landscape of secondary bladder cancer (SBC) after radiotherapy for prostate cancer (PCa). External beam radiotherapy (EBRT) poses an increased risk for SBC, while brachytherapy seems to be associated with smaller increased risks for SBC due to its targeted radiation delivery, sparing the surrounding bladder tissue. Secondary cancers in the bladder are the most frequently diagnosed secondary cancers in the PCa patient population treated with radiotherapy. Patient-related factors are pivotal, with age emerging as a dual-edged factor. While advanced age is a recognized risk for bladder cancer, younger PCa patients exhibit higher susceptibility to radiation-induced cancers. Smoking, a well-established bladder cancer risk factor, increases this vulnerability. Studies highlight the synergistic effect of smoking and radiation exposure, amplifying the likelihood of genetic mutations and SBC. The latency period of SBC, which spans years to decades, remains a critical aspect. There is a strong dose-response relationship between radiation exposure and SBC risk, with higher doses consistently being associated with a higher SBC risk. While specific models for therapeutic radiation-induced SBC are lacking, insights from related studies, like the Atomic Bomb survivor research, emphasize the bladder's sensitivity to radiation-induced cancer. Chemotherapy in combination with radiotherapy, although infrequently used in PCa, emerges as a potential risk for bladder cancer. Bladder cancer's complex epidemiology, encompassing risk factors, treatment modalities, and cancer types, provides a comprehensive backdrop. As research refines understanding, we hope that this review contributes to guide clinicians, inform patient care, and shape preventive strategies on SBC.

Keywords: Secondary bladder cancer (SBC); radiotherapy; prostate cancer (PCa); risk factors

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Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies affecting men worldwide. With an aging population and advances in early detection, the incidence of PCa continues to rise (1). In the past decades, treatment modalities for PCa have evolved significantly, offering patients a range of therapeutic options. Among these, radiotherapy has emerged as a primary treatment modality, providing curative and palliative benefits to PCa patients. Despite its efficacy, radiotherapy is not without its complexities and potential risks.

Radiotherapy for PCa involves the targeted delivery of ionizing radiation to the eradicate cancer cells, typically through external beam radiotherapy (EBRT) or brachytherapy. This focused approach has proven to be

highly effective in controlling localized disease and has even extended to the management of locally advanced cases. However, this form of treatment carries the inherent risk of damaging surrounding healthy tissues. A growing concern has surfaced with the increasing use of radiotherapy in PCa treatment: the risk of radiation-induced secondary bladder cancers (SBC) (2,3). Observational studies have consistently shown that individuals who have undergone radiotherapy for PCa face an increased risk of developing SBC (4-6). This observation raises critical questions regarding the etiology, risk factors, and management of these secondary malignancies. Understanding the complexities and risk factors associated with the development of SBC following radiotherapy for PCa is crucial for both clinicians and patients.

Bladder cancer, the most common cancer in the urinary system, in itself has a complex epidemiological profile (7). Established risk factors include advanced age, cigarette smoking, male gender, familial predisposition, and exposure to occupational carcinogens (8). Bladder cancer can be categorized into two types: non-muscle-invasive and muscle-invasive (9). Muscle-invasive bladder cancer involves the infiltration of cancerous cells into the muscular wall, necessitating more aggressive treatment. In contrast, non-muscle invasive bladder cancer is confined to the inner layers of the bladder lining and is generally managed through less invasive approaches.

This review aims to identify the various risk factors associated with the development of SBC in patients who have undergone radiotherapy for PCa. By analysing the existing body of literature, we shed light on the complex interplay of factors that contribute to the development of SBC.

Radiotherapy treatment for PCa

Radiotherapy is an important treatment modality for PCa, offering patients a range of curative and palliative benefits. This approach involves the precise delivery of ionizing radiation to eliminate cancer cells within the prostate gland. Radiotherapy for PCa can be administered using two primary techniques: EBRT or brachytherapy (10). In EBRT, high-energy X-rays are directed at the prostate from outside the body, allowing for precise dose distribution and minimizing damage to surrounding healthy tissues (11). Several distinct types of EBRT are utilized in the treatment of PCa, each with its unique characteristics. Conventional 3-dimensional conformal radiation therapy (3D-CRT) is a traditional method that shapes radiation beams to match the size and contours of the prostate. It employs three-dimensional imaging and treatment planning for precise tumor targeting. Intensity-modulated radiation therapy (IMRT) takes precision to the next level by adjusting the intensity of radiation beams from multiple directions, minimizing exposure to nearby critical structures like the bladder and rectum, which reduces the risk of side effects (12). Image-guided radiation therapy (IGRT) offers real-time imaging during treatment to ensure accurate radiation delivery, adapting to any positional changes in the prostate (13). Volumetric modulated arc therapy (VMAT) is a recent advancement that delivers radiation continuously while the machine rotates around the patient, resulting in shorter treatment times and improved precision (11). Stereotactic body radiation therapy (SBRT), also referred to as stereotactic radiosurgery, administers high radiation doses in a limited number of sessions (11). It's frequently used for low-risk PCa due to its convenience and effectiveness or in case of oligometastatic disease. EBRT can be used as a standalone treatment or in combination with other therapies, such as hormone therapy or brachytherapy, to enhance its effectiveness. As advances in treatment planning and delivery continue to reduce side effects and improve precision, EBRT remains an attractive and versatile option for many PCa patients.

Brachytherapy involves the precise delivery of radiation therapy by placing radioactive sources directly within the prostate gland. Two main types of brachytherapy are employed in PCa treatment: low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy (14). LDR brachytherapy, also known as permanent seed implantation, involves the permanent placement of tiny radioactive seeds, typically containing isotopes like iodine-125 or palladium-103, directly into the prostate. These seeds emit a constant, low dose of radiation over an extended period. LDR brachytherapy is particularly suitable for patients with low to intermediate-risk PCa, as it offers excellent long-term cancer control with relatively low rates of urinary and rectal side effects (15). In contrast, HDR brachytherapy utilizes temporary catheters to deliver high doses of radiation to the prostate over a shorter period. The radioactive source is removed after each session, reducing radiation exposure to surrounding tissues. HDR brachytherapy can be combined with EBRT in patients with intermediate to high-risk PCa. This combination approach enhances the precision of radiation delivery and allows for higher radiation doses to the tumor (16). Both LDR and HDR brachytherapy have demonstrated high rates of cancer control and relatively

low rates of severe side effects. Both methods have proven highly effective in controlling localized disease and have even expanded to the management of locally advanced cases. Radiotherapy plays a pivotal role in the comprehensive management of PCa, and the choice of radiotherapy type (EBRT or brachytherapy) often depends on the patient's cancer stage, overall health, individual preferences, and availability of the treatment technique in the treating institute (17).

Irradiation of the bladder

In the context of adverse effects of radiotherapy for PCa, the bladder has a prominent role due to its proximity to the prostate gland (18). During treatment planning, the precise delivery of radiation to the prostate by minimizing radiation exposure to surrounding healthy tissues is of paramount importance. The bladder, being one of the primary adjacent organs, is particularly vulnerable to the side effects of radiation. As the prostate and the bladder share anatomical closeness, there is a risk of unintentional radiation exposure to the bladder during PCa radiotherapy, which can lead to various urinary complications (19). These may include irritative symptoms, such as urinary frequency and urgency, and in some cases, the potential development of secondary malignancies, notably bladder cancer. Thus, meticulous treatment planning and the use of advanced radiation techniques are essential to mitigate these risks, optimizing the therapeutic benefits of radiotherapy while safeguarding the integrity of the bladder, and preserving the patient's quality of life. In the following section, we will discuss the most important treatment-related and patient-related risk factors for SBC.

Treatment-related risk factors for SBC

EBRT

Large population-based studies have consistently reported an increased risk for SBC after EBRT, also after adjustments for age and calendar period at treatment (20-23). In a systematic review, Murray *et al.* [2014] reported the risk of developing an SBC post irradiation for PCa. They compared the risk to the general population and non-irradiated patients (5). Notably, studies specifically investigating SBC risks in comparison to non-irradiated PCa patients revealed significantly elevated risks. An important side note on these numbers, is that in the years 1990 and earlier, it was common to treat localized PCa patients standard with pelvic fields with elective nodal irradiation and therefore estimated SBC risks from older studies cannot be translated to the current situation.

It has been argued that a prostatectomy cohort is not a valid comparison group for EBRT because it concerns healthier patients with less comorbidity and less smokers, which are both risk factors for various cancers including bladder cancer. In a study by Eifler *et al.* [2012] (24), they observed that the risk of dying from cancer after radical prostatectomy was significantly lower compared to the general population with a standardized mortality ratio (SMR) of 0.45 for cancer in general and 0.47 for bladder cancer. In a study conducted by our research group (25), we calculated relative risks for SBC for EBRT patients compared to both the general population and prostatectomy patients, and we found a relative risk of 1.33 and 1.81 respectively (*Table 1*), which also suggests that the risk is overestimated using a prostatectomy comparison group. It is also noteworthy that in our comparison with a prostatectomy group, there was a significant increase in the risk of second lung cancer, likely attributed to poorer comorbidity/smoking profiles. This was not the case for the general population comparison. In the study of Eifler *et al.*, the risk of dying from lung cancer risks was largely reduced (SMR of 0.31). In a randomized control trial by Aksnessæther *et al.* (26), PCa patients receiving androgen deprivation therapy (ADT) were compared to patients receiving ADT + EBRT. An increased risk of SBC among patients receiving EBRT was found, with a relative risk point estimate of 2.54 and a confidence interval of 1.1–5.6. These findings, when considered alongside those from retrospective cohort studies, underscore the consistent elevation in risk associated with pelvic radiotherapy. The findings of the main studies exploring SBC risk after EBRT are summarized in *Table 1*.

In the past two decades EBRT techniques rapidly evolved, applying smaller safety margins, using IMRT techniques, and introducing daily monitoring of patient and tumor position (adaptive radiotherapy). This might also have had an impact on SBC risks. Unfortunately, many studies are limited in their specific information regarding what type of EBRT was used. Research outcomes regarding the impact of advanced EBRT on SBC risk remain indecisive. In broad terms, it is believed that advanced EBRT techniques tend to reduce the average bladder radiation dose and minimize the volume of the bladder exposed to intermediate-dose radiation, but may increase

Table 1 Studies examining SBC risk in PCa patients receiving EBRT

Study	Type of data	Comparison group	No. of patients receiving EBRT	Median follow-up, years	Risk of SBC	Magnitude of SBC risk
Wu, 2022 (20)	SEER registry	Non-irradiated patients	97,799	10.5	Increased	HR: 1.60 (95% CI: 1.50–1.70), P<0.01
Davis, 2014 (21)	SEER registry	General population	25,569	Not specified	Increased	SIR: 1.42 (95% CI: 1.28–1.58)
Guo, 2019 (22)	SEER registry	Non-irradiated patients	143,679	6.1	Increased	HR: 1.41 (95% CI: 1.33–1.51), P<0.01
Abern, 2013 (23)	SEER registry	General population	83,110	5.4	Increased	SIR: 1.14 (95% CI: 1.08–1.20)
Aksnessæther, 2020 (26)	Randomized controlled trial	PCa patients receiving androgen deprivation therapy	429	12.2	Increased	HR: 2.54 (95% CI: 1.14–5.60), P=0.023
Jahreiß, 2021 (25)	Netherlands cancer registry	Radical prostatectomy	42,069	5.2	Increased	sHR: 1.83 (95% CI: 1.63–2.05), P<0.01
Jahreiß, 2021 (25)	Netherlands cancer registry	General population	42,069	5.2	Increased	SIR: 1.33 (95% CI: 1.26–1.44)

SBC, secondary bladder cancer; PCa, prostate cancer; EBRT, external beam radiotherapy; CI, confidence interval; SEER, the surveillance, epidemiology, and end results; HR, hazard ratio; SIR, standardized incidence ratio; sHR, subhazard ratio.

exposure of bladder volumes to (very) low dose levels. Consequently, this reduction might be associated with a decreased risk of developing SBC but to our knowledge, this has not been confirmed yet with clinical data (5,27). Exploring the impact of treatment technique on SBC risk remains complex, with varying results among different studies. In a large nationwide cohort study carried out in the Netherlands, calendar periods were used to represent different EBRT eras (25). The study revealed that the highest risk for SBC was associated with the 3D-CRT era, but differences with other technique eras were not significant. Despite a reduction in risk during the advanced EBRT era, the study observed a persistent risk of SBC. Upon closer examination of SBC risk after IMRT versus 3D-CRT at multi- and single-center level, no significant differences were observed between IMRT and 3D-CRT (28,29). The findings across the studies demonstrate a consistent trend of lower risks for second pelvic cancers, particularly bladder SBC, compared to earlier treatment eras such as 3D-CRT. This indicates a potential advantage of advanced EBRT techniques in mitigating the occurrence of secondary cancers in the pelvis.

Brachytherapy

Studies examining the risk of secondary primary cancers in general have consistently found that the probability of developing a secondary cancer after PCa brachytherapy is lower than that following EBRT (5,30-32). This can be attributed to several factors. Brachytherapy offers a more targeted and precise delivery of radiation, minimizing exposure to surrounding tissues, including the bladder (33). It allows for dose escalation while sparing nearby organs, and typically involves a shorter treatment duration. In their systematic review, Murray *et al.* [2014] also examined the likelihood of developing SBC subsequent to brachytherapy for PCa. In general, the evidence from patients treated with brachytherapy or EBRT + brachytherapy is encouraging, and less suggestive of an increased risk of second cancers, especially when compared to the risk following EBRT. However, there have been studies suggesting an increased risk of bladder cancer, particularly in the first years of follow-up (34-36). A subsequent paragraph will address factors related to the latency period for the development of SBC. Ultimately, the choice between brachytherapy and EBRT should be based on a thorough assessment of the patient's and tumor unique characteristics and a careful consideration of the potential risks and benefits of each treatment option.

Dose exposure and radiation-induced SBC risks

Within the context of radiation-induced SBC, the dose-response relationship plays a crucial role, with existing

literature consistently indicating that higher dose exposures are associated with elevated SBC levels compared to lower or no dose exposures (37). The excess relative risk per Gray (ERR per Gy) serves as a quantitative measure delineating the precise relationship between dose exposure and excess risk. To the best of our knowledge, currently there are no ERR models based on exposure to fractionated therapeutic radiation published. However, insightful data from the Atomic Bomb survivor studies has emphasized the bladder's sensitivity to radiation-induced cancer, revealing discernible differences between male and female populations. Grant *et al.* [2017] reported on the radiation risks of all solid cancers while focusing on the shape of the dose response, which further contributed to our understanding of the intricate relationship between radiation exposure and bladder cancer risk (38). These findings collectively underscore the importance of discerning dose-response dynamics for effective risk assessment and management in the context of radiation-induced bladder cancers. Groot *et al.* [2018] contributed valuable information regarding the risk of solid cancer after treatment of testicular germ cell cancer, including relevant data on high/low dose exposure and SBC risks (39). These findings highlight the need to understand how doses of radiation relate to the risk of bladder cancer, which is crucial for effective risk assessment and management in cases of radiation-induced bladder cancers. Abern *et al.* investigated the characteristics of SBC after PCa radiotherapy in a large review of SEER data and reported on significance differences for the distributions of sublocations (more trigone cases) and pathology [more carcinoma in situ (CIS) cases and more non-urothelial case] (23).

Chemotherapy

The primary treatment of PCa does not include the treatment of chemotherapy + EBRT. This differs from other tumor sites, such as testicular cancer and non-Hodgkin lymphoma, where radiotherapy in the pelvic area is occasionally complemented with chemotherapy to achieve superior tumor control. Nevertheless, it is crucial to highlight that chemotherapy has been recognized as a potential risk factor for the onset of bladder cancer (40). This association arises from the potential dysregulation of normal cells in organs characterized by rapid cell turnover. Literature reports specifically point to the induction of bladder cancer by cyclophosphamide chemotherapy (41). As of now, there is no evidence supporting the occurrence of SBC induced by the combined treatment of EBRT + chemotherapy, primarily attributed to the infrequency of this treatment regimen for PCa.

Patient-related risk factors for SBC

Age

Advanced age is a common factor associated with heightened risks across numerous cancer types, and this is particularly evident for bladder cancer. Data from a large population-based study determining the effect of age on survival in bladder cancer found that about 40% of diagnosed cases is older than 75 years and only about 10% is younger than 55 years (37). Likewise, an extensive review study determined that being at advanced age is acknowledged as the primary and most significant risk factor for the development of bladder cancer (7). Contrary to this, multiple studies suggest that the risks of radiation-induced cancers are more pronounced in younger individuals due to the characteristics of youthful tissue (2,42). In the study conducted by de Gonzalez *et al.* [2015], it was demonstrated that the likelihood of developing a second cancer in a region exposed to high radiation doses, such as the bladder, diminishes with increasing age at the diagnosis of PCa (42). This risk even becomes statistically insignificant for patients diagnosed with PCa at the age of 75 years or older. However, despite the observed trend of reduced risk of radiation-induced cancers with increasing age, it is essential to consider the interplay of specific relative risks alongside the potential acceleration of second cancers in older patients with pre-existing risk factors such as smoking. While younger patients face a prolonged risk window, older patients may experience an accelerated onset of second cancers due to these factors. This underscores the complexity of assessing the risk-benefit ratio across different age groups and risk profiles. Given that the majority of the PCa population is aged 65 years and above, it is crucial to note that while advanced age itself may not elevate the risk, the presence of other risk factors like smoking could contribute to an increased likelihood of second cancers during the post-radiotherapy follow-up period.

Smoking

Smoking is an established risk factor for the development of bladder cancer. Smoking is intricately linked to bladder cancer through the presence of carcinogens in tobacco smoke (43). These include aromatic amines and polycyclic

aromatic hydrocarbons, which induce DNA damage in bladder cells, fostering genetic mutations and cancer development. Direct contact of tobacco-related carcinogens irritates the bladder lining, and their metabolism in the liver generates reactive compounds. Chronic inflammation, abnormal cell proliferation, and weakened immune responses further contribute to the cancer risk (44). The combination of smoking and radiation exposure, as in the case of PCa patients undergoing EBRT, may further elevate the risk of bladder cancer (45). Smoking introduces additional carcinogens into the body, compounding the DNA damage caused by radiation. This synergistic effect increases the likelihood of genetic mutations and ultimately SBC. Although numerous cohort studies employing extensive registry data often lack comprehensive information about the smoking status of patients, they consistently underscore its crucial role as a confounding factor in secondary cancer development after radiotherapy. Studies exploring secondary cancer risk, with detailed patient smoking data, overwhelmingly identify it as a significant predictor for the development of SBC (45,46). Shiota and colleagues (45) investigated the combinational effect of EBRT for PCa and smoking on the risk of developing SBC. They found an interaction between active smoking and SBC and concluded that smoking history should be considered a criterion to opt for radical prostatectomy rather than EBRT (45). In a study carried out by Boorjian *et al.* (46), the presence of smoking was also found to significantly increased the probability of developing an SBC, especially in combination with radiotherapy.

Latency period of SBC

The latency period concerning SBC subsequent to radiotherapy for PCa is defined as the duration between exposure to ionizing radiation and the onset of a SBC. This timeframe can vary, from several years to decades, and is influenced by factors such as radiation type, dose, and individual patient characteristics. A study by Brenner *et al.*, has demonstrated a significant increased risk of SBC at least 5 years following irradiation, 15% after more than 5 years, and 34% after 10 years (2). While second cancers, particularly those induced by radiotherapy for PCa, exhibit a long latency period, their relevance remains pronounced, especially considering the age-related susceptibility of patients. As treatment modalities evolve, more recent research findings provide important insight into the changing landscape of second cancer risks, offering more accurate reflection of the current treatment protocols. However, the long latency period of second cancers complicates the assessment of newer treatment protocols.

Strengths and limitations

The review presents a comprehensive examination of the risk factors associated with SBC following radiotherapy for PCa, encompassing treatment modalities, dose exposure, and patient-related risk factors. However, it is limited by the reliance on historical data, the potential biases inherent in comparing treatment cohorts, and the lack of extensive exploration of emerging technologies, which is attributed to the necessary follow-up time required for studying SBC. Despite these limitations, the review underscores the importance of risk assessment, patient education, and preventive measures in clinical practice.

Conclusions

In conclusion, this review explored the landscape of SBC following radiotherapy for PCa. The review highlights the nuanced relationship between treatment modalities and SBC risk, noting that EBRT, particularly historical methods like 3D-CRT, poses an increased SBC risk. Advanced EBRT techniques seem to mitigate risks, but uncertainties persist. Conversely, brachytherapy demonstrates a lower incidence of second cancers due to targeted radiation delivery. While bladder cancer is more frequently observed in older patients, it is noteworthy that radiation-induced cancers tend to occur more often in younger patients. Furthermore, the probability of developing an SBC is further exacerbated by smoking. Dose-response dynamics reveal a consistent association between higher radiation doses and elevated SBC levels. Although specific models for therapeutic radiation-induced SBC are lacking, insights from related studies emphasize the bladder's sensitivity to radiation-induced cancer. As ongoing research refines our comprehension, this review may play a role in guiding clinicians, educating patient care, and influencing the development of preventive strategies.

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Footnote

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