Secondary malignancies following radiotherapy for prostate cancer

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Abstract: Human exposure to sources of radiation as well as the use of radiation-derived therapeutic and diagnostic modalities for medical reasons has been ongoing for the last 60 years or so. The carcinogenetic effect of radiation either due to accidental exposure or use of radiation for the treatment of cancer has been undoubtedly proven during the last decades. The role of radiation therapy in the treatment of patients with prostate cancer is constantly increasing as less-invasive treatment modalities are sought for the management of this widely, prevalent disease. Moreover the wide adoption of screening for prostate cancer has led to a decrease in the average age that patients are diagnosed with prostate cancer. Screening has also resulted in the diagnosis of low-grade, less-aggressive prostate cancers which would probably never lead to complications or death from the disease. Radiotherapy for prostate cancer has been linked to the late occurrence of second malignancies both in the true pelvis and outside the targeted area due to low-dose radiation scatter. Secondary malignancies following prostate irradiation include predominantly bladder cancer and, to a lesser extent, colon cancer. Those secondary radiation-induced bladder tumors are usually aggressive and sometimes lethal. Care should be given to the long-term follow up of patients under radiation therapy for prostate cancer, while the indications for its use in certain cases should be reconsidered.

Keywords: brachytherapy, prostate cancer, radiation therapy, secondary bladder cancer

Radiation and malignancies

Radiation-induced malignant transformation is a problem that has emerged recently, or at least has been recognized recently, in the area of oncology. The association between radiation and malignancies was initially observed in the population that survived the World War II bombings. The role of radiation as a precursor of malignancy has been established in subsequent studies of Japanese survivors of the atomic bomb, survivors of the Chernobyl nuclear accident, after occupational exposure to radiation, and following the use of radiation in medicine [Brenner and Hall, 2007; Suit *et al.* 2007; Preston *et al.* 2003].

Environmental radiation exposure, DNA damage and risk of malignancies

The risk of malignancy after radiation varies between different animals and between different strains of the same species, and even tissues vary in their sensitivity to radiation. Suit and

colleagues reviewed the data on the effects of radiation in cell cultures, animal studies and in humans exposed to radiation. In cell cultures, a linear increase of transformations was noted as radiation increased from 1 to 7 Gy [Suit *et al.* 2007].

Older studies have suggested a long latency period between radiation exposure and the development of clinical cancer although the increased risk is life long. Quilty and Kerr reported the median latency period between the delivery of pelvic radiation and the diagnosis of bladder cancer to be 30 and 16.5 years using low-dose and high-dose radiation, respectively [Quilty and Kerr, 1987].

However, recent studies have estimated a mean latency period of 5 years from radiation exposure to radiation-induced cancer [Suit *et al.* 2007; Boice and Lubin, 1997]. Studies on patients

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who survived the release of radioactivity after the accident at the Chernobyl nuclear facility show an increase in DNA damage, DNA damage-repair mechanisms, and urinary bladder lesions [Romanenko *et al.* 2003, 2002; Yamamoto *et al.* 1999].

The same studies have shown that a 73% rate of urothelial carcinoma in a cohort of patients with benign prostatic hyperplasia (BPH) or chronic cystitis, while the rate of bladder dysplasia was 97%, compared with no carcinomas and a 27% rate of dysplasia in unaffected areas [Romanenko *et al.* 2003]. The incidence of bladder cancer increased from 26.2 to 43.3 per 100,000 between 1986 and 2001 (after the Chernobyl accident) [Pavlova *et al.* 2001].

An issue that had gone largely unrecognized in the past is the effect of imaging studies in the development of radiation-induced malignancies. It has been shown that the lowest radiation dose absorbed in the tissue that can cause cancer is around 35 mSv or 1 mGy, which is equal to three or four abdominal computed tomography (CT) scans. A recent controversial study came up with the disconcerting finding that 1.5–2% of cancer cases in the USA are caused by radiation from diagnostic CT scans. It was also estimated that one third of those CT scans were not based on medical need, challenging the current indications on the use of imaging modalities [Brenner and Hall, 2007].

Radiotherapy-induced malignancies

In the clinical setting the existence of an association between therapeutic radiation and secondary malignancies has been clearly observed in patients treated with external beam radiation therapy (EBRT) for cervical cancer. The latency period between exposure to therapeutic radiation and occurrence of radiation-induced malignancy was estimated to be between 5 and 15 years [Suit *et al.* 2007].

Patients were diagnosed with new tumors of different histology than squamous cell cervical cancer and in many cases the new tumors were located outside the irradiated field. This phenomenon was attributed to low-dose radiation scatter [Senkus *et al.* 2000; Ohno *et al.* 1997; Kleinerman *et al.* 1995; Filatova, 1990].

Another example of radiation-induced malignancy is the occurrence of lethal breast sarcomas

following radiation given after lumpectomy for breast ductal carcinoma *in situ* (DCIS). The aim of adjuvant radiation is to obtain local control of the disease, although this is performed without a documented overall survival benefit. These radiation-induced sarcomas have been estimated to occur in approximately 1/200 to 1/1000 patients who receive radiation therapy [Mills *et al.* 2002; Choy *et al.* 1993; Wijnmaalen *et al.* 1993].

The issue of second cancers following therapeutic radiation for a wide variety of malignancies is currently receiving increased attention as it is well recognized that patients who receive radiation therapy have an increased long-term risk for developing second primary cancers compared with patients who do not receive radiation therapy. Radiation therapy has been linked to occurrences of secondary malignancies, including leukemia, sarcomas, thyroid carcinoma, lung carcinoma, and bladder carcinoma [Kendal and Nicholas, 2007; Kleinerman *et al.* 1995].

Radiotherapy for prostatic carcinoma

Prostate cancer is the leading type of cancer and the second leading cause of death in Western men. It was estimated that 218,890 new cases of prostate cancer and 27,050 deaths from the disease occurred in the USA in 2007. The prevalence of prostate cancer was estimated to be 1,832,000 in 2002 [Jemal *et al.* 2007]. Radical prostatectomy and radiation therapy in the form of EBRT, brachytherapy, or the combination of EBRT followed by brachytherapy are considered definitive therapies for patients with localized prostate cancer. Radical prostatectomy is the preferred treatment in younger, healthier patients with a longer life expectancy who have a higher likelihood of organ-confined disease. Surgery is associated with a significant risk of serious early complications such as incontinence and erectile dysfunction. Most complications related to surgery have an initial impact with a gradual return to preoperative function [Blasko *et al.* 1993].

Radiation therapy is an alternative treatment and is considered the optimal choice for older, frailer patients at risk for complications from surgery as well as for patients in whom the likelihood of organ-confined disease is lower. Radiation therapy can also be delivered as adjuvant therapy for biochemical local relapse following surgical

treatment of prostate cancer. Radiation for prostate cancer can be currently applied by a variety of modalities. EBRT can be delivered by three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT; high dose), or proton beam.

These new radiation delivery modalities (IMRT, 3D-CRT) have been designed to allow dose escalation with reduced toxicity. The goal of any form of radiation delivery technique is to target only the prostate with high doses of radiation. Dosimetric studies have established IMRT as superior to 3D-CRT in terms of target coverage, conformity, and sparing of normal tissues. Furthermore, IMRT is superior in terms of functional sparing of critical organs while offering survival outcomes equivalent to those of 3D-CRT. However, concern has been raised regarding its carcinogenic potential.

The issue with IMRT is that it increases the integral dose to normal tissues by spreading out radiation dose so that a larger volume of tissue receives lower, more carcinogenic radiation doses. IMRT might therefore be expected to pose a greater carcinogenic risk than 3D-CRT. It has been estimated that IMRT to the prostate is associated with a three-fold increased risk for a second cancer compared with 3D-CRT [Ruben *et al.* 2008; Kry *et al.* 2005; Thilmann *et al.* 2004; Nutting *et al.* 2001].

Brachytherapy, or interstitial radiation therapy, is an alternative treatment option for prostate cancer patients, particularly for those with less-aggressive features, although the role of brachytherapy still continues to evolve. Brachytherapy can be delivered by a variety of isotopes such as I-125 and Ir-192 [Henry *et al.* 2010; Edgren *et al.* 2006].

Neugut and colleagues were the first to report an increased risk for secondary cancers after radiation for prostate cancer [Neugut *et al.* 1997]. The latency period between radiation exposure and radiation induced secondary tumors ranged from 5 to 15 years [Thompson *et al.* 1994; Jao *et al.* 1987].

In a review of the data from the Surveillance, Epidemiology and End Results (SEER) Medicare Program, in 269,069 men with prostate cancer, 9.9% were diagnosed with a heterochronous secondary cancer. The mean follow up was

7 years, and the median number of days was 2342 (6.4 years) [Moon *et al.* 2006]. In this study it was shown that men who received EBRT as their only form of therapy had statistically significant increased odds of secondary cancers at several sites potentially related to radiation therapy, including the bladder, rectum, and lung.

Men who received EBRT also had statistically significantly higher odds of secondary cancers occurring at sites in the upper body and other areas not directly related to radiation therapy, such as the cecum, transverse colon, brain, stomach, skin, and lung, compared with men who did not receive radiation therapy.

A recent review on the risks of secondary malignancies following delivery of radiation therapy confirmed a modest increase in secondary cancers associated with radiation for prostate cancer. It was estimated that approximately 1/70 patients undergoing radiation and surviving more than 10 years will develop secondary cancer. The most common sites for secondary cancers are the bladder and rectum. Men who received radiation therapy in the form of the radioactive implants or isotopes, either in isolation or in combination with beam radiation, did not appear to have significantly different odds of secondary cancer occurring at any of the 20 most common sites [Moon *et al.* 2006].

Another study based on data from SEER shows that the risk of secondary primary cancer (SPC) was lowest in the group who underwent brachytherapy and greatest in the group who had undergone EBRT. The patients who had undergone a combination of EBRT and brachytherapy had an intermediate SPC risk between the other two groups [Abdel-Wahab *et al.* 2008].

Rectal cancer after radiation therapy for prostate cancer

The risk of developing cancer of the rectum after radiation therapy for prostate cancer is similar to the risk of having a first-degree relative with colorectal cancer. There is evidence that radiation shifts the patients from normal to moderate risk for rectal cancer. Baxter and colleagues reported a significant increase in the development of rectal cancer, indicating that the effect was specific to directly irradiated tissue. The observed hazard ratio for radiation therapy and subsequent rectal

cancer was 1.7 [Baxter *et al.* 2005]. Results from the SEER database estimated the relative risk of rectal cancer developing after EBRT, brachytherapy, and EBRT–brachytherapy compared with radical prostatectomy to be 1.26, 1.08, and 1.21, respectively [Nieder *et al.* 2008].

On the other hand, a large analysis of 33,831 patients who received radiation for prostate cancer did not reveal the presence of measurable risk for the subsequent development of rectal cancer [Kendal *et al.* 2006].

It seems that there is a relatively increased risk of rectal cancer for patients that underwent radiation therapy for prostate cancer. However, it is still not clear whether this risk should be solely attributed to the effects of radiation alone.

Bladder cancer after radiation therapy for prostate cancer

There is evidence that patients diagnosed with prostate cancer share an increased relative risk for primary bladder cancer occurrence irrespective of the treatment modality used [Chun, 1997; Liskow *et al.* 1987].

Epidemiological studies show a higher rate (5–6% versus 3.7%) of bladder cancer in patients receiving radiation for prostate cancer compared with patients who underwent surgery or watchful waiting [Moon *et al.* 2006]. Bladder cancer cases diagnosed following prostatic radiation therapy differ in histology and biological behavior from bladder cancers diagnosed in patients with prostate cancer who did not receive radiation therapy. Histology in these cases shows an undifferentiated malignant tumor which does not resemble prostate adenocarcinoma. Radiation has been shown to be associated with the *in vitro* progression of low-grade urothelial tumors to high-grade tumors and a higher rate of p53 mutations [Romanenko *et al.* 2002; Yamamoto *et al.* 1999; Pazzaglia *et al.* 1994].

In the vast majority, the secondary bladder carcinomas are high grade and muscle invasive at diagnosis. Moreover, bladder cancer-specific survival is worse in the population of patients who present with secondary bladder cancer following radiation for prostate cancer versus patients not treated with radiation [Kendal *et al.* 2007; Brenner, 2006; Moon *et al.* 2006].

Studies have suggested an increased bladder cancer risk after radiation for prostate cancer with a risk ratio of approximately 1.5 [Boorjian *et al.* 2007; Moon *et al.* 2006; Brenner *et al.* 2000].

This increased risk was reported after primary and adjuvant EBRT [Chrouser *et al.* 2005]. Although radiation-treated patients had more high-grade and muscle-invasive tumors, there was no survival difference compared with patients with a history of other prostate cancer treatments [Sandhu *et al.* 2006].

The study by Sandhu and colleagues included 100 patients diagnosed with bladder cancer after a diagnosis of prostate cancer. Fifty-eight of those patients were treated with radiation therapy. The mean time between the diagnosis of bladder cancer and prostate cancer was 62 months in the radiation therapy group and 34 months in the nonirradiated group. At the time of diagnosis, 56 of the 58 patients (97%) who received radiation therapy had high-grade urothelial carcinoma, *versus* 27 (64%) in those not irradiated. Thirty (52%) of the patients with radiation therapy had muscle-invasive bladder cancer, *versus* 17 (40%) of those not irradiated. The overall survival rate was slightly worse for the irradiated patients [Sandhu *et al.* 2006].

A study by Bostrom and colleagues retrospectively evaluated 34 patients who underwent cystectomy for bladder cancer and had a history of irradiation for prostate cancer. In 86% of cases hematuria was the initial symptom while 53% of the patients were found to harbor muscle-invasive disease following cystectomy. The method of urinary diversion used was the ileal conduit [Bostrom *et al.* 2008].

Regarding the risks of surgical treatment, the mortality rate of patients undergoing radical cystectomy ranges from 2.9% to 7% according to recent series [Bostrom *et al.* 2008; Sandhu *et al.* 2006; Stein and Skinner, 2003]. In radical cystectomy cases there is an increased risk of intra-operative rectal injury, presumably due to the lack of planes posterior to the prostate and the need for sharp dissection. The complication rates, around 10%, were similar in various studies for patients undergoing radical cystectomy following definitive therapy for prostate cancer [Bostrom *et al.* 2008; Schuster *et al.* 2003; Kim and Steinberg, 2001].

Current studies have shown that the interval between prostate and bladder cancer is significantly longer in the radiotherapy group. This delay in the diagnosis of bladder cancer in those treated with radiotherapy is probably due to the belief that hematuria after prostate radiotherapy is a normal finding which leads to a delayed cystoscopy. Furthermore, since radiation is delivered by nonurologists and the follow up is done by nonurologists, perhaps the signs and symptoms of bladder cancer are poorly understood, even though the prostate cancer is managed appropriately with serial serum prostate-specific antigen tests and digital rectal examination. In addition some tests for invasive bladder cancer, e.g. urinary cytology and the bladder tumor antigen test, can be falsely positive in the setting of radiation therapy, making those tests difficult to interpret [Crane *et al.* 1999; Wiggishoff and McDonald, 1972].

With regard to brachytherapy one would expect that, given that it is more targeted than EBRT, the risk of secondary bladder cancers would be less. On the contrary, even with brachytherapy, the odds ratio for bladder malignancies seems to be rising following years after treatment for prostate cancer [Liau *et al.* 2006].

Conclusions

Radiation-induced malignancies represent a reality. Radiotherapy is associated with a modest increase in secondary cancers. In the treatment of prostate cancer, the risk of dying from a secondary radiation-induced bladder cancer may be greater than the risk of dying from the primary prostatic tumor following surgery or watchful waiting. Although the overall risk of secondary cancers is not high enough to question or defer the need for radiotherapy in prostate cancer, there is concern regarding the adverse effects of radiation therapy in low-risk patients with minimal risk of dying from prostate cancer. With regards to bladder cancer, patients with prostate cancer treated with radiation therapy should be monitored closely, over a period of up to 15 years, because of the delay in diagnosis, the more aggressive presentation of bladder cancer, and the subsequent worse survival.

Conflict of interest statement

The authors have no conflict of interest to declare in connection with this work.

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