Radiation-induced Second Malignancies

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Abstract. *Background: The number of patients with second malignancies is growing and they represent about one in six out of all new cancers. Second malignancies can be categorized into three major groups according to the predominant etiological factor(s): (i) treatment-related, (ii) part of a syndrome and (iii) those due to shared etiologic exposures. Patients and Methods: This article focuses on radiation-induced malignancies with illustrative cases of thyroid, rectal cancer and sarcoma. Results: The detection and management of radiation-induced malignancies of some case scenarios are presented. Second malignancies are detected within previous radiation field and the time intervals from previous tumor vary from 8 to 21 years. Conclusion: Clinicians should aim to reduce radiation-induced malignancies by careful selection of patients and radiation techniques before radiotherapy. Subsequent vigilant follow-up and investigations can detect these radiation-induced malignancies early and, hence, result in successful treatment.*

When a tumor occurs within the radiation field of a previous malignancy, differential diagnoses include: (i) local recurrence of original tumor, (ii) field effect for unstable epithelium, *e.g.* bladder tumor after radiotherapy to the whole bladder or vaginal cancer after radiotherapy of a previous cervical cancer, (iii) new primary and (iv) radiation-induced second malignancy.

The number of patients with second malignancies is growing, with these now representing about one in six of all new cancers reported to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program (1). Second malignancies can be categorized into three major groups according to the predominant etiological factor(s): (i) treatment-related, (ii) part of a syndrome and (iii) shared etiological exposures, especially tobacco and excessive alcohol intake and other factors such as, genetic susceptibility, environmental exposures and host effects including gene-environment interactions (2).

This article focuses on radiation-induced malignancies and common examples are listed in Table I (3). Case scenarios are presented. Practical guidance to detection and treatment options including surgery, chemotherapy and re-irradiation (4) will be herein discussed.

Case Scenarios

Table II lists some cases seen by the authors. All second malignancies in the Table are within previous radiation field. Both previous radiation doses and time intervals to second malignancies vary greatly.

The first patient in Table II was diagnosed in 2005 with adenocarcinoma of the left breast, stage T1 N1. She underwent lumpectomy and axillary dissection. One out of twenty-two nodes were involved. It was a T1 tumor, grade 2. Lymphovascular invasion was negative. The tumor was estrogen- and progesterone receptor-positive. The patient received adjuvant external beam radiotherapy in 2005 with a dose of 50 Gy in 25 fractions to the entire left breast by a 6 MV photon and a 12 MeV electron boost of 10 Gy in 5 fractions to the lumpectomy site. She also received adjuvant tamoxifen. The patient remained well after that for eight years. In the winter of 2012, she started to notice some purplish discoloration of the skin of the lower half of the left breast. A biopsy showed angiosarcoma. She underwent investigations included CT scan of the chest, abdomen and pelvis showing skin thickening in the left breast with an approximately 2 cm spiculated mass involving the left breast tissue laterally. There was a 6-mm pulmonary nodule seen at the left base

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Table I. *Common examples of radiation-induced malignancies.*

Initial cancer	Radiation-induced malignancies
Low-grade glioma	Meningioma, sarcoma
Retinoblastoma	Osteosarcoma
Nasopharyngeal carcinoma	Oral cavity, particularly tongue
Breast cancer	Esophageal cancer, angiosarcoma
Prostate cancer	Bladder, rectal cancer
Ewing's sarcoma	Osteosarcoma
Hodgkin lymphoma	Thyroid, breast, stomach cancer

peripherally, as well as a few other tiny subpleural nodular densities. These were entirely nonspecific at that point but could be assessed on follow-up. There was no lymphadenopathy. The intra-abdominal solid organs were normal in appearance. The tumor had grown in the last six months. Upon examination, the left breast was tender only on palpation and it was not painful, usually for the patient. A wide local excision of the tumor was performed on November 12, 2013 and no graft was required at that time. The lesion was grossly removed but the superior margin was less than 0.5 mm. The surgeon performed a re-resection. Four months later she developed multiple bone metastases involving the cervical spine and received palliative radiotherapy 20 Gy in 5 fractions. She died five months after diagnosis of angiosarcoma.

The second patient had a Hodgkin's lymphoma in 1981 when he was 16 years of age, treated with mantle and inverted-Y radiation to 35 Gy/20 fractions plus a boost of 5 Gy/2 fractions to the lower neck with a cobalt machine. He was well until 2002 when a high-grade papillary carcinoma, possibly insular carcinoma, was found. A total thyroidectomy was performed in June 2002 followed by radioactive iodine ablation (30 mCi). He developed nodal recurrence and, hence, a right neck dissection was performed in November 2002. He then developed an occipital skull metastasis with generous excision in January, 2005 followed by postoperative local radiotherapy 56 Gy/28 fractions as the patient was afraid of wide field radiotherapy to the whole skull or brain. He developed bilateral neck node recurrences and had bilateral neck dissection and right hemilaryngectomy in May 2005 in Toronto, followed by radioactive iodine therapy in Saskatoon in August 2005. He also completed 40 Gy/25 fractions in May 2006 to the upper and right lower neck. Later, he developed a left parasagittal brain metastasis and was treated by excision in January 2007. He then had a resection of a right cerebellar metastasis by mid-July 2007 and 50.4 Gy/28 fractions to the cerebellum. His surgery was complicated by respiratory distress requiring intubation and a tracheostomy tube was placed. Further recurrence occurred in the posterior fossa but no more radiation could be safely given. He expired at the age of 44 from the thyroid cancer.

The third patient was diagnosed with an adenocarcinoma of the prostate in May, 1997 at the age of 57. He had a radical prostatectomy and the distal margin was positive. He presented to the cancer clinic again in 2002 with a slowly rising PSA. There was no conclusive evidence of distant metastases. He completed salvage radiotherapy to pelvis 60 Gy/30 fractions on January 27, 2003. He started androgen deprivation therapy in March 2005 in an intermittent manner. By November 2007, he was found to have an early stage rectal adenocarcinoma and abdomino-perineal resection was performed. He did not require any adjuvant chemotherapy or radiotherapy. In March 2009, his PSA rose to 51.1 μg/l and bicalutamide was added to leuprolide. He also had four doses of zoledronic acid. He was put on fragmin due to pulmonary embolism. He then developed a low-grade neoplasm of bladder, treated surgically in February 2008. The patient became bed-ridden in the summer of 2009. He had repeated biopsies of a right groin mass and the conclusion was recurrent prostatic adenocarcinoma. He was started on docetaxel chemotherapy and had some initial improvement in the fact that the patient was able to walk again. Since October 2009, he started having pain in the right inguinal area, which was an 8 cm long×10 cm wide fixed metastatic mass in the lower anterior abdominal wall. There was some vague swelling above the pubic area. Palliative radiotherapy was arranged. As accurate as possible, the staff reproduced the previous treatment setup. The patient understood that a perfect reproduction of the previous treatment might not be feasible and occasionally some small bowel loops could move into the area and got retreated. He completed 30 Gy in 10 fractions to the upper pelvis and 20 Gy/10 fractions to the lower pelvis on 22 January 2010. The patient underwent radiation uneventfully. The radiation helped his pain. He died of metastatic prostate cancer at 70 years of age.

Discussion

Oncologists should aim to reduce radiation-induced malignancies by careful selection of patients for radiotherapy and radiotherapy treatment techniques. Subsequent vigilant follow-up and investigations can detect these radiation-induced malignancies early and, hence, resulting in successful treatment.

Decision of initial therapy for prostate cancers is a good example. The risk of post-radiation second malignancy becomes a factor for consideration when different treatment options are available. Some authors felt that risk of post-radiation second malignancies is significantly increased (5, 6). The series by Brenner *et al.* published in 2000 used data from the Surveillance, Epidemiology and End Results Program registry to compare the risk of second malignancy in 51,584 men treated with radiotherapy and 70,539 surgically-treated men. Overall, the use of radiotherapy

Table II. *Case scenarios*.

Age, sex, year at presentation of first malignancy	Type of first malignancy	Treatment of first malignancy	Time interval to second malignancy	Type of second malignancy	Treatment of second malignancy	Outcome
79, female, 2005	Breast adeno-carcinoma	Radiotherapy to breast and tamoxifen	8 years	Left breast angio-sarcoma	Surgery and skin graft	Died of angio-sarcoma at 87 years of age
16, male, 1981	Hodgkin lymphoma, nodular sclerosing type	Radiotherapy (neck was included)	21 years	High grade papillary carcinoma possibly insular subtype	Surgery, radioactive iodine ablation and radiotherapy	Died of thyroid cancer at 44 years of age
57, male, 1997	Prostate adeno-carcinoma	Prostate bed salvage radiotherapy	10 years	Rectal adeno-carcinoma	Abdomino-perineal resection only	Died of prostate cancer at 70 years of age

Table III. *Strategy for management of radiation-induced malignancies*.

• History-dose, technique, location and time of previous irradiation
• Examination-post-irradiation changes of overlying skin (fibrosis, telangiectasia), tattoo marks
• Investigation-computerized tomography, magnetic resonance, positron emission tomography scans to document localized disease before contemplating radical radiotherapy again
• Multidisciplinary discussion in tumor board is recommended
• Surgery is generally the preferred modality
• Re-irradiation is offered when no other viable treatment options are available
• Re-irradiation if needed to be done, should be carefully planned

Table IV. *Strategy for re-irradiation of radiation-induced malignancies*.

• Informed consent and proper documentation
• Highly conformal and precise radiotherapy e.g. stereotactic radiotherapy, intensity-modulated radiotherapy, proton therapy
• Calculation of biological effective dose (BED) is mandatory
• Use 2 Gray (Gy) or lower (hyperfractionation)
• Control of diabetes and hypertension, if any
• Management of radiation complications in a timely manner
• Organizational structure
-institutional guideline of tolerance doses
-institutional program of quality assurance
-late effect clinic

rather than surgery was associated with an increase of one solid tumor per 125 men at risk by five years; this increased to one tumor per 70 men at risk for men surviving >10 years. The excess risk was predominantly from bladder and rectal cancer, as well as from in-field sarcomas.

In the Connecticut registry, the risk of second malignancy after prostate radiotherapy was 5.8% but many patients had other risk factors, like smoking. The actual risk is not higher in patients younger than 70 years with localized disease (<T2c) who often must choose between surgery and radiation (7). Some felt that the concept of excess risk is non-significant, especially in comparison to surgery that result in higher complication rates like urinary incontinence (8). Other criticisms for the reported increased rate of secondary malignancies are: (i) that the vast majority of secondary cancers occurred outside of the radiation field (84%) and/or (ii) within 3 years of radiotherapy (97%) suggesting they were not caused by radiation and (iii) most of these patients had lifestyles with predisposing risk factors.

Readers have to separate the results of external beam radiotherapy from brachytherapy. The latter has a highly conformal dose distribution, limiting radiation exposure of surrounding normal tissues. The rate of second malignancy after brachytherapy is much lower (9).

After curative cancer treatment, patients are often sent back to family physicians for follow-up with guidelines; an example is that developed by the Saskatchewan Cancer Agency (10). These guidelines should include symptoms and signs of recurrence, as well as complications for referral to the cancer clinic. The oncologists should also send a discharge letter with specific recommendations for the individual patient if a second malignancy is common. These help family physicians to become familiar with the prevention and detection of second malignancies. Multi-disciplinary team approach is required for management of these malignancies (Tables III and IV).

Conclusion

Physicians should be familiar with the prevention, detection and management of radiation-induced malignancies. Multi-disciplinary team approach is required for management of these malignancies.

Conflicts of Interest

The Authors declare no financial support and no funds received.

References

1 http://seer.cancer.gov/csr/1975_2007/
2 Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P and Travis LB: Second malignant neoplasms: assessment and strategies for risk reduction. J Clin Oncol *30*: 3734-3745, 2012.
3 Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P and Travis LB: Second malignant neoplasms: assessment and strategies for risk reduction. J Clin Oncol *30(30)*: 3734-3745, 2012.
4 Nieder C, Andratschke NH and Grosu AL: Increasing frequency of reirradiation studies in radiation oncology: systematic review of highly cited articles. Am J Cancer Res *3*: 152-158, 2013.
5 Brenner DJ, Hall EJ, Curtis RE and Ron E: Prostate radiotherapy is associated with second cancers in many organs, not just the colorectum. Gastroenterology *129*: 773-774, 2005.
6 Brenner DJ, Curtis RE, Hall EJ and Ron E: Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer *88(2)*: 398-406, 2000.
7 Movsas B, Hanlon AL, Pinover W and Hanks GE: Is there an increased risk of second primaries following prostate irradiation? Int J Radiat Oncol Biol Phys *41*: 251-255, 1998.
8 DiBiase SJ and Roach M III: In: UpToDate, Ross ME (Deputy Editor), UpToDate, Waltham, MA, 2000-13. [www.uptodate.com (last accessed 12 Dec 2013)].
9 Liauw SL, Sylvester JE, Morris CG, Blasko JC and Grimm PD: 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 *66*: 669-673, 2006.
10 http://www.saskcancer.ca/Default.aspx?DN=2edee9d1-7797-40b3-bb49-56f4c3905169

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