

Alcohol as a Potential Contributing Factor in Radiation Complications

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Introduction

Various predisposing situations or conditions have been associated with a heightened risk of serious complications following therapeutic irradiation (XRT). Some examples include diabetes,¹ ataxia telangiectasia,² collagen vascular diseases such as scleroderma, lupus, or CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia),^{3,4} or prior abdominal/pelvic surgeries⁵ when XRT is to be directed to the abdomen or pelvis.

Malaise and colleagues suggested that various tumor types have inherently different radiosensitivities.^{6,7} A collaboration between a French group and an M.D. Anderson Cancer Center group indicated that there is an appreciable individual inherent difference in radiosensitivities for normal tissue cells.⁸

Peters and coworkers have examined a possible inherent sensitivity of head and neck squamous cell carcinomas by attempting to correlate radiation sensitivity of cultured tumor cells with response of the tumors *in vivo*. In principle, the *in vitro* radiation sensitivity of a given tumor could be used to adjust the final radiation dose to the individual head and neck cancer patient. There was a tendency for cells irradiated *in vitro* from patients who failed treatment to be more radioresistant, but the correlation was rather imperfect.^{9,10}

We would suggest that radiation sensitivity of normal structures or tumors could be dependent on environmental or nutritional factors modifying the *in vivo* milieu, as well as inherent genetic factors. Oxygenation status has long been noted to influence the effect of radiation on tissues.^{2,10} We report and discuss here a case of serious complications following treatment for prostate cancer, in which a contributing factor would appear to be alcohol consumption.

Case Report

The patient was a 53-year-old male who had a prostate specific antigen (PSA) level of 26.19 on September 13, 2000. Biopsy was positive for Gleason's score 7 adenocarcinoma in 6/6 cores bilaterally, cores varying from 25–100% involvement. Perineural invasion was noted. A computed tomography (CT) scan was negative for enlarged lymph nodes, and a bone scan on November 16, 2000 was regarded as probably negative, with minimal uptake at L3 regarded as degenerative changes. The patient denied hematuria, dysuria, hesitancy, or weak stream. He complained of nocturia 2–3 times per night and denied changes in bladder or bowel habits. Past medical history included chronic obstructive pulmonary disease, arthritis, vertigo, peptic ulcer disease, some left hand numbness, and gastroesophageal reflux disease. His social history consists of living with his mother, ongoing smoking of 1.5 packs per day for 33 years. The patient described himself as a light social drinker (1–2 beers 1 or 2 nights a week). Family history includes several relatives, including his father, who died of cancers (type unknown). Initial examination observed a large nodular prostate, which they described as T2b (correctly T2c on present system). The patient received one shot of goserelin, but discontinued it, objecting to the hot flashes. When scheduled to start XRT in April 2001, he failed to show up. A subsequent examination one month later noted obliteration of a sulcus and classed the patient as T2b/T3. The patient ultimately started XRT in June 2001, took 2 break periods during XRT, and completed XRT in August. At examination just prior to the start of XRT, it was thought there was clear extension of tumor out of the gland; hence stage would be T3. He ultimately received 7,027 cGy tumor dose in 39 fractions of 18 megavolt X-rays. The patient repeatedly declined resumption of hormonal therapy. Side effects at completion of XRT did not immediately seem overly severe; he complained of fatigue, some rectal soreness, and an occasional episode of diarrhea. At 1 month after treatment he seemed more concerned

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with urinary symptoms including burning on urination, frequency, and nocturia 3–4 times per night. Although hormonal therapy had been discontinued prior to starting XRT, examination of the gland at 1 month suggested that it had diminished in size appreciably and had less prominent nodularity. However, the patient also complained of erectile dysfunction (ED) at this time. Examined again at 2.5 months after XRT, the patient had no palpable tumor nodule and a decline in PSA levels to 1.1. The patient again complained of persistent fatigue, ED, hot flashes, and urinary urgency. At 6-month follow-up, the prostate was negative for suspicious nodule and PSA remained low at 1.0. The patient continued to complain of ED, no sexual arousal, urgency without incontinence, and an enlarging waistline; however, fatigue and hot flashes were beginning to abate. At 9 months follow-up, his prostate was negative for suspicious nodule and PSA continued to decline to 0.52, but the International Prostate Symptom Score (IPSS) seemed to be gradually worsening at 19/35. At 1 year follow up, the prostate was negative for suspicious nodule and the PSA remained low, but prominent complaints included urgency at stool or urination. Two and a half months later, in November of 2002, the patient encountered bowel obstruction, leading to the resection of the terminal portion of the small bowel and the proximal portion of the large bowel. The patient was seen in February 2003, at which point he complained of diarrhea (difficult to control by loperamide), and worsening urinary symptoms with IPSS rising to 33/35, including urgency to the point of incontinence. Colestipol was added to the patient's medications and in May 2003, the patient's diarrhea was still well controlled and urinary symptoms had abated with an IPSS score of 8/35.

History was reviewed again, with the patient denying diseases such as diabetes or scleroderma, and heavy alcohol consumption. Prostate remained negative on exam. By October 2003, the patient complained of "terrible pain" in the low pelvic area and had been placed on narcotic pain medications. The prostate continued to remain negative, the PSA low, and the patient continued to smoke. Seen again in January of 2004, the patient revised some of his earlier history, commenting that he had cut back on his significant drinking for the past year. Further questioning led the patient to admit to consumption of approximately 6–7 beers per day during the period of his radiation treatment and for the 1.5 years post-XRT, including the time of bowel obstruction. Interim cystoscopy had revealed significant bladder damage, presumably XRT-related, and he continued on narcotic pain medications for pelvic pain. His prostate remained negative for suspicious nodule and his PSA low at 0.25. When the patient was seen again in May 2004, he informed us of 2 surgical procedures he underwent in the pelvic area—an apparent cystectomy for

a dysfunctional bladder and drainage of a pelvic abscess—qualifying him as the patient with the most serious set of late complications we have seen. The problem of pelvic pain did resolve following these surgical procedures. The patient was fairly comfortable and apparently without active cancer when he was seen in September 2004 at 3 years follow-up after XRT.

The patient was seen in April and August of 2005; at the time he was 3 years and 11 months after XRT. Although he was doing relatively well clinically, he went through a series of 3 successive PSA increases to 1.27, thus encountering biochemical failure by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition (Table 1). The doubling time for the rising PSA pattern was approximately 8 months. The patient was informed of his PSA failure condition, and the pros and cons of early versus later hormonal therapy was discussed. In view of his worse-than-usual experience

Table 1. Prostate Specific Antigen (PSA) Values with Associated Events

Date	PSA (ng/mL)	Comments
9/13/2000	26.19	Done elsewhere
10/25/2000		Bx+ Gleason's score 3 + 4 = 7 in 6/6 cores, 25–100%
March 2001		Received only shot of goserelin hormonal therapy
5/15/2001	3.57	
8/22/2001		Completed XRT
9/21/2001	1.11	
11/16/2001	1.07	
2/21/2002	1.00	
5/21/2002	0.52	
8/30/2002	0.53	
2/7/2003	0.22	
5/8/2003	0.69	PSA bounce
10/6/2003	0.49	
1/12/2004	0.25	
5/18/2004	0.45	
9/8/2004	0.58	
8/18/2005	1.27	PSA failure, ASTRO definition

ASTRO=American Society for Therapeutic Radiology & Oncology; Bx=biopsy; PSA=prostate specific antigen; XRT=irradiation.

with side effects and complications with both hormonal therapy and XRT, he declined active intervention, choosing to be observed.

Discussion

Prostate cancer often progresses in a more indolent fashion than other cancers, so that some observers would advocate no aggressive intervention for the older patient with multiple other serious comorbidities, and a low-risk prostate cancer is unlikely to progress rapidly. A retrospective analysis of an observational series showed that with 15 years of follow-up, men with Gleason's score 2–4 cancers had little risk of dying of prostate cancer, whereas men with Gleason's score 7–10 cancers had a high risk of dying of this disease.¹¹ High-risk prostate cancer has often been defined as a single feature of Gleason's score 8–10, PSA higher than 20, or T stage higher than T2b; or a combination of intermediate risk factors such as Gleason's score 7 and PSA 10–20 or clinical stage T2b.¹² There are computational models, such as those produced by Roach, for predicting the risk of more advanced disease, such as lymph node positivity, from the extent of the foregoing factors.¹³ Such a model would suggest our patient had quite high-risk prostate cancer, with a greater than 40% risk of involved lymph nodes. Apart from the high-risk features incorporated in the Roach model, perineural invasion has been found to be an additional risk factor associated with an increased rate of relapse following XRT.¹⁴ D'Amico's data on prostate cancer as a specific cause of death within 10 years would suggest that our patient had a 45% risk of prostate cancer death within 10 years.¹²

RTOG protocol 9413 addressed 2 important points in the treatment of moderately high-risk prostate cancer patients; 1) size of XRT fields, and 2) the potential benefit of neoadjuvant/adjuvant hormonal therapy along with XRT. Patients were selected to have at least a 15% risk of pelvic lymph node involvement by use of the Roach formula: percent chance of lymph node involvement = $2/3(\text{PSA}) + ([\text{Gleason's score} - 6] \times 10)$. Patients were randomized to 4 arms: XRT fields covering only the prostate with a small margin and without neoadjuvant/adjuvant hormonal therapy, the same small fields with neoadjuvant/adjuvant hormonal therapy, initially large pelvic fields without neoadjuvant hormonal therapy, and initially large pelvic fields with neoadjuvant/adjuvant hormonal therapy. The last arm was superior to the other 3 in progression-free survival (although this has become less clear with longer follow-up). If patients with involved pelvic lymph nodes are all destined to progress and die of prostate cancer, there should have been no advantage to the use of large pelvic fields for the initial 4,500 cGy. This implies that lymph node involvement may be a fea-

ture of high-risk disease, but does not make the patient entirely incurable.¹⁵ This important study also suggests a synergism between neoadjuvant/adjuvant hormonal therapy and pelvic XRT, such that a dose of 4,500 cGy to a limited pelvic tumor burden outside the prostate has a useful impact. Our patient was thus treated with a management plan, which has been recommended for high-risk prostate cancer; his heavy alcohol consumption may have also contributed to the radiosensitization of his tumor by an undefined extent.

The normal digestion of lipids in the gastrointestinal tract involves a cyclical reuse of bile salts, the so-called enterohepatic circulation of bile salts (or acids). Bile acids are synthesized from cholesterol in the liver, stored in the gallbladder, and expelled into the duodenum when a fatty meal is ingested. They function in the small bowel by helping to break up fat into small micelles with more surface area available to enzymes involved in the digestion of fats. Reabsorption in the distal ileum is accomplished by the apical sodium-dependent bile acid transporter (ASBT). A truncated version of ASBT at the basolateral surface of the enterocyte facilitates transfer of bile acids into the portal circulation, and the enterohepatic circulation is completed by a sodium-dependent bile acid transporter at the basolateral surface of the hepatocytes.¹⁶ Failure to reabsorb bile acids in the terminal ileum causes them to be emptied into the colon, where they have a cathartic action causing water and electrolyte secretion which manifests as diarrhea.^{16–18} Constipation can be associated with low loss of bile acids into the colon, whereas diarrhea is associated with high loss of bile acids into the colon.^{16,19} There are multiple causes of ileal malabsorption of bile acids causing diarrhea including a congenital anomaly in which there is a mutation in the ileal ASBT gene,²⁰ Crohn's disease, ileal surgery as a chronic sequel to significant gastroenteritis, or radiation enteritis.^{16,21} Sequestration of bile salts by agents such as cholestyramine resin or colestipol can be useful for controlling diarrhea in a reasonable percentage of cases of diarrhea resulting from bile acid malabsorption due to the foregoing reasons.¹⁷ Bile acid malabsorption can be diagnosed by testing procedures such as measurement of retention of a synthetic bile salt labeled with ⁷⁵Se,²² but it may be a simple and practical approach to prescribe a trial course of a sequestrant such as cholestyramine or colestipol for a patient when it is suspected that diarrhea may be secondary to the effects of XRT or surgery on the ileum. This approach solved one problem for our patient.

Moderate alcohol consumption may be beneficial to health in certain ways, as has been suggested for red wine consumption and coronary heart disease in the so-called "French paradox".^{23,24} However, heavy alcohol consumption has been implicated as a causative factor in several human disease processes involving various organs. An

epidemiologic study of external factors causing deaths in the United States ranked alcohol (100,000 deaths) third in a list of 9 factors behind tobacco (400,000) and diet and activity patterns (300,000 deaths).²⁵ It had been noted in a prospective cohort study that patients with a history of chronic alcohol abuse have a significantly higher risk of developing acute respiratory distress syndrome than other patients, and these patients then have a significantly higher in-hospital mortality rate.²⁶ An animal model was set up in which control rats were given regular water to drink, and the experimental group were given 20% alcohol for a period of at least 3 weeks. Exposure of alcoholic rat lung to an endotoxin caused greater injury than it did to control lungs. Glutathione (GSH) was found to be depleted in lung lavage fluid, lung tissue, and plasma of the alcoholic group. Treatment of the alcoholic rats with GSH precursors S-adenosyl-methionine (SAM) and N-acetylcysteine (NAC) could partially reverse this process.²⁷ SAM is also known to be depleted by oxidative stress associated with alcoholism early in the evolution of alcoholic liver disease, and supplementation with SAM can contribute to reversal of the process.²⁸ There is a decreased pool of GSH in the mitochondria of hepatocytes from ethanol-fed animals, and this is associated with diminished transport of GSH into the mitochondria. The hepatocytes are then more susceptible to cell death induced by oxidative stress. These changes can be reversed by incubation with GSH monoethyl ester.²⁹ Mitochondrial function is important to maintain the normal functions of hepatocytes, especially energy levels. NAC supplementation can restore cytosolic, but not mitochondrial, GSH levels in hepatocytes from alcoholic animals, whereas SAM feeding can restore GSH in both compartments, and also partially restore ATP levels.³⁰ GSH is known as an endogenous protectant against the toxic effects of XRT as well as various toxic chemical agents, and it would be expected that any agent, such as alcohol, which leads to depletion of GSH would render a variety of tissues more susceptible to damage from XRT.²

In an effort to explore the postulated interaction of XRT and alcohol mechanistically, we studied the interaction *in vitro* using HepG2 cells. Cells irradiated in the presence of ethanol underwent apoptosis at a greater rate, and this was accompanied by decreases in GSH, increases in malondialdehyde, and increases in caspase-3.³¹

Ethanol induces oxidative stress, resulting in a GSH decrease, among other things, by enhancing superoxide radical production, but also by increasing a free iron pool involved in the catalysis of the Haber-Weiss reaction, which produces more aggressive prooxidant radicals.³² Reactive oxygen species produced by ethanol would then induce damage in various tissues by mechanisms such as the production of peroxides in membrane lipids.³³ The complications generated in our patient could be secondary

not only to the increased impact of XRT during treatment associated with GSH depletion at that time, but also to the generation of increased levels of reactive oxygen species during the year and a half after treatment, when his major complications appeared.

PSA failure is an interesting problem in itself; so when is it of sufficient significance to warrant another active intervention? Our patient, who had experienced unusually troubling side effects and complications with both hormonal therapy and XRT was loathe to consider active treatment recommendations, and with a PSA level less than 2, it may not be of great urgency to persuade the patient. Critz and coworkers have used a 125-I brachytherapy implant boost along with 4,500 cGy external beam XRT and noted that a substantial fraction (35%) show a transitory "bounce" in PSA levels after treatment followed by a subsequent decline without further treatment.³⁴ A group from M.D. Anderson Cancer Center has suggested that for high-risk prostate cancer patients, a definition of PSA failure as 2 units above the existing nadir value may have greater utility than the ASTRO definition of 3 successive rises,³⁵ and this has become the essence of the newer "Phoenix" definition of PSA failure. Consider, for instance, that a series of PSA values reading 0.01, 0.02, 0.03, and 0.04 would constitute failure by the ASTRO consensus definition, though this would be slim evidence to justify another active intervention. The analysis of Kestin and coauthors³⁶ would suggest that a rise of 3 above the nadir is predictive of an approaching clinical failure, and warrants serious consideration of treatment. Analyses by D'Amico and collaborators would suggest that pretreatment high-risk disease parameters and a short doubling time in PSA rise post XRT would predict a high risk for prostate cancer death.³⁷ Sartor and colleagues noted an increased risk for PSA failure being followed by the appearance of clinical distant metastases for patients with a PSA doubling time of less than 6 months.³⁸ Parker and Dearnaley set a break point at 8 months in the PSA doubling time as predictive of progression to metastases.³⁹ Our patient's situation would seem not too threatening in terms of his PSA level not being 2 or 3 above nadir, however it raises some concern in that he was a high-risk patient initially, and his doubling time may be close to the break points predicting a high risk of metastases.

Conclusions

We present the case of a patient treated for high-risk prostate cancer with a moderate dose of XRT to pelvic fields with boost, and a suboptimum schedule of hormonal therapy. He apparently obtained good control of his cancer for approximately 4 years, with further course to be decided, but at the cost of unusually severe late com-

plications of treatment. We believe that his unsuspected high level of alcohol consumption had an important radiobiologic consequence, depleting his endogenous GSH, and increasing levels of reactive oxygen species. This probably improved our ability to gain response in the tumor, but also led to unusually severe late complications in the urinary and digestive tracts. We suggest adding heavy alcohol consumption to the list of conditions that one should be aware of as increasing the hazard of serious late complications when employing XRT. Damage to the ileum secondary to surgical resection or pelvic XRT can impair the enterohepatic circulation of bile salts, resulting in a late effect of troublesome chronic diarrhea, and this can be effectively treated by a sequestrant such as colestipol or cholestyramine resin. There are several indicators available to help guide one in making a recommendation as to when to suggest active intervention following PSA failure; these include a rise of 2 or 3 units above the nadir value, or a short PSA doubling time of less than 6 or 8 months.

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Review

Alcohol and Other Factors Related to Late Prostate Radiation Injury

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Prostate cancer is the most common cancer diagnosed among men in the United States other than nonmelanomatous skin cancer. In 2008, an estimated 186,000 men had been diagnosed with prostate cancer.¹ Radiation therapy (RT) is one of the main treatment modalities, with 33% of newly diagnosed patients undergoing some form of radiation.

Fortunately, most men tolerate RT extremely well, with excellent quality of life scores post-therapy.² However, severe late normal tissue injury does occur. In dose escalation trials using conformal planning, doses of 74+ Gy resulted in a grade 3 or higher late rectal toxicity of 2–3%^{3,4} and a late bladder grade 3 or higher toxicity of 3–4%.^{4,5} Increasing dose beyond 74 Gy was related to higher risks of late normal tissue toxicity.^{3,5} Four-field whole pelvis irradiation has been associated with a 4% risk of grade 3 or higher bowel obstruction.⁶ Finally, the combination of whole pelvis irradiation and neoadjuvant androgen deprivation therapy (ADT) was found to have an increased risk of bowel toxicity in an updated analysis of a phase III study (RTOG 9413) conducted by Lawson and colleagues.⁷ In summary, the frequency of late toxicity is related to dose, field size, and potentially hormone use.

In the presented case, Matthews and coauthors⁸ describe a patient who developed severe urinary symptoms ultimately requiring cystectomy, a small bowel obstruction, and erectile dysfunction (ED) after moderate dose radiation (albeit given with conformal planning). He did, however, have multiple factors, which could have potentiated radiation effects.

ADT Use: In addition to the intriguing results found in RTOG 9413, testosterone suppression often continues long past the elimination of the luteinizing hormone-releasing hormone agonist.⁹ While most common in older men, persistent testosterone suppression may have contributed to the patient's ED.

Early Severe Symptoms: Studies have shown a correlation between severe acute toxicity and risk of late toxicity. Zelefsky and coworkers⁵ found that late grade 2 or higher

gastrointestinal toxicities increased from 10% to 19% in patients with grade 2 or higher acute gastrointestinal toxicity. Gastrointestinal toxicity rose from 7% to 19%.

Family History of Multiple Cancers: A family history of cancer raises the possibility of a genetic mutation, which could cause radiosensitization. Studies in prostate and breast cancer have found an increased rate of acute toxicity in patients with polymorphisms of the XRCC1, TP53, and other DNA repair genes.^{10,11}

Alcohol Use: Matthews and colleagues⁸ introduce the potential radiosensitizing effect of alcohol by means of glutathione depletion. This is an interesting suggestion, with little else in literature discussing toxicities of RT as related to alcohol use. In vitro, oxidative stress and glutathione depletion enhances radiation injury to tumor cells. Alcohol may affect toxicity in other ways—its diuretic effect may worsen urinary symptoms. Patients who depend on alcohol may have less coping skills and are less able to follow recommendations for treating side effects when they occur.

Alcohol use is often not well quantified, particularly in cancers beyond the aerodigestive tract, but would, however, be deserving of further clinical study. Our take-home message from this case is that, even though prostate irradiation is generally exceedingly well tolerated, it does not come without side effects and an informed discussion of rare potential side effects is necessary.

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