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Psychiatric Care of the Radiation Oncology Patient

Emily G. Holmes^a, Jordan A. Holmes^b, and Eliza M. Park^{a,c}

^aDepartment of Psychiatry, University of North Carolina, 101 Manning Drive, Chapel Hill, NC, 27514

^bDepartment of Radiation Oncology, University of North Carolina, 101 Manning Drive, Chapel Hill, NC 27514

^cLineberger Comprehensive Cancer Center, University of North Carolina, 101 Manning Drive, Chapel Hill, NC, 27514

Abstract

Background—In recent decades, psychiatrists have become increasingly involved in the care of patients with cancer. Psychiatrists are often less familiar with the field of radiation oncology than with other medical specialties. Therefore, it is beneficial for consulting psychiatrists to be familiar with the basic principles of radiation therapy (RT) and its potential neuropsychiatric sequelae.

Methods—We performed a PubMed search to identify articles describing neuropsychiatric symptoms resulting from RT, including anxiety, claustrophobia, posttraumatic stress disorder, and neurocognitive impairment. We also searched for other sequelae of RT that may produce psychiatric symptoms such as radiation necrosis and endocrinopathies. We provided a basic introduction to the delivery of RT.

Results—Psychiatrists may be involved in the treatment of patients before, during, or after RT, and each phase of treatment produces unique considerations. Anxiety about the treatment, especially the need for immobilization with a mask, can be treatment-limiting. Adverse effects from treatment including cognitive impairment and endocrinopathies can result in psychiatric symptoms.

Conclusions—Consulting psychiatrists should be familiar with the basic principles of RT and the neuropsychiatric sequelae that may result from the treatment. Further research is needed to identify strategies to help patients tolerate RT and to identify additional preventive and therapeutic options for RT-induced cognitive impairment.

Keywords

cancer; oncology; neuropsychiatry; radiation therapy

Corresponding author: Emily Holmes, Emily.Holmes@unhealth.unc.edu, P: 984-974-3820, 170 Manning Drive, 3rd Floor, Campus Box #7305, Chapel Hill, NC 27599-7305.

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Introduction

Psychiatrists are increasingly involved in the care of cancer patients.(1) Understanding basic principles of cancer care helps psychiatrists understand the oncology-specific needs of these patients. Radiation therapy (RT) is associated with unique neuropsychiatric sequelae; however, some psychiatrists may be less familiar with this field.

This review summarizes basic principles of RT, focusing on the unique features of RT relevant to psychiatrists treating adult patients.

Overview of RT

General Principles

RT uses focused beams of energy to kill cancer cells. RT is one of the three primary cancer treatment modalities (along with surgery and chemotherapy). It may be delivered as a single treatment modality or in conjunction with surgery and/or chemotherapy, depending on the cancer site and stage. The radiation oncologist chooses who to treat, determines the total dose of radiation, and oversees the delivery of the radiation plan. Treatment goals range from palliation to full cure. Radiation oncologists see patients weekly during treatment to manage side effects and continue to follow some patients for years after treatment.(2)

RT with or without chemotherapy can be curative for some cancers including head and neck, lung, anal, prostate and some gynecologic cancers. In these situations timely and uninterrupted completion of RT is paramount. Studies in multiple disease sites have found that delays in initiation of treatment and interruptions or early termination of treatment adversely affect local control and overall survival.(3–7)

Radiation causes DNA damage in cells. Compared to normal cells, cancer cells are more vulnerable because they have missing or malfunctioning DNA repair mechanisms. However not all DNA damage imparted to normal cells is repaired, resulting in side effects (Table 1). Therefore, the total dose of radiation is often ‘fractionated’ or divided into multiple daily treatments to allow normal cells to recover between treatments. The number of treatments can vary from a single treatment to daily treatments for up to eight weeks. RT can be delivered using three different approaches: external beam RT (EBRT), brachytherapy, and intraoperative RT (IORT).(2)

EBRT—EBRT uses a linear accelerator or other source of high energy radiation to deliver electrons, photons, or particulate radiation to the tumor. Radiation oncologists attempt to maximize the radiation dose to the tumor while minimizing the dose to surrounding normal tissues. For small, well-defined tumors, stereotactic radiation is a technique used to maximize tumor kill while reducing side effects. Stereotactic radiosurgery (SRS), used for intracranial targets, and stereotactic body RT (SBRT), which targets extracranial tumors, use high doses of very precise radiation delivered in fewer treatments. SRS and SBRT can be delivered using a linear accelerator or a proprietary system such as the CyberKnife (Accuray, Sunnyvale CA) or Gamma Knife (Elekta, Stockholm Sweden).(2) Charged particle radiation including proton radiation has shown some promise in reducing toxicity

from EBRT, but proton centers are currently relatively rare and protons are of unproven benefit in most cancers.

Brachytherapy—Brachytherapy delivers radiation directly to a tumor via the surgical insertion of radioactive seeds or catheters into or in close proximity to the tumor. Radioactive seeds remain inside the patient permanently, but are not delivering a meaningful amount of radiation after the planned treatment course; radioactive catheters are removed. Brachytherapy more directly targets the tumor and allows for higher radiation doses because the radiation does not pass through normal tissues. Brachytherapy is most often used in prostate and gynecologic malignancies; often it is given with EBRT.(2)

IORT—IORT is the delivery of radiation during surgery, allowing the physician to shield internal structures, such as the intestines. IORT is particularly useful for abdominal and pelvic tumors.(2)

RT of the Brain

The neuropsychiatric complications of RT most often result from radiation to the head and neck and the brain. Therefore, we mostly focus on RT that directly affects these structures.

Patients typically receive brain radiation for one of three reasons: (1) treatment of primary central nervous system (CNS) or head and neck tumors, (2) treatment of CNS metastases, and (3) prophylactic treatment for certain malignancies that commonly spread to the brain (i.e. small cell lung cancer and some hematologic malignancies).

Cancer prognosis is important to note when considering the risks and benefits of radiation. The prognosis for primary CNS tumors can vary from imminently terminal to curative.(8, 9) However, CNS metastases often indicate a poor prognosis; without treatment, median survival is typically measured in weeks to months, and even with treatment, usually less than a year.(10) When radiation is used prophylactically, the prognosis can vary widely depending on the underlying malignancy.

RT can be delivered to the whole brain (WBRT), part of the brain, or to a focal tumor using SRS. WBRT and partial brain RT are used when there are many lesions, or the disease process is diffuse. WBRT and partial brain RT are usually delivered in daily treatments for one to five weeks, during which the patient must lie very still for 10–20 minutes.

SRS usually involves 1–5 sessions during which the patient lies on a table for up to an hour or more to receive radiation. SRS generally has >70% local control of targeted lesions, but median survival remains poor due to systemic or intracranial disease progression.(10)

Due to the need for precise delivery of radiation, the patient's head must be completely immobilized during treatment, usually with a thermoplastic mask that is molded to the patient's face and neck, or, in the case of patients undergoing Gamma Knife treatment, with a frame that is attached to the patient's skull by a neurosurgeon. The immobilization device is fixed to the treatment table to provide precise alignment and reduce patient motion (Figure 1).

Neuropsychiatric Symptoms

Distress

Some patients may have concerns about RT that can delay or prevent treatment. Common concerns include worries about side effects such as fatigue or pain. Patients also have misperceptions, including fears that RT will cause infertility or make the patient radioactive and dangerous to others, or that the patient will receive an overdose of radiation. These misperceptions more often occur when a patient's knowledge about radiation comes from the media.(11)

Anxiety and Depressive Disorders

In a systematic review of 93 studies of psychosocial functioning amongst RT patients the median prevalence of anxiety disorders was 20%, 49%, and 17% before, during, and after treatment, respectively. The median prevalence of depression prior to treatment was 15%, rising to 33% during treatment, and remaining elevated at 27% after treatment. Premorbid depression and anxiety, impaired functioning, pain, concurrent chemotherapy, and laryngectomy were associated with decline.(12) Limitations of this study include the heterogeneity of the included studies, which used a variety of screening instruments and examined patients at different time points in treatment. However, this study provides a helpful framework for understanding the potential trajectory of psychiatric symptoms for patients undergoing RT.

Post-Traumatic Stress Disorder

Case 1. Ms. M was a 38 year-old woman scheduled to receive her second brachytherapy treatment for endometrial cancer. Before the treatment started she developed a panic attack and was unable to proceed with RT. She disclosed to the psychiatric consultant that she had been raped as a child and that the invasive treatment triggered symptoms of hypervigilance and anticipatory anxiety. With increased support from psychiatry, she was ultimately able to complete treatment.

Brachytherapy for gynecological cancers requires a transvaginal or transperineal approach, which can be distressing for some patients, especially patients with a trauma history.(14) Compared with EBRT alone, treatment with brachytherapy improves survival when combined with EBRT for cervical cancer.(13) In one small study of 50 patients, brachytherapy for cervical cancer was associated with symptoms of acute stress disorder (ASD) and posttraumatic stress disorder (PTSD). One week after treatment, 15 of 50 patients demonstrated ASD symptoms and 20 of 49 patients had PTSD symptoms three months after treatment. For patients, the most distressing aspect of treatment was the period between fractionations that required immobility with the transvaginal applicator in place. (15) Brachytherapy techniques vary by institution, so a limitation of this study is that these results may not be generalizable to institutions that use a different technique.

Anxiety and Claustrophobia

Case 2. Ms. A was a 40 year-old woman with a history of sexual trauma referred for RT for definitive treatment of a pituitary adenoma, status post multiple surgical resections and

ongoing optic chiasm impingement. She was unable to tolerate the immobilizing mask even with 5mg of lorazepam. Treatment was attempted via conscious sedation, but she stopped coming to appointments. Ultimately she received RT under general anesthesia and was able to complete her treatment course.

The delivery of RT can result in a range of psychological symptoms, from mild anxiety to debilitating anxiety and panic attacks. The mask can be uncomfortable, and wearing the mask has been identified as one of the worst aspects of treatment for head and neck cancer. (16) The patient's response to the mask can lead to delays, interruptions, and even cessation of RT. Risk factors associated with interruption of RT include the use of psychoactive medications and history of an anxiety attack.(17)

No studies have estimated the incidence of treatment interruptions due to anxiety or claustrophobia caused by the immobilization devices, but it may help to extrapolate from the magnetic resonance imaging (MRI) literature. In one study 4.3% of patients were unable to complete MRI due to anxiety and claustrophobia.(18)

There are no guidelines on the treatment of anxiety during RT, though a few small studies have examined potential interventions. Patient education, guided imagery, meditation, and relaxation therapy may reduce distress.(19–23) Massage may temporarily reduce anxiety, though it may not produce lasting improvements.(24) Music therapy seems to improve subjective reports of anxiety but not objective measures.(25, 26) In our experience, it can be helpful for patients to have practice sessions with the mask as a form of exposure therapy prior to treatment.

Often radiation oncologists are comfortable with providing a benzodiazepine to help patients undergo RT. Most patients are able to tolerate the treatment and will easily be able to wean off the benzodiazepine as they become more comfortable with the treatments. However in our experience, a small number of patients with psychiatric co-morbidity will struggle with treatment even with a benzodiazepine. These patients can develop tolerance and require escalating doses due to the need for daily treatments over the course of weeks.

At higher doses, benzodiazepines may induce a state of moderate or deep sedation, which could place the patient at risk for respiratory depression, hypoxia, and vital sign instability. Due to these risks, moderate and deep sedation require more intensive medical monitoring. The psychiatrist should be familiar with his or her institution's policies about moderate sedation when prescribing high dose benzodiazepines for anxiolysis and recognize when additional medical monitoring is necessary.

In some rare cases, the patient may need to undergo conscious sedation or even general anesthesia to receive treatment, incurring additional cost and risk to the patient. The long term risks of receiving daily general anesthesia over the course of weeks are unknown, though there are concerns it may be harmful.(27)

Cases of severe anxiety that limit RT represent an opportunity for psychiatrists to intervene early and aggressively. With aggressive intervention, the psychiatrist may be able to utilize behavioral strategies and prescribe antidepressants or other non-benzodiazepine anxiolytics

to help treat anxiety and panic attacks. This could potentially reduce the total benzodiazepine dose and the need for conscious sedation or general anesthesia, while preventing delays or interruptions in treatment. Research is urgently needed to improve treatment outcomes for this patient population.

Neurocognitive Effects

Radiation of the brain and head and neck has been shown to have a number of effects on cognition. Changes from baseline in learning, memory, and recall are seen as early as six to eight weeks following RT and lasting up to 12 months.(28–30) These effects, which may reflect vasogenic edema, are reversible in some cases.(31)

Though beyond the scope of this review, it is important to mention that pediatric patients are especially vulnerable to the neurocognitive sequelae of RT. There are several excellent review articles that the reader may consult if interested in this particular topic.(32, 33)

Several risk factors make some patients more vulnerable to the cognitive risks of CNS radiotherapy. Higher doses of radiation may result in poorer cognitive outcomes.(34) Compared with younger adults, older adults are more at risk of developing neurocognitive effects from radiation to the head and neck.(35) Additionally, WBRT confers greater risk than does SRS. A small randomized controlled trial (RCT) with 58 patients comparing SRS alone with SRS in combination with WBRT was terminated prematurely by the data monitoring committee because patients receiving SRS and WBRT had much greater declines in total memory and executive function. In this study, 7 of 11 patients (64%) who received SRS and WBRT had a statistically significant drop in learning and memory as measured by the Hopkins Verbal Learning Test compared with only 4 of 20 patients (24%) of patients in the SRS group.(30) However, it is using a more focal treatment may result in worse overall cancer control; in this study 73% of patients who received SRS and WBRT were free from CNS recurrence at 1 year compared with only 27% of patients who received SRS alone. Other factors likely contribute to the risk of cognitive impairment including the brain lesions themselves; medications; the concomitant use of chemotherapy, immunotherapy, and other anti-neoplastic agents; and other comorbidities such as vascular disease and diabetes.

A Cochrane Review was conducted to synthesize the literature on the prophylaxis and treatment of radiation-induced neurocognitive effects. Unfortunately, the few RCTs on this topic have been limited by high attrition and low statistical power. Only six studies were included in the Cochrane review, and these studies could not be analyzed by a meta-analysis due to heterogeneity.(36) Table 2 compares four RCTs of potential pharmacological agents for the prevention and treatment of cognitive impairment associated with RT.(37–40) None of these studies demonstrated significant improvement in the primary outcomes, but memantine showed some benefit for secondary outcomes for prophylaxis of cognitive impairment. Donepezil, methylphenidate, and modafinil showed some benefit in secondary outcomes.

Further research is needed to help guide clinicians in the prevention and treatment of radiation- induced cognitive impairment. Given the current evidence, it may be reasonable for a psychiatrist to initiate a trial of memantine, methylphenidate, or donepezil to target

cognitive complaints, fatigue, and mood in this patient population. This should be done in conjunction with the patient, weighing potential risks and benefits, considering overall prognosis, and understanding that this would be an off-label use of the medication.

Radiation Necrosis

Cerebral radiation necrosis is a rare but serious complication of RT. It can occur anywhere from six months to years after treatment. It manifests as cell death and edema around the site of the tumor and, depending on the location, can produce discreet neurological deficits and/or symptoms of increased intracranial pressure, such as headaches. There have been reports of radiation necrosis manifesting as psychiatric symptoms, including depressive symptoms, mood lability, paranoia, delirium, and cognitive impairment.(41) Treatment for radiation necrosis can range from watchful waiting, to treatment with corticosteroids or bevacizumab, to surgical resection of the area of necrosis in the worst cases.(42, 43)

Endocrinopathies

Endocrine abnormalities due to pituitary and hypothalamic dysfunction occur in up to 75% of patients who undergo RT of the brain and head and neck, and these patients remain at risk months to years after treatment.(44–46) A discussion of the common presenting symptoms of endocrinopathies is beyond the scope of this review, but as with endocrinopathies caused by other etiologies, endocrinopathies resulting from RT can present with neuropsychiatric symptoms. Therefore, the psychiatrist should have high suspicion for endocrinopathies in patients who have received radiation to the brain, head, and neck.

The most common endocrinopathies include hypothyroidism, hyperprolactinemia, and hypogonadism.(45–47) Hyperparathyroidism is another late complication of head and neck irradiation.(48) The American Cancer Society recommends that patients who have received radiation for head and neck cancer undergo screening for thyroid abnormalities every 6–12 months; there are no recommendations for screening for other endocrine abnormalities, which are likely under-recognized.(45, 49)

Approach to the Psychiatric Patient Receiving RT

A psychiatrist may be involved in the treatment of a patient before, during, or after RT. Here, we provide recommendations for this patient population:

- Know the basics of the RT plan including the radiation site and anticipated side effects. Know if the patient is receiving WBRT, partial brain RT, or SRS.
- Anticipate that the immobilization mask will be difficult for some patients to tolerate. Treat depression and anxiety aggressively, especially when these symptoms interfere with treatment.
- Anticipate cognitive side effects in patients who receive cranial RT, especially WBRT. Weigh risks and benefits and consider prophylaxis with memantine or treatment with modafinil, methylphenidate, or donepezil.
- Abrupt worsening in psychiatric symptoms or failure to respond to treatment should prompt consideration of other etiologies including radiation necrosis and

endocrinopathies. Discuss these concerns with the oncologists and consider further laboratory testing or imaging.

Conclusions

This review summarizes the basic principles of RT that may be helpful to the psychiatrist. The psychiatrist should be familiar with the distress that can be caused by the immobilization mask during treatment and the various sequelae after RT that may result in neurocognitive impairment and psychiatric symptoms. There is need for further research to guide treatment of anxiety caused by the mask and the adverse neurocognitive effects.

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Figure 1.
The thermoplastic mask.

TABLE 1

Common side effects of radiation to the head and neck and the brain

Side Effects from Head and Neck Radiation
Acute side effects
Fatigue
Skin irritation
Hair loss
Sore throat/mucositis
Changes in taste
Dry mouth
Long term side effects
Permanent dry mouth
Permanent hair loss
Neck fibrosis
Dental complications
Side Effects from Brain Radiation
Acute side effects
Fatigue
Skin irritation
Hair loss
Nausea or headaches
Long term side effects
Permanent hair loss
Neurocognitive effects
Cataracts
Endocrinopathies
Damage to optic structures

TABLE 2
Randomized controlled trials of pharmacological interventions targeting cognitive impairment associated with cranial radiation therapy

	Interventions	Duration	Primary Outcome	Results	Comments
Prophylaxis					
Brown et al.	Memantine (5–20mg daily) vs. placebo	24 weeks	HVLT-R DR	No difference in primary outcome; memantine had longer time to cognitive decline, and better scores on tests of executive function, processing speed, and delayed recognition	Double-blinded; Possibly underpowered
Kaleita et al.	Modafinil 200 mg daily vs. Modafinil 400mg daily	8 weeks	Not specified	Improvements from baseline in TMT, SDM, VF, depression, and fatigue	Double-blinded; results pooled and compared against baseline scores; only 87% had received RT
Treatment					
Gehrig et al.	Arm 1: methylphenidate 5mg twice daily Arm 2: methylphenidate SR 18mg daily Arm 3: modafinil 200mg daily	4 weeks	Cognitive function (WAIS-III Digit Span and Digit Symbol, TMT, HVLT-R, GP-D, MAE, COWA)	No difference in primary outcome; methylphenidate improved attention and modafinil improved processing speed; both improved mood, QoL, and fatigue	Open-label design increases risk for bias; only 83% of patients had received RT
Rapp et al.	Donepezil (5–10mg daily) vs. placebo	24 weeks	Cognitive composite (HVLT-R, mROCF, TMT, COWA, DST, GP-D)	No difference in primary outcome; memory, motor speed, and dexterity were improved in the donepezil group	Double-blinded

Abbreviations: COWA = Controlled Oral Word Association; DST = Digit Span Test; GP-D = Grooved Pegboard-Dominant hand; HVLT-R=Hopkins Verbal Learning Test-Revised; HVLT-R DR = Hopkins Verbal Learning Test-Revised Delayed Recall; MAE = Multilingual Aphasia Examination; mROCF = modified Rey-Osterreith Complex Figure; RCTs = Randomized Controlled Trials; RT = Radiation Therapy; SDM = symbol digit modalities; TMT = Trail Making Test; VF=verbal fluency; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition;