FROM TREATMENT TO TRAUMA: FIRST-LINE CANCER TREATMENT AND CANCER-RELATED POST-TRAUMATIC STRESS DISORDER

by

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This thesis was prepared under the direction of the candidate's thesis advisors, Dr. Chitra Chandrasekhar and Dr. Julie Earles, and has been approved by the members of his supervisory committee. It was submitted to the faculty of The Honors College and was accepted in partial fulfillment of the requirements for the degrees of Bachelor of Science in Biological and Physical Sciences and Bachelor of Arts in Liberal Arts and Sciences.

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ABSTRACT

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The epidemiology of cancer-related PTSD is well-documented, but the effect of first-line cancer treatments on the prevalence and severity of PTSD has yet to be consolidated. Unlike many other traumatic events preceding the onset of post-traumatic stress disorder (PTSD), the cancer experience has ongoing stages of diagnosis, treatment, and survivorship that each present their own stressors. Due to the multifaceted nature of cancer-related trauma, it is important to understand how each component of the experience plays a role in the onset of mental illness. Thus, I review the existing literature to elucidate how the biochemical changes induced by chemotherapy, radiation, and surgery influence the onset and prevalence of cancer-related PTSD. In being informed of the physiological processes underlying treatment and their implications for mental health, patients and clinicians alike can better predict the psychological changes that occur alongside cancer treatment.

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Introduction

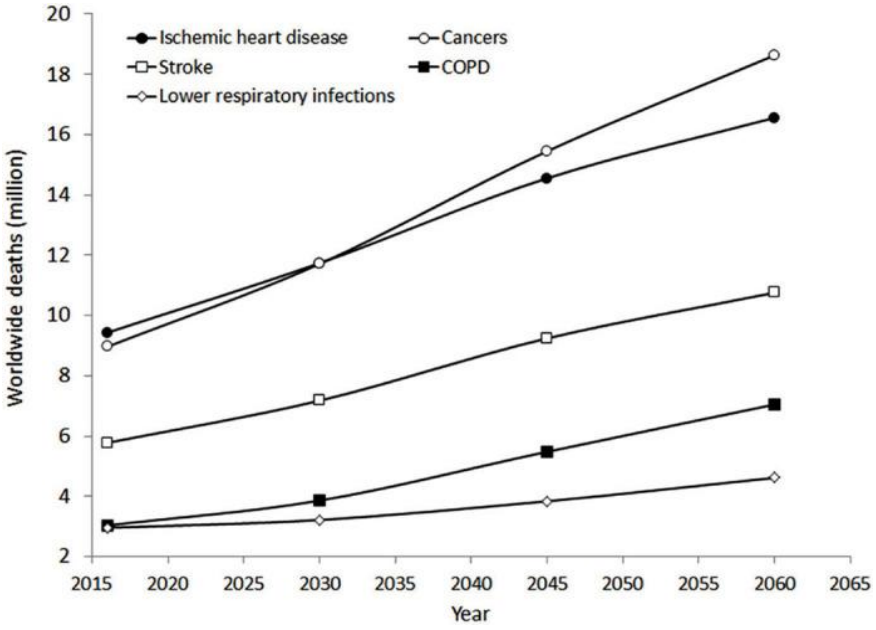
Post-traumatic stress disorder (PTSD) is a psychiatric disorder that arises in response to a traumatic event. Lasting longer than a month after the stressful incident, its symptoms include intrusive thoughts, frequent avoidance of reminders to the event, worsened changes in thought or mood, and changes in arousal (American Psychiatric Association, 2013). An estimated 3.6% of U.S. adults suffered from PTSD in 2016, with a higher yearly prevalence in women (5.2%) compared to men (1.8%) (Kessler, 2005b). The estimated lifetime prevalence of PTSD is 6.8% (Kessler, 2005a).

In the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM–5), the American Psychiatric Association (2013) has updated the criteria necessary for clinicians to diagnose patients with PTSD. One of the most notable changes that has occurred since the third edition of the DSM is the description of the first diagnostic criterion, Criterion A, which defines what can be considered a traumatic event. Unlike in previous editions, the DSM-5 identifies life-threatening illnesses as sources of trauma that can induce PTSD in patients. The diagnostic criteria for PTSD are: (A) exposure to a traumatic event; (B) intrusive symptoms associated with the event such as dissociation and recurring, upsetting memories; (C) frequent avoidance of reminders, including thoughts, feelings, and situations, that bring up memories of the event; (D) negative changes in thought or mood that worsened following the experience; (E) changes in physical arousal after the event, such as difficulty concentrating or hypervigilance; (F) symptomology for at least a month; (G) considerable distress and impediment to daily life; and (H) the symptoms are not due to the physiological effects of a medical condition or

substance use. Traumatic events are defined by the DSM–5 as those that "involved death or threatened death, actual or threatened serious injury, or threatened sexual violation" (American Psychiatric Association, 2013). In light of this reconceptualization of PTSD criteria, the current literature has broadened such events since the DSM-III to include patients with medical diagnoses, beyond the traditionally studied population of war veterans and disaster victims (Mundy & Baum, 2004). A cancer diagnosis qualifies under this criterion, as cancer is currently the second highest cause of death worldwide (8.97 million deaths in 2016), after ischemic heart disease, and is projected to be the leading cause of death by 2060 (~18.63 million deaths) (Mattiuzzi & Lippi, 2019). These trends are portrayed in Figure 1.

Figure 1.

Predicted Epidemiological Trends of Top Five Causes of Death From 2016 to 2060



Note. From "Current Cancer Epidemiology," by C. Mattiuzzi & G. Lippi, 2019, *Journal of Epidemiology and Global Health*, *9*(4), p. 220 (https://doi.org/10.2991/jegh.k.191008.001).

Unlike many stressful events, which generally occur a single time with a fixed end point, the cancer experience involves ongoing stages of diagnosis, treatment, and survivorship that each provide their own respective myriad of challenges and worries related to future-oriented health outcomes (Greimel et al., 2013; Kangas et al., 2002; Mehnert & Koch, 2007). Sources of pathological stress can include physical symptoms, psychosocial stressors, and financial difficulties. Many of these variables are inextricably connected to the cancer treatment process, in which various combinations of first-line treatment options are employed based on the characteristics of the particular diagnosis. However, there exists a current gap in the literature that reviews the specific biochemical implications of medical cancer treatments on the prevalence and severity of PTSD. Oncological treatment currently relies on three broad categories of first-line treatment: chemotherapy, surgery, and radiation therapy. I will review the biochemical basis of each treatment. In this thesis, I hypothesize that the physiological changes induced by the first-line treatments of chemotherapy, surgery, and radiation therapy facilitate the onset of cancer-related PTSD. First, I will review the biochemical basis of each treatment.

Biochemistry of Traditional First-Line Cancer Treatments

Chemotherapy

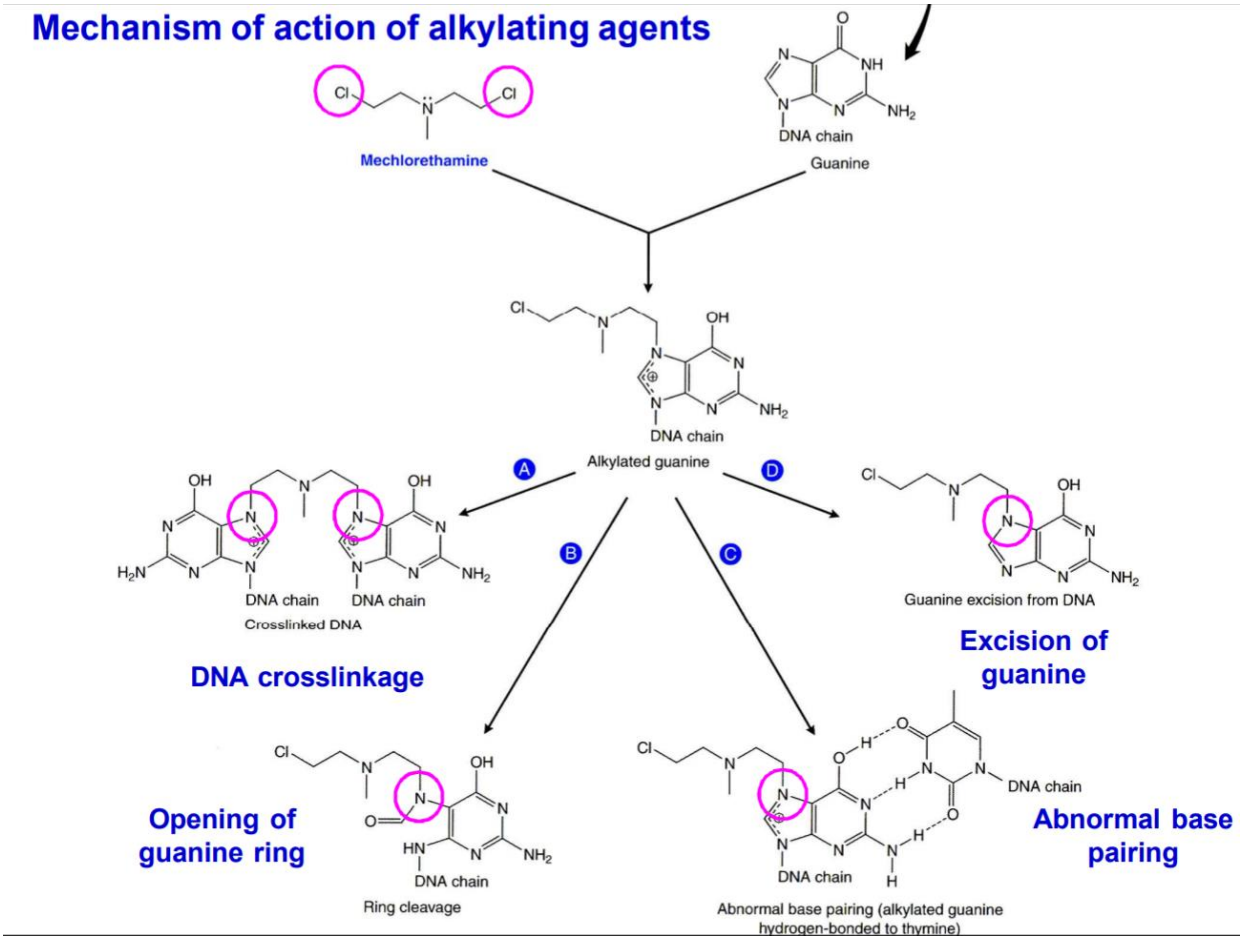
The German chemist Paul Ehrlich was the first to coin the term “chemotherapy” in the early 20th century, when nitrogen mustards and antifolate drugs were adopted as the first chemotherapeutic agents (DeVita & Chu, 2008). These drugs are traditionally characterized by their cytotoxic and/or cytostatic effects, by which they are administered to interfere with mitosis. Within the body, they can initiate numerous cellular responses and thus inhibit the proliferation and survival of cancer cells (Lowe & Lin, 2000). Such cell-damaging events include the targeting of cell-cycle checkpoints, catastrophic cell death, long-term arrest, and apoptosis.

Cellular pathways inducing apoptosis, or programmed cell death, and the events preceding their activation are the most well-studied; thus, many chemotherapeutic agents are manufactured to trigger common apoptotic pathways. Categories of medications are defined based on the differences in their mechanisms of action and include alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, mitotic inhibitors, and corticosteroids. To overview the diversity of molecular processes by which the cell cycle is inhibited, I will briefly cover the biochemistry behind alkylating agents, antimetabolites, and anti-tumor antibiotics.

Alkylating agents react such that an electrophilic alkyl group or a substituted alkyl group covalently binds to cellular nucleophilic sites (Tew, 2018). Reactions within this category can occur either through S_N1 or S_N2 reactions, with different biochemical implications for each. S_N1 reactions are where carbonium ion intermediates are formed with electrophilic properties. Chemotherapeutic agents that fall under this definition include nitrogen mustards and nitrosoureas (Colvin, 2003). S_N2 reactions are distinct from S_N1 in that the carbonium ion is not created, but instead a transition complex composed of the reactants is formed. These interactions encourage the covalent linking of these alkyl groups to DNA bases, interfering with cell cycle machinery through processes such as cross linkage, abnormal base pairing, and excision of the DNA strand (Warwick, 1963). This mechanism of action is delineated in Figure 2.

Figure 2.

Mechanism of Action of Alkylating Agents



Note. From Line.17qq.com (https://line.17qq.com/articles/tscsuaaqx.html).

Antimetabolites include compounds that interfere with metabolites, which are chemicals necessary for normal cellular metabolism (Smith, 1997). Oftentimes, these drugs are analogs that are similar in structure to their metabolite targets and engage in competitive inhibition (Peters et al., 2000). For instance, antifolates are a type of antimetabolite that resemble reduced folates, which plays a major role in one-carbon metabolism and the biosynthesis of purines, proteins, and thymidylate (Lee & Chu, 2018). These chemotherapeutic compounds become incorporated into

the primary structure of the DNA sequence because of their close resemblance to DNA bases. Upon recognition of these errors during the S phase of mitosis, cell cycle checkpoints halt the duplication of genetic material. The anti-metabolic effects of these compounds do not discriminate between cells that exhibit cancer or normal growth; however, cancers with higher growth fractions are disproportionately affected due to their heightened rate of cell division.

While antimetabolites are preferable for intervention within the S phase of mitosis, anti-tumor antibiotics differ in that they are cell-cycle non-specific. Thus, this class of drugs is generally employed for tumors with low growth fractions. Three general modes of action for anti-tumor antibiotics have been elucidated. First, intercalation between DNA bases disturbs the proper structure of the double helix and prevents DNA polymerase from binding to the structure. Second, anthracyclines can undergo an oxidoreductase-catalyzed reaction to form free radicals that can cause either DNA scission or DNA intercalation. However, the production of free radicals can give rise to peroxides, superoxide, and hydroxyl radicals that may cause heart damage (Doroshow, 1983). Lastly, anthracycline acts as an inhibitor of topoisomerase II, which catalyzes a breakage and resealing reaction to prevent DNA tangling. Inhibition is accomplished by stabilizing the cleavable complex formed between topoisomerase II and DNA. The second step of the breakage-reunion reaction, which is the rejoining of the DNA strands that were initially cleaved by topoisomerase II, is prevented, thereby allowing genetic damage to persist (Chen et al., 1984; Tewey et al., 1984).

The success of specific chemotherapy regimens is not always replicable due the significant heterogeneity among distinct types of cancers and between individual patients (Airley, 2009). Chemotherapy in particular does not yield consistent degrees of success across cancer subtypes. In an ideal mechanism of action, neoplastic cells should be the only target.

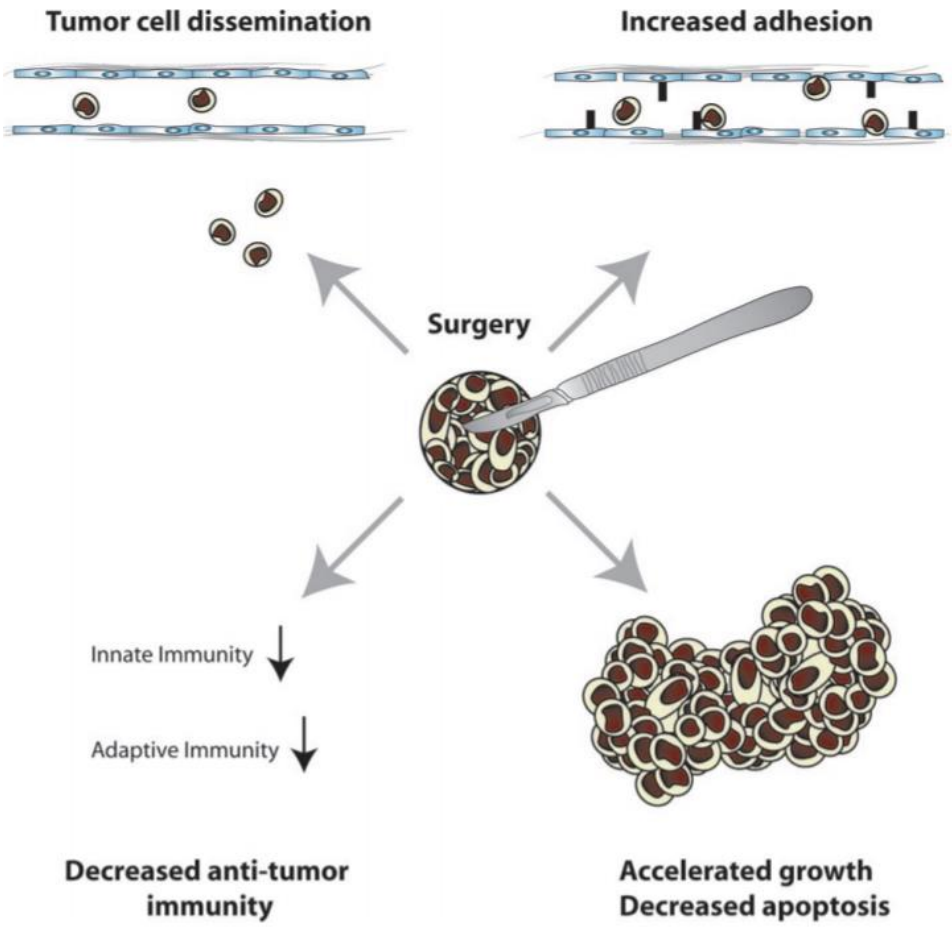
However, this treatment's non-specificity and the issue of local, regional, and systemic chemotherapeutic drug resistance confers systemic toxicity. Debilitating side effects across most organ systems, including the nervous, cardiovascular, and pulmonary organs, may occur as a byproduct of this toxicity (Livshits et al., 2014). It is through these secondary symptoms that much of the psychological distress associated with the cancer experience arises.

Surgery

Until the late 20th century, surgical intervention was generally guided by the principles of William S. Halsted, an American surgeon who believed that the bloodstream was of little importance in the dissemination of tumor cells and that the tumor was autonomous from its host (Halsted, 1907). Once laboratory research began formulating a scientific, rather than anecdotal, basis for tumor biology, a new thesis emerged that recognized cancer's ability to metastasize through the vascular and lymphatic system (Fisher, 2008). In better understanding the conditions by which metastasis can occur, recent research has shown that surgery resection or extirpation can not only introduce harmful complications but can also create an environment encouraging tumor growth. Numerous studies suggest that surgical trauma associated with a breadth of operations and cancer subtypes can accelerate tumor development (Demicheli et al., 2008; Murthy et al., 1989; Georges et al., 2007). For instance, colorectal cancer (CRC) is one of the most prevalent forms of cancer, and the preferred treatment is surgical removal of the colorectal carcinoma (Weitz et al., 2005). However, surgically-induced CRC metastases have been experimentally demonstrated to be provoked via several main methods, as outlined by Figure 3 from van der Bij et al. (2009). The mechanisms by which CRC can cause distant metastasis can also be extrapolated across a breadth of cancer subtypes.

Figure 3.

Factors Promoting Surgery-Induced CRC Metastasis



Note. From "The Perioperative Period is an Underutilized Window of Therapeutic Opportunity in Patients With Colorectal Cancer," by G. J. van der Bij et al., 2009, *Annals of Surgery*, *249*(5), p. 728 (https://doi.org/10.2991/jegh.k.191008.001). Copyright 2009 by Lippincott Williams & Wilkins.

The first of these mechanisms is tumor cell dissemination, caused by physical damage to localized tumors. Once disturbed by surgical manipulation, cancer tissue sheds tumor cells within the bloodstream and thus encourages new metastatic disease (Yamaguchi et al., 2000;

Nishizaki et al., 1990). Second, increased tumor cell adhesion promotes circulating tumor cell implantation via inflammatory responses and the exposure of extracellular matrix (ECM) components. Upon physical trauma, pro-inflammatory cytokines including TNF-α and IL-1β enhance the adhesion of cancer cell lines to monolayers of human mesothelial and endothelial cells (Ziprin et al., 2003; ten Kate et al., 2004). Additionally, ECM exposure occurs as a result of surgical damage to peritoneal surfaces via both direct and indirect means. This allows for the β1-integrins, the primary adhesion subunits of tumor cells, to anchor and begin the metastatic process (Oosterling et al., 2008).

Third, recurrent and metastatic tumors after surgery have been observed to exhibit increased tumor growth, increased proliferation rate, and decreased apoptosis (Peeters et al., 2006). Abnormal changes in pathways of gene expression are implicated in post-surgical metastasis as well. Coffey et al. (2005) found elevated expression of phosphoinositide-3 kinase (Pi3k), which is crucial for cell survival, within recurrent tumors, contributing to reduced apoptosis and chemoresistance. Lastly, decreased anti-tumor innate and adaptive immunity occurs in the early stages of the postoperative phase, providing a brief time window for free-floating tumor cells to implant and grow. Immunosuppression is observed in the activity of natural killer cells, macrophages, and T helper 1 cells following surgery and results in lowered cytotoxicity (Da Costa et al., 1998b; Berguer et al., 1999; Rushfeldt et al., 1999). The levels of anti-tumor activity in NK cells are correlated with the degree of injury, underscoring the degree to which surgical technique can play a role in eventual metastasis (Da Costa et al., 1998a).

While surgery can certainly threaten remission through systemic alterations, advances in surgical technology within the past few decades have led to improved outcomes with regards to survivorship (Coffey et al., 2003). Optimization of these procedures results in minimized

surgery-induced trauma, number of complications, and frequency of tumor recurrence (Lacy et al., 2008). Continued developments within the field of surgery technology will likely decrease the aforementioned injuries from treatment. For the time being, other treatments such as immunotherapy may be employed in the postoperative phase to compensate for surgery-induced shortcomings. IFN-α and the granulocyte-macrophage colony-stimulating factor are examples of immunomodulators that are clinically proven to reduce perioperative immunosuppression (Oosterling et al., 2006; Mels et al., 2001). The biochemical changes in the period following surgery have implications for the onset of post-traumatic stress disorder, as pro-inflammatory and immune dysfunctional states are linked to PTSD occurrence (Neigh & Ali, 2016).

Radiation

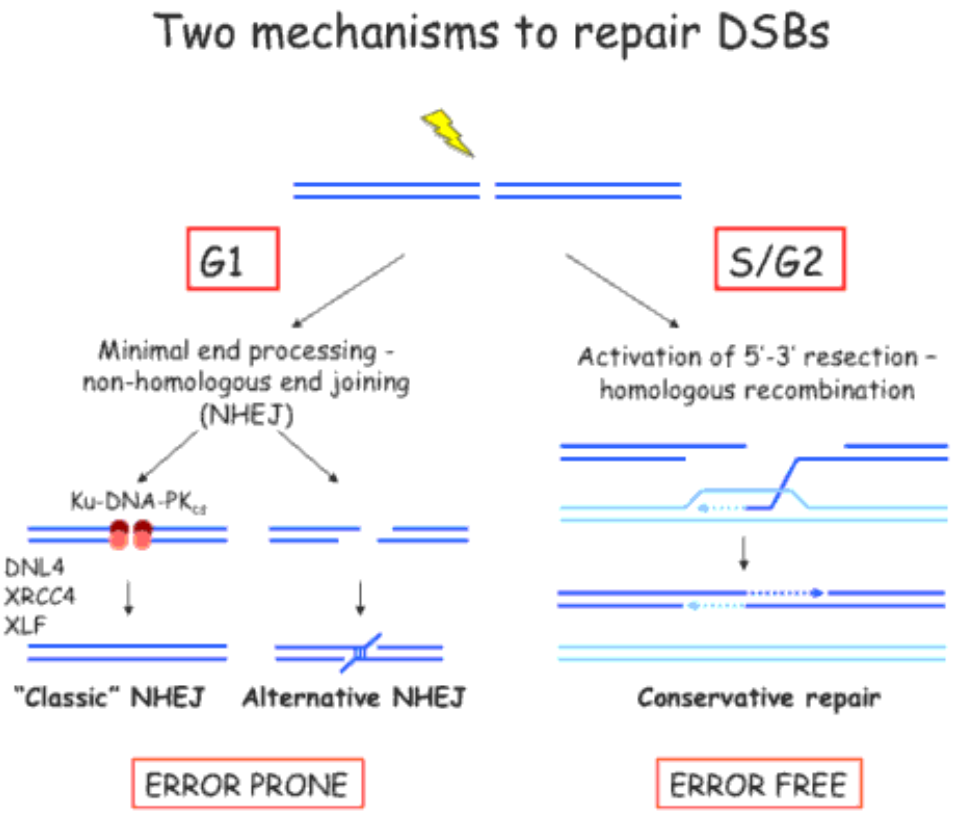
Radiation therapy differs from chemotherapy in that radiation can attack tumors locally, while chemotherapy has a systemic scope of influence. Contact with biological tissue results in free radicals or ionizations, which eventually precipitate into DNA damage (Airley, 2009). Specifically, ideal radio-therapeutic technology emits a wavelength lower than 10^{-6} cm, exciting electrons in the target tissue and thus resulting in ionization (Jones & Symonds, 2019). Within most biological contexts, water is abundant and thus radiation usually results in an ionized water molecule, represented by $H_2O^{+\bullet}$. Hydroxyl radicals, represented by $^{\bullet}OH$, are formed when the ionized water molecule reacts with other water molecules. These new radicals are of the greatest concern to clinical treatment, as it is these $^{\bullet}OH$ species that interact with DNA by damaging the sugar phosphate backbone and/or the nitrogenous bases. Additional molecular events that can also result from this biochemical reaction include single or double-stranded breaks and DNA-DNA or DNA-protein crosslinks.

Of the various structural impediments that are caused by radiation, the most relevant and cytotoxic threat to genomic integrity is double-stranded breaks (DSBs) (Han & Yu, 2010; Hoeijmakers, 2001). This type of DNA lesion occurs when two single stranded breaks are formed approximately 10-20 base pairs apart (Mahaney et al., 2009). The aberrations to chromosomal material disrupt proper gene functioning, having downstream effects on normal protein synthesis and eventually provoking cell death (Rich et al., 2000). Numerous DNA repair pathways exist to combat damage caused by naturally confronted factors, including UV radiation, various chemical agents, or metabolism (Negritto, 2010). Therefore, an emerging field of interest within cancer treatment is the administration of drugs that target these pathways, namely the homologous recombination (HR) and non-homologous end joining (NHEJ) pathways (Kavanagh et al., 2013).

While much of the pathways are not fully understood and continue to be elucidated, the HR pathway is known to be employed only in the presence of an undamaged sister chromatid, using the structurally intact homologous DNA to act as a template that will re-synthesize the genetic material damaged by the DSB (Hendrickson, 1997). This prerequisite implicates that HR can only occur during the S and G2 phases of the cell cycle. Within the G1 phase, the NHEJ pathway dominates over the HR pathway and does not necessitate the presence of homology. A heterodimeric complex is formed that interacts with various kinases and recruits many NHEJ-related factors to identify DNA ends formed by DSBs and to process them for sufficient ligation (Kavanagh et al., 2013). Both these pathways are depicted in Figure 4. Should therapeutics target the individual steps or factors involved in these pathways, such as the Ku70 or Ku80 proteins of the NHEJ complex, radiotherapy administered in tandem can result in greater clinical efficacy.

Figure 4.

Mechanism of HR and NHEJ Pathways for DSB Repair



Note. From "Research at the Symington Laboratory," by L. Symington (https://microbiology.columbia.edu/symington-lab-research).

Cancer-Related PTSD

A brief review of literature concerning cancer-related PTSD (CR-PTSD) will follow. Symptomology of post-traumatic stress using the DSM-IV criteria has been notably observed in a breadth of cancer types, including melanoma, Hodgkin's disease, breast cancer, and mixed-diagnosis samples (Gurevich et al., 2002). PTSD symptoms disproportionately affect cancer patients, as current research finds an incidence rate of 20% among cancer patients with recent diagnosis (Mehnert & Koch, 2007; Mundy & Baum, 2004). This rate is significantly greater than

the lifetime prevalence of PTSD among the general population, which is approximately 6.5% (Pietrzak et al., 2011). While PTSD diagnosis in cancer patients is an emerging field that is currently understudied, it is imperative that clinicians are able to diagnose PTSD within their cancer patients because of its associated intrusive thinking and avoidant behavioral patterns. These psychological aspects contribute to issues with compliance and adherence to clinical recommendations (Ma et al., 2008).

Numerous empirical factor analyses have been conducted to identify the categories of psychosocial responses associated with CR-PTSD. These investigations utilized the responses of cancer patients that were collected via the PTSD PCL-C, a standardized self-report rating scale designed for the assessment of traumas experienced by civilians (Weathers et al., 1993). Each study reported its own particular factor model of symptoms, which may be attributed to the unique trauma experiences found across each sample. Despite the variation across these studies, analysis of the results as a collective show that common patterns of symptom responses include some form of re-experiencing, numbing, arousal, and avoidance (Smith et al., 1999; Cordova et al., 2000; DuHamel et al., 2004; Shelby et al., 2005). Cancer-specific and treatment-specific variables that contribute to the development of PTSD symptoms include the degree of life threat, as breast cancer patients with more progressive disease and longer periods of hospitalization tended to experience more PTSD symptoms (Jacobsen et al., 1998). Additionally, more intensive treatment, such as autologous bone marrow transplantation, was associated with more prevalent CR-PTSD symptomatology than more standard treatment options such as surgery, chemotherapy, or both (Jacobsen et al., 1998; Fields et al., 1994; Peters et al., 1993).

Demographic risk factors for CR-PTSD include younger age, lower income, less formal education, pre-existing lifetime PTSD, and prior negative life stressors and/or psychological

problems (Cordova et al., 1995; Mehnert & Koch, 2007; Green et al., 2000; Green et al., 1998). Social aspects that precipitate PTSD symptoms include constraints on discussing one's illness and poor social support (Abbey et al., 2014). Coping mechanisms also may affect incidence, as dissociation, emotional suppression and avoidance, and rumination are linked to PTSD symptoms. O'Connor et al. (2011) found that the strongest predictors of severe post-traumatic stress symptoms in breast cancer patients at 15 months post-surgery were low social status, previous physical and mental illness, axillary lymph node involvement, and reduced physical functioning at 3 months. Bone marrow transplant patients have also exhibited heightened PTSD symptom severity with weaker social support and higher avoidance coping (Jacobsen et al., 2002). Lastly, CR-PTSD symptoms can also be time-sensitive with regards to one's cancer survivorship timeline. An increased severity of these symptoms is associated with a more recent treatment completion and cancer recurrence (Andrykowski & Cordova, 1998; Butler et al., 1999). It is important to note, however, that post-traumatic stress symptoms do not necessarily equate to a formal PTSD diagnosis. Further research must be conducted to affirm the implications of such risk factors for the official onset of this disorder as dictated by DSM-5 criteria.

Of notable relevance to the COVID-19 pandemic is how social isolation during treatment influences PTSD onset and severity. Some cancer therapies, especially intensive inpatient surgeries, necessitate lengthy periods of isolation or hospitalization that may last from hours to days, thus acting as barriers to social support. The medical treatment setting can evoke stress responses and feelings of loneliness by demanding reduced personal agency, general lack of privacy, and great unfamiliarity to what patients deem most comfortable (Hall & Hall, 2013). PTSD onset then becomes more likely, as research shows that both social and emotional

loneliness are longitudinally associated with post-traumatic stress symptoms and that this relationship may be bidirectional in its causality (Fox et al., 2021). Quarantine restrictions, such as those in the present pandemic, stifle attempts at sufficient coping via social support, usurp comfort within one's own home, and trigger more severe PTSD symptoms for at least 1 month after the beginning of quarantine enforcement (Fawaz & Samaha, 2020; Brooks et al., 2020). As a result, cancer patients undergoing treatment during quarantine may experience worse PTSD-related symptoms than what would be typically observed. To protect against or minimize adverse reactions to confinement, clinicians should consider recommending more electronic media engagement to bolster one's social support network, psychoeducation regarding the importance of coping strategies, and goal-directed activities such as learning a skill or creating (Jurblum et al., 2020).

Biochemical Basis of Cancer-Related PTSD

While not definitively established, the pathophysiology underlying CR-PTSD is likely mediated by a conglomerate of various hormonal pathways and systemic changes, rather than isolated to a single mechanism of action. For one, the immune system is an important domain for CR-PTSD onset. Of particular interest is the proliferation of pro-inflammatory cytokines in response to cancer. These proteins provide both beneficial and detrimental effects toward disease progression, paradoxically amplifying immune response against neoplastic cells while also simultaneously encouraging tumor growth and metastasis (Dinarello, 2006).

Several studies have uncovered correlations between hormonal stress responses and serum levels of these cytokines. When administered with INF-α, a key cytokine in early immune response, both humans and animals experienced strong behavioral side effects known as "sickness behavior" that involves anhedonia, anorexia, decreased social exploration, fatigue,

impaired sleep, and cognitive dysfunction (Yamano et al., 2000; Musselman et al., 2001). This set of behaviors strongly overlap with those resulting from the cancer experience. Maes et al. (1999) found increased levels of IL-6 signaling in PTSD patients. IL-6 and other cytokines heighten the activity of dopaminergic neurons in the hippocampus and bolster the integrity of catecholaminergic neurons (Kushima et al., 1992; Zalcman et al., 1994). Because these cells are believed to be involved in fear, encoding of fear memories, trauma retrieval, and sensitization, pro-inflammatory cytokines' influence on the hippocampal-amygdala neural network may act as a means by which CR-PTSD is elicited (Grillon et al., 1996). Research suggests that the proper functioning of anxiety-regulating monoamine neurotransmitter systems and the hypothalamic-pituitary-adrenal (HPA) axis is also affected by cytokine action (Miller et al., 2008). Through negative feedback regulation of the HPA axis, glucocorticoid resistance occurs and eventually evolves into elevated glucocorticoid levels via desensitization (Rustad et al., 2012). The resulting HPA dysregulation and heightened IL-6 concentration impairs the uptake of monoamines such as serotonin, dopamine, and norepinephrine (Miller, 2009). Previous studies show that PTSD patients exhibit numerous serotonin-related deficiencies, including lower concentrations of serotonin and lower density of platelet serotonin uptake sites (Heim & Nemeroff, 2009). Additionally, higher dopamine levels disrupt fear conditioning in the mesolimbic system and elevated norepinephrine has been shown to increase arousal, fear encoding, startle response, and response to memories (Sherin & Nemeroff, 2011). Current literature generally supports the monoamine hypothesis, which posits that these monoamine neurotransmitters are the underlying pathophysiological basis for depression, mania, and overall affective states (Hirschfeld, 2000; Barchas & Altemus, 1999; Schildkraut & Kety, 1967). Considerable comorbidity is observed with PTSD and other psychiatric disorders, especially major depressive disorder (Brady et al.,

2000). Thus, evidence suggests that the onset of PTSD can be exacerbated by the recruitment of pro-inflammatory cytokines that are mobilized for immunological cancer defense, providing a neurobiological reason for elevated PTSD prevalence among cancer patients.

While the biochemical changes of cancer and its treatment predispose one to CR-PTSD, research indicates that a reverse relationship between these variables may also be possible, in which PTSD can provoke tumorigenesis. In this emergent area of study, however, the current findings are not completely consistent with this hypothesis (Gradus et al., 2015). Despite this, Arnaboldi et al. (2017) argue that the studies conducted by Antonova et al. (2011), Chida et al. (2008), and Lillberg et al. (2003) that support this hypothesis are more significant because each attempted to discern mediating variables between cancer development and psychosocial stress. However, closely related is the finding that stressful life events correlate with breast cancer incidence. Cortisol, the primary stress hormone, has a sustained and heightened concentration during stressful life events. This hormone is crucial for mammary gland formation and estrogen regulation, explaining why evidence currently points toward life stress affecting tumors that are breast-specific (Antonova et al., 2011). As future investigations are performed, researchers may find new interactions between psychosocial factors and different cancer types. Thus, it is essential that clinicians approach patient care with a holistic approach and with consideration of the social determinants of health.

Cancer Treatment and CR-PTSD

Chemotherapy and CR-PTSD

Chemotherapy is notorious for its harmful side effects, which most often includes nausea, vomiting, fatigue, dry mouth, loss of appetite, changes in taste, hair loss, and constipation (Altun & Sonkaya, 2018). Physical and emotional distresses induced by such symptoms act as sources

of trauma that can eventually confer PTSD within certain patients. Firstly, for patients with cancers that are lymphoproliferative or immunologically mediated, chemotherapeutic agents with immunosuppressive properties are often recommended (Rasmussen & Arvin, 1982). In a study by Verma et al. (2016), depletion of immune cell levels in breast cancer patients were sustained for longer than 9 months post-chemotherapy. During this period, patients are advised to remain hypervigilant with regards to hygiene and potential disease exposure in order to compensate for their increased susceptibility to infection. Several empirical and clinical studies within the past few decades suggest that hypervigilance to threat and attentional biases are essential for the maintenance of PTSD (Kimble et al., 2014). Indeed, facilitated detection and interference in disengaging from threatening stimuli are demonstrated in PTSD patients, indicating that heightened attentional bias is internalized within their behavior (Pineles et al., 2007; Beck et al., 2001). In light of this, Conoscenti et al. (2009) identify hypervigilance as a gateway to posttraumatic disturbance and, in turn, as crucial to understanding the etiology of PTSD.

However, a recent study of a nationwide cohort by Jiang et al. (2019) found that PTSD is a risk factor for numerous incident infections. This finding is consistent with current literature that psychological stress leads to dysfunction of the HPA axis and epigenetic changes that impair immune function via changes in gene expression (Uddin et al., 2010). Therefore, a forward feedback loop exists in which initial immunosuppression via chemotherapy causes a patient's hypervigilance towards infection. This behavior facilitates greater psychological distress and/or PTSD onset, which leads to a greater risk for infection through further immune deficiency.

Secondly, numerous studies confirm an association between cognitive dysfunction and PTSD. Colloquially dubbed "chemobrain," chemotherapy-induced cognitive impairment is a common symptom that harms quality of life and causes functional decline in daily life, especially

with regards to memory, attention, verbal learning, and information processing speed (Boykoff et al., 2009; McAllister et al., 2004). Initially, chemotherapeutic neurotoxicity was thought to be the main reason for chemobrain symptoms to arise (Ahles & Saykin, 2007). This hypothesis was placed under scrutiny when cognitive impairment was observed prior to chemotherapy, prompting Hermelink et al. (2017) and Vardy et al. (2015) to find that cancer-related post-traumatic stress partially mediates cognitive dysfunction irrespective of chemotherapy. These results suggest that the trauma stemming from the event of cancer diagnosis, rather than the pathophysiological changes from chemotherapeutic medication, is the main cause of "chemobrain." Research on PTSD in veterans supports this notion, as high severity of PTSD symptoms predicts greater cognitive impairment (Qureshi et al., 2011; Clouston et al., 2016).

Thirdly, psychosocial sources of trauma that arise from chemotherapy are also essential to consider when discussing the cancer experience. Chemotherapy-induced alopecia plays a crucial role in one's identity, is considered a visible sign of illness, and confers an additional source of trauma for the patient (Cash, 2001; Freedman, 1994). Breast cancer patients with hair loss who were interviewed by Trusson and Pilnick (2017) cited a struggle to maintain a sense of self-perception in the wake of their new cancer identity because "by the time they lost their hair, they were struggling to keep a sense of themselves." It is important to note, however, that much of patients' psychological distress was provoked from the social contexts in which they lived. Participants who opted out of wearing wigs were often met with uncomfortable attention, and for patients who covered their baldness, their motive was to preserve the relationships of the people they interacted with. Many women were afraid of scaring their children or losing the romantic interest of significant others, despite affirmations to the contrary (Harcourt & Frith, 2008). Additionally, participants expressed concern about the stigma they would receive from

neighbors, due to the association of baldness with illness and with incarceration in asylums and prisons. Therefore, the compounding personal and social stressors related to chemotherapy-induced alopecia become incorporated into a patient's daily life, establishing a firm foundation on which CR-PTSD can occur.

Lastly, the cyclic and prolonged nature of chemotherapy treatment provides a textbook setting for classically conditioned responses against treatment-related stimuli. Patients undergoing intravenous chemotherapy will repeatedly be exposed to aversive stimuli, including treatment-induced side effects or painful procedures, over the course of several months or longer. Neutral stimuli, such as sounds, smells, or sights associated with the treatment site, will become paired with trauma-related stimuli and may contribute to fear, arousal, and anxiety throughout chemotherapy and even after treatment completion (PDQ® Supportive and Palliative Care Editorial Board, 2019). For instance, 15% to 65% of chemotherapy patients become nauseated when expecting treatment, a symptom known as anticipatory nausea. Reported predictors of this phenomenon include detection of the distinctive chemical odor in chemotherapy clinics, the color of chemotherapy drugs, the sight of oncologists, and the voice of nurses (Nesse et al., 1980; Redd et al., 1993; Divgi, 1989). The specific odor stimulus is generalized to elicit the conditioned nausea response from similar scents. Within a sample of Hodgkin's disease survivors, 63% reported anticipatory nausea and 80% experienced anxiety from 6 months to 140 months after treatment completion (Cella et al., 1986). Patients do not only experience nausea within the clinic, but also in other contexts. In those with a history of anticipatory nausea, cancer patients became nauseated when mental images of chemotherapy treatments were induced (Redd et al., 1993). These results align with current theories suggesting that psychological, neurological, and physiological systems all play a role in the etiology of this symptom (Roscoe et

al., 2011). Guidelines by the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend behavioral therapy via systematic desensitization, hypnosis, relaxation exercises, cognitive distraction, yoga, or acupuncture/acupressure (Natale, 2018).

Surgery and CR-PTSD

As observed in the prevalence of PTSD in cancer patients, post-surgical PTSD rates are significantly higher than that of the general population and range variably from 8-51% (Deatrich & Boyer, 2015). The rates of PTSD after surgery across several diagnoses are depicted in Table 1. Current data suggest that cancer patients who also require surgery do not have a higher PTSD rate, indicating that prevalence rates for patients with cancer or patients with PTSD are not additive. However, it remains to be investigated whether the severity of PTSD symptoms is heightened when patients undergo both cancer and cancer-related surgical treatment, compared to if patients either only had cancer or underwent surgical operation for a non-cancer issue.

Table 1.

Post-surgical PTSD rates among different patient populations

Medical condition requiring surgery	Rates of PTSD
Breast cancer	8–20 %
Gynecologic cancer	16–34 %
Cardiac	8–20.1 %
Traumatic injury	8–51 %

Note. Adapted from "Post-traumatic Stress Disorder Related to Surgery: Prevalence and Risk Factors," by K. G. Deatrich and B. A. Boyer, 2015, *Comprehensive Guide to Post-Traumatic Stress Disorder*, p. 2 (https://doi.org/10.1007/978-3-319-08613-2_42-1). Copyright 2015 by Springer International Publishing Switzerland.

For surgical cancer patients, the severity of both post-traumatic stress and PTSD rates are correlated with more advanced or malignant disease (Deatrich & Boyer, 2015). For instance, a study of gynecologic cancer found PTSD cases in 34% of advanced cancer patients, 16% of early cancer patients, and 15% of benign disease groups (Posluszny et al., 2011). Additionally, prostate cancer patients scored higher on the Davidson Trauma Scale than those with benign prostate hyperplasia, who scored similar to the general population (Anastasiou et al., 2011). The physical and financial demands of surgery may certainly contribute to PTSD symptoms, but a more likely source of psychological distress is derived from the potential for tumor recurrence and the diagnosis itself post-treatment (Taylor et al., 2011; Mehnert & Koch, 2007). Some studies suggest that the anticipatory and uncertainty aspects of surgical care contribute to distress, as PTSD rates and PTSD symptoms wane with time post-surgery (Posluszny et al., 2011). Emerging research employing the new DSM-5 criteria has found that the intolerance of uncertainty, defined as an inability to tolerate the unpleasant response triggered by the observed absence of information, is significantly associated with overall PTSD symptom severity, along with other anxiety disorders (Raines et al., 2019).

The perceived risk of a surgery, in terms of both success and subsequent complications, has implications for the degree of psychological stress incurred in patients. This risk is generally gauged as a function of the threat to life of the disease in question. Thirty-two percent of those undergoing abdominal aortic repair/coronary artery bypass, 25% undergoing secondary peritonitis, and 15% undergoing native valve replacement were reported to have PTSD-related symptoms (Jeantieu et al., 2014). These symptoms have further implications for prognosis, as in another sample of coronary artery bypass grafting patients, depression, PTSD, and comorbid depression and PTSD are associated with greater risk of death to a degree that is similar to well-

established physical health risk factors (Dao et al., 2010). Thus, high-risk surgeries as a collective may have a role in PTSD onset and vice versa. Because tumor surgery is perceived as high-risk and generally has more danger than elective procedures, psychiatric morbidity during the cancer experience should be thoroughly vetted by clinicians. Lung cancer patients who were treated with surgical resection had a PTSD symptom prevalence rate of 51%, as measured by the Impact of Event Scale - Revised, and postoperative pain seemed to trigger the development of these symptoms (Jeantieu et al., 2014). This finding is in agreement with previous research showing that increased pain at discharge is closely related to PTSD and depression after 1 year (Archer et al., 2016). A study of breast cancer patients found that 83% of the CR-PTSD group received modified radical mastectomy versus 47% of the subsyndromal CR-PTSD group and 38% of the non-PTSD group, showing that surgical intervention may mediate the prevalence of CR-PTSD (Shelby et al., 2008).

A small body of research investigating psychological sequelae in parents of children undergoing surgery for cancer and non-cancer diseases indicates that PTSD onset is not limited to the bearer of the disease being treated, but may occur intergenerationally. In a study by Karadeniz Cerit et al. (2017) on mothers whose children underwent oncological surgery, the rate of PTSD among mothers was found to be 21.7%. PTSD-diagnosed mothers more often expressed some form of guilt, such as believing they were "being punished or tested," than non-PTSD mothers. Non-cancer studies found that six months after their children were treated with cardiopulmonary bypass surgery, 14.9% of mothers and 9.5% of fathers developed PTSD, with mothers experiencing more severe symptoms (Helfricht et al., 2008). In daughters whose mothers were battling breast cancer, 13% reported PTSD-related symptoms and were significantly more likely to experience these symptoms if their mothers also exhibited them

(Boyer et al., 2002). Cognitive-behavioral therapy aimed at resolving maladaptive feelings of guilt may result in improved psychological outcomes.

Tumor recurrence enabled by the biophysiological processes underlying surgery-induced metastasis also has effects on CR-PTSD. The mere fear of recurrence may be a contributor to CR-PTSD symptoms, as a higher fear of recurrence is associated with more PTSD symptoms (Black & White, 2005). Black and White (2005) note that "an individual's fear of recurrence may be perceived as a 'sense of serious current threat,' thus affecting their appraisals and memory of the trauma and increasing the possibility of them experiencing post-traumatic stress symptoms." Upon diagnosis of a novel tumor, the patient will unfortunately have to cope with both familiar and new physical, psychosocial, and financial stressors, which may cause more severe psychological trauma than the initial diagnosis. Indeed, 80% of recurrent cancer patients reported PTSD-related symptoms compared to 20% of early-stage cancer patients (Gurevich et al., 2002). Thus, to help to cope with cancer, it is imperative that appropriate screening and psycho-educational intervention is pursued upon tumor recurrence in surgical and non-surgical patients alike (Okamura et al., 2005).

Radiation and CR-PTSD

Several studies purport the effects of radiation on overall psychiatric morbidity. Currently, the literature on radiotherapy and CR-PTSD is under-investigated in comparison to the other two major cancer treatments. However, it is known that radiotherapy confers considerable physical and psychological distress. Acute physical side effects include fatigue, skin changes, and site-specific effects (e.g. mouth and gum sores or tooth decay for head and neck treatment) (Cancer.Net Editorial Board, 2020). The distress incurred provokes 13% of cancer patients being treated with radiation to seek psycho-oncology support during their

treatment (Riedl et al., 2018). The actual proportion of radiotherapy patients that would benefit from such intervention is likely to be greater. One-third of all radiotherapy patients experience psychosocial function decline over the course of radiation treatment, during which a study found a temporal relationship between rates of distress, depression, and anxiety (Hess & Chen, 2014). As these factors are often comorbid with PTSD, these results indicate that radiotherapy may influence the onset of CR-PTSD; however, to my knowledge, no empirical study isolating a potential association between radiotherapy and CR-PTSD exists as of yet.

Preliminary evidence does support the notion that radiotherapy plays a role in CR-PTSD onset. Within a sample of 3343 breast cancer patients, a status of having received or waiting to receive radiotherapy was associated with higher risk of severe PTSD symptomatology at 3 months (O'Connor et al., 2011). Upon follow-up of these same patients at 15 months, however, the association between post-traumatic stress symptoms and radiotherapy disappeared. The long-term absence of PTSD within this group may imply that symptoms stem from other acute side effects or experiences that are precipitated by treatment. Shorter follow-up intervals would better elucidate how the severity and/or prevalence of PTSD-related symptoms change as a function of time since radiation completion.

One of these acute side effects is cancer-related neuropathic pain. Lema et al. (2010) assessed how neuropathic pain, defined as pain resulting from a lesion, damage, or dysfunction of the somatosensory nervous system, was induced by cancer treatment and its implications for patient outcomes. Reduced quality of life, resulting treatment delays, dose reductions, and discontinuations are some of the dangerous consequences of neuropathy. In particular, toxic neuropathic pain, which may be introduced by radiotherapy as well as chemotherapy, can manifest into neurological dysfunction. The uncertainty that accompanies the loss of physical

control of one's body may be distressing enough for some patients to eventually develop PTSD or related symptoms. Ideally, the upcoming decades will introduce further mechanisms underlying how radiotherapy contributes to CR-PTSD, allowing for better informed patient care.

Treatments and Future Directions for CR-PTSD

Therapies specifically curated for PTSD in cancer patients have yet to be formally established (PDQ® Supportive and Palliative Care Editorial Board, 2019). Furthermore, the current body of research on treatments for CR-PTSD is limited, as a 2019 review focusing on the treatment of cancer-related traumatic stress found only eight studies covering this specific topic (Dimitrov et al., 2019). Despite this, there remain pre-existing interventions for general PTSD patients and for those facing personal crises. One of the most difficult steps taken to remedy this disorder is the acceptance and pursuit of professional help, as avoidant coping is a frequent technique by which patients attempt to grapple with their trauma. However, this strategy exacerbates the risk of maintaining or worsening PTSD symptoms in the months following the traumatic event (Pineles et al., 2011). Once treatment is pursued, symptoms and overall psychological distress can be reduced with psychotherapy or medication, and treatment via one means can often amplify the beneficial effects of the other.

Regarding CR-PTSD specifically, cognitive-behavioral therapy (CBT), which aims to guide changes in unhelpful thinking or behavioral patterns and provide better coping strategies, has shown clinical merit in reducing PTSD symptom scores. In a randomized clinical trial (RCT) of hematopoietic stem-cell transplantation survivors, those who completed telephone-administered CBT reported decreased avoidance, fewer intrusive thoughts, lower distress, and fewer depressive symptoms across a 12-month period (DuHamel et al., 2010). Kangas et al. (2012) found that CBT and supportive counseling helped reduce PTSD, depression, and/or

anxiety symptoms, but CBT benefitted up to 67% of patients while supportive counseling only helped 25%. Another effective intervention for CR-PTSD is eye movement desensitization and reprocessing (EMDR) therapy. This treatment "encourages the patient to briefly focus on the trauma memory while simultaneously experiencing bilateral stimulation (typically eye movements), which is associated with a reduction in the vividness and emotion associated with the trauma memories" (American Psychological Association, 2017). Studies by Jarero et al. (2015) and Capezzani et al. (2013) concluded that cancer patients experienced reduced PTSD symptomatology, whether in active or follow-up care. When comparing the clinical efficacy of EMDR and CBT, Capezzani et al. (2013) found that patients with EMDR were more likely to have a post-treatment absence of PTSD. Other promising treatments that are corroborated with scant evidence and require further investigation include complementary/alternative-oriented intervention and telephone counseling (Dimitrov et al., 2019).

Pharmacologic treatment may provide greater benefit for PTSD cases that are more severe. Three main classes of medications have caused improved psychological outcomes for patients suffering from PTSD. Several RCTs have demonstrated the effectiveness of selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline in reducing intrusive thoughts and hyperarousal in PTSD patients (PDQ® Supportive and Palliative Care Editorial Board, 2019). While prescribed open label, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine can offer improvements across all symptom clusters of PTSD. Lastly, monoamine oxidase inhibitors (MAOIs) are a common form of treatment that are better than placebos for short-term symptoms (Davidson et al., 2009). These are especially beneficial for patients exhibiting both PTSD and depressive symptoms (PDQ® Supportive and Palliative Care Editorial Board, 2019).

In summary, the effects of first-line cancer treatments that are discussed in this thesis can direct further, much-needed research and care towards alleviating CR-PTSD symptoms. An increasingly prevalent issue, CR-PTSD must be treated through a holistic lens and consider all factors that may affect patients' mental well-being. Central to my thesis is the notion that cancer is a multifaceted experience in which sources of trauma extend far beyond the pathophysiology of the disease itself and includes the phases of treatment and survivorship. To improve health outcomes across a patient's lifespan, clinicians can seek to minimize the side effects of chemotherapy, surgical trauma, and radiation therapy that can each contribute to psychological distress and PTSD symptoms within their patients.

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