Platinum Study Newsletter

SUMMER 2025

INSIDE THIS ISSUE:

Stay connected with The Platinum Study Team! If you have moved, changed your email address, or have a new phone number, please notify your clinic or study team or you may share your contact information with the current study headquarters at Indiana University by:

- **Calling us toll-free at 833-770-8700**
- **Emailing us at ptstudy@iu.edu**

The Platinum Study Update

We thank you for your ongoing support of The Platinum Study. Because of your participation, The Platinum Study has made critical and important contributions to the practice of oncology and clinical literature in terms of information that helps you, the study participant, and the almost 6,000,000 patients each year who are eligible to receive the platinum drugs. The Principal Investigator, Dr. Lois B. Travis, was asked to represent the study at the 2024 annual meeting of the American Society of Clinical Oncologists (ASCO) in Chicago. A copy of her presentation ("Long-term Survivorship in Testicular Cancer: The Platinum Study)" can be found on the study website https://cancer.iu.edu/patients/surviving/platinum-study/index.html. Dr. Travis and other Platinum Study colleagues also published an invited review paper titled "Adolescent and Young Adult Germ Cell Tumors: Epidemiology, Genomics, Treatment, and Survivorship" in the Journal of Clinical Oncology. Co-authors included Drs. Darren Feldman (Memorial Sloan Kettering Cancer Center) (MSKCC) and Chunkit Fung (University of Rochester). A link to this publication is also provided on the study website.

In the last year, we have added two experts in cognitive science to our research team: Drs. James Root and Tim Ahles from MSKCC in New York City. Dr. Root is profiled in this newsletter. Together with Drs. Root and Ahles, we published a research article on cognitive function titled "Cognitive Function in Long-term Testicular Cancer Survivors: Impact of Modifiable Factors," with a link to the final paper also on The Platinum Study website.

An ongoing challenge identified by our advisory board and reviewed in our last newsletter, is that the rate of survey completion in The Platinum Study II is relatively low against national benchmarks. The standard is that around 80% of all patients enrolled in the initial phase of any cohort study should also complete subsequent questionnaires so that longitudinal data can be obtained. Thus, if you have not yet consented to Part II of the study, or if you have consented but have not completed your questionnaire, we would like you to know that your responses are extremely important. Please let us know how we can help you complete these by contacting us by phone at 833-770-8700 or by e-mail at ptstudy@iu.edu. Thank you again to all the study participants who have answered the questionnaire and continue to provide important data. If you would like to request that a specific clinical or research topic be discussed in the newsletter, please let us know by contacting us at the above phone or email.

FEATURED CLINICIAN: DR. JAMES C. ROOT, PhD

Dr. James C. Root, Attending Neuropsychologist at Memorial Sloan Kettering Cancer Center (MSKCC) and Professor of Psychology at Weill Cornell Medical College, received his PhD from the New School for Social Research in New York City. He completed his predoctoral residency in neuropsychology at Yale, and postdoctoral training at Columbia and Cornell in neuropsychology and neuroimaging, respectively. Dr. Root's clinical expertise is in the assessment

of cognitive abilities (e.g., memory, attention, language, executive functioning) in adults following cancer diagnosis and treatment. His research similarly focuses on the cognitive effects of cancer and its treatment within MSKCC's Neurocognitive Research Laboratory, with over 100 publications and multiple book chapters devoted to this work. Dr. Root utilizes neuropsychological, neuroimaging, and psychophysiological assessment to investigate the effects of cancer and its treatment on cognition, as well as on brain structure and function. For The Platinum Study, he has advised on interpretation of neurocognitive outcomes and specific factors including hearing loss, that might be associated with a greater risk of cognitive dysfunction. He is also working in close collaboration with Platinum Study researchers on future research proposals with similar aims, again focusing on testicular cancer and platinum-based chemotherapies and the extent to which an effect on cognition exists. This proposal will use novel neurocognitive measures, developed and validated by Dr. Root, with proven sensitivity to cancer-related cognitive dysfunction. Dr. Root's previous NIH-funded project focused on improving sensitivity to cognitive changes in survivorship using novel, cognitive-experimental and psychophysiological methods. His currently NIH-funded research explores how a history of cancer and treatment may alter the trajectory of cognitive aging in later life and associated risk factors. Dr. Root has trained and mentored over 60 graduate students as part of the MSKCC Neuropsychology Externship Program over the past 15 years, in addition to multiple postdoctoral fellows as part of an NIH funded training program in the Department of Psychiatry and Behavioral Sciences at MSKCC.

Clinician's Corner: Cancer-Related Cognitive Dysfunction by Dr. James C. Root, PhD

Cognitive decline following cancer diagnosis and treatment is of one of the greatest concerns in cancer survivors. Once termed "chemo-fog" or "chemo-brain" given the suspicion that chemotherapy agents might be the primary culprit, we now refer to cognitive changes following treatment as cancer-related cognitive dysfunction (CRCD). This is due to the fact that many chemotherapy agents cannot cross into the brain to have a direct effect, that many survivors not treated with chemotherapy also experience changes in cognition, and that many other factors may be involved in cognitive changes. These include surgical stress and anesthetic exposure, hormonal therapy in the case of breast and prostate cancers, and the use of newer treatments (tyrosine kinase inhibitors (TKIs); CAR-T cell therapy) that also appear to be related to changes in cognition. The role of systemic inflammation brought on by the cancer itself, and potentially by treatment, and associated increases in neuroinflammation are also being investigated. Recent work even suggests that the features of some cancers (tumor stage, size, molecular characteristics) may impact cognition before any further adjuvant treatment. Regardless of the cause, survivors who experience such cognitive changes - inattention, forgetfulness, word-finding changes in planning and organization – that are of sufficient severity may be referred to a neuropsychologist for formal testing. Neuropsychological assessment consists of an in-depth clinical interview followed by administration of performance-based cognitive measures that measure specific domains of cognitive function. Results can help determine the reason for cognitive decline, rule out other potential causes, and can be useful in their role in treatment planning for remediation, which might include cognitive rehabilitation, changes in lifestyle, and pharmacological treatment in some cases. It is important to note that not all survivors are affected nor are some affected to the same extent as others. Likely risk factors may include increasing age, genetic susceptibilities known and unknown, unrelated neurological problems like a history of head injury or repeated concussions, psychosocial and environmental stressors, and accrual of other medical conditions e.g., hypertension, diabetes, cardiovascular disease that either lay the groundwork or exacerbate cognitive changes with age. If you experience cognitive difficulties following cancer diagnosis and treatment that are of sufficient concern, a discussion with your primary care provider or oncologist will help to guide subsequent referrals and treatment plans to evaluate and address these difficulties.

Summary of Publications

Cognitive Function in Long-term Testicular Cancer Survivors: Impact of Modifiable Factors

Dinh Jr. P.C., Monahan P.O., Fung C., Sesso H.D., Feldman D.R., Vaughn D.J., Hamilton R.J., Huddart R., Martin N.E., Kollmannsberger C., Althouse S., Einhorn L.H., Frisina R., Root J.C., Ahles T.A., Travis L.B.

Background: Cognitive dysfunction is a potential adverse health outcome in testicular cancer survivors. There are several known risk factors for impaired cognition in the general population, and this study was the first to examine their impact on cognitive function in long-term testicular cancer survivors.

What we did: A total of 678 testicular cancer survivors given cisplatin-based chemotherapy completed comprehensive survey assessments of multiple measures (e.g., sociodemographics, health measures, and health outcomes), including self-reported cognition. Statistical analyses were performed to determine the relationship between potential risk factors and cognitive dysfunction.

What we found: Cognitive dysfunction (defined by problems in the ability to think, concentrate, or remember items in the past 7 days) was self-reported by approximately 14% of study participants. Cognitive dysfunction was associated with several factors: hearing loss, neuropathic pain, fatigue, anxiety/depression, being on disability, or being retired.

What does the study mean: This study identified several factors associated with self-reported cognitive decline among testicular cancer survivors given cisplatin-based chemotherapy. Knowledge of these risk factors enables providers to better identify survivors who might benefit from closer monitoring, counseling, and care to prevent or reduce cognitive dysfunction, perhaps especially by targeting hearing loss, neuropathic pain, fatigue, and anxiety/depression.

This study was published in the Journal of the National Cancer Institute (JNCI) Cancer Spectrum, available at https://pmc.ncbi.nlm.nih.gov/articles/PMC11424079/pdf/pkae068.pdf.

Factors Associated with Longitudinal Progression of the Cumulative Burden of Morbidity and Overall Mortality After Cisplatin-based Chemotherapy for Testicular Cancer

Kerns S.L; Dinh P.C., Jr.; Monahan P.O.; Stump T.; Fung C.; Sesso H.D.; Feldman D.R.; Hamilton R.J.; Vaughn DJ.; Huddart R.; Kollmannsberger C.; Martin N.E.; Nevel K.; Kincaid J.; Einhorn L.H.; Travis L.B.

Background: We previously characterized the cumulative burden of morbidity (CBM) in the Platinum Study by assessing the severity of 21 adverse health outcomes (AHO). Since some health outcomes occur later in life, such as cardiovascular disease, and others, like neuropathy and hearing loss, may worsen over time, it is critical to assess these over time.

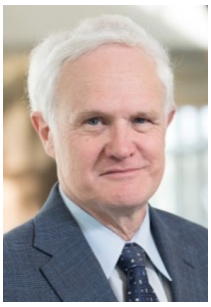
What we did: We compared survey responses between Platinum Studies 1 and 2 (median: 7 years later). Worsening trends over time for AHO and CBM scores were identified. We also tested whether certain health behaviors and AHO at Platinum Study 1 were later associated with an increased risk of mortality.

What we found: Of the 616 participants who completed both Platinum Studies 1 and 2, 23% experienced worsening trends of the CBM score. These worsening trends were driven by treatment-related AHO: tinnitus, hearing loss, Raynaud's phenomena, neuropathy, and neuropathic pain. Lack of aerobic physical activity and obesity were associated with both worsening neuropathy and worsening neuropathic pain. 29 deaths occurred among the 1,830 participants surviving at least 5 years from their cancer diagnosis; the median age was 48 years. Participants who reported no aerobic physical activity, no low-impact physical activity, and neuropathic pain experienced worse rates of death. Lowered physical activity was identified as a mediator (i.e., intermediate step) between neuropathic pain and mortality.

What does the study mean: This study identified worsening trends in health outcomes and the modifiable risk factors that influence these trends. Lack of physical activity (specifically aerobic physical activity) stood out as an important factor that affected both worsening trends of health outcomes and rates of death. Clinical monitoring of testicular cancer survivors with risk factors and continued messaging on the importance of physical activity are needed to prevent poor health outcomes.

The full published version of this article can be accessed on our website at:
https://cancer.iu.edu/patients/surviving/platinum-study/research-updates.html

Featured Clinican: Kurt Kroenke, M.D.



Dr. Kroenke is a highly valued member of the Platinum Study research team. He is a Chancellor's Professor of Medicine at Indiana University (IU) and a Research Scientist at IU's Regenstrief Institute. He is a past President of both the Society of General Internal Medicine and the Association for Clinical Research Training. An internationally respected expert in physical and psychological symptoms, Dr. Kurt Kroenke's expert in physical and psychological symptoms, Dr. Kurt Kroenke's major research interests include pain, depression, and anxiety. He has developed multiple patient-reported outcome measures that have beentranslated into 100 or more languages and used internationally, including the Patient Health Questionnaire-9 (PHQ-9) depression scale, General Anxiety Disorder-7 (GAD-7) anxiety scale, and Pain, Enjoyment of Life and General Activity pain scale. The PHQ-9 and GAD-7 are now used by the U.S. Centers for Medicare and Medicaid Services, Department of Veterans Affairs, and Food and Drug Administration as national guidelines; they are also incorporated into electronic that investigate pain. Chronic pain is one of the most common problems seen in primary care. Dr. Kroenke's work in this area examines the impact of treating depression and anxiety on pain, assesses stepped care to optimize pain and mental health care effectiveness, and tests novel collaborative and telecare management. Dr. Kroenke has received multiple international awards for his work. These include the 2015 European Association of Psychosomatic Medicine Alison Creed Lifetime Achievement Award. In 2018, he was the recipient of the Society of General Internal Medicine's Robert J. Glaser award, the organization's highest honor. He has mentored more than 40 fellows and junior faculty and has more than 450 peer-reviewed research publications.

Principal Investigator's Corner: Lois B. Travis, M.D., Sc.D.

The 2024 Report by the Lancet Standing Commission on Dementia Prevention, Intervention and Care concluded that 12 potentially modifiable risk factors for dementia account for about 45% of all cases. We bring this article to your attention because one of the top two risk factors is hearing loss, which is also a potential side effect of platinum treatment and can be treated. In brief, the the identified risk factors for dementia and percent of dementia in the general population caused by these risk factors follow. In midlife, the risk factors are hearing loss (7%), high LDL cholesterol (7%), depression (3%), traumatic brain injury (3%), physical inactivity (2%), diabetes (2%), smoking (2%), hypertension (2%), obesity (1%), and excessive alcohol (1%). In later life, the risk factors are social isolation (5%), air pollution (3%), and visual loss (2%). In early life, the one identified risk factor to date is less education (5%). What is a 'modifiable risk factor'? Typically, the term refers to something that can be changed. For example, if you have hearing loss, you can obtain a hearing aid. If your cholesterol is elevated, your doctor can discuss dietary modifications and/or prescribe statins for you. If you are obese, you can lose weight. If you are not physically active, you can try to be more active and work with your physician to develop a plan that is right for you. These risk factors are important to control in all individuals, including cancer survivors. For participants in The Platinum Study, a prior column in the 2023 Newsletter by our hearing scientist, Dr. Victoria Sanchez, further addressed hearing loss.

Reference: Livingston G, et al. Dementia Prevention, Intervention, and Care: 2024 Report of the Lancet Standing Commission. Lancet (London, England). 2024; 404(10452): 572-628. Epub 20240731. PMID: 39096926.