Original Article

Self-reported cognitive impairments and quality of life in patients with gastrointestinal stromal tumor: Results of a multinational survey

Robert J. Ferguson, PhD [1,2]; Jessica Manculich, BS[1]; Hsuan Chang, BS[1]; Nikita J. Sareen, BS[1,3]; Beth E. Snitz, PhD[4]; Lauren Terhorst, PhD[5]; Dana H. Bovbjerg, PhD [1,6]; and Anette U. Duensing, MD [3,7]

BACKGROUND: Cancer-related cognitive impairment (CRCI) has long-term effects on survivor quality of life, but CRCI research on patients with gastrointestinal stromal tumor (GIST) is lacking. The aims of this study were to investigate CRCI and concomitant quality of life among patients with GIST. **METHODS:** An online survey was used to assess CRCI in adult patients with GIST using the validated Functional Assessment of Cancer Therapy-Cognitive-v.3. Age, education, demographically indexed IQ, general health, and quality of life factors (e.g., fatigue, emotional distress) were also assessed. The online survey was administered through five international GIST and sarcoma support organizations. **RESULTS:** Over the 3-month recruitment period, the survey was completed by 485 participants: mean age, 57.80 (SD, 11.51), median 5 years after diagnosis. A majority (63.91%) reported experiencing cognitive symptoms with a significant negative quality of life impact. Controlling for age, patients with GIST ≥5 years after diagnosis reported worse cognitive function than those <5 years after diagnosis ($p < .05$) but did not differ in educational level or IQ. Whereas longer term survivors were more likely to have been treated with tyrosine kinase inhibitor (TKI) therapies, there was no observed association of TKI therapy with self-reported cognitive impairments. **CONCLUSIONS:** A majority of GIST patients report cognitive symptoms that have a negative impact on quality of life, with longer term survivors (≥5 years) tending to report more cognitive impairments. Given the success of TKI therapy to substantially increase overall survival of patients with GIST, addressing CRCI in clinical practice may improve long-term GIST survivor function and quality of life. ***Cancer*** **2022;128:4017-4026**

KEYWORDS: cancer-related cognitive impairment, gastrointestinal stromal tumor (GIST), neurocognitive outcomes, quality of life, tyrosine kinase inhibitor therapy.

INTRODUCTION

Cancer-related cognitive impairment (CRCI) affects nearly one-half of all cancer survivors and has an adverse impact on overall quality of life (QOL).[1–4] The degree of cognitive change related to CRCI is usually mild to moderate but can be long-lasting.[5–8] Central nervous system malignancies, including primary brain tumors or metastatic lesions, can have direct influences on cognitive function through neural disruption, but non–central nervous system cancers and their treatments produce CRCI through multiple etiologies.[9–11] Direct neurotoxic effects of systemic chemotherapies,[12] genetic polymorphisms, inflammatory, and other immune mediators[1,11,13–16] have all been identified as candidate mechanisms.[9,11] Whereas a majority of CRCI research (79%) has focused on breast cancer survivors (primarily treated with chemotherapy and/or hormonal therapies),[17] a variety of cancer populations have been reported to have cognitive impairment. This includes lung cancer, testicular cancer (e.g., treated with androgen deprivation therapies), and hematologic malignancies (e.g., treated with chemotherapeutic agents, hemopoietic stem cell transplants).[11,18–20]

Corresponding Authors: Robert J. Ferguson, PhD, Division of Hematology/Oncology, University of Pittsburgh School of Medicine, Biobehavioral Cancer Control, UPMC Hillman Cancer Center, Shadyside Medical Building, Suite 604, 5200 Centre Ave, Pittsburgh, PA 15232 (fergusonrj2@upmc.edu). Anette U. Duensing, MD, Department of Pathology, University of Pittsburgh School of Medicine, Cancer Therapeutics Program, UPMC Hillman Cancer Center, Research Pavilion, Suite G.17, 5117 Centre Ave, Pittsburgh, PA 15213 (aduensin@pitt.edu).

Nikita J. Sareen's current address: University of Florida, College of Medicine, Gainesville, Florida, USA

Hsuan Chang's current address: Hsuan Chang does not currently have an academic or corporate affiliation

[1]Biobehavioral Cancer Control Program, UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA; [2]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [3]Cancer Therapeutics Program, UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA; [4]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [5]School of Health and Rehabilitation Sciences Data Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [6]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [7]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.34469, **Received:** January 28, 2022; **Revised:** August 2, 2022; **Accepted:** August 3, 2022, **Published online** September 20, 2022 in Wiley Online Library (wileyonlinelibrary.com)

To date, there is no research exclusively examining CRCI among individuals with gastrointestinal stromal tumor (GIST). This may be due to its low incidence of 10 to 15 cases per million and historically low survival.[21–24] The primary treatment for GIST is surgical resection, and survival of patients with metastatic or inoperable GIST has been poor because of a lack of responsiveness to chemotherapy and radiotherapy.[25,26] Because the majority of GISTs are caused by oncogenic mutations in the *KIT* receptor tyrosine kinase, US Food and Drug Administration approval of the KIT inhibitor imatinib mesylate (Gleevec) dramatically improved overall survival (OS).[27–32] Over the past 20 years, daily oral imatinib has become the standard first-line treatment for patients with metastatic and/or inoperable GIST. In contrast to classical chemotherapy, patients ordinarily have to adhere to imatinib therapy indefinitely or until resistance occurs.[33] Imatinib-resistant tumors are treated with the second- and third-line tyrosine kinase inhibitors (TKI) sunitinib (Sutent) and regorafenib (Stivarga), respectively.[34–36] Ripretinib (Qinlock) has recently been approved as a fourth-line treatment.[37] Imatinib is also approved for adjuvant treatment (3 years) in patients who undergo complete resection of their GIST with a high risk of recurrence.[30–32] Given the long time patients with GIST receive TKI treatments, it is possible that they are at increased risk for CRCI as a side effect of that exposure. Whereas proinflammatory cytokine activity has been associated with CRCI among long-term survivors,[11,38–40] it is known that TKIs used to treat GIST inhibit platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) signaling, which play a role in vascularization, neurogenesis, and memory.[41] A previous cross-sectional study focusing on patients with renal cell carcinoma found that 30 patients treated with sunitinib or sorafenib scored significantly lower on tests of verbal response generation than no-treatment patients and healthy controls. Although four GIST patients were included in the TKI group of this study, it likely has limited relevance to this patient population.[42]

Considering continued improvements in OS associated with TKI treatment, but current lack of knowledge of cognitive impairment among individuals with GIST, we evaluated CRCI and associated QOL in this patient population. We used the innovative approach of deploying an online survey (consisting of valid and reliable CRCI and QOL measures) accessible through patient/survivor websites and social media announcements from well-established international patient organizations with combined global reach. The first aim of this research was to estimate the rate of self-reported cognitive impairment that had a negative impact on QOL among patients with GIST.[1,11] A second aim was to evaluate possible influences of TKI therapies on self-reported cognitive symptoms and general QOL.

MATERIALS AND METHODS

Study design

A cross-sectional, international online survey ("A web-based survey of cognitive dysfunction and other patient-reported outcomes in people with GIST") was developed that incorporated valid and reliable self-report questionnaires assessing CRCI symptoms, and co-occurring symptoms that may affect cognition and overall QOL (e.g., fatigue, depression, anxiety, sleep quality, pain). We also assessed TKI therapy history, age, education level, physical limitations, general health status, and IQ (using indexing of demographic variables).[43] The survey was deployed using secure software (Qualtrics) approved by the University of Pittsburgh for use in research, which uses an IP address as a unique case identifier, survey entry, and exit. All data were anonymous and used safe-harbor data management methods. Each participant was required to complete online written consent before responding to survey items. This study was approved by the University of Pittsburgh's institutional review board (#PRO17060551).

Participants

The survey was distributed through five international GIST and sarcoma support organizations (GIST Support International, GIST Cancer Research Fund, Sarcoma Patients EuroNet, Das Lebenshaus, and The Life Raft Group) with administrative permission to post the survey on their websites and social media channels (email, Facebook, Twitter). The survey was open from May 15 to August 15, 2018. Potential participants were asked to click a link to review information about the study before completing informed consent. Inclusion screening questions consisted of self-reporting a diagnosis of GIST, legal age of consent (≥18 years), and ability to read and understand English.

Measures

Demographic and medical history variables were assessed with forced-choice responses and free text. Cognitive function was assessed by the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog, version 3) questionnaire, which is a valid and reliable measure of self-reported cognitive symptoms and other aspects of cognitive symptom experience across four scales: Perceived Cognitive Impairments (PCI), Perceived Cognitive Abilities, Comments from

Others (or perceptions of others commenting on patient memory dysfunction), and Impact on Quality of Life (IQOL).[44] Higher FACT-Cog scores indicate better cognitive function/QOL. For assessment of anxiety, depression, fatigue, sleep quality, and pain interference, we used fixed-item short-forms available through the Patient-Reported Outcomes Measurement Information System (www.healthmeasures.net). Each measure assesses eight items over the previous 7 days and is scaled with a 1 (never) to 5 (always) Likert-type rating and a possible raw score range of 8 to 40. Higher scores correspond to higher levels of the measured domain (higher anxiety score = more anxiety). We also assessed self-reported health (physical limitations and general health) using the Medical Outcomes Study 36-Item Short-Form Health Survey (higher scores = better health).[45]

Statistical analysis

Preliminary screening and sample characteristics

Before analysis, we assessed data distributions, bivariate relationships among variables, and amounts of missingness. We examined demographic and medical variables using descriptive statistics (means, SD, and standard error for continuous variables, frequencies, and percentages for categorical variables). To estimate precancer overall cognitive function of the sample, we used demographic indexing to identify estimated Full Scale, Verbal, and Performance IQ.[43,46,47] We used the US Northeast region as a proxy for individuals from non-US regions because it likely represents European and Canadian respondents most closely, which were the most frequent non-US respondents (see Barona Index Formula, Supplemental Materials).

CRCI and QOL impact

CRCI was defined as the proportion of patients with GIST who reported a score of ≤10 on the FACT-Cog IQOL scale. This cutoff is derived from previous breast cancer research and represents approximately 1 SD below the IQOL mean for a sample of breast cancer survivors, a proportion of whom had known impairment as assessed by neurocognitive testing (lower score = worse QOL).[44] The intent of using the IQOL cutoff was to identify a clinically meaningful level of cognitive symptom impact burden on QOL in this survey using self-report measures (Supplemental Materials). This IQOL cutoff score has been used as an inclusion criterion and marker of significant symptom burden for a past randomized control trial for cognitive-behavioral treatment of CRCI[48] and an ongoing trial (NCT04586530) in breast cancer survivors. We also conducted Pearson product moment correlations between PCI, IQOL, fatigue, depression, anxiety, and other QOL measures to evaluate potential associations with self-reported cognitive impairment.

CRCI impact and time since diagnosis

We were also interested in the possible impact of time since GIST diagnosis on PCI (whether cognition worsens with time). We dichotomized time as patients with GIST ≥5 years vs. those reporting <5 years. Student *t* tests were used to examine differences in PCI. Factors that could influence cognition such as Full Scale IQ (FSIQ) and those within the Barona index (such as age and education) were examined as possible covariates that could influence reported cognitive symptoms. When including covariates, we used analysis of covariance to examine PCI differences. Cohen's *d* was used to estimate size of effect.

TKI therapy, perceived cognitive impairments, and QOL impact

Last, to determine potential impact of TKI therapy on cognitive impairments, we used Student *t* tests to compare PCI scores and QOL variables among individuals reporting having been on vs. not having been on imatinib or other TKI therapy as well as those having completed adjuvant imatinib therapy. We note that some individuals reported only being on one TKI therapy, whereas others reported being on additional therapies over time (not mutually exclusive in all cases). For example, some individuals in the clinical setting were initially treated with imatinib but went on to other second or third-line TKI therapies on progression. All analyses were performed using Statistical Packages for the Social Sciences (SPSS, v. 27) using an alpha of 0.05.

RESULTS

Preliminary screening and sample characteristics

A total of 859 individuals provided signed consent for the online survey. One respondent was <18 years of age, 228 did not respond to any items, and 145 respondents did not complete the survey, leaving a final study sample of 485 participants (Fig. 1). We evaluated comparisons between those completing the entire survey ($n = 485$) to those who did not complete all survey items ($n = 145$) on demographic and other variables using Student *t* tests. Individuals in the "incomplete" group who reported age ($n = 139$) were 2.95 years younger (54.85; SD = 13.41) than the "completer" group (57.80; SD = 11.51; $p = .01$), and the incomplete group

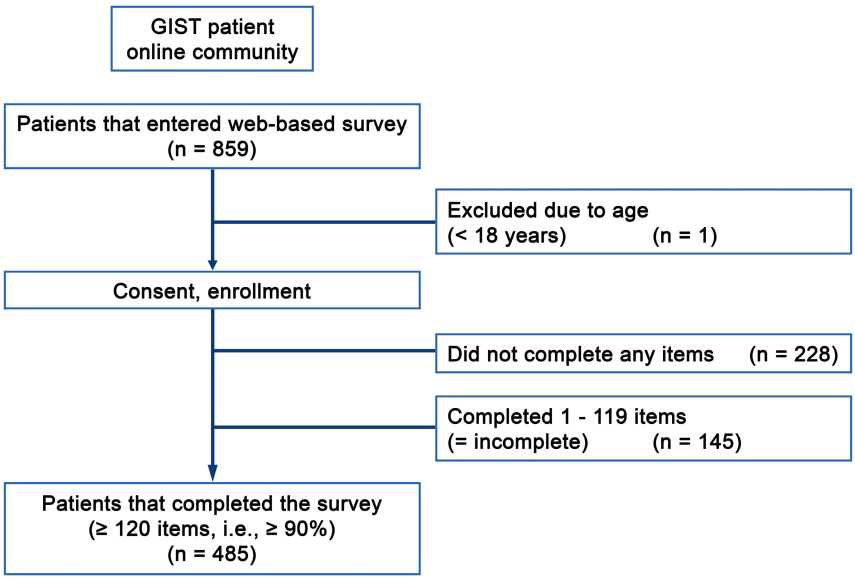

Figure 1. Flow diagram of survey participation.

who recorded enough data (n = 111) had a lower FSIQ (108.74; SD = 6.07) than the completer group (110.53; SD = 5.38; p = .002). Although statistically significant, the closeness in age and IQ may have had no clinically meaningful influence on self-reported cognitive symptoms. The 75 individuals in the incomplete group with valid PCI data (51%) scored significantly higher on the FACT-Cog PCI (fewer cognitive problems; 54.96; SD = 14.58) than those completing the entire survey (35.64; SD = 21.41, p = .001). However, 49.3% of those in the incomplete group scored within 1 SD of the completer group mean. A similar result was found with the FACT-Cog IQOL, where a small number of "incomplete" individuals (n = 31; 21.38%) had valid IQOL scores and scored higher (11.90; SD = 4.31) than the 485 completing the survey (7.73; SD = 5.76, p = .001). Given the small number of individuals and distributions of these differences in FACT-Cog outcomes, it is questionable if the incomplete group's PCI or IQOL data would have had a substantive impact on final outcomes. There were no other statistically significant differences between those not completing and those completing the survey on any other self-report measures.

The mean age of participants in the final sample was 57.8 years (SD = 11.51), and 71.8% were female (n = 348; three individuals did not indicate sex; Table 1). There were no significant sex differences on PCI (female [F] = 35.35/male [M] = 36.37; p = .64); IQOL (F = 7.78/M = 7.56; p = .70), or years of education (F = 15.58/M = 15.66; p = .83). Most identified as Caucasian (88.7%), followed by 6% Asian, 2.3% Hispanic, 1.6% Native American, and 1.2% African American. Regions represented were the United States (74.4%), Europe (15.3%), Canada (3.5%), Australia (2.9%), Asia (2.5%), and Africa (0.8%). Fifty percent of the sample was college-educated or equivalent (median = 16 years of education), and the mean full-scale IQ was estimated at 110.53 (SD = 5.38). The median number of years since initial GIST diagnosis at the time of survey completion was 5 years, with 140 (28.8%) participants reporting metastatic disease.

CRCI and QOL impact

A total of 310 participants (63.91%) had a score ≤ 10 on the FACT-Cog IQOL scale, representing a majority of individuals who reported cognitive symptoms with a substantive negative QOL impact (Table 2). There was no sex difference. In contrast to much of the CRCI literature, PCI was not found to correlate with anxiety, depression, fatigue, sleep disturbance, pain interference, or other factors commonly found to influence self-reported cognitive impairment.[49] PCI was strongly correlated with IQOL (r = .84; p < .001) as might be expected, because both measures are subscales of the FACT-Cog.

Perceived cognitive impairments and time since diagnosis

We compared individuals who were ≥ 5 years since diagnosis vs. <5 years since diagnosis on PCI (5 years was found

TABLE 1. Sample Demographic and Charactistics

Characteristic	Participants (N = 485) Mean/No. (%/SD)
Age, y	
Mean	57.8 (11.5)
Range	20–91
Female	348 (71.8%)
Male	137 (28.2%)
Ethnicity	
African American	6 (1.2%)
Asian	29 (6.0%)
Caucasian	430 (88.7%)
Hispanic	11 (2.3%)
Native American	8 (1.6%)
Primary residence	
Africa	4 (0.8%)
Asia	12 (2.5%)
Australia	14 (2.9%)
Canada	17 (3.5%)
Europe	74 (15.3%)
United States	361 (74.4%)
Education	
<High school	3 (0.6%)
High school	61 (12.6%)
Some college/university	135 (27.8%)
College	156 (32.2%)
>College	130 (26.8%)
Estimated Full Scale IQ	110.5 (5.4)
Range	92.4–120.7
Estimated Verbal IQ	110.5 (5.5)
Range	92.5–120.5
Estimated Performance IQ	108.1 (4.3)
Range	93.4–116.4
Years Because GIST Diagnosis	
Mean	6.3 (5.2)
Range	0–26
Median	5.0
Metastatic disease	140 (28.8%)
TKI therapy (Imatinib) anytime during course of disease	433 (89.3%)
Initial surgery	431 (88.9%)

Abbreviations: GIST, gastrointestinal stromal tumor.

to be the median number of years since diagnosis for the entire sample). The mean number of years since diagnosis in the ≥5 year group was 9.93 (SD = 4.41), whereas those in the lower half (<5 years) were a mean of 2.01 years (SD = 1.31) postdiagnosis ($t(478) = -25.74$, $p < .001$). Patients with GIST ≥5 years postdiagnosis were older (M = 59.40; SD = 11.52) than those diagnosed <5 years (M = 55.95; SD = 11.20; $t(475) = -3.30$, $p < .001$). With age as a covariate, one-way analysis of covariance demonstrated that patients with GIST in the ≥5-year survival group reported significantly worse cognitive function (lower PCI scores; M = 33.91; SD = 20.20) than those <5 years since diagnosis (M = 37.83; SD = 22.74; $p < .05$). Of interest, patients with GIST who were ≥5 years since diagnosis reported lower anxiety ($p < .001$) and lower depression ($p < .01$), despite reporting worse cognitive function than those <5 years since diagnosis. The groups did not differ on IQOL, years of education, IQ, fatigue, sleep, pain interference, physical limitations, or general health (Table 2).

TKI therapy, perceived cognitive impairments, and QOL impact

Current imatinib

Not all participants reported how long they were on imatinib therapy when asked, but among those who did (n = 161), the median duration was 3 years (range, ≤1–15). Comparing individuals reporting active imatinib therapy at the time of survey completion (n = 268) vs. those who reported *never* having been on imatinib or other TKI therapy (n = 45), we found no significant differences in PCI. Likewise, no significant differences were observed in IQOL, education, IQ, time since diagnosis, anxiety, depression, fatigue, pain, physical limitations, or general health (Fig. 2). Individuals currently on imatinib therapy were approximately 4.5 years older (58.79; SD = 10.48) than those reporting never having been on imatinib or any other therapy (54.22; SD = 11.29; $p < .01$).

Current other TKI therapies

After progression on first-line imatinib therapy, treatment is generally switched to second- and later-line TKIs. Respondents who reported being on other TKI therapies at the time of survey completion (e.g., sunitinib, regorafenib; Supplemental Table, Supplemental Figure) were not different in PCI or IQOL score from those reporting never having been on imatinib or who were on current imatinib therapy (Fig. 2). However, those on other TKIs did report significantly worse general health, physical limitations, pain interference, and fatigue than both other groups (Fig. 2). Moreover, they also reported significantly more depression ($p < .01$) and sleep disturbance ($p < .001$) as well as marginally worse anxiety ($p = .06$) than those on current imatinib therapy and marginally worse anxiety ($p = .08$) and depression ($p = .08$) than individuals with no history of imatinib or any TKI therapy (Fig. 2).

Completed adjuvant imatinib

Individuals who completed imatinib therapy with no additional therapy (n = 45) did so an average of 5.4 years (SD = 3.70) before the survey. Participants in this group were older (60; SD = 10.11) than those with no reported treatment. The former also reported more years since time of diagnosis than the latter group (7.69; SD = 3.69; Fig. 2). When compared with all other respondents, those who completed adjuvant imatinib generally reported the

TABLE 2. Perceived Cognitive Impairments and other Outcomes for Total Sample, and Time Since Diagnosis Groups (≥5 years and <5 years)

Measure	Total sample (SD) N = 485	Time since diagnosis (y, SD)[a] ≥5 n = 259	<5 n = 221	p	d
Age	57.80 (11.51)	59.40 (11.52)	55.95 (11.20)	<.001	0.30
Years of education					
(median, 16 y)	15.60 (3.59)	15.84 (3.66)	15.33 (3.52)	.13	0.14
Estimated full-scale IQ					
	110.53 (5.38)	110.93 (5.37)	110.02 (5.30)	.07	0.10
Years since diagnosis					
(median, 5 y)	6.29 (5.19)	9.93 (4.41)	2.01 (1.31)	<.001	2.43
FACT-Cog					
PCI	35.64 (21.41)	33.91 (20.21)	37.83 (22.74)	<.05	0.18
IQOL	7.73 (5.76)	7.30 (5.61)	8.23 (5.95)	.078	0.16
Other QOL					
Anxiety	16.4 (7.33)	15.4 (6.87)	17.55 (7.71)	<.001	0.29
Depression	15.85 (7.30)	15.00 (6.90)	16.8 (7.70)	<.01	0.25
Fatigue	24.74 (8.74)	24.70 (8.75)	24.71 (8.79)	.99	0.001
Sleep Disturbance	21.6 (8.28	21.42 (8.10)	21.78 (8.57)	.64	0.04
Pain Interference	15.85 (8.85)	16.09 (8.63)	15.47 (9.15)	.44	0.07
Physical Limitations	45.89 (43.24)	48.85 (42.96)	43.72 (43.67)	.25	0.12
SF-36 General Health	48.16 (22.27)	47.22 (22.67)	49.45 (21.98)	.28	0.10

Abbreviations: FACT-Cog, Functional Assessment of Cancer Therapy – Cognitive; IQOL, Impact on Quality of Life; PCI, Perceived Cognitive Impairment; QOL, quality of life; SF-36, Short-Form 36.
[a]5 missing cases in the "time since diagnosis" variable.

least interference with QOL measures across categories, including PCI and IQOL, although the latter was not significant (Fig. 2). Those who previously completed imatinib therapy reported significantly less fatigue than all other groups as well as fewer physical limitations than those on current imatinib therapy ($p < .05$) and those on current other TKI therapy ($p < .001$). Individuals who completed adjuvant imatinib also had less sleep disturbance ($p < .05$), pain interference ($p < .001$), and trends toward less anxiety and depression (both $p < .1$) than those on current other TKI therapies. There was no significant difference on Full Scale IQ.

DISCUSSION

To our knowledge, this is the first large-scale study of perceived cognitive impairment among individuals with GIST. In our sample of 485 participants, 63.91% of patients with GIST reported cognitive symptoms with a significant, "high-negative" impact on QOL. The mean FACT-Cog PCI score of participants in this group was 24.25 (SD = 15.48; Fig. 3). However, TKI therapies were not found to be associated with perceived cognitive impairment. We found no significant difference in PCI among individuals reporting being on imatinib therapy from those never on or who previously completed imatinib therapy. Furthermore, respondents on other TKI therapies (e.g., sunitinib, regorafenib) at the time of survey completion did not significantly differ in self-reported cognitive impairment from those on past or current imatinib therapy, or no therapy at all. Notably, however, those who reported having completed adjuvant imatinib treatment, had the least interference with QOL measures across categories, even compared with those with no current or prior TKI treatment. This could be due to lower disease and/or treatment burden than the other groups at the time of survey completion. Further investigation to identify specific clinical factors underlying this observation, such as verification of no evidence of disease status, is required. By contrast, respondents on TKI therapies other than imatinib did report more noncognitive QOL problems such as physical limitations, poorer general health, pain interference, sleep problems, and emotional distress. This may be because individuals on these agents had more advanced disease.

The degree of self-reported cognitive impairment in our sample of GIST patients is generally worse than that found in other CRCI studies. For example, the mean FACT-Cog PCI score for our entire sample was 35.64 (SD = 21.41; Table 2, Fig. 3). This is substantially lower (worse) than that of a recent large sample of breast cancer survivors 36 months after diagnosis ($N = 343$; pooled M = 63.45; SD = 14.75; Fig. 3).[50] Although there was greater variability of PCI scores in our sample than in the breast cancer sample, the PCI variable among patients with GIST was normally distributed. Moreover, participants in the breast cancer study were similar in age (M = 55.6 years) and racial composition to our sample suggesting that this

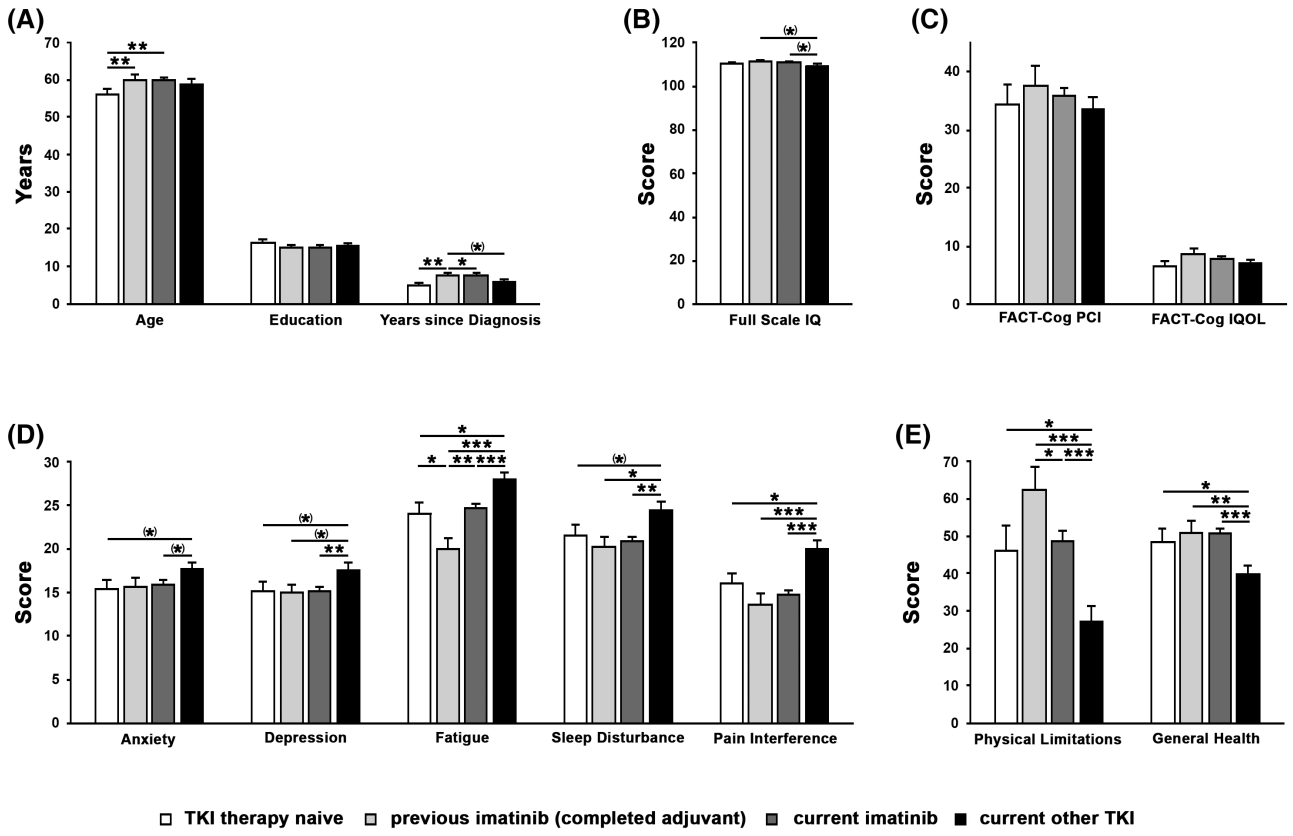

Figure 2. Comparisons of individuals on imatinib therapy (n = 268, dark gray bars) or individuals on TKI therapy other than imatinib (n = 80, black bars) at the time of survey completion to those individuals reporting never being exposed to imatinib or any other TKI (n = 45, white bars), and to those reporting previous completion of imatinib therapy (n = 45, light gray bars) on demographic, cognitive, and quality of life outcomes. Higher FACT-Cog PCI and FACT-Cog IQOL scores denote less perceived cognitive impairment and better quality of life. Similarly, higher SF-36 Physical Limitations and General Health scores denote better quality of life (t score; M = 50; SD = 10). In contrast, higher scores for Anxiety, Depression, Fatigue, Sleep Disturbance, and Pain Interference denote worse experiences for these outcomes. Columns; mean ± SE; asterisks denote the following significances: *trend ($p < 0.1$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ (Student t test, 2-tailed). Abbreviations: IQOL indicates Impact on Quality of Life; PCI, Perceived Cognitive Impairment; SE, standard error; TKI, tyrosine kinase inhibitor.

is a valid comparison. We believe our sample is a fair representation of the wider GIST patient population, given that it was demographically similar to other GIST studies, albeit with a higher representation of women (71.8%) and a slightly younger age.[22,30]

We did find that patients with GIST in our sample who reported being ≥5 years since diagnosis, whether or not they were on TKI therapy, reported significantly more cognitive symptoms than those with <5 years. This suggests an effect of disease duration on cognitive symptoms, which was independent of age, education, IQ, and emotional distress. In contrast, those ≥5 years since time of diagnosis reported less anxiety and depression than those diagnosed <5 years, despite reporting more cognitive impairment. This latter result is consistent with the finding that long-term cancer survivors often report levels of emotional distress comparable to the general population.[51] It may explain why we found that our self-report measure of cognitive symptoms (FACT-Cog PCI) did not correlate with anxiety or depression. This is contrary to most CRCI research, in which self-report measures of cognitive symptoms often correlate with measures of emotional distress, and less so with objective neurocognitive tests.[49]

The mean PCI score of 35.64 for the entire sample points to a notable clinical concern for patients with GIST when compared with breast cancer or other survivorship groups.[50] Why individuals with GIST report more cognitive symptoms is not known. Because our study was advertised as assessing "GIST and cognition," it is possible that we attracted a disproportionate number of people with cognitive complaints, thereby potentially leading to a lower mean PCI score. In contrast, the goal of the previously cited comparison study in breast cancer survivors

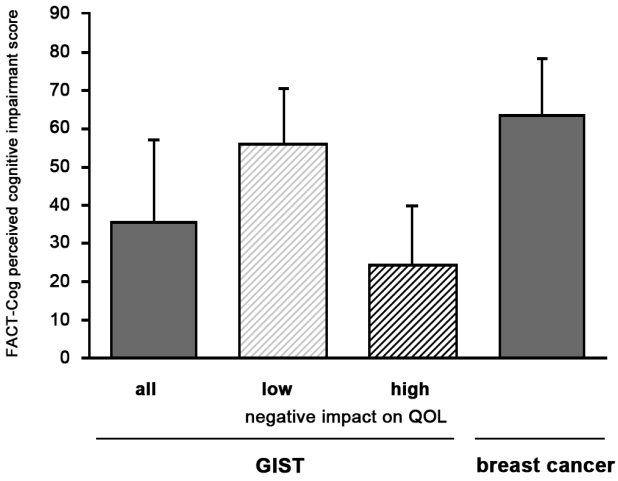

Figure 3. GIST and breast cancer patient PCI score comparisons (lower score indicates worse cognitive function). Note: 36-month posttreatment breast cancer data are derived from Wagner et al.[51] GIST indicates gastrointestinal stromal tumor; PCI, Perceived Cognitive Impairment; QOL, quality of life.

was to evaluate for long-term endocrine therapy outcomes and thus did not specifically target CRCI.[50] Nevertheless, the difference in mean PCI scores between our sample and the breast cancer cohort was 27.81 points, exceeding the GIST sample SD (21.41) by 1.3-fold. Therefore, this large clinically meaningful difference[52] is unlikely to result from sample bias alone.

Our cohort of patients with GIST reported a long time of survival at study completion compared with the aforementioned breast cancer sample reported by Wagner et al.[50] Notably, patients with inoperable/metastatic GIST follow a long course of daily oral TKI therapy, in contrast to breast cancer therapies that typically consist of shorter standard regimes. TKI therapies that are used to treat GIST, such as sunitinib and regorafenib, exert inhibitory effects on VEGF signaling, which plays a role in neurogenesis and memory.[41] It may be that VEGFR inhibition (or inhibition of PDGFR signaling by imatinib) exerts enduring microvascular damage that affects cognition. However, our survey results demonstrate no differences in cognitive symptoms among those who were exposed or not exposed to imatinib or other TKIs. The question of whether those exposed to TKIs acquire durable microvascular changes from VEGFR or PDGFR inhibition requires further biological examiniation.[9,10,42]

Another possible mechanism of CRCI involves proinflammatory cytokines. In particular, interleukin-6 has been associated with reduced hippocampal function among long-term cancer survivors.[11,39,40] Interleukin-6 release can result from cell death following cancer treatment, in conjunction with other stressors,[53,54] and has been associated with self-reported cognitive symptoms.[55] It is possible that there is prolonged cytokine and immune response with increased time since diagnosis leading to cognitive change. Furthermore, genetic factors, such as single-nucleotide polymorphisms, could influence vulnerability to long-term cognitive symptoms. For example, the brain-derived neurotrophic factor val66met polymorphism was found to interfere with hippocampal neurogenesis[56] and associated with reduced memory performance in a noncancer sample.[57] Evaluating genetic markers among long-term GIST survivors could potentially identify those at increased risk for CRCI.

The present study has limitations. First, it was based solely on a self-report measure of cognitive function. Future research should evaluate cognitive function among patients with GIST using standardized neuropsychological tests as well as age- and education-matched cancer and noncancer control groups. This would more accurately determine the degree of neurocognitive impairment and CRCI prevalence in this population. Second, the lack of medical record review as well as not taking into consideration any past or present neurologic history or medications that could affect self-reported cognitive symptoms is a limitation. However, medical record review of medication dosing may not equate to actual patient dosing because of medication adherence problems.[58] Third, our sample had a generally high level of education (59% reported college and postgraduate education). Thus, our results may be limited in generalizability to individuals with less formal education. Furthermore, we did not use the forced response feature to advance in our online survey. This could have led to some selection bias of more cognitively distressed individuals who were more motivated to complete the survey in its entirety, whereas those less distressed did not complete the survey. Finally, this study is a cross-sectional "snapshot" of individuals at various stages of GIST. A longitudinal design evaluating neurocognitive performance of patients who start TKI therapy with those who do not with assessment of other factors (e.g., genetic polymorphisms) could better illuminate the prevalence and trajectory of CRCI among patients with GIST.

Although this initial research on cognition and GIST has limitations, the FACT-Cog is one of the most widely used self-report measures of cognitive symptoms in the CRCI literature.[44,49,50] Neuropsychological tests completed in controlled laboratory conditions may not capture patient experience of daily cognitive difficulty under increased performance demands with multiple distractions

that self-report measurement can. The current study is thus important because it provides a description of the QOL impact of CRCI among patients with GIST, especially in light of increasing length of OS because of the high success of TKI therapies. We believe this first broad assessment of CRCI among those with GIST is a valid picture of patient QOL and is a starting point for further clinical investigation with more complete neuropsychological evaluation.

AUTHOR CONTRIBUTIONS

Robert J. Ferguson: Conceptualization, investigation, analysis, project administration, and writing. **Jessica Manculich:** Project administration, methodology, data curation, and analysis. **Hsuan Chang:** Data curation. **Nikita J. Sareen:** Data curation and analysis. **Beth E. Snitz:** Conceptualization, investigation, review, and editing. **Lauren Terhorst:** Review, analysis, and editing. **Dana H. Bovbjerg:** Conceptualization, methodology, investigation, review, and editing. **Anette U. Duensing:** Conceptualization, investigation, analysis, project administration, and writing.

ACKNOWLEDGMENTS

Grant support comes from the GIST Cancer Research Fund (GCRF, to Anette U. Duensing), the Out of the Woods Foundation (to Anette U. Duensing), the Shadyside Hospital Foundation (to Anette U. Duensing and Robert J. Ferguson), Pittsburgh Cure Sarcoma (to Anette U. Duensing and Robert J. Ferguson) and NIH/NCI P30CA047904 (UPMC Hillman Cancer Center). We also gratefully acknowledge the GIST and sarcoma patient organizations (GIST Support International, the GIST Cancer Research Fund, Sarcoma Patients EuroNet, Das Lebenshaus, and the Life Raft Group) for their promotion and dissemination of the online questionnaire. Finally, we thank all patients for participating in our study and taking the time to fill out our survey.

FUNDING INFORMATION

Funding for this project was in part based on a grant from the GIST Cancer Research Fund (A.U.D.), the Out of the Woods Foundation (A.U.D.), the Shadyside Hospital Foundation (A.U.D. and R.J.F.), and Pittsburgh Cure Sarcoma (A.U.D. and R.J.F.). Both A.U.D. and R.J.F. are in part supported by the Cancer Center Support Grant of the National Institutes of Health/National Cancer Institute P30CA047904.

CONFLICTS OF INTEREST

Robert J. Ferguson is the lead author of *Memory and Attention Adaptation Training (MAAT)*, which is an evidence-based cognitive-behavioral therapy for treatment of cancer-related cognitive impairment, published by Oxford University Press. All other authors made no disclosures.

REFERENCES

1. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin*. 2015;65(2):123-138.
2. Janelsins MC, Heckler CE, Peppone LJ, et al. Longitudinal assessment of cancer-related cognitive impairment (CRCI) up to six-months post-chemotherapy with multiple cognitive testing methods in 943 breast cancer (BC) patients and controls. *Am Soc Clin Oncol*. 2017;35(15 Suppl):10014.
3. Zafar SY, McNeil RB, Thomas CM, Lathan CS, Ayanian JZ, Provenzale D. Population-based assessment of cancer survivors' financial burden and quality of life: a prospective cohort study. *J Oncol Pract*. 2015;11(2):145-150.
4. Országhová Z, Mego M, Chovanec M. Long-term cognitive dysfunction in cancer survivors. *Front Mol Biosci*. 2021;8:770413.
5. Janelsins MC, Heckler CE, Peppone LJ, Ahles TA, Mohile SG, Mustian KM, Palesh O, O'Mara AM, Minasian LM, Williams AM, Magnuson A, Geer J, Dakhil SR, Hopkins JO, Morrow GR Longitudinal trajectory and characterization of cancer-related cognitive impairment in a nationwide cohort study. *J Clin Oncol* 2018;36(32):JCO2018786624, 3231, 3239.
6. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol*. 2010;28(29):4434-4440.
7. Jim HS, Phillips KM, Chait S, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012;30(29):3578-3587.
8. Ahles T, Saykin A, Furstenberg C, et al. Quality of life of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy or local therapy. *J Clin Oncol*. 2005;23(19):4399-4405.
9. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer*. 2007;7(3):192-201.
10. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*. 2014;26(1):102-113.
11. Ferguson RJ, Bender CM, McDonald BC, Root JC, Kucherer S. Cognitive Dysfunction. Cognitive dysfunction. Handbook of cancer survivorship. 2nd ed. Springer; 2018:199-225.
12. Kesler SR, Blayney DW. Neurotoxic effects of anthracycline-vs nonanthracycline-based chemotherapy on cognition in breast cancer survivors. *JAMA Oncol*. 2016;2(2):185-192.
13. McAllister TW, Ahles TA, Saykin AJ, et al. Cognitive effects of cytotoxic cancer chemotherapy: predisposing risk factors and potential treatments. *Curr Psychiatry Rep*. 2004;6(5):364-371.
14. Patel SK, Wong AL, Wong FL, et al. Inflammatory biomarkers, comorbidity, and neurocognition in women with newly diagnosed breast cancer. *J Natl Cancer Inst*. 2015;107(8):djv131.
15. Williams AM, Shah R, Shayne M, et al. Associations between inflammatory markers and cognitive function in breast cancer patients receiving chemotherapy. *J Neuroimmunol*. 2018;314:17-23.
16. Bender C, Sereika S, Brufsky A, et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. *Menopause*. 2007;14(6):995-998.
17. Bray VJ, Dhillon HM, Vardy JL. Cancer-related cognitive impairment in adult cancer survivors: a review of the literature. *Cancer Forum*. 2017;41:46-54.
18. Jones D, Vichaya EG, Wang XS, Sailors MH, Cleeland CS, Wefel JS. Acute cognitive impairment in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplant. *Cancer*. 2013;119(23):4188-4195.
19. McGinty HL, Phillips KM, Jim HS, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2014;22(8):2271-2280.
20. Gonzalez BD, Jim HS, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. *J Clin Oncol*. 2015;33(18):2021-2027.
21. von Mehren M. Management of gastrointestinal stromal tumors. *Surg Clin*. 2016;96(5):1059-1075.
22. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. *Cancer Epidemiol*. 2016;40:39-46.
23. Kindblom LG, Meis-Kindblom J, Bümming P, et al. Incidence, prevalence, phenotype and biologic spectrum of gastrointestinal stromal cell tumors (GIST)-a population-based study of 600 cases. *Ann Oncol*. 2002;13:157.
24. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):298-302.
25. Jakhetiya A, Garg PK, Prakash G, Sharma J, Pandey R, Pandey D. Targeted therapy of gastrointestinal stromal tumours. *World J Gastrointest Surg*. 2016;8(5):345-352.
26. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol*. 2004;22(18):3813-3825.
27. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science*. 1998;279(5350):577-580.

28. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 2001;61:8118–8121.
29. Demetri GD, Von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347(7):472-480.
30. Joensuu H, Eriksson M, Hall KS, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307(12):1265-1272.
31. DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373(9669):1097-1104.
32. Mei L, Du W, Idowu M, Von Mehren M, Boikos SA. Advances and challenges on management of gastrointestinal stromal tumors. *Front Oncol*. 2018;8:135.
33. Ben Ami E, Demetri GD. A safety evaluation of imatinib mesylate in the treatment of gastrointestinal stromal tumor. *Exp Opin Drug Safety*. 2016;15(4):571-578.
34. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368(9544):1329-1338.
35. George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *J Clin Oncol*. 2012;30(19):2401-2407.
36. Demetri GD, Reichardt P, Kang Y-K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):295-302.
37. Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(7):923-934.
38. Lange M, Joly F, Vardy J, et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol*. 2019;30(12):1925-1940.
39. Pusztai L, Mendoza TR, Reuben JM, et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine*. 2004;25(3):94-102.
40. Hoogland AI, Nelson AM, Gonzalez BD, et al. Worsening cognitive performance is associated with increases in systemic inflammation following hematopoietic cell transplantation. *Brain Behav Immun*. 2019;80:308-314.
41. Cao L, Jiao X, Zuzga DS, et al. VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet*. 2004;36(8):827-835.
42. Mulder SF, Bertens D, Desar IM, et al. Impairment of cognitive functioning during sunitinib or sorafenib treatment in cancer patients: a cross sectional study. *BMC Cancer*. 2014;14(1):219.
43. Barona A, Reynolds C, Chastain R. A demographically based index of premorbid intelligence for the WAIS-R. *J Consult Clin Psychol*. 1984;52(5):885-887.
44. Wagner LI, Sweet J, Butt Z, Lai J-s, Cella D. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J Support Oncol*. 2009;7(6):W32-W39.
45. Rand Corporation. 36-Item Short Form Survey (SF-36). Accessed September 9, 2022. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html
46. Ferguson R, Sigmon ST, Pritchard AJ, et al. A randomized trial of videoconference-delivered CBT for survivors of breast cancer with self-reported cognitive dysfunction. *Cancer*. 2016;122:1782-1791. doi:10.1002/cncr29891
47. Ferguson RJ, McDonald BC, Rocque MA, et al. Development of CBT for chemotherapy-related cognitive change: results of a wait list control trial. *Psychooncology*. 2012;21(2):176-186.
48. Ferguson RJ, Sigmon ST, Pritchard AJ, et al. A randomized trial of videoconference-delivered cognitive behavioral therapy for survivors of breast cancer with self-reported cognitive dysfunction. *Cancer*. 2016;122(11):1782-1791.
49. Bray VJ, Dhillon HM, Vardy JL. Systematic review of self-reported cognitive function in cancer patients following chemotherapy treatment. *J Cancer Surviv*. 2018;12(4):537-559.
50. Wagner LI, Gray RJ, Sparano JA, et al. Patient-reported cognitive impairment among women with early breast cancer randomly assigned to endocrine therapy alone versus chemoendocrine therapy: results from TAILORx. *J Clin Oncol*. 2020;38(17):1875-1886.
51. Brandenbarg D, Maass SW, Geerse OP, et al. A systematic review on the prevalence of symptoms of depression, anxiety and distress in long-term cancer survivors: Implications for primary care. *Eur J Cancer Care*. 2019;28(3):e13086.
52. Yost KJ, Eton DT. Combining distribution-and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Professions*. 2005;28(2):172-191.
53. Wang X-M, Walitt B, Saligan L, Tiwari AF, Cheung CW, Zhang Z-J. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. *Cytokine*. 2015;72(1):86-96.
54. Chae J-w, Ng T, Yeo HL, et al. Impact of TNF-α (rs1800629) and IL-6 (rs1800795) polymorphisms on cognitive impairment in Asian breast cancer patients. *PLoS One*. 2016;11(10):e0164204.
55. Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol*. 2004;26(7):955-969.
56. Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav*. 2006;5(4):311-328.
57. Hariri AR, Goldberg TE, Mattay VS, et al. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J Neurosci*. 2003;23(17):6690-6694.
58. Kaptein AA, Schoones JW, van der Meer PB, et al. Psychosocial determinants of adherence with oral anticancer treatment: 'we don't need no education'. *Acta Oncol*. 2021;60(1):87-95.