Nature and Extent of Cognitive Dysfunction in Cancer Survivors

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How prevalent is cognitive dysfunction in cancer survivors?

- $\frac{1}{3}$ to $\frac{2}{3}$ of patients report cognitive dysfunction (Joly et al., 2010)
- May be as high as 70% of survivors (Boykoff, et al. 2009)
- Frustrating
- Upsetting
- frightening
Survivor Perspective

- “you have to fight to make yourself remember numbers, words, places that you go. Sometimes I would leave the house to go somewhere and I really couldn’t remember how to get there... it almost made me break down because of the fact that you think you are losing your mind”

Boykoff et al. 2009)
Impact of Dysfunction

- Diminished independence
- Limited ability to manage responsibilities
- Difficulty or inability to return to work or previous position/level of responsibility
- Early retirement
- Avoidance of social situations or reducing participation in social conversations
- Strain on family, friends

Boykoff et al. 2009)
Responses from Medical Community

- Lack of acknowledgement to denial from medical community of the existence of cognitive dysfunction
- Agreement that cognitive impairment exists but stating that ‘everything will be fine’
- Attributing changes to age, menopause
- Lack of knowledge on how to manage symptoms

Boykoff et al. 2009)
FACT-Cog

- My memory is as good as it has always been
- I have forgotten names of people soon after being introduced
- Words I wanted to use seemed to be on the “tip of my tongue”
- My mind is as sharp as it has always been
- My thinking is as fast as it has always been
- I have had trouble finding the right word(s) to express myself
- I have walked into a room and forgotten what I meant to get or do there
- I have been able to bring to mind words that I wanted to use while talking to someone
- I have tried to do things (like writing lists or keeping a calendar) so these problems would not interfere
- I have had trouble forming thoughts
- I have had to use written lists more often than usual so that I would not forget things

Jacobs et al. (2007)
FACT-Cog

- Hematopoetic stem cell transplant N= 101
- Age= 52 years, Ed= 13.8
- F.u. 6 – 12 months post transplantation
- FACT-cog and neuropsychn evaluation
  - No relationship between FACT-cog and neuropsychn results (except for other noticed)
Cognition and Breast Cancer studies

- Early studies indicated cognitive impairments might be very common (Reid-Arndt, 2006)
- Attention and Memory
  - Cross sectional
  - Self-report
  - Small sample sizes, selective sample sizes
  - Brief batteries, no baseline
- Self reported impairments correlate with subjective reports of distress more than objective performance deficits, both prior to and after chemotherapy (Cimprich et al, 2005 & Vandam et al, 2004)
- Restricted conclusions
Cognition and Breast Cancer studies

- Attention and processing speed (digit span, digit symbol)
- Visual and verbal memory (WMS-LM, RVLT)
- Executive Functions (Trails B, Stroop)
- Meta-analysis indicated largest effects were for verbal memory and executive functions (C. Anderson-Hanley et al., 2003)
### Areas of Cognitive Domain

#### Table: Neuropsychological findings of breast cancer patients and cognitive functioning studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Verbal memory</th>
<th>Language</th>
<th>Motor</th>
<th>Processing speed</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>Weinreb and Dienst et al</td>
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<td>Van Dam et al</td>
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<td>Schagen et al</td>
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<td>Tchen et al</td>
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<td>Wold et al</td>
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</table>

- Black square, clear evidence of cognitive compromise.
- Gray square, nonsignificant trend toward cognitive compromise.

Effect sizes -0.30 - -0.37

Marin et al., 2009)
Cognition and Breast Cancer studies

Duration?

- Some studies indicate continued cognitive impairments 5 – 10 years post chemotherapy (e.g. forgetfulness, increased distractibility, problems concentrating) (Ganz et al, 2002; Ahles et al., 2002)
- Other studies indicate that cognitive impairments noted 2 years post treatment were no longer present 4 years post-treatment (Schagen et al, 2002)
Baseline Assessment

- 35% of breast cancer patients (N=84) evaluated after needle biopsy or surgery prior to chemotherapy demonstrated cognitive impairments (Wefel et al., 2004)

- A subsequent longitudinal study (N=18) of breast cancer patients found 33% of patients with cognitive impairment prior to chemo, 61% at 6mos post chemo., 50/50 decline/improve at 18 months (Wefel et al., 2010)
Cognitive Impairment in Breast Cancer

Wefel et al., 2010

20% impaired

N=42

3 months

7 months

13 months
Cognitive Impairment in Breast Cancer

**Figure 3.** The frequency of acute treatment-related changes in cognitive function based on the practice effect adjusted reliable change index is depicted.

**Figure 4.** The frequency of late emerging changes in cognitive function based on the practice effect adjusted reliable change index is depicted.
Duration of cognitive impairment?
Duration of cognitive impairment?

- Unknown
- Some studies suggest lasting impairments for many years - up to 20 years
- Study of N=1,300 (18mos) N=1,059 (36 mos) Chinese women BCA, mid 50s: logical memory, verbal fluency, stroop.
  - Improvements observed at 18mos and 36 mos post treatment. Older age, lower ed assoc. with less improvement on verbal fluency. (Zheng, 2014)
Duration of cognitive impairment?

- Neurocognitive function of Hematopoietic cell transplantation - followed for 5 years
  - N=92 survivors tested 80 days, 1 and 5 years post-transplant with controls tested at same intervals
  - Follow up patients continued to show improvement up to 5 years post transplant in all areas except for motor dexterity and a small effect for verbal recall
A. COWAT
B. DSST
C. HVLT
D. HVLT- delay
E. Grooved Pegboard dom.
F. Grooved Peg. Non-dom
G. Trails A
H. Trails B

Syrjala et. al, 2011
Variables to be considered

- Age

- Neural integrity

- Cognitive Impairment
  - Attention span
  - Concentration
  - Memory
  - Organizational ability
  - Arithmetic skills
  - Language skills

- Diminished Quality of Life
  - Activities of daily living
  - Interpersonal relationships
  - Work/profession
  - Future Education

- Hormonal Therapy
  - Anxiety
  - Depression
  - Fatigue

- Olin, JJ, 2001
PRE-MORBID/ BASELINE CHARACTERISTICS

N= 39 control, N=46 chemotherapy, N=64 no chemo) (Ahles et al., 2010)
Impairment of cognitive function in Breast cancer: High Dose vs Standard Dose

Table 6. Percentage of patients with deviant neuropsychologic test scores

<table>
<thead>
<tr>
<th>No. tests failed (impairment determination)†</th>
<th>CTC (n = 34)</th>
<th>FEC (n = 36)</th>
<th>Control (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 (not impaired)</td>
<td>23 (68%)</td>
<td>30 (83%)</td>
<td>31 (91%)</td>
</tr>
<tr>
<td>≥3 (impaired)</td>
<td>11 (32%)</td>
<td>6 (17%)</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

Chi-squared test: $P = .043$§

Van Dam et al., 1998
Animal Studies on effects of Chemotherapeutic agents on cognition

(methotrexate, paclitaxel, 5-fluorouracil, cyclophosphamide)

Most but not all studies show impairments in learning and memory.
Mechanisms of Action

- Neurogenesis - cytostatics inhibit cell division
- Oxidative stress - (carboplatin, cyclophosphamide) and antioxidants block cog. Impairments when co-admin (Konat, 2008)
- 5-FU decreases myelin sheaths (speed of information processing)
- Inflammation – cytokines (MTX activates microglia, but no BZ receptor activity despite cog. Impairment) (Siegers, 2010)
- Blood flow – anti-angiogenic effect of cytostatic agents
Hippocampal blood vessel density decrease: methotrexate

**Figure 2.** Optical density of EBA-positive blood vessels in the dentate gyrus of the hippocampus of control rats (open bar, n = 12); animals treated with MTX, sacrificed 1 week after treatment (grey bar, n = 8); and animals treated with MTX, sacrificed 3 weeks after treatment (black bar, n = 8). One-way ANOVA revealed a significant group effect ($F_{2,26} = 3.747, P < 0.05$). Post-hoc test revealed that blood vessel density was significantly decreased in both MTX-treated groups (sacrificed 1 week or 3 weeks after treatment, $P < 0.05$).

(Seigers et al., 2010)
Fig. 10. Cytokine levels in hippocampal tissue from animals sacrificed 5 days after treatment with MTX (dark grey bar, n = 8), and 20 days after treatment with MTX (closed bar, n = 8). The cytokine levels of animals treated with MTX are represented as percentage of controls. MTX did not suppress the levels of any cytokine measured 5 days or 20 days after treatment compared to the levels in control animals.
FDG Altered frontal, cerebellar, BG, activity in Breast Cancer Survivors 5-10 yrs Post chemo

Fig. 3 Level of metabolism in lentiform nuclei (normalized to whole-brain activity) measured in subjects undergoing chemotherapy + tamoxifen therapy tended to be lower (by 7–8%, $P<0.01$) than the level seen in all other control groups, including those subjects who received chemotherapy without tamoxifen, as well as those who received no chemotherapy for their breast cancer, and a reference group without chemotherapy or breast cancer

Silverman et al. 2006
Pre/Post Chemotherapy Changes in White matter (DTI) in BCa

Parietal superior longitudinal fasiculus

Deprez et al. 2012
Variables to be considered

Olin, JJ, 2001

Chemotherapy

Intelligence

Education

Genetics

Menopause

Hormonal Therapy

Anxiety

Depression

Fatigue

Cognitive Impairment

Attention span
Concentration
Memory
Organizational ability
Arithmetic skills
Language skills

Neural integrity

Diminished Quality of Life

• Activities of daily living
• Interpersonal relationships
• Work/profession
• Future Education

Age

Olin, JJ, 2001)
Fatigue

- 75-96% of patients suffer from chemotherapy-induced fatigue
  - Tiredness despite adequate rest or sleep
  - Lasts well beyond treatment period
  - Most common symptom

- Strong association between fatigue and perceived cognitive impairment

- Lack of association between fatigue and objective assessment
Anxiety & Depression

- Depression incidence in cancer patients (6% to 50%)
  - Depression rates generally improve (i.e. decrease) following treatment
  - Only patients with ongoing symptoms demonstrate high levels of depression
- Studies do not find an association between objective cognitive performance and depression/anxiety
- Studies do find an association between subjective perception of cognitive impairment and depression/anxiety
Hormone effects

- Pre-mature menopause
  - Human studies demonstrating cognitive changes associated with lack of estrogen
  - Animal studies showing impact on neuronal growth, branching & cognition with hormone withdrawal

- Hormone treatment
  - Aromatase inhibitors (anastrozol, letrozole, exemestane)
  - SERMS (tamoxifene, raloxifene)
  - Prostate cancer (androgen deprivation)
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  - SERMS (tamoxifen, raloxifene)
  - Prostate cancer (androgen deprivation)
Cognitive changes with Endocrine therapy in Breast Cancer: SERMS

- **MORE** N=7478  No effect on cog. Fxn
  - Raloxifene, placebo
- **CoSTAR** N=1498  Cog. Testing similar in both groups
  - Tamoxifene, raloxifene
- **P-1** N=13,388  little difference between groups
  - Tamoxifen, placebo
- TEAM & BIG studies show decline with tamoxifen
Estradiol increased spine synapse density

Wooley et al., 1997
Post GDX- Testosterone maintains synapses in hippocampus

Leranth et al., J. Neurosci. 2003
Cognitive changes with Endocrine therapy in Breast Cancer: AIs

- Greater cognitive decline has been shown with anastrozole as compared to tamoxifen
- Lesser cognitive decline with exemestane and letrozole
- Studies vary with regard to sample size, methods
Intermittent Androgen Suppression (IAS)

Combined treatment:

- LHRH (GnRH) agonist – leuprolide acetate 7.5 mg IM injection every 4 weeks
  - Inhibits LH/FSH secretion from the pituitary
- Flutamide 250mg p.o. three times daily
  - Androgen receptor antagonist – competes w/ T/DHT for AR
- IAS cycles androgen withdrawal (6-9 months) with an “off treatment” period
- Treatment is reinstated as the prostate specific antigen (PSA) reaches a threshold
**Study Design**

- **Start Medication**
  - 9 month Treatment
  - Baseline Cognitive Testing & PET
  - Month 1 Cognitive Testing & PET
  - Pre-Baseline Cognitive Testing

- **Stop Medication**
  - 3 months or longer washout
  - Month 9 Cognitive Testing & PET
  - Month 12 Cognitive Testing
  - Re-start Medication If PSA rises
Cognitive Battery

- Verbal memory - paragraph recall, proactive interference word list
- Spatial Memory - Route test
- Spatial abilities - Block design, Mental Rotation
- Executive Functions - verbal fluency, Stroop, SOPT
Mental Rotation

Cherrier et al. (2009)

* p < .05
Profile of Moods State: Fatigue-Inertia

Cherrier et al. (2009)

* p < .05
Profile of Moods State: Depression

Cherrier et al. (2009)

* p < .05
Cherrier et al. (2009)

Visual Analog Scale: Irritability

Time

Baseline  On Treatment  Off Treatment

Score

IAS
Control

* p < .05
Environmental Memory Task

Encoding (movies)

Survey

Route

Recognition (slides)

Correct

Rearranged

Correct

Rearranged

Shelton et al, 2002, 2007)
Fig. a (left) Region of reduced Activation during Tx Compared to baseline

Fig. b (right) Difference scores (time2 – time1) for Mixed effects GLM Z scores. Neg = decrease Pos= increase
Encode- environmental memory Task
Recog- environmental memory Task
Match- mental rotation task

(Cherrier et al., 2009)
SCORE: Study Design

- **Start ADT**
- **9 month ADT**
- **Stop ADT and Start T or placebo**
- **T or P**
- **No treatment**

- Baseline Cognitive Testing
- Month 1 Cognitive Testing
- Month 9 Cognitive Testing
- Month 10 Cognitive Testing
- Month 15 Cognitive Testing

- Pre-Baseline Cognitive Testing
How to treat cognitive dysfunction?

- Are there any other obvious medical or health conditions that can be addressed or treated?
  - Anxiety, Depression, fear of recurrence
  - Diabetes, heart disease, BMI/weight
  - Alcoholism, drug use, smoking
  - Sleep, sleep apnea, fatigue, anemia
- Psychosocial factors that need to be addressed?
  - Stress
    - Work/life balance?
    - What was the previous baseline
Research findings on treatments:

- Very few published studies on interventions or methods to prevent or treat cognitive dysfunction in cancer
  - Historical literature in brain injury/rehabilitation
  - Other neurological disorders - multiple sclerosis, dementia/MCI, epilepsy
  - Childhood cancers
Pharmacological interventions

- Psychotropic medications
  - Depression
  - Avoid anti-anxiety medication (Benzodiazepines)
- Cognitive Enhancers
  - Cholinesterase inhibitors & AD medications
  - Gingko
- Statins & anti-inflammatory
- Stimulants- ADHD
  - Methylphenidate study neg. for BC (lower et al., 2009)
- Eythropoeitin (evidence neg for cancer)
- Vitamins
Modafinil

- Medication for ‘narcolepsy’ improves attention and alertness, unique CNS stimulant
- Advanced cancer patients N=28 with high fatigue, 4 days on placebo vs modafinil then crossover (Lundorff et al., 2009)
  - Psychomotor speed & sequencing (TMT) improved as well as depression and drowsiness
- BC patients with fatigue N=68 22 months post tx, four weeks on modafinil then cross over to m or placebo (Kohli et al., 2009)
  - Improved on a computerized test of attention and memory
Cognitive Rehabilitation

- Some evidence of intervention success in children (Butler et al.)
- Memory and Attention Adaption Training (MAAT)
  - N=29 BC three years post Tx, complaints of memory and attention problems (Ferguson, 2007)
  - 4 individual monthly visits with phone contact (education, relaxation, schedule, workbook)
  - Improvement in self report and Neuropsych measures post TX, & 2 and 6 months f.u.
CARES study

- Currently enrolling cancer patients
  - 1yr or more post treatment (no transplant)
  - Stable on medications (serms/ais ok)
  - Not currently undergoing treatment for ca
  - Able to undergo cognitive testing

- Pre-Tx evaluation 7 weeks of Tx, post Tx evaluation
significant improvement on verbal memory and attention (working memory) compared to baseline (p<.05) and compared to control (interaction effect) p<.05

Cherrier et al., 2014
Participants in the treatment group endorsed significant improvement on all subscales of the FACT-cog and increased use of cognitive strategies compared to baseline ($p<.05$) and compared to control (interaction effect) $p<.05$)

Cherrier et al., 2014
**BOOST: Post Treatment Questionnaire**

1 = strongly disagree    5 = strongly agree

<table>
<thead>
<tr>
<th>Rating</th>
<th>Statement</th>
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<tbody>
<tr>
<td>4</td>
<td>Better understanding of how memory and attention work</td>
</tr>
<tr>
<td>5</td>
<td>More confident about trying new solutions to address memory and attention difficulties</td>
</tr>
<tr>
<td>4</td>
<td>Learned new solutions for dealing with daily memory failures</td>
</tr>
<tr>
<td>4</td>
<td>My ability to remember information has improved</td>
</tr>
<tr>
<td>4</td>
<td>Overall I am better able to cope with cognitive difficulties</td>
</tr>
<tr>
<td>4</td>
<td>I enjoyed working and learning in a group setting</td>
</tr>
<tr>
<td>1</td>
<td>I would prefer to have online/computerized training</td>
</tr>
<tr>
<td>1</td>
<td>This treatment could be more effective using a computer format</td>
</tr>
</tbody>
</table>

Cherrier et al., 2014
WORKING MEMORY TASK

Memory Set
500 ms
100 ms

Mask
100 ms

Maintenance
500 ms

Probe
500 ms

Fixation
1500 ms

3 Item
14.45 trials/block
24 s/block
17 blocks/run

3 Item
5 Item Memory Load

7 Item

3 7 5
3 5 7
7 3 5
5 7 3
PAIRED ASSOCIATES TASK

Control trials intermixed in item and relational blocks

Together previously?
Which side %?

16 trials/block
4.8 s/trial

Together previously?
Both Old?

6 s/trial
4 trials/block

Relational
Recombined
Intact
New

Item
Recombined
Old/New
New

Both Old?

CABI
CLAY
RAIN
BAR
FRA
PILO
SHIR
Rain
CLAY
Tree

Both Old?

Which side %?

CLO
RAIN
PILO

Both Old?

GRA
BOO
REL
ME

Both Old?

SAU
REN

Both Old?

Trained participants showed a significant improvement in accuracy in the Relational condition (p<.001), but not in the Item condition (p=.67) of the Paired Associates task.

Cherrier et al., 2014
Participants also showed a non-significant improvement in accuracy within higher-load, but not lower-load trials in the Working Memory Task.

Cherrier et al., 2014
Other interventions

- Exercise
  - Exercise improves cognition in older adults and those with mild memory impairments (Baker et al., 2010, Liu-Ambrose, 2010; Davis, 2010)
  - Exercise may improve fatigue, pain, and overall health and quality of life in cancer survivors and those undergoing treatment (McTiernan, 2004; Denmark-Wahnefried et al, 2003)
- Increases regional capillary density, neural metabolic capacity, BDNF
Other interventions

- Meditation - alert, restful state
- Requires focused attention, increased sense of control
  - Used to help with chronic pain, anxiety, depression, smoking cessation
  - EEG studies have found neurophysiological modulations associated with meditation practice
  - fMRI studies have shown brain activation changes with increasing meditation practice
  - Improvements in attention, cognitive flexibility
  - An option for mobility restricted or challenged patients

Biegler et al., 2009
Summary:

- 50 – 70% patients experience subjective cognitive complaints – related to anxiety, depression, other physical symptoms
- 10 – 30% objectively measured impairments
- Patients can improve over time, including years post treatment
- Pre-morbid factors should be taken into consideration
- Cognition can be accurately measured with norm based tests
Summary:

- Causes of cognitive dysfunction are likely multi-factorial
- Interventions (targeted) can be effective