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Vienna, Austria
Supportive care makes excellent cancer care possible

MASCC/ISOO
Annual Meeting on Supportive Care in Cancer

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#MASCC18
Neurocognitive Deficits in Older Cancer Patients

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Conflicts of Interest

- None
Background

• By 2030 close to 70% of cancer patients will be 65 years of age and older

• Age-related diseases include cognitive impairment and dementia, osteoporosis, diabetes, frailty, and sarcopenia

• The effect of chemotherapy on cognitive processes will be superimposed on age-related mild cognitive impairment (MCI) and dementia

• Given that many cancer patients have received cancer therapy, they may exhibit cognitive impairment and neurocognitive deficits earlier in life.

• Cultural and societal concerns
Definition

- Dementia is a general term for a “gradual decline in cognitive capacity severe enough to interfere with daily life”.

- The prevalence of dementia increases with age, from 15.0% of those aged 71–79 years to 37.4% of those aged 90 and older.

- Up to 74% of primary care physicians may not recognize cognitive impairment and when they do, the patient is in the moderate to severe stage of dementia.
DNA damage

Chemotherapy

Androgen deprivation therapy

Mitochondrial Damage

Chronic inflammation

Depression

Metastatic cancer

Strokes

Comorbidity

NEUROCOGNITIVE DEFICIT
Cognitive Impairment and Neurocognitive Deficits

Chemotherapy induced cognitive impairment (CCI) may develop in any of the 3 groups listed above.

Cognitive Impairment

Mild Cognitive Impairment (MCI)
Minor neurocognitive Deficit

Depression, Delirium
Organic brain syndrome, Post CVA

Dementia
Major Neurocognitive Deficit
# Criteria for Diagnosis

<table>
<thead>
<tr>
<th>Abnormal MoCA</th>
<th>Cognitive Impairment</th>
<th>National Institute of Aging</th>
<th>DSM V</th>
<th>Minor neurocognitive deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal MoCA + Loss of ≤ one IADL</td>
<td>Mild Cognitive Impairment (MCI)</td>
<td></td>
<td></td>
<td>Major neurocognitive deficit</td>
</tr>
<tr>
<td>Abnormal MoCA + Loss of 2 or more IADLs*</td>
<td>Dementia</td>
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</table>

MoCa = Montreal cognitive assessment, IADL = independent activity of daily living, DSM = Diagnostic and statistical manual of mental disorders version V, Abnormal MoCA = < 26 or <20 if ethnic minority. Folstein Mini mental state exam (MMSE) has also been used in the literature. * Deficits in 2 or more cognitive domains such as executive function, antegrade amnesia, aphasia, attention, abstraction, orientation, acalculia, apraxia, among others.
NCCN Guidelines Version 2.2017
Older Adult Oncology

APPROACH TO DECISION MAKING IN THE OLDER ADULT

Is the patient at moderate or high risk of dying or suffering from cancer considering his or her overall life expectancy?\(^a,b\)  
\[ \begin{align*} 
\text{No} & \quad \text{Symptom management/supportive care} \quad \text{(See NCCN Guidelines for Palliative Care)} \\
\text{Yes} & \quad \text{Obtain information from:} \\
& \quad \quad \text{- Patient's proxy} \\
& \quad \quad \text{- Advance directive} \\
& \quad \quad \text{- Living will} \\
& \quad \quad \text{- Health care power of attorney} \\
& \quad \quad \text{- Clinician's documentation} \\
& \quad \quad \text{- Consider consult from ethics committee or social worker or consider palliative care (See NCCN Guidelines for Palliative Care)} \\
\end{align*} \]

Does this patient have decision-making capacity?\(^c,d\)  
Patients must have the ability to:  
\begin{itemize} 
\item Understand the relevant information about proposed diagnostic tests or treatments 
\item Appreciate their situation (including their underlying values and current medical situation) 
\item Use reason to make a decision 
\item Communicate a consistent choice\(^e\) 
\end{itemize}  
\[ \begin{align*} 
\text{No} & \quad \text{Assess the patient's goals and values regarding the management of his or her cancer} \\
\text{Yes} & \quad \text{Are the patient's goals and values consistent with wanting anti-cancer therapy?}\(^f\) \\
\end{align*} \]

\[ \begin{align*} 
\text{No} & \quad \text{Symptom management/supportive care (See NCCN Guidelines for Palliative Care)} \\
\text{Yes} & \quad \text{Assessment of Risk Factors (See OAQ-2)} \\
\end{align*} \]
# Assessment of Cognitive Function

**WHEN TO ASSESS FOR COGNITIVE FUNCTION**

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would impaired cognitive function affect the planning or delivery of care? (e.g., impact life expectancy or risk/benefit, impact adherence to treatment plan)</td>
<td>Reassess periodically or when considering treatment plan changes</td>
</tr>
<tr>
<td>Is the medical team concerned about decision-making capacity? See <a href="#">OAO-1</a></td>
<td>Consult with a clinician experienced in cognitive evaluation (i.e., geriatrician, neurologist, geriatric psychiatrist, neuropsychologist, occupational therapist) OR Initiate the evaluation yourself See <a href="#">OAO-F (2 of 2)</a></td>
</tr>
<tr>
<td>Does the patient have a history of recent delirium or late onset of depression?</td>
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<tr>
<td>Does the medical team suspect impaired cognitive function?</td>
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<tr>
<td>Has the patient or patient's family suggested that the patient has impaired cognitive function?</td>
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Instrumental Activities of Daily Living

- **Original IADLS**
  - Heavy housekeeping
  - Laundry
  - Cooking
  - Financial Management
  - Taking own medications
  - Using the telephone
  - Arranging for transportation
  - Shopping

- **Brody’s Adaptation**
  - Financial management
  - Taking own medications
  - Using the telephone
  - Arranging for transportation
  - Shopping

- **NO GENDER BIAS**
STEPS IN DIAGNOSING NEUROCOGNITIVE DEFICITS

Presentation + Risk factors
A decline in cognitive abilities
Slow progression over months or possibly years
Knowledgeable informant

Prior concussion(s)
Diabetes mellitus
Hypertension
Hyperlipidemia
Recurrent depression
Alcohol/substance abuse
Family history of dementia

Functional assessment + Abnormal cognitive score

IADLs
1. Managing their finances
2. Taking their own medications
3. Arranging for transportation
4. Using the telephone
5. Shopping

No delirium
MoCA < 26 for whites
< 20 if African American or Latino

Mild neurocognitive deficit (MCI)
IADLs = intact or missing one
IADLs = missing 2 or more

Major neurocognitive deficit (dementia)
MCI = mild cognitive impairment; IADL = independent activities of daily living; ADL = activities of daily living
MAJOR NEUROCOGNITIVE DEFICIT

- Cognitive deficits precede cancer diagnosis
- Cognitive deficits date back years
- Families will not recognize cognitive impairment, inquire about finances, driving, MVA, taking own medicines. etc
- Interpret findings in the setting of educational, occupational level, and ethnicity

CHEMOTHERAPY INDUCED COGNITIVE IMPAIRMENT

- Cognitive deficits follow cancer care (months)
- Patient and/or families recognize a recent change in cognition
Mini Cog

- 4 items
- Clock drawing
- 3 item recall

- Comprehensive lit review 3 studies n = 1620
  - Sens 99% spec 93%
  - Sens 76% spec 89%
  - Sens 99% spec 83%

Montreal Cognitive Assessment (MoCA)
Cognitive Testing in African Americans

- Mini Mental State Examination (MMSE)
- Blessed Orientation Memory Concentration Test (BOMC)
- Neurobehavior Cognitive Status Examination (NCSE)
- Cambridge Cognitive Examination (CAMCOG)
- Montreal Cognitive Assessment (MoCA)

Lampley Dallas, JNMA 2001: 93:9
Folstein Mini Mental State Exam

- Ethnic bias
- In spite of education-adjustment, bias continues
- Does not detect early dementia
- Some studies suggest that 21 would be a better threshold for African Americans and possibly down to 18.
- Bias results in higher false positive rates for African Americans as compared to whites. Specificity of MMSE is lower in African Americans
- specific questions that are biased: WORLD spelling
  - No ifs ands or buts

Lampley Dallas, JNMA 2001: 93:9
Blessed Orientation Memory Concentration Test

- It tests Orientation, Memory and Concentration
- 6 Item scale, takes 2-3 min and has a total score of 28.
- Normal score 0 to 6 or 0 to 8; 9 questionable, 10 + dementia
- BOMC and MMSE misclassified more African Americans than whites
- BOMC 62% MMSE 42% misclassification for African Americans

- Short Portable Mental Status Questionnaire (SPMSQ), BOMC identifies patients at earlier stage than SPMSQ.
- BOMC apparently misclassified African Americans twice as often as SPMSQ

Welsh, Neurology 1995 45: 2207-2215
Lampley Dallas, JNMA 2001: 93:9
Montreal Cognitive Assessment

- MoCA was developed in Quebec, Canada among whites with a mean 13.3 ± 3.6 years of education.
- It is the scale best designed to identify Mild cognitive Impairment
- Scores may be lower in ethnic minorities (Score = 20)
- Scores may be lower in ethnic minorities. In a community of African Americans the mean MoCA 19.8 ± 3.8. If 26 is set as a cutoff for impairment, 93.5% of subjects would be considered impaired.
- Among AA with HS education, participants who were
  - < 55 years MoCA 20.5
  - 55 – 60 years 19.8 ± 3.8
  - 65 + years of age MoCA 18.7
- In Latinos with low education (< 5 years of school) add 5 points

*Journal of Aging Research. 2015;2015:872018.*
MD Anderson Cohort

N=455, mean age 86 +/- 8; MoCA screen and exam, MCI 30%, dementia 33%
Prevalence of dementia is 2-fold higher than in non-cancer patients
Factors Associated with Neurocognitive Deficits

- NCD: 33% Major NCD; 31% Minor NCD
- Multimorbidity (CCI > 4) p = 0.04
- Prior stroke p = 0.03
- Metastases p = 0.04
- Warfarin use p = 0.03

Prevalence of Neurocognitive Deficits

Edwards BJ  https://doi.org/10.1016/j.jgo.2018.02.010
Caveats on Interpretation

- MoCA created on white HS graduates (threshold 26) in Canada
- Ethnic minorities: MoCA 20 (African Americans and Latinos)
- If you use a cut-off of 26, you miss 90% of African Americans
- Latinos with less than 5 years of education, you can add 5 points
- Repeat testing should be no closer than 6 months
DELIRIUM

• Definition:

• Acute or subacute onset of attention and cognitive changes associated with fluctuating sensorium. It may be accompanied by hyper- or hypoactivity.

• Predisposing factors: cognitive or sensory impairment, advanced age, male gender, Parkinson’s disease, depression,

• Precipitating factors: infections, SIRS, strokes, myocardial infarction, heart failure, acidosis, hepatic failure, dehydration, advanced cancer, corticosteroids.
Delirium

The Confusion Assessment Method (CAM) Diagnostic Algorithm

**Feature 1: Acute Onset or Fluctuating Course**
This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: is there evidence of an acute change in mental status from the patient’s baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

**Feature 2: Inattention**
This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

**Feature 3: Disorganized thinking**
This feature is shown by a positive response to the following question: Was the patient’s thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

**Feature 4: Altered Level of consciousness**
This feature is shown by any answer other than “alert” to the following question: Overall, how would you rate this patient’s level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.
• Depression as a cause or risk factor for dementia

• Depression as a consequence of dementia

• Depression as a coincidental finding in dementia

Bennett, Maturitas 2014 Oct;79(2):184-90
<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Evidence for</th>
<th>Evidence against</th>
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<tbody>
<tr>
<td>Depression being an independent risk factor in developing dementia</td>
<td>Owensby et al. [17]</td>
<td>Becker et al. [35]</td>
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<td></td>
<td>Disi et al. [21]</td>
<td>Loppa et al. [36]</td>
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<td></td>
<td>Cao et al. [22]</td>
<td>Li et al. [37]</td>
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<td></td>
<td>Da Silva et al. [23]</td>
<td>Brommelhoff et al. [38]</td>
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<td>Szynska et al. [24]</td>
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<td></td>
<td>Georgi et al. [25]</td>
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<td></td>
<td>Dobson et al. [41]</td>
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<td></td>
<td>Chem et al. [42]</td>
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<td></td>
<td>Barnes et al. [28]</td>
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<td></td>
<td>Fernández-Martínez et al. [1]</td>
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<td></td>
<td>Butiers et al. [32]</td>
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<td>Depression affecting the threshold for manifesting dementia</td>
<td>Rapp et al. [15]</td>
<td>Bhalla et al. [16]</td>
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<tr>
<td>Dementia or cognitive impairment being a feature of depression</td>
<td>Gatt et al. [44]</td>
<td>Becker et al. [35]</td>
</tr>
<tr>
<td>Depression being a prodrome of dementia</td>
<td>Li et al. [37]</td>
<td>Geerling et al. [25]</td>
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<td></td>
<td>Lenzi et al. [29]</td>
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<td>Brommelhoff et al. [38]</td>
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<tr>
<td>Depression being a reaction to cognitive decline</td>
<td>Jajodia and Borders [45]</td>
<td>Study with a pre/post survey design finding no significant changes in depression, regardless of diagnostic outcome or dementia severity.</td>
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<tr>
<td>Dementia and depression simply sharing common risk factors</td>
<td>Mathers et al. [50]</td>
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<td></td>
<td>World Health Organisation and Alzheimer’s Disease International [52]</td>
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<td></td>
<td>Heus and Heun et al. [54]</td>
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<td></td>
<td>Yip et al. [55]</td>
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<td>Prospective follow up study showing risk factors for depression in the elderly</td>
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<td>Case control study showing risk factors for dementia</td>
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IMAGING IN ALZHEIMERS DISEASE
IMAGING IN VASCULAR DEMENTIAS
PET IMAGES IN ALZHEIMERS DISEASE

Neurobiol Aging.
RESULTS

• MCI and dementia are commonly encountered in older cancer patients
• Issues to consider:
  • Chemotherapy induced cognitive impairment- is there a greater decline with cancer care if NCD is present at baseline
  • Decisional capacity- of concern when patient is in moderate stage dementia (Major NCD)
  • Memantine has been successful preventing Cranial XRT cognitive impairment
  • Major NCD will exert an effect on clinical outcomes
Operationalizing Cognitive Assessment

- Self-administer ADL, IADL, and Patient Health questionnaire (PHQ-9). Social support MOS
- History of concussions, strokes, T2DM, HTN, hyperlipidemia, substance abuse, family hx dementia. Assess for delirium
- Testing: quick screen Mini Cog, MoCA
- Testing: B12, VDRL, TSH/T4
- Imaging: CT brain, MRI, PET Scan
- Discussion about Rx.
RCT of Memantine to prevent XRT related cognitive impairment

Methods

- Patients received 37.5 Gy of WBRT (15 fractions of 2.5 Gy). Study drug administration was to commence no later than the third day of WBRT.
- Patients were randomly assigned to receive memantine or placebo orally for 24 weeks and escalating doses over the first 4 weeks.
- Memantine was slowly titrated to the maintenance dose of 10 mg BID.
- The dose was lowered to 5 mg orally twice daily if creatinine clearance fell below 30 mL/min and was held if the creatinine clearance was less than 5 mL/min with a weekly recheck of laboratory values.
At 24 weeks there is
Less decline in delayed recall (p=0.0587)

Longer time to cognitive decline (hazard ratio 0.78, 95% CI 0.62–0.99, p < 0.01);

Superior executive function at 8 (p < 0.008) and 16 weeks (p < 0.004) and

Superior processing speed (p < 0.024)

Superior delayed recognition (p < 0.012) at 24 weeks.
Meta-Analyses of Efficacy of Acetyl cholinesterase inhibitors on Major NCD

Strohle, Am J Geriatr Psychiatry 23:12, December 2015
Meta analyses to assess the Efficacy of Exercise on Minor Neurocognitive Deficit

Records identified through database searching (N = 1315)

Additional records identified through other sources (N = 8)

Records after duplicates removed (N = 939)

Records screened (N = 939)

Full-text articles assessed for eligibility (N = 29)

Studies included in qualitative synthesis (N = 4)

Studies included in quantitative synthesis (meta-analysis) (N = 4)

Records excluded (N = 910)

Full-text articles excluded, with reasons (N = 25)

- Outcome (N = 14)
- Design (N = 4)
- Intervention (N = 5)
- Sample (N = 2)

J Geriatr Psychiatry 23:12, December 2015
Drug treatments resulted in a small pooled effect on cognition (SMCR: 0.23, 95% CI: 0.20 to 0.25) in AD studies (N = 45, 18,434 patients) and no effect in any of the MCI studies (N = 5, 3,693 patients; SMCR: 0.03, 95% CI: 0.00 to 0.005).

Strohle, Am J Geriatr Psychiatry 23:12, December 2015
Exercise and Major Neurocognitive Deficit

Exercise interventions had a moderate to strong pooled effect size (SMCR: 0.83, 95% CI: 0.59, 1.07)
Conclusion

- Neurocognitive deficits are common in older cancer patients
- Dementia is 2-fold higher in cancer patients than in patients without cancer
- Identification is critically important for decision making
- Management is possible
- Prevention of CCI?
- Exercise is beneficial