Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
Supplemental Methods

1. Serum parameters:

Participants provided blood samples for measurement of: hemoglobin, leukocytes, neutrophils, lymphocytes, platelets, creatinine, bilirubin, aspartate transaminase (AST), alanine-transaminase (ALT), alkaline phosphatase, thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), thyroxin (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen or testosterone. Vitamin B1, vitamin B12, folate, and albumin were measured as surrogate markers for nutritional status. In addition, blood was drawn for measurement of 10 cytokines (interleukin[IL]-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, and GM-CSF) at baseline and 24mo using LiquiChip Human10-cytokine kit (Qiagen, Valencia, CA), according to manufacturer’s instructions. Time-of-day of blood draw was not controlled. Participants went to the blood lab at their convenience on the day that their assessment was scheduled.
## eTable 1 - Neurocognitive domains, tests, and brief task description

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual capacity &lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>WAIS-III Vocabulary</td>
<td>Provide definitions of words.</td>
</tr>
<tr>
<td></td>
<td>Even/odd split half for alternate forms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WAIS-III Matrix Reasoning</td>
<td>Complete visual puzzles engaging nonverbal abstract problem solving, inductive and spatial reasoning.</td>
</tr>
<tr>
<td></td>
<td>Even/odd split half for alternate forms</td>
<td></td>
</tr>
<tr>
<td>Concentration/Short-term attention span &lt;sup&gt;1&lt;/sup&gt;</td>
<td>WMS-III Digit span forward</td>
<td>Repeat sequences of digits in same order.</td>
</tr>
<tr>
<td></td>
<td>WMS-III Spatial span forward</td>
<td>Touch blocks tapped by examiner in the same order.</td>
</tr>
<tr>
<td>Visual memory &lt;sup&gt;3&lt;/sup&gt;</td>
<td>BVMT forms 1 and 3 Total Recall</td>
<td>Reproduce studied designs immediately after three 10 second exposures.</td>
</tr>
<tr>
<td></td>
<td>BVMT forms 1 and 3 Delayed Recall</td>
<td>Reproduce and recognize figures studied 25 minutes earlier.</td>
</tr>
<tr>
<td>Verbal memory &lt;sup&gt;4&lt;/sup&gt;</td>
<td>HVLT-R forms 1 and 5 Total Recall</td>
<td>Recall a list of spoken words immediately after three readings.</td>
</tr>
<tr>
<td></td>
<td>HVLT-R forms 1 and 5 Delayed Recall</td>
<td>Recall the list of words 25 minutes later.</td>
</tr>
<tr>
<td>Processing speed &lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>DKEFS Color naming</td>
<td>Say aloud colors that X’s are printed in as quickly as possible.</td>
</tr>
<tr>
<td></td>
<td>DKEFS Word reading</td>
<td>Read aloud words printed on a page as quickly as possible.</td>
</tr>
<tr>
<td></td>
<td>Trail Making Test A</td>
<td>Connect in sequence numbers randomly distributed on a page.</td>
</tr>
<tr>
<td>Executive function/Working Memory &lt;sup&gt;3,5,6&lt;/sup&gt;</td>
<td>DKEFS - Stroop Inhibition</td>
<td>Participant is required to suppress a habitual response in favor of an unusual one.</td>
</tr>
<tr>
<td></td>
<td>Trail Making Test B</td>
<td>Connect in alternating sequence numbers and letters randomly distributed on a page.</td>
</tr>
<tr>
<td></td>
<td>WMS-III Digit Span Backward</td>
<td>Repeat sequences of digits in reverse order.</td>
</tr>
<tr>
<td></td>
<td>WMS III Spatial Span Backward</td>
<td>Touch blocks tapped by examiner in reverse order.</td>
</tr>
<tr>
<td>Motor dexterity &lt;sup&gt;7&lt;/sup&gt;</td>
<td>Grooved Pegboard Test-Dominant &amp; Non-dominant Hand</td>
<td>Insert pegs into slots on a board as quickly as possible. Pegs must be rotated and angled properly to fit.</td>
</tr>
</tbody>
</table>

WAIS = Wechsler Adult Intelligence Scale. WMS = Wechsler Memory Scale. BVMT = Brief Visuospatial Memory. HVLT-R = Hopkins Verbal Learning Test Revised. DKEFS = Delis-Kaplan Executive Function System.

### eTable 1 References
3. eTable 2 - Characteristics of participants who completed all assessments (baseline, 6, 12, and 24 months)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Patients</th>
<th>Controls</th>
<th>Effect Size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Median (range) 58 (41-73)</td>
<td>55 (41-75)</td>
<td>0.33 [-1.08, 1.74]</td>
</tr>
<tr>
<td></td>
<td>Mean (std) 57.5 (7.6)</td>
<td>54.9 (8.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distribution (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>9 (18)</td>
<td>9 (26)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>20 (40)</td>
<td>14 (40)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>19 (38)</td>
<td>11 (31)</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male (%)</td>
<td>39 (78)</td>
<td>30 (86)</td>
</tr>
<tr>
<td>Education (coded#)</td>
<td>&lt; high school</td>
<td>9 (18)</td>
<td>2 (6)</td>
</tr>
<tr>
<td></td>
<td>high school +/- college</td>
<td>20 (40)</td>
<td>9 (26)</td>
</tr>
<tr>
<td></td>
<td>university degree</td>
<td>12 (24)</td>
<td>17 (49)</td>
</tr>
<tr>
<td></td>
<td>post graduate degree</td>
<td>9 (18)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>0</td>
<td>32 (64)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>18 (36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cigarette History (Pack Years)</td>
<td>Median (range) 7.5 (0-80)</td>
<td>0 (0-56)</td>
<td>0.80 [0.44, 1.17]</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>Never Smoker</td>
<td>23 (46)</td>
<td>23 (66)</td>
</tr>
<tr>
<td></td>
<td>≤10 pack-years</td>
<td>7 (14)</td>
<td>5 (14)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 pack-years</td>
<td>20 (40)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Alcohol Units Per Week</td>
<td>Mean (SD)</td>
<td>13.6 (12.6)</td>
<td>6.7 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>9 (0-70)</td>
<td>9 (0-20)</td>
</tr>
<tr>
<td></td>
<td>≤10</td>
<td>35 (70)</td>
<td>30 (86)</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>15 (30)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Number of Comorbidities (heart disease, renal disease, hypertension, diabetes)</td>
<td>0</td>
<td>34 (68)</td>
<td>31 (89)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7 (14)</td>
<td>4 (11)</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>9 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Remote Concussion</td>
<td>N (%)</td>
<td>11 (22)</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

### Disease and Treatment

| Site                  | Hypopharynx | 2 (4) | - | NA |
|                      | Oropharynx | 42 (84) | | |
|                      | Laryngeal | 1 (2) | | |
|                      | Nasal Cavity | 1 (2) | | |
|                      | Unknown Primary | 4 (8) | | |

| HPV Status            | Positive | 36 (72) | - | NA |
|                      | Negative | 5 (10) | | |

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<table>
<thead>
<tr>
<th></th>
<th>Unknown</th>
<th>9 (18)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>47 (94)</td>
<td></td>
</tr>
<tr>
<td><strong>Max Radiation dose to target</strong></td>
<td>70 Gy in 35 Fractions</td>
<td>44 (88)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>Max RT dose to brain</strong></td>
<td>Median Cmax Gy (range)</td>
<td>56 (0.7-77.4)</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Systemic Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin +/- 5FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31 (62)</td>
<td>1 (2)</td>
<td>12 (24)</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>

Std=Standard Deviation; ECOG=eastern cooperative oncology group
* At least university education versus less than university
† >10 pack-years of smoking versus ≤10 pack-years of smoking
‡ >10 units of alcohol / week versus ≤10 units of alcohol / week
# ≥1 comorbidity versus 0 comorbidities
NA=Not applicable
4. eTable 3 – Standardized Regression Based (SRB) scores of all participants.
The differences between patients (P) and controls (C), adjusted for baseline performance, depression, age, and education.

<table>
<thead>
<tr>
<th>Variables: Mean SRB score (std)</th>
<th>6 month</th>
<th>12 month</th>
<th>24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>C</td>
<td>d CI</td>
</tr>
<tr>
<td>Intellectual Capacity SRB</td>
<td>-0.43 (0.95)</td>
<td>0.00 (0.89)</td>
<td>-0.46 [-0.64, -0.30]</td>
</tr>
<tr>
<td>Concentration SRB</td>
<td>-0.19 (1.08)</td>
<td>0.00 (0.90)</td>
<td>-0.19 [-0.37, -0.00]</td>
</tr>
<tr>
<td>Verbal Memory SRB</td>
<td>-0.15 (1.00)</td>
<td>0.00 (0.89)</td>
<td>-0.16 [-0.33, 0.02]</td>
</tr>
<tr>
<td>Visual Memory SRB</td>
<td>0.26 (0.66)</td>
<td>0.00 (0.90)</td>
<td>0.35 [0.22, 0.49]</td>
</tr>
<tr>
<td>Processing Speed SRB</td>
<td>0.00 (1.32)</td>
<td>0.00 (0.89)</td>
<td>0.00 [-0.22, 0.22]</td>
</tr>
<tr>
<td>Executive Function SRB</td>
<td>-0.10 (0.68)</td>
<td>0.00 (0.86)</td>
<td>-0.14 [-0.27, -0.00]</td>
</tr>
<tr>
<td>Motor Dexterity SRB</td>
<td>-0.22 (1.06)</td>
<td>0.00 (0.89)</td>
<td>-0.22 [-0.40, -0.04]</td>
</tr>
<tr>
<td>Global Cognitive Function Composite Score</td>
<td>-0.35 (0.94)</td>
<td>0.00 (0.89)</td>
<td>-0.38 [-0.55, -0.22]</td>
</tr>
</tbody>
</table>

std=Standard Deviation; P = Patients; C = Controls; d=Cohen’s d; CI=95% confidence interval
5. eTable 4—Standardized Regression Based scores of participants who completed all assessments (50 patients; 35 controls).
The differences between patients (P) and controls (C), adjusted for baseline performance, age, and education.

<table>
<thead>
<tr>
<th>Variables: Mean SRB score (std)</th>
<th>6 month</th>
<th>12 month</th>
<th>24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>C</td>
<td>d [CI]</td>
</tr>
<tr>
<td>Intellectual Capacity SRB</td>
<td>-0.45 (1.01)</td>
<td>0.00 (0.91)</td>
<td>-0.47 [-0.67, -0.27]</td>
</tr>
<tr>
<td>Concentration SRB</td>
<td>-0.17 (1.15)</td>
<td>0.00 (0.91)</td>
<td>-0.16 [-0.39, 0.06]</td>
</tr>
<tr>
<td>Verbal Memory SRB</td>
<td>-0.27 (1.03)</td>
<td>0.00 (0.91)</td>
<td>-0.28 [-0.48, -0.07]</td>
</tr>
<tr>
<td>Visual Memory SRB</td>
<td>0.26 (0.68)</td>
<td>-0.00 (0.91)</td>
<td>0.34 [0.17, 0.50]</td>
</tr>
<tr>
<td>Processing Speed SRB</td>
<td>-0.16 (1.22)</td>
<td>0.00 (0.91)</td>
<td>-0.15 [-0.38, 0.09]</td>
</tr>
<tr>
<td>Executive Function SRB</td>
<td>-0.11 (0.71)</td>
<td>0.00 (0.87)</td>
<td>-0.14 [-0.31, 0.02]</td>
</tr>
<tr>
<td>Motor Dexterity SRB</td>
<td>-0.22 (1.14)</td>
<td>0.00 (0.91)</td>
<td>-0.21 [-0.43, 0.01]</td>
</tr>
<tr>
<td>Global Cognitive Function</td>
<td>-0.46 (0.98)</td>
<td>0.00 (0.90)</td>
<td>-0.49 [-0.69, -0.29]</td>
</tr>
</tbody>
</table>

std=Standard Deviation; P = Patients; C = Controls; d=Cohen’s d
6. eTable 5 – Self reported Symptoms

<table>
<thead>
<tr>
<th>Self-Reported Symptoms</th>
<th>Mean (std)</th>
<th>Baseline</th>
<th></th>
<th>6 month</th>
<th></th>
<th>12 month</th>
<th></th>
<th>24 month</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>C</td>
<td>Effect Size [95% CI]</td>
<td>P</td>
<td>C</td>
<td>Effect Size [95% CI]</td>
<td>P</td>
<td>C</td>
<td>Effect Size [95% CI]</td>
</tr>
<tr>
<td>Cognition (FACT-COG)</td>
<td>102.1 (22.3)</td>
<td>116.9 (14.8)</td>
<td>-0.71 [-1.07, -0.35]</td>
<td>101.5 (23.1)</td>
<td>110.7 (18.2)</td>
<td>-0.47 [-0.86, -0.09]</td>
<td>100.1 (23.2)</td>
<td>114.7 (13.0)</td>
<td>-0.81 [-1.20, -0.41]</td>
</tr>
<tr>
<td>Fatigue (FACIT-F)</td>
<td>41.5 (4.4)</td>
<td>37.5 (2.8)</td>
<td>0.58 [0.21, 0.94]</td>
<td>37.7 (10.6)</td>
<td>45.7 (5.7)</td>
<td>-1.00 [-0.63, -1.38]</td>
<td>40.3 (9.8)</td>
<td>46.3 (5.1)</td>
<td>-0.82 [-1.22, -0.43]</td>
</tr>
<tr>
<td>Head &amp; Neck symptoms (FACT-HN)</td>
<td>10.48 (9.05)</td>
<td>NA</td>
<td>NA</td>
<td>18.12 (7.64)</td>
<td>NA</td>
<td>NA</td>
<td>15.98 (7.64)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>6.99 (3.95)</td>
<td>3.35 (2.86)</td>
<td>1.04 [0.68, 1.40]</td>
<td>4.77 (3.84)</td>
<td>3.83 (3.19)</td>
<td>0.24 [-0.15, 0.63]</td>
<td>5.63 (4.34)</td>
<td>2.83 (2.88)</td>
<td>0.75 [0.36, 1.15]</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>3.86 (3.77)</td>
<td>1.33 (2.10)</td>
<td>1.02 [0.66, 1.37]</td>
<td>4.21 (3.89)</td>
<td>2.53 (2.26)</td>
<td>0.43 [0.04, 0.82]</td>
<td>4.24 (3.85)</td>
<td>1.86 (2.0)</td>
<td>0.79 [0.39, 1.18]</td>
</tr>
</tbody>
</table>

std=Standard Deviation; P = Patients; C = Controls; d=Cohen’s d
FACT-Cog= Functional Assessment of Cancer Therapy (FACT)-Cognitive Function Total. FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue. FACT-HN= FACT head and neck. HADS= Hospital Anxiety and Depression scale; Dep = Depression subscale. For consistency of interpretation and ease of reading, all questionnaires scored such that lower scores indicate fewer symptoms.
### eTable 6 - Median and (interquartile range) of serum variables

<table>
<thead>
<tr>
<th>P</th>
<th>Baseline</th>
<th>6 month</th>
<th>12 month</th>
<th>24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect Size [95% CI]</td>
<td>Effect Size [95% CI]</td>
<td>Effect Size [95% CI]</td>
<td>Effect Size [95% CI]</td>
</tr>
<tr>
<td>B12</td>
<td>340</td>
<td>286 [0.68]</td>
<td>386 [0.75]</td>
<td>479 [0.64]</td>
</tr>
<tr>
<td></td>
<td>(251, 420)</td>
<td>(235, 367)</td>
<td>(290, 538)</td>
<td>(342, 611)</td>
</tr>
<tr>
<td>FA</td>
<td>1362</td>
<td>1474 [-0.07]</td>
<td>1585 [0.72]</td>
<td>1454 [-0.74]</td>
</tr>
<tr>
<td></td>
<td>(1120, 1779)</td>
<td>(1096, 1863)</td>
<td>(1161, 1898)</td>
<td>(1165, 2014)</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>1.76 [-0.30]</td>
<td>2.09 [0.73]</td>
<td>2.82 [-0.74]</td>
</tr>
<tr>
<td></td>
<td>(1.0, 2.0)</td>
<td>(1.15, 2.44)</td>
<td>(1.41, 3.08)</td>
<td>(1.99, 5.10)</td>
</tr>
<tr>
<td>T4</td>
<td>14</td>
<td>12 [-0.29]</td>
<td>14 [-0.67]</td>
<td>13 [-0.35]</td>
</tr>
<tr>
<td></td>
<td>(13, 15)</td>
<td>(11, 14)</td>
<td>(12, 14)</td>
<td>(13, 14)</td>
</tr>
<tr>
<td>Free testost</td>
<td>25.7</td>
<td>27.2 [-0.07]</td>
<td>20.8 [-0.72]</td>
<td>23.7 [-0.15]</td>
</tr>
<tr>
<td></td>
<td>(20.8, 33.7)</td>
<td>(21.2, 34.6)</td>
<td>(17.9, 27.3)</td>
<td>(20.3, 28.1)</td>
</tr>
<tr>
<td>IL2</td>
<td>0.41</td>
<td>0.82 [-1.18]</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>(0.27, 0.69)</td>
<td>(0.51, 0.35)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>IL6</td>
<td>1.15</td>
<td>0.84 [-0.32]</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>(0.86, 1.76)</td>
<td>(0.58, 1.52)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>IL8</td>
<td>3.31</td>
<td>3.39 [-0.33]</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>(2.39, 5.98)</td>
<td>(2.81, 4.16)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>IL12</td>
<td>0.33</td>
<td>1.09 [-1.03]</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>(0.01, 1.38)</td>
<td>(0.87, 1.53)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>TNF-a</td>
<td>4.40</td>
<td>4.00 [-0.13]</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>(3.43, 5.55)</td>
<td>(3.17, 5.04)</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

P = Patients; C = Controls; FA-folic acid. TSH-thyroid stimulating hormone. Testost-testosterone. IL-interleukin. TNF-tumor necrosis factor.
NE = not evaluated
Patients
Declined (n=53)
Enrolled but not tested* (n=10)
*due to change in treatment schedule

Eligible Patients=161
Patients approached=143
(18 missed in clinic)

Baseline
Patients (P)=80
Controls (C)=40

6-month
P=77, C=38
NC results available: P=65, C=38

12-month
P=69, C=35
NC results available: P=62, C=35

24-month
P=63, C=35
NC results available: P=56, C=35

Controls
Withdrawn (n=2)
Deceased (n=1)

Patients
Deceased (n=4)
Withdraw - non-medical (n=3)
Withdraw - progression (n=1)
Missed neurocog test (n=6)
Non-verbal neurocog test only (n=3)
Incomplete neurocog tests (n=1)
Missed neurocog tests (n=5)

Patients
Deceased (n=2)
Withdraw - non-medical (n=2)
Withdraw - progression (n=1)
Inadequate neurocog tests (n=6)
Missed neurocog tests (n=11)
Non-verbal neurocog test only (n=1)

Controls
Withdrawn (n=2)
Deceased (n=1)

Patients
Deceased (n=1)
Withdrawn - non-medical (n=2)
Missed neurocog test (n=11)
Non-verbal neurocog test only (n=1)