Neurocognitive Dysfunction in Patients with Head and Neck Cancer

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- I have no significant relationships to disclose

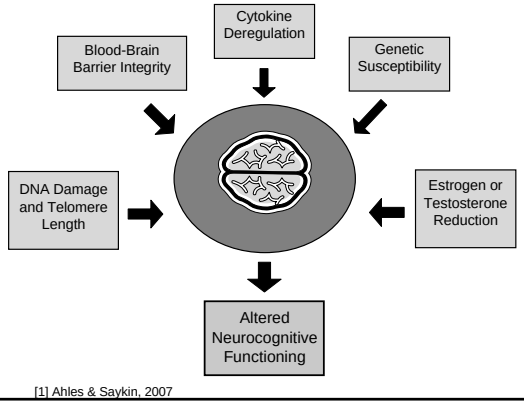
Learning Objectives

- Discuss the prevalence and incidence of neurocognitive dysfunction in head and neck cancer patients
- Identify the most commonly affected neurocognitive domains
- Describe factors associated with neurocognitive dysfunction in head and neck cancer patients

Neurocognitive Function in Cancer

- Cancer patients experience changes in neurocognitive function during and after treatment
- Up to 40% have impairment before starting treatment
- Improvement after treatment but may persist in a subgroup of patients
- Limited studies in patients with head and neck cancer

Lancet Oncology October 2007



[1] Ahles & Saykin, 2007

Specific Factors Contributing to Neurocognitive Dysfunction in HNC Patients

- Radiation-induced microvascular injury
- Hypothalamic-pituitary dysfunction
- Thyroid dysfunction

Pathogenesis of Radiation-Induced Neurocognitive Dysfunction

- Microvascular injury
  - Endothelial damage
  - Hyaline thickening
  - Fibrinoid necrosis of the vessel wall
  - Thrombosis
  - Infiltration of macrophages

[2] Abayomi, 2002

Pathogenesis of Radiation-Induced Neurocognitive Dysfunction

- Increased risk
  - Hypertension
  - Diabetes
  - Smoking
  - Hyperlipidemia

[2] Abayomi, 2002

Studies of Neurocognitive Function

- Neurocognitive function after radiation therapy (RT) for nasopharyngeal cancer (NPC)
- 16 patients treated for NPC with RT only
- 21 patients awaiting RT for NPC
- Cross-sectional; Median duration post-RT: 5.5 years (2.5 – 10.2 years)
- Hong Kong

[3] Lee et al.,1989

Studies of Neurocognitive Function

- Compared to controls, post-RT patients
  - Lower scores on full scale IQ, verbal IQ, and performance IQ
  - Poorer performance on verbal and visual memory
  - Increased subjective memory complaints
  - More difficulties with comprehension and non-verbal concept formation

[3] Lee et al.,1989

Studies of Neurocognitive Function

- 17 patients with histologically confirmed chordomas and low-grade condrosarcomas of the skull base
- Prospective longitudinal
- Neuropsychological testing after surgical resection/biopsy before RT, 6 months, 2 years, and 4 years after treatment

[4] Glosser et al., 1997)

Studies of Neurocognitive Function

- No decline in IQ, memory, auditory or visual attention, language, or visuospatial abilities
- Progressive psychomotor slowing in 10 patients (59%)
- Trend for association of psychomotor slowing with increased RT doses in brainstem, right and left temporal lobes combined, and in the substantia nigra

[4] Glosser et al., 1997)

Studies of Neurocognitive Function

- Neurocognitive function in patients with NPC treated with RT
- 27 patients with NPC post-RT; 28 patients with NPC awaiting RT; 35 normal adult controls (matched for age and education)
- Cross-sectional; Median duration post-RT 1.7 years
- Taiwan

[5] Hua et al., 1998

Studies of Neurocognitive Function

- Patients with NPC treated with RT had impairments in the following domains:
  - Auditory attention/concentration
  - Verbal learning
  - Verbal memory
  - Visual memory
  - Visuospatial-visuoperceptual abilities
  - Manual dexterity

[5] Hua et al., 1998

Studies of Neurocognitive Function

- Neurocognitive function in patients treated with RT for paranasal sinus tumors
- 19 patients
- Cross-sectional; 20 months to 20 years post-treatment
- Impaired performance defined as > 1.5 SD below the normative mean
- CT or MRI for clinical symptoms (*n* = 6)

[6] Meyers et al., 2000

Studies of Neurocognitive Function

Domain	Impaired (%)
Verbal Memory •Long term storage •Consistent retrieval •Delayed recall	 58% 69% 80%
Executive Function	35%
Visual Motor Speed	35%
Fine Motor Coordination •Right hand •Left hand	 33% 27%

[6] Meyers et al., 2000

Studies of Neurocognitive Function

- RT dose associated with impaired memory – delayed recall ($r = -0.55$, $p < .03$) but not other tests
- Total volume of brain irradiated not associated with performance
- Among 6 patients with scans, 2 had documented cerebral necrosis; 3 had cerebral atrophy
- 8 patients unable to perform usual activities

[6] Meyers et al., 2000

Studies of Neurocognitive Function

- Compare neurocognitive function in patients with and without temporal lobe necrosis at least 1 year after RT for NPC
- 53 patients treated between 1968 and 1997
- 31 patients with TLN; 22 patients without TLN; 31 healthy adults matched for age and education
- Hong Kong

[7] Cheung et al., 2000)

Studies of Neurocognitive Function

- Patients without TLN performed similarly to controls
- Patients with TLN had significant impairment in the following domains:
  - Verbal and visual memory
  - Motor ability
  - Planning
  - Cognitive ability
  - Abstract thinking

[7] Cheung et al., 2000

Studies of Neurocognitive Function

- Neurocognitive function in patients with NPC who were post-RT at least 2 years
- 40 patients with documented temporal lobe injury (TLI); 20 without TLI; 19 healthy adults matched for age and education
- Initial assessment and follow-up assessment in 17 patients (10 TLI, 7 no TLI) an average of 28 months later (range 11 – 42 months)
- Hong Kong

[8] Lam et al., 2003)

Studies of Neurocognitive Function

- Initial Assessment
  - Patient groups had lower scores on information and comprehension subtests
  - Patient groups had lower scores on verbal and visual memory tests
  - 60% of patients with TLI had subjective memory problems compared to 55% without TLI
- Follow-Up Assessments
  - Trend toward improved verbal memory; significant decline in visual memory (worse in TLI patients)

[8] Lam et al., 2003

Studies of Neurocognitive Function

- Neurocognitive function before and after RT-based therapy in patients with NPC
- 30 patients treated with intensity-modulated RT with or without chemotherapy
- Prospective longitudinal design; Assessments before RT and an average of 18 months post-RT (range 12 – 26 months)
- Taiwan

[9] Hsaio et al., 2010

Studies of Neurocognitive Function

- 76% had significantly lower scores post-RT
- Significant decline the in the following domains:
  - Short-term memory
  - Language abilities
  - List-generating fluency
- Patients with mean RT dose > 36 Gy to temporal lobes had greater decline
- Patients in whom V60 of temporal lobes was greater than 10% had greater reduction

[9] Hsaio et al., 2010

Studies of Neurocognitive Function

- Neuropsychological performance in patients after RT-based therapy for SCC (excluded nasopharyngeal)
- 10 patients (5 RT only; 5 CCR with cisplatin)
- Cross-sectional; 20 months post-treatment (range 9 – 41 months)

[10] Gan et al., 2011

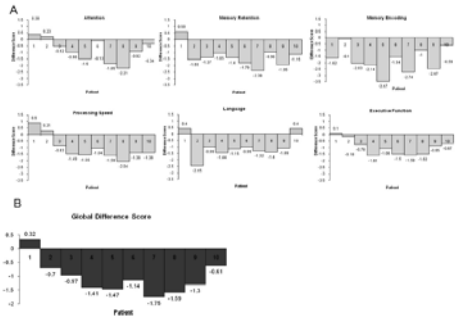


Fig. 1. Difference scores for individual patients. For each patient, (A) difference score (D-score) for each cognitive domain and (B) global difference score shown. Score of 0 represents performance at level expected from intelligence quotient subtests; score of −1.0 represents underperformance by one standard deviation (SD) and score of +1.0 represents overperformance by one SD.

[10] Gan et al., 2011, p. 129

Studies of Neurocognitive Function

- 9 of the 10 patients had cognitive dysfunction in multiple domains
- Memory was severely affected
- Global difference score not correlated with time since treatment

[10] Gan et al., 2011

Table 3. Radiation dosimetry to brain for individual patients

		Maximal dose (Gy)								
Pt. No.	Mean dose (Gy) to whole brain	Whole brain	Frontal lobe	Parietal lobe	Temporal lobe	Occipital lobe	Thalamus	Pituitary	Hypothalamus	Cerebellum
1	1.36	36.05*	<1.00	<1.00	1.53	<1.09	1.00	1.05	1.13	36.05*
2	< 1.00	1.65	<1.00	<1.00	< 1.00	< 1.00	<1.00	<1.00	<1.00	<1.00
3	2.14	40.64*	1.86	<1.00	6.54	7.59	1.57	3.92	3.70	32.74*
4	1.74	38.99*	1.25	<1.00	3.61	9.22	1.75	2.15	1.95	37.76*
5	3.55	51.33*	2.02	<1.00	46.99*	27.11*	1.93	3.78	2.64	48.45*
6†	2.85	45.84*	1.93	<1.00	5.29	10.98*	2.18	2.96	3.30	45.84*
7†	4.07	51.76*	2.80	<1.00	11.36*	19.01*	2.41	3.74	3.32	51.76*
8†	2.71	44.28*	1.83	<1.00	3.80	3.28	1.43	2.66	2.10	44.28*
9†	4.83	57.77*	2.22	<1.00	40.08*	28.47*	2.60	3.64	3.58	57.77*
10†	4.27	54.42*	2.31	<1.00	30.54*	9.13	2.31	3.75	3.15	46.31*

Abbreviation: Pt = patient.
* Radiation dose ≥ 10 Gy.
† Chemoradiotherapy patient.

[10] Gan et al., 2011, p. 130

Studies of Neurocognitive Function

- Correlation between increasing RT dose to temporal lobes and worse performance on memory encoding
- Correlation between increasing RT dose to cerebellum and manual dexterity
- Trend for CCR patients to have greater neurocognitive dysfunction

[10] Gan et al., 2011

Studies of Neurocognitive Function

- Neurocognitive function in HNC patients treated with RT-based therapy
- Prospective longitudinal design
- *N* = 24 (14 CCR with cisplatin; 6 RT with panitumumab; 4 RT only)
- Post-op and nasopharyngeal excluded
- Multiple domains and self-report measures
- Change in neurocognitive function ≥ 1 SD

[11] Razak et al., 2011

Studies of Neurocognitive Function

- No baseline data presented
- At 1 year
  - 6 (25%) patients had decline in at least one neurocognitive domain; 3 had decline in multiple domains
  - Memory and attention were most affected
  - 5 patients had improvement
  - No correlation with radiation dose to brain
  - 46% reported decline in neurocognitive function

[11] Razak et al., 2011

Studies of Neurocognitive Function

- Neurocognitive function in sample with mixed head and neck cancer
- Prospective, longitudinal design
- Neuropsych assessments at baseline and 3-months post-treatment
- Delirium assessments at scheduled treatment visits

[12] Bond, Dietrich, & Murphy, 2011

Patient Characteristics *(N = 70)*

	n	(%)
Male	57	(81)
Caucasian	64	(91)
Married	53	(76)
High School/College	61	(87)
Oropharynx	39	(56)
Current Smoker	22	(31)
Alcohol Misuse (AUDIT score ≥ 8)	10	(14)

	Mean	SD	Range
Age (years)	55	8.92	33 – 70
# of Comorbidities	4	2.74	0 – 17
Estimated IQ (NAART)	104	8.94	82 – 122

Baseline Neurocognitive Impairment Based on Global Deficit Score (*N* = 70)

	n	(%)
Global Deficit Score < 0.5	37	(52.9)
Global Deficit Score ≥ 0.5	33	(47.1)

[12] Bond, Dietrich, & Murphy, 2011)

Rates of Baseline Neurocognitive Impairment by Domain

Domain (Measure)	*n*	Mild to Moderate (T-score 39 – 30) *n* (%)	Moderate to Severe (T-score ≤ 29) *n* (%)	Total *n* (%)
Global Function (MMSE)	68	16 (23.5)	1 (1.5)	17 (25.0)
Attention (TMT A)	69	14 (20.2)	2 (2.8)	16 (23.0)
Executive Function(TMT B)	69	15 (21.7)	7 (10.1)	22 (31.8)
Processing Speed(Symbol Digit)	70	12 (17.1)	7 (10.0)	19 (27.1)
Verbal Learning(RAVLT – Total)	70	20 (28.6)	5 (7.1)	25 (35.7)
Verbal Memory(RAVLT – Delayed Recall)	70	16 (23.1)	5 (7.2)	21 (30.3)
Verbal Fluency (Action Verb Fluency)	70	14 (20.0)	3 (4.3)	17 (24.3)

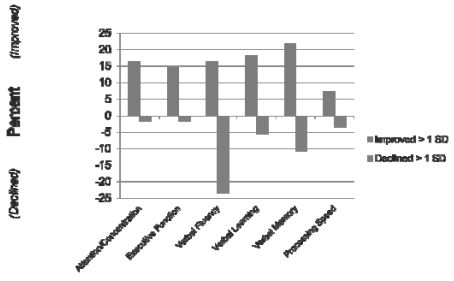
[12] Bond, Dietrich, & Murphy, 2011

Baseline Neurocognitive Function in Patients Who Completed and Who Did Not

Domain (Measure)	3-Month Post-Treatment Assessment (*n* = 55) Median	No 3-Month Post-Treatment Assessment (*n* = 15) Median	*p* value
Global Function (MMSE)	47.6	40.3	.010
Attention (TMT A)	48.0	40.5	.022
Executive Function(TMT B)	47.0	36.0	.041
Processing Speed(Symbol Digit)	48.1	37.9	.002
Verbal Learning(RAVLT – Total)	46.9	39.1	.002
Verbal Memory(RAVLT – Delayed Recall)	47.2	39.2	.085
Verbal Fluency (Action Verb Fluency)	47.4	46.2	.830

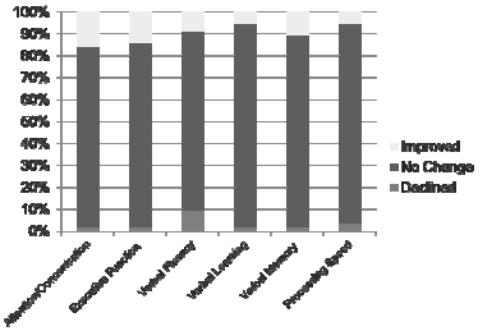
[12] Bond, Dietrich, & Murphy, 2011

Changes in Neurocognitive Function Based on T-score Change > 1 SD (*N* = 55)



[Bond et al., Unpublished Data]

Changes in Neurocognitive Function Based on Reliable Change Index (*N* = 55)



[Bond et al., Unpublished Data]

Incidence of Delirium & Subsyndromal Delirium During Cancer Treatment

	# of Cases	(%)
Delirium	6/69	(8.6)
Subsyndromal Delirium	29/64	(45.3)
Patient Report at End of Study	18/58	(31.0)

[13] Bond, Dietrich, Shuster, & Murphy, 2011

Discussion

- 47% of patients with head and neck cancer had impaired overall neurocognitive function at baseline
- > 25% of patients exhibited impairment in verbal learning, verbal memory, executive function, and processing speed
- 3 months post-treatment; decline in small number, improvement in some, majority unchanged
- Delirium and delirium symptoms common

Conclusions

- Most studies done in patients with NPC and base of skull tumors
- Recent studies include patients with other tumor sites (exclude patients with NPC)
- Earlier studies cross-sectional designs with assessments at varying times post-treatment
- Recent studies longitudinal prospective designs with baseline assessments
- Small sample sizes

Conclusions

- Inconsistent results
- Neurocognitive domains most commonly affected
  - Verbal and visual memory
  - Executive function
  - Processing speed
  - Attention/concentration
  - Motor function
- Patients receiving RT for non-NPC/skull base tumors may receive incidental brain RT

Implications for Practice

- Pre-existing deficits may affect treatment tolerance and compliance
- Patients may have difficulty comprehending and learning information about their diagnosis and treatment
- Patients may not be able to fully understand and consent to plan of care
- Patients may not be able to manage complex supportive care activities

Implications for Practice

- Patients may not be able to monitor and report symptoms and other problems
- Patients require increased caregiver support resulting in increased caregiver burden

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