Cancer-Related Cognitive Impairment: Mechanisms and Clinical Implications

Léa Henriette[1], Vincent Richard[1,2] & Giovanni Briganti[1]

[1] Department of Computational Medicine and Neuropsychiatry, University of Mons, Belgium

[2] Department of Medical Oncology, CHU HELORA - Kennedy site, Mons, Belgium

INTRODUCTION

Cancer survivorship has grown substantially: over **18 million** Americans now live beyond a cancer diagnosis, projected to exceed 26 million by 2040 (1). This shift reframes cancer as a chronic condition, with enduring physical and psychosocial sequelae.

Cancer-Related Cognitive Impairment (CRCI) encompasses cognitive changes in patients without cerebral metastasis, most frequently affecting attention, working memory, language, processing speed and executive function (2).

⚠ While commonly attributed to chemotherapy, CRCI is also associated with hormonotherapy and immunotherapy.

COGNITIVE DOMAINS

Meta-analyses yield inconsistent findings across domains (2-6).

Most affected domains post-chemotherapy :

Memory · **Processing Speed** · **Attention** · **Executive Function**

Discrepancies arise from heterogeneous neuropsychological test classification reported in each studies.

Ex : The Digit Span Forward is widely categorised under Attention, yet primarily measures working memory (Johnstone et al., 1995; Mirsky et al., 1991).

⚠ Common guidelines for neuropsychological test classification in meta-analyses are urgently needed (6).

UNDERLYING MECHANISMS

Four interconnected mechanisms form a cascade: therapy-induced neuroinflammation drives downstream structural & functional changes (7).

NEUROINFLAMMATION

Persistent microglial activation creates a pro-inflammatory brain environment outlasting treatment (≥6 months post-chemo), disrupting neural plasticity (7-8).

DEMYELINATION

Neuroinflammatory cascade degrades myelin, slowing neural signal conduction and impairing processing speed (9).

CEREBRAL ATROPHY

Neuronal loss in hippocampus & prefrontal cortex directly correlates with memory and executive function deficits (10-11).

NEUROTRANSMITTER DISRUPTION

Disruptions to dopaminergic, serotonergic & renin-angiotensin signaling underlie co-occurrence with depression & fatigue (12).

Table 1. Cytokine profile : differential associations with cognitive domains.

CYTOKINE	COGNITIVE ASSOCIATION
IL-1β	Slower response speed (13)
IL-6	↑ subjective complaints; ↓ verbal memory; ↓ hippocampal volume (11)
TNF-α	Subjective memory complaints; ↓ hippocampal volume (14)

TEMPORAL EVOLUTION

21–28% show objective impairment before chemotherapy. (15-16)

PRE-TREATMENT

61% show persitent deficits. (15)

POST-TREATMENT

ACTIVE TREATMENT

65% exhibit acute decline peaking in memory, executive function & processing speed. (15)

MEASUREMENT

SUBJECTIVE VS. OBJECTIVE PREVALENCE

- **Objective measures**
- **Self-report questionnaires**

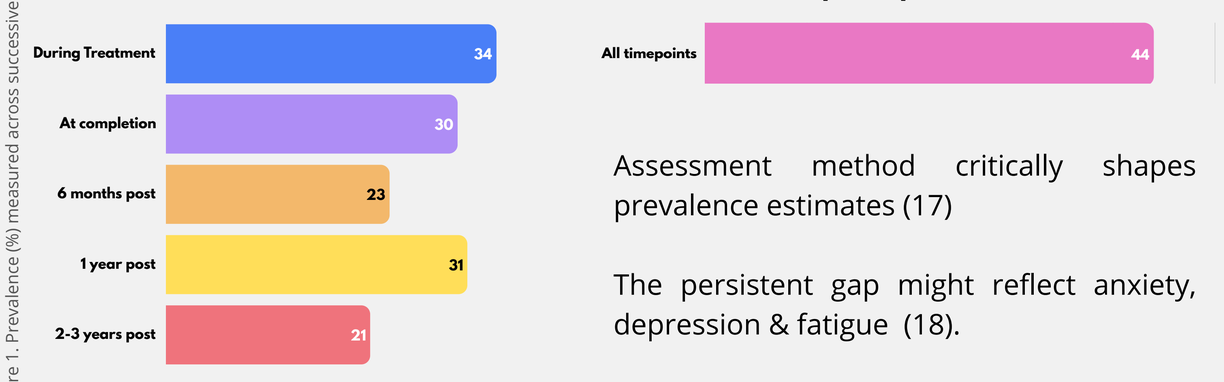

Figure 1. Prevalence (%) measured across successive timepoints.

Assessment method critically shapes prevalence estimates (17)

The persistent gap might reflect anxiety, depression & fatigue (18).

PSYCHOLOGICAL FACTORS

Psychological variables actively contribute to CRCI onset and maintenance (19).

- **Anxiety & depression** correlated with both objective & subjective CRCI (20)
- **Death anxiety** in 43%; linked to depression (49%) & demoralization (67%) (21)
- **Fatigue & anxiety** increase risk of perceived attention & memory impairment (22)
- **Poor sleep quality** → worse cognition; moderated by optimism (23)
- **Insomnia** in 51.9%; 79% report cognitive symptoms (24)
- **Loneliness** significantly correlated with diminished cognition across all domains (25)

LIMITATIONS

- No consensus on neuropsychological test classification across studies (6)
- Lack of baseline assessments prevents characterising pre-existing deficits
- Literature predominantly based on breast cancer
- Measures confounded by anxiety, depression & fatigue (18)

PERSPECTIVES

- Establish common guidelines for neuropsychological test classification (6,26)
- Systematic inclusion of pre-treatment baseline neuropsychological assessments
- Integrate psychological & social factors (sleep, loneliness) into CRCI clinical models

CONCLUSION

CRCI is a multifactorial, heterogeneous syndrome arising from the interplay of neurotoxic, neuroinflammatory, psychological and social mechanisms. Prevalence ranges from 21–65% depending on time-point and assessment method.

KEY TAKE-AWAY

Neuropsychological testing alone is insufficient. A standardised, multimodal approach, integrating objective measures, self-report measures and biomarkers is essential to fully characterise CRCI.

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