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Post-operative cognitive dysfunction in cancer patients: A narrative review

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Shilpi Agarwal,[1] Rakesh Garg[2]
[1]Senior Resident, Department of Onco-Anaesthesiology, Pain and Palliative Medicine, Dr BRAIRCH, AIIMS, India
[2]Associate Professor, Department of Onco-Anaesthesiology, Pain and Palliative Medicine, Dr BRAIRCH, AIIMS, India

Correspondence: Rakesh Garg, Department of Anaesthesiology, Pain and Palliative Care, Dr BRAIRCH, All India Institute of Medical Sciences, Room No. 139, Ist floor, Ansari Nagar, India, Tel +91 9810394950, Email drrgarg@hotmail.com

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Introduction

Cancer patients requires multimodal management for an optimal outcome. The cancer patients may require surgical interventions with or without chemotherapy, radiotherapy, and targeted biological therapies. The advancement in these therapies have led to long term survival of cancer patients. Surgeries are increasingly being performed for different cancers which otherwise was not feasible in earlier days because of advancement of the surgical procedures and optimization of tumour extent using the adjuvant therapies. However, each of these interventions may be associated with adverse effects and complications. There is dire need to understand, manage and prevent the adverse effects of such treatments. This remains essential for improving the quality of life and overall outcome. One of the such debilitating adverse event in the postoperative period is post-operative cognitive dysfunction (POCD).

POCD is a syndrome defined as a decline in cognitive function on a set of neurological tests from before to after surgery. Its manifestations are subtle and manifold depending upon the cognitive domains involved. The reported incidence of POCD varies due to lack of formal criteria for diagnosis of POCD. The various factors leading to POCD in cancer patients are demographic factors such as advanced age and comorbidities, genetic, immune factors and treatment related of which surgery and anaesthesia play a significant role.[1-5]

Risk factors for POCD in cancer patients

The complex interaction between the demographic factors, biological, genetic, and immune function increases the risk of cognitive dysfunction in cancer patients. These interaction remains responsible for occurrence of POCD and is affected by various factors (Table 1). It can be explained as the seed which is the cancer, the soil is the person who has the cancer and the pesticides are the treatments which these patients undergo for management of cancer.

Immune function: Cancer patients have increased levels of circulating cytokines. Interleukins are one component of a complex cancer-induced cytokine cascade. In most clinical studies in cancer patients, the Interleukin-6 (IL-6) serum level has been reported to be increased. This is indicative of influence of cancer on markers of immune system. On the other hand, inflammation and immune dysfunction has been associated in the pathology of cognitive dysfunction.[1] It has been reported that the oncologic treatment like chemotherapy leads to increased levels of cytokines.[2] Cytokines produced peripherally can cross the blood brain barrier via saturable transporters or by passive diffusion through spaces between vascular endothelial cells. These cytokines activate microglia and astrocytes. Also, presence of increased central nervous system inflammatory reactivity has been reported to affect cognitive function.[3] The mechanism includes neuronal activity impact, neuron toxicity or neuron degeneration. These all alteration may results in impaired cognitive function in cancer patients.[3]

Demographic factors: Age is commonly associated with increased risk of cognitive decline. In an observational prospective study on elderly cancer patients with age greater than 65 years undergoing surgery for a solid malignant tumour, the incidence of POCD was increasingly observed at 3 months follow up using neuropsychological tests. Of the investigated potential risk factors for POCD to develop such as gender, Charslon Comorbidity score and type of surgery, only age had a significant influence on the development of early POCD.[4] Ageing may be associated with medical comorbidities like cardiovascular and diabetes mellitus. Other factors such as low educational level is a possible risk factor for POCD to develop.[5] Cancer patients may develop psychological factors after diagnosis such as stress, anxiety, depression, fatigue and sleep disturbances which may hamper cognitive performance. In a study of 50 patients of breast cancer who received either chemotherapy or radiation treatment were assessed with regards to worry and assessed with functional magnetic resonance imaging (MRI) and measures of cognitive function.[6] The pre-treatment worry was associated with alterations in brain function and the cognitive function in both treatment groups.[6]

Table 1 Risk Factors for POCD in Cancer Patients

Parameters	Factors
Cancer related	Immune suppression
	Advanced Age
	Pre-existing comorbidities
Patient related	Low level of education
	Psychological Factors like stress, anxiety after diagnosis
	Genetic (Apo E4 allele)
Treatment related	Surgery: Extensive surgical procedures, intraoperative and postoperative complications
	Anaesthesia: Marked disturbance of homeostasis, long acting anaesthetics
	Neoadjuvant and adjuvant chemotherapy
	Hormonal therapy
	Radiotherapy

Genetic: Presence of APO E4 allelle and catechol-o-methyl-transferase (COMT) genotypes predisposes to risk of postoperative cognitive dysfunction. The literature reports an association between ApoE4 and POCD in patients undergoing surgery requiring anaesthesia using volatile anaesthetics.[7] The inhalational agents have an impact on neuronal repair and plasticity. COMT Val nucleotide polymorphism is related to lesser release of dopamine in prefrontal cortex and thus cognitive dysfunction.[8]

Treatment related: Although the treatment modalities have increased the survival in cancer patients, but they also increase the risk of associated comorbidities including cognitive dysfunction. Many patients receive neoadjuvant and adjuvant chemotherapy, radiation therapy and hormonal therapy before or after surgery.

A. ***Hormonal therapy*** in breast cancer patients leads to treatment induced menopause and cognitive decline. In one study in breast cancer patients use of adjuvant endocrine therapy along with chemotherapy was associated with worse performance on measures of processing speed and verbal memory.[9] A prospective study showed that there was deterioration in verbal memory and executive function in post-menopausal patients with breast cancer taking tamoxifen for one year but not in those taking the aromatase inhibitor, exemestane, compared to healthy controls.[10] In another study on breast cancer patients it was shown that postoperative hormonal therapy with an aromatase inhibitor prevents the recovery of neurological damage after surgery. The thalamic volume reduction and attentional dysfunction which occurred shortly after surgery did not recover in 6 months in those receiving hormonal therapy after surgery. Even if hormonal therapy does not have direct neurotoxic effects, hormonal therapy prevents recovery of neuronal damage caused by other neurotoxic agents, such as an anaesthesia, inflammation and chemotherapy.[11]

B. ***Radiation therapy*** induced cognitive changes can affect the quality of life. Radiation therapy can lead to tissue early or late changes in brain. These injurious effect can lead to changes like demyelination or white matter necrosis. In addition, functional deficits like progressive impairments in memory, attention, and executive function may also occur. These structural and functional changes have been observed to have profound effects on quality of life (QOL) of cancer survivors.[12]

C. ***Chemotherapy****:* Chemotherapy-associated cognitive dysfunction, often referred to as "chemobrain," includes subjectively reported and objectively measured problems with cognition following chemotherapy. Few patients experience long-term cognitive effects after chemotherapy treatment; however, these effects generally appear to be modest in severity, and for most survivors, cognitive impairment may diminish over time.[13] But many patients undergo surgery after receiving chemotherapy so this may increase the effects of chemobrain and increase the chances of developing POCD. In a study of 107 elderly patients of gastric or colorectal cancer, patients were divided into two groups one receiving chemotherapy before surgery and another did not receive chemotherapy.[14] Cognitive functions were assessed 1 day prior to surgery and at 3 days postoperatively. It was shown that chemotherapy preoperatively increased the chances of early postoperative cognitive dysfunction in elderly patients.[14] Many studies that have compared individuals treated with chemotherapy to healthy control populations at various time intervals have shown that some chemotherapy regimens lead to impaired cognitive function. Patients with breast cancer receiving adjuvant therapy were compared with healthy women with regards to fatigue, menopausal symptoms, and cognitive dysfunction.[15]. The authors reported that the occurrence of cognitive dysfunction was more in patients receiving chemotherapy at follow up of 2 years.[15] Memory, attention, psychomotor function processing speed, and executive function appear to be commonly affected. The proposed mechanisms of chemobrain are neurotoxic injury resulting from chemotherapeutic agents, vascular ischemia due to vascular obstruction, and neurotransmitters changes.[14-16] The chemotherapeutic drugs like carmustine, cisplatin, cytarabine, ifosfamide, lomustine, methotrexate, procarbazine, and temozolomide can cross the blood brain barrier. This enhances direct toxicity to brain cells and thus risk of cognitive dysfunction.[16]

D. ***Surgery and anaesthesia***: Surgery induced stress response leads to release of neuroendocrine factors and changes related to neuroinflammation, which may influence neuronal functioning, increased levels of glucocorticoids such as cortisol and cytokines lead to inflammatory response.[17] Anaesthetic related central nervous system toxicity such as volatile anaesthetic induced apoptosis and B amyloid formation lead to cognitive impairment. The duration of surgery and anaesthesia, intraoperative factors like hypoxia, hypercarbia, hypotension, and marked disturbance of homeostasis are risk factors resulting in POCD.[18] Many cancer surgeries are extensive and of long duration leading to major blood loss resulting in hypotension. In certain cancer surgeries, such as lobectomies and pneumonectomies there are increased chances of hypoxia and hypercarbia. Certain orthopaedic procedures like total knee replacement have an increased risk of microemboli after tourniquet release leading to increased risk of POCD.[19] Similarly, in cardiac surgery, the cause of POCD is microemboli during cardio-pulmonary bypass.[20] Thus we assume that cancer surgeries have increased risk of microemboli due to increased chances of thrombosis in cancer patients and may predispose to POCD. The influence of surgery on brain structure and cognitive function was studied magnetic resonance imaging (MRI) in 32 postmenopausal females with breast cancer and compared with 20 age-matched controls. A significant interaction between regional grey matter volume (rGMV) in the thalamus and one attention domain subset was reported. So they concluded that impact on brain structure including thalamus may occur after surgery and may lead to the attentional dysfunction.[21]

Prevention and treatment

POCD is viewed as a syndrome of brain dysfunction caused by diverse factors rather than a single disease caused by a specific etiology. It requires a multicomponent intervention that addresses the diverse factors that contribute to its genesis. Various strategies have been reported in the literature (Table 2). It is beneficial to address issues of anxiety, depression, fatigue, and sleep disturbance in cancer patients which act as potential confounding factors in cognitive decline. The perioperative measures include use of minimally invasive surgeries, intraoperatively homeostasis should be maintained avoiding complications, use of short acting anaesthetics and multimodal analgesia techniques to avoid narcotics. Biofeedback and cognitive-behavioural therapy have also been investigated for reducing chemotherapy-associated cognitive dysfunction. The memory and attention deficit has been reported after chemotherapy in breast cancer patients.[22] It was also reported that improvements in cognitive function, quality of life and standard neuropsychological test performance occurred with increasing time on follow-up.[22] Modafinil, a neural stimulant has been reported to improve cognitive performance in breast cancer survivors by enhancing some memory and attention skills.[23]

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Table 2 Perioperative strategies for prevention and treatment of POCD

Parameters	Factors
Patient related	Address psychological issues in cancer patients.
	Perioperative cognitive training.
Surgery related	Minimally invasive techniques.
	Meticulous techniques to avoid complications.
Anaesthesia related	Short acting anaesthetics.
	Perioperative maintenance of homeostasis
	Multimodal analgesia.

Conclusion

Various patient related characteristics including genetic factors, and biological factors may play a role in the predisposition of POCD in cancer patients. Its pathogenesis is multifactorial, with the immune response to surgery probably serving as a trigger. Meticulous perioperative care to prevent intra and postoperative complications can reduce the risk of POCD. Cancer treatment related cognitive impairment is a prevalent side effect of cancer treatments that can persist for years following treatment and negatively affect quality of life in cancer survivors.

Conflicts of interest

There is no conflict of interest.

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