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Understanding cognition in older patients with cancer

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Abstract

Cancer and neurocognitive disorders, such as dementia and delirium, are common and serious diseases in the elderly that are accompanied by high degree of morbidity and mortality. Furthermore, evidence supports the under-diagnosis of both dementia and delirium in older adults. Complex questions exist regarding the interaction of dementia and delirium with cancer, beginning with guidelines on how best measure disease severity, the optimal screening test for either disorder, the appropriate level of intervention in the setting of abnormal findings, and strategies

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aimed at preventing the development or progression of either process. Ethical concerns emerge in the research setting, pertaining to the detection of cognitive dysfunction in participants, validity of consent, disclosure of abnormal results if screening is pursued, and recommended level of intervention by investigators. Furthermore, understanding the ways in which comorbid cognitive dysfunction and cancer impact both cancer and non-cancer-related outcomes is essential in guiding treatment decisions. In the following article, we will discuss what is presently known of the interactions of pre-existing cognitive impairment and delirium with cancer. We will also discuss identified deficits in our knowledge base, and propose ways in which innovative research may address these gaps.

Keywords

Cognition; Delirium; Dementia; Mild cognitive impairment; Confusion assessment method (CAM); Competency; Decision-making capacity; Screening; Prevention; Treatment

1. Introduction

There is a rising incidence of both cancer and neurocognitive disorders with aging. The prevalence of dementia is estimated to be around 6% in persons older than 65 years and 30% of persons older than 90 years.[1] The actual prevalence of dementia may be significantly different, as studies have shown that dementia is underdiagnosed in many patients. Despite the fact that the benefit of routine screening for cognitive impairment in older adults is unclear,[2] older patients with cancer represent a vulnerable subset, where assessment of decisional capacity is essential. Although patients with dementia may be able to relay preferences in regard to daily activities and care, they may lack the ability to make more complex decisions such as those involving cancer treatment. The implications of even mild cognitive impairment are significant, given that these patients may be at high risk for developing dementia.[3] In the setting of cancer treatment decisions hold significant consequences, patients must be able to demonstrate a high degree of understanding and ability to process information in order to proceed with active treatment.

Delirium is also a common, often under-recognized [4] neuropsychiatric problem associated with substantial morbidity, mortality, and a high potential impact on decision-making ability. The vast majority of studies on the prevalence and impact of delirium have focused on hospitalized general medicine or postoperative patients, as opposed to older adults with cancer. The lack of awareness of delirium incidence and prevalence is especially problematic in the outpatient setting where much of cancer care is delivered.[5]

Both dementia and delirium can contribute significantly to morbidity and mortality in the elderly and are important factors for patients in a number of treatment settings. The coexistence of cancer and dementia or delirium has dramatic implications on treatment decisions and outcomes. The objective of this article is to identify and address gaps pertaining to the diagnosis, screening, and treatment of cognitive impairment and delirium in the older adult cancer patient population. The case study in Table 1 illustrates how these conditions may present, and the issues that arise. This manuscript will address gaps in

knowledge and how dedicated research in this area can help close these gaps. In addition, issues related to protection of patients with cognitive impairment in research are discussed.

2. GAP 1: The optimal way of identifying and measuring pre-existing cognitive impairment in older adults with cancer is not known

Dementia is often misdiagnosed. One study found that the diagnosis of dementia was missed in 21% of patients on a general medical ward, and 20% of patients without dementia were misdiagnosed with the condition.[6] The presence of several diagnostic classification schemes may lead to different diagnostic conclusions. A study of 1879 people aged 65 years and older enrolled in the Canadian Study of Health and Aging revealed that the prevalence of dementia can differ by a factor of 10 depending on which diagnostic criteria are used, which has important implications for treatment and research.[7] Although several definitions for dementia exist, the definition set by the Diagnostic and Statistical Manual (DSM) provides a reasonable framework readily applicable to clinical practice.[8] According to the DSM-5, a diagnosis of dementia requires significant cognitive impairment in at least one of 6 domains apparent from history and clinical assessment (learning and memory, language, executive function, complex attention, perceptual-motor function, and social cognition). The identified deficit(s) must represent a decline from a previous level of function, and interfere with independence in everyday social and occupational function. The major dementia syndromes include Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, and Parkinson disease with dementia. Less common disorders include progressive supranuclear palsy and dementia related to Huntington's disease. Alzheimer's dementia is the most common subtype of dementia in the general elderly population. It represents 60–80% of dementia cases, with a prevalence of 5–7% in most counties.[9] Vascular dementia represents the second most common form of dementia, comprising approximately 10–20% of cases in North American and Europe, with an estimated prevalence of 1.2–4.2% in patients 65 and older.[10,11] In patients with cancer, the precise incidence of various subtypes of dementia is unknown. However, using SEER Medicare data, the incidence of memory loss (defined as impairment causing interference with daily activities) and dementia has been found to be around 12%.[12] Each subtype is clinically distinguishable by history, physical signs/symptoms, and imaging. Disturbances are insidious and progressive in the case of neurodegenerative dementias such as Alzheimer's, as revealed through serial cognitive function exams examinations, and cannot be accounted for by another mental disorder (such as depression, schizophrenia, or delirium).[13] Given the prevalence of depression, it is particularly important for practitioners to concurrently screen for depression at the time of initial evaluation.

Garnering increasing attention is the entity of mild cognitive impairment (MCI). Findings of longitudinal population studies, applying varied definitions of MCI, estimate that the prevalence of MCI in the general elderly population is anywhere from 3% to 19%, and the risk of MCI progressing to dementia in a 2-year time-frame is 11–33%.[14,15] MCI is generally recognized as cognitive decline that is greater than expected for a patient's age but does not impact function in daily life.[15,16] Table 2 highlights several different definitions applied to cognitive impairment syndromes.[17]

General consensus-based guidelines recommend that providers use cognitive assessment tools when evaluating older patients with cancer to screen for baseline impairments, to evaluate cognitive capacity, with comprehensive work-up pursued in those with abnormal scores.[18] Assessment of cognitive function is included as a domain in the comprehensive geriatric assessment (CGA). Several tools are available (summarized in Loh et al. in this supplement), although not all have been fully tested or compared for predictive validity or impact on outcomes.[19] Several studies have shown that the incidence of cognitive impairment (CI) as detected by screening undertaken during the CGA ranges between 24% and 38%.[20–23] Thein and colleagues demonstrated in a retrospective chart review of 191 patients that the overall prevalence of CI, including dementia, using the Mini-cog tool, was 35%.[24] In another prospective study in which 50 patients were administered a CGA at baseline, 27% were found to have cognitive impairment.[22,25] However, evidence is also available supporting a lower rate of cognitive impairment in the older patient with cancer considered functionally normal by the Karnofsky Performance Status, with one study showing that the incidence of cognitive dysfunction as rated by the Blessed Orientation Memory Concentration Test (BOMC) was less than 10%.[26] Comprehensive neuropsychological testing is not necessary for all patients but may be useful for diagnosis and evaluation of decision-making capacity in patients with substantial cognitive impairment, including dementia, those with significant brain damage (stroke, head injury), or other neurological disease.

More observation and registry studies are needed to gain better understanding of the prevalence and incidence of dementia and cognitive impairment in patients with cancer. Using SEER Medicare data, Mohile and colleagues were able to demonstrate a comparable presence of memory loss and dementia in elderly patients with a history of cancer and those without a history, of 11.6% and 10.4%, respectively (p-value = 0.1773).[12] Further studies are needed that apply a designated set of validated criteria to newly diagnosed elderly patients with cancer, placing focus on the full spectrum of cognitive impairment, not restricted to dementia alone. In order to capture the diagnosis to begin with, studies comparing the positive and negative predictive values of various screening methods in this population are also imperative.

3. GAP 2: The impact of underlying cognitive impairment on cancer care is unclear

Another deficit pertaining to treatment of cancer in patients with pre-existing cognitive impairment is the impact on subsequent treatment and disease-related clinical outcomes. Few published studies have evaluated outcomes in patients with cognitive dysfunction who receive systemic therapy. Patients with cognitive impairment may have greater difficulty understanding the nature of the diagnosed cancer and its prognosis, in addition to the risks and benefits associated with treatment. Furthermore, such deficiencies may cause difficulty processing instructions on treatment regimens and reporting side effects that could impact their treatment and disease-related outcomes. They may also have a difficult time expressing their cancer-related syndrome burden, which impacts delivery of appropriate palliative interventions such as analgesia and subsequently diminishes quality of life. In most cases,

patients with mild cognitive impairment/dementia have intact decision-making capacity and require clear communication from a medical provider regarding various options and provisional support from their families and/or caregivers. Prior studies have shown that patients with comorbid physical and mental illness are at greater risk for morbidity and mortality, which would apply to the cancer patient population as well.[27] A more recent study found that 61% of patients with dementia had significant physical illness.[28] Furthermore, studies have shown that patients with dementia have a shorter life expectancy than is often times estimated by both clinicians and family members, which should be taken into account during clinical decision making for cancer treatment.[29] However, further research is needed to determine whether patients with mild cognitive impairment are at heightened risk for adverse effects from cancer treatment, and how pre-existing impairment impacts decision-making.

Several studies report an association between a diagnosis of pre-existing dementia with diagnosis of cancer at a later stage. One study of 17,500 older patients with colon cancer found that a pre-existing diagnosis of dementia was associated with lower odds of undergoing diagnostic tissue biopsy, higher odds of having unstaged cancer, and subsequent lower likelihood of receiving curative intent therapies.[30] A second study of 50,460 older patients with breast cancer revealed that dementia was independently associated with a diagnosis of later-stage breast cancer.[31] Raji and colleagues conducted a retrospective cohort study of patients with breast, colon, and prostate cancer that also showed an association between pre-existing dementia and diagnosis of disease at later stages. Furthermore, they also showed that the effect of cancer stage at diagnosis on mortality was significantly higher in older patients with pre-existing dementia.[32]

Further studies are needed to understand how the presence of pre-existing cognitive impairment or dementia affects chemotherapy-related adverse effects, hospitalization, post-treatment surveillance, cancer recurrence, and patient-reported outcome measures. Studies accomplishing this could be of various types, including observational, case–control, and cohort studies and cross-sectional studies. Ultimately, such studies would further allow us to best determine the degree to which a diagnosis of cognitive impairment or dementia may impact cancer treatment.

4. GAP 3: There are no standard procedures to manage abnormal cognitive screening test results that are found during research studies

Cognitive impairment is underdiagnosed in older adults with cancer. However, as cognitive screening is increasingly incorporated into clinical care and research of older adults with cancer, clinicians and investigators must consider the implications of an abnormal cognitive screen on treatment decisions. If cognitive screening is performed, particularly within the context of clinical research, there are ethical issues that may arise around disclosure, responsibilities of the research team and health care providers, and whether the research and treatment consent can be considered valid. No current framework exists to address these issues leading to a lack of uniformity in dealing with these issues across different institutions.

There is currently no consensus as to whether researchers are obligated to or should inform patients and/or their primary care professional about results of cognitive testing done within the context of clinical research. Some institutions mandate disclosure of incidentally found cognitive findings, while others do not. Generally, researchers have an obligation to disclose incidental findings either to a clinician or the patients themselves, which may have "clinically important implications on patient health".[33] Differences in policies may stem from the uncertain implications of an abnormal cognitive screen, as a positive cognitive screen does not equate to a diagnosis of dementia. Depending on the cognitive test used, the specificity for dementia can range from 50% to 96%.[34–36] With further testing, patients may be found to have normal cognition (false positive), MCI, or dementia.[2] In addition, other conditions, such as depression, delirium, and medications, can result in a positive cognitive screen and must be ruled out.

The uncertain benefit of earlier MCI diagnosis likely also factors into the complex decision to disclose or not disclose positive results. MCI, by definition, has no impact on a patient's ability to function independently. Although patients with MCI are at higher risk of developing dementia, the likelihood of this ranges considerably.[3,37–39] Furthermore, there are currently no effective pharmacological interventions for MCI,[36,37] although optimization of vascular risk factors, cognitive stimulation, and engagement of community resources may be beneficial.[37,40] Even for patients diagnosed with dementia, it is unclear whether pharmacologic intervention translates into a clinically significant benefit.[36] While the psychological impact related to a false-positive cognitive screening test is unknown,[36] several studies suggest that patients fear a diagnosis of dementia due to the potential stigma associated with this diagnosis,[40–43] as well as the possible impact it may have on their ability to drive and live independently.[44] It should be noted that some patients may not wish to know if they have abnormal cognitive screening and that 48–67% of patients who have a positive cognitive screen refuse to undergo further testing.[41,45,46] Thus, given that abnormal cognitive screening does not imply a diagnosis of dementia and that earlier diagnosis of cognitive impairment may not translate into better outcomes, it is unclear whether or not these results need to be conveyed to patients or their primary care physician.

The decision to disclose findings to a patient is further complicated in situations in which the researcher has no therapeutic relationship to the patient, such as in testing of volunteers used for controls. In these cases, it unclear what responsibility the researcher may have to the subject, and whether results should be relayed directly to the patient from the researcher, or if such information would best come from a physician with whom the patient has an established therapeutic relationship with, such as their primary care physician, who can explain the implications of the test result and arrange for further testing if necessary.

Finally, if patients are found to have cognitive impairments, this may have significant implications on the treatment plan and the validity of the patient's consent. The presence of cognitive impairment, particularly dementia, can influence both the potential benefits of chemotherapy, particularly in the adjuvant setting, as well as its potential harms. Chemotherapy can worsen cognition in some patients, which would be undesirable. Patients with cognitive impairment may have more difficulty understanding the risks and benefits of treatment and adhering to complex cancer treatment regimens. This is particularly relevant

in the current era where obtaining written informed consent prior to undertaking treatment is becoming increasingly common in clinical practice. In clinical research, rigorous procedures exist to ensure patients are well informed about the risks and benefits of participation in research, for the purpose of protecting patients. Yet these consent forms and procedures are often complex and may be difficult for patients with cognitive impairments to understand.

However, a diagnosis of cognitive impairment or dementia does not necessarily mean that the patient is incapable of making decisions and consenting.[47,48] In fact, most patients with MCI and many patients with early dementia are still able to understand the risks and benefits of treatment and of being involved in research, although this ability may fluctuate and vary depending on the task and complexity of the decision.[48,49] It is important that researchers do not automatically exclude patients with any cognitive impairment from clinical research, but that every effort be made to ensure that patients enrolled in studies do have the capacity to consent. Broadly, patients are deemed to have the capacity to make a decision if they demonstrate understanding of the situation, appreciate how the decision affects them personally, and are able to express a choice and the reasoning behind the choice.[50] The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) is a commonly used instrument to determine decision-making capacity.[51] In patients who are not capable of providing consent for research purposes, the American Geriatric Society suggests that a surrogate decision maker should be able to consent for research on the patient's behalf.[48] However, patient assent (agreement) or dissent for a particular decision should still be sought. In those studies that pose a greater than minimal risk and which do not have a reasonable likelihood of direct benefit to the patient, the American Geriatric Society suggests that these studies should not be offered patients who do not have the capacity to consent.[48]

A common strategy is needed to guide researchers on how best to handle abnormal cognitive screening findings. It is important that all stakeholders, including patients as well as regulatory bodies, be involved in providing guidance on the development of standardized protocols to address this important issue. As part of this process, it will be important to determine the threshold of cognitive impairment that is felt to have clinically significant implications on patient health, and at which researchers are obligated to inform patients, caregivers, and patients' physicians. In the absence of existing guidelines/framework, we propose that patients should be asked prior to testing whether they wish to know the results of their cognitive screen if positive and that patients and investigators should discuss the potential implications of such a result prior to consenting for testing.

5. Gap 4: Patients with cancer are not routinely screened for delirium or delirium risk

Delirium is a condition that can lead to serious complications including increased morbidity and mortality,[52,53] functional[54] and cognitive decline,[55,56] and caregiver burden and distress.[57–59] It is characterized by an acute onset of disturbances in attention, awareness, and cognition that are not caused by a pre-existing cognitive disorder.[60] Making the diagnosis of delirium is complicated by similarity in presentation to other disease processes.

Similar to delirium, Lewy Body Dementia is characterized by fluctuating effects on mental functions, particularly in alertness and attention.[61] Sundown syndrome is another distinct clinical entity formally recognized in the DSM-V that can be difficult to distinguish from delirium. It occurs more frequently in the cognitively impaired or institutionalized patient population but is characterized by behavioral disturbances and mood alteration that occurs specifically in the later afternoon or evening.[62] It is important to discern the prevalence and impact of delirium in older patients with cancer since the risk of delirium is associated with both increased age[63] and malignancy.[64] Estimates of the prevalence of delirium in patients with cancer range widely from 10% to 50% among inpatients undergoing cancer surgery[65–69] and 20% to 90% among patients with advanced cancer receiving palliative care.[70–73] Without routine evaluation for delirium in outpatient cancer clinics, it is difficult to estimate the true prevalence of delirium among patients with cancer.

Screening for delirium in patients with cancer may be challenging since cancer itself may cause similar symptoms such as lethargy and decreased awareness, two potential signs of hypoactive delirium. Hypoactive delirium is the most common subtype and is more likely to be underdiagnosed compared with hyperactive or mixed delirium.[4,74] Delirium can be clinically assessed using a variety of screening instruments, with the Confusion Assessment Method[75] being the most well-validated and widely used approach. The diagnosis is established according to DSM-5 [60] or ICD-10 criteria.[76] Delirium severity is commonly measured using the Memorial Delirium Assessment Scale (MDAS),[77] Delirium Rating Scale-Revised 98 (DRS-R-98)[78] or CAM-S, which is the only delirium severity tool that has been validated against clinical outcomes.[75] More research is needed to understand how to best apply delirium screening tools to community-dwelling patients with cancer. Delirium is also difficult to retrospectively identify in clinical research utilizing secondary data analysis. A validated chart-based delirium instrument demonstrated a sensitivity of 74% and specificity of 83%.[79] This may limit what can be learned about delirium from large population-based cancer databases, where sensitivity analyses would be important to determine the potential impact of underrecognition or misclassification.

In addition to provider assessments of delirium in patients with cancer, family caregiver perspectives outside the formal clinic environment may provide unique information on delirium symptoms in between visits. In one of the few studies of delirium in cancer outpatients, caregivers of patients with head and neck cancer retrospectively reported higher rates of delirium compared with provider clinical assessments.[5] To incorporate the family perspective, the developers of the CAM created a second delirium screening instrument to be administered by caregivers, the Family-CAM (FAM-CAM).[80] The FAM-CAM has a sensitivity of 86% and a specificity of 98% compared with the CAM and is designed to be used in conjunction with or confirmed by providers. The implementation of the FAM-CAM and other caregiver-based delirium assessment tools to identify delirium in community-dwelling patients with cancer needs to be further investigated.

To fill this gap, researchers need to first determine the true incidence of delirium among patients with cancer in order to identify the extent of the problem. Researchers also need to investigate the optimal screening tool to use in this specific patient population. The CAM has been validated in the inpatient hospital and emergency room settings but additional

studies of the CAM in outpatient cancer treatment centers are needed. Targeted screening and monitoring of high-risk patients for delirium would likely be the optimal approach in outpatient cancer treatment center. The recommended frequency of repeated delirium assessments is also unknown. Once screening for delirium has been performed, oncologists need education and training on how to respond to a positive result to confirm the diagnosis of delirium, to minimize its duration and complications, and to develop a plan to prevent its recurrence. Oncology nurses may be well poised to assist with this effort since nurses have been instrumental in delirium screening and prevention in hospitalized patients through multidisciplinary programs such as the Hospital Elder Life Program.[81] To improve identification of delirium in large cohorts, clinical trials of older patients with cancer should also consider adding an assessment of delirium as a patient-centered adverse event.

6. Gap 5: Too few studies focus on the prevention and treatment of delirium in older adults with cancer

Patients with cancer are at increased risk for delirium compared with those without cancer due to potential direct effects of cancer on the central nervous system from brain metastases or paraneoplastic syndromes, uncontrolled symptoms such as pain, nausea, and constipation, and toxicity from chemotherapy[82] and supportive medication including opiates, benzodiazepines, anti-emetics, diphenhydramine, and corticosteroids. These supportive medications commonly used in cancer care may be of concern in older patients with cancer, who are at higher risk for delirium. Cancer and its treatment may also augment traditional delirium risk factors including multimorbidity, polypharmacy, infections, metabolic derangements, insomnia, and malnutrition. A recent study of geriatric assessment for older patients prior to cancer surgery found that the Charlson Comorbidity Index, the dependence on IADLs, and a history of falls predicted postoperative delirium.[83] Preoperative cognition and severity of the surgical procedure have also been shown to be independent risk factors for postoperative delirium after cancer surgery.[84]

Delirium has been shown to be preventable in 30–40% of cases.[81,85] Several successful strategies for delirium prevention have been developed including the multicomponent non-pharmacologic Hospital Elder Life Program,[81,86] proactive geriatric consultation,[87] and exercise and rehabilitation interventions.[88,89] A recent meta-analysis concluded that multicomponent non-pharmacologic delirium interventions in non-cancer-specific populations were effective.[90]

Despite the advances in delirium prevention in non-cancer settings, studies of delirium prevention in patients with cancer have been limited, and the few interventions studied have not demonstrated efficacy (Table 3). Gagnon and colleagues tested a multicomponent delirium prevention intervention for inpatient hospice patients with terminal cancer.[91] The intervention consisted of a delirium risk assessment, nursing reorientation, and family education about delirium, but it was not effective at decreasing delirium incidence or severity. Hempenius et al. conducted a randomized controlled trial of a geriatric liaison intervention to prevent postoperative delirium after elective surgery for a solid tumor.[92] Again, there was no difference in the incidence of delirium between the intervention and

usual care groups. Concerns have been raised about the potency of the interventions in both of these studies.

To fill this knowledge gap, studies on delirium prevention in older patients with cancer are key since the treatment of delirium after its onset is challenging. The American Geriatrics Society postoperative delirium guideline also emphasizes the importance of delirium prevention.[93] Interventions for randomized clinical trials need to be of adequate potency and the optimal delirium endpoint should be selected carefully to accurately measure hypoactive, hyperactive, and mixed delirium without overweighting agitation. Discussion with stakeholders and pilot studies conducted with multidisciplinary input should be undertaken prior to randomized studies. Pragmatic trials of proven interventions (Table 3) applied to patients with cancer should be considered because the results can potentially be disseminated in real-world oncology settings. However, this trial design may require a large sample size, produce less definitive results, and be significantly influenced by confounding factors. Quality improvement trials studying the incidence of delirium before and after an intervention may be useful for interventions where effectiveness and cost-effectiveness have been established. This type of trial design may produce convincing local evidence but may be susceptible to temporal trends and may not be generalizable to other settings. Furthermore, studies on how to optimize oncologic supportive medications in older adults to minimize delirium are needed to develop more specific evidence-based guidelines.

Once delirium has occurred, management commonly begins with an evaluation of potential precipitating and aggravating factors and correction of any modifiable risk factors to minimize complications and the duration of symptoms. Pharmacologic treatment for hyperactive delirium such as haloperidol or atypical antipsychotics may be necessary if non-pharmacologic strategies for agitation are not sufficient. Older patients are more susceptible to side effects from antipsychotics and patients with cancer may have numerous comorbidities and potential drug interactions to consider as well. As with delirium screening and prevention, studies of pharmacologic treatments for delirium specifically in patients with cancer are few and sample sizes have been small.[94] To better understand how to treat delirium in older patients with cancer, qualitative studies to address barriers and challenges to implementing behavioral and pharmacologic treatments for delirium in oncology are needed. The development of effective education and training materials on delirium treatment for oncologists and studies of the feasibility of implementing proven treatment approaches in an oncology setting will help advance our ability to decrease the burden of delirium on patients with cancer.

7. Conclusion

With the growing aging population, the number of older adults with both cancer and cognitive impairment is predicted to increase. The major challenge faced by health care providers will be the optimal way to both address and manage these co-existing conditions. Decision making and interventions will ultimately be best facilitated by early identification of cognitive impairment. Finally, further research is needed to determine how best to identify and monitor these conditions and understand the ways in which cancer-related and quality-of-life outcomes are impacted. Included in Table 4 is a summary of key research priorities

that will enable health care providers to better understand the implications of comorbid cognitive dysfunction and cancer in elderly patients.

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Table 1

Case study.

Case	Mr. HF is a 70-year-old Caucasian man with a 50-pack-year smoking history and past medical history of hypertension and hyperlipidemia. He was diagnosed with metastatic lung cancer to the bone after presenting with a progressive mild cough over the course of 2 months. Imaging revealed a large right-middle-lobe lung mass measuring 4 cm, with associated mediastinal lymphadenopathy. Bronchoscopy was performed soon thereafter, confirming the diagnosis of non-small cell adenocarcinoma, EGFR/ALK non-mutated. PET-CT demonstrated multiple bone lesions consistent with metastatic involvement. On initial evaluation by his medical oncologist to consider treatment options, he reported that apart from mild cough, he felt very well. His medical comorbidities of hypertension and hyperlipidemia were well managed for a number of years with medications. He was formerly employed as an attorney and had been retired for the past 15 years. He was accompanied to his appointment by his daughter but stated that he lived alone since losing his wife to a sudden heart attack 1 year prior. He noted that he was doing well in the adjustment period of living alone, taking care of his house, grocery shopping, preparing his own meals, and spending much of his free time with his young grandchildren who lived nearby and also volunteering his time at a free legal clinic in his community. He denied any feeling of sadness or anxiety. Upon further probing, his daughter did express that her father had periodic issues with his memory at time, such as social plans they made together. Lately, he also had been requesting her oversight in paying bills and managing his finances. After further discussion, the plan was to start him on first-line systemic therapy with doublet therapy that included carboplatin/pemetrexed. Two weeks after receiving his first cycle of treatment, he was brought to the emergency room (ER) by his daughter for evaluation of new onset confusion and difficulty performing even simple activities of daily living (bathing, feeding himself, etc). He had noted disturbances in his sleep pattern 1 week prior and had been taking lorazepam to help him fall asleep. His daughter was uncertain but believed he has been taking lorazepam regularly. In the ER, he was alert and oriented only to his name and was unsure of time or place. He was slightly agitated and combative when physical exam was attempted. Vital signs were within normal limits. MRI of the brain was performed revealing no abnormalities. Labs (including complete metabolic panel, B12, folic acid, TSH) revealed no abnormalities.
Questions	What other assessments could have taken place at his initial evaluation, prior to starting treatment (*GAP 1*)? What does an abnormal screening test of cognitive impairment mean in this patient population and what are the implications in treatment decision making (*GAP 2*)? *GAP 1: The optimal way of identifying and measuring pre-existing cognitive impairment in older adults with cancer is not known.* *GAP 3: There are no standard procedures to manage abnormal cognitive screening test results that are found during research studies.* What is known about the patterns of cancer care for patients with cognitive impairment? (*GAP 2*) *GAP 2: The impact of underlying cognitive impairment on cancer care is unclear.* Are there any risk factors for the development of delirium and should routine screening be done (*GAP 4*)? Are there ways to treat or prevent delirium in older adults with cancer (*GAP5*)? *GAP 4: Patients with cancer are not routinely screened for delirium.* *GAP 5:There are too few studies focus on the prevention and treatment of delirium in older adults with cancer.*

Table 2

Definitions of cognitive impairment syndromes.

Term	Diagnostic criteria	Source
Age-associated memory impairment	Subjective and objective memory impairment compared with that of a young adult	Crook et al. [95]
Benign senescent forgetfulness	Complaints of memory	Kral et al.[96]
Age-related cognitive decline	Objective decline in cognitive function not otherwise specified	DSM 5[13,60,97]
Aging-associated cognitive decline	Age-adjusted impairment in any cognitive task	Levy et al.[98]
Mild neurocognitive decline	Impairments in memory, learning, perceptual-motor, linguistic, or executive functioning	DSM V[13,97]
Mild cognitive decline	Impairment in cognitive tests of learning, concentration or memory secondary to a defined illness	ICD-10[76]
Mild cognitive impairment	Subjective and objective memory impairment in the absence of dementia adjusted for age and education	Peterson et al.[99]
Cognitive impairment—no dementia	Impairments in memory, learning, perceptual-motor, linguistic, or executive function in the absence of clinically diagnosed dementia	Graham et al. [100]
Delirium	Acute and fluctuating impairments inattention and global cognitive functioning	DSM 5[60]

Table 3

Delirium risk factor identification and prevention studies in (A) cancer-specific and (B) non-cancer-specific populations.

Study	Study population	Intervention	Delirium measure	Outcome	Comments
(A) Cancer-specific studies					
Delirium risk factor identification: Korc-Grodzicki et al.[83] (retrospective single-center cohort study)	416 patients aged ≥75 years undergoing major surgery for a solid tumor in the US. Median age, 80 years (range 75–98 years).	Preoperative geriatric assessment	Confusion Assessment Method (CAM)[75]	Postoperative delirium identified in 19% of patients. Delirium associated with the Charlson Comorbidity Index (adjusted OR = 1.82, 95% CI = 1.05–3.15) and IADL dependence (adjusted OR = 2.07, 95% CI = 1.18–3.64).	Geriatric assessment may be a useful tool to identify patients with cancer at high risk for postoperative delirium for future delirium prevention trials.
Delirium risk factor identification: Hempenius et al. [84] (retrospective multicenter observational study)	251 patients aged >65 years undergoing elective surgery for a solid tumor in the Netherlands. Mean age (SD): 74.2 (6.4) years.	Preoperative Groningen Frailty Indicator (GFI)[101]	Inouye chart-based delirium instrument[79]	Postoperative delirium identified in 18.3% of patients. Delirium associated with preoperative GFI cognitive functioning (adjusted OR = 23.36, 95% CI = 5.33–102.36) and severity of surgery (intermediate surgery OR = 15.44, 95% CI = 1.70–140.18; major surgery adjusted OR = 45.01, 95% CI = 5.22–387.87).	Preoperative cognition and severity of surgery are important delirium risk factors and may be useful to identify high-risk patients for future trials.
Delirium prevention: Gagnon et al. [91] (nonrandomized multicenter trial)	1,516 patients with cancer residing in 7 Canadian palliative care units. Mean age (SD): 67.6 (13) years intervention group vs 69.1 (12.9) years usual care group.	Multicomponent preventive intervention (nurse identification of delirium risk factors, patient and family delirium symptom education, routine patient reorientation) vs usual care	Confusion Rating Scale (CRS) [102]	Incidence of delirium was 49.1% in the intervention arm vs 43.9% in the usual care arm ($p = 0.045$). After controlling for confounders, there was no difference in incident delirium ($p = 0.66$).	Delirium prevention intervention may have lacked potency.
Delirium prevention: Hempenius et al. [92] (multicenter randomized controlled trial)	251 patients age >65 years undergoing elective surgery for solid tumor in the Netherlands. Mean age (SD): 77.45 (6.72) years intervention group vs 77.63 (7.69)	Geriatric liaison intervention (preoperative geriatric consultation with individualized treatment plan, daily geriatric nurse visits during admission) vs usual care	Delirium Observation Scale (DOS) [103]	Postoperative delirium identified in 11.9% of patients. No difference in the incidence of delirium in the intervention	Delirium prevention intervention may have lacked potency.

Study	Study population	Intervention	Delirium measure	Outcome	Comments
	years usual care group			group (9.4%) vs the usual care group (14.3%), OR = 0.63, 95% CI = 0.29–1.35.	
(B) Non-cancer-specific studies					
Delirium prevention: Inouye et al. [81] (single-center matched controlled trial)	852 hospitalized general medicine patients in the US. Mean age (SD): 79.6 (6.1) years intervention group vs 79.8 (6.2) years usual care group; 3% with cancer.	Multicomponent preventive intervention—Hospital Elder Life Program (interdisciplinary standardized management of six delirium risk factors: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, dehydration) vs usual care	CAM	9.9% of the intervention group developed delirium vs 15.0% of the usual care group (matched OR = 0.60, 95% CI = 0.39–0.92). Once delirium occurred, there was no difference in the severity of delirium or recurrence.	Studies that adapt this efficacious multicomponent intervention to cancer populations are needed.
Delirium prevention: Marcantonio et al. [87] (single-center randomized trial)	126 patients aged ≥65 years admitted emergently for surgical repair of hip fracture in the US. Mean age (SD): 79 (8) years.	Proactive geriatrics consultation (daily visits with targeted recommendations per structured protocol) vs usual care	CAM	Postoperative delirium occurred in 32% of intervention patients vs 50% of usual care patients (RR = 0.64, 95% CI = 0.37–0.98).	The efficacy of proactive geriatrics consultation should also be studied in hospitalized and community-dwelling patients with cancer.
Delirium prevention: Caplan et al. [88] (randomized controlled trial)	104 Australian hospitalized patients referred for geriatric rehabilitation randomized to home rehab (early discharge) vs hospital rehab. Mean age (SD): 83.9 (7.8) years home rehab vs 84.0 (7.0) years hospital rehab.	Home rehab (multidisciplinary outreach team including nurses, physical therapists, occupational therapists, and providers plus an acute admission substitution service) vs hospital rehab (geriatric rehab ward care)	CAM	Home rehab group had lower odds of developing delirium (OR = 0.17, 95% CI = 0.03–0.65) and shorter duration of rehab (15.97 vs 23.09 days, p = 0.0164).	The home-based rehab intervention is a valuable example of decreasing delirium risk in the outpatient setting. Potential applications of this intervention to outpatient cancer care should be studied.

Table 4

Summary of key research priorities to better understand cognition in older patients with cancer.

1. Define the optimal way to identify and measure pre-existing cognitive impairment in older patients with cancer.
a. Cognitive assessment tools should be utilized both in clinical practice and in research studies to screen for baseline impairments and assess cognitive capacity. Abnormal scores warrant a comprehensive evaluation.
b. More observational and registry studies are needed to better estimate the prevalence and incidence of dementia and cognitive impairment in patients with cancer.
2. Conduct further studies on the impact of pre-existing cognitive impairment or dementia on cancer treatment and toxicity, hospitalization, post-treatment surveillance, and cancer recurrence.
3. Develop a standardized framework on how to manage abnormal cognitive screening results performed for research purposes.
a. Standardized framework should include guidelines on obtaining patient preferences for disclosure of abnormal test results at study enrollment, threshold of clinically significant cognitive impairment, when to disclose abnormal results and to whom.
a. Improve detection of delirium in older patients with cancer with improved screening and monitoring of high-risk patients in the outpatient setting, and improved screening and monitoring of all older patients in inpatient settings. Delirium screening tools need to be studied in community-dwelling patients with cancer to better estimate the incidence of delirium during cancer treatment.
b. Family caregiver reported outcomes may provide unique information on delirium symptoms in between clinical assessments.
c. Improved methods to assess delirium risk in patients with cancer.
4. Conduct more studies focused on the prevention and treatment of delirium in older patients with cancer.
a. Delirium interventions for randomized controlled trials need to be of adequate potency and require stakeholder and multidisciplinary input.