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OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary

Risk Assessment Tools for Adult Cancer Patients Undergoing Chemotherapy

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BACKGROUND

Approximately 60 percent of new cases and 70 percent of mortality from cancer occur in patients ≥65 years of age (SEER Cancer Statistics Review: 1975-2000). As a result, the care of older patients constitutes an important part of the everyday practice for the adult oncologist. Despite the high incidence of cancer in this group, older patients have been underrepresented in clinical trials that set the standards for care in oncology practice (Hutchins 1999, Yee 2003, Trimble 1994). Less data exist regarding the risks and benefits of cancer treatment in this population, and there are few guidelines that specifically address the evaluation and treatment of the older patient. Older patients are less likely to receive all types of standard cancer therapies compared to younger individuals (Christman 1992, Hurria 2003, Mandelblatt 2000, Newcomb 1993, Schrag 2001). Possible reasons include concerns regarding increased toxicity, competing causes of morbidity and mortality, lack of access to care, and physician or patient preference. Information about specific issues may guide interventions that can improve the ability to undergo cancer treatment.

ASK THE QUESTION

Question 1: In elderly cancer patients (>/= 65 years) undergoing chemotherapy, what assessment tool is most valid for identifying high risk patients (i.e. high cost, cancer recurrence, mortality)?

SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, Cochrane Database of Systematic Reviews, PsycINFO, and National Guideline Clearinghouse, also looked at references and citing articles

Ovid MEDLINE search strategy included:
1 cancer.mp. or exp Neoplasms/ (1763645)
2 chemotherapy.mp. (232147)
3 ((((high adj3 risk) or high) adj3 cost) or mortality).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (414106)
4 patient outcome assessment/ (2270)
5 assessment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (774658)
6 4 or 5 (774658)

7 ((((older adj1 adult*) or older) adj1 patient*) or elderly or geriatric).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (174520)
8 1 and 2 and 3 and 6 and 7 (109)
9 limit 8 to yr="2006 -Current" (88)

Cochrane Database of Systematic Reviews search strategy included:
1 (assessment or screening).mp. [mp=title, abstract, full text, keywords, caption text] (9042)
2 chemotherapy.mp. (962)
3 (elderly or geriatric or geriatrics or older adult or older pateitn).ti,ab,kw. (106)
4 (cancer or neoplasm or neoplasms or metastatic).ti,ab,kw. (1033)
5 1 and 2 and 3 and 4 (9)
6 limit 5 to last 10 years (8)

PsycINFO search strategy included:
1 chemotherapy.mp. (4966)
2 exp Measurement/ (304737)
3 (elderly or geriatric or geriatrics or older adult or older patient).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (78945)
4 (cancer or neoplasm or neoplasms or metastatic).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (55353)

5 1 and 2 and 3 and 4 (6)
6 limit 5 to yr="2006 -Current" (6)

Filters/limits included research articles published in English in the last 10 years

CRITICALLY ANALYZE THE EVIDENCE

The literature search did not result in any articles focused on the outcomes of cost or cancer recurrence. Of the seven relevant studies identified, six of them evaluated the ability of the Comprehensive Geriatric Assessment (CGA) to predict mortality.

The CGA is defined as a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional limitations of a frail older person in order to develop a coordinated plan to maximize overall health with aging (Stuck 1993, Devons 2002). The CGA is an in-depth, multidimensional evaluation that provides the clinician with information on a patient's life expectancy, risk of morbidity, physiological age and overall health (Min 2006). Although the CGA was not originally intended for use in an oncologic population (Reuben 1995), this tool's ability to disclose information related to a patient's underlying disease processes and other age-related factors, may allow oncologists to foresee how cancer care can be complicated due to certain age-related factors (Elsawy 2011). These factors include a patient's functional capacity, polypharmacy, nutritional status, cognitive function, geriatric syndromes and comorbidities (Elsawy 2011).

The typical domains of a CGA include evaluations of functional status, comorbid medical conditions, cognitive status, psychological state, social support, nutritional status, and a review of the medication list. Consensus guidelines from both the National Comprehensive Cancer Network (NCCN) and the International Society for Geriatric Oncology (SIOG) recommend the routine use of a geriatric assessment for the older patient with cancer (defined as age 65 or older) (Hung 2013, Siu 1996). However, although a CGA is helpful for physicians to develop a coordinated plan for cancer treatment and to guide appropriate interventions for specific problems, it can be time consuming and may not be practical for all patients.

CGA Domains Most Predictive of Cancer Outcomes:

A systematic review (Ramjuan 2013), and a prospective observational study (Aaldriks 2016) sought to identify CGA domains most predictive of important cancer-specific outcomes. In predicting mortality, the systematic review found that all domains of the CGA were significant. Most frequently, however, **the following domains were reported for predicting mortality**: **nutritional status** (HR = 1.84–

2.54), **the presence of geriatric syndromes such as depression** (HR = 1.51–1.81), **and functional status** (HR = 1.04–1.33). With regards to chemotherapy-related toxicity, similar findings were obtained where functional status (OR = 1.71–2.47) and the presence of geriatric syndromes, such as impaired hearing (OR = 1.67, 95% CI 1.04–2.69), had the most significant predictive value. Only one study reported on the incidence of post-operative complications for which **severe comorbidity was found to be highly associated with experiencing severe complications** (OR = 5.62, 95% CI 2.18–14.50), while **functional status was found to be significantly associated with experiencing any complication** (OR = 4.02, 95% CI 1.24–13.09) (Ramjuan 2013). The results of this review indicate that **certain CGA domains, such as nutrition, functional status and the presence of geriatric syndromes, may play a particularly important role in predicting adverse events**, including treatment-related toxicity and death.

A prospective observational study (Aaldriks 2016) found that **two items of the Mini Nutritional Assessment (MNA) and one of the Groningen Frailty Indicator (GFI) ('declining food intake in past 3 months', 'using > 3 prescript drugs', and 'dependence in shopping') independently predicted for mortality**. In comparison with patients without any positive item on the three-item GPI, patients with one, two or three positive items had hazard ratios (HRs) of 1.58, 2.32, and 5.58, respectively (all $p < 0.001$) (Aaldriks 2016). This study concludes that **time saving could be accomplished by identifying those individual items that classify elderly cancer patients at risk for feasibility of chemotherapy and for mortality**. These findings suggest that with only three items of the MNA, feasibility of chemotherapy can be predicted, and the three-item GPI may help to identify elderly cancer patients at elevated risk for mortality.

Four studies tested the ability of the CGA to predict important cancer-related outcomes in specific populations. The studies are summarized below:

Hematological Malignancies:

A systematic review attempting to assemble available evidence on the relevance of a geriatric assessment in the treatment of older patients with hematological malignancies found that geriatric impairments were associated with a shorter overall survival in a relevant proportion of studies (instrumental activities 55%, nutritional status 67%, cognitive capacities 83%, objectively measured physical capacity 100%). Comorbidity, physical capacity and nutritional status retained their significance even in multivariate analyses in 50%, 75%, and 67% of analyses respectively, whereas age and performance status lost their predictive value in most studies (Hamaker 2014) .This review demonstrates that a geriatric assessment can detect multiple health issues, even in patients with good performance status. Impairments in geriatric domains appear to have predictive value for mortality.

Solid Malignancies:

A systematic review focused on current literature regarding CGA in elderly patients with solid malignancies who receive chemotherapy, revealed: (i) up to 64% of elderly patients suffer from severe toxicity caused by polychemotherapy, (ii) **nutritional status, functionality**

and comorbidity are often associated with worse outcome, (iii) CGA reveals (unknown) geriatric problems in more than 50% of elderly patients with cancer and (iv) 21%–53% of chemotherapy regimens are being modified based on CGA (Versteeg 2014). The review concluded that the value of CGA in predicting toxicity and mortality in older patients with cancer undergoing treatment with chemotherapy has not been proven. It may be valuable in revealing geriatric problems, but current evidence for its usefulness to guide treatment decisions in patients with solid malignancies is limited.

Non-Hodgkin Lymphoma (NHL):

A small prospective observational study of 44 cancer patients with NHL evaluated whether a CGA, in addition to the age-adjusted International Prognostic Index, is of additional prognostic value. The study found that **abnormal MNA and GFI scores and low hemoglobin level were associated with not being able to complete the intended chemotherapy**: odds ratio (OR) 8.29 (95% [CI]: 1.24 – 55.6; p = 0.03), 9.17 (95% CI: 1.51 – 55.8; p = 0.02) and 5.41 (95% CI: 0.99 – 29.8; p = 0.05). **Frailty by GFI and low hemoglobin were associated with worse survival**, with a hazard ratio (HR) of mortality of 2.55 (95% CI: 1.07 – 6.10; p = 0.04) and 4.90 (95% CI: 1.76 – 13.7; p = 0.002), respectively (Aaldriks 2015).

Breast Cancer:

A small prospective observational study of 55 elderly patients with advanced breast cancer evaluated the prognostic value CGA, and found that **inferior MNA and GFI scores were associated with increased hazard ratios for mortality**: 3.05 (95% confidence interval [CI]: 1.44-6.45; p = 0.004) and 3.40 (95% CI:1.62-7.10; p = 0.001), respectively. Physical aspects of frailty worsened during the course of chemotherapy. **Laboratory values were not associated with assessment scores nor were they predictive for mortality** (Aaldriks 2013).

Aside from the CGA, one other risk prediction tool was identified in the literature. A larger prospective observational study of 160 elderly patients with inoperable or metastatic solid cancer, tested the Multidimensional Prognostic Index (MPI). It found that **increasing mortality rates after 6 and 12 months of follow-up coincided with higher MPI scores**. The MPI-related hazard ratios were higher at 6 months of follow-up than at 12 months, a high MPI being associated with a HR of 8.09 (95% CI = 3.75–17.48, p < 0.001) at 6 months as opposed to 5.66 (95%CI = 2.87–11.16, p < 0.001) at 12 months.

Conclusion: Overall, there is moderate quality evidence to support using CGA, or components of CGA, for disclosing important cancer-specific outcomes.

PICO Question 1: In elderly cancer patients (>/= 65 years) undergoing chemotherapy, what assessment tool is most valid for identifying high risk patients (i.e. high cost, cancer recurrence, mortality)?	Lower Quality Rating if: ☒ Studies inconsistent

Author/Date/ Journal	*Purpose of Study*	*Study Design*	*Sample& Setting*	*Outcomes*	*Design Limitations*	(*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)* ☐ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)* Increase Quality Rating if: ☐ Large Effect Level of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low
Aaldriks et al, 2016, *Acta Oncologica*	To identify individual items in the CGA that classify elderly cancer patients at risk for feasibility of chemotherapy and for mortality	Prospective observational study Patients older than 70 years of age were assessed before the first chemotherapy administration. GA consisted of the Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State Examination (MMSE). Predictive individual items for feasibility of chemotherapy and mortality were entered in the multivariable logistic regression and Cox-regression models, and a three-item sum scale was constructed: the Geriatric Prognostic Index (GPI).	494 elderly cancer patients	Two items of the MNA and one of the GFI (‘ declining food intake in past 3 months ’ , ‘ using > 3 prescript drugs ’ , and ‘ dependence in shopping ’) independently predicted for mortality. In comparison with patients without any positive item on the three-item GPI, patients with one, two or three positive items had hazard ratios (HRs) of 1.58, 2.32, and 5.58, respectively (all p < 0.001).	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☒ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Aaldriks et al, 2015, *Leukemia and Lymphoma*	Investigate whether a geriatric assessment (GA), in addition to the age-adjusted International Prognostic Index, is of additional prognostic value in non-Hodgkin	Prospective observational study GA was administered before the start of chemotherapy. GA was composed of the Mini Nutritional Assessment (MNA), Groningen Frailty	44 patients aged 70 years or older with NHL receiving rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)	abnormal MNA and GFI scores and low hemoglobin level were associated with not being able to complete the intended chemotherapy: odds ratio (OR) 8.29 (95% [CI]: 1.24 – 55.6; *p* = 0.03), 9.17 (95% CI: 1.51 – 55.8; *p* = 0.02) and 5.41 (95% CI:	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not	

	lymphoma	Indicator (GFI), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Mini Mental State Examination (MMSE) and levels of albumin, creatinine, lactate dehydrogenase (LDH) and hemoglobin		0.99 – 29.8; *p* = 0.05) frailty by GFI and low hemoglobin were associated with worse survival, with a hazard ratio (HR) of mortality of 2.55 (95% CI: 1.07 – 6.10; p = 0.04) and 4.90 (95% CI: 1.76 – 13.7; p = 0.002), respectively	representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☒ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Aaldriks et al, 2013, *Breast*	To evaluate the prognostic value of geriatric assessment in older patients with breast cancer treated with chemotherapy	Prospective observational study Patients were Assessed by Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State Examination (MMSE). Levels of albumin, hemoglobin, creatinine and lactate dehydrogenase were measured	Fifty-five patients with advanced breast cancer aged 70 years or older	Inferior MNA and GFI scores were associated with increased hazard ratios for mortality: 3.05 (95% confidence interval [CI]: 1.44-6.45; p = 0.004) and 3.40 (95% CI: 1.62-7.10; p = 0.001), respectively. Physical aspects of frailty worsened during the course of chemotherapy. Laboratory values were not associated with assessment scores nor were they predictive for mortality	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☒ For prognostic study, sample not defined at common point in course of disease/condition	

					☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Hamaker et al, 2014, *Leukemia Research*	Assemble all available evidence on the relevance of a geriatric assessment in the treatment of older patients with haematological malignancies	Systematic Review	15 studies in which a geriatric assessment was used to detect health issues or to address the association between baseline geriatric assessment and outcome	Geriatric impairments were associated with a shorter overall survival in a relevant proportion of studies (instrumental activities 55%, nutritional status 67%, cognitive capacities 83%, objectively measured physical capacity 100%). Comorbidity, physical capacity and nutritional status retained their significance even in multivariate analyses in 50%, 75%, and 67% of analyses respectively, whereas age and performance status lost their predictive value in most studies. One study found an association between comorbidity and chemotherapy-related non-haematological toxicity. In another study a pronounced association between summarised outcome of geriatric assessment and chemotherapy-related toxicity as well as response to treatment was described	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Giantin et al, 2013, *Journal of Geriatric Oncology*	Test the Multidimensional Prognostic Index (MPI) in elderly cancer patients with locally	Prospective observational study	160 patients ≥70 years with inoperable or metastatic solid cancer consecutively	Increasing mortality rates after 6 and 12 months of follow-up coincided with higher MPI scores	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional,***	

	advanced or metastatic disease		admitted to Program of Geriatric Oncology in Padove, Italy and assessed by a multidisciplinary team and received a basal CGA to calculate the MPI score	The MPI-related hazard ratios were higher at 6 months of follow-up than at 12 months, a high MPI being associated with a HR of 8.09 (95% CI = 3.75–17.48, p < 0.001) at 6 months as opposed to 5.66 (95%CI = 2.87–11.16, p < 0.001) at 12 months	***longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☒ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Ramjaun et al, 2013, *Geriatric Oncology*	To identify Comprehensive Geriatric Assessment (CGA) domains most predictive of important cancer-specific outcomes	Systematic Review	9 studies published in English or French between May 1997 and May 2012, in which a CGA was conducted in patients over the age of 65 initiating cancer treatment All studies must have assessed the following: nutritional, cognitive and functional status, polypharmacy,	In predicting mortality all CGA domains were found to be significant. Most frequently, however, the following domains were reported for predicting mortality: nutritional status (HR = 1.84–2.54), the presence of geriatric syndromes such as depression (HR = 1.51–1.81), and functional status (HR = 1.04–1.33). With regards to chemotherapy-related toxicity, similar findings were obtained where functional status (OR = 1.71–2.47) and the	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

			comorbidities and the presence of geriatric syndromes	presence of geriatric syndromes, such as impaired hearing (OR = 1.67, 95% CI 1.04–2.69), had the most significant predictive value. Only one study reported on the incidence of post-operative complications for which severe comorbidity was found to be highly associated with experiencing severe complications (OR = 5.62, 95% CI 2.18–14.50), while functional status was found to be significantly associated with experiencing any complication (OR = 4.02, 95% CI 1.24–13.09).		
Versteeg et al, 2014, *Annals of Oncology*	Summarize current literature that is available on GA in elderly patients with solid malignancies who receive chemotherapy	Systematic Review	13 studies of patients 65 years or older, with a diagnosis of solid malignancy, treated with chemotherapy, submission to GA, either designed to study prediction of treatment toxicity or mortality or to evaluate the role of GA in the decision-making process	The studies revealed: (i) up to 64% of elderly patients suffer from severe toxicity caused by polychemotherapy, (ii) Nutritional status, functionality and comorbidity are often associated with worse outcome, (iii) GA reveals (unknown) geriatric problems in more than 50% of elderly patients with cancer and (iv) 21%–53% of chemotherapy regimens are being modified based on GA	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☒ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.