



# Fighting diagnostic and therapeutic nihilism in the elderly with cancer

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**Abstract:** Palliative care in geriatric cancer patient is a severely under investigated and stigmatized topic. Presumptions and lack of clinical, validated data, lead to a poor or at least not optimal care for this specific and vulnerable population. The nihilism in the field of palliative geronto-oncology is a major contributor to a reduced quality of life among elderly with cancer and their families. Assumptions towards their compliance, accessibility to the treatment and their outcomes often lead to an undertreatment in terms of palliation, which is mostly falsely equalized with end-of-life and hospice care. However, an early palliative management of geriatric patients should always be aimed first—for symptomatic treatment, but also potentially including interventions and active anti-tumor therapies. Nevertheless, gerontopalliation should also assure comfort, closeness, hope and security for relatives. This review illustrates the stand of the knowledge, relevant problems, chances, necessary developments, perspectives and research directions on the area of geriatric palliative care, especially in terms of the outcomes and improved quality of life for this specific population, with applicability for not only oncologists, but any involved physicians, such as internists, palliative and geriatric care specialists. With the rapid progress in precision and personalized medicine, there are new perspectives opening for geriatric cancer patients.

**Keywords:** Palliative care; elderly; cancer; geriatric oncology; geriatric palliation

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## Fighting diagnostic and therapeutic nihilism in the elderly with cancer—why?

### *Geriatric oncology*

Geriatric oncology is a new field of medicine, with a rapidly growing importance, providing designated approaches to elderly oncological patients (1). It is especially aiming at providing a higher quality, both in patients under an active cancer or a palliative treatment. In addition to the

corresponding adaptation of cancer treatment, the targeted treatment of age-related comorbidities is one of important focuses.

Advanced age is the main risk factor for cancer (2,3). Thus, the majority of oncological patients are already older at the time of diagnosis, so that the neoplasm is often not the only disease, but there are various preexisting, usually chronic comorbidities and with varying frequency, polypharmacy, as well as not well treatable problems,

such as sarcopenia, malnutrition due to in appetite or cognitive decline, drowsiness, gait deceleration and social problems, such as loss of independence and participation in life (4). Due to this enormous complexity and the great interindividual variance, caring for older patients with cancer is a challenge in daily practice. In this heterogeneous patient collective, the thoroughly diagnostic work up—including the cancer diagnosis and the age-related changes, the careful selection of therapeutic measures, and adequate concomitant therapy are crucial. Thus, geriatric oncology requires a team work of a multidisciplinary, multi-professional team in various venues, e.g., geriatricians, surgical/medical/radiation oncologists, internists, palliative care specialists at local oncology practices, ambulances, clinics and centers. The goal is to provide recommendations of a therapeutically concept that is individually adapted to the pre-existing conditions and situation of the patient, ensuring a better therapy tolerance and better quality of life during that therapy (5).

Geriatric syndromes in old-age cancer patients are not only to be considered in oncological therapy decisions, but also directed to a targeted management. If a geriatric complex treatment can be realized, functional improvements are expected (6). Thus, despite being there for a short period of time, geriatric oncology data already show that the assessment and subsequent interventions can reduce toxicity and mortality through specific therapy and improve quality of life (7).

#### *Aging and cancer—epidemiology, demography, cancer as disease of old age*

The National Institute on Aging recently described the phenomenon of demographic development as a “silver tsunami”. Approximately 50 % of newly diagnosed cases occur in elderly over 65 years and this percentage is expected to increase to 70% by 2030. Cancer incidence is 12 to 36 times higher in individuals over 65 years of age as compared to younger adults. Despite the high incidence rate in this population, older patients are mostly underrepresented in practice-changing clinical trials (8).

Some specialists claim that if people were to live up to 150 years of age, we would probably almost all get cancer or die due to cancer. The advances of medicine in other fields allow people to reach high age, which has however a positive correlation to cancerogenesis: the constant regeneration of human organism through mitosis and

miosis leads to inevitable mistakes, repair failure and mutations in oncogenes (9,10). With age, the damage accumulates and the body's repair tools lose their effect (11-13). Many cancers never appear clinically and would only be detected on autopsies, e.g., in 100 years old men, 85% have prostate cancer (14). Pre-forms of leukemia are also found in 20 percent of older people (15). Clearly, also the lifestyle (smoking, alcohol, physical inactivity) and the nutrition of the last decades lead to a significant increase in cancer incidence. However, it is crucial to also consider the component of screening and early diagnosis, which improved and is greatly available in developed countries—the relative number of cancer cases may not be objectively higher, but the actual diagnosis number (16-18).

Another theory linking aging and genes is the shortening of telomeres. Shortening of the telomeres could be associated with the aging process (19). In the group of over-60s, those with shorter telomeres were three times more likely to die from heart disease and eight times more likely to die from infectious diseases. Many neoplasms are associated with shortened telomeres, for example in the pancreas, the bones, the prostate and bladder, the lungs, the kidneys, the head and neck (20-22). A common feature of human cancers is the overexpression of telomerase, a ribonucleoprotein complex that is responsible for maintaining the length and integrity of chromosome ends. The extremely hypermitotic cancer cells need this protective mechanism (23,24). A prospective study reported measured telomere length in 787 healthy participants, 92 of which developed cancer within ten years. The cancer rate was 60% higher than the average for those with short telomeres and five times higher than in participants with long telomeres (25).

It was long not known whether telomere shortening is simply a sign of aging or is it actively contributing to the aging process (26). According to the recent research from Australia, it is rather telomeres' health (structure of the DNA segment) than the length (27). Telomeres usually form a loop structure in which the ends of the chromosomes are hidden. As the telomere loops unfold, the end of the chromosome is exposed and the cell perceives it as broken DNA. The telomere loop can only be formed with difficulty by shortening it. While in cancer cells, this can actually be a therapeutic target, since telomeres can alter their structure in response to chemotherapy, making them more susceptible.

Overall, it is most likely that a combination of

**Table 1** List of SIOG guideline and recommendations

Disease	Professional society	Literature
Chronic lymphocytic leukemia	International Society for Geriatric Oncology	Eichhorst <i>et al.</i> 2017
Multiple myeloma	International Myeloma Working Group	Rajkumar <i>et al.</i> 2014
Diffuse large B-cell lymphoma	International Society for Geriatric Oncology	Hamlin <i>et al.</i> 2015
Prostate cancer	International Society for Geriatric Oncology	Albrand <i>et al.</i> 2017
Colorectal cancer	International Society for Geriatric Oncology	Audisio <i>et al.</i> 2015
Lung cancer	European Organization for Research and Treatment of Cancer	Gridelli <i>et al.</i> 2014
Breast cancer	International Society for Geriatric Oncology	Wildiers <i>et al.</i> 2012

various physiological processes contributes to aging and carcinogenesis: oxidative stress, glycation, telomere shortening, and others (12,28).

#### What role does biological age play?

The aspect of biological age is very controversial. It is difficult to set a strict limit to categorize old, oldest old and elderly, since the physiological and mental decline of health is individual (29). While some cases of hardship can be described as retirees with a good conscience, many oldest old patients look and act much less senile than the chronological age indicates.

Partially, the (further below) multi-dimensional geriatric assessment are framing these aspects and help to discriminate between biologically old and still elderly patients. These assessments examine the life situation regardless of age, including mobility, cognition, emotional mood, social environment etc., to be included in the therapy decision.

#### Oldest old—lack of care due to lack of evidence

Oncologists are faced with the challenge of customizing treatment adjustment that would be optimal for each individual older patient, while taking into consideration the heterogeneity of comorbidities, functional status, disabilities and geriatric conditions. This constitutes a barrier of enrollment into RCTs that are mostly performed on middle-aged patients who have just one disease and therefore focus on monopathology. The difficulty of dealing with old patients in trials is mainly attributed to high prevalence of comorbidities and treatment-related toxicity in older population, but also due to a number of ethical issues (free will, informed consent etc.) and drop out or lost-to-follow up rates. As a result, there is limited evidence-

based information as well as inadequate guideline on the risk/benefit ratio that specifically address the evaluation and treatment for elderly (30,31).

Some professional societies have already set up sections dedicated to the needs of older people, which provide a list of tools for physicians to optimize therapy and adjust to patients' wishes and needs, exceeding the purely medical needs. Nevertheless, so far apart from several general recommendations (32,33), there are no stringent guidelines that would support or lead the physicians in their decision making (*Table 1*). This is because most RCT and bigger studies exclude elderly and oldest old patients (34-36). If one transfers these results to old, often chronically ill and multimorbid patients, that is on the one hand often not scientific ally founded and possibly even risky. Due to the poor evidence, there are still no S3 (as it is the case for dementia or diabetes in oldest old patients), albeit they are urgently needed, since the majority of patients are diagnosed with cancer beyond the age of 65 or higher (the age itself is not the crucial point, but rather the comorbidities), while they represent only 36% of RCT participants (37). Since this group is massively underrepresented, subgroup analyzes from larger studies are currently the most powerful evidence, although they cannot answer many questions. In addition, they can only provide answers for a population matching to the included group of patients. This tremendous inadequacy in study situation leads to an inadequate care: old patients receive regimes of anti-tumor therapies without a proper knowledge of the potential multimorbidity-adjusted side effects, whether a dose-adjustment is effective and whether an alternative management would be more beneficial.

Recently, a study of breast cancer patients reports that in fact a lower dosage of cyclophosphamide (plus anti-HER2) are superior to docetaxel in terms of geriatric-oriented

outcomes of ADL (Activities of Daily Living) and IADL (Instrumental ADL). Controversies arise since these end points are not the most valid and representative assessment tools, as well as because the sample only contained 80 patients (38,39).

Another study from the USA confirmed that for most palliative patients (mean age 69), chemotherapy has no discernible influence on risk of death. While for patients with ECOG Performance Status 2 or 3 at baseline, chemotherapy did not bring any quality of life benefits one week before death, for those of ECOG 0 and 1, it significantly worsened the quality of life (40). These findings urge to reconsider the standard treatment advise towards a better balance between the quality and quantity of life in specific patient groups—those who are fit, but approaching death, as not to spend the last weeks or months of a lifetime on largely ineffective therapies and their side effects. As a general timeframe, 6 months prior to death were mentioned (40). The leading physician is however always required to conduct a clear discussion about prognosis, goals, fears and sustainable compromises (41).

#### *Oldest old cancer patients' special needs*

One of the biggest challenges for physicians is to establish a report with the patient and find a difficult balancing act to weigh together carefully what do older patients need to consider when choosing cancer therapies. Concomitant diseases can significantly influence the course of therapy and since the physical conditions in older cancer patients vary greatly, the effect of the medication is much more difficult to predict (42). However, besides of these concerns, frequently, the patients themselves express the desire for age-appropriate or no treatment in order to avoid the renunciation of exhausting therapies. In cases of early diagnoses of slowly growing tumors, e.g., prostate cancer, the decision to refrain from interventions is reasonable (43). In palliative cases, this rationale is not applicable and requires a high level of personalized approach.

Another important element for geriatric cancer patients is the special in- and outpatient care. Most patients require longer and more frequent hospitalizations, leading to decline in cognitive functions, sarcopenia and muscle wasting, logically requiring an intensive follow-up in outpatient setting, including support in everyday life, rehabilitation etc. (44,45). The recovery is usually of a slow progress, so the patients (and caregivers) should be prepared for what to expect after the therapy as to organize support before

the therapy starts. Depression following radical surgeries, such as mastectomy, should also be considered (46).

#### *Clinical challenges and pitfalls in palliative care of geriatric cancer patients*

The public often perceives the value of cancer treatment in terms of survival, yet for geriatric patients, it is necessary to address independence, quality of life and the avoidance of toxic side effects due to the remaining lifetime (32).

Besides of the heterogeneity in old age and difficult decision of an appropriate tumor therapy in old age, further challenging situations that require convincing arguments, are present. When determining a therapy goal, ethical issues and the relevance of preserving of human dignity are arbitrate. Informed consents (ICs) of affected parties are only effective if they meet certain requirements of data protection law. The IC is only effective if the person concerned knows exactly to what he/she agrees to. Especially the voluntary basis must be clearly and understandably explained. It must be pointed out to the person concerned that his/her consent is entirely of free-will, that is why he/she can refuse it or revoke it without implications. In case of geriatric patients, however, this might be problematic to assess to what extent the comprehension of the person concerned can be ensured so that the effectiveness of the consent is guaranteed. Many are simply overwhelmed by the flood of information or are cognitively impaired (which is not always obvious at the consultation). To give consent, patients must have legal and clinical capacity (47-50). Doctors who wish to receive informed consent must be able to provide qualified information and to provide comprehensive information on both the risks and benefits of the intervention and to answer appropriate questions. From an ethical and legal perspective, it is imperative that physicians are committed to ensuring that patients are aware of the current state of health, including the probable course if no treatment is given, potentially helpful treatments, including a description and explanation of the potential risks and benefits, assessment of the doctor about the best alternative etc. Physicians, families, patients, nurses and further health professionals have to be aware of that and have a sufficient ethical competence, as they have to often face autonomy conflict in over- or under-treatment or end-of-life situations, where discontinuing or refraining from therapies is being agreed upon. Single experiences of even somnolent patients receiving chemotherapy, resulting in a temporary bettering and thus a chance for a last farewell,

provide a base for entrusting that not every tumor therapy in palliative stage is futile.

Furthermore, therapy limitation is frequently misunderstood as a complete therapy cessation. However, comfort therapy can also include active substances, such as electrolyte substitution for alleviating thirst, benzodiazepines for anxiety etc. (51).

Last but not least, aged individuals have an already developed individual personality, as well as crystallized their priorities, goals and purposes in life. On this background, it is important to promote the active competence with an affirmative attitude.

Trust of the patient in the physicians aim to seek for the best treatment for him/her, is the cornerstone of a good care. In some patients this might be active cancer treatment, in others the best treatment can be not to provide active cancer treatment. In every patient, standard palliative care should be included in any case.

#### *Undertreatment of geriatric cancer patients*

Despite tremendous advancements in the medical care options, geriatric cancer patients are still not optimally diagnosed and/or treated. This is based—besides of the lack of data as described above—on various preconceptions and mostly the fear (of both patients and physicians) of unwanted side effects of the therapy. Ultimately, the life expectancy of patients is underestimated (52).

Several registry studies confirmed that there is a severe underdiagnosis and undertreatment for this specific population—an almost ironic seeing strong efforts in various disciplines towards choosing wisely and “less is more”.

In colorectal cancer, no or almost no patients over 80 received adjuvant therapy, despite the fact that the life expectancy is higher than time-to-recurrence (53). Newer insights suggest that 5FU-based adjuvant therapies are indeed not beneficial, however, other regiments such as UFT (Tegafur/Uracil) and oral capecitabine were favorable (54-56). An US cohort study actually confirmed that chronic diseases, which are mostly a barrier to application of adjuvant colorectal cancer therapies, are not significant and the adjuvant treatment leads to a better survival (median patients' age 76) (57). This report was contradictory to an earlier study based on a SEER data extraction (58). Thus, some insecurity about of whether to apply standard protocols for geriatric patients is advisable or not, remains controversial. However, one has to consider the rapid progress of treatment management and be critical to studies

from before the last decade. Similar information has been gathered for NSCLC, encouraging clinicians to apply adjuvant chemotherapies in elderly as they have a similar safety profile and lead to a survival benefit (48,59,60). Due to their common co-morbidities, less platinum-based regimens are used, but fit patients may also receive a standard regimen adapted to their kidney function. The additional administration of bevacizumab has similar advantages in the elderly patients as in the younger ones in both tumor entities, when considering patients included into clinical trials (61-63).

#### **Fighting diagnostic and therapeutic nihilism in the elderly with cancer—how to?**

##### *Early and late onset palliative care*

A significant feature of this specific discipline is that it provides a venue for doctors to discuss patient's preference and treatment goal so that the treatment plan reflects these essential aspects of care. Palliation is often misunderstood as end-of-life care in terminal phases or as pain/symptom management only. Meanwhile, palliative care, especially in older patients, is aimed to exculpate families or caregivers, as well as in avoid unnecessary hospitalizations.

A recent metanalysis reported an overall benefit in quality of life for cancer patients who are under early palliative care treatment, despite an increased pain occurrence and loss of appetite. There was no impact on depression or survival (64). However, these results need to be validated in a bigger cohort, which is still not available. For a general population (not only geriatric patients), similar outcomes, but including a survival benefit, have been reported in the North America and Belgium (65-67). Some authors claimed that an early palliative intervention is not only beneficial in terms of symptomatic treatment, but actually reduces mortality and morbidity in cancer patients (68,69). Nevertheless, the results have been widely discussed and attention has been pointed to an attentive interpretation of these, because of numerous confounders (70). Oorschot *et al.* recently evaluated the effects of integrated palliative care in newly diagnosed stage 4 pulmonary and GI tumor patients, looking at the change in quality of life, depression score and consulted end-of-life care preferences within 12 and 24 weeks (T2), reporting a clear benefit in all aspects (71). These reports are more imminent based on the fact that for elderly cancer patients, pain management is the cornerstone of palliative care. The Hospitalized Elderly Longitudinal



Project (HELP) showed that one third of patient subjects experienced severe pain in the last months of their lives (72). However, the evaluation of pain has always been and remains a challenge for clinicians due to its both physical and emotional component (73,74). Existing evaluations of pain evaluation are mainly based on patients' self-report, which is particularly problematic in geriatric patients, especially in individuals with cognitive impairment (75-77). Validation of effective pain assessment system relying on behaviors observation is urgently needed (78).

Although elderly account for approximately 50% of all cancer patients, their pain management is often neglected, even in Western countries. A study from Italy analyzed the underlying causes of this neglect, pointing to an underestimation of patients' sensitivity to pain, the overestimation of pain tolerance and their benefit from opioids (79-81).

### **Geriatric assessments**

As mentioned before, most geriatric old tumor patients can benefit from a cytotoxic treatment. The basis for the treatment decision must be scientifically valid and allow to select the appropriate treatment protocols.

Over the last decades, oncologists and geriatricians developed such instruments, which allow to capture comprehensive patient factors to aid in clinical management, individualized intervention plan, and optimized decision-making process—geriatric assessments. Therefore, we can observe an increasing call of experts for a new concept for the integration of these simple tools in order to assess the geriatric risk profile of the patients.

The cancer-specific geriatric assessments evaluate the individual's functional status, comorbidities, cognition, psychological status, social functioning, support, and nutritional status. Information gained serves as the basis for treatment planning and anticipating the possible consequences of cancer and its treatment on an older adult cancer survivor (31,32,82).

One study conducted a comparison of the G8 and Triage Risk Screening Tool (fTRST).

In patients  $\geq 70$  years of age with a newly diagnosed malignancy. Both scales showed a high sensitivity (86.5% to 91.3%), moderate negative predictive value (61.3% to 63.4%) and strong prognostic value for functional decline on ADL and IADL, and the OS. They are simple and useful instruments in older patients with cancer for identifying patients with a and have a strong prognostic value for functional decline and OS (83).

CRASH study provided further insights assessments of this specific population. It identified several predictors, such as hemoglobin, creatinine clearance, self-esteem for one's own health, the CIRS-G-index for the cancer stage and comorbidities, the performance, the Mini-Mental Status Examination (MMSE), the Mini Nutritional Assessment (MNA) for non-hematologic toxicity and albumin, LDH and diastolic blood pressure for hematological toxicity (84).

Applying geriatric assessments has already been recommended by national and international professional societies in order to identify deficiencies and plan targeted support, as well as to ensure better compliance.

A further focus is on cross-sectorial collaboration, so that the patient can follow on a competent outpatient care after inpatient therapy.

Current research focus on the approach to base interventions on the results of geriatric assessment, which is standard in general geriatric medicine, however not yet in geriatric oncology. Currently at least four RCTs are on the way to demonstrate, that geriatric assessment based geriatric interventions improve outcome in elderly cancer patients.

### **Conclusions and perspectives**

While ageism is still one of the main reasons for discrimination of geriatric patients, there is a need for an increasing awareness of geriatric oncology among patients and health professionals. Special divisions of palliative care need to be understood as centers for more than end-of-life and hospice care. Especially early palliative management of geriatric patients should aim to relieve physical and psychological symptoms, while also providing closeness, hope, security and comfort for relatives. Symptomatic treatment might include interventions and active anti-tumor therapies. The individual assessments of risks and benefits, as well as a considerate judgment and integration of patient's wishes should be prioritized in decision making. Sometimes, advocacy can improve life (quality over quantity) and appropriate training should be offered to crucial actors, also with regards to their interactions and team work (nurses, palliative/oncology/internal medicine/GP/geriatrics health professionals, caregivers etc.) With the rapid progress in precision and personalized medicine, there are new perspectives opening for geriatric cancer patients.

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## References

- Magnuson A, Dale W, Mohile S. Models of Care in Geriatric Oncology. *Curr Geriatr Rep* 2014;3:182-9.
- Mazzola P, Radhi S, Mirandola L, et al. Aging, cancer, and cancer vaccines. *Immun Ageing* 2012;9:4.
- Harman D. The aging process: major risk factor for disease and death. *Proc Natl Acad Sci U S A* 1991;88:5360-3.
- Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol* 2013;75:685-705.
- Wedding U. Geriatric oncology. *Z Gerontol Geriatr* 2019;52:75-86.
- Colditz GA, Wei EK. Preventability of Cancer: The Relative Contributions of Biologic and Social and Physical Environmental Determinants of Cancer Mortality. *Annu Rev Public Health* 2012;33:137-56.
- Magnuson A, Allore H, Cohen HJ, et al. Geriatric assessment with management in cancer care: Current evidence and potential mechanisms for future research. *J Geriatr Oncol* 2016;7:242-8.
- White MC, Holman DM, Boehm JE, et al. Age and cancer risk: a potentially modifiable relationship. *Am J Prev Med* 2014;46:S7-15.
- DeGregori J. Challenging the axiom: Does the occurrence of oncogenic mutations truly limit cancer development with age. *Oncogene* 2013;32:1869-75.
- Finkel T, Serrano M, Blasco MA. The common biology of cancer and ageing. *Nature* 2007;448:767-74.
- Andersen SL, Terry DE, Wilcox MA, et al. Cancer in the oldest old. *Mech Ageing Dev* 2005;126:263-267.
- Vijg J, Suh Y. Genome Instability and Aging. *Annu Rev Physiol* 2013;75:645-68.
- Maslov AY, Vijg J. Genome instability, cancer and aging. *Biochim Biophys Acta* 2009;1790:963-9.
- Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. *N Engl J Med* 2009;360:1310-9.
- Gandjour A, Greb J, Bomsdorf E, et al. Impact of demographic changes on healthcare expenditures and funding in the EU. *Appl Health Econ Health Policy* 2005;4:1-4.
- Belpomme D, Irigaray P, Sasco AJ, et al. The growing incidence of cancer: Role of lifestyle and screening detection (Review). *Int J Oncol* 2007;30:1037-49.
- Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. *Lancet* 2019;393:169-82.
- Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998-2005.
- Calado RT, Young NS. Telomere Diseases. *N Engl J Med* 2009;361:2353-65.
- Rudolph KL, Chang S, Lee HW, et al. Longevity, stress response, and cancer in aging telomerase-deficient mice. *Cell* 1999;96:701-12.
- Chin K, de Solorzano CO, Knowles D, et al. In situ analyses of genome instability in breast cancer. *Nat Genet* 2004;36:984-8.
- McGrath M, Wong JYY, Michaud D, Telomere Length, Cigarette Smoking, and Bladder Cancer Risk in Men and Women. *Cancer Epidemiol Biomarkers Prev* 2007;16:815-9.
- Shay JW, Wright WE. Role of telomeres and telomerase in cancer. *Semin. Cancer Biol* 2011;21:349-53.
- Artandi SE, DePinho RA. Telomeres and telomerase in cancer. *Carcinogenesis* 2010;31:9-18.

25. Willeit P, Willeit J, Mayr A, et al. Telomere Length and Risk of Incident Cancer and Cancer Mortality. *JAMA* 2010;304:69.
26. Wu X, Amos CI, Zhu Y, et al. Telomere dysfunction: a potential cancer predisposition factor. *J Natl Cancer Inst* 2003;95:1211-8.
27. Van Ly D, Low RRJ, Frölich S, et al. Telomere Loop Dynamics in Chromosome End Protection. *Mol Cell* 2018;71:510-25.e6.
28. Tallen G, Soliman MA, Riabowol K. The cancer-aging interface and the significance of telomere dynamics in cancer therapy. *Rejuvenation Res* 2007;10:387-95.
29. Sehl M, Sawhney R, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part II. *Cancer J* 2005;11:461-73.
30. Lichtman SM. Guidelines for the treatment of elderly cancer patients. *Cancer Control* 2003;10:445-53.
31. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011;29:3457-65.
32. Wildiers H, Heeren P, Puts M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595-603.
33. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: An update on SIOG recommendations. *Ann Oncol* 2015;26:288-300.
34. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of Patients 65 Years of Age or Older in Cancer-Treatment Trials. *N Engl J Med* 1999;341:2061-7.
35. Trimble EL, Carter CL, Cain D, et al. Representation of older patients in cancer treatment trials. *Cancer* 1994;74:2208-14.
36. Yee KWL, Pater JL, Pho L, et al. Enrollment of older patients in cancer treatment trials in Canada: Why is age a barrier? *J Clin Oncol* 2003;21:1618-23.
37. Le Saux O, Falandry C, Gan HK, et al. Inclusion of elderly patients in oncology clinical trials. *Ann Oncol* 2016;27:1799-804.
38. Litvak DA, Arora R. Treatment of Elderly Breast Cancer Patients in a Community Hospital Setting. *Arch Surg* 2006;141:985.
39. Geyer CE. Clinical trials in older, less fit populations: an unmet need? *Lancet Oncol* 2018;19:271-2.
40. Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. *JAMA Oncol* 2015;1:778.
41. Biskup E, Cai F, Vetter M, et al. Oncological patients in the intensive care unit: Prognosis, decision-making, therapies and end-of-life care. *Swiss Med Wkly* 2017;147:w14481.
42. Given B, Given CW. Older adults and cancer treatment. *Cancer* 2008;113:3505-11.
43. Foster JA, Salinas GD, Mansell D, et al. How does older age influence oncologists' cancer management? *Oncologist* 2010;15:584-92.
44. van Dam R, Van Ancum JM, Verlaan S, et al. Lower Cognitive Function in Older Patients with Lower Muscle Strength and Muscle Mass. *Dement Geriatr Cogn Disord* 2018;45:243-50.
45. Prado CM, Purcell SA, Alish C, et al. Implications of low muscle mass across the continuum of care: a narrative review. *Ann Med* 2018;50:675-93.
46. Zhang C, Hu G, Biskup E, et al. Depression Induced by Total Mastectomy, Breast Conserving Surgery and Breast Reconstruction: A Systematic Review and Meta-analysis. *World J Surg* 2018;42:2076-85.
47. Miller FG, Joffe S. Evaluating the Therapeutic Misconception. *Kennedy Inst Ethics J* 2006;16:353-66.
48. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: Defining the therapeutic misconception. *PLoS Med* 2007;4:e324.
49. Hougham GW, Sachs GA, Danner D, et al. Empirical Research on Informed Consent with the Cognitively Impaired. *IRB* 2003;25:S26-32.
50. Fields LM, Calvert JD. Informed consent procedures with cognitively impaired patients: A review of ethics and best practices. *Psychiatry Clin Neurosci* 2015;69:462-71.
51. Alexander K, Goldberg J, Korc-Grodzicki B. Palliative Care and Symptom Management in Older Patients with Cancer. *Clin Geriatr Med* 2016;32:45-62.
52. Swaminathan D, Swaminathan V. Geriatric oncology: problems with under-treatment within this population. *Cancer Biol Med* 2015;12:275-83.
53. Potosky AL, Harlan LC, Kaplan RS, et al. Age, Sex, and Racial Differences in the Use of Standard Adjuvant Therapy for Colorectal Cancer. *J Clin Oncol* 2002;20:1192-1202.
54. Yang L, Ma Q, Yu YY, et al. Efficacy of Surgery and Adjuvant Therapy in Older Patients With Colorectal Cancer. *Medicine (Baltimore)* 2014;93:e266.
55. Kahn KL. Adjuvant Chemotherapy Use and Adverse Events Among Older Patients With Stage III Colon Cancer. *JAMA* 2010;303:1037.
56. Yoshitani S, Takashima S. Efficacy of postoperative UFT (Tegafur/Uracil) plus PSK therapies in elderly patients with resected colorectal cancer. *Cancer Biother Radiopharm* 2009;24:35-40.
57. Gross CP, McAvay GJ, Guo Z, et al. The impact of



- chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. *Cancer* 2007;109:2410-9.
58. Yancik R, Wesley MN, Ries LA, et al. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. *Cancer* 1998;82:2123-34.
  59. Cuffe S, Booth CM, Peng Y, et al. Adjuvant chemotherapy for non-small-cell lung cancer in the elderly: a population-based study in Ontario, Canada. *J Clin Oncol* 2012;30:1813-21.
  60. Früh M, Rolland E, Pignon JP, et al. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. *J Clin Oncol* 2008;26:3573-81.
  61. Yoshida M, Muro K, Tsuji A, et al. Combination chemotherapy with bevacizumab and S-1 for elderly patients with metastatic colorectal cancer (BASIC trial). *Eur J Cancer* 2015;51:935-41.
  62. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): An open-label, randomised phase 3 trial. *Lancet Oncol* 2013;14:1077-85.
  63. Leighl NB, Zatloukal P, Mezger J, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). *J Thorac Oncol* 2010;5:1970-6
  64. Haun MW, Estel S, Rücker G, et al. Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev* 2017;6:CD011129.
  65. Vanbutsele G, Pardon K, Van Belle S, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol* 2018;19:394-404.
  66. Dalgaard KM, Bergenholtz H, Nielsen ME, et al. Early integration of palliative care in hospitals: A systematic review on methods, barriers, and outcome. *Palliat Support Care* 2014;12:495-513.
  67. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: A cluster-randomised controlled trial. *Lancet*.2014;383:1721-30.
  68. El-Jawahri A, Greer JA, Temel JS. Does Palliative Care Improve Outcomes for Patients with Incurable Illness? A Review of the Evidence. *J Support Oncol* 2011;9:87-94.
  69. Rocque GB, Cleary JF. Palliative care reduces morbidity and mortality in cancer. *Nat Rev Clin Oncol* 2013;10:80-9.
  70. Ishiki H, Yamaguchi T, Matsumoto Y, et al. Effect of early palliative care: complex intervention and complex results. *Lancet Oncol* 2018;19:e221.
  71. van Oorschot B. Frühe Mitbetreuung nichtheilbarer Krebspatienten durch Palliativteams bessert die Lebensqualität und fördert Gespräche über Versorgungswünsche am Lebensende. *Strahlentherapie und Onkol* 2018;194:178-80.
  72. Somogyi-Zalud E, Zhong Z, Lynn J, et al. Elderly Persons' Last Six Months Of Life: Findings from the Hospitalized Elderly Longitudinal Project. *J Am Geriatr Soc* 2000;48:S131-9.
  73. Wade JB, Price DD, Hamer RM, et al. An emotional component analysis of chronic pain. *Pain* 1990;40:303-10.
  74. McCracken LM, Vowles KE. A Prospective Analysis of Acceptance of Pain and Values-Based Action in Patients With Chronic Pain. *Health Psychol* 2008;27:215-20.
  75. Miu DKY, Chan KC. Under-detection of pain in elderly nursing home residents with moderate to severe dementia. *J Clin Gerontol Geriatr* 2014. doi:10.1016/j.jcgg.2013.09.001.
  76. Fries BE, Simon SE, Morris JN, et al. Pain in U.S. nursing homes: Validating a pain scale for the Minimum Data Set. *Gerontologist* 2001;41:173-9.
  77. Tse MMY, Ho SSK. Pain management for older persons living in nursing homes: A pilot study. *Pain Manag Nurs* 2013;14:e10-21.
  78. Puntillo K, Pasero C, Li D, et al. Evaluation of pain in ICU patients. *Chest* 2009;135:1069-74.
  79. Gaither JR, Leventhal JM, Ryan SA, et al. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. *JAMA Pediatr* 2016;170:1195-201.
  80. Corsi N, Roberto A, Cortesi L, et al. Prevalence, characteristics and treatment of chronic pain in elderly patients hospitalized in internal medicine wards. *Eur J Intern Med* 2018;55:35-9.
  81. Fanelli G, Cherubino P, Compagnone C. Opioid use for chronic pain management in Italy: results from the Orthopedic Instant Pain survey project. *Orthop Rev (Pavia)* 2014;6:5309.
  82. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007;25:1824-31.
  83. Kenis C, Milisen K, Flamaing J, et al. Performance of two geriatric screening tools in older patients with cancer. *J Clin Oncol* 2014;32:19-26.
  84. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: The chemotherapy risk assessment scale for high-age patients (CRASH) score. *Cancer* 2012;118:3377-86.

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