

# Challenge of cancer in the elderly



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## ABSTRACT

Despite the sustained trend of decreasing overall cancer incidence, the number of elderly patients with cancer will considerably increase in the coming years, as the incidence of cancer is elevated 11-fold after the age of 65 years compared to adults up to 65 years. This soon-to-erupt tsunami of elderly patients with cancer requires adequate treatment, for which guidelines and evidence-based data are still scarce, given the longlasting under-representation of elderly patients with cancer in cancer trials. Older adults present not only with the physiological decreases of organ functions related to age, but also with an individual burden of comorbidities, other impairments and social factors that might impact on their potential for undergoing cancer care. Close collaboration with gerontologists and other health professionals to assess the personal resources and limitations of each person enables providing adequate therapy to elderly patients with cancer. There are promising achievements in each of the requirements listed, but a huge, holistic effort has still to be made.

## INTRODUCTION

In the years to come, the incidence of the elderly diagnosed with cancer in Europe and throughout the world will rapidly increase. This short educational review aims at illustrating the challenges for treating elderly patients with cancer in Europe, challenges caused by the high number of patients being awaited, by considering their age-related metabolic changes, comorbidities, the lack of guidelines and by listing some of the efforts already achieved to solve this huge problem. As of today, the incidence of malignancies after the age of 65 years has increased 11-fold compared to younger adults.<sup>1 2</sup> Nearly 80% of all cancers are diagnosed in persons beyond the age of 55 years.<sup>2</sup> The median age of diagnosis in many tumours lies beyond the age of 60 years, for example, hormone-sensitive breast cancer, multiple myeloma, renal, prostate and colon cancer.<sup>3–7</sup> Moreover, as socioeconomic and medical progress contribute to the decrease in death from other causes, the relative impact of cancer on mortality will increase further. A small study conducted in 2014 by the health and life sciences university (UNIT) in Tirol

in collaboration with the Austrian Society for Hematology and medical Oncology<sup>8</sup> showed an increase in prevalence of patients living with cancer of 38% in 2020 as compared with 2014, most of them elderly—despite a continuous reduction of incidence per 100 000 people from 465.3 to a prevision of 451 in 2020. Even in a country with a low-threshold healthcare system, and with one of the highest densities of physicians per population in Europe, this will result in a severe shortage of trained healthcare professionals, for example, not only cancer surgeons, radiation oncologists and medical oncologists, but also in all other professions involved that are needed to take care of this huge population of elderly patients with cancer to come. This situation might not be unique to Austria, but similar in all European countries—and should give rise to a common European effort to respond to this predictable increased demand together.

## METHODS

To illustrate the challenge of providing adequate cancer treatment for elderly persons, a PubMed search of the published English literature was done, using the search terms ‘elderly’, ‘cancer’, ‘clinical trial’ and ‘geriatric assessment’, including also manual searches on references in articles to these topics.

### Improving the evidence base for treating elderly patients with cancer

However, also today, despite the high prevalence of malignancies in elderly people, administering the optimal treatment to elderly patients with cancer remains challenging. Until recently, most therapeutic trials in oncology did not admit elderly patients; previously because of age limits, recently because of exclusion criteria prohibiting the admission of patients with comorbidities. A recent survey on health-related quality of life (HRQOL) in elderly patients with cancer, pooling data from 25 EORTC randomised trials involving more than 6000 patients included just 9% of patients aged 70 years or

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older (n=539).<sup>9</sup> This low proportion of elderly patients with cancer admitted into therapeutic trials reflects the paradox situation that cancer treatments are generally not tested in the population with the highest patient incidence. Most registration trials include only marginally the population that will be the majority of patients treated after registration of the drug. With increasing age and comorbidities, drug tolerance may decrease and the toxicity of therapies might increase.<sup>10–12</sup> The scarcity of data and the lack of guidelines contribute to a situation where therapeutic nihilism, undertreatment and overtreatment of elderly patients with cancer still occur. The survey of Quinten *et al* further showed that the domains of HRQOL impaired by cancer treatment vary with age: whereas younger patients reported more about impaired social and role functioning and financial problems, older patients reported on appetite loss, constipation and reported about impaired physical functioning, but of less pain than younger patients.<sup>13–15</sup> However, this deficit has now been recognised, and recently, efforts in all domains of oncology have been made to provide reliable information on treating elderly persons with different cancers, for example, to cite a few, a comprehensive review on radiotherapy in elderly,<sup>16</sup> or chemotherapy in elderly<sup>17–19</sup> breast cancer,<sup>20–21</sup> prostate cancer,<sup>22</sup> colorectal cancer,<sup>23–25</sup> esophageal cancer,<sup>26</sup> gastric cancer,<sup>27</sup> glioblastoma,<sup>28</sup> bladder cancer<sup>29</sup> and myeloma.<sup>30</sup> The American Society of Clinical Oncology (ASCO) appointed a subcommittee of the Cancer Research to improve the evidence base for treating older adult patients with cancer: an ASCO statement consisting of five recommendations to reach the goal of providing evidence-based guidelines for treatment of elderly patients with cancer was formulated, published and will be activated.<sup>31</sup> In Europe, the Task Force for the Elderly of the EORTC has agreed on a position paper to broaden the knowledge on treating elderly patients in 2010,<sup>2</sup> held a workshop on adequate trial methodology for elderly patients with cancer, developed a screening module useful for oncologists to identify ‘fit’ older adults and to distinguish them from ‘vulnerable’ and ‘frail’ elderly that should undergo a full geriatric assessment,<sup>32</sup> further developed treatment trials for elderly patients with cancer in collaboration with nearly all the ‘organ’ groups of the EORTC, and launched several translational research projects on evaluating potential biomarkers of ageing.<sup>33–34</sup>

### What are the barriers for the treatment of elderly with cancer?

Every human being has indeed his personal genetic configuration, and even before birth and with the first breath, the environment starts its influences on this individual and he/she starts his/her interaction with the individual environment including lifestyle choices, nutrition and exercise, exposure to sun, toxins and all other environmental factors, thus unravelling our uniqueness. The longer we live, the more each person

becomes elaborated, ‘sculptured’, and the elderly are more visibly singular than younger adults, children and babies.

With advancing age all organ systems are affected and accumulate changes leading to age-related diseases and ultimately to organ failures. These changes can be studied in laboratory animals during their usually shorter life span, and more extensively in humans. Ageing occurs in the stress field between exposures and resiliency at an individual rhythm, resulting in a diversity of different individual biological age in chronologically equal old individuals. The National Health and Nutrition Survey III (NHANES III) addressed the determination of the biological age by a set of 21 biomarkers. This cross-sectional study included more than 9000 people aged 30–75 years, and was conducted between 1988 and 1994. It showed that their algorithm proposed by Klemmer and Doubal far outperformed the prediction of mortality by chronological age.<sup>35–36</sup> The algorithm investigated in the NHANES study was used to study biological ageing in young adults in a birth cohort in 1972–1973 comprising 1037 persons all born in Dunedin, the second largest city in the south island of New Zealand, that were followed within the Dunedin Longitudinal Study at age 38 years to determine their individual pace of ageing.<sup>37</sup> The biological age of the persons in this cohort at the chronological age of 38 years was normally distributed between 28 and 61 years, with an SD of 3.2 years. The individual pace of ageing was calculated from longitudinal analysis of 18 biomarkers collected across the chronological ages of 26, 32 and 38 years, revealing a variability of the pace of ageing of nearly 0 to more than 3 years per chronological year. Study members with accelerated pace of ageing performed less well on objective tests of physical functioning, had more difficulties with balance, less grip strength, and showed poorer cognitive functioning in their fluid intelligence than their biologically younger peers. A potential surrogate marker for assessing microvascular ageing could consist in evaluating loss of integrity of retinal vessels, as narrower arterioles are seen in persons with increased stroke risk, and wider venules in persons with increased risk for dementia.<sup>38</sup> The biomarkers used for calculation of the biological age in the NHANES and in the Dunedin study include, among other things, routine laboratory measures as HbA1C, creatinine clearance, blood urea nitrogen, high-sensitivity C reactive protein, cholesterol, apolipoprotein B, white blood cell count, as well as functional capacities as cardiorespiratory fitness, forced expiratory volume in the first second, mean arterial blood pressure, body mass index and some more sophisticated parameters such as telomere length.

The gap between the chronological and the biological ages of an individual might be significant, and explains why considering only the chronological age in an elderly person may lead to insufficient estimates of organ functions in a given individual. Moreover, lifestyle factors were proven to modify biomarkers of DNA

damage and telomere dysfunction. Song *et al*<sup>39</sup> showed in 103 persons that tobacco smoking and increased body mass index correlate with increase of the expression of oxidative DNA damage after telomere shortening, and with elevated levels of p16<sup>INK4a</sup> in blood, whereas exercise has a preventive effect.

All described factors, and presumably numerous not mentioned, and perhaps today unknown factors explain the difficulties in choosing an optimal individual treatment for an aged individual with cancer.

### Biomarkers of ageing

It is an appealing conception to identify biomarkers of ageing that would be helpful to assess the physiological reserves of a given individual, guiding medical interventions. The big epidemiological ageing studies, NHANES III, and the Dunedin study, used unspecific, established, robust laboratory and functional tests to determine the physiological age of an individual. Geriatric research has identified several biological markers potentially able to reflect the physiological age of a person.<sup>33</sup> Still, the diagnostic and prognostic value of these markers has yet not been prospectively proven:

- ▶ Among the markers proposed, the length of telomeres as measured in circulating lymphocytes is one of the best documented and proved biological markers of ageing. Telomeres are highly repetitive DNA sequences situated at the ends of the chromosomes; for vertebrates, the sequence is TTAGGG which is repeated approximately 2500 times in humans. During cell division, telomeres are truncated and shorten at cell division. However, the enzyme, telomerase, is able to replenish telomere sequences but is not expressed in somatic cells. Telomere length works like a molecular clock reporting the actual remaining cell proliferation capacity. Shorter telomeres of circulating lymphocytes have been found in patients with cardiovascular diseases, COPD, dementia, osteoporosis and were associated with a higher mortality rate. The association with frailty is less clear from the literature.<sup>40</sup>
- ▶ Elevated plasma interleukin 6 level is the most prominent of age-related inflammation markers, 'inflammaging', related to increased mortality, cardiovascular diseases and with frailty.<sup>41 42</sup> Interleukin 6 is secreted mainly by T cells but also by osteoblasts and smooth muscle cells, and mediates the formation of other proinflammatory markers, such as C reactive protein and tumour necrosis factor  $\alpha$ , and was found to be associated with all-cause and cardiovascular mortality in studies of older adults,<sup>43</sup> and is to date the best documented marker of inflammaging.
- ▶ Besides several other cytokines and chemokines associated with ageing, some hormonal blood levels show consistent decrease with age and have been found to be associated with frailty, as the growth hormone and its peripheral effector insulin-like growth factor 1 (IGF-1) or somatomedin C, a peptide hormone

secreted primarily by the liver, with anabolic effects on almost all tissues.<sup>44</sup>

In a recent prospective trial on 82 young (median age 40 years) and 162 old (median age 76 years) patients with non-metastatic breast cancer, Brouwers *et al* studied the relation between ageing biomarkers and the outcomes of a geriatric assessment in the older patients. They found that telomere length and IGF-1 correlated more with calendar age, whereas interleukin 6 more reliably increased with clinical markers of frailty.<sup>40</sup> This study marks the start of a new era of exploratory studies in elderly with cancer.

### Age-related changes in pharmacokinetics

Ageing induces changes in functional organ capacities that should be considered for the planning and dosing of therapies, for example, drug therapies. Age-related changes in organ functions may affect all pharmacokinetic and pharmacodynamic parameters. For orally taken drugs, this starts with decreased production of saliva and gastric acid, gastric gland, anapepsia and decreased production of all digestive enzymes, and a decrease of perfusion of the gastrointestinal tract, all contributing to a high variability of gastrointestinal uptake of drugs. As the perfusion of the liver also decreases with age, the metabolism of drugs might be prolonged favouring increased toxicity.<sup>45 46</sup> When, due to decreased synthesis albumin concentration in blood is reduced, drug concentrations of drugs with high plasma protein binding may dramatically increase. Moreover, changes in body composition contribute to a smaller plasma volume, increasing the concentration of water-soluble drugs and decreasing the concentration of liposoluble drugs. Age-related decrease of creatinine clearance of approximately 1% per year should be considered. Dosage of renally excreted drugs should be adjusted to the reduced renal function; this can easily be achieved by using web-based services.<sup>47</sup>

### Geriatric assessment improves decision-making

The need to consider all resources, but also all impairments of elderly patients, and prior ranking the person's wishes and fears in decision-making for oncological therapy has become widely accepted. To achieve this goal, multidimensional geriatric assessment offers approved tools suitable to measure and to communicate fitness or frailty of a given person.<sup>48-52</sup> A comprehensive geriatric assessment (CGA) includes a series of standardised tests, evaluating aspects of patient functioning, impairments and social supports, covering cognitive performance, mobility and balance, emotional health and substance abuse, nutritional status and needs, comorbidities and services required and received. Taking into account all these issues is mandatory for exploring all potential sources of problems but also the resources of a given patient at the start of a challenging new therapy. Several studies have shown that a geriatric assessment unravels unknown significant geriatric issues in up to

half of elderly newly diagnosed persons with cancer. In a survey of the American Centers of Disease Control and prevention, 80% of older adults have at least one chronic condition, and more than 50% have two or more.<sup>53</sup> Geriatric interventions were shown to improve survival duration, improve the quality of life, decrease hospital admissions and referrals to nursing homes.<sup>54</sup>

In patients with cancer, the scores obtained by geriatric assessment were shown to correlate with the length of survival and ability to predict toxicity of cancer therapy.<sup>17 18 55–59</sup> Hamaker *et al* showed that geriatric assessment revealed at least one geriatric syndrome (eg, pressure ulcers, incontinence, falls, functional decline and delirium<sup>60</sup>) in 93% of 72 patients referred for geriatric consultation by oncologists in a Dutch teaching hospital.<sup>61</sup> Patients were aged from 57 to 94 years, in median 82 years. The consultation led to the diagnosis of previously undiagnosed conditions in 49% of patients. At least one geriatric, non-oncological intervention was instigated in 56% of patients, and changes in the oncological treatment plan were proposed in 82% of patients, approved in 92% by leading to a less intense therapy in 42% of patients, supportive care only in 19%, and a more intense therapy in 39% of patients. These results show that a geriatric assessment influences oncological treatment decisions in directions, limiting treatment intensity in vulnerable patients, as well as preventing undertreatment of fit patients. In fact, a randomised trial comparing treatment adjusted according to the results of geriatric assessment with any ‘standard treatment’, regardless if this ‘standard’ would be adjusted to physiological changes of metabolism with age or not, appears unlikely to be conducted. It remains doubtful how such a trial could be performed within the frame of the Helsinki Declaration.

### **Establishing collaboration between geriatricians and oncologists to optimise care for elderly patients with cancer**

Nevertheless, performing a geriatric assessment before decision-making for the therapy of elderly patients with cancer requires expertise and time. All domains of the CGA provide independent, useful information. Therefore, abbreviated forms or screening tools will not provide the same information as a full CGA, which is not a solution, but a platform to communicate deficits and resources of a given patient. Geriatric knowledge is mandatory to interpret these results: which deficits need to be addressed and how successful an intervention—mostly continuous support in one or more identified domains—will allow stabilising or improving the affected domain. The stabilisation obtained will then allow the patient to undergo an intervention or drug therapy with an improved safety level. Geriatric medicine is an extremely demanding, diverse, multidimensional and rapidly evolving field of medicine. For optimal patient care, being treated by a team formed by oncologists collaborating with geriatricians working in collaboration

with services assuring mobile home care or institutional care would probably be a more realistically achieved scenario than finding the one omniscient specialist (and succeeding to get in touch with such a highly demanded person). Belgium has institutionalised the collaboration between oncology and geriatric medicine by integrating liaison persons into the oncological units on a nationwide basis to perform geriatric assessments, and to facilitate geriatric interventions in older patients with cancer. This helps to establish referral pathways for all issues that might impact on a patient’s tolerance to therapy. This initiative was started some years ago and has yet allowed accumulating data on more than 8000 elderly patients with cancer.<sup>54 62</sup> In this huge cohort of patients, a full geriatric assessment was suggested by screening with the G8 test in nearly 80%,<sup>63 64</sup> and after the full CGA, geriatric recommendations were again given in nearly 80% of patients.

For oncologists, treating the tumour is the primary goal of their expertise, and waiting for a significant number of oncologists to acquire, in addition, the holistic expertise of geriatricians to the always rapidly changing field of oncology is highly improbable, and even if an increased number of colleagues are aware of the huge demand, the number of elderly patients with cancer requiring treatment in a few years will result in a severe shortage of oncologists and impair their capacities of training in a second demanding broad medical specialty such as geriatric medicine. Given the lack of data on the treatment of the elderly with cancer, there is a huge unmet need for improving the evidence level of cancer treatments in the elderly, thus, results from high-quality trials guiding further treatments and exploring the potential of new drugs and new ways of targeted drug delivery especially in the population of older adults.

### **Trial designs for elderly patients with cancer**

Older adults are highly heterogeneous in all domains of physical and psychological functioning and, to date, there are very few results allowing answers to which treatment interventions provide net benefit to which kind of patients. Future trials will have to answer which patients respond to which treatment and what side effect burden has to be expected. For elderly patients with cancer, the most important outcomes of their treatment might substantially differ from the current standard outcome measures in clinical oncology. Time to treatment failure, even overall survival time might be perceived as less important than the preservation of independence and of quality of life.<sup>65</sup> The consideration of this change in priorities requires choosing different trial designs with different end points from standard oncological trials. Adequate documentation of the functional capacities and CGA results of elderly trial participants is a prerequisite for making the trial results applicable for future patients. The treatment outcome in elderly patients with cancer may be modulated adversely by treatment side effects impacting on QOL and decreasing



independence; the elderly might also suffer from comorbidities, and their condition might deteriorate from cancer-unrelated causes. Such composite influences might better be recorded by composite end points allowing integrating several aspects into the trial outcome measures and not being restricted to time of event durations, but also QOL and functional capacity. Such designs do not require huge numbers of patients, but elaborated statistical planning is mandatory.<sup>66</sup>

Getting older patients into trials could be achieved by several strategies. Abolishing age limits and avoiding restrictive exclusion criteria could allow recruitment of older patients into conventional oncological trials, taking care to include, prospectively, all necessary information on functional capacities and comorbidities. An alternative would be to create specific (small) trials in prespecified elderly populations. This is the path currently followed by the elderly task force of the EORTC who developed a bunch of several trials investigating new treatment opportunities in elderly patients with cancer, including the Minimal data set, CGA results, careful monitoring of treatment toxicity, QOL and functional capacity, using treatments with limited expected toxicity as antibodies, tyrosine kinase inhibitors or liposomal drugs<sup>67</sup> in collaboration with nearly all other EORTC groups for now nearly all tumours. Moreover, the predictive value of the stratification by biomarkers of ageing should be explored as a second end point in future trials. Of note, getting elderly patients into research trials also assumes their informed consent and, de facto, also the consent of their proxies. Getting informed consent also is mandatory to providing adequate, understandable information on the research to the potential participants, and to contribute to a research-favourable 'climate' among the general public, in order to avoid the feeling of being used like a laboratory animal. Actual informed consent sheets are overloaded with text formulated by lawyers employed by the pharmaceutical industry, which indeed have another focus of interest than clarity and usability of the text.

## CONCLUSION

During the next few years, the numbers of elderly patients with cancer will increase. To cope with this complex demand implies an assumption of this task in its overwhelming complexity, and to build the collaborations necessary for it. Treating elderly patients with cancer according to their physical health, and according to their preferences, will afford starting with a geriatric assessment, then to perform geriatric interventions if necessary, and then to plan individually for the best-suited therapy, according to data coming from evidence-generating cancer treatment studies for the elderly that mostly still have to be done.

**Collaborators** Marcus Köller.

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