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Review

Geriatric oncology: a clinical approach to the older patient with cancer

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Abstract

Due to the ageing of the population and the sharp increase in life expectancy, cancer in the older person has become an increasingly common problem in the Western world. Although several authors have stressed that elderly cancer patients deserve special attention as a target group for research efforts, older aged patients are still less likely to be offered participation in clinical trials. The cellular and molecular mechanisms regulating the physiological process of ageing and senescence are far from understood, although inflammation is likely to play an important role, at least in some cancers. In addition, the relationship between ageing and cancer risk is also far from understood. One of the most intriguing aspects of ageing is how different the ageing process is from person to person; the basis for this variation is largely unknown. Population-based studies and longitudinal surveys have shown that comorbidity and physical and mental functioning are important risk factors; thus, a meaningful assessment of comorbidity and disability should be implemented in clinical practice. Modern geriatrics is targeted towards patients with multiple problems. Such patients are not simply old, but are geriatric patients because of interacting psychosocial and physical problems. As a consequence, the health status of old persons cannot be evaluated by merely describing the single disease, and/or by measuring the response, or survival after treatment. Conversely, it is necessary to conduct a more comprehensive investigation of the 'functional status' of the aged person. A geriatric consultation provides a variety of relevant information and enables the healthcare team to manage the complexity of health care in the elderly; this process is referred to as the Comprehensive Geriatric Assessment (CGA). The use of CGA is now being introduced into oncological practice. The definition of frailty is still controversial and represents a major issue of debate in clinical geriatrics. As the frail population increases, clinical trials in frail persons are needed. The usefulness of these trials requires a consensus as to the definition of frailty. Clearly, the management of older persons with cancer requires the acquisition of special skills in the evaluation of the older person and in the recognition and management of emergencies as well as experience in geriatric case management.

Keywords: Ageing; Cancer; Elderly patients; Geriatric evaluation; Comprehensive geriatric assessment

1. The ageing of the population and the risk of cancer

The age distribution of a population greatly affects its burden of disease and disability, including cancer incidence and mortality. Accordingly, due to the ageing of the population, cancer in the older person has become an increasingly common problem in the Western world, and a sharp increase in life expectancy was registered in the last century [1,2]. Life expectancy at birth increased, among men, from 48.0 years in 1900 to 71.0 in 1980; among women, the gain was bigger, from 51.0 to 77.7 years [3]. This major improvement registered among women, compared with men, was mainly due to the marked reduction in maternal mortality and to the strong increase in smoking-related deaths recorded among men since the 1950s.

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Time trends of expected years of life at age 65 years are of substantial interest to assess the cancer burden in the older population. Between 1900 and 1980, elderly men experienced an average advantage in their life expectancy of nearly 3 years, from 11.1 to 14.0 years. In elderly women, such a gain was more pronounced, i.e. 6 years (from 11.9 to 17.9 years).The longest life expectancy above 65 years was registered in Japan (15.7 years in men and 19.3 in women) and in Nordic countries (14.6 years in men and 18.7 in women). For future decades, it has been estimated that in industrialised countries life expectancy may reach 90 years for women [4,5]. Predicted gains in life expectancy among men are more limited, due to the greater impact on survival of tobacco use [6].

Although the most striking feature of the epidemiology of many cancers is the rapid increase in the incidence and mortality rates with age, the relationship between ageing and cancer risk is complex and far from understood. Cancer rates increase sharply with age in both sexes: the incidence of cancer is 12–36 times higher in individuals aged 65 years or older than in individuals aged 25–44 years, and 2–3 times more common than in persons aged 45–64 years [7]. Mortality data show a very similar picture: approximately 70% of deaths attributable to all cancers occur in men and in women aged 65 years or older. It is worth noting that 35% of cancer deaths in men and 46% of cancer deaths in women occurred in those aged 75 years or older.

The relationship between ageing and cancer is similar for most cancers, and it is well described by the multistage model [8]. Most of the cellular changes necessary for oncogenesis depend on the environment, and may occur in relation to the year of birth (i.e. the birth cohort effect), or to particular calendar periods (i.e. the period effect, such as the recreational exposure to sun rays observed since the 1960s).

Although the age–incidence curve model is appropriate for most cancer types, for others, namely childhood and hormone-related cancers (for instance, breast, endometrium and ovarian cancers), the multistage model is inappropriate [9]. Overall, strong evidence has been obtained on the carcinogenic mechanism inferring that ageing should not be considered as a determinant of cancer *per se*, but as a surrogate marker of the duration of exposure to relevant carcinogenic factors. Among cigarette smokers, the incidence of lung cancer increases as the fourth power of duration of smoking, and with age as such. It is thus possible to show that cancer is not causally related to ageing [10].

From the public health point of view, clinicians will be treating an increasing number of older patients with cancer. In Italy, it can be estimated from population-based incidence and survival data that between 200 000 and 300 000 elderly patients are living with cancer, and that by 2020, 70% of all cancers will be diagnosed in those aged 65 years or older [11]. On the whole, elderly cancer patients experience an increased relative risk of death compared with young adult patients (particularly, the overall 1-year risk among women and for non-Hodgkin's lymphomas in both sexes) [12] and the optimal treatment for elderly patients with cancer is not known.

2. The different attitude towards the older person with cancer

Despite advances in cancer treatments, during the 1970s and 1980s most of the improvements in cancer mortality were restricted to persons under 50 years of age [13]. However, recently, Levi and colleagues reported a positive change in mortality trends at age 65–84 years, for males in the United States (US) (−2.3%) and for both sexes in the European Union (EU) (males −5.5% and females −4.5%) [14].

Several authors have stressed that elderly cancer patients deserve special attention as a target group for research efforts, and clinicians will be treating more older patients as the populations of industrialised countries age [3]. However, although the drawbacks of excluding elderly cancer patients from randomised trials were emphasised as early as 1980 [15], older patients are still less likely to be offered participation in clinical trials [16]. Several reasons have been proposed to explain the differences in the management of elderly cancer patients, including communication skills, diverging treatment decision-making attitudes, psychosocial issues and the illness experience itself, as well as physicians' and family attitudes [17]. Unfortunately, there are still several barriers that limit cancer treatment in the elderly, but most of them are potentially surmountable. These encompass, among others, limitations in the doctor–patient relationship, inadequate and inaccurate health information, attitudes barring treatment, such as patient anxiety, and the attitude of the community, that influence the compliance of elderly cancer patients to the overall medical approach.

3. The relationship between cancer and ageing

Although several hypotheses have been postulated, the cellular and the molecular mechanisms regulating the physiological process of ageing and senescence have not been fully elucidated [18]. Ageing cannot be considered to be directly responsible for the carcinogenic process, but some mechanisms (Table 1) highlight the relationship between cancer and ageing.

Since carcinogenesis is a lengthy process often occurring over several years, patients generally need to be older in order to develop cancer. Tumours which

involve relatively few carcinogenic stages, like melanomas, peak around age 45 years for women and 60 years for men [19], while tumours like prostate cancer or non-melanomatous skin cancer, requiring numerous intermediate stages, steadily increase after age 80 years [19,20].

The susceptibility of older cells to environmental carcinogens may facilitate some molecular changes, like the formation of DNA adducts, DNA hypomethylation and genetic instability. These are observed in both aged cultured cells and in tissues from older animals [21,22]. Other changes, such as the shortening of telomeres, reduced telomerase activity and activation of the *p16* antioncogene, may oppose carcinogenesis [23–25].

A specific increase in susceptibility to environmental carcinogens with increasing age, in both humans and rodents, has been reported for the cutaneous, lymphatic, hepatic and nervous tissues [19,20,26–30]. Since older persons develop more cancers, it is reasonable to assume that ageing tissues are more susceptible to late-stage carcinogens [31] and we can pose the question of whether various forms of cancer present differently in the elderly [3].

Understanding the role of immunosenescence in cancer development is incomplete; in some cases, such as lymphomas and other highly immunogenic tumours, immunosenescence may favour the development of cancer, but in other cases, including breast cancer, it may delay neoplastic growth [32]. Some authors have hypothesised that specific aspects of immunosenescence might be responsible for the levelling off in cancer incidence among the 'oldest old' (i.e. $\geqslant$85 years of age) [33]. Senescent cells lose the ability to undergo apoptosis and thus may live indefinitely, like cancer cells. Paradoxically, proliferative senescence, that is the loss of self-replicative ability by a cell, may predispose to cancer. In addition, senescent cells release both tumour growth factors (heregulin) that stimulate tumour growth and metalloproteinases, that favour metastatic spreading [34,35].

Current evidence seems to indicate that the immune system of extremely old people contains T cells which, by losing some properties (coactivator molecules, helper function), resemble 'primitive' natural killer (NK) cells, and have a phenotype that is intermediate between T and NK cells. Hence, human immunosenescence can be envisaged as a complex situation in which the reshaping of T lymphocyte sub-populations could be responsible for an increase of natural immunity, due to the high proportion of cells having a NK and a T/NK phenotype, which are capable of reacting with autoantigens, including those of cancerous cells. Moreover, these cells could be also responsible for changes in the pattern of cytokine secretion (secretion of interleukin-4 (IL-4) and interferon-gamma (INF-γ), which could cooperate in yielding a progressively more hostile environment for the growth of cancer cells. This situation could be responsible for the decreased incidence of cancer in the 'oldest old', and studies on the immune system of the 'oldest old' and centenarians could help in understanding the complex relationship between the immune system and cancer [36].

4. Do various forms of cancer present differently in the elderly?

The behaviour of some neoplasms, including acute myeloid leukaemias (AML), non-Hodgkin's lymphoma (NHL), ovarian and breast cancers, varies with age [3,37–39] (Table 2). This observation contradicts the commonly held tenet that cancer is more indolent in older individuals.

The influence of the age of the tumour host on cancer growth was shown by Ershler and colleagues [40]. These authors injected the same load of B16 melanoma and Lewis lung carcinoma into younger and older mice and found that the survival was shorter and the number of metastases higher in the younger animals.

In humans, circumstantial evidence suggests the presence of both a 'seed' and a 'soil' effect. The worst prognosis of AML is accounted for by a higher prevalence of multidrug resistance 1 in the myeloblasts of persons aged 60 years and over and of stem cell leukaemias [41]. The worst prognosis of NHL may be due to the serum concentrations of interleukin-6 (IL-6), which increases with age [42] and is an independent prognostic factor for this disease [43].

In the case of breast cancers, the prevalence of well differentiated, hormone-receptor-rich tumours increases with age, whereas both ovarian failure and immunosenescence may slow/inhibit the growth of breast cancers [44].

5. The complex interaction of ageing and inflammation

Ageing is associated with an accumulation of inflammatory cytokines (tumour necrosis factor (TNF)-alpha,

Table 1
Mechanisms accounting for the association of cancer and ageing

Length of time of the carcinogenic process
Increased susceptibility of ageing tissues to environmental carcinogens •Molecular changes associated with ageing •Experimental data •Epidemiological data
Environmental conditions that favour the growth and the spread of cancer •Proliferative senescence •Immunosenescence

IL-6, cytokine antagonists and acute phase proteins), as well as a decreased production of insulin-like Growth Factor 1 [42,45,46]. Epidemiological studies suggest that chronic low-grade inflammation in ageing promotes an atherogenic profile, favours age-associated disorders (e.g. Alzheimer's disease, atherosclerosis, type 2 diabetes, etc.) and increases the risk of death.

Accordingly, the disregulated production of inflammatory cytokines has an important role in the process of ageing. *In vivo* infectious models show delayed termination of inflammatory activity and a prolonged fever response in elderly humans, suggesting that the acute-phase response is altered in ageing [47]. Epidemiological studies have revealed that minimal acute-phase changes predict poor prognoses in many conditions and predict disability and mortality in the elderly.

These findings have usually been interpreted to indicate that inflammatory processes of some kind play a role in these situations. In fact, a minimal acute-phase response does not necessarily establish the existence of an inflammatory process, but may reflect a variety of non-inflammatory states, including obesity, sleep disturbance, depression, chronic fatigue, and low levels of physical activity. Therefore it has been proposed that a minimal acute-phase response may also be a marker of biologic ageing [48].

Chronic inflammation has been proposed as a biological mechanism underlying the decline in physical function that occurs with ageing. Some authors examined the cross-sectional and prospective relationships between markers of inflammation, IL-6 and C-reactive protein (CRP), with several measures of physical performance in older persons. The conclusions of these studies were that, although IL-6 has been shown to predict the onset of disability in older persons and both IL-6 and CRP are associated with the mortality risk, these markers of inflammation have only limited associations with physical performance, except for walking measures and grip strength at baseline, and do not predict changes in performance 7 years later [49]. Although it is reasonable to expect that a biochemical profile of ageing may become available in the not so distant future, at present, we lack a valuable biomarker of ageing for clinical purposes. Current methods to assess ageing are summarised in Table 3 [50].

6. Evaluating older patients for clinical purposes

One of the most intriguing aspects of ageing is how different the ageing process is from person to person: some maintain their physical and cognitive abilities throughout a long life (successful ageing), while others lose these abilities rather early in adult life. In a very small subgroup of individuals, their functional status even appears to improve over time [51,52]. The basis for this variation is largely unknown [53].

Many population-based studies and longitudinal surveys have shown that comorbidity and physical and mental functioning are important risk factors to assess one's health status [54]. In clinical practice, a meaningful assessment of comorbidity may be obtained with a comorbidity index. The inclusion of comorbidity data in epidemiological analyses, using the Chronic Disease Score, derived from medication usage, has showed some advantages over other measures [55], while the Charlson scale [56] and the Chronic Illness Rating Scale (CIRS-G) [57] are also widely accepted.

The relationship between low levels of physical activity and the occurrence of disabilities has been clearly shown by epidemiological studies. Appropriate physical exercise should be prescribed to older persons, and even

Table 2
Age and changes in cancer prognosis

Neoplasm	Age-related changes in prognosis	Mechanism (s)
Acute myelogenous leukaemia (AML)	Worse: •Increased resistance to chemotherapy •Increased mortality during induction	Seed effect: Increased prevalence of MDR1-expressing cells; Increased prevalence of stem-cell leukaemia
Non-Hodgkin's lymphoma (MHL)	Worse: •Decreased duration of complete remission	Soil effect: Increased circulating concentrations of interleukin-6
Breast cancer	More indolent disease	Seed effect: •Increased prevalence of hormone-receptor-rich, well differentiated tumours Soil effect: •Decreased production of sexual hormones •Immunosenescence
Celomic ovarian cancer	Worse: •Decreased duration of remission •Decreased survival	Unknown

MDR1, multidrug resistance 1.

to the frail elderly, since the positive effects of exercise, including training of endurance, strength and coordination, on the cardiovascular system, the lung, the musculo-skeletal system, metabolism and the immune system are now well established [58].

Physical activity remains a key factor predicting non-disability before death. A 2-fold increased likelihood of dying without disability among the most physically active group compared with sedentary adults was observed providing encouraging evidence that disability prior to death is not an inevitable part of a long life, but may be prevented by moderate physical activity [59]. The importance of preventive interventions to reduce functional limitations, requires preventive and rehabilitative measures to be individualised [60]. For example, a proper assessment and treatment of memory troubles associated with age, reduces the degree of disabilities in daily living even without dementia, and allows identification of subjects at a higher risk of Alzheimer's disease who may benefit from preventive interventions [61].

Social support and social networks have also been shown to exert significant effects on health and functioning among elderly persons [62].

A critical figure in the management of the older person is the caregiver, that in geriatric terms is the person responsible for managing the daily life of the functionally-dependent older person, including medical care [63–65]. Many older individuals who are independent at the beginning of their (cancer) treatment, may become temporarily dependent as a result of treatment complications. Thus, it is prudent to assure the presence of the caregiver at the initiation of treatment. By providing timely assistance in cases of emergency and reliable access to medical care, by monitoring the nutrition and the activity of the older person, by acting as a spokesperson for the family and mediating possible family conflicts, the role of the caregiver in the management of the older person is invaluable. It behoves the health professional to ascertain that a caregiver is available and to train and support that caregiver [66].

Table 3
Assessment of ageing

Laboratory assessment	
Serum creatinine	Non-specific
Serum Osmolarity	Non specific
Circulating levels of cytokines (IL-6, TNF)	Non-sensitive to the early stages of ageing
Cystine/acid soluble thiol ratio	Non-specific; may be altered by cancer and malnutrition
D-Dimer levels	Non-specific
Serum growth hormone/insulin-like growth factor 1 levels	Experimental
Physical assessment	
Stature	Non-specific; maybe influenced by nutrition and osteoporosis
Hand-grasp	In an individual situation may predict development of functional disability
Lower extremities strength	Experimental
Raising from chair	Useful to establish certain difficulties in movement; no relationship to functional dependence or life-expectancy
Comprehensive Geriatric Assessment (CGA)	
Functional status	
Activities of Daily Living and Instrumental Activities of Daily Living (IADL)	Relationship to life-expectancy, tolerance of chemotherapy, dependence
Comorbidity	
Number of comorbid conditions and comorbidity indices	Relationship to life-expectancy and tolerance of treatment
Mental status	
Folstein minimental status	Relationship to life-expectancy and dependence
Emotional conditions	
Geriatric Depression Scale (GDS)	Relationship to survival; may indicate motivation to received treatment
Nutritional status	
Mininutritional assessment (MNA)	Reversible condition; possible relationship to survival
Polypharmacy	Risk of drug interactions
Geriatric syndromes	Relationship to survival
Delirium, dementia, depression, falls, incontinence, spontaneous bone fractures, neglect and abuse, failure to thrive.	Functional dependence

IL-6, interleukin = 6; TNF, tumour necrosis factor.

Older individuals are likely to be both undernourished and overmedicated [67,68], both conditions may interfere with the effectiveness and safety of treatment. The concept of 'therapeutic burden', which encompasses the number of concurrent medications as well as the dose of medications administered, has assumed considerable importance in the understanding of drug therapy in older individuals. Drug therapy provides improvement in quality and quantity of life, but is also a major source of morbidity for the aged patient.

Nutritional status and the needs of elderly people are associated with age-related biological and often socioeconomic changes. Decreased food intake, a sedentary lifestyle, and reduced energy expenditure are critical risk factors for malnutrition, especially protein and micronutrients. Malnutrition is associated with the risk of developing a number of age-related diseases. A potential role for dietary antioxidants in the reduction of diseases such as vascular dementia, cardiovascular disease and cancer has been reported [69].

7. The lesson of geriatrics

Modern geriatrics is the study of the medical aspects of old age and the application of knowledge related to the biological, biomedical, behavioural and social aspects of ageing to perception, diagnosis, treatment and care of older persons. The speciality of geriatric medicine is better utilised if targeted towards patients with multiple, interacting problems brought on by disease or ageing and resulting in a progressive reduction of reserve of multiple organ systems, disability (i.e. functional impairment and dependency), comorbidity, frailty and geriatric syndromes. Such patients are not simply old, but are geriatric patients because of interacting psychosocial and physical problems.

Diseases in the elderly, may appear with atypical signs and symptoms, such as incontinence, confusion, loss of mobility, asthenia, memory failure and psychosis. In some cases, a silent presentation may occur [70]. Older persons are extremely susceptible to iatrogenic disease from a variety of sources, including: polypharmacy, inactivity, and failure to adopt preventive and restorative rehabilitation principles. Comorbid diseases are common and their contribution makes the picture more complex [71].

As a consequence, the health status of old persons cannot be evaluated by merely describing the single disease, and/or by measuring the response or survival after treatment. Conversely, it is necessary to conduct a more comprehensive investigation of the 'functional status' of the aged person. The assessment of the functional status is defined as the measurement of a patient's ability to complete functional tasks, that range from simple self care in activities of daily living (ADL) [72] to more complex instrumental activities of daily living (IADL) [73], and fulfil social roles. ADLs include feeding, grooming, transferring and toileting. IADLs include shopping, managing finances, housekeeping, laundry, meal preparation, ability to use transportation and telephone and ability to take medications. Independence, or the degree of dependence in the ADL and IADL scales, determines whether an older person can eventually live alone without a caregiver. As for social roles, these include the ability to use transportation, the ability of requiring help in cases of urgent need and the ability of living in an interpersonal context. Each impairment in the physical, social or psychological dimension which gives rise to functional limitations is defined as disability.

8. Geriatric assessment in clinical practice

As age from a clinical perspective is highly heterogeneous and poorly reflected by chronological age, the clinical evaluation of the older person is influenced by several factors and is a key step in the clinical decision process [66].

A geriatric consultation provide a variety of relevant information and enables the healthcare team to manage the complexity of health care in the elderly [74]; this process is referred to as the Comprehensive Geriatric Assessment (CGA). The first published report on geriatric assessment programmes was originated by a British geriatrician, Marjory Warren, who developed the concept of specialised geriatric assessment units during the late 1930s [75]. Since then, the concept of CGA has spread to Europe and the US and the use of standardised assessment scales is now recommended [76–78]. In 1988, the American College of Physicians stated that "the maintenance of patients' functional well-being is a fundamental goal of medicine practice and CGA is an essential element of clinical diagnosis, a major determinant of therapeutic choices, a measure of their efficacy and a guide in the planning of care for elderly" [79].

CGA is defined as a multidimensional, often interdisciplinary, diagnostic process aimed at determining the medical, psychological and functional capabilities of elderly persons in order to develop an overall plan for treatment and long-term follow-up. It differs from the standard medical evaluation because: (1) it focuses on frail elderly people with their complex problems; (2) it puts emphasis on the functional status and on their quality of life; and (3) it benefits from the use of an interdisciplinary team.

In the geriatric setting, several studies have supported the effectiveness of CGA in improving functional status, reducing hospitalisation, decreasing medical costs and prolonging survival [76,80–85], but others have failed to demonstrate such favourable effects. The meta-analysis by Stuck and colleagues, including 28 controlled trials on 4959 elderly subjects and 4912 elderly controls

allocated to one of five CGA approaches, showed a positive effect of the CGA, and the authors recommended its use within interdisciplinary units [77].

9. The frail patient

The definition of frailty represents a major issue in clinical geriatrics. Although the term frailty has been increasingly used since the 1980s in the medical literature, its actual meaning is still not well defined. Different authors emphasise different aspects of frailty, and frailty includes the following notions:

- Being dependent on others
- Being at a substantial risk of dependency and other adverse health outcomes
- Experiencing the loss of 'physiological reserves'
- Having many chronic illnesses
- Having complex medical and psychosocial problems
- Having 'atypical' disease presentations
- Being able to benefit from specialised geriatric programmes

The potential adverse outcome resulting in frailty have been well outlined by Fried and Walston [86]. The concept of frailty include problems such as falls, injuries, susceptibility to acute illnesses, worse disability and dependence, institutionalisation and death. Frailty is considered irreversible, but this may change with a better understanding of the biology of frailty and the development of new forms of treatment. Rockwood and colleagues [87] defined as frail those patients who depend on others for activities of daily living, or who are at a high risk of becoming dependent. Another definition of frailty, or 'unstable disability' was proposed by Campbell and colleagues [88], frailty is considered as a decline in the reserve of multiple organ systems, which places the frail person 'at risk' for disability or death with minor stresses.

Hammerman [45] reported that frailty arises from an altered metabolic balance manifested by cytokine overexpression and hormonal decline. Thus, the search for a serum marker that can identify frailty has been instigated and it has been reported that high serum IL-6 levels predict future disability in elderly people [89]. Similarly, somatic mitochondrial DNA mutations, which are eventually accumulated in postmitotic cells and lead to senescence [90], low testosterone levels [91] or low cholesterol levels [92] have been proposed to play a role in the development of frailty. Finally, Fried and colleagues hypothesised that frailty is a sort of wasting syndrome, characterised by weakness, low grip strength, low energy, slow gait speed, and low activity levels that are able to predict early an adverse outcome [93].

In any case, two aspects of frailty deserve recognition: frailty is a chronic condition, not an acute change in functional status, and the median survival of the frail person is in excess of 2 years [94]. Many older cancer patients are frail and need effective palliation; this may include treatment with low doses of chemotherapy [95]. Oncologists inexperienced in the assessment of older individuals are led to also consider as frail persons with moderate disability who may benefit from aggressive cancer treatments. Thus, as the frail population increases, clinical trials including this subgroup are needed. The usefulness of these trials requires a consensus on the definition of frailty.

10. The older patient in the oncological setting

The application of the CGA and the identification of frailty have great importance not only in geriatrics, but also in the oncological setting and its use is now being adapted to older cancer patients [96–99]. The global functional assessment may provide an important estimate of life expectancy, i.e. a critical step in the process of therapeutic decisions in elderly cancer patients. Oncologists should be able to intervene and to target interventions by choosing between aggressive or palliative treatments, and to prevent toxicity. To understand frailty could lead to a stratification of elderly cancer patients for entering optimal treatment strategies and/or clinical trials. The seminal early works on defining tasks essential for the evaluation of the global health care of aged persons, i.e. functional status, ADL and IADL disabilities, comorbidity, frailty, led to the introduction, validation [98] and use of these measures.

The recognition of the importance of the assessment of functional status may be regarded as the introduction of 'geriatric thinking' into the healthcare of older persons with cancer and optimal training of future medical oncologists should include a better understanding of the clinical and research problems of managing older persons [100].

The CGA may help in the management of older individuals with cancer in at least three areas: detection of frailty, treatment of unsuspected conditions, and removal of social barriers to treatment [101].

In the case of the older cancer patient, the CGA presents the following advantages:

- Gross estimate of life-expectancy [102–113].
- Gross estimate of functional reserve and tolerance of chemotherapy [98,99,107].
- Recognition of reversible comorbid conditions that may interfere with cancer treatment.
- Recognition of special social economic needs that may interfere with cancer treatment.
- Management of nutrition and medications.

- Adoption of a common language in the management of older cancer patients; this is essential both for the retrospective evaluation of quality of care and for the prospective assessment of outcome in clinical trials.

11. The older cancer patient and clinical trials

There are very few clinical trials for older populations and few patients are referred to existing trials: thus, a major effort should be made to enter older persons into treatment protocols [114].

To date, most data are derived from retrospective studies, which are often affected by a selection bias [115,116]. This leads to the conclusion that older patients with good performance status, minor comorbidities, which have been selected for entry into clinical trials, can tolerate cancer treatments as well as young adults. Other studies have indicated that elderly patients are treated less aggressively, inadequately or not at all, even when no comorbidities or other age-related factors are identified [117–121]. These studies do not provide adequate information on the global health status of elegible patients. Therefore, such results cannot be applied to the older population as a whole.

Older patients who are able to tolerate standard doses of chemotherapy appear to experience survival that is not substantially different from that achieved in younger patients. However, older patients who cannot tolerate standard treatment present a poorer outcome. New regimens with lower toxicity and comparable effectiveness are needed, especially for patients with poor a performance status [122].

Since the role of age *per se* in the decisional process is negligible, new strategies need to be validated and more elderly patients should be included in clinical trials. Studies aimed at evaluating toxicity, the activity of the new regimens, the overall survival, the possible prognostic factors, the quality of life and the prognostic relevance of CGA in elderly patients with cancer are warranted.

CGA allows identification of three broad groups of elderly patients possibly requiring different clinical approaches: (1) persons who are totally independent and without serious comorbidity; (2) frail persons; (3) persons dependent in some IADL, with or without severe comorbidity. Patients of the first group are good candidates for most forms of standard cancer treatment; the patients of the second group are nearly always candidates for palliative care only, including treatment with single-agent chemotherapy; finally, for the remaining patients, individualised approaches and specific clinical trials are needed: these patients are at increased risk of treatment complications and require special considerations, like dose adjustment based on renal and liver functions and identification of a reliable care-giver.

The proper selection of patients may greatly improve the results and the toxicity related to cancer treatment in the elderly. We recommend the adoption of some form of geriatric assessment in the evaluation of any patient who is 70 years and older. Much work needs to be done to understand how to use CGA in the oncological setting. A CGA scale should be integrated into the research protocols of the cooperative groups. The challenge is that the proposed scales need to be reasonably short, reproducible, and measurable [99].

Treatment guidelines for older patients are clearly needed, including advice on whether to treat at all and whether to use single agents or combination therapy. To date, very few data are available on the tolerance of chemotherapy in patients over 75 years old, data regarding elderly patients entering phase I trails are evermore scarce [123]. This exclusion may affect the applicability of the recommended dose to the majority of elderly cancer patients. Similarly, data on the effectiveness of treatment in frail patients or patients with severe comorbidity are limited. In order to assess if a conventional therapy is better than a reduced intensity regimen, new randomised studies, that take into account the global health of individual patient, are needed.

The adoption of statistical methodologies devoted to older subjects appear fundamental in the development of clinical research in older cancer patients. Such methods need to balance toxicity and activity, survival duration and quality of survival, define the optimal dose for each individual patient, and also define new, age-related treatment endpoints.

12. Conclusions

The management of older persons with cancer requires the acquisition of special skills in the evaluation of the older person and in the recognition and management of emergencies as well as experience in geriatric case management. In addition, the oncologist treating the older cancer patients should be cognizant of new insights into the biology of ageing and be able to apply these advances to patient management as well as to the formulation research questions specific for older individuals. Aware of these imperatives, the American Society of Clinical Oncologists (ASCO) is supporting a number of fellowships in geriatric oncology throughout the major training programmes in the USA. The goals of these programmes are to train clinical scientists to be able to address the most compelling problems of cancer in the older patients and to sensitise practitioners of oncology to the issues of cancer in the elderly. Cooperation between oncologists and geriatricians, as is being developed within large cooperative European Groups, is another strategy being implemented to

improve the management and treatment of the elderly with cancer.

The ageing of the general population and subsequent increase in cancer in the elderly mandate that special attention is given at both the National and European Community levels. Dedicated grants, for basic and clinical research in this field, should be promoted to improve our understanding of the complex relationships between ageing and cancer, to produce a new medical landscape and to change physicians attitudes toward older patients. In the meantime, any oncologists should be aware of the unique interfaces of cancer and ageing and should strive to become able to manage these interactions in the clinical setting.

References

1. World Health Organization (WHO). *World Health Statistics Annual*. Geneva, WHO, 1987.
2. Murray CJL, Lopez Ad. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997, **349**, 1498–1504.
3. Yancik R, Ries LAG. Aging and cancer in America: demographic and epidemiologic perspectives. *Hematol/Oncol Clin, North Am* 2000, **14**, 17–23.
4. Yancik RM, Ries L. Cancer and age: magnitude of the problem. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology,* 2nd edn. London, Harwood Academic, 1998, 95–103.
5. Franceschi S, La Vecchia C. Cancer epidemiology in the elderly. *Crit Rev Oncol Hematol* 2001, **39**, 219–226.
6. Negri E, La Vecchia C, Decarli A. Cancer mortality in Italy. *Tumori* 2002, **88**, 89–94.
7. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. *Cancer Incidence in Five Continents, vol. VII. IARC Sci Publication No. 143*. Lyon, IARC, 1997.
8. Armitage P, Doll R. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. *Br J Cancer* 1961, **11**, 161–169.
9. Stanta G, Campagner L, Cavallieri F, Giarelli L. Cancer of the oldest old: what we have learned from autopsy studies. *Clin Ger Med* 1997, **13**, 55–68.
10. Peto R, Parish SE, Gray RG. There is no such thing as ageing, and cancer is not related to it. In Likhacev A, Anisimov V, Montesano R, eds. *Age-related Factors in Carcinogenesis: Proceedings of a Symposium*. Lyon, IARC, 1985, 45–53.
11. Balducci L, Extermann M. Cancer and aging. An evolving panorama. *Hematol Oncol Clin North Am* 2000, **14**, 1–16.
12. Vercelli M, Quaglia A, Casella C, Parodi S, Capocaccia R, Martinez Garcia C. Relative survival in elderly cancer patients in Europe. EUROCARE Work Group. *Eur J Cancer* 1998, **34**, 2264–2270.
13. Balducci L, Lyman GH. Cancer in the elderly: epidemiologic and clinical implications. *Clin Geriatr Med* 1997, **13**, 1–14.
14. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Changed trends of cancer mortality in the elderly. *Ann Oncol* 2001, **12**, 1467–1477.
15. Begg CB, Cohen JL, Ellerton J. Are the elderly predisposed to toxicity from cancer chemotherapy? An investigation using data from the Eastern Cooperative Oncology Group. *Clin Trials* 1980, **3**, 369–374.
16. Kemeny M, Muss HB, Kornblith AB, Peterson B, Wheeler J, Cohen HJ. Barriers to participation of older women with breast cancer in clinical trials. *Proc Am Soc Clin Oncol* 2000, **19**, 2371.
17. Maly RC. Qualitative research for the study of cancer and age. *Hematol Oncol Clin North Am* 2000, **14**, 79–88.
18. Schmidt K. Physiology and pathophysiology of senescence. *Int J Vitam Nutr Res* 1999, **69**, 150–153.
19. Glass AG, Hoover RN. The emerging epidemics of melanoma and squamous cell skin cancer. *J Am Med Ass* 1989, **262**, 2097–2100.
20. Balducci L, Pow-Sang J, Friedland J, Diaz JI. Prostate cancer. *Clin Ger Med* 1997, **13**, 283–307.
21. Anisimov VN, Gvardina OE. *N*-Nitrosomethylurea-induced carcinogenesis in the progeny of male rats of different ages. *Mutat Res* 1995, **316**, 139–145.
22. Randerath K, Liehr JG, Gladeck A, Randerath E. Age-dependent covalent DNA alteration (I compounds) in rodent tissues: species, tissue and sex specifications. *Mutat Res* 1989, **219**, 121–133.
23. Collins K. Mammalian telomeres and telomerase. *Curr Opin Cell Biol* 2000, **12**, 378–383.
24. Liggett WH, Sidransky D. Role of the P16 tumor suppressor gene in cancer. *J Clin Oncol* 1998, **16**, 1197–1206.
25. Anisimov VN. Age as a risk factor in multistage carcinogenesis. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, Harwood Academic, 1998, 157–178.
26. Kraupp-Grasl B, Huber W, Taper H, Schulte-Hermann R. Increased susceptibility of aged rats to hepatocarcinogenesis induced by the peroxisome proliferator nafenopin and the possible involvement of altered liver foci occuring spontaneously. *Cancer Res* 1991, **51**, 666–671.
27. Ebbesen P. Papilloma development on young and senescent mouse skin treated with 12-tetradecanoylforbol-13-acetate. In Likhacev A, Anisimov V, Montesano R, *et al*, eds. *Age-related Factors in Carcinogenesis. IARC Scientific Publication No. 58*. Lyon, France, IARC, 1985, 167–170.
28. Barbone F, Bovenzi M, Cavallieri F, Stanta G. Air pollution and lung cancer in Trieste, Italy. *Am J Epidemiol* 1995, **141**, 1161–1169.
29. Monfardini S, Carbone A. Non-Hodgkin's lymphomas. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, Harwood Academic, 1998, 577–595.
30. Flowers A. Brain tumors. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, Harwood Academic, 1998, 703–720.
31. Balducci L. Geriatric Oncology: challenges for the new century. *Eur J Cancer* 2000, **36**, 1741–1754.
32. Goodwin J, Burns E. Immunological changes of aging. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, Harwood Academic, 1998, 213–222.
33. Bonafè M, Valesin S, Gianni W, Marigliano W, Franceschi C. The unexpected contribution of immunosenescence to the levelling off of cancer incidence and mortality in the oldest old. *Crit Rev Oncol Hematol* 2001, **39**, 227–233.
34. Campisi J. Cancer and age: the double sword of proliferative senescence. *J Am Ger Soc* 1997, **45**, 482–488.
35. Warner HR. Aging and regulation of apoptosis. *Curr Top Cell Regul* 1997, **35**, 107–121.
36. Franceschi C, Monti D, Sansoni P, Cossarizza A. The immunology of exceptional individuals: the lesson of centenarians. *Immunol Today* 1995, **16**, 12–16.
37. Lancet JE, Willman CL, Bennett JM. Acute myelogenous leukemia and aging: clinical interactions. *Hematol Oncol Clinics North Am* 2000, **16**, 251–268.
38. The International Non-Hodgkin's Lymphoma prognostic

factors project: a predictive model for aggressive non-hodgkin's lymphoma. *N Engl J Med* 1993, **329**, 87–94.
39. Thigpen JT. Gynecologic cancer. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, Harwood Academic, 1998, 721–732.
40. Ershler WB. Tumor-host interactions, aging and tumor growth. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, Harwood Academic, 1998, 201–211.
41. Willman CL. The prognostic significance of the expression and function of multidrug resistance transporter proteins in acute myeloid leukaemia: studies of the Southwest Oncology Group Leukemia Research programm. *Semin Hematol* 1997, **34**, 25–36.
42. Hamermann D, Berman JW, Albers GW, Brown DL, Silver D. Emerging evidence for inflammation in conditions frequently affecting older adults: report of a symposium. *J Am Ger Soc* 1999, **47**, 995–999.
43. Preti HJ, Cabanillas F, Talpaz M, Jucker SL, Seymour JF, Kurzrock R. Prognostic value of serum interleukin-6 in diffuse large cell lymphoma. *Ann Intern Med* 1997, **127**, 186–194.
44. Balducci L, Silliman RA, Diaz N. Breast cancer: an oncological perspective. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*, 2nd ed. London, Harwood Academic (in press).
45. Hamermann D. Toward an understanding of frailty. *Ann Intern Med* 1999, **130**, 945–950.
46. Cohen HJ, Pieper CF, Harris T. Markers of inflammation and coagulation predict decline in function and mortality in community dwelling elderly. *Proc Am Ger Soc* 2001, **S1** (abstr A3)..
47. Bruunsgaard H, Pedersen M, Pedersen BK. Aging and proinflammatory cytokines. *Curr Opin Hematol* 2001, **8**, 131–136.
48. Kushner I. C-reactive protein elevation can be caused by conditions other than inflammation and may reflect biologic aging. *Cleve Clin J Med* 2001, **68**, 535–537.
49. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci* 2000, **55**, M709–M715.
50. Balducci L. The comprehensive geriatric assessment in the management of the older person with cancer. *Eur J Gerontol* (in press).
51. Craig Rubin D, Sizemore T, Loftis PA, Loret de Nola N. A randomized, controlled trial of outpatient geriatric evaluation and management in a large public hospital. *J Am Ger Soc* 1993, **41**, 1023–1028.
52. Stuck AE, Aronow HU, Steiner A, *et al*. A trial of annual in-home comprehensive geriatric assessment for elderly people living in the community. *N Engl J Med* 1995, **333**, 1184–1189.
53. Christensen K. Why do we age so differently? *Lakartidningen* 1999, **96**, 5099–5102.
54. Fratiglioni L, Von Strauss E, Winblad B. Epidemiology of aging with focus on physical and mental functional ability. *Lakartidningen* 2001, **98**, 552–558.
55. MacKnight C, Rockwood K. Use of chronic disease score to measure comorbidity in the Canadian Study of Health and Aging. *Int Psychogeriatr* 2001, **13**, 37–142.
56. Charlson ME, Pompei P, Ales K, Mackenzie CR. A new method of classifying comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987, **40**, 373–383.
57. Miller MD, Paradis CF, Houck PR, *et al*. Rating chronic medical illness burden in geropsychiatric practice and research: application of the cumulative illness rating scale. *Psychiatric Res* 1992, **41**, 237–248.
58. Nikolaus T. Effect of physical activity on functional performance. *Z Gerontol Geriatr* 2001, **34**, 44–47.
59. Leveille SG, Guralnik JM, Ferrucci L, Langlois JA. Aging successfully until death in old age: opportunities for increasing active life expectancy. *Am J Epidemiol* 1999, **149**, 654–664.
60. Pientka L. Knowledge for prolonging longevity without disability. *Z Gerontol Geriatr* 2001, **34**, 38–43.
61. Dartigues JF, Fabrigoule C, Barberger-Gateau P, Orgogozo JM. emory, aging and risk factors. Lessons from clinical trials and epidemiologic studies. *Therapie* 2000, **55**, 503–505.
62. Unger JB, McAvay G, Bruce ML, Berkman L, Seeman T. Variation in the impact of social network characteristics on physical functioning in elderly persons: MacArthur Studies of Successful Aging. *J Gerontol B Psychol Sci Soc Sci* 1999, **54**, S245–S251.
63. Weitzner MA, Haley WE, Chen H. The family caregiver of the older cancer patient. *Hematol Oncol Clin* 2000, **14**, 269–282.
64. Haley WE, Ehrbar L, Schonwetter RS. Family caregiving issues. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. London, Harwood Academic, 1998, 805–812.
65. Hayman JA, Langa KM, Kabeto MU, *et al*. Estimating the cost of informal caregiving for elderly patients with cancer. *J Clin Oncol* 2001, **19**, 3219–3225.
66. Balducci L, Extermann M. A practical approach to the older patient with cancer. Current problems. *Cancer* 2001, **25**, 1–76.
67. Guigoz Y, Vellas B, Garry PJ. Mininutritional assessment: a practical assessment tool for grading the nutritional state of elderly patients. In Guigoz Y, Vellas B, Garry PJ, eds. *Facts, Research, Interventions in Geriatrics, 1997*. New York, Serdi, 1997, 15–60.
68. Corcoran MB. Polypharmacy in the older patient. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. London, Harwood Academic, 1998, 525–532.
69. Meydani M. Nutrition interventions in aging and age-associated disease. *Ann N Y Acad Sci* 2001, **928**, 226–235.
70. Fox RA, Pxty J. *Geriatric and the Problem Solving Approach. Medicine in the Frail Elderly: A Problem Oriented Approach*. London, Arnold, 1993 1–13.
71. Guralnik JM, LaCroix AZ, Everett DF, Kovar MG. *Aging in the Eighties: The Prevalence of Comorbidity and Its Association with Disability. Advance Data from Vital and Health Statistical 1989, No. 170*. National Center of Health Statistic, Bethesda, USA.
72. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970, **10**, 20–30.
73. Lawton MP, Brody E. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969, **9**, 179–186.
74. Fratino L, Ferrario L, Redmond K, Audisio RA. Global Health care: the role of geriatrician, general practitioner and oncology nurse. *Crit Rev Oncol Hematol* 1998, **27**, 101–109.
75. Matthews DA. Marjory Warren and the origin of British geriatrics. *J Am Geriatr Soc* 1984, **32**, 253–258.
76. Hendriksen C, Lund E, Stremgard E. Consequences of assessment and intervention among elderly people: a 3 year randomised controlled trial. *Br Med J* 1984, **289**, 1522–1524.
77. Stuck AK, Siu AL, Wieland DG, Adams J, Rubenstein LZ. Comprehensive geriatric assessment. A meta-analysis of controlled trials. *Lancet* 1993, **342**, 1032–1036.
78. Working Group of the Royal College of Physicians and the British Geriatric Society. *Standardised Assessment Scales for Elderly People*. London, Royal College of Physicians, 1992.
79. Health and Public Policy Committee. American College of Physicians. Comprehensive geriatric assessment for elderly patients. position paper. *Ann Intern Med* 1988, **1**, 70–73.
80. Applegate WB, Miller ST, Graney MJ, Elam JT, Burns R, Akins DE. A randomised controlled trial of geriatric assessment unit in a community rehabilitation hospital. *New Engl J Med* 1990, **322**, 1572–1578.
81. Bernabei R, Landi F, Gambassi G, *et al*. Randomised trial of impact of model of integrated care and case management for older people living in the community. *Br Med J* 1998, **316**, 1348–1351.

82. Alessi CA, Stuck AE, Aronow HU, *et al*. The process of care in preventive "in home" comprehensive geriatric assessment. *J Am Ger Soc* 1997, **45**, 1044–1050.
83. Tinetti ME, Baker DI, McAvay G, Claus EB, Garret P, Gottschalk M. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med* 1994, **331**, 821–827.
84. Inouye SK, Bogardus ST, Charpentier PA, *et al*. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999, **340**, 669–676.
85. Reuben DB, Franck JC, Hirsch SH, McGuigan KA, Maly RC. A randomized clinical trial of outpatient geriatric assessment (CGA), coupled with an intervention, to increase adherence to recommendations. *J Am Ger Soc* 1999, **47**, 269–276.
86. Fried LP, Walston J. Frailty and failure to thrive. In Hazzard WR, Blass JP, Ettinger WH, Halter JB, Ouslander JG, eds. *Principle of Geriatric Medicine and Gerontology,* 4th ed. New York, McGraw Hill, 1999, 1387–1402.
87. Rockwood K, Fox RA, Stolee P. Frailty in elderly people: an evolving concept. *Can Med Assoc J* 1994, **150**, 489–495.
88. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. *Age Ageing* 1997, **26**, 315–318.
89. Ferrucci L, Harris TB, Guralnik JM, *et al*. Serum IL-6 and the development of disability in older persons. *J Am Geriatr Soc* 1999, **47**, 639–646.
90. Wallace DC. Mitochondrial diseases in man and mouse. *Science* 1999, **283**, 1482–1488.
91. Morley JE, Kaiser FE, Sih R, Hajjar R, Perry 3rd HM. Testosterone and frailty. *Clin Geriatr Med* 1997, **13**, 685–695.
92. Ranieri P, Rozzini R, Franzoni S, Barbisoni P, Trabucchi M. Serum cholesterol levels as measure of frailty in elderly patients. *Exp Aging Res* 1998, **24**, 169–179.
93. Fried LP, Tangen C, Walston J, *et al*. Frailty on older adults: evidence for a phenotype. *J Gerontol Med Sci* 2001, **56**, M146–M156.
94. Rockwood K, Stadnyk K, Macknight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet* 1999, **353**, 205–206.
95. Balducci L, Stanta G. Cancer in the frail patient: a coming epidemic. *Hematol Oncol Clin North Am* 2000, **14**, 235–250.
96. Repetto L, Comandini D. Cancer in the elderly: assessing patients for fitness. *Crit Rev Oncol Hematol* 2000, **35**, 155–160.
97. Exterman M, Aapro M. Assessment of the older cancer patient. *Hematol Oncol Clin North Am* 2000, **14**, 63–77.
98. Monfardini S, Ferrucci L, Fratino L, Del Lungo I, Serraino D, Zagonel V. Validation of a multidimensional evaluation scale for use in elderly cancer patients. *Cancer* 1996, **77**, 395–401.
99. Repetto L, Fratino L, Audisio RA, *et al*. The Comprehensive Geriatric Assessment adds information to ECOG Performance Status in elderly cancer patients: a GIOGer study. *J Clin Oncol* 2002, **20**, 494–502.
100. Bennet JM, Sahasrabudhe DM, Hall WJ. Medical oncology and geriatric medicine it is time to fellowship integration. *Ann Oncol* 1998, **9**, S16–S18.
101. Balducci L, Beghè C. The application of the principles of geriatrics to the management of the older person with cancer. *Crit Rev Oncol Hematol* 2000, **35**, 147–154.
102. Reuben DB, Rubenstein LV, Hirsch SH, Hays RD. Value of functional status as predictor of mortality. *Am J Med* 1992, **93**, 663–669.
103. Inoyue SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA* 1998, **279**, 1187–1193.
104. Siu AL, Moshita L, Blaustein J. Comprehensive geriatric assessment in a day hospital. *J Am Ger Soc* 1994, **42**, 1094–1099.
105. Barbeger-Gateau P, Fabrigoule C, Helmer C, Rouch I, Dartigues JF. Functional impairment in instrumental activities of daily living: an early clinical sign of dementia? *J Am Ger Soc* 1999, **47**, 456–462.
106. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Int Med* 1994, **120**, 104–110.
107. Piccirillo JF, Feinstein AR. Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. *Cancer* 1996, **77**, 834–842.
108. Manton K. A longitudinal study of functional change and mortality in the United States. *J Gerontol* 1988, **43**, S153–S161.
109. Eagles JM, Beattie JAG, Restall DB, Rawlinson F, Hagen S, Ashcroft GW. Relationship between cognitive impairment and early death in the elderly. *Br Med J* 1990, **300**, 239–240.
110. Bruce ML, Hoff RA, Jacobs SC, Leaf PJ. The effect of cognitive impairment on 9-year mortality in a community sample. *J Gerontol* 1995, **50**, P289–P296.
111. Folstein ME, Folstein SE, McHugh PR. A mini mental state: a practical method for grading the cognitive status of patients for the clinician. *J Psychiatr Res* 1975, **12**, 189–198.
112. Covinsky KE, Kahana E, Chin MH, Palmer RM, Fortinsky RH, Landefeld CS. Depressive symptoms and three year mortality in older hospitalized medical patients. *Ann Int Med* 1999, **130**, 563–569.
113. Lyness JM, King DA, Cox C, Yoedino Z, Caine ED. The importance of subsyndromal depression in older primary care patients. Prevalence and associated functional disability. *J Am Ger Soc* 1999, **47**, 647–652.
114. Kimmick GG, Muss HB. Systemic therapy for older women with breast cancer. *Oncology (Huntingt)* 2001, **15**, 280–291 [discussion 291–292, 295–296, 299]..
115. Repetto L, Venturino A, Vercelli M, *et al*. Performance status and comorbidity in elderly cancer patients compared to a young neoplastic and an elderly non-neoplastic population. *Cancer* 1998, **82**, 760–765.
116. Satoh H, Ishikawa H, Funayama Y, *et al*. Management of small cell lung cancer in elderly. *Anticancer Res* 1999, **19**, 4507–4510.
117. Ashkanani F, Eremin O, Heys SD. The management of cancer of the breast in the elderly. *Eur J Surg Oncol* 1998, **24**, 396–402.
118. Muss HB. Breast cancer in older women. *Semin Oncol* 1996, **23**(Suppl. 2), S82–S88.
119. Kennedy BJ. Cancer research and the aging population. *Oncol Issues* 2000, **15**, 20–28.
120. Goodwin JS, Hunt WC, Samet JM. Determinants of cancer therapy in elderly patients. *Cancer* 1993, **72**, 594–601.
121. Goodwin JS, Samet JM, Key CR, Humble C, Kutvirt D, Hunt C. Stage at diagnosis of cancer varies with the age of the patient. *J Am Geriatr Soc* 1986, **34**, 20–26.
122. Johnson DH. Small cell lung cancer in the elderly patient. *Semin Oncol* 1997, **24**, 484–491.
123. Monfardini S, Sorio R, Kaye S. Should elderly cancer patients be entered in dose-escalation studies? *Ann Oncol* 1994, **5**, 964–966.