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Treatment of cancer in old age, shortcomings and challenges

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Abstract

The burden of cancer in old age is increasing as a result from both the expanding number of older persons in the population and the high and still increasing cancer incidence in this group. The goal of this article is to outline the shortcomings and challenges of the management of cancer in the elderly. Several factors contribute to the complexity of this management, such as the enormous heterogeneity in this population, increased co-morbidity, reduced functional status, increased frailty and different treatment goals from those in younger patients. Other problems include the lack of data on the efficacy and toxicity of cancer treatment in this age group, the lack of awareness of life-expectancy and the lack of an easy applicable and validated frailty scale. Improvement of the quality of oncological care in this age group could be achieved by initiation of clinical trials specifically directed at the elderly, in which a frailty scale is implemented. The results of these trials may lead to more evidence-based decision making in cancer treatment in the elderly. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Cancer; Cancer treatment; Frailty

Currently over 60% of newly diagnosed cancers occur in patients over 65 years of age [1].

This percentage is increasing as earlier in this decade 55% of all malignancies were identified in this group, while about 20 years ago it was only 50% [1]. Tumour registry data obtained in 1997 by the nine comprehensive cancer centres in our country established that cancer is most common in the elderly, as 28% of new patients was aged between 65 and 74 years and 30% was 75 years or older [2]. Combined with a still expanding number of older

persons, the magnitude of the cancer burden in the aged is clear. Survival data from 17 European countries demonstrated that elderly with cancer face a worse prognosis than younger patients [3]. This inferior prognosis may be the product of several factors, such as differences in biological behaviour of the tumour, decreased DNA-repair and age-related host factors as hormone receptors and circulating hormone levels, and mostly these cannot be affected [4]. However, as least as important are the observed age-related differences in diagnostic procedures and therapy [5–8], upon which still is room for improvement. These age-related differences derive from both patient- and doctor-related factors. Examples of patient-related factors are co-morbidity, co-medication, ethnicity, educational level, cognitive status,

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access to transportation, social support and the results of physiological decline, whereas doctor-related factors include attitude, know-how, assumptions, generalizations and prejudice. Because of this, the pro's and cons for diagnostic procedures and treatment options in older patients are not always properly balanced. About 10–15% of the elderly experience an optimal ageing without occurrence of co-morbidity ('old and fit'). When cancer is diagnosed in a person within this group, the calendar age should not be an argument in therapeutic decisions, and the first choice in oncological care should be the prevailing standard treatment. However, in frail older patients counter-arguments about treatment can be considerable, and decisions regarding treatment should be weighed carefully. In this article we outline our view with respect to optimal oncological care for older patients. Specific issues on medical treatment such as alterations in pharmacodynamics or pharmacokinetics are beyond the scope of this review.

Diagnostic procedures and filters for referral

The basis of adequate oncological care comprises careful diagnostic examinations followed by sufficient staging procedures, as stage governs both treatment and prognosis. However, in older patients the diagnostic work-up is often less extensive compared to their younger counterparts, so that there is a higher proportion of unstaged disease in the elderly [5]. It can be assumed that there is a similar difference in diagnostic approaches in the preceding phase in which a histological diagnosis has not been obtained. An essential key in diagnosing a disease is a thorough physical examination. Although older patients visit a doctor more frequently than younger patients, and consequently undergo more often a general physical examination, the number of gynecological examinations declines [9]. This could be the result of the misperception that older patients might reject such examinations. In a survey regarding the attitude of doctors and of older patients towards rectal examinations, the majority of patients considered it an important examination and did not find it disagreeable [10]. The literature suggests several reasons why in older patients less intensive

diagnostic procedures are performed. Some of these are patient-related while others are doctor-related [11,12].

Examples of patient-related factors are ignorance of (non-specific) symptoms or attributing them to normal ageing or to co-morbid conditions. Other factors are the assumption that cancer is contagious, or the overwhelming idea that cancer is not a treatable disease.

Examples of doctor-related factors are the lack of knowledge of the normal process of ageing and of life-expectancy, stereotyped opinions, and therapeutic nihilism. All these factors also contribute to referral filters, of which the exact magnitude and underlying mechanisms still have to be unraveled. Older patients are probably less frequently referred to tertiary cancer centres, while differences in diagnostic and therapeutic approach between tertiary cancer centres and general hospitals are very likely. In a retrospective study of ovarian cancer patients, differences were observed in background and experience of surgeons: in the patient group over 80 years old, only 14% were treated by a gynaecologic oncologist, 29% by an obstetrician/gynaecologist and 31% by a general surgeon [13]. These figures were 23, 56 and 14%, respectively for patients under 60 years. Another illustration of the existence and influence of referral filters are the results of a study comparing performance status and co-morbidity in older cancer patients (>70 years), younger cancer patients (<70 years) and non-cancer patients [14]. Older cancer patients intriguingly exhibited a better functional status and less co-morbidity than older patients with non-neoplastic disease. In this study the selection of patients probably influenced the results as the cancer patients were recruited from specialised cancer centres, whereas the non-cancer patients were recruited from geriatric or general medicine departments. In our country referral filters have been found too. The variation in referral for postoperative radiotherapy for endometrial carcinoma stage I was mainly determined by differences in opinion between referring gynaecologists [15]. In prostate cancer patients, the decision of urologists to use radical prostatectomy was not only determined by patients' age and tumour characteristics, but also by the type of hospital in terms of case-load [16].

The management of older patients with cancer

varies between countries. Differences in incidence as well as percentage of histologically verified cancer between neighbouring countries do not reflect genuine differences but have to be attributed to dissimilar management. If survival data are considered as endpoint for management, the lower survival for elderly, as well as younger patients, in Eastern European countries compared to other European countries, probably reflects the difference in access to and quality of care [3]. The various management of cancer in old age not only results from disparity in economical resources but also from another cultural point of view. For example, the concept of 'Tenju-Gann' or 'natural end cancer' has recently been advocated [17]. Tenju-gann is derived from the Japanese words 'ten' which means heaven and 'ju' which means 'celebrated long life' and considers the development of cancer at very old ages as more or less inevitable. Sometimes the result may be a peaceful death with minimal suffering. This concept, probably more accepted in non-Western countries, rejects aggressive treatment, but may also preclude appropriate diagnostic procedures and therefore causes surrogate decisions [17,18].

In our opinion, a proper approach to each older patient starts with a complete evaluation of the symptoms and signs, which have to be clarified satisfactory, and in which the occurrence of a malignancy always has to be considered. Referrals to medical specialists have to be accomplished if necessary. After the diagnosis of cancer has been confirmed histologically, or is thought to be very likely, complementary diagnostic procedures are only warranted when there are therapeutic consequences. These therapeutic consequences, chemotherapy, surgery, radiotherapy, were recently reviewed by Turner et al. [7]. Those therapeutic consequences are determined by the life-expectancy, contra-indications if any, as well as by the patients' acceptance of the treatment proposed.

Lack of data

A major obstacle in selecting the optimal cancer treatment for older patients is the lack of sound data on the efficacy and toxicity of therapy, as well as on quality of life. This is because few studies are

specifically aimed at older cancer patients, who have been underrepresented in common cancer trials. For example, the overall accrual in the South-West Oncology Group trials between 1993 and 1996 for patients 65 years of older was only 25%, whereas the corresponding proportion of cancer in the general population in this age group was 63% [19].

As well as age restrictions related to inclusion criteria, other reasons elucidated for this underrepresentation are the exclusion due to co-morbidity, advanced stage of disease, lower level of education, the idea that older patients have less benefit from aggressive treatment, the lack of financial, social, and logistic support for participation in a trial as well as low referral [20,21]. Considering this underrepresentation of older patients, the interpretation of these trials needs to be viewed with caution, because a selection bias, including only the 'best' elderly, likely influences the results.

Life-expectancy

During the last century, life-expectancy has gradually increased. For the Dutch population, the mean life-expectancy for a male septagenarian is 11 years, for an octogenarian 6 years, and for a nonagenarian it is still 3 years. For females these figures are even more impressive, 15, 8 and 4 years, respectively [21]. Against this, the variability of the life-expectancy is increased, which decreases confidence of individual predictions. The heterogeneity within the older population, usually defined as everyone aged over 65 years, partly results from the wide age range. In addition, the age at which patients are considered 'elderly' varies in the literature. In geriatric medicine often the limit of 65 years is mentioned, whereas in the European literature on cancer in the elderly often the age limit of 70 years is used. Some authors advocate to distinguish the 'young old' (65–74 years), the 'older old' (75–84 years) and the 'oldest old' (85 years or older) [1]. Subdivision in age groups is primarily important for research purposes, which secondarily can influence individual treatment decisions. For example, after comparison of clinical and histological characteristics and outcome of Dutch Non-Hodgkin lymphoma patients, patients with indolent lymphoma are considered 'elderly'

when they are older than 70 years whereas in aggressive lymphoma this occurs when patients are older than 65 years [22]. The life-expectancy is crucial in decisions regarding oncological treatment. For example, in a 90-year-old person suffering from a bowel obstruction due to a sigmoid tumour, a surgical resection will be performed as the profit and loss account will in the short term go in favour of profit. However, when the histological examination reveals a Dukes-C colon carcinoma, no adjuvant chemotherapy will be proposed because any benefit manifests after several years [23].

Co-morbidity

Next to life-expectancy, co-morbidity deserves attention. In the Netherlands, the increase in life-expectancy observed between 1983 and 1994 is mainly based on an increase of 'unhealthy years', although the severity of this 'ill health' declined [21]. The rise in unhealthy life-expectancy particularly is related to the corresponding increase in age-dependent diseases, whose pathogenesis directly involves normal ageing [24]. Examples are cardiovascular diseases, osteoporosis and Alzheimers' disease. The incidence and prevalence of these age-dependent diseases gradually increase with ageing, and in many cases the transition between physiological ageing and age-dependent disease is ill-defined. They form a major part of co-morbidity and strongly influence life-expectancy, quality of life and frailty as well as decisions regarding treatment.

Tumour registry data for 7600 cancer patients in the United States showed in patients aged between 55–64, 65–74 and over 75 an increase in the mean number of co-morbidities from 2.9 to 3.6 and 4.2 [1]. In contrast, the number of patients without any co-morbidity declined in these groups from about 10 to 6% and 4%, respectively. In a Dutch series of 3864 lung cancer patients, the prevalence of co-morbidity was higher in patients aged over 70 years (69%) compared with patients aged below 70 years (52%) [25]. The most frequent concomitant diseases were cardiovascular (23%), chronic obstructive pulmonary disease (22%), other malignancies (15%), hypertension (12%) and diabetes mellitus (7%). A comparable increasing prevalence of relevant comorbid

conditions with increasing age was observed in colorectal and prostate cancer patients in our country [16,26]. The assessment of co-morbidity is important for decisions regarding treatment and the expected toxicity profile, but has also implications for prognosis. The number of co-morbidities were predictive of early mortality in colon- and breast cancer [27,28]. In breast cancer patients suffering from three or more concomitant diseases the all cause mortality appeared 4-fold higher than in the patients without comorbid conditions [28]. In Dutch colorectal cancer patients, co-morbidity did not affect the resection rate but did negatively influence short-term survival [26].

A consequence of the enhanced co-morbidity is the accompanying, often abundantly provided, co-medication. A cross-sectional study in three general practices in the Netherlands showed that one third of all patients aged over 65 years used two or more drugs [29]. This polypharmacy can lead to drug interactions interfering with cytotoxic agents, and therefore should be considered in terms of treatment decisions.

Functional status

Ageing is often associated with a decline in functional status, which refers to the ability to perform tasks, and includes basic activities of daily life (BADL) such as eating, bathing, dressing and movement but also more complex activities such as using the telephone, shopping, housekeeping, handling finances (instrumental activities of daily life, IADL). In a Danish cross sectional study, the physical abilities evaluated by changes in activities of BADL gradually inclined with ageing without leveling off [30]. Functional limitations, low physical activity as well as cognitive impairment have been identified as risk factors for receiving inadequate treatment for cancer [31]. Cancer in itself is associated with impairment in BADL and IADL, but these reductions are less important than the limitations observed in other chronic conditions such as ischaemic heart disease, chronic pulmonary disease and rheumatoid arthritis [32].

Functional status should be evaluated accurately for several reasons. First, in oncological trials func-

tional status is often assessed by the Karnofsky score or the ECOG performance score, which are known for their predictive value for outcome. However, these quite crude scales probably underrate functional impairment in older persons. Second, physical functioning prior to the diagnosis appeared to be a predictor of physical functioning during and after treatment in geriatric cancer patients [33]. Last, physicians underestimate the functional disabilities and psychological problems of their patients [34,35].

Frailty

In geriatrics, the judgment of the 'general condition', considering multiple domains prevails.

Frailty is a metaphysical notion implying this 'general condition'. The frailty concept is an umbrella, covering multiple domains, such as co-morbidity, functional and sensory impairment, incontinence, mobility, falls, nutrition, cognitive functioning, psychological factors and social support [36–38]. Until now, no agreement has been accomplished about the ultimate definition of frailty. Moreover, a valid assessment of frailty is still lacking.

Co-morbidity and functional status are important determinants in cancer treatment with respect to efficacy, toxicity and survival, as discussed above. Previously, they appeared independent variables in older cancer patients, and should be measured separately [39].

However, one might question whether the the Karnofsky or WHO-scales used in oncological research for functional status are sensitive enough for use in older patients. In addition, co-morbidity and functional status comprise only two domains and a more comprehensive multi-domain evaluation is advocated [40,41]. This comprehensive screening however, is time-consuming and seems not always necessary. An alternative would be the 'Multidimensional Assessment for Cancer in the Elderly' primarily designed for oncological-geriatric research [42].

In the past, simple clinical screening instruments of frailty appeared useful in case-finding as well as in predicting outcome [37,43]. Frailty appeared to be more predictive of mortality and nursing home utilization than age or diagnostic groups in hospital-

ised patients [37]. Rockwood et al. reported a dose-response curve between frailty and institutionalisation as well as survival with their frailty scale, which probably under-rates psychosocial issues [43].

In geriatric oncology often the frailty definition according to Balducci is used (Table 1) [44].

This definition is for rapid screening very helpful, although a few comments can be made. In our opinion, age over 85 years should be considered more as a risk factor for frailty than as an absolute criteria. Prospective data using this frailty scale in cancer patients are not yet available, although some of the items proved predictors of survival. The frailty definition does not include a grading of the severity of frailty, which could be helpful for individual treatment decisions.

For these reasons, an easy applicable, validated assessment of frailty is urgently required. After implementation in clinical trials, this assessment could guide decisions regarding anti-cancer treatment. In case of recording a frailty score below a certain level A, treatment will be beneficial and coincide with acceptable toxicity, while in case of a frailty score above a certain level B, treatment will be unwise. In case of a frailty score between A and B, treatment can be considered, but intensive supportive care measures have to be taken.

Besides the prediction of efficacy and toxicity, this brief frailty assessment could even be a predictor of survival. The frailty value could be evaluated regularly, because several determinants can be influenced by interventions, such as nutrition.

Table 1
Frailty (according to Balducci): the presence of any of these criteria establishes frailty

Age	85 years and older
ADL	Dependence in one or more
Comorbidity	One or more
Geriatric Syndromes	One or more
	Delirium
	Dementia
	Depression
	Osteoporosis
	Incontinence
	Falls
	Neglect and abuse
	Failure to thrive

Acceptance of therapy

A noteworthy aspect of care for older cancer patients is their acceptance of the treatment proposed. In several studies age-related differences concerning the profit and loss account of treatment have been demonstrated. Older patients did not differ from younger patients in acceptance of aggressive chemotherapy aiming either cure or palliation, but were less willing to accept toxicity (with negative impact on quality of life) for survival time [45]. Bremmes et al. [46] sketched a hypothetical situation to untreated cancer patients at their first admission for receiving chemotherapy. "You have been referred to our oncological unit for treatment of a malignant tumour. The treatment is toxic and has numerous side-effects and drawbacks".

Patients under 40 years would accept this toxic treatment with hardly any benefit such as the reduction of symptoms (8%), life prolongation (3 months) and chance of cure (7%). In contrast, patients older than 60 years accepted this treatment only for a 50% chance of reduction of symptoms, a life prolongation of 12 months and a chance of cure of 50%. When a comparable hypothetical case was proposed to lung cancer patients who previously received chemotherapy, again a difference in minimal survival threshold for acceptance of treatment was established, namely 4.5 months for patients younger than 60 years and 9 months for patients older than 70 years [47]. In this study, also a choice was given between chemotherapy and supportive care. Remarkably, only 22% of all patients chose chemotherapy, in the group of patients younger than 60 years 65% chose supportive care and in the patients older than 70 years this percentage increased to 85%. These kind of studies have not only been performed in settings using chemotherapy. Among 148 patients with prostate cancer 26% preferred surveillance over surgery even when there was a small 10-years benefit of surgery [48].

Fortunately quality of life assessments receive increasing attention. Frequently used and validated scales are the EORTC QLQ-C30, the FACT scale and the Rotterdam symptom check list [49–52]. However, the interpretation of data obtained by surveys of quality of life need some consideration and pitfalls can be recognized. Statistically signifi-

cant changes do not always correspond with clinically relevant changes [53]. There is still a lack of large databases enclosing normal values for 'healthy' persons, different age groups and certain patient populations [53]. The subjective grading of experienced changes in quality of life is not constant. Cultural factors influence quality of life and especially in multicentre studies this might confuse results [54]. Generally, symptom relief is highly valued and is usually associated with improvement of quality of life [55]. In optimal oncological care, the quality of life at presentation and the patients' expectations and desires about their lives have to be elucidated before treatment is started and probably even before far reaching examinations have been arranged. In case of abandoning anti-tumour therapy, adequate palliative care should be provided. Paralleling differences in cancer treatment, differences in palliative care between age groups have been recognized, in which older patients often come off badly compared to younger patients [6,56].

Future perspectives

The issue of oncological care in old age is extensive and complex, and requires more attention and education of health care staff [7]. Oncologists should be aware of the pros and cons of cancer treatment, which in turn should be assessed by validated instruments. It is to be hoped that a frailty-indicator will be developed, which can be implemented in oncological research.

Challenges for research comprise studies directed specifically at older patients. In these studies, geriatric and frailty assessments should be taken along with quality of life as a primary endpoint. This should provide grounds for treatment decisions, and lead to evidence-based geronto-oncology. However, because of the enormous heterogeneity in the older population, the evidence achieved will not unequivocally correspond with the best treatment for the individual patient. Patients will still require some individual balancing of treatment options.

Leading on from the fact that oncological care to, only a few, children is provided by special paediatric oncologists, we advocate the emergence of special geronto-oncologists, in the first instance for academ-

ic centres. These geronto-oncologists should not only provide care to older cancer patients but also play an important role in clinical research and education of oncologists in referring centres and community based physicians. This may lead to tailored oncological care for older persons, so that the lamentation from the Lancet in 1990 "Cancer in the elderly, why so badly treated" [57] can be definitely abandoned in the new century.

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