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Lung Cancer in Elderly

Anne Dagnault and Jean Archambault

*Radiation Oncology Department, CHUQ-Hôtel-Dieu de Québec,
Canada*

1. Introduction

Lung cancer is one of the leading causes of cancer in the population. The aging population is a reality. More and more, in oncology, we are facing challenges about management of cancer in this important population. In this chapter, we will review data on lung cancer and aging. We will explore how to evaluate this particular population to offer them the best treatment possible, bearing in mind that some adjustment may be necessary compared to younger population.

2. Definition of the elderly

2.1 Chronologic aging

The cut-off point for an adult to be considered “elder” is not well defined. According to most of the literature, age 70 years is used as a chronologic marker for definition of elderly population. This is also the age most commonly used in the clinical trials in oncology as a limit for recruitment (Balducci, 2000).

2.2 Physiologic aging

In fact, elderly should be referring to a state either than a chronological age. It is well known that with time, especially at or around 70 years of age, a number of age-related physiologic changes occur affecting the physiologic reserve of the person. Many of these changes may affect the tolerance to cancer treatment as; decreased renal and liver functions, decreased volume of distribution, immune response and intestinal absorption (Avery et al., 2009). Talking more specifically about lung function, age-related pulmonary changes include a decreased response to hypoxemia or hypercapnia, decreased elasticity of the lung tissue, increased ventilation-perfusion mismatch, and decreased forced expiratory volume (Gonzalez-Aragoneses et al., 2009).

3. The aging population

Population age is increasing in developed country. In the United States, in 2000, there were 35 million persons aged over 65 years old. This proportion is expected to continue to increase from 40 million in 2010 to 81 million in 2040 (U.S. Census Bureau). In Canada, the situation is similar. In 2036, Statistics Canada estimates the population of persons aged 70 years and older to be situated between 10 and 10.8 million.

The National institute of Aging has characterised the aging of the American Society as a “silver tsunami for which we are unprepared” (Fried & Hall, 2008).

4. Cancer as an aging problem

It is recognized that the risk of cancer increases with age. In Canada, 43% of all new cancer cases and 61% of cancer deaths will occur among those who are at least 70 years old. Figure 1 represents the number of new cases of cancer for Canadian males together with the corresponding age-standardized rates for 1981-2006 and estimates to the year 2010. It shows that despite the relative stability in age-standardized rates, the number of new cancer cases continue to rise steadily as the Canadian population grows and ages. The figure shows the major contribution of the population’s growth and the aging population to the rising numbers of new cases from cancer.

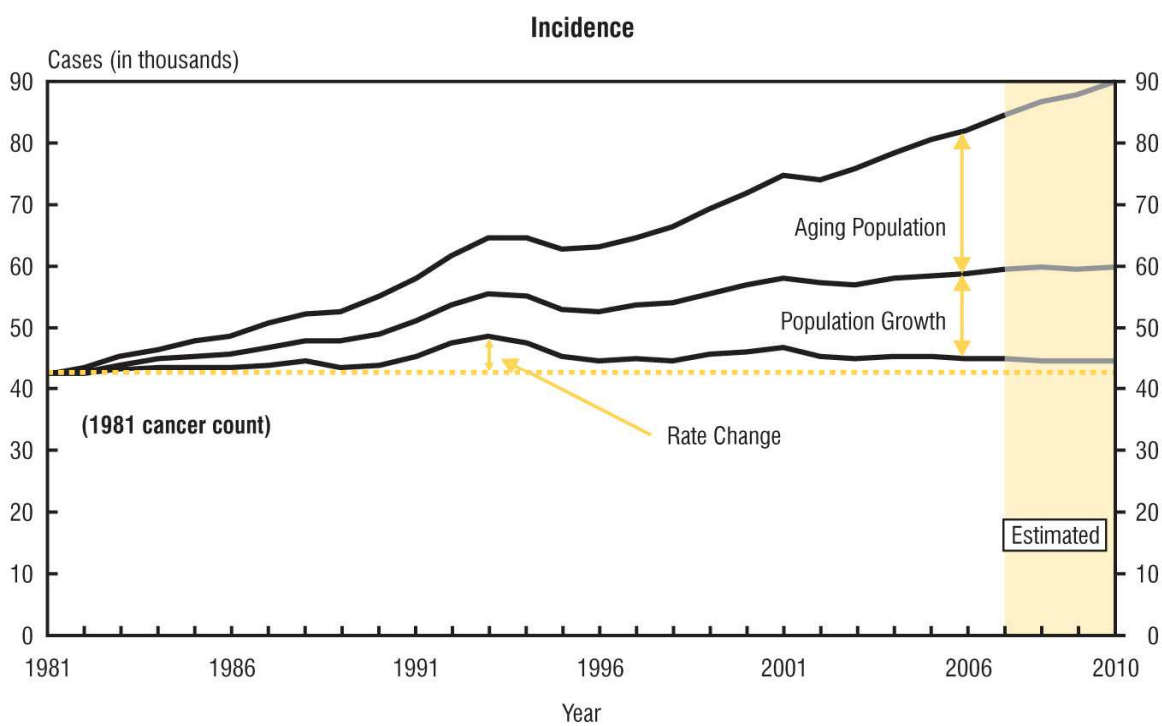


Fig. 1. Incidence of cancer for Canadian males with age-standardized rates (1981-2006) (from Canadian Cancer Statistics 2010).

The lowest line represents the total number of new cancer cases that would have occurred each year if the population size and age structure had remained in the same as it was in 1981, reflecting the impact of changing risk. The middle line represents the number of new cases that would have occurred if the age structure had remained the same as it was in 1981, reflecting the impact of changing risk and population growth. The top line, the actually occurring number of new cancer cases, represents the combined impact of changes in risk, population growth and the aging of population. This figure is similar for new cancer cases of adjuvant chemotherapy rates in male and female. It indicates the importance of the impact of the aging population on the growth in the number of cancer cases that has occurred over the last 30 years (Canadian Cancer Statistics 2010).

5. Lung cancer in elderly

In Canada, both in men and women, lung cancer is the second most common cancer (13.9%) after prostate cancer in men and breast cancer in women. In 2010, it represents 24,200 new cases. More than half of all newly diagnosed cases will occur among people aged 70 years and older. More importantly, lung cancer is the leading cause of cancer death in both sex representing 20,600 deaths. Lung cancer deaths peak at age 70-79 years for both male and female in Canada.

In United States, median age for diagnosis for lung cancer was 71 years of age from 2004 to 2008 according to SEER data. 29% of cases were in persons aged between 75 and 84 and 8.3% were older than 85 years old. In the same period, the median age at death for cancer of the lung and bronchus was 72 years of age, with 30.7% between ages 75 and 84 and 9.6% in persons older than 85 years.

6. Evaluation of the elderly cancer patient

6.1 Oncologic evaluation

On the oncologic point of view, evaluation of an elderly patient should be exactly the same as for a younger one. Clinical and pathological stage of disease should be determined with the same accuracy. The complete workup for lung cancer includes at least a complete history and physical examination, a bronchoscopy, a CT scan of the chest and upper abdomen and blood tests for assessment of liver and renal function. CT scan of the head should be done if there are any suspicions of metastasis, or in advanced cases, as well as a complete bone scan. Ideally, patients must have a Pet-Scan to complete the workup. As for younger patients, biopsy of the tumour for histology is always mandatory.

When surgery or radiation therapy treatment are anticipate, pulmonary function test are essential to determine the capacity of the patient to tolerate those procedure.

Unfortunately, in the elderly population, lung cancers are less susceptible to be diagnosed at an early stage and the evaluation is more often incomplete. More than 20% of cancers in patients aged more than 85 years of age are diagnosed on a clinical or radiologic basis without pathologic confirmation (Goddwin & Osborne, 2004).

6.2 Geriatric evaluation

The geriatric assessment of a patient is also a diagnostic process. It may be done by an individual clinician, but more often, the geriatric evaluation involve a more intensive multidisciplinary program. This is often referred to a comprehensive geriatric assessment (CGA). The optimal goal is to evaluate the patients' global and functional status, in order to improve treatment decisions and outcomes. His use is now recommended by the International Society of Geriatric Oncology (SIOG) for all cancer patient aged more than 70 years old. This recommendation is based on the evidence that the incidence of geriatric problems increases sharply after 70 in cancer patients (Extermann et al., 2005, as cited in Balducci et al., 1990). The CGA permits to detect unaddressed problems, improve older cancer patients functional status and possibly their survival. The SIOG was not able to recommend any specific tool or approach above others for this assessment (Extermann et al., 2005).

Whatever the approach or the tools used to complete a CGA, different aspects should be included as; functional status, comorbid medical conditions, cognitive and nutritional status, psychological state, social support and review of the medication.

6.3 Components of a comprehensive geriatric assessment

6.3.1 Functional status

Functional status represents the patient's ability to perform daily activities. The more commonly used performance status score are the Karnofsky or Eastern Cooperative Oncology Group (ECOG) scales. In older patients, these scores were showed to under-represent the degree of functional impairment (Repetto et al., 2002). For that reason, it is important to include the autonomy for Activities of Daily Living (ADL), such as feeding, grooming, transferring and toileting and for the Instrumental Activities of Daily Living (IADL) such as shopping, housekeeping, managing finances, preparing meals and taking medications in the evaluation of functional status for these patients.

A study of 566 patients with advanced non-small cell lung cancer age ≥ 70 years receiving chemotherapy explores the impact of functional status on the overall survival. Improved overall survival was associated with independence in IADLs and higher quality of life scores. Limitations in basic ADLs and the presence of comorbidity were not predictors of a decrease in overall survival (Maione et al. 2005). However, limitation in basic ADLs was previously shown to predict chemotherapy toxicity and postoperative survival and morbidity (Extermann & Huria, 2007).

6.3.2 Comorbidities

In cancer patients, comorbidity can be seen as a competitive cause of death. It is well known that with increasing age, the number or comorbid medical conditions increases. It is important to consider these comorbid conditions in life expectancy and potential treatment tolerance when balancing the risks and benefits of them. Charlson Comorbidity Index (CCI) is a way to assess the number and severity of comorbid condition (Charlson et al., 1987).

Additional issues regarding the treatment of elderly cancer patients are the presence of geriatric syndromes as; dementia, delirium, depression, falls, neglect and abuse, failure to thrive, incontinence and spontaneous bone fracture.

A review of the National Cancer Institute of Canada (NCI) Clinical Trials Group in 2008 analyzed 1,255 patients enrolled in two large, prospectively randomized trials of systemic chemotherapy for NSCLC. Patients aged 65 and older were more likely to have a CCI score of ≥ 1 (42 % versus 26%). Age did not influence overall survival, but the Charlson Comorbidity Index ≥ 1 appeared prognostic for poorer survival (Asmis et al., 2008). The impact of comorbidity was recently studied in a population of 83 untreated lung cancer patients over the age of 70. It was shown that they have a high prevalence of comorbidity but these may not cause patient's death (Gironés et al., 2011).

6.3.3 Cognitive status

Cognitive deficits are associated in the geriatric population with an increase in mortality of over 150% at 5 years. They are also associated with an increase risk of complications, depression, and functional decline.

Cognitive deficits and dementia in oncology patient is often unrecognized. However, it was demonstrated that 25-50% of older patients with cancer had abnormalities in screening cognitive exam that warranted further evaluation. Cognitive dysfunction can have significant impact in the pathway of cancer treatment; dysfunction on the ability to weigh the risks and benefits of cancer therapy, compliance with treatment, and recognition of the signs of toxicity that require medical attention (Extermann & Hurria, 2007). It was

previously demonstrated than even when treated in a specialized geriatric oncology program, cognitively impaired patients had a survival of cancer one third of that of nonimpaired patients in various tumor type and stages, even if they received similar treatments (Extermann & Hurria, 2007, as cited in Callen et al. 2004). Therefore, screening for cognition should be part of the evaluation in the elderly patient afflicted with lung cancer.

6.3.4 Nutritional status

The importance of malnutrition on overall survival and morbidity is well known in the general cancer population. It is also demonstrated that aging is a factor for an increase risk of malnutrition. Other than mortality, poor nutritional status can have an impact on the quality of life, response to chemotherapy, and any other medical complications.

6.3.5 Psychological state

Many reports have shown that the incidence of psychological distress is approximately one-third of older patient with cancer. Studies of geriatric assessment show that 14% to 40% of older patients have depressive symptoms (Extermann & Hurria, 2007). A large epidemiologic studies of 24,696 older breast cancer in the SEER database (ages 67 to 90 years) revealed that a recent diagnosis of depression put them at risk for receiving less-than-definitive treatment for their cancer, and they also experienced shorter survival (Extermann & Hurria, 2007 as cited in Goddwin et al, 2004). In addition, depressive symptoms have impact on quality of life, increased utilization of healthcare resources and can affect treatment compliance.

6.3.6 Social support

Social support is a major factor that puts patients at risk for psychological distress. Even monthly telephone call was shown to reduce depression in older patients with cancer. This method was demonstrated to reduce significantly anxiety ($p < 0.0001$), depression ($p = 0.0004$), and overall distress ($p < 0.0001$) compare to no similar support (Extermann & Hurria, 2007 as cited in Kornblith et al., 2006).

6.3.7 Review of the medication

Polypharmacy is a significant problem in the geriatric population. Many physiologic changes in the elderly may have impact on pharmacokinetic; a decrease in total body water, an increase in body fat, a decrease in renal function, decrease in hepatic mass and blood flow, and decrease in bone marrow reserve. The combination of those changes and polypharmacy is associated with an increase risk of drug interactions, adverse drug events and problem with compliance. Therefore, it is essential to regularly review the medication list to discontinue any unnecessary medications and avoid potential drug interactions.

6.4 Impact of the CGA

Many trials have studied the impact of a CGA on outcome of elderly patients with cancer. A meta-analysis of 28 controlled trials had demonstrated that CGA if linked to geriatric interventions reduced early re-hospitalisation and mortality in older patients through early identification and treatment of problems (Pallis et al. 2010, as cited in Stuck et al., 1993). In a

recent French study it was shown that comprehensive geriatric evaluation did significantly influence treatment decisions in 82% of the older cancer patients. In this 161 patients group, with a median age of 82.4 years, cancer treatment was change in 79 patients (49%), including delayed therapy in 5 patients, less intensive therapy in 18% and more intensive therapy in 28% of patients (Chaïbi et al. 2010).

It is interesting to notice that even a simplified geriatric assessment, adapted to cancer and quicker to perform than a CGA was recently demonstrated effective in patients with thoracic cancer. It is an important aid to decision-making in the management of elderly patients with bronchial cancer (Cudennec et al., 2010).

| Aim | Method |
|--|---|
| Social evaluation | Place of residence: home, type of residence for an elderly, dependent patient Helpers, aids around the home |
| Iatrogenic risk | Number and classes of drugs |
| Existence of ≥3 co-morbidities significant in geriatrics | Dementia, confusion, depression, incontinence, falls, malnutrition, progressive heart failure, other cancer |
| Nutritional status | Loss of weight over the previous 3 months (≥5%), albuminemia levels |
| Cognitive functions | Mini Mental State Examination (MMSE), Clock drawing task |
| State of mind | Mini-Geriatric Depression Scale (mini-GDS) |
| Risk of fall | Timed “Get up and go” test |
| Sense organs | Vision and hearing |
| Autonomy | Instrumental Activities of Daily Living (IADL) |

Table 1. Simplified Geriatric Assessment of patients with bronchial cancer (Cudennec et al., 2010).

7. Surgery

Surgery remains the mainstay of treatment for early stage NSCLC. Unfortunately, according to most published reports, elderly have a significant lower resection rates compared to younger patients and age is one of the factor influencing the decision for surgical treatment. Sigel retrospectively analyzed 27 850 patients with stage I lung cancer. The rate of lung surgery was 95% for patients less than 60 years and 79% in patients > 80 years (Sigel et al., 2009). An analysis of Riquet showed that patients older than 70 years of age represents 21.7% of patients who had surgery for lung cancer, patients of 75 years and older represents 8.8% and older than 80 years old are only 1.9% in proportion (Riquet et al., 2001).

These observations are still true, even considering the significant improvement in anesthesia, in technical procedures of lung resection and post-operative care that greatly enhanced the security of the surgery, even in a frail population. In patients with stage I and II, surgical option is still the prefer treatment option. The 5-year overall survival rates for pathological stage I range between 67% for pT1pN0 and 57% for pT2pN0 tumors. The corresponding values based on clinical stage are 61% for cT1cN0 and 37% for cT2cN0.

7.1 Evaluation and selection of patients

Patients must have a very good evaluation and adequate scrutiny is necessary to evaluate those who will really benefit from surgery. Preoperative assessment of cancer in the elderly (PACE) incorporates validated instruments including the CGA, an assessment of fatigue and performance status and an anaesthesiologist's evaluation of operative risk. It is considered to be a valuable tool in enhancing the decision process concerning the candidacy of elderly patients for surgical intervention. It also reduce inappropriate age-related inequity in access to surgical intervention (PACE, 2008).

7.2 Different types of surgery are used for the elderly. But which one is better?

Survival data from the SEER database with patient of all ages shown that survival for lung cancer stage I and II were 56 and 34% respectively (Chang et al., 2007). The most important question regarding surgical resection for lung cancer is how aggressive should it be? The choice of the type of surgery is particularly important in the elderly. Right pneumonectomy is likely to be avoided in octogenarians (Broks et al., 2007; Port et al., 2004; Van Meerbeeck et al., 2002), but low rate of pneumonectomy in different series make this difficult to assess. As an indication, the British Thoracic Society Guidelines indicates that pneumonectomy is associated with higher risk of mortality.

The sublobar pulmonary resection remains controversial in patients of any age. In a SEER analysis of 14,555 patients with stage I or II NSCLC, it was showed that benefit of a lobectomy was not evident for patients older than 71 years compared with limited resection (Meryet al., 2005). Okami did a non-randomized study to evaluate the different types of surgery in the elderly patients. A total of 764 patients, including 133 elderly and 631 younger patients had lobectomy or sublobar resection. The survival after sublobar resection was significantly lower than that after standard lobectomy in the younger group (64% vs 90.9%). Comparatively, no difference was seen in the elderly (67.6% vs 74.3%). However, locoregional recurrences were higher in patients with sublobar resection than lobectomy in young and older patients (Okami et al., 2009). A phase III study regarding this specific topic would be necessary to confirm this information.

Another study done in Pittsburg has compared lobectomy to the segmentectomy for stage I lung cancer. In a subgroup of 99 octogenarian patients, the segmentectomy was associated with an improvement of the 3-year survival ($p=0.02$) (Schuchert et al., 2009).

7.3 The impact of comorbidities on surgical outcomes

A review of 10,761 patients with lung cancer stage IA showed the age of 67 years or more as an independent factor associated with long-term survival worse after surgery. One of the major criticisms of this study is that patients were not stratified based on their functional status or their comorbidities. It is known that these two factors are associated with advanced age and are predictors of mortality in elderly patients suffering from lung cancer (Maione et al., 2005; Frasci et al., 2000; Asmis et al., 2008; Schuchert et al., 2009).

In another study of 126 patients 70 years of age or older with lung cancer, the Charlson Comorbidity Index has been performed in patients for lung surgery. A low score was a predictor of major complications after surgery (Birim et al., 2003). Some studies in patients older than 80 years of age were also conducted (Brokx et al., 2007; Okami et al., 2009; Wada et al., 1998). At the Mayo Clinic, 294 patients aged between 80 and 94 years underwent pulmonary resection and their 1-year survival was 80% and 2-year survival was 62% (Dominguez-Ventura et al., 2007).

A review of 297 articles was done by Chambers (2010) to consider the impact of lung resection on morbidity, mortality and postoperative quality of life for patients aged over 70 years. They found twelve articles to answer this question. The collective analysis of these 12 articles showed a five-year survival following surgery for early stages in those under age 70 between 69 and 77%, for those over 70 years, the five-year survival ranges from 59 to 78%. The 30-day mortality rate was 5.7% in patients younger than 70 years against 1.3 to 3.3% in those over 70 years, length of hospital stay after thoracoscopy was respectively 4.6 and 4.9 to 5.2 days. The post-operative lung functions were also equivalent between the two groups. FEV₁ decreased 13% compared to 18% in patients older than 70 years ($p=0.34$) comparing the functional vital capacity decrease were equivalent between both groups (9% vs 14%).

Lung function was also compared among young and elderly patients after lobectomy for early stage NSCLC. Changes in FEV₁ and functional vital capacity were not significant although postoperative complications occurred in 32% of younger patients and 48% in the elderly (Sullivan et al., 2005).

8. Adjuvant chemotherapy

The use of adjuvant chemotherapy in the elderly is increasingly popular (Wang et al., 2008). In a SEER database, 25.8% of patients aged between 66 and 69 years received adjuvant treatment compared to 19.8% for those aged 70 to 74, 13.7% for those of 75 to 79 and only 9% for patients older than 80 years old. In the LACE meta-analysis of 4,584 patients with adjuvant chemotherapy, the hazard ratio for mortality was 0.89 and favored chemotherapy, with a 5-year absolute survival benefit of 5.4%. The authors concluded that the benefit of chemotherapy is similar between the elderly and their younger counterpart (Pignon et al., 2006). Another meta-analysis of the impact of adjuvant chemotherapy done by the Non-Small Cell Lung Cancer Collaborative Group and regrouping 52 trials with 9,387 patients between 1963 and 1992 has showed the same absolute benefice on survival of 5% at 5 years. The odds ratio for survival is similar between the different groups of age (Cochrane review, 2000).

Pepe et al. at ASCO meeting in 2006 presented an age-specific evaluation of BR10 study, a phase III trial with patients with stage Ib and II NSCLC and comparing four cycles of cisplatin and vinorelbine with observation. 155 patients of the 482 enrolled in this study were aged 65 years and older. Baseline characteristics were similar between age cohorts except for the histology with more elderly patients with squamous cell cancer. In general, elderly received a lower mean dose intensity of chemotherapy. Overall survival was in favor of the younger patients, but chemotherapy led still to a benefit effect compared with standard observation in elderly. There were few patients aged over 75 and without regard to treatment, survival was still poor at 26% at 5 years (Pepe et al., 2007).

Other studies have been conducted on adjuvant chemotherapy, but the elderly subgroup was either absent, very little or without subgroup analysis as in the IALT study (Arriagada et al., 2004), Anita study (Douillard et al., 2006), Italian study Alpi (Scagliotti et al., 2003), Big Lung Trial (Waller et al., 2004) and CALGB (Strauss et al., 2004, 2006).

Because studies on this subject are retrospective, it is still difficult to conclude on the exact role of surgery in elderly patients with lung cancer. However, surgery should be considered for patients in good condition. Lobectomy is preferable to the limited resections if patients are medically fit (Alberts et al., 2007). Pneumonectomy is associated with greater morbidity and mortality and should only be performed in a highly selected group of patients. With

few conclusive results available from studies of adjuvant chemotherapy in elderly, it is difficult to conclude that it should be a standard treatment for older people. However, we can possibly extrapolate from studies done with younger patients and use it in selected patients aged less than 75 years of age.

9. Radiotherapy

It was demonstrated that nearly 25% of patients with disease stage I or II did not have surgery, most often because of significant comorbidities, patient preferences or poor lung functions (Bach et al., 1999; Spiro et al., 2002). For elderly who are not candidates for surgery, radiation therapy is possible. Unfortunately, it usually gives poor results with a 5-year survival estimated at between 6 to 14% (Razet al., 2007; Wisnivesky et al., 2005). In this section, the curative as well as palliative indication for radiation will be discussed.

Radiation therapy has been shown to improve outcomes compared to best supportive care alone (Raz et al., 2007). A subgroup analysis, in the study of Morita, assessed the impact of age in relation with survival in irradiated patients. One hundred and forty-nine patients older than 80 years with stage I lung cancer were included in this analysis. The survival was lower in older patients compared with younger. The 3- and 5-years actuarial survival was 15.4% and 7.7% in octogenarians versus respectively 38.2% and 25.2% in younger ($p=0.035$) (Morita et al., 1997). Similar results were found by Sibley (Sibley et al., 1998). However, a retrospective study from 6 studies of EORTC with 1,208 patients has shown no difference in overall survival between patients older or younger of 70 years (Pignon et al., 1998). Other retrospective studies compared treatment outcomes in younger and older patients. The North Central Cancer Treatment Group studied the impact of age (≥ 70 years versus younger) with two different schedules of radiation, either daily or twice per day, combined with concurrent chemotherapy. The 2-year survival rates were 39% in younger and 36% in the elderly and at 5-year, it was 18% versus 13% in patients ≥ 70 years ($p=0.4$). Toxicity of grade 4 or more were significantly higher in older patients (81%) than in younger ones (62%). The conclusion of this study was that toxicity is higher in elderly, but the survival is similar. Thus for fit patients this treatment can be proposed (Schild et al., 2003).

In the treatment of locally advanced NSCLC, the standard of care is radiation with chemotherapy based on cisplatin. Two major trials demonstrated a survival advantage for the use of induction chemotherapy prior to radiation therapy (Dillman et al., 1990; Sause et al., 2000). After the publication of these results, studies have been done to test the combined treatment. These studies shown that combined chemoradiotherapy is more effective compared to radiation alone (Dillman et al., 1990; Furuse et al., 1999). Elderly were in general excluded from these studies and few trials have been done about the role of combined chemoradiation in this particular population. A phase II study in 40 elderly patients with unresectable stage III or medically inoperable stage I and II lung cancer treated with concurrent carboplatin and radiation was done. For stage IIIA/IIIB patients, the median survival time was 15.1 months and 1- and 2-year actuarial survival rates were 52.6% and 20.5%, respectively. For stage I/II patients, 1- and 3-year actuarial survival rates were 90.9% and 69.3%, respectively (Atagi et al., 2000).

A phase III trial was performed by Atagi in 2005 with patients older than 70 years with stage III NSCLC. Patients were randomly assigned to either radiation therapy (dose of 60 Gy) with concurrent carboplatin or radiation therapy alone. 4 patient's death may have resulted

from poor compliance in the design of the radiation fields. This trial was closed early with only 46 randomised patients.

A retrospective study of Langer (2002b) examined 104 patients older than 70 years with good performance status and minor weight loss receiving either sequential chemotherapy followed by daily radiotherapy, concomitant chemotherapy with daily radiotherapy or concomitant chemotherapy with twice daily radiation in phase III RTOG protocol 94-10. Concurrent treatment was proved to be favourable in the elderly, but toxicities were increased in this group. Median survival was 22.4 months for concurrent therapy with daily radiation, 16.4 months for concurrent chemotherapy with twice daily radiation treatment and 10.8 months for sequential treatment ($p=0.069$).

Patients over 70 years of prospective studies performed by CALGB were retrospectively analyzed by Rocha Lima (2002). In CALGB 9130, patients were randomised between vinblastine and cisplatin followed by radiation alone at dose of 60 Gy or neoadjuvant vinblastine and cisplatin followed by concurrent radiation with carboplatin. 22% of the patients enrolled in this study had between 70-79 years and no patients had more than 80 years of age. Age was not found to be a factor in survival or response rate, but elderly had more neutropenia and renal toxicity of grade 3 or more.

Hayakawa (2001) showed an alteration of performance index in only 5% of patients between 75-79 years and 8% in those more than 80 years when they are treated with radiation alone of 60 Gy. Another study presenting results about toxicity in 51 patients older than 65 years shows no augmentation of the toxicity in these patients in function with age, but survival was significantly correlated with performance status and importance of comorbidities (Fiorica et al., 2010).

Retrospective case series of older patients treated with curative radiation alone have demonstrated a median survival of up to 37 months for stage I-II and 8 months pour stage III (Bonfili et al., 2009; Lonardi et al., 2000; San José et al., 2006 & Tombolini et al., 2000).

It is recommended to provide elderly patients with advanced lung cancer disease in good general condition radiotherapy combined with chemotherapy. Concomitant treatment gives better results, but it is also more toxic to patients. For those that concomitant treatment is not possible, chemotherapy may be given before sequential radiotherapy. If the general condition of the patient or his comorbidities do not allow use of chemotherapy, he should receive radiation therapy alone either for curative or palliative purpose.

9.1 Radiotherapy planning

9.1.1 Treatment volume

There would be an increase of interruption of radiation treatment with the increased volume of the radiation field in patients over 80 years (Zachariah et al., 1997). For patients over 90 years, Ikeda (1999) showed that radiotherapy is better tolerated if treatment is limited to the macroscopic volume. In Pergolizzi (2002), 40 patients with stage IIIA, aged older than 75 years, were treated with involved field with median dose of 60 Gy. The overall survival was 18% at 3-years and 12% at 5 years.

9.1.2 Radiation technique

Technique of radiation could also influence the response to treatment in elderly population. Thus, Park's study evaluate whether complex radiotherapy planning with 3D techniques was associated with improvement outcomes in elderly compared with intermediate analysis

with 2D planning. They found a better survival in patients treated with a more complex planning (Park et al., 2010).

In 2008, Yu conducted a multicenter prospective study in older patients with Intensity Modulated Radiotherapy (IMRT), an inverse planning technique. 80 patients had stage I and II disease and were medically inoperable or refused surgery. Patients received 66 Gy to involved field including primary tumor and clinical enlarged nodes. Objective response rate was 88.6%, with 1-, 2- and 5-year overall survival rates of 65.8%, 55.7% and 25.3% respectively and local progression-free survival was 84.8%. Toxicity was minimal. This study confirms that involved field radiation is a reasonable treatment for elderly patients.

9.2 Stereotactic radiation

Stereotactic body irradiation (SBRT) is a technique that utilizes precisely targeted radiation to tumor while minimizing radiation to adjacent normal tissue. This is accomplished by using multiple beams (typically 10 to 12) or large angle arc rotations. This technique is promising in the elderly. SBRT accurately delivers highly hypofractionated doses of radiation. High biologically effective radiation doses are generally of advantage with regard to tumor cell kill and local tumor control. SBRT is in general well tolerated and local control is similar than for patients treated with surgery.

In Zimmermann study, 68 patients were treated with a mean dose of 37.5 Gy in 3-5 fractions. The mean age was 76 years. Actuarial local tumor control at 1, 2 and 3 years was 96%, 88% and 88%. Disease-specific survival was 96%, 82% and 73% at 1, 2, and 3 year follow-up. 2 patients died by local tumor progression and a total of 8 patients died from their lung cancer disease. 55% of patients had mild acute and subacute toxicities (Zimmerman 2006). In Indiana University study, patients received in a phase I trial 66 Gy in 3 fractions for T2 tumors. The maximum tolerated dose was not reached for T1 tumors at 60 Gy in 3 fractions (McGarry et al., 2005; Timmerman et al., 2003). A RTOG multicenter study treated 59 patients with T1-T2N0 tumor with 54 Gy in 3 fractions. Three-year local control of the tumor was 98%. The three-year disease-free and overall survivals were 48% and 56% respectively (Timmerman, 2010).

In general, the results for stereotactic radiotherapy appear better than those of standard radiotherapy. Local control at 3 years vary from 86-95% (Baumann et al., 2006, 2009; Onishi et al., 2007; Xia et al., 2006; Zimmermann et al., 2006) for patients treated with SBRT while for external radiotherapy, local recurrences are more than 50% (Rowell et al., 2001 & Qiao et al., 2003) with 5-years survival around 10 to 30%.

Moreover a Palma analysis on 875 elderly patients shown that SBRT introduction was associated with an improvement of 16% in the use of radiation, and a decline in the number of untreated elderly patients (Palma et al., 2010).

9.3 Palliative radiation

The main goal of palliative radiation is to decrease the pulmonary symptoms of the patients. The number of treatment may vary according to the general functional status of the patients. According to a review of 13 randomized trials, no significant difference was observed for specific symptom control end points, but there is an improvement in survival favoured with high dose radiotherapy. For good functional status patients, it is recommended to use a palliative dose of radiation with a biological effective dose (BED) of at least 35 Gy₁₀ (Fairchild et al., 2008). Another review of 12 randomized controlled studies recommends a

short course (one or two fraction) of hypofractionated radiotherapy for the majority of the patients. Selected patients with good performance status should be considered for higher dose regimens as this could increase their survival (Toy et al., 2003).

9.3.1 Brachytherapy as palliation

Another way to treat lung cancer disease is using palliative brachytherapy. This treatment is effective to treat endobronchial disease. This often causes cough, hemoptysis and dyspnea. Stout compared external beam radiation therapy (EBRT) with endobronchial brachytherapy. He showed that EBRT offers a better palliation. Furthermore, there was slightly improved in survival (Stout et al., 2000). However, some patients cannot be treated with external beam radiation and brachytherapy could be offered to them. This approach seems to be more effective than other types of treatment, such as cryotherapy, cauterization or phototherapy, which only superficially destruct cancer cell (Hetzel et al., 1985; Sutedja et al., 1994; Walsh et al., 1990). High-dose rate brachytherapy is cost-effective and convenient owing to its short irradiation time and the fact that it can be provided on an outpatient basis. Endobronchial brachytherapy treats tumors up to 1-cm deep with 100% of prescribed dose and a decreasing dose can reach up to 2-cm deep.

A retrospective study with inoperable endobronchial lung cancer or metastasis had shown a significant improvement of symptoms and a good survival. 85% of patients had an improvement of the dyspnea during or shortly after the end of the treatment. Hemoptysis was stopped in all 23 patients of the study and 77% of them had an improvement of their cough. Patients had received 4 weekly fractions of 5 Gy each time. The complication rate during treatment was low (Dagnault et al., 2010).

Thus, for palliation, hypofractionated external beam radiation therapy and brachytherapy are alternatives to proper treatment for the relief of symptoms.

10. Chemotherapy

The treatment of advanced lung cancer requires chemotherapy. The standard combination is based on a combination of platinum and either vinorelbine, gemcitabine, paclitaxel or docetaxel. Few studies have yet been made to assess the best chemotherapy agents in elderly people. Many of the available data are from analysis of subgroups. The American College of Chest Physician guidelines recommends chemotherapy for stage IV NSCLC for selected patients older than 70 years. They caution that the benefits of chemotherapy in patients over 80 years of age are unknown and recommend instead a case by case assessment (Socinski et al., 2007).

The first important question is to determine if older people tolerates chemotherapy as well as younger patients and if the outcome of the treatments is the same. Some studies have been done in this direction. Nguyen (1999) compared cisplatin and gemcitabine to cisplatin alone and showed that tolerance to treatment and outcome of patients were identical for patients aged more or less than 70 years. In a subset analysis of an Eastern Cooperative Oncology Group study (ECOG 5592) patients received cisplatin and etoposide or paclitaxel. A total of 574 patients were included in this trial, which 15% were 70 or older. The response rate, the time to progression and the survival rate did not differ across groups but there was higher hematological and neuropsychiatric toxicities in the elders. There was no difference in the quality of life (Langer et al., 2002a). In the CALGB 7730 trial, 561 patients received paclitaxel compared to paclitaxel and carboplatin. The total of patients aged more than 70

years included in this trial was 27% or 155 patients. In that study, there was no formal subgroup analysis based on age, but the general data revealed no obvious difference between age groups (Lilenbaum et al., 2005). Further studies with subgroup analysis showed similar results (Belani et al., 2005; Earle et al., 2001; Hensing et al., 2003; Iberti et al., 1995; Langer et al., 2003; Rocha Lima et al., 2002). We can then conclude that the survival benefit is similar in elderly as in younger patients.

10.1 Importance of patient evaluation for chemotherapy treatment

As previously discussed, age by itself should not be a factor to decide if a patient will receive or not chemotherapy treatment. That decision should be taken considering the global functional status of the patients and his comorbidities, particularly cardiovascular and pulmonary ones. Aging is associated with several physiologic changes in organ function. Those changes could alter drug pharmacokinetics and they could have an impact on cytotoxic chemotherapy toxicity and tolerability (Wildiers et al., 2003). Thus, it is always mandatory to know the serum creatinine, but also the creatinine clearance to assess renal function, particularly for chemotherapy agents whose main route of elimination is by the kidney, as platinum derivatives and methotrexate. It is also important to evaluate the bone marrow reserve as this reserve may diminish with increasing age, and the risk of neutropenia increases with age (Langer et al., 2002; Rocha Lima et al., 2002).

10.2 Single-agent chemotherapy versus best supportive care

This question was evaluated in elderly patients with advanced/metastatic NSCLC in the Italian phase III trial, Elderly Lung Cancer Vinorelbine Italian Group Study (ELVIS) (Ardizzoni et al., 2005). Patients over 70 years of age were randomly assigned to either receive vinorelbine (30 mg/m² on days 1 and 8) or to receive best supportive care (BSC). Even if the accrual of this study was poor, with only 161 evaluable patients, it demonstrated that there was a significant advantage of survival in the vinorelbine arm ($p=0.03$). The median survival was 21 weeks for BSC versus 28 weeks for vinorelbine. Survival rates were 41% at 6 months for control arm compared to 55% in the vinorelbine arm. At 12 months, survival was respectively 14% for BSC and 32% with vinorelbine. This study also shown that patients receiving chemotherapy had a significant benefit in disease-related quality-of-life (QoL) measures (decreased pain $p=0.02$, decreased dyspnea $p=0.05$). Toxicity was acceptable. Only 5 of 71 older patients discontinued treatment secondary to severe toxic events (3 patients had constipation grade 3, 1 patient had constipation grade 4 and 1 patient had grade 2 heart toxicity). Even if 4 patients had a grade 4 leukopenia, treatment had not been interrupted.

10.3 Type of single-agent chemotherapy

Others chemotherapy were tested to find the best one in elderly patients. A phase III trial of West Japan Thoracic Oncology Group Trial (WJTOG 9904) randomized 182 patients older than 70 years between two agents: docetaxel (60 mg/m² on day 1) or vinorelbine (25 mg/m² on days 1 and 8). Patients received 4 cycles every 21 days. Median survival was not significantly different between two arms with docetaxel group being 14.3 months compared to 9.9 months with vinorelbine ($p=0.138$). However, others outcomes were significantly in favour of docetaxel. Thus, the progression-free survival was 5.5 months versus 3.1 months ($p<0.001$) and the response rate was 22.7% compared to 9.9% ($p=0.019$). Even if no

significant differences in global QoL were observed between the two groups, it is interesting to notice that patients in the docetaxel group had a significant greater improvement in overall symptom score than those in vinorelbine group. One disadvantage of docetaxel is that it induces significantly severe neutropenia more frequently. To conclude, docetaxel in monotherapy can be considered as an option of treatment in older patients (Kudoh et al., 2006). A phase 2 study performed in older patients compared gemcitabine and docetaxel and these agents had comparable efficacy and tolerability profiles (Leong et al., 2007).

In 2010, a phase II trial was published on the role of single-agent vinorelbine in patient older than 70 years with poor performance status (ECOG 2 or more). Forty-three patients received oral vinorelbine at the dose of 60 mg/m² on days 1 to 8 every 3 weeks. Overall response rate was 18.6%, median time to progression was 4.0 months and median overall survival was 8.0 months. This treatment was safe, without grade 3 or 4 toxicity, exception of a single non-febrile grade 3 neutropenia. Therefore, vinorelbine is safe for elderly patient, even in those with poor performance status (Camerini et al., 2010). Previously, another study with docetaxel in monotherapy, comparing weekly to 3-weekly administration, had also conclude that this treatment is effective and well tolerated in older patients, even with poor performance status (Lilenbaum et al., 2007).

An international expert panel ruled in favour of the use of single-agent chemotherapy in the elderly cancer patient. A third-generation agent is recommended for patients with any performance status and a platinum-based chemotherapy is recommended for those with performance status 0 or 1 and no contre-indications for comorbidities (Gridelli et al., 2005).

10.4 Combination versus single-agent chemotherapy

When studies revealed that single-agent chemotherapy improved survival, the search for more effective treatment continued and studies with combinations of chemotherapy have been done. Few randomized trials compared a combination of chemotherapy to a single agent. A French Intergroup study randomly assigned 451 patients of 70-89 years with performance status 0-2 that previously had untreated stage III or IV disease. Patients received a combination of carboplatin (AUC 6 on day 1) plus paclitaxel (90 mg/m², days 1, 8 and 15) every 4 weeks for a total of four cycles or a single agent (gemcitabine or vinorelbine, as predetermined by each institution). Gemcitabine (1,150 mg/m²) or vinorelbine (30 mg/m²) were given on days 1 and 8 for 5 cycles, every 3 weeks. At ASCO meeting in 2010, preliminary results were presented. For the first 313 patients, overall survival was significantly better in the combination arm with 10.4 months versus 6.2 months for single agent chemotherapy. Progression-free survival was significantly improved with combination chemotherapy (6.3 versus 3.2 months) and this difference was significant. The combined treatment was well tolerable even if neutropenia grade 3 and 4 were more frequent with the combination chemotherapy (Quoix et al., 2010).

A phase III study done by The South Italian Cooperative Oncology Group (SICOG) randomized patients between vinorelbine (30 mg/m² days 1 and 8 every 3 weeks), versus vinorelbine/gemcitabine (vinorelbine 30 mg/m² and gemcitabine 1,200 mg/m², days 1 and 8 every 3 weeks). In this study an interim analysis of survival with the first 60 patients was done. This analysis showed a significant survival advantage for the combination arm, with median survival of 29 weeks versus 18 weeks for the single arm. Following these results, the study was closed prematurely. The estimated 6-months and 1-year survival were 56% and 30% for the combination group and 32% and 13% in the single-agent arm ($p < 0.01$). Patients receiving monotherapy treatment had more symptoms and deterioration of quality of life.

Toxicity for the combination arm resulted in grade 3-4 neutropenia and thrombocytopenia in 38% and 13% respectively, and it was more prevalent than in the vinorelbine arm (Fraschi et al., 2000).

The Cancer and Leukemia Group B reported results of a phase III trial (CALGB-9730) that compared a combination of carboplatin and paclitaxel with paclitaxel in monotherapy. In this study, in which 155 patients had over 70 years, the response rate was 36% versus 21% respectively. The median survival was better in patients treated with the combination compared with monotherapy (8.0 vs 5.8 months respectively- non significant) (Lilenbaum et al., 2005).

Docetaxel and cisplatin doublet was compared with docetaxel in monotherapy in a phase III trial for elderly patient with NSCLC (Ansari et al., 2007). The planned sample size was 115 patients per arm, but the study was closed when the planned interim analysis showed that the doublet may be beneficial for patient aged 70 to 74 years.

However, results remain conflicting about the impact of a combination of chemotherapy. Multicenter Italian Lung cancer in the elderly Study (MILES) is another randomized study that involves patients aged 70 years or older. 698 patients were randomly assigned to gemcitabine alone (1,200 mg/m² days 1 and 8, every 3 weeks), vinorelbine alone (30 mg/m² on days 1 and 8, every 3 weeks) or gemcitabine (1,000 mg/m²) plus vinorelbine (25 mg/m²) both administrated on days 1 and 8 every 3 weeks (Gridelli et al., 2003). In this study, there was no difference between each single-agent and the combination arm for progression-free survival and overall survival. The estimated 1-year survival was 38% and 28% for patients respectively with vinorelbine and gemcitabine alone. In the combination arm, the overall survival was 30%. Median survival was 36 weeks for vinorelbine, 28 weeks for gemcitabine alone and 30 weeks for the combination. Toxicities were more frequent in the patients receiving combination chemotherapy. Thus, the combination of vinorelbine and gemcitabine was not shown to be more effective than single agent vinorelbine or gemcitabine in elderly patients with NSCLC (Gridelli et al., 2003).

A study analysed the baseline assessment of functional status, comorbidity and quality of life in elderly patients randomised in MILES trial. The presence of comorbidity was assessed with a checklist of 33 items, items 29 and 30 of the European Organisation for research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 were used for the quality of life and the Charlson scale was used to summarize cormorbidity. Better values of activities of instrumental activities of daily living (IADL) ($p=0.04$) and of baseline quality of life ($p=0.0003$) were significantly associated with better prognosis. Two others factors, either activities of daily living (ADL) and the Charlson scale score had no prognostic value (Maione et al., 2005).

An analysis from SEER data on patients with NSCLC over 65 years old evaluated the role of chemotherapy. Of over 21,000 patients evaluated, only 25.8% received first-line chemotherapy. After adjusting for comorbidities, age and performance status, patients with chemotherapy had an increased adjusted 1-year survival rate of 27% when compared to those without chemotherapy (11%) and a reduction of the adjusted risk of death, with a hazard ratio of 0.558. In this study, the use of combination of platinum agents was associated with an increase survival at 30.1% compared with single-agent at 19.4% (Davidoff et al., 2010).

A meta-analysis involving 2,867 patients of randomized controlled trial had shown superior results for efficacy and tolerability of docetaxel compared with vinorelbine or vindesine (Douillard et al., 2007; Laporte et al., 2007). The overall survival was 11% greater in patients

with doxorubicin compared with vinorelbine-based regimen (HR 0.89). This benefit was observed when docetaxel was used with or without a platinum agent as part of the regimen. In this meta-analysis, the benefit of docetaxel was at least as much important in older patients than in younger (Laporte et al., 2007).

In conclusion, for fit elderly patients, combination chemotherapy with a platinum-based regimen can improve survival without much toxicity. For patients without a good performance status a single-agent may be proposed.

10.5 Second-line therapy

No definitive studies have been conducted in the second-line setting in older patients with NSCLC. A phase II study has shown utility of docetaxel as second-line therapy. Tibaldi's trial demonstrated an objective response rate of 21% (Tibaldi et al., 2006). A subset analysis of a phase III trial compared docetaxel with pemetrexed, in 86 patients older than 70 years. This study demonstrated an objective response rate of 6% and a median overall survival of 9.5 months in the pemetrexed group and 7.7 months in docetaxel (not statistically significant) (Weiss et al., 2006).

10.6 EGFR-tyrosin kinase inhibitors

Over the last years, many biologic and targeted therapies have been approved. Molecules which target epidermal growth factor receptor (EGFR) include erlotinib and gefitinib. Some monoclonal antibodies are also now approved for the use in lung cancer like cetuximab which targets EGFR and bevacizumab which targets the vascular endothelial growth factor (VEGF).

Thanks to their oral administration and their toxicity profile, the EGFR may be alternative treatments in chemotherapy-naïve elderly. In a phase II trial, chemotherapy-naïve patients older than 75 years with advanced NSCLC received gefitinib in monotherapy. The primary objective of this study was the objective response rate. 49 patients were eligible. The response rate was 25% with median survival of 10 months and 1-year survival of 50%. Skin disorders were the most frequent adverse side effects, in 76% of patients (Ebi et al., 2008).

A phase II trial, INVITE, compared gefitinib versus vinorelbine in chemotherapy-naïve elderly patients with advanced non-small-cell lung cancer. 97 patients were randomly assigned to gefitinib and received 250 mg/d orally and 99 patients received vinorelbine (30 mg/m² infusion on days 1 and 8 of a 21-day cycle). The primary endpoint was progression-free survival and the hazard ratio was 1.19 (gefitinib versus vinorelbine). Overall survival was 2.7 months for gefitinib versus 2.9 months for vinorelbine and hazard ratio was 0.98. Disease control rates were 43.3% for gefitinib and 53.5% for vinorelbine. The quality of life (QoL) was also analysed in this study. There was no statistical difference between gefitinib and vinorelbine for pulmonary symptom improvement (PSI) and QoL. The improvement of overall QoL and PSI were 24.3% and 36.6% for gefitinib and 10.9% and 31.0% for vinorelbine respectively. 54 patients had EGFR FISH-positive and the hazard ratio were 3.13 for PFS and 2.88 for OS (Crinò et al., 2008).

A phase III trial, TOPICAL, compared erlotinib versus placebo in chemotherapy-naïve patients with poor performance status who were not candidate for first line chemotherapy. Overall survival was not significantly different between both groups (Lee et al., 2010).

For elderly patients whose tumor contains an EGFR mutation, it is recommended to treat with an EGFR TK inhibitor, as erlotinib or gefitinib, rather than chemotherapy.

Regarding the use of bevacizumab, few subsets analyses were done. In ECOG 4599, patients over 70 years were randomized to carboplatin and paclitaxel, with or without the addition of bevacizumab. The overall incidence of severe or fatal (grade 3 to 5) toxicity was significantly higher (87% versus 61%) in those receiving bevacizumab and treatment-related deaths were more frequent (6.3% versus 2.6%). This trial revealed a trend toward improvement in disease response (29% versus 17 %) and progression-free survival (5.9 versus 4.9 months), without benefit in overall survival (Ramalingam et al., 2008).

11. Conclusion

Lung cancer is already a significant problem in our population. It is one of the major causes for cancer mortality in the younger population, even more in the elderly. The aging population will continue to grow and the proportion of elderly with lung cancer will increase in coming decades. Oncologist will have to develop their abilities to better evaluate them and to give them the appropriate treatment for their condition. Actually, no specific assessment tool is proved to be better than other, but we demonstrated the importance of a form of CGA and all his components in the evaluation of these persons.

Many treatment options are available and proved to be effective in the elderly. It can vary from standard treatment, as for younger patient, to more adapted treatment, in regard to the general functional status of the person and his comorbidities.

For patients with early stage disease, surgery remains the treatment of choice with or without adjuvant chemotherapy. When it is not possible, radiation therapy is an excellent alternative, well tolerated with limited side effects. In case of advanced disease, radiation combined or not to chemotherapy is the option, according to the general functional status of the patient. Palliative treatment, either radiation or chemotherapy can also be offered to the elderly patient, according to their symptoms and wishes.

A good evaluation of the patient and realistic goal for treatment remain essential in this population, but treatment decisions based solely on chronological age is no longer acceptable at this time.

12. References

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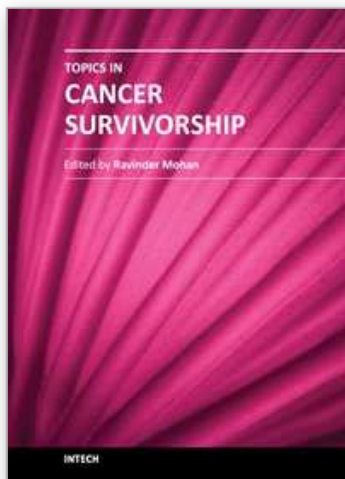
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Cancer is now the leading cause of death in the world. In the U.S., one in two men and one in three women will be diagnosed with a non-skin cancer in their lifetime. Cancer patients are living longer than ever before. For instance, when detected early, the five-year survival for breast cancer is 98%, and it is about 84% in patients with regional disease. However, the diagnosis and treatment of cancer is very distressing. Cancer patients frequently suffer from pain, disfigurement, depression, fatigue, physical dysfunctions, frequent visits to doctors and hospitals, multiple tests and procedures with the possibility of treatment complications, and the financial impact of the diagnosis on their life. This book presents a number of ways that can help cancer patients to look, feel and become healthier, take care of specific symptoms such as hair loss, arm swelling, and shortness of breath, and improve their intimacy, sexuality, and fertility.

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Phone: +86-21-62489820
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