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Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology

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Non-small-cell lung cancer (NSCLC) is a very common disease in the elderly population and its incidence in this particular population is expected to increase further, because of the ageing of the Western population. Despite this, limited data are available for the treatment of these patients and, therefore, the development of evidence-based treatment recommendations is challenging. In 2010, European Organization for Research and Treatment of Cancer (EORTC) took an initiative in collaboration with International Society of Geriatric Oncology (SIOG) and created an experts panel that provided an experts' opinion consensus paper for the management of elderly NSCLC patients. Since this publication, important new data are available and EORTC and SIOG recommended to update the 2010 recommendations. Besides recommendations for surgery, adjuvant chemotherapy and radiotherapy, treatment of locally advanced and metastatic disease, recommendations were expanded, to include data on patient preferences and geriatric assessment.

Key words: elderly, NSCLC, age, EORTC, SIOG

introduction

The median age at diagnosis of non-small-cell lung cancer (NSCLC) is ~70 years in the Western world [1]. However,

despite the high incidence of lung cancer in the elderly, it is known that these patients are under-represented in clinical trials and, therefore, it is difficult to reach evidence-based clinical recommendations for them [2]. This scarcity of robust data on elderly NSCLC patients precludes the development of level 1 evidence-based recommendation for treatment. However, it is clear that therapeutic decisions in the elderly should not be based just on chronological age but should take into account patient's life expectancy and preferences, functional age,

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presence of comorbidities and estimated benefits and risks [3]. For these reasons, the European Organization for Research and Treatment of cancer (EORTC, Elderly Task Force and Lung Cancer Group) and the International Society for Geriatric Oncology (SIOG) have developed an opinion paper based on a consensus, by a panel of experts, on available evidence [4]. Since the previous publication, we believe that important data have been reported and, therefore, these recommendations need to be updated. Table 1 presents the 2010 and 2013 recommendations.

search strategy and selection criteria

A bibliographic search of the Medline database was conducted for papers published from 2008 to 2013 with the keywords 'non-small-cell lung cancer', 'elderly', 'older', 'aged', 'age', 'surgery', 'chemotherapy' and 'radiotherapy', 'erlotinib', 'gefitinib' and 'bevacizumab'. The same selection criteria were applied as in the previous publication [4]. A consensus was reached among all authors for the recommendations. We did not use the level of evidence and grade of recommendation according to ASCO guidelines because age cut-offs varied and several data were based on retrospective analyses.

epidemiology and prognosis of NSCLC in the elderly

NSCLC is a disease of the elderly. It is estimated that ~50% of newly diagnosed cases occur in patients older than 70 years of age [5]. It is also important to underline that although mortality from NSCLC in younger patients is decreasing, it is still increasing among the elderly and particularly in older female patients [5].

Initial presentation of NSCLC is similar between younger and older patients (≥ 70 years), with no significant difference observed concerning initial symptoms at diagnosis [6]. Time between initial symptoms, diagnosis and start of treatment is similar between younger and older patients [6]. A retrospective series reported by Sterlacci et al. compared clinical characteristics (PS, smoking status, Hgb, LDH and CRP levels), pathological features (histology, stage, differentiation and Ki-67 expression) and clinical course of disease after resection in 383 NSCLC patients with operable disease (< 70 years, $n = 283$; ≥ 70 years, $n = 100$) [7]. Patients were selected on the basis of tissue availability. The authors failed to identify any difference between the two age groups in terms of clinical and pathological characteristics. The only exception was that elderly patients were more likely to be anaemic (Hgb < 12 mg/dl) and more likely to have PS > 1 . However, these differences could be attributed to the fact that elderly have more comorbidities and a decline in organ function, and not to differences in the biology of the disease [3]. Disease-free survival and rate of disease recurrence was not different between young and older patients and age had no impact on prognosis in the multivariate analysis [7]. A similar report by Goodgame et al. with 781 NSCLC patients with stage I disease (≥ 70 years, $n = 286$) failed to demonstrate any difference in pathological characteristics (T classification, median tumour size, histology, grade) and in recurrence rate [8]. It should be mentioned that the median age of these cohorts of patients was well below that of the general population. Elderly patients are more likely to be diagnosed with stage I disease but, most probably, this is because elderly seek more frequently medical consultation

because of coexisting medical problems or because of understaging due to more conservative staging, and not because of differences in the biology of the disease [9]. Elderly are also more likely to be diagnosed with squamous histology, although the reason for this difference is not quite clear [7, 8, 10] and more significant mediastinal lymph node involvement [11].

Biomarker expression was also compared between younger and older patients participating in the BATTLE programme [12]. There was no statistically significant difference in biomarker expression between patients aged < 65 years versus those aged ≥ 65 years; however, patients aged ≥ 70 years had less epidermal growth factor receptor (EGFR) high-polysomy ($P = 0.05$) and lower immunohistochemistry expression of nucleic RXR α ($P = 0.046$).

screening

The publication of the National Lung Screening Trial (MSLT) provided evidence that low-dose CT-based screening could reduce lung cancer-specific mortality by ~20% [13]. Approximately 18% of the patients included in this study were 65–69 years of age and 9% were 70–74 years old.

The median age at diagnosis of lung cancer is ~71 years [14]. This means half of all cases will be diagnosed above the age of 71. For the Western population, the estimated life expectancy at the age of 70 is ~18 years [15], and the risk of developing lung cancer appears to increase in a linear fashion with age [16]. Therefore, if incidence of lung cancer is increasing with age and a 70-year-old patient has a life expectancy of more than 10 years, then screening of these patients is justified. Based on these data, the American Association of Thoracic Surgery (AATS) recommends annual screening up to the age of 79 [17, 18]. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines support that screening is reasonable for selected high-risk individuals older than 74 years of age who are eligible for definitive treatment [19].

On the other hand, it should be underlined that decisions about screening should take into consideration the presence of competing morbidities and patient heterogeneity, potential harms of screening (over-diagnosis, false-positive cases, potential harms of diagnostic tests and the harms of disease treatment) and patient preferences. A comprehensive geriatric assessment approach, estimating life expectancy of an elderly patient, could help the decision to perform lung cancer screening or not [3]. There is limited information regarding the preferences of the elderly for deciding to undergo screening, the process of being screened and the health status associated with being or not being screened [20]. A small study assessed the attitudes towards screening of 116 older adults [21]. Attitudes about continuing cancer screening were favourable and factors important to consider stopping include: age, deteriorating or poor health, concerns about the effectiveness of the tests and physician's recommendations. Another study collected information on older adults' views of screening cessation and found that, for many older adults, stopping screening is a major decision, but continuing screening is not. A physician's recommendation to stop may threaten patient trust so that the authors concluded that effective strategies to reduce non-beneficial

Table 1. Recommendations for the management of elderly NSCLC patients

	2010 Recommendation	2013 Recommendation
Screening		Screening for lung cancer can be offered to elderly individuals at high risk for lung cancer. Screening decisions should be based on patient's life expectancy, the presence of competing comorbidities that could hamper diagnostic tests or administration of treatment and patients' preference.
Early-stage disease		
Surgery	Surgical options should not be discarded for elderly patients based solely on their chronological age. Tumour stage, patient life expectancy, PS and the presence of comorbidities should be taken into account when deciding to treat or not treat an elderly patient with surgery. Whether elderly patients should be offered lobectomy as a 'standard of care' or more limited procedures (i.e. wedge resection) is not clear, although retrospective data indicate that both these procedures yield similar outcomes. Pneumonectomy should be avoided or carried out with caution, given the higher rate of mortality reported with this procedure.	Surgical treatment should not be denied to elderly patients just on the basis of chronological age. Limited resections and omission of systematic mediastinal lymphadenectomy can be considered in the elderly on the basis of retrospective data. Pneumonectomy should be avoided when possible given the higher mortality associated with this procedure. We strongly recommend referral to high-volume centres. VATS might be an option for elderly since it is associated with lower incidence of postoperative morbidity. For elderly patients who are not operable for medical reasons, SABR could represent an alternative with less adverse events and similar outcome, although prospective data are needed. SABR is preferable compared with conventional RT.
Adjuvant chemotherapy	Despite receiving a lower total chemotherapy dose, elderly patients seem to derive the same benefit from adjuvant chemotherapy as younger patients do, with no significant increase in toxicity. Given this, adjuvant chemotherapy should not be denied to patients on the basis of age. Treatment decisions should take into account the estimated absolute benefit, life expectancy, treatment tolerance, cognition, presence of comorbidities and patient preferences. Less information is available regarding the real benefit and tolerability of these regimens for patients aged >75 years and the risk versus benefit has not been studied adequately. It should be noted that these are retrospective data based on highly selected patients and their extrapolation to the general elderly population should be made with caution.	Adjuvant chemotherapy is associated with survival benefit in the elderly and therefore is should not be denied to these patients. Little information is available regarding the real benefit and tolerability of adjuvant treatment of patients over 80 years of age and the risk-benefit ratio has not been studied adequately. It should be noted that these are retrospective data based on highly selected patients and their extrapolation to the general elderly population should be made with caution.
Neoadjuvant chemotherapy	–	The results of randomized trials do not support the use of neoadjuvant chemotherapy rather than immediate surgery followed by adjuvant chemotherapy in the general NSCLC population. Furthermore, limited data support that neoadjuvant chemotherapy in the elderly may increase the incidence and severity of postoperative complications.
Adjuvant RT	There is nearly a complete lack of data, both prospective and retrospective, regarding the role of postoperative adjuvant RT, especially for elderly NSCLC populations. Given the lack of demonstrated benefit for the use of RT in the general population, adjuvant RT is also not recommended for elderly NSCLC patients. When used with curative intent in elderly patients not suitable for surgery, RT is well tolerated and older and younger patients benefit in a similar way.	Given the lack of demonstrated benefit for the use of RT in the general population, adjuvant RT is also not recommended for elderly NSCLC patients.
Locally advanced disease	Concurrent CMRT approach should be offered to elderly patients with locally advanced NSCLC. Nevertheless, given the lack of prospective randomized trials, specifically	CMRT (either sequentially or concurrently) can be considered as an option in elderly patients although it should only be

Continued

Table 1. Continued

	2010 Recommendation	2013 Recommendation
	<p>designed for the elderly population, and given the higher risk of toxicity in elderly patients, treatment decision should be based on PS, absence of significant comorbid diseases and patient's life expectancy.</p> <p>Trials specifically designed for the elderly population are urgently needed and patients should be encouraged to participate in such clinical trials.</p>	<p>used in selected, fit patients. Data are limited in the elderly and should be considered with caution.</p>
Advanced/metastatic disease		<p>Prospective trials support the use of carboplatin-based doublets in fit elderly patients. For less fit patients, single-agent treatment (gemcitabine, vinorelbine, taxanes) represent a valid option. There are no data to support that any single agent offers an OS benefit compared with the other ones, Very limited data are available for octogenarians and, therefore, no specific recommendations can be made for this group.</p>
Chemotherapy	<p>For the elderly population, the available data indicate that third-generation single agent should be used as first-line NSCLC treatment. Published data support the use of vinorelbine, gemcitabine or docetaxel monotherapy. Docetaxel produces higher PFS when compared with vinorelbine but without a difference in OS. Very limited data are published regarding octogenarians and, thus, no specific recommendations can be made for this particular age group.</p>	<p>Prospective trials support the use of carboplatin-based doublets in fit elderly patients. For less fit patients single-agent treatment (gemcitabine, vinorelbine, taxanes) represent a valid option.</p> <p>There is no data to support that any single agent offers an OS benefit compared with the other ones.</p> <p>Very limited data are available for octogenarians and, therefore, no specific recommendations can be made for this group.</p>
Targeted agents	<p>Given that the addition of bevacizumab to standard cytotoxic chemotherapy in elderly population results in significant toxicity, while it is not clear whether it offers a survival benefit or not, prospective studies to assess the therapeutic index of the combination of chemotherapy with a targeted agent in the elderly are needed, before definitive recommendations regarding their use can be made.</p> <p>Erlotinib monotherapy is active and relatively well tolerated in elderly patients with advanced NSCLC. Nevertheless, because these data are based on phase II trials, further investigation in the context of randomized phase III trials of selected patients based on validated molecular markers (e.g. EGFR mutations) are needed.</p>	<p>It is not clear whether bevacizumab offers a survival benefit in the elderly when combined with standard cytotoxic chemotherapy, while it may result in slightly higher toxicity in the elderly compared with younger patients. Therefore, the benefit-risk ratio should be taken into account before deciding to administer bevacizumab to elderly patients.</p> <p>EGFR tyrosine kinase inhibitors are associated with significant benefit and minimal toxicity in molecularly selected elderly patients and therefore are strongly recommended as first-line treatment in patients with EGFR mutations. In EGFR wild-type patients, chemotherapy should be preferred to TKIs as first-line treatment.</p>
Second-line treatment	<p>There is lack of prospective data regarding the role of second-line treatment in elderly NSCLC population. On the basis of retrospective data, age alone should not prevent the administration of second-line therapy and pemetrexed or erlotinib could be considered as second-line treatment of elderly NSCLC patients.</p> <p>A thorough evaluation of the patient should be done on the basis of life expectancy, expected benefit, comorbidities and patient's preferences.</p>	<p>On the basis of retrospective data, age alone should not prevent the administration of second-line therapy in elderly NSCLC patients. Same agents as in the general population can be considered.</p>
Patient's preferences	–	<p>Adequate information and participation of the patient and family members is important for elderly NSCLC patients. Treatment decisions should be taken after clear information is given to the patient regarding prognosis of the disease, treatment options, benefit-risk ratio of the proposed treatment and the potential negative effect of over- and under-treatment.</p>

Continued

Table 1. Continued

2010 Recommendation	2013 Recommendation
Geriatric assessment –	A CGA-based approach for the evaluation of elderly NSCLC patients is strongly recommended. This approach can be used for the estimation of life expectancy, for the detection of undetected health problems and improve the outcome and patients' compliance. Data do not support the use of screening tools. Minimal dataset is recommended in all trials including elderly patients.

PS, performance status; VATS, video-assisted thoracoscopic surgery; SABR, stereotactic body radiation; RT, radiotherapy; PORT, postoperative RT; CMRT, chemoradiotherapy; OS, overall survival; PFS, progression-free survival; EGFR, epidermal growth factor receptor; CGA, comprehensive geriatric assessment.

screening may include discussion of the balance of risks and benefits, complications or burdens [22].

Regarding the risk of over-diagnosis, it has been estimated that overall about 10% of screened-detected lung cancers are indolent tumours with volume-doubling time more than 600 days most of whom Positron emission tomography (PET) negative and of a non-solid type [23]. To avoid risk of overtreatment, a reasonable proposal for older adults with indolent screened cancers is to maintain a conservative management (observation or SABR) and no surgical resection considering the long time required for these nodules to become clinically dangerous.

recommendation

Although European recommendations regarding the role of screening in the general lung cancer population do not exist yet, screening might be an option for elderly individuals at high risk for lung cancer. Screening decisions should be based on patient's life expectancy, the presence of competing comorbidities that could hamper diagnostic tests or administration of treatment and patients' preference. Further investigation in the context of prospective trials is needed in order to have a more clear picture about the role of screening in elderly lung cancer patients.

early-stage disease

surgery

Since the previous recommendation numerous studies have further proved the feasibility of surgical treatment of lung cancer in the elderly and even in octogenarians [24–27]. However, the likelihood of elderly patients with early-stage disease not receiving any treatment significantly increases with age [28]. It has been noted that age more than comorbidities had an impact on the likelihood of being offered surgical treatment. In this report, elderly patients without significant comorbidities were offered less frequently surgery compared with younger patients with significant comorbidities [28]. Similar results were reported by a smaller series by Palma et al. [29] emphasizing that there is clearly a treatment bias related to age in elderly patients with

early-stage NSCLC. However, population-based data from the Netherlands demonstrated that the number of elderly NSCLC patients undergoing surgical resection increased between 1989 and 2009 [30] and, in addition, the authors noted an improvement in median survival between 2001 and 2009 [31]. This phenomenon of potential treatment bias may be related to the local surgical expertise in caring for the elderly. In an analysis of a linked Medicare-SEER database, Gray et al. found that <63% of patients >65 years of age underwent surgery in low-surgery volume geographic areas, while >79% underwent surgery in high-surgery geographic areas [32].

Although case-control studies suggest that elderly patients might have a higher risk of postoperative mortality, this is not supported by data from large randomized trials [26]. A case-control study by Rivera et al. with more than 3000 patients demonstrated that postoperative mortality was higher in elderly (≥70 years) patients at every end point compared with younger counterparts [30-day mortality, 3.6% versus 2.2% ($P = 0.01$); 60-day mortality, 4.1% versus 2.4% ($P = 0.003$); 90-day mortality, 4.7% versus 2.5% ($P = 0.0002$)] [26]. However, this conclusion was not confirmed by a report by Chambers et al. [33]. Both reports yielded no significant differences between younger and older patients in terms of hospital length of stay and incidence of postoperative complications [26, 33]. Postoperative morbidity was associated with age above 75 years, male sex, higher comorbidity index, larger tumours and treatment in hospitals with low volume of surgical procedures [34]. Even when postoperative morbidity and mortality was higher in older patients, levels were on a low rate in both groups, with surgery being an option of elderly patients with early-stage NSCLC. Anticipated operative mortality for elderly patients undergoing thoracic surgery has been steadily decreasing. The landmark multi-institutional study of operative mortality following thoracotomy and lung resection by the Lung Cancer Study Group in 1983 found a linear relationship with 30-day mortality and age. In patients under the age of 60 years, the mortality rate was 1.3%; 60–69 years, 4.1% and over 70 years, 7.1%, all significantly different ($P < 0.01$) [35]. Twenty-five years later, the operative mortality for early-stage lung cancers in the ACOSOG Z0030 trial was 1.4% [36]. These procedures were carried out by thoracotomy,

but at high-volume academic centres with board-certified thoracic surgeons.

Minimally invasive techniques can produce even lower operative mortality. McKenna et al. reported in his largest series of minimally invasive lobectomies to date with 1048 cases out of 1100 minimally invasive anatomic resections, the majority of which (92.3%) were for primary lung cancer. The mean age of the patients was 72 years. Perioperative mortality was only 0.8% and the morbidity rate was 15% [37]. Similar results were reported by other retrospective series [38], and from the lung cancer screening trials [13, 39], with all these trials reporting an operative mortality rate of 0.5%–1%. This low mortality rate could be attributed to the participation of high-volume centres with experience using minimally invasive techniques. To graphically illustrate the importance of these figures, an operative mortality of 7% equals one death for every 14 patients, while an operative mortality rate of 0.8% is one death in every 125 patients. That is a remarkable change in 25 years!

There are conflicting data in regards to long-term outcomes in elderly lung cancer patients treated with surgery. A collective analysis of the literature by Chambers et al. revealed no significant difference in 5-year survival rates following surgery for early-stage disease between younger and older patients [stage I NSCLC 5-years overall survival (OS): <70 years, 69%–77%; >70 years, 59%–78%] [33]. On the other hand, a study based on data of more than 10 000 patients from the SEER registry showed that patients older than the median age of 67 years had worse 5-year survival than younger patients (absolute 5-year OS: 52% versus 65%; $P < 0.0001$) [40]. This was confirmed by a smaller study from Wong et al. [41]. However, both of these studies did not stratify for functional status and comorbidities at the time of surgery. Of interest, Gray et al. were able to link the long-term survival rates of elderly lung cancer victims to the volume of surgery within their treating institution. Thus, lung cancer-specific mortality was reduced in high-volume centres with an adjusted OR of 0.86 (95% CI 0.82–0.91) for each 10% increase in surgery rates [32]. Billmeier et al. found that the risk of a poor outcome 1 year after lung cancer surgery was not a function of age alone, but an association between age and stage of disease. The risk of nursing home admission, severe functional impairment or death was low (16%) for patients younger than 75 years and for those 75 years or older with stage I disease; intermediate (33%) for patients 75 years or older with stage II–IIIA disease and no or mild comorbidities; high (60%) for those 75 years or older with stage II–IIIA disease and moderate or severe comorbidities [39].

Regarding the type of operation, although lobectomy is considered the standard of care for stage I disease [42] several retrospective reports published after our previous recommendation support that for elderly patients more limited resections can be justified and results to similar long-term survival and better functional results compared with lobectomy [43–45]. Also some data support that systematic mediastinal lymphadenectomy may be spared in elderly patients as it may not be associated with a survival benefit [46], although it does not increase perioperative morbidity and mortality [47]. Pneumonectomy is associated with higher risk of postoperative morbidity and mortality in the elderly and should be avoided [48, 49]. Also it should be emphasized that outcomes are associated with the expertise of each

surgical centre as it has been reported sites with high expertise achieve better results. Thus referral of elderly patients to high-volume centres for surgical treatment is recommended [32].

We have to underline that all studies discussed in this section are based on retrospective data and are subject to selection bias; therefore, their conclusions should be interpreted with caution.

video-assisted thoracoscopic surgery

The less invasive nature of video-assisted thoracoscopic surgery (VATS) makes this procedure attractive for elderly patients. A number of recent retrospective studies reported significantly shorter length of hospital stay in patients operated with VATS and less postoperative complications, compared with open procedure [50–52]. A case-control study by Cattaneo et al. with 333 NSCLC patients aged ≥ 70 demonstrated that VATS approach had significantly lower rate of complications compared with open procedures (28% versus 45%; $P = 0.04$) and a shorter median length of stay (5 days, range 2–20 versus 6 days, range 2–27; $P < 0.001$) [53]. No patients undergoing VATS lobectomy had higher than grade 2 complications, whereas 7% of complications in the thoracotomy group were grade 3 or higher. No perioperative deaths were reported in the VATS group compared with a mortality rate of 3.6% (3 of 82) in the open thoracotomy arm.

radiotherapy

Although surgery is the treatment of choice for early-stage NSCLC, a significant proportion of elderly patients are medically inoperable due to co-existing comorbidities, refuse or are not offered surgery [28]. For these patients, radiotherapy (RT) represents a therapeutic alternative. A recent report based on the SEER registry with data from more than 6000 patients demonstrated that use of RT resulted in overall and lung cancer-specific survival improvement compared with untreated patients [54]. However, it should be noted that the magnitude of benefit was moderate (~6-month improvement in median OS). A potential explanation for this modest result is that this study did not analyse results according to RT technique. Currently, both conventional RT and stereotactic ablative body radiation therapy (SABR) are available for the treatment of inoperable (e.g. patients with poor lung function) patients with peripheral early-stage NSCLC. SABR is a form of high-precision RT technique allowing the delivery of very high doses of radiation to the tumour over a short period of time, which is particularly attractive to the elderly (typically 3–8 fractions). SABR is associated with local control ~90% as opposed to <50% with conventional RT [55]. It should be noted that most of the available evidence to support SABR is in patients with peripheral tumours and that there is paucity of prospective multicentre data in patients with central tumours [56].

A population-based study from the Netherlands demonstrated that the introduction of SABR was associated with an increase in RT use, a reduction in the proportion of untreated elderly and an improvement in OS [57]. Importantly, there was no reduction in the proportion of elderly patients undergoing surgery. There is no randomized data comparing surgery to SABR in early-stage NSCLC. A population-based matched-pair comparison of SABR versus surgery in 120 elderly (≥ 75 years) NSCLC stage I patients demonstrated no difference in OS (OS at 1 and 3 years was 75%

and 60% after surgery, and 87% and 42% after SABR, respectively; log-rank $P = 0.22$) [58]. Thirty-day mortality was 8.3% after surgery and 1.7% after SABR. A comparison of five different treatment strategies in 10 923 patients, aged ≥ 66 years (median age 75 years) was reported by Shivarni et al. [59]. Treatment distribution was lobectomy (59%), sublobar resection (11.7%), conventional radiation (14.8%), observation (12.6%) and SABR (1.1%). In Cox regression analysis with a median follow-up time of 3.2 years, SABR was associated with the lowest risk of death within 6 months of diagnosis [HR 0.48; 95% confidence interval (CI) 0.38–0.63; referent is lobectomy]. After 6 months, lobectomy was associated with the best overall and disease-specific survival. In the propensity-score-matched analysis, survival after SABR was similar to that after lobectomy (HR 0.71; 95% CI 0.45–1.12; referent is SABR). Conventional radiation and observation were associated with poor outcomes in all analyses.

recommendation. Surgical treatment should not be denied elderly patients on the basis of chronological age. Elderly patients with diagnosed or suspected early-stage lung cancer with robust functional status should be referred for surgical evaluation. They should also be referred for radiation oncology evaluation as an alternative treatment option.

Elderly patients with moderately impaired functional status and diagnosed or suspected early-stage lung cancer should be provided access to a multi-specialty care team. This team should include the ability to provide minimally invasive surgical techniques for diagnosis, staging and treatment; surgery within a high-volume centre; radiation oncology techniques including SABR and other locally ablative techniques. Furthermore, this multi-specialty team should allow evaluation by specialists trained in the care of geriatric patients.

adjuvant (and neoadjuvant) chemotherapy

Since our previous report, Cuffe et al. presented the results of a population-based study in Canada, with 2763 elderly NSCLC patients (≥ 70 years). Use of adjuvant chemotherapy in the elderly increased from 3.3% (period 2001–2003) to 16.2% (period 2004–2006), although it remained lower compared with younger patients (period 2004–2006, 42.7%; $P < 0.001$). The cisplatin/vinorelbine combination was the most frequently used doublet across all age groups; however, a trend in the use of carboplatin-based regimens as carboplatin plus paclitaxel was seen for elderly patients [60]. Adjuvant chemotherapy administration was associated with a significant survival benefit in the elderly (although not for patients older than 80 years, $n = 282$) with tolerability similar to that of patients < 70 years [60]. No difference in quality of life (QoL) between elderly and non-elderly patients receiving adjuvant chemotherapy has been documented [61].

Rivera et al. reported the results of a case-control study ($n = 81$, patients ≥ 75 years versus $n = 81$, patients < 75 years) of patients treated with neoadjuvant chemotherapy [62]. Incidence and severity grade of postoperative complications was higher in the elderly group, with no significant difference in the type of operation and postoperative mortality.

recommendation

Adjuvant chemotherapy is associated with survival benefit in the elderly and therefore should not be denied to these patients. Treatment decisions should take into account the estimated absolute benefit, life expectancy, treatment tolerance, presence of comorbidities and patient preferences. Little information is available regarding the real benefit and tolerability of adjuvant treatment of patients over 80 years of age and the risk-benefit ratio has not been studied adequately. It should be noted that these are retrospective data based on highly selected patients and their extrapolation to the general elderly population should be made with caution. Furthermore, limited data support that neoadjuvant chemotherapy in the elderly may increase the incidence and severity of postoperative complications.

postoperative adjuvant RT

Since the previous recommendation, no new data were published supporting the role of post-operative RT (PORT). Using the SEER registry Wisnivesky et al. identified 1307 elderly NSCLC patients with N2 disease [63]. Overall, 710 patients (54%) received PORT. PORT administration was not associated with a survival benefit.

recommendation

Given the lack of demonstrated benefit for the use of RT in the general population, adjuvant RT is also not recommended for elderly NSCLC patients. The potential effectiveness of PORT should be tested further in prospective randomized trials.

locally advanced disease

A consistent finding of recent publications is that elderly patients with locally advanced NSCLC are more likely to receive no treatment [28, 64–66]. In one large series by Davidoff et al. based on SEER registry ($n = 6325$ patients, ≥ 66 years), 34% of these patients received no treatment at all [66], while a similar series by Wang et al. based on Veterans Affairs Central Cancer Registry ($n = 4635$ patients, ≥ 65 years) reported that 35% of patients received no treatment [28]. Patients who received combined modality treatment [chemoradiotherapy (CMRT) either sequentially or concurrently] had better survival compared with patients who received single modality treatment [64–66], but at the cost of higher toxicity and mortality [66].

Despite a concerted effort to remove age cut-off from inclusion criteria in clinical trials, evidence to support CMRT (particularly concurrent CRT) in the elderly is limited [67]. Recently, Atagi et al. reported the results of a randomized, controlled, phase III trial by the Japan Clinical Oncology Group conducted specifically in the elderly (JCOG0301). A total of 200 patients (≥ 70 years) with unresectable stage III NSCLC were randomly assigned to CMRT (60 Gy plus concurrent low-dose carboplatin) or RT alone [68]. Median age was 77 in both groups. Median OS was significantly longer in the combined modality arm [CMRT versus RT: 22.4 months (95% CI 16.5–33.6) versus 16.9 months (95% CI 13.4–20.3)], respectively (HR: 0.68, 95.4% CI 0.47–0.98, $P = 0.0179$). Toxicity was higher in the CMRT group than in the RT alone group, and there were seven treatment-related deaths:

three (3.0%) in the chemoradiotherapy group and four (4.0%) in the RT group. This is the first prospective randomized study to prove the feasibility of CMRT and the clinical benefit associated with this therapeutic strategy in the elderly. However, it should be underlined that the control arm (RT only) is not considered standard in fit, elderly patients and that the chemotherapy regimen used (daily carboplatin) is not considered standard concurrent treatment of locally advanced disease [69]. Furthermore, this study included only Asian, good performance status patients (96.4% of patients had PS 0 and 1), with limited comorbidities (patients with chronic obstructive pulmonary and 'uncontrolled' heart disease were excluded), so its results cannot be safely generalized to Western population. This study did not include a geriatric assessment of patients. Therefore, we cannot assess the functional status of these patients and thus extrapolation of its conclusions to the general elderly population should be made with caution [70]. We consider it difficult to define CMRT as the new standard of care for elderly patients just on the basis of a single phase III trial.

recommendation

CMRT (either sequentially or concurrently) can be considered as an option in elderly patients although it should only be used in selected, fit patients. Data are limited in the elderly and should be considered with caution. Treatment decisions should take into account patient's life expectancy, presence of comorbidities, functional limitations and patient's preferences.

advanced/metastatic disease

chemotherapy

Since the previous recommendation, further studies proved that chemotherapy is feasible and beneficial for elderly NSCLC patients with advanced/metastatic disease [71–74]. On the other hand, it should be noted that elderly had higher rates of adverse events (AEs) during chemotherapy, adjusted rate ratios 1.70 (95% CI 1.19–2.43) for 65- to 74-year-old patients, and 1.34 (95% CI 0.90–2.00) for patients aged 75 or older, compared with patients younger than 55 years and this observation was independent of comorbidity [75]. This could be the reason for the significant under-treatment of elderly patients in clinical practice [28, 73].

single-agent treatment

A prospective phase III trial compared single-agent docetaxel to single-agent vinorelbine in patients older than 65 years and failed to demonstrate any difference between the two treatments [76]. Median time to tumour progression was 2.3 and 1.9 months ($P = 0.298$), and the median OS was 6.1 and 3.9 months ($P = 0.090$) in the docetaxel and vinorelbine arms, respectively. However, this study was prematurely terminated because of low accrual and, therefore, its conclusions should be interpreted with caution but given the difference would be worth exploring.

platinum-based doublets

Two prospective trials have evaluated the role of platinum-based doublets in the elderly. The first trial reported by Quoiq et al.

compared a monthly carboplatin and weekly paclitaxel doublet chemotherapy regimen with monotherapy (either vinorelbine or gemcitabine) in elderly (aged 70–89) patients with advanced NSCLC. The primary end point was OS and a total of 451 patients were enrolled. Median age was 77 years and median follow-up was 30.3 months (range 8.6–45.2 months). Median OS was 10.3 months for doublet chemotherapy and 6.2 months for monotherapy (HR 0.64, 95% CI 0.52–0.78; $P < 0.0001$); 1-year survival was 44.5% (95% CI 37.9–50.9) and 25.4% (95% CI 19.9–31.3), respectively. Progression-free survival (PFS) was also significantly prolonged in the doublet arm (6.0 versus 2.8 months; $P < 0.001$). Toxic effects were more frequent in the doublet chemotherapy group than in the monotherapy group and more toxic deaths were observed in the doublet versus single-agent arm (6.6% versus 1.8%, respectively; $P = 0.035$) [77].

This is the first prospective randomized trial that demonstrated a clear benefit in favour of a platinum-based doublet in elderly NSCLC patients. This trial has been criticized because there was a significant imbalance in prognostic factors between the two groups. Weight loss more than 5% and the body mass index (BMI) ≤ 20 were significantly more frequent in the single-agent arm than in the doublet arm ($P = 0.048$ and $P = 0.023$, respectively). Weight loss is known to be a negative prognostic factor for OS in NSCLC [78] and low BMI is associated with an increased risk of mortality [79]. Another issue is that this study did not evaluate whether the addition of a platinum compound to single-agent treatment offers a benefit but compared two completely different arms (paclitaxel/carboplatin versus gemcitabine or vinorelbine). However, the most important issue is that although the population included in this study is older than those included in general studies without upper age limit, it cannot be considered as representative of the general older population. The majority of these patients (80%) had an activities of daily life (ADL) score of 6 of 6 and 75% a Charlson comorbidity index (CCI) of ≤ 2 which are not common characteristics of the general older population, but only of the 'healthy' (fit) subgroup [80].

Moreover, a phase III trial reported by a Japanese group at the ASCO Annual 2011 meeting, comparing a combination regimen of weekly docetaxel plus weekly cisplatin versus single-agent docetaxel (every 3 weeks), failed to demonstrate any benefit for the combination regimen [81]. This study enrolled 276 patients, but was prematurely terminated after an interim analysis demonstrated that the probability the combination would be superior to single-agent arm at the time of final analysis was very low. The median OS of the platinum and single-agent groups were 13.3 and 17.3 months, respectively (HR: 1.557; 95% CI 0.976–2.485). This trial used a weekly regimen of platinum–docetaxel that cannot be considered as standard. Also, the combination arm used lower dose intensity of docetaxel (20 mg/m², days 1, 8, 15 q28 days) compared with single-agent arm (60 mg/m², day 1, q21 days). This trial is not fully published yet. Thus, there is still lack of data regarding the role of platinum-based doublets and especially in non-fit older patients.

A recent phase III trial randomly assigned 1052 NSCLC patients to carboplatin (AUC6, day 1 q 3 weeks) and either nab-paclitaxel (100 mg/m² weekly [nab-P/C]) or solvent-based paclitaxel (200 mg/m² day 1 q 3 weeks [sb-P/C]) [82]. The primary end point was overall response rate (ORR). An age-specific subgroup analysis of that trial (≥ 70 years, $n = 156$)

yielded a trend towards higher PFS in favour of nab-P/C (median 8.0 versus 6.8 months, HR 0.687, $P=0.134$), while overall survival (OS) was significantly improved (median 19.9 versus 10.4 months, HR 0.583, $P=0.009$) [83]. A retrospective series with 15 318 Medicare patients who received first-line treatment observed a moderate OS benefit associated with the use of carboplatin–paclitaxel doublet versus carboplatin combined with either gemcitabine or docetaxel [74]. Finally, a small randomized phase II study compared a platinum-containing doublet (carboplatin/pemetrexed) versus a platinum-free doublet (pemetrexed/gemcitabine) in 110 elderly (≥ 70 years) NSCLC patients [84]. Both arms contained bevacizumab (15 mg/kg) that was continued until progression after the completion of six chemotherapy cycles. A significant benefit was observed in favour of the platinum-containing regimen (pemetrexed/gemcitabine versus carboplatin/pemetrexed: median time to tumor progression (TTP): 4.7 versus 10.2 months; median OS: 7.5 versus 14.8 months, respectively).

A small retrospective study evaluated the role of 17 different variables and concluded that four of them had prognostic significance for OS: comorbidities ($P < 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status (PS) ($P = 0.02$), first-line chemotherapy cycles ($P < 0.001$) and serum albumin level ($P = 0.04$) [85].

octogenarians

Practically, no new data were published since our last publication regarding treatment of this particular group. Therefore, more data are needed in order to develop treatment recommendations for these patients.

recommendation. Prospective trials support the use of carboplatin-based doublets in fit elderly patients. No phase III comparative trials of single agent versus cisplatin-based doublets are currently available. For less fit patients, single-agent treatment (gemcitabine, vinorelbine, taxanes) represents a valid option. There are no data to support any single agent offering an OS benefit. Very limited data are available for octogenarians and, therefore, no specific recommendations can be made for this group. Performance status, comorbidities, life expectancy and patient’s preference should be taken into account when developing a treatment strategy.

targeted agents

bevacizumab

The results of two phase IV trials (SAiL and ARIES) were published after the publication of the previous expert’s opinion

paper. SAiL (Safety of Avastin in Lung) was an open-label, single-arm study, ($n = 2212$) which assessed the safety and efficacy of first-line bevacizumab in combination with standard chemotherapy. A pre-planned age-specific subgroup analysis was carried out in patients older than 65 years ($n = 623$) [86]. The incidence of bevacizumab-related AEs of special interest (bleeding, hypertension, proteinuria) was similar between the two age groups. Serious AEs were reported in 45.3% and 34.7% of older and younger patients, respectively. Median OS was similar in older and younger patients (14.6 months in both age groups), as were TTP (8.2 versus 7.6 months), response rate (49.3% versus 52.4%) and disease control rate (89.3% versus 88.4%). Similar results were seen in a post hoc comparison of the older than 70 years and 70 years or younger subgroups: TTP was 8.6 months versus 7.7 months, respectively; OS was 14.6 months in both subgroups; response rate was 49% and 52%, respectively; incidence of AEs of special interest was comparable.

ARIES is another phase IV trial assessing bevacizumab efficacy and safety among a broader population of NSCLC patients in a real-world setting [87]. The study enrolled almost 2000 patients with advanced NSCLC whose first-line therapy included bevacizumab ($n = 650$ elderly, ≥ 70 years). Older patients had similar AE rates compared with the total population with the exception of arterial thromboembolic events (ATE) that were slightly increased in patients ≥ 70 years (3% versus 2% for older and younger patients, respectively). Median PFS was 6.7 months and OS was 13.6 months for the entire cohort and were similar for the older patients subgroup (6.8 and 12.6 months, respectively).

A retrospective, cohort study with 4168 Medicare beneficiaries, aged 65 years or older was recently reported by Zhu et al. [88]. The primary outcome of the study was OS and the study failed to demonstrate any difference between the bevacizumab containing and bevacizumab free arms.

EGFR tyrosine kinase inhibitors

Three single-arm phase II trials evaluated the role of gefitinib in patients with EGFR mutation-positive tumours (Table 2) [89–91]. All of these trials confirmed the significant activity of gefitinib in molecularly selected patients with no significant toxicity. Of special interest is the trial of Inoue et al. that enrolled very old (>80 years) patients or patients with PS 3–4 and demonstrated significant benefit even for these patients [90]. Similarly, a randomized phase II trial of erlotinib versus vinorelbine in elderly (70 years or older) demonstrated a significant OS benefit in the EGFR mutation-positive sub-population [92]. On the contrary, a randomized phase II trial of erlotinib versus

Table 2. Phase II trials of gefitinib in EGFR mut (+) elderly patients

Study	Age	N	ORR	PFS (median)	OS (median)
Maemondo et al. [89]	≥ 75 years	31	74.2%	12.1 months	33.8 months
Inoue et al. [90]	≥ 75 years PS 2–4/ >80 years PS 1–4/ <70 years PS 3–4	30	66%	6.5 months	17.8 months
Asami et al. [91]	≥ 75 years	17	59%	12.9	Not reached

PS, performance status; PFS, progression-free survival; OS, overall survival.

gemcitabine versus erlotinib/gemcitabine combination in 146 unselected elderly (≥ 70 years) patients failed to demonstrate any benefit in favour of erlotinib or the combination compared with single-agent gemcitabine [93]. A retrospective analysis of VeriStrat status of this trial demonstrated that gemcitabine was superior in patients with VeriStrat poor status, while, in patients with VeriStrat good status, erlotinib might be an option and warrants further investigation [94]. A small, single-arm phase II study failed to demonstrate significant activity of the combination of erlotinib and bevacizumab in elderly or PS 2 patients with NSCLC [95].

An age-specific subgroup analysis of unselected elderly patients (≥ 70 years, $n = 485$) participating in a phase IV erlotinib study demonstrated a disease control rate of 79%, a median PFS of 4.6 months and a median overall survival OS of 7.3 months [96].

recommendation. In keeping with other age groups, bevacizumab (outside carboplatin and paclitaxel regimens) does not offer a survival benefit in the elderly when combined with standard cytotoxic chemotherapy, but it does result in higher toxicity in the elderly compared with younger patients. EGFR tyrosine kinase inhibitors are associated with significant benefit and minimal toxicity in molecularly selected elderly patients and therefore are strongly recommended as first-line treatment in patients with EGFR mutations. In EGFR wild-type patients, chemotherapy should be preferred to TKIs as first-line treatment as in all age groups.

second-line treatment

Wu et al. retrospectively reviewed and analysed data of 293 young (< 70 years), and 168 patients (≥ 70 years) who were treated with second-line treatment (both chemotherapy and EGFR TKIs) in the context of clinical trials of their department [97]. No significant differences were observed in both efficacy and toxicity between the two age groups. No age-specific data exist for second-line treatment.

recommendation

Age alone should not prevent the administration of second-line therapy in elderly NSCLC patients.

patients' preferences

Although clinical information is very important for older cancer patients, a significant proportion of them do not receive enough information [98]. Elderly patients might have misinterpretations about the disease and the expected benefit from treatment and thus it is crucial for them to be provided with clear and detailed information. Elderly NSCLC patients want to be involved in the decision making and also need to involve family members in the processes of diagnosis and prognosis disclosure and decision making, and this should be respected and taken into account by treating physicians [99, 100].

Many NSCLC patients judge moderate survival benefits sufficient to make chemotherapy worthwhile (e.g. absolute increases of 10% in survival rates or 6 months in life

expectancies) [101]. The majority of elderly patients expect to receive aggressive treatment although a small but clinically significant portion chose not to receive the offered treatment [99, 102]. For the majority of elderly patients, survival is the main treatment objective [99].

recommendation

Adequate information and participation of the patient and family members is important for elderly NSCLC patients. Treatment decisions should be taken after clear information is given to the patient regarding prognosis of the disease, treatment options, benefit-risk ratio of the proposed treatment and the potential negative effect of over- and under-treatment.

palliative care

Most of patients in advanced stage finally die of their lung cancer. Involvement of palliative care is therefore an essential part of treatment. In a pivotal trial, Temel et al. analysed the effect of early integration of palliative care in parallel to usual oncological care. As expected, they demonstrated an improvement of HRQoL and depression at 3 months in patients treated with palliative care right from the beginning in addition to usual oncological care. Surprisingly patients treated with early integration of palliative care lived 2.3 months longer than those treated with usual care [103]. The median age of patients was 65 years; age-related subgroup analysis is not reported.

recommendation

Palliative care should be integrated in the care of elderly patients with advanced NSCLC at the time of diagnosis, independent of age.

geriatric assessment

Elderly cancer patients represent a very heterogeneous group and their functional status cannot be predicted solely on the basis of chronological age [3]. Comprehensive Geriatric Assessment (CGA) is a well-established comprehensive approach for the evaluation of the older patient developed initially in the field of geriatrics and then applied also to cancer elderly patients [104]. It is a multidimensional and multidisciplinary approach that includes the evaluation of several domains: functional status, cognitive, emotional and social function, comorbidity, polypharmacy and geriatric syndromes [70]. A meta-analysis of 28 controlled trials not restricted to cancer patients (4959 subjects allocated to one of five CGA types and 4912 controls) demonstrated that CGA, if linked to proper geriatric interventions, reduced early re-hospitalization and mortality in older patients through early identification and treatment of health problems [105]. There is a great heterogeneity in studies on CGA in cancer patients and no phase III randomized trials are available. CGA, however, has an important role in estimating the life expectancy of the older cancer, which is of crucial importance when planning therapeutic strategy. It can also reveal previously unknown geriatric problems, if followed by targeted interventions can improve QoL and compliance to therapy [106, 107]. Recent studies demonstrated that some

CGA domains can predict the risk of chemotherapy toxicity [108, 109]. Despite these benefits CGA is not routinely used in clinical practice because it is a time and man-power consuming process that is not always reimbursed by health systems. For that reason, several abbreviated screening tools have been developed (e.g. VES-13 [110, 111], G8 [112], GFI [113]) to screen older patients for potential problems, who require a full CGA [70]. However, a systematic review by Hamaker et al. demonstrated insufficient sensitivity and specificity for those screening instruments [114]. A large recent trial reported by Kenis et al. ($n = 1967$ cancer patients, ≥ 70 years old) demonstrated that CGA in older patients with cancer is feasible for large numbers in busy clinics, and has a significant impact on the detection of unknown geriatric problems, leading to geriatric interventions and adapted treatment [80]. In a systematic review, Puts et al. identified 73 studies reporting on data on CGA in cancer patients. Six of nine studies reported an association of results of CGA with toxicity of chemotherapy, 8 out of 16 studies reported an association with mortality, and two of four studies reported a change of treatment recommendations after knowledge of results in 40%–50% of patients [115]. A CGA-based approach is also recommended by the International Society for Geriatric Oncology (SIOG) [116] and the EORTC [3].

recommendation

A CGA-based approach for the evaluation of elderly NSCLC patients is strongly recommended. This approach can be used for the estimation of life expectancy, for the detection of undetected health problems, and improves the outcome and patients' compliance. If health problems are detected with the screening tool, then a full CGA should be recommended.

conclusions

Chronological age should not be the basis of treatment decisions in elderly NSCLC patients. On the contrary, a multidimensional, multidisciplinary CGA can lead to better tailored treatment taking into account, patient's life expectancy, the functional, cognitive and emotional status of the patient and the presence of comorbidities. Patient's preferences should be incorporated into treatment decisions. Several prospective studies in the locally advanced and metastatic setting support that age-specific clinical trials are feasible and provide reliable data that can guide treatment decisions. More efforts should be taken to develop such studies in other disease stages including patients who are more representative of the general elderly population and not only very fit patients.

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Maintenance strategies in stage IV non-small-cell lung cancer (NSCLC): in which patients, with which drugs?

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Four to six cycles of platinum-based chemotherapy are currently recommended for the first-line treatment of advanced non-small-cell lung cancer (NSCLC). Several studies have assessed the benefit of maintenance therapy following platinum-based first-line therapy, to improve disease control, and thus, progression-free and overall survival with minimal toxicity and maintenance or improvement of quality of life of patients. We review here clinical trials evaluating continuation maintenance therapy or switch maintenance therapy in locally advanced or metastatic NSCLC, to highlight the achievements made and critical issues faced. Based on the available results and limitations of these trials, maintenance therapy should be considered a good treatment strategy for a limited subgroup of patients. Maintenance therapy should be personalised according to the characteristics of patients and their disease, taking into account the data available for the agents used in this setting.

Key words: non-small-cell lung cancer, continuation maintenance, switch maintenance, early second line

Introduction

In advanced non-small-cell lung cancer (NSCLC) patients, the backbone treatment is based on a platinum-based doublet therapy that yields better overall survival (OS), quality of life (QoL) and control of symptoms than best supportive care (BSC) [1]. Historical median OS after first-line treatment is 8–10 months, with a 1-year survival rate of 33% and a progression-free survival (PFS) of 3–5 months [2–5]. The last decade has seen a considerable change in the field of systemic treatment.

First, the molecular characterisation of lung cancer has led to the approval of targeted therapies that improve PFS, response rate and QoL in small subsets of patients. These targeted treatments include epidermal growth factor receptor (*EGFR*)

tyrosine-kinase inhibitor (TKI) (erlotinib or gefitinib) if the tumour harbours an *EGFR*-activating mutation, and the anaplastic lymphoma kinase (*ALK*) inhibitor crizotinib for tumours with *ALK* rearrangements [6–8].

Moreover, the platinum-based doublet can be optimised by adding bevacizumab (Avastin®, Roche). This approach has been shown to improve PFS in selected patients with non-squamous NSCLC [9].

The benefits on OS of second-line single-agent drugs (pemetrexed, docetaxel or *EGFR*-TKI) have also been validated (Figure 1) [2, 6, 7, 10–12].

For years, attention has focused on prolonging first-line therapy benefit, in a strategy described as the ‘maintenance’ strategy. The prolongation of one or more of the drugs used in the first-line treatment (continuation maintenance) or the introduction of another agent with no cross-resistance (switch maintenance or early second-line) is designed to improve PFS and

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