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Review article

Multidisciplinary treatment of lung cancer in older patients: A review

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ABSTRACT

Lung cancer is the leading cause of cancer death worldwide. Older patients represent approximately half of the patient population and optimal management of these patients is challenging. In early-stagenon-small cell lung cancer (NSCLC), lobectomy should be considered in fit older patients. For unfit patients, stereotactic body radiotherapy (SBRT) represents a good alternative. While data on the benefit and risk of concurrent chemo-radiotherapy (cCRT) in older patients with locally advanced NSCLC is conflicting, age alone should not preclude cCRT. Multidisciplinary collaboration is essential for appropriate patient selection. In limited disease small cell lung cancer (SCLC), older patients appear to benefit similarly from standard treatment compared to their younger counterparts, however, with a higher risk of toxicity. Appropriately selected older patients with lung cancer seem to derive as much benefit from active oncological treatment as their younger counterparts. Geriatric screening tests and comprehensive geriatric assessments (CGA) can be helpful when choosing between treatment strategies. Older patients are at risk for under-treatment; this should be avoided by proper selection and multidisciplinary management. This review outlines the management of lung cancer in older patients.

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Contents

1. Introduction

Lung cancer is the leading cause of cancer death worldwide. Each year, more people die of lung cancer than of colon, breast, and prostate

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cancers combined [1]. Non-small cell lung cancer (NSCLC) is the most common histology (85%) [2]. Depending on tumour stage, surgery, radiotherapy, and systemic therapy alone or in combination represent standard treatment options [3,4]. While older patients (>70 years of age) represent approximately half of the patient population [5], this subgroup is under-represented in clinical trials where the median age is typically around 60 years [6].

Older patients do not tolerate treatments as well as their younger counterparts [7,8], which may be caused by higher rates of comorbidities as well as decreased regenerative capacity and organ function [9]. Providing optimal treatment for older patients is challenging. Geriatric screening tests, comprehensive geriatric assessments (CGA), and guideline-concordant treatment are tools to optimize lung cancer management in older patients [10–14]. Less than half of older patients receive guideline-concordant treatment according to a pooled analysis of SEER-data. Yet, survival was increased in the patients who received guideline concordant care [15]. For the purpose of this review we have followed the International Society of Geriatric Oncology's (SIOG's) definition of older patients as patients 70 years of age and older.

2. Non-Small Cell Lung Cancer

2.1. Early-Stage NSCLC: AJCC Stage I and II

According to a meta-analysis, standard treatment of stage IA NSCLC consists of a lobectomy [16]. It is associated with the best long-term outcomes in fit older patients in an unadjusted survival analysis [17]. However, a retrospective analysis suggested that sub-lobar resections achieve similar survival rates when compared with lobectomy in older patients with stage I NSCLC with tumours of <2 cm diameter and with low Forced Expiratory Pressure in one Second (FEV1) [18]. However, this could not be confirmed in a larger SEER database analysis [17].

When surgery is considered too risky in older patients, e.g. due to poor pulmonary function, stereotactic body radiotherapy (SBRT) represents a good alternative. SBRT should be considered in patients with advanced age with multiple comorbidities which preclude surgical resection, as the tolerability appears to be better compared to surgery [17,19–21]. According to cohort studies (propensity score matched/matched pairs), SBRT has demonstrated favourable results, particularly when compared to conventional fractionated radiotherapy, observation only or sub-lobar resection [17,19–21]. However, these results were not confirmed by a systematic review and meta-analysis of sixteen studies containing 11,540 patients where a sub-lobar resection was associated with significantly improved overall survival compared to irradiated patients ($p < 0.05$) [22,23]. While newer techniques are being investigated, such as protons and carbon-ions [24], these have not found their way into clinical practice yet. Three randomized trials of SBRT vs. resection in patients with operable stage I NSCLC (STARS [NCT00840749], ROSEL [NCT00687986], and ACOSOG Z4099 trial [NCT01336894] [22]) closed early due to poor accrual. While a pooled analysis [25] of the first two studies demonstrated a favourable trend in survival towards SBRT, results should be interpreted with caution due to the small sample sizes of the trials. Retrospectively, frailty is associated with lower overall survival in older patients treated with SBRT but should not be viewed as a contraindication as disease free survival and overall survival were better compared to no active treatment [26]. According to a registry-based study, SBRT could be applied safely even in patients over the age of 80 years old [27]. Recent retrospective data comparing 30- and 90-day mortality of surgery and SBRT showed differences in favour of SBRT, especially in patients older than 71 years [28].

Although, active treatment confers similar survival advantages in both younger and older patients, older patients are still at risk of under-treatment [29]. Survival after radical treatment for early-stageNSCLC depends on factors such as tumour stage, performance status, gender, and radiotherapy (RT) dose, but not on age [30]. SBRT introduction and implementation has led to a higher proportion of older patients receiving potentially curative treatment, leading to improved overall survival [31]. The introduction of multi-disciplinary teams and tumour boards can increase the proportion of actively treated older patients [32].

When feasible, surgery followed by chemotherapy can be considered standard treatment in stage II NSCLC. However, there is no universally accepted standard for older patients with stage II disease, especially when surgery is not reasonably possible. While data for this subset is limited, treatment would typically involve radiotherapy (conventionally fractionated, hypofractionated, or stereotactic radiotherapy), often in combination with chemotherapy (for N+) when possible. Adjuvant immunotherapy may also be considered for selected patients.

2.2. Locally Advanced NSCLC (AJCC Stage III)

Concurrent chemo-radiotherapy (cCRT) is the standard treatment for many patients with locally advanced NSCLC [4]; its use is however not universally implemented for older patients.

Patients included in randomized controlled trials and represented inmeta-analyses establishing cCRT were mostly under 70 years old [33–35].

A randomized phase III study was conducted to assess whether cCRT with carboplatin resulted in longer survival than radiotherapy alone in patients older than 70 years [36]. The median overal survival (OS) for cCRT and RT alone was 22.4 and 16.9 months ($p = 0.0179$), progression-free survival (PFS) was significantly longer with cCRT (8.9 vs. 6.8 months, $p = 0.009$). These results were confirmed by a recently published meta-analysis [37]. Studies addressing cCRT in older patients concluded that grade 3–4 haematological toxicity and grade 3 infections were increased with cCRT, but lung toxicity was not increased [36,37].

While the above-mentioned studies show the benefit of cCRT in older patients, pooled analysis of individual patient data on cCRT for Stage III NSCLC in older vs. younger patients (cut-off 65 years) demonstrated that older patients experienced shorter OS, more toxicity, more treatment discontinuation, and a higher rate of death during treatment [7]. Recent comparative effectiveness [38] and phase-II-data suggest that simultaneous treatment could cause shorter overall survival in older patients [NCT01166204] [39]. Therefore, older patients should be selected carefully for a cCRT approach [40]. Sequential chemoradiation (CRT) could be a viable alternative to cCRT, although overall survival has shown to be inferior in a meta-analysis [35].

While data on the benefit and risk of cCRT in older patients are conflicting, age alone should not preclude cCRT, and a multidisciplinary team could help to select appropriate patients. Evidence shows that treatment, as it is applied to younger patients, could be used for fit older patients. However, there is insufficient evidence that this is an appropriate approach for unfit older patients. Recently, the Pacific trial showed a longer progression free survival in patients with NSCLC stage III treated with durvalumab after cCRT compared to placebo. There was no age restriction in this study, and the median age was 64 years (range 23–90 years) but age-related results showed that the experimental arm may not be as efficacious in older adults. Older patients were not analysed separately [41].

2.3. Adjuvant Systemic Treatment

Adjuvant systemic therapy significantly improves survival in patients with NSCLC [42]. Age alone should not disqualify an older patient from adjuvant chemotherapy in NSCLC, although data demonstrating a survival benefit is missing for patients >75 years of age [43]. The decision to treat should include the expected benefit and the increased risk of serious adverse events [44,45]. In the absence of specific trials for older patients, we must rely on retrospective data and subgroup analyses. Post hoc subgroup analyses inherently lack power due to small numbers of older patients included. One such small subgroup analysis of a randomized trial even suggested that

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adjuvant cisplatin-containing chemotherapy could be harmful for patients 75 years or older [46].

Another retrospective analysis was performed on populations which included individual patient data of 4584 patients randomized in cisplatin based adjuvant trials [43]. Impact on overall survival, treatment delivery, and toxicity were investigated according to age. Older patients (≥70 years old) made up 9% of the patients, and were compared to both the young group (<65 years old, 71%) and an intermediate group (65–69 years old, 20%). The result of this analysis showed that selected older patients had similar survival benefits and toxicity rates including toxic death rates from chemotherapy compared to their younger counterparts. Separate SEER-Medicare database analyses revealed that up to 83% of older patients were actually treated with carboplatin instead of cisplatin. These analyses did not show significant survival differences between cisplatin and carboplatin but slightly less side effects in carboplatin treated patients [47,48].

Potentially, better tolerated new systemic treatment options such as immunotherapy are of particular interest in older patients [49]. Various studies are currently testing whether checkpoint-inhibitors or other targeted therapies could improve clinical outcomes in the adjuvant as well as in the neoadjuvant setting [50]. One recent study showed a DFS benefit for EGFR mutant patients who were given gefitinib targeted therapy compared to chemotherapy [51]. Like in the metastatic setting, these drugs have a better toxicity profile and are better tolerated in older patients.

2.4. Treatment for Metastatic NSCLC

As in younger patients, platinum-based doublet chemotherapy is associated with a survival benefit compared with vinorelbine or gemcitabine monotherapy in older patients with advanced NSCLC [52]. However, a recent Asian study of docetaxel plus cisplatin versus docetaxel monotherapy failed to demonstrate any survival advantage as first-line chemotherapy for advanced NSCLC in older patients [53]. Further information about treatment outcomes of cisplatin-basedchemotherapy in older patients with lung cancer are available from subgroup analyses of patients with metastatic disease who participated in large cooperative group studies, but again, likely represent a highly selected group of older patients [54–56]. These studies mostly showed similar treatment outcomes for older patients with similar or slightly increased toxicity rates in selected older patients who fulfilled the stringent inclusion criteria of clinical trials.

Responses to palliative radiotherapy in older patients are similar to those in younger patients [57]. However, the QUARTZ-trial comparing best supportive care with or without whole brain radiotherapy (WBRT) in patients with brain metastases from NSCLC only showed a survival benefit for irradiated patients younger than 60 years and Karnofsky Performance Status (KPS) of >70% in a subgroup analysis [58]. For patients at risk for neurocognitive disorders methods of minimizing WBRT associated neurotoxicity like the use of NMDA (*N*-methyl-D-aspartate) receptor antagonist memantine and/or hippocampal-sparing radiation techniques may become standard options in the future [59].

Trials evaluating targeted therapy in patients with EGFR mutations or ALK translocations have constantly demonstrated better tolerability and quality of life compared to platinum-based chemotherapy. Therefore, these treatments should also be suitable for a more vulnerable population such as patients with poor performance status or older patients [60].

As immunotherapy with checkpoint inhibitors represents a relatively novel treatment option for patients with metastatic NSCLC, limited data is available on the safety and efficacy of these agents in older patients. While a recent trial suggested good tolerability [61], another study demonstrated increased toxicity and worse outcomes [62]. Specific trials for older patients are needed to further explore the role of immunotherapy in this population. Recent phase III trials have demonstrated an overall survival advantage of immunotherapy as second line treatment compared to docetaxel or, most recently, as first line treatment in patients whose tumours express high levels of PDL-1 or if added to standard platinum-based chemotherapy. All these trials enrolled relatively young (median age ranging from 63 to 65 years) as well as exclusively fit patients (PS 0–1) [63–70]. Due to the underrepresentation of older patients in these trials, only limited conclusions can be drawn because the majority of these studies did not analyse older patients separately. In the IMPOWER 150 trial, only 9% (n = 64) were older than 75 years of age, which does not allow meaningful conclusions to be drawn [66]. In this study, the addition of immunotherapy to first line carboplatin/paclitaxel and bevacizumab appeared to be beneficial with regards to PFS benefit, both in younger and also in patients aged 75 or older (hazard ratio 0.78). In the absence of sufficient data on the older population in these trials, it has to be noted that with the addition of immunotherapy to chemotherapy, toxicity rates were higher and tolerability of such an approach in older patients needs further evaluation. On the other hand, in a European single-arm, phase 2 trial (CheckMate 171) testing nivolumab in previously treated patients with metastatic squamous NSCLC, the subgroup of patients aged 70 years or older ($n = 155$) had a 56% rate of treatment related adverse events (TRAEs) and only 16 (6%) discontinued due to TRAEs [61]. These results indicate that anti-PD1 monotherapy tolerability in patients aged 70 or older may be comparable to the overall population.

2.5. NSCLC Geriatric Assessment

Retrospective analyses have demonstrated that comprehensive geriatric assessments (CGA) in older patients in addition to neuropsychological evaluations and blood tests help in predicting survival [10] and chemotherapy associated toxicity [11]. CGAs can better predict the risks of chemotherapy toxicity than KPS [71]. In a prospective study, treatment allocation based on CGAs in older patients with advanced NSCLC failed to improve the treatment failure free survival (primary endpoint) or OS, but reduced treatment toxicity [72]. This can be an important surrogate marker of quality of life.

Although the use of CGA for treatment allocation is currently not standard, their use may facilitate an individualized approach. As CGAs are time consuming, screening tools such as the G8 or Vulnerable Elders Survey (VES)-13 may be suitable to select patients for a CGA [12]. These short geriatric screenings include multiple tools to evaluate the need for a full comprehensive assessment, an estimation ofthe ability for self-care, risk assessment regarding excess treatment related toxicity, and early mortality [13]. All older patients with lung cancer should have a CGA done if possible, and if resources are an issue, they should at least get a CGA screening test to select those requiring a full CGA [14].

3. Small Cell Lung Cancer (SCLC)

The incidence of SCLC is gradually decreasing as the prevalence ofsmoking is declining [73]. Almost 40% of all SCLC patients are over70 years old and 10% are older than 80 years [74]. Without therapy, the overall survival is limited from weeks to a few months [3]. Fiveyearoverall survival (5y-OS) for lung cancer independent of histology is 18.1% [5], whereas 5y-OS for SCLC is only 6.6%. For limited disease SCLC (LD-SCLC), 5y-OS is 12.1%; and only 1.6% for extensive disease (ED-SCLC) [3]. About 70% will present with ED-SCLC at time of diagnosis [75].

3.1. SCLC Limited Disease

The standard treatment for LD-SCLC is cCRT [76,77]. Older patients appear to benefit similarly from treatment compared to their younger counterparts, but with increased toxicity [56]. According to a meta-analysis including older trials [76], no survival benefit was observed for patients over 65 years, but this subgroup analysis should be

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interpreted with caution. There are no randomized phase III studies available comparing combined chemo-radiotherapy to chemotherapy alone in the older population with LD-SCLC [78], but retrospective data suggest that age does not have an impact on the efficacy of combined treatment in contrast to the mentioned meta-analysis [79]. For example, Corso et al. showed that CRT has better results compared to chemotherapy alone in older patients after stratification for comorbidities, nodal status, radiation once/twice daily or concomitant/sequential treatment [78]. Subset analyses of CRT treatment sequence showed a survival benefit with cCRT over sequential CRT. The subset analysis restricted the chemotherapy cohort to patients for whom CRT was explicitly recommended but not delivered in an effort to reduce selection bias. The cohort was reduced to 8.9% of the original cohort (335 patients), but a survival benefit for CRT persisted.

In the CONVERT trial, radiation once daily up to 66 Gy did not provide a survival benefit or more severe adverse events compared to radiation twice daily up to 45 Gy [80]. 15% of patients were >70 years old with a median age of 62 years, but there were fewer older patients in the twice-daily-group. A separate report on outcome in the older population from this study showed similar results for older patients [81]. A phase II trial demonstrated similar outcomes with less esophagitis in patients treated once daily to 70 Gy with 2 Gy daily compared with radiation twice daily [82], however with no specific focus on older populations.

A large retrospective cohort study (SEER-Medicare Database) of 10,428 patients aged 65 years and older who were diagnosed with SCLC between 1992 and 2001, showed that 67.1% of patients received chemotherapy, and 41.6% received etoposide with carboplatin or cisplatin with or without other agents. One third of older patients with SCLC never received chemotherapy, and one sixth were never referred to a medical oncologist. These results indicate that the use of chemotherapy is limited in this vulnerable population. Definitive conclusions regarding survival benefit are difficult due to the retrospective nature of this analysis [83]. Evidence from a retrospective analysis of data from two randomized trials suggests that response rates to chemotherapy in the older patients are comparable to younger patients [56]. Chemotherapy regimens used are the same as in younger patients [84]. Therefore, while standard treatment for limited disease small cell lung cancer consists of cCRT once or twice daily, older patients should be selected carefully for combined treatment.

3.2. LD SCLC- Prophylactic Cranial Irradiation (PCI)

PCI should be part of standard care in LD SCLC in case of complete or good partial remission after primary treatment. According to a meta-analysis, there was an overall survival benefit in patients receiving PCI (25% of study participants were 65 years old or older) [85]. Based on additional data from a SEER-database analysis, older patients, who received PCI, had better survival than patients who did not receive PCI [86]. While age alone should not rule out PCI, it should be used with caution in older patients as they are at higher risk for neurocognitive deterioration [3].

3.3. Extensive Disease SCLC

ED SCLC is highly responsive to chemotherapy, but median survival is less than one year [87,88]. First line treatment in older patients consists of Carboplatin/Etoposide [73,89] or Cisplatin/Etoposide [90]. A trial including patients up to 75 years of age showed doubling of the 1y OS with PCI, as well as reduced rates of brain metastases at one year if no routine MRI of the brain was performed before the start of chemotherapy [91]. PCI in older patients with SCLC results in a longer survival, according to a pooled analysis of four prospective trials [92]. However, in a Japanese trial, PCI did not result in longer overall survival compared with observation in patients with ED SCLC (median age 69 years, maximum age 86 years) [93]. Regarding PCI, risk of overtreatment should be avoided [94] and PCI is currently controversially discussed for ED SCLC even for younger patients. As mentioned previously, numerous approaches are being investigated to preserve neurocognitive function in patients receiving WBRT, these methods may prove most valuable in subsets of patients with relatively good prognoses – i.e. in prophylactic cranial irradiation.

The use of thoracic RT (TRT) in ED SCLC remains controversial and patients have to be chosen carefully for this approach which slightly increases survival rates [95–97]. The only two prospective studies included patients with a median age of 60 and 63 years, respectively, <10% were 75 years old or older. Given the overall poor prognosis, the older population with ED-SCLC require an individualized approach [98] and multidisciplinary team in the decision making in order to avoid both, over- and under-treatment.

4. Summary/Conclusion

Older patients with lung cancer should be discussed in a multidisciplinary setting. Selected older patients with lung cancer seem to derive as much benefit from active oncological treatment as their younger counterparts. Under-treatment is a risk in this patient population and should be avoided. Patient selection is of great importance as many older patients have other medical issues that need to be taken into account before selecting the appropriate treatment. This remains a challenging task as data for this specific population is scarce. While newer agents are being investigated in the neoadjuvant, concurrent or adjuvant setting, we should not lose sight of the fact that a major impact on survival and quality of life in potentially curative stages is still achieved by established local treatments (i.e. radiotherapy, surgery). While emerging treatments may provide improved outcomes with limited toxicity, patient preference should remain at the centre of our attention, especially in an older population where tolerability and logistics may significantly impact patient satisfaction. Having a multidisciplinary team and performing CGAs could help select appropriate treatments with improved outcomes (including quality of life) and reduce toxicities. Effective treatment should not be withheld based on age alone.

Author Contributions

M. Putora and M. Radovic contributed to the study concept. M.Glatzer, F. Minervini, M. Früh, A. Rittmeyer, R. Kanesvaran, M. Radovic and M. Putora contributed to manuscript preparation, editing, and review. All authors have no conflicts of interest to declare.

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