



Management of stage IIIA non-small cell lung cancer in elderly patients: should we do differently? – a narrative review

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Abstract: Lung cancer is the second most common cancer in males, after prostate cancer, and the third in females after breast and colorectal malignancies. The incidence of cancer increases with aging and, because of the increase of life expectancy, the incidence of lung cancer in the elderly is becoming increasingly important. Even if lung cancer has a high prevalence among patients older than 65 years, geriatric patients are often at risk for insufficient treatment because of lack of data on outcomes after multimodality treatment. The supposed impact of age in geriatric population is probably very overestimated and therefore several trials have included no patients older than 65. In our current society, the population is getting older worldwide and simultaneously the surgical demand of elderly patients is becoming increasingly pressing. Patients with stage IIIA disease are a heterogeneous group requiring often a multimodality treatment tailored to each patient. A multidisciplinary approach to select patients and plan the best treatments is nowadays a cornerstone in order to have good surgical outcomes and reduce morbidity and mortality rates. Improve the selection of elderly patients who can benefit from multimodal treatment in stage IIIA non-small cell lung cancer (NSCLC) will be a challenge of the future.

Keywords: Non-small cell lung cancer in elderly (NSCLC in elderly); lung cancer multimodality treatment; stage IIIA lung cancer

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Introduction

The world's population is gradually getting older and therefore the surgical demand in geriatric patients is growing fast. About 60% of patients diagnosed with lung cancer are 65 years or older and the majority of cancer-related deaths occur within this age population. More than 50% of non-small cell lung cancer (NSCLC) cases are diagnosed in patients older than 65 years and about 30% in patients older than 70 years (1).

In 2003 lung cancer was the second leading cause of cancer death in octogenarians; nevertheless, there is evidence that this patient population is at risk for inadequate management because of a reluctance to perform surgery due to concerns about age-related comorbidities and outcomes (2). Geriatric patients are usually underrepresented in clinical trials and therefore there is a lack of data on outcomes of multimodal strategies (3,4). Although the standard treatment of locally advanced non-small-cell lung cancer (NSCLC) is a

multimodal therapy approach (5), very few trials focus on elderly patients (6).

The most commonly used cutoff to define elderly patients is the age of 70 and above (7).

However, since the median life expectancy continues to lengthen in developed countries, providing the best treatment for elderly has gained importance. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://ccts.amegroups.com/article/view/10.21037/ccts-20-128/rc>).

Methods

We performed a literature research in PubMed including articles from January 1 1997 to June 30 2020, using the following search words alone or in combination: NSCLC, stage IIIa, lung surgery in the elderly, neoadjuvant and adjuvant, multimodal approach in the elderly for lung cancer. We excluded papers in language other than English.

The risk/benefit balance of surgery in elderly

A frequently asked question from our patients about the possibility to perform surgery is “am I too old for lung surgery?” Elderly patients are a very heterogeneous group. The answer is not simple even for the most experienced and passionate surgeon. A well-reasoned balance between surgery and other treatments or even the choice of no treatment at all should be done.

Birim and colleagues reported, in their retrospective study of 126 patients older than 70, acceptable mortality (3.2%) and morbidity (minor complication rate: 57%; major complication rate 13%). The study showed a 5-year survival rate of 37% and a 10-year survival of 15%. The median survival time was 3.8 years. In the multivariate analysis smoking (odds ratio, 2.6; 95% CI, 1.1 to 6.2), chronic obstructive pulmonary disease (odds ratio, 2.7; 95% CI, 1.7 to 5.9), and pathologic stage (stage IIIA, odds ratio, 2.9; 95% CI, 1.4 to 6.2) significantly influenced overall survival (8).

Dominguez-Ventura and his group from Mayo Clinic reported in a retrospective analysis of 379 patients older than 80 an operative mortality of 6.3% with complications occurring in 182 patients (48.0%) (9). At the time of follow up (median 2.3 years), 114 patients were alive (30%).

The feasibility of lung surgery in the elderly was confirmed by Dillman in 2009 who clearly stated in the conclusion of his paper that curative surgery should be not

denied simply because of age (10). They reported a median follow-up and survival at the time of median follow-up of 23 months and 77% for the group with patients between 80 and 89 years old, 31 months and 74% for the 70–79 group. Several studies have reached the same conclusions although it is particularly difficult to make a clear statement about the balance of pro versus contra of lung surgery in elderly affected by stage IIIA lung cancer. First of all, there are no focused studies on this stage. Moreover the available literature to date mainly consists of retrospective studies with several limitations.

The minimally invasive approach with video-assisted thoracoscopic surgery (VATS), especially using uniportal technique, has made surgery attractive for elderly patients reducing postoperative pain and in hospital length of stay. A recent retrospective analysis of 1,100 VATS lobectomies performed on patients with a mean age of 71.2 published by McKenna and colleagues demonstrated low rates of mortality (<1%) and morbidity, with 84.7% of patients exhibiting no significant complications (11).

A paper published by Cattaneo *et al.* with 333 patients aged ≥ 70 who underwent surgery due to NSCLC demonstrated that VATS approach had significantly lower rate of complications compared with open surgeries (28% versus 45%; $P=0.04$) and a reduced length of stay (5 days, range 2–20 versus 6 days, range 2–27; $P<0.001$) (12).

According to several studies, stage IIIA should not be considered in expert hands an absolute contraindication to a thoracoscopic approach with curative intentions (13–16).

An accurate selection of the patients along with the expertise of the surgeons do not appear to affect the perioperative morbidity rates and the oncologic efficacy.

Neo-adjuvant treatments in the elderly

Multimodality treatments in patients with Stage IIIA lung cancer have clearly demonstrated clinical benefits on overall and disease-free survival (17–19). As a point of fact, a multimodal strategy is seldom offered to elderly patients due to several concerns about comorbidities and possible toxicity.

Rivera *et al.* compared the mortality and complications rate of 81 elderly patients (>75 years) with younger counterparts. Although the mortality was comparable, the incidence of postoperative major complications was higher in elderly patients group (22.2% *vs.* 14.8%, $P=0.03$) likewise they experienced a longer length of stay (14.9 *vs.* 12 days, $P\leq 0.01$). However the authors concluded that

surgical resection after neo-adjuvant treatment should be recommended to elderly patients although it should be taken in account that post-operative morbidity is not negligible (20).

Marquez-Medina and his group published a paper in 2014 comparing the tolerance to induction chemotherapy or chemo-radiation followed by surgery or definitive radiotherapy in subjects younger and older than 70 years with NSCLC. No difference was observed in postoperative mortality and moreover age *per se* did not affect efficacy or tolerance of the multimodal treatment (21). The same results were reported two years later by Yang who did not observe any difference in 30-day or 90-day mortality (3).

Coate and his group from Toronto reported that in patients undergoing multimodal therapy including surgery there was no statistically significant association between toxicity from chemotherapy and age (4).

Bongiolatti and colleagues conducted a retrospective study comparing patients <70 with patients ≥70. They analyzed mortality, morbidity and oncological outcomes of lung resection after neoadjuvant treatment for NSCLC concluding that age *per se* is not a risk factor who should place limits on the application of a multimodality approach in elderly patients (22). Concurrently, D'Angelillo *et al.* have reported on the safety and feasibility of a neoadjuvant treatment combining radiotherapy and chemotherapy (carboplatin or gemcitabine). The rate of hematological and non-hematological grade 3 toxicity was 7.9% and 2.6% respectively, and the response rate was 72.6% (23).

Chemoradiation

Sequential or concurrent radio-chemotherapy is commonly used in locally advanced NSCLC, but data on their efficacy and toxicity in elderly population is very limited.

Only few prospective trials focused their attention on this important topic while most studies are actually of retrospective nature and are thus clearly subject to selection bias and thus making their conclusions inconsistent.

Atagi and his group reported a response rate of 50% with hematological toxicities (leukopenia 71%, neutropenia 55%, thrombocytopenia 29% and anemia 34%) in elderly patients who received radiotherapy along with low dose daily carboplatin (24). Moreover, Nakano found a response rate of 82% with a median overall survival of 23 months in elderly patients affected with locally advanced NSCLC treated with thoracic radiation and cisplatin (25).

Asmis and colleagues retrospectively analyzed 1,255

patients who received systematic chemotherapy due to NSCLC. The most important prognostic factor associated with poor survival was the presence of comorbidities rather than age >65 years (26).

The LACE meta-analysis included five major studies investigating the use of platinum-based chemotherapy in an adjuvant setting. This analysis demonstrated the same outcomes in patients older than 60 years compared with the younger counterparts, despite it should be taken in account that, in the older patients group, doses and duration of chemotherapy were lower (27). Nonetheless, two included studies, JBR10 and the Big Lung Trial, enrolled a small number of patients older than 75 years (23 and 8, respectively) (28,29).

Even if the above-mentioned publications show some benefit of cRCT in elderly patients, individual data analysis on chemoradiation therapy for Stage III NSCLC in patients older than 70 versus younger patients demonstrated that older patients experienced worse OS, more toxicities, more treatment discontinuation and a higher mortality rate during treatment (30).

Immunotherapy

The advent of immunotherapy in clinical practice has significantly impacted survival of patients with locally advanced NSCLC. Trials using targeted therapies have been demonstrated a favorable toxicity profile differing from classical chemotherapy drugs and therefore the use of immunotherapy could represent a safe option in older patients.

Most of studies with Immune Checkpoint Inhibitors for NSCLC included only small subgroups of patients aged ≥65.

Comparable efficacy of immunotherapy in patients older than 65 and younger counterparts emerged from a meta-analysis of nine randomized controlled trials, in which patients with NSCLC were treated with nivolumab, pembrolizumab or atezolizumab in comparison with chemotherapy/targeted therapy (31).

Galli *et al.* published a case series including 290 patients with 3 subgroups: patients aged <70, 70–79 and ≥80 years old.

Response rate (P=0.9470), median progression free survival (P=0.2020) and overall survival did not differ according to age (P=0.9144) and toxicity was comparable among the subpopulations (P=0.6493) (32).

However, to date there is no larger trial, investigating the

efficacy and safety of immunotherapy exclusively in elderly patients.

Conclusions

Several risk factors like lower values of forced expiratory volume in 1 second (FEV1), diffusing capacity for carbon monoxide (DLCO), history of coronary artery bypass graft surgery and chronic obstructive pulmonary disease could affect post operative outcomes in elderly (33). Age should not be considered an absolute contraindication for the treatment of stage IIIA elderly patients anymore. Innovations in surgery, radiation therapies and new immunotherapies have reduced toxicities and related morbidities expanding the potential cohort of possible patients that can be treated. Nevertheless, it has become apparent that especially in older patients, a patient-tailored and multidisciplinary approach should be used to define the risk-benefit balance. According to our experience, a comprehensive geriatric assessment (CGA) is mandatory in order to potentially stratify elderly patients affected by Stage IIIA NSCLC with the aim to reduce post-operative morbidity and mortality.

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