Review

Assessment of the External Validity of the National Comprehensive Cancer Network and European Society for Medical Oncology Guidelines for Non–Small-Cell Lung Cancer in a Population of Patients Aged 80 Years and Older

Nicolò Matteo Luca Battisti, Marina Sehovic, Martine Extermann

Abstract

Non–small-cell lung cancer (NSCLC) is a disease of the elderly, who are under-represented in clinical trials. This challenges the external validity of the evidence base for its management and of current guidelines, that we evaluated in a population of older patients. We retrieved randomized clinical trials (RCTs) supporting the guidelines and identified 18 relevant topics. We matched a cohort of NSCLC patients aged older than 80 years from the Moffitt Cancer Center database with the studies' eligibility criteria to check their qualification for at least 2 studies. Eligibility > 60% was rated full validity, 30% to 60% partial validity, and < 30% limited validity. We obtained data from 760 elderly patients in stage-adjusted groups and collected 244 RCTs from the National Comprehensive Cancer Network (NCCN) and 148 from the European Society for Medical Oncology (ESMO) guidelines. External validity was deemed insufficient for neoadjuvant chemotherapy in stage III disease (27.37% and 25.26% of patients eligible for NCCN and ESMO guidelines, respectively) and use of bevacizumab (13.86% and 16.27% of patients eligible). For ESMO guidelines, it was inadequate regarding double-agent chemotherapy (25.90% of patients eligible), its duration (24.10%) and therapy for Eastern Cooperative Oncology Group performance status 2 patients (17.74%). For NCCN guidelines external validity was lacking for neoadjuvant chemoradiotherapy in stage IIIA disease (25.86% of patients eligible). Our analysis highlighted the effect of RCT eligibility criteria on guidelines' external validity in elderly patients. Eligibility criteria should be carefully considered in trial design and more studies that do not exclude elderly patients should be included in guidelines.

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Introduction

Western countries are progressively aging[1] and elderly patients suffer from a higher burden of cancer.[1] Age is the most important risk factor for cancer and its prevalence will progressively increase in the elderly population,[2] urging the need for better treatment strategies in this setting. Although patients aged older than 80 years are a small percentage of trial patients, this fraction is rapidly growing and represents 17.8% of non–small-cell lung cancer (NSCLC) patients.[3]

The under-representation of elderly patients in clinical trials[4] because of strict eligibility criteria about performance status (PS) and organ dysfunction, competing comorbidities, and logistic barriers[5-7] limit the solidity of the evidence supporting the optimal management of NSCLC in this specific population.

Randomized clinical trials (RCTs) and systematic reviews are the highest level of evidence. If applicable and relevant to a definable group of patients in a particular clinical setting, they can be defined clinically useful and externally valid. According to the Consolidated Standards of Reporting Trials (CONSORT) statement, external

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Senior Adult Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

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Address for correspondence: Nicolò Matteo Luca Battisti, MD, PhD, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom
E-mail contact: nicolo.battisti@rmh.nhs.uk

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validity should be addressed in reporting RCTs.[8] Its lack of consideration is the most frequent criticism for RCTs, systematic reviews, and guidelines,[9-14] accounting for the underuse of treatments beneficial in trials and recommended in guidelines in routine practice.[15-19] A conceptual approach to assess the external validity of therapeutic research has already been proposed.[20] However, it cannot be easily formalized because it is a complex situation in which previous knowledge, statistical considerations, biological plausibility, and eligibility criteria all have a place. Therefore there is no consensus about how to assess external validity, although this necessarily includes the review of studies' eligibility criteria.

The 2 most commonly used guidelines for the management of NSCLC in Western countries are: the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC[21] in the United States and the European Society for Medical Oncology (ESMO) guidelines for early and locally advanced[22] and for metastatic NSCLC[23] in Europe. The aim of this study was to quantify and qualify the evidence of such guidelines in a population of elderly patients, and assess their external validity in a population of patients aged 80 years and older.

Materials and Methods

We defined the evidence base for the management of NSCLC patients according to the RCTs included in the NCCN and ESMO guidelines because these studies translate into clinical treatment decisions. We used the most recent version of both guidelines at the time of the research and analysis (NCCN guidelines version 4.2014 of June 2014,[21] ESMO guidelines for early and advanced stage disease of July 2013,[22] and ESMO guidelines for metastatic disease of August 2014[23]).

We retrieved the original articles through PubMed and Web of Science. For every systematic review or meta-analysis of multiple RCTs, we retrieved and included all individual studies once. Their eligibility criteria were examined. If authors referred to previous publications for eligibility criteria, they were retrieved from ClinicalTrials.gov.[24]

We identified several questions regarding the management of NSCLC and translating into clinical recommendations stated by the guidelines. We summarized such topics as follows: (1) video-assisted thoracic surgical (VATS) lobectomy versus open thoracotomy and lobectomy in operable NSCLC; (2) lobectomy versus limited resection in operable NSCLC; (3) lymph node sampling versus mediastinal lymph node systematic dissection in operable NSCLC; (4) neoadjuvant chemoradiotherapy with surgery versus chemoradiotherapy alone in stage IIIA cT1-3N2 NSCLC; (5) neoadjuvant chemotherapy versus adjuvant chemotherapy in operable NSCLC; (6) concurrent versus sequential chemoradiotherapy in stage III unresectable NSCLC; (7) double-agent versus single-agent first-line chemotherapy in stage IIIB to IV epidermal growth factor receptor (EGFR)- and anaplastic lymphoma kinase (ALK)-negative NSCLC; (8) platinum-based versus nonplatinum-based first-line chemotherapy in advanced/metastatic in stage IIIB to IV EGFR- and ALK-negative NSCLC; (9) cisplatin-based versus carboplatin-based first-line chemotherapy in stage IIIB to IV EGFR- and ALK-negative NSCLC; (10) optimal duration of first-line chemotherapy in stage IIIB to IV EGFR- and ALK-negative NSCLC; (11) best second-line therapy in stage IIIB to IV EGFR- and ALK-negative NSCLC; (12) combination of bevacizumab with first-line chemotherapy in stage IIIB to IV EGFR- and ALK-negative NSCLC; (13) maintenance therapy after first-line chemotherapy in stage IIIB to IV EGFR- and ALK-negative NSCLC; (14) best first-line treatment in patients with Eastern Cooperative Oncology Group (ECOG) PS 2 and stage IIIB to IV EGFR- and ALK-negative NSCLC; (15) adjuvant chemotherapy after surgery versus surgery in stage Ib to III resected NSCLC; (16) neoadjuvant chemotherapy before surgery versus surgery in stage III NSCLC; (17) use of tyrosine kinase inhibitors (TKIs) as first-line therapy in EGFR-mutated advanced/metastatic NSCLC; and (18) use of crizotinib as first-line therapy in ALK-rearranged advanced/metastatic NSCLC.

We retrieved a cohort of patients aged 80 years and older from the Total Cancer Care (TCC) database, at the Moffitt Cancer Center and Research Institute of Tampa, Florida, from January 1, 2000 to October 31, 2014, because electronic medical records were implemented in 2000 and we aimed to test the most recent data. Potential biases regarding the recording of clinical parameters such as PS were addressed by confirmation through the analysis of the medical records.

We matched these patients with the RCT eligibility criteria, answering each question to determine what proportion of elderly patients would have been eligible for such studies. Information on patient characteristics, tumor characteristics, treatment, follow-up, and outcomes were recorded for all patients. We considered all the recent changes in the Tumor, Node, Metastases staging system for NSCLC and converted each patient's stage to the system in use at the time he or she would have enrolled in a specific trial. Comorbidities were rated according to the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[25] and level 3 and 4 conditions were considered as severe. The Moffitt laboratory reference ranges were used for comparison when the studies required patients to have "normal" ranges of values without defining them.

We calculated what proportion of elderly patients from the TCC database would have been eligible for at least 2 trials, on the basis of their eligibility criteria, for each question, which assured reproducibility and generalizability of the evidence.[26,27] Positive results from at least 2 trials are required by regulatory agencies for treatment approval or to increase the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) of evidence.[28] There is no standard definition or cutoff for an evidence base for treatment, and defining external validity is nonstandardized. Studies on guidelines' application typically consider $>$ 60% to 80% as acceptable. Our study was inspired by similar research conducted by van de Water et al on a population of elderly breast cancer patients.[29] Therefore, the evidence base was considered present if $>$ 60% of patients would have been eligible for the trials; partial if a proportion between 30% and 60% would have been eligible; and limited if $<$ 30% would have been included in the studies. In patients for whom an evidence base was deemed present, we concluded that recommendations from the guidelines, on the basis of such trials, could be extrapolated. To further qualify the evidence, we evaluated the most influential eligibility criteria within each guideline's recommendation.

Results

Overall, 760 NSCLC patients older than 80 years of age were included in the study. The mean age at the time of first presentation