Concurrent systemic therapy with radiotherapy for the treatment of poor-risk patients with unresectable stage III non-small-cell lung cancer: a review of the literature

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Background: There is no consensus on the therapeutic approach to poor-risk patients with unresectable stage III non-small-cell lung cancer (NSCLC), despite the increasing number of these patients in current clinical practice. In terms of survival, the combination of concurrent systemic therapy with standard radiotherapy might be advantageous over radiotherapy alone. The purpose of this review is to ascertain the feasibility, safety and efficacy of the combination of concurrent systemic therapy and standard radiotherapy in these patients.

Methods: A computer-based literature search was carried out using PubMed and Science Direct for relevant publications; data reported at major conferences in abstract form were also included.

Results: In unresectable stage III NSCLC, advanced age, poor performance status, weight loss and comorbidities are factors that influence treatment options and disease outcomes in clinical practice. Prospective studies including poor-risk
patients have been reviewed. Trials specifically recruiting poor-risk patients have been separated into those using chemotherapy and those using targeted agents with or without chemotherapy. Only two phase III studies specifically including poor-risk patients have been published. Some recent studies suggested that tolerable radio-sensitizing therapy combined with radiotherapy can provide longer survival outcomes than those reported earlier with chemo-radiotherapy or with radiotherapy alone.

Conclusions: There is an unmet need to develop well-designed clinical trials with tolerable combinations of systemic therapy and radiotherapy specifically tailored to this lung cancer population. Such trials should incorporate careful comorbidity measurement and, in older adults, a validated geriatric assessment.

Key words: non-small-cell lung cancer, stage III, chemo-radiotherapy, poor-risk patients, EGFR inhibitors, elderly patients

introduction

Concurrent chemo-radiotherapy (CTRT) is the standard treatment of good performance status (PS) patients with unresectable stage III non-small-cell lung cancer (NSCLC). An individual patient data meta-analysis comparing concurrent CTRT with sequential CTRT demonstrated that concurrent CTRT decreases locoregional progression and provides an absolute benefit in overall survival of 4.5% at 5 years. Concurrent CTRT is associated with higher rates of radiation oesophagitis, which is largely reversible, but there is no increase in the risk of radiation-related lung toxicity [1].

However, patients with characteristics predicting poor tolerance to treatment and poor prognosis are generally referred to in the literature as ‘poor-risk’ patients and have in the main been excluded from clinical trials evaluating concurrent CTRT. In most phase III studies, eligibility criteria include a maximum age of 70–75 years, Eastern Cooperative Oncology Group (ECOG) PS ≤ 1, weight loss <5% or ≤10% in the previous 3 months, adequate organ function (renal, hepatic, haematopoietic, pulmonary or cardiac) and the absence of major comorbidities. These are summarized in Table 1 [2–9]. In addition, a population-based study from a Dutch Cancer Registry showed that 57% of patients were not eligible for concurrent CTRT based on comorbidities and age [10].

Further data from population-based studies suggest that elderly patients with locally advanced NSCLC are less likely to receive active treatment compared with their younger counterparts [11–13].

Table 1. Summary of exclusion selection criteria in large (≥200 patients) phase III clinical trials of concurrent chemo-radiotherapy in stage III NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Performance status (PS)</th>
<th>Upper age limit</th>
<th>Maximum weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9410 [2]</td>
<td>Karnofsky ≥ 70</td>
<td>–</td>
<td>5%</td>
</tr>
<tr>
<td>WJTOG [3]</td>
<td>ECOG ≤ 2</td>
<td>74</td>
<td>–</td>
</tr>
<tr>
<td>GLOT-GFPC-NPC 9501 [4]</td>
<td>ECOG ≤ 1</td>
<td>70</td>
<td>10%</td>
</tr>
<tr>
<td>CALGB 39801 [5]</td>
<td>CALGB ≤ 1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SWOG 0023 [6]</td>
<td>ECOG ≤ 1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HOG LUN 01-24 [7]</td>
<td>ECOG ≤ 1</td>
<td>–</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>OLCG 0007 [8]</td>
<td>ECOG ≤ 1</td>
<td>75</td>
<td>–</td>
</tr>
<tr>
<td>WJTOG 0105 [9]</td>
<td>ECOG ≤ 1</td>
<td>75</td>
<td>–</td>
</tr>
</tbody>
</table>

*5% of enrolled patients actually had ECOG PS 2.

†12% of enrolled patients actually had weight loss >10%.

There is no consensus on the therapeutic approach for poor-risk patients with unresectable stage III NSCLC, despite the increasing number of these patients in clinical practice. Radiotherapy alone is still the standard treatment of patients with less than optimal risk characteristics according to the Radiation Therapy Oncology Group (RTOG) [14].

The purpose of this review is to ascertain whether radiotherapy with concurrent systemic therapy is feasible, safe and effective in patients with poor-risk characteristics.

methods

A literature search was carried out using PubMed and Science Direct databases up to July 2013 with the search terms: ‘locally advanced lung cancer’, ‘stage III’, ‘chemotherapy’, ‘radiotherapy’, ‘poor-risk’ and ‘elderly’. Proceedings of the major conferences were also searched for abstracts using the same keywords. The reference sections of selected papers were manually searched for relevant publications.

poor-risk factors influence treatment options and disease outcomes

age

Advanced age is a well-recognized factor of clinical limitations. As age increases, there is a decline in physiological reserve, functional status and cognition, whereas comorbidities tend to increase. These age-related changes can influence tolerance to and the overall risk-benefit ratio of cancer treatment [15]. In addition, social support and nutrition are factors that may influence treatment outcomes in older adults. All these elements should
be considered and developed into geriatric assessment tools to characterize older adults [16, 17]. The implementation of such tools in clinical trials is being developed [18].

performance status

Poor PS, according to ECOG or Karnofsky scales (KPS), is a recognized adverse prognostic factor in lung cancer and it has been the only assessment of general health at baseline when enrolling patients to clinical trials.

The influence of a poor PS has been studied extensively in the setting of advanced disease, where it has been identified as a factor that decreases tolerance to treatment and survival [19, 20]. PS has also emerged as a prognostic factor in stage III NSCLC [21], but only the subset of patients with a good PS (KPS ≥70, ECOG ≤1) have as a rule been included in clinical trials, consequently there is paucity of outcome data in patients with PS 2.

weight loss

Weight loss is associated with increased treatment complications and has consistently been associated with decreased survival in stage III NSCLC [21]. Some of the key concurrent CTRT clinical trials excluded patients with pre-treatment weight loss ≥5–10%. Nevertheless, it is not known whether pre-treatment weight loss is an independent prognostic factor and whether it should be used as the single criterion for denying patients standard treatment in the stage III setting. Indeed, it is still a selection criterion in some concurrent CTRT trials within some cooperative groups, such as RTOG.

comorbidities

Comorbidities are common in lung cancer [22] and it is generally assumed that patients with pre-existing pulmonary disease, particularly chronic obstructive pulmonary disease (COPD), are at increased risk of radiation toxicity [23, 24]. Although in most CTRT studies poor pulmonary function is an exclusion criterion, the data relating pre-morbid physiology to radiation toxicity and survival are limited. The ERS-ESTS task force on fitness for radiotherapy in lung cancer concluded that safe lower limits of respiratory function for radical radiotherapy have not been as well defined as they have for surgery [25].

Comorbidities are consistently more prevalent in the elderly [26] and are largely under-represented in clinical trials [27]. There is a paucity of data on the impact of comorbidities on stage III NSCLC clinical trial patients. Investigators from the Medical College of Wisconsin examined the influence of comorbidities in study enrolment in stage III NSCLC patients treated with radiotherapy alone or with CTRT [28]. They hypothesized that comorbidities were largely responsible for the under-representation of older patients in clinical trials, including trials without an upper age limit. They retrospectively analysed 171 patients with a KPS ≥70 and found that although 29% of patients were considered eligible for CTRT studies they were not enrolled and 33% did not meet eligibility criteria for any RTOG studies. The most common ineligibility reasons were weight loss (67%) and comorbidities (63%). In patients meeting study eligibility requirements a higher comorbidity score measured by the Cumulative Index Rating Scale for Geriatrics (CIRS-G) and age ≥70 years were independent factors influencing RTOG study enrolment. This study confirmed that older and comorbid patients are not well represented in clinical trials. In addition, extremely severe comorbidity (CIRS-G4) appeared to be an independent factor for predicting poor survival. The conflicting results on the outcomes of elderly patients in RTOG trials might be due to the fact that comorbidities were not measured in those trials. Currently, several scales measuring comorbidity are available for use [29].

The impact of comorbid conditions on the outcome of patients with stage III NSCLC was a secondary end point in the RTOG 0213 study [14]; a phase II study recruiting poor-risk patients. Unfortunately, this trial closed early as it failed to recruit enough patients. Only 5 of the expected 122 patients were recruited.

subgroup analysis of poor-risk patients in trials of concurrent chemo-radiotherapy

elderly patients

A subset analysis from RTOG phase I–III trials of radiotherapy alone, sequential CTRT and concurrent CTRT showed that for patients >70 years, concurrent CTRT did not improve outcome and was associated with an increased risk of grade 4 and 5 toxicities [30–33]. In contrast, more favourable results have been reported recently in a subgroup analysis comparing the outcome of elderly patients (≥70 years old) with their younger counterparts (Table 2). The RTOG 9410 study is a landmark three-arm trial comparing sequential CTRT with two concurrent CTRT arms (once-daily and twice-daily radiotherapy) that demonstrated an advantage for once-daily concurrent CTRT over the other two arms [2]. In this study, elderly patients were as likely to derive benefit from concurrent treatment as younger patients with no significant difference in survival between age groups in any of the three arms. It should be noted that only 17% of the patients included were >70 years and that the study mandated KPS ≥70 and weight loss ≤5%. In terms of toxicity, rates of grade ≥3 neutropenia (in all arms) and grade ≥3 oesophagitis (in the concurrent arms) were higher in the elderly. Furthermore, elderly patients treated with hyperfractionated radiotherapy were less likely to complete treatment [33].

Similarly, a subgroup analysis of a phase III North Central Cancer Treatment Group (NCCTG) study of once-daily versus twice-daily concurrent CTRT showed that elderly patients had survival rates equivalent to those of younger patients [34]. Two- and 5-year survival rates were 39% and 18% versus 36% and 13%, respectively, in patients <70 and ≥70 years, respectively (P = 0.4). Grade 4 haematological toxicity was more pronounced in the elderly group (78% versus 56%, P = 0.003) as was grade 4 pneumonitis (6% versus 1%, P = 0.02), but there was no difference in rates of grade >2 oesophagitis or rates of treatment-related deaths.

A CALGB phase III study evaluated the addition of weekly carboplatin during thoracic radiotherapy after induction cisplatim/vinblastine chemotherapy in patients with stage III NSCLC and PS 0–1 [38]. Carboplatin failed to improve survival compared with radiotherapy alone. Elderly patients had a
Table 2. Summary of retrospective subset analysis of clinical trials of chemo-radiotherapy for stage III NSCLC patients comparing treatment efficacy and toxicity between elderly patients and their younger counterparts

<table>
<thead>
<tr>
<th>Study</th>
<th>Trials retrospectively analysed</th>
<th>Age groups</th>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movsas [30]</td>
<td>6 RTOG phase II–III trials of RT alone, sequential CTRT and concurrent CTRT</td>
<td>≥70 years, 144 (15%) &lt;70 years, 835</td>
<td>Patients ≥70 years had the best quality-adjusted survival with RT alone, while patients &lt; 70 years achieved the best survival results with CTRT</td>
<td>Toxicity was not analysed according to the age groups (≥70 and &lt;70 years)</td>
</tr>
<tr>
<td>Werner-Wassik [31]</td>
<td>9 RTOG phase I–III trials of RT alone, sequential CTRT and concurrent CTRT</td>
<td>≥70 years, 429 (21%) &lt;70 years, 1565</td>
<td>Patients ≥70 years had significantly worse survival than younger patients (P &lt; 0.001)</td>
<td>Toxicity was not analysed according to the age groups (≥70 and &lt;70 years)</td>
</tr>
<tr>
<td>Langer [32]</td>
<td>3 RTOG phase II–III trials of RT alone, sequential CTRT and concurrent CTRT</td>
<td>≥70 years, 114 (15%) &lt;70 years, 635</td>
<td>Patients ≥70 years did not benefit from increasing therapeutic intensity and achieved better outcome with sequential CTRT and less intensive CT</td>
<td>≥G3 toxicities were higher with intensified treatments (≥G4 AEs were limited to patients receiving a combined modality treatment)</td>
</tr>
<tr>
<td>Langer [33]</td>
<td>RTOG phase III trial comparing sequential CTRT and concurrent CTRT (q.d. or b.i.d.)</td>
<td>≥70 years, 104 (17%) &lt;70 years, 488</td>
<td>Median survival in the elderly favoured concurrent CTRT (MST 22.4 months in concurrent q.d. CTRT)</td>
<td>Short-term toxicities (G3 neutropenia and G3 oesophagitis) were higher in elderly patients, whereas long-term toxicities were similar between both age groups</td>
</tr>
<tr>
<td>Schild [34]</td>
<td>NCCTG phase III trial comparing q.d. RT versus b.i.d. RT split-course concurrently with CT</td>
<td>≥70 years, 63 (26%) &lt;70 years, 181</td>
<td>Elderly patients had similar survival benefit to their younger counterparts (2- and 5-year survival rates were 36% and 13% in elderly patients versus 39% and 18% in &lt;70-year patients)</td>
<td>≥G4 AEs more frequent in elderly patients (81% in ≥70 versus 62% in &lt;70); ≥G4 myelosuppression and ≥G4 pneumonitis were significantly higher in elderly patients</td>
</tr>
<tr>
<td>Rocha–Lima [35]</td>
<td>CALGB 9130 phase III trial comparing concurrent CTRT versus sequential RT after induction with CT</td>
<td>≥70 years, 54 (22%) &lt;70 years, 196</td>
<td>Elderly patients had similar survival benefit compared with younger patients (MST 13.4 months in ≥70 years versus 10.9–15.4 months in &lt;70 years)</td>
<td>Elderly patients had significantly higher ≥G3 haematological and renal toxicity, but did not experience higher rates of gastrointestinal or pulmonary toxicity</td>
</tr>
<tr>
<td>Jalal [36]</td>
<td>HOG LUN phase III trial comparing consolidation docetaxel versus observation following concurrent CTRT</td>
<td>≥70 years, 64 (26%) &lt;70 years, 179</td>
<td>Elderly patients had similar survival benefit to the younger (MST 17.1 months in ≥70 years versus 22.8 months in &lt;70 years, P = 0.15)</td>
<td>Older patients had higher rates of ≥G3 AEs, hospitalization and treatment discontinuation. Rates of ≥G3 oesophagitis and pneumonitis were not higher in ≥70 years compared with &lt;70 years patients</td>
</tr>
<tr>
<td>Takigawa [37]</td>
<td>OLCSG phase III trial comparing two different cisplatin-based CT regimens (MVP versus DP) with concurrent RT</td>
<td>≥70 years, 52 (26%) &lt;70 years, 148</td>
<td>Survival benefit was similar between both age groups (DP arm: MST 27.5 months in ≥70 years versus 25.6 months in &lt;70 years)</td>
<td>Rate of ≥G4 AEs (myelosuppression, oesophagitis and pneumonitis) was similar among the age groups, although the frequency of pneumonitis tended to be higher in the older group</td>
</tr>
</tbody>
</table>

*Patients with lower KPS (50–70) had the worst quality-adjusted survival. This group of patients achieved higher median and quality-adjusted survival with either sequential or concurrent CTRT.

AE, adverse event; CTRT, chemo-radiotherapy; CT, chemotherapy; HOG LUN, Hoosier Oncology Group; KPS, Karnofsky Performance Status; MST, median survival time; NCCTG, North Central Cancer Treatment Group; OLCSG, Okayama Lung Cancer Study Group; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.
similar median overall survival (13.4 months) compared with patients <70 years (13.5 months). Grade ≥3 myelosuppression and renal toxicity were significantly higher in elderly patients ($P = 0.028$ and 0.0025, respectively); however, they did not experience higher rates of gastrointestinal or pulmonary toxicity [35]. The HOG LUN 01-24 trial compared consolidation docetaxel versus observation following concurrent CTRT in 166 non-progressing patients with stage III NSCLC [7]. The trial was terminated early when an interim analysis demonstrated futility of docetaxel. Consolidation docetaxel did not improve survival and toxicity was greater in the experimental arm compared with the observation arm. Patients ≥70 years ($n = 64$) had similar median survival (17.1 months) compared with younger patients (22.8 months, $P = 0.15$), but experienced higher rates of grade 3 and 4 toxicity (neutropenia, dehydration, anorexia and fatigue) and hospitalization during CTRT [36]. Furthermore, older patients were less able to complete CTRT due to toxicity (11% versus 3%; $P = 0.02$).

The OLCSG 0007 trial compared concurrent CTRT with docetaxel and cisplatin (DP) to concurrent CTRT with mytomycin C, vindesine and cisplatin (MVP) in Japanese patients with stage III NSCLC with a maximum age of 75 years [8]. There was a trend towards improved survival in the DP arm compared with the MVP arm ($P = 0.059$) and rates of grade 3 febrile neutropenia were significantly increased in the MVP arm. When patients were split into two age groups (≥70 and <70 years), survival of older patients in the DP and MVP arms were similar to that of younger patients (median survival time 27.5 versus 25.6 and 22.9 versus 23.4 months, respectively). When compared with younger patients, older patients did not experience a significantly higher rate of grade ≥3 neutropenia, febrile neutropenia, oesophagitis or pneumonitis [37].

weight loss
In the CALGB 39801 study in which weight loss was not a selection factor, there was a significant statistical difference in survival when comparing patients ≥5% versus <5% weight loss ($HR = 1.92, 1.33–2.76, P < 0.01$) [39].

trials for poor-risk patients
The first published study testing a concurrent CTRT approach for poor-risk patients with stage III NSCLC was conducted by the Southwest Oncology Group (SWOG S9429) [40]. Patients were eligible if they were excluded from cisplatin-based protocols because of poor pulmonary or renal function, history of congestive heart failure, hearing loss, peripheral neuropathy, or weight loss. In this randomized phase II study, 60 patients with PS 0–2 were treated with carboplatin and etoposide for two cycles given concurrently with thoracic radiotherapy, 1.8–2.0 Gy daily to a total dose of 61 Gy. There were no treatment-related deaths, the median overall survival was 13 months [95% confidence interval (CI) 11–14 months] and the 2-year survival rate was 21%. A subsequent single-arm phase II study conducted by the same cooperative group studied the addition of three cycles of consolidation paclitaxel after concurrent CTRT [41]. The CTRT regimen and eligibility criteria were the same as in the previous SWOG trial. Eighty-seven patients started treatment and 54 received paclitaxel consolidation. There were eight treatment-related deaths and median overall survival was 10.2 months (95% CI 7.2–12.6 months) and the 2-year survival rate was 25%. The addition of consolidation paclitaxel resulted in more toxicity, without any improvement in survival. The increase in fatal toxicity in the second SWOG study was attributed to the inclusion of a higher proportion of patients with PS 2 (48%) compared with the first study (18%).

Semrau et al. [42] treated 66 patients considered poor-risk (based on age ≥70 years, poor PS, weight loss and comorbidities) with two cycles of carboplatin or cisplatin every 4 weeks plus 3 weekly doses of low-dose vinorelbine per cycle and concurrent radiotherapy up to 63 Gy in 35 fractions. One- and 2-year survival was 53% and 24%. The treatment was well tolerated with 4.5% of grade 3–4 oesophagitis and 3% of grade 4 pneumonitis.

The Spanish Lung Cancer Group protocol 00-05 was a phase II randomized trial comparing sequential versus concurrent CTRT in poor-risk patients with inoperable stage III NSCLC [43]. Eligible patients had at least one of the following characteristics: age ≥75 years, PS 2, weight loss ≥5%, creatinine clearance <60 ml/min, a comorbid condition precluding the patient from being treated in a protocol for fit patients. Forty-six patients were treated in the concurrent CTRT arm with two cycles of carboplatin plus vinorelbine regimen and thoracic radiotherapy (60 Gy in 30 fractions). Toxicity was low and the median overall survival was 16.8 months.

The Japanese Clinical Oncology Group study 9812 was a phase III trial randomly assigning patients >70 years (median age 77 years, range 71–84 years) with stage III NSCLC to either radiotherapy alone (including elective nodal irradiation) or in combination with concurrent daily carboplatin [44]. This trial was stopped early, when only 46 patients had been randomized, due to four treatment-related deaths. A new phase III trial (JCOG0301) was initiated with a similar design to JCOG9812, but including a strict radiotherapy quality-assurance programme [45]. Two hundred patients older than 70 years with unresectable stage III NSCLC were randomized in this phase III study. Patients ≥71 years (age range 71–93 years) were included if deemed unsuitable for cisplatin-based chemotherapy. Patients were randomly assigned to concurrent CTRT (60 Gy in 30 fractions plus concurrent low-dose carboplatin 30 mg/m² per day, 5 days a week for 20 days) or radiotherapy alone. The trial was stopped early as a result of the second planned interim analysis. The concurrent CTRT group achieved a higher median overall survival (22.4 months, 95% CI 16.5–33.6) compared with the radiotherapy alone group (16.9 months, $P = 0.0179$). However, toxicity was more pronounced in the CTRT group including grade 3–4 haematological toxicity (neutropenia 55% versus 0%, thrombocytopenia 28% versus 2% and grade 3 infection 12.5% versus 4.1%). Incidences of grade 3–4 pneumonitis and late lung toxicity as well as treatment-related deaths (3% versus 4%) were similar between groups. All these studies have been summarized in Table 3.

An elderly specific concurrent CTRT trial is recruiting in France. In this Groupe Francais de Pneumo-Cancerologie (GFPC) phase II study, stage III NSCLC patients older than 70 years and PS ≥1 and assessed as fit by a geriatric assessment are treated with concurrent CTRT that consists of weekly cisplatin
**Table 3. Summary of clinical trials assessing concurrent chemo-radiotherapy in poor-risk patients with stage III NSCLC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients’ characteristics</th>
<th>Treatment</th>
<th>N</th>
<th>Treatment completion rate</th>
<th>Median survival, months (95% CI)</th>
<th>Toxic deaths</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG S9424 [40]</td>
<td>Not eligible for CDDP-based treatment and/or severe COPD (72%); PS 2 or poor nutritional status (17%); renal insufficiency (12%); hearing loss (13%); controlled CHF (12%); peripheral neuropathy (8%)</td>
<td>CBDCA, VP16 × 2 cycles with chest RT (61 Gy)</td>
<td>60</td>
<td>87%</td>
<td>13 (11–14)</td>
<td>0</td>
<td>50% ≥G3 leucopenia, 23% ≥G3 thrombocytopenia, 15% ≥G3 oesophagitis, ≥G3 pneumonitis not observed</td>
</tr>
<tr>
<td>SWOG S9712 [41]</td>
<td>Not eligible for CDDP-based treatment and/or severe COPD (31%); PS 2 or poor nutritional status (38%); renal insufficiency (13%); hearing loss (15%) or controlled CHF (3%)</td>
<td>CBDCA, VP16 × 2 cycles with chest RT (61 Gy) and consolidation with paclitaxel × 3 cycles</td>
<td>87</td>
<td>82% completed CTRT and only 46% consolidation</td>
<td>10.2 (7.2–12.6)</td>
<td>8%</td>
<td>During concurrent CTRT: 42.5% ≥G3 neutropenia, 7% G3 oesophagitis, 3% ≥G3 pneumonitis; During consolidation CT: 9.6% ≥G3 neutropenia, 1.5% ≥G3 pneumonitis</td>
</tr>
<tr>
<td>Semrau [42]</td>
<td>Poor-risk factors: PS 2; cardiac, pulmonary or renal failure; extensive weight loss or age 71–78 years</td>
<td>CDDP/CBDCA, VNR × 2 cycles with chest RT (63 Gy)</td>
<td>66</td>
<td>62%</td>
<td>14 (11–17)</td>
<td>0</td>
<td>Most toxic deaths related to infection 42% ≥G3 leucopenia, 27% ≥G3 thrombocytopenia, 3% ≥G3 oesophagitis, 3% G3 pneumonitis</td>
</tr>
<tr>
<td>SLCG 00-05 [43]</td>
<td>Patients with at least one of the following: &gt;75; PS 2 (26%); weight loss &gt;5% (29%); renal insufficiency (26%); other comorbidities (70%)</td>
<td>CBDCA, VNR × 2 and sequential RT (60 Gy); CBDCA, VNR × 2 with concurrent RT (60 Gy)</td>
<td>45</td>
<td>93%</td>
<td>16.8 (9.5–24)</td>
<td>0</td>
<td>Sequential arm: 14% ≥G3 neutropenia, 14% ≥G3 dyspnoea, no ≥G3 oesophagitis; Concurrent arm: no ≥G3 haematological toxicity, 9% ≥G3 dyspnoea, 2% ≥G3 oesophagitis</td>
</tr>
<tr>
<td>JCOG 0301 [45]</td>
<td>Patients not eligible for CDDP-based treatment and/or age ≥71 years. Few patients with PS 2 (3.5%) and &gt;5% weigh loss (16%) were included</td>
<td>RT alone (60 Gy); Chest RT (60 Gy) with daily low-dose CBDCA</td>
<td>100</td>
<td>93%</td>
<td>16.9 (13.4–20.3)</td>
<td>4%</td>
<td>RT arm: ≥G3 pneumonitis, acute 3.1% and late 5.3%; CTRT arm: 57.3% ≥G3 neutropenia, 29.2% ≥G3 thrombocytopenia, 1% ≥G3 oesophagitis, ≥G3 pneumonitis 1% acute and 6.5% late</td>
</tr>
</tbody>
</table>

AE, adverse event; CBDCA, carboplatin; CDDP, cisplatin; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CTRT, chemo-radiotherapy; JCOG, Japanese Clinical Oncology Group; PS, performance status; SLCG, Spanish Lung Cancer Group; SWOG, Southwestern Oncology Group; RT, radiotherapy; VNR, vinorelbine; VP16, etoposide.
and oral vinorelbine concurrently with thoracic radiotherapy (66 Gy in 33 fractions) (RACCOSSA, GFPC 08-06). The primary end point is early treatment tolerance [46].

**trials with biological or targeted therapies**

The RTOG tested in a phase III study the efficacy of β-interferon in 123 poor-risk patients with stage III NSCLC (RTOG 93-04) [47]. Patients had either KPS 50–70 or >70 and at least 5% weight loss over the preceding 3 months. In both arms thoracic radiotherapy (60 Gy in 30 fractions) was given and patients randomized to the investigational arm were given β-interferon by IV bolus 3 days a week on weeks 1, 3 and 5. There was no significant difference in survival, but the use of β-interferon led to greater rates of both acute and late treatment-related toxicity.

The combination of epidermal growth factor receptor (EGFR) inhibitors with radiotherapy has been explored over the last 10 years [48]. The monoclonal antibody cetuximab and the tyrosine kinase inhibitors such as gefitinib and erlotinib have been tested (Table 4). Some of the studies with these agents, which are in general better tolerated than standard systemic chemotherapy, have been carried out in patients with poor-risk characteristics. It is unknown how best to integrate these agents into CTRT protocols and whether the addition of those agents might improve the outcomes in unselected patient populations [53].

The NCCTG conducted a phase II study which tested cetuximab plus radiotherapy in elderly and/or poor performance status patients with stage III NSCLC [49]. Fifty-seven patients with either age ≥65 years and PS ≤2 or younger patients with PS 2 received cetuximab at standard weekly doses with concomitant thoracic radiotherapy (60 Gy in 30 fractions). The primary end point was survival at 11 months. Forty of 57 patients (70%) lived ≥11 months, thus exceeding the anticipated survival rate of 50%. There were no treatment-related deaths, and the median survival was 15.1 months (95% CI 13.1–19.3 months).

The NEAR trial investigated the combination of intensity-modulated radiotherapy and cetuximab in patients with stage III NSCLC deemed unfit for concurrent CTRT due to comorbidities [50]. In this phase II study, patients received a loading dose of cetuximab (400 mg/m²) 1 week before radiotherapy followed by weekly infusions (250 mg/m²) given concurrently with thoracic radiotherapy (66 Gy in 33 fractions). This was followed by a 13-week maintenance period. The study enrolled 33 patients with a median age of 71 years (range 57–82 years). Median overall survival was 19.5 months, with an estimated 1- and 2-year survival of 66.7% and 34.9%, respectively. Only one patient developed grade 3 pneumonitis.

Using a similar treatment approach, the SWOG group reported a pilot study (SWOG S0429) of weekly cetuximab and thoracic radiotherapy for poor-risk stage III NSCLC [51]. Patients with PS 0–1, poor pulmonary function (FEV1 <2 l) and/or comorbidities prohibiting concurrent CTRT, or PS 2 were eligible. A loading dose of cetuximab (400 mg/m²) was given in week 1, followed by weekly cetuximab (250 mg/m²) with thoracic radiotherapy (64.5 Gy in 36 fractions), and maintenance weekly cetuximab (250 mg/m²) for 2 years or until evidence of disease progression. Twenty-four patients with a median age of 72.9 years were recruited. The estimated 1-year overall survival was 55% (95% CI 32% to 72%) and estimated MS was 14 months (95% CI 8–24 months). Toxicity was moderate and there were no grade 5 adverse events.

The CALGB published a stratified phase II trial which studied the addition of gefitinib to sequential or concurrent CTRT in unresectable stage III NSCLC with wild-type or mutated EGFR [52]. Patients were treated with two cycles of induction paclitaxel and carboplatin plus gefitinib. Poor-risk stratum 1 (≥5% weight loss and/or PS 2) received standard high-dose radiotherapy (66 Gy) with gefitinib 250 mg daily. Good-risk stratum 2 (≤5% weight loss and PS 0–1) received the combination of radiotherapy and gefitinib plus weekly paclitaxel (50 mg/m²) and carboplatin (AUC 2). Consolidation gefitinib until progression was started after all toxicities were ≤2. The study was closed early after only 21 patients had been accrued in the poor-risk stratum 1 and 39 in the good-risk stratum 2. Strikingly, poor-risk patients had a median survival of 19 months (95% CI 9.9–28.4), whereas median survival of good-risk patients was 13 months (95% CI 8.5–17.2). Survival of good-risk patients with tumours harbouring an EGFR mutation was equally disappointing. There was no clear increase in acute high-grade in-field radiotherapy toxicities in either arm. Two patients died during induction chemotherapy (one in each stratum) from febrile neutropenia and pneumonia.

The CALGB 30605 study is a recently completed phase II study, which tested two cycles of induction chemotherapy with carboplatin and nab-paclitaxel followed by concurrent erlotinib and radiotherapy (66 Gy) in patients who poor-risk characteristics (PS 2 and or weight loss ≥10%). Mature results from this study are awaited.

**discussion and future directions**

Fit older adults with unresectable stage III NSCLC appear to have a similar survival benefit from standard concurrent CTRT as younger patients with increased rates of haematological toxicity, but it should be noted that age-specific subgroup analyses were not pre-planned in the trials detailed above. Moreover, only a small proportion of elderly patients were included in those studies, which were not powered to detect minor differences in outcomes between age-specific subgroups. Finally, the elderly patients included in these studies are not fully representative of the average elderly patients as PS was generally restricted to 0–1, few patients were ≥75 years and almost none ≥80 years. In the absence of reliable information from clinical trials, we currently rely on clinical judgement and multidisciplinary discussion to select elderly patients for concurrent CTRT. The need for a validated characterization of fit elderly patients was first discussed several years ago [54] and the geriatric assessment should help in selecting those patients likely to benefit for the standard treatment approach regardless of their chronological age.

The JCOG 0301 study [45] is of great interest because it was the first published randomized phase III trial specifically addressing concurrent CTRT in an elderly population and because it demonstrated that the use of low-dose radio-sensitizing chemotherapy led to better survival than radiotherapy alone. However, its applicability to a standard elderly population should be discussed since 96.5% of the patients enrolled had a PS of 0–1 and
Table 4. Summary of clinical trials assessing concurrent treatment with EGFR-targeted agents and thoracic radiation in poor-risk patients with stage III NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients’ characteristics</th>
<th>Treatment</th>
<th>N</th>
<th>Treatment completion rate</th>
<th>Median survival, months (95% CI)</th>
<th>Toxic deaths</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCTG N0422</td>
<td>≥65 years (93%) or &lt;65 years PS 2 (21%)</td>
<td>Cetuximab weekly concurrent with chest RT (60 Gy)</td>
<td>58</td>
<td>86%</td>
<td>15.1 (13.1–19.3)</td>
<td>0</td>
<td>53.4% ≥ G3 toxicity (9% dyspnoea or fatigue and 7% rash or dysphagia)</td>
</tr>
<tr>
<td>NEAR [50]</td>
<td>Refused or unfit for conventional CTRT. COPD (60%); Coronariopathy (53%)</td>
<td>Cetuximab weekly concurrent with chest IRMT RT (66 Gy) and then 13-week maintenance with cetuximab</td>
<td>30</td>
<td>90%</td>
<td>19.6 (11.5–24.7)</td>
<td>10%</td>
<td>36.6% G3 toxicity (most common G3 AE was pneumonia) and 1 G4 (pericardial effusion) 3 G5 AE (1 sepsis, 1 pulmonary embolism and 1 bacterial endocarditis) considered unrelated with the treatment</td>
</tr>
<tr>
<td>SWOG S0429 [51]</td>
<td>Poor pulmonary function and/or comorbidities precluding CTRT or PS 2 (23%)</td>
<td>Cetuximab weekly concurrent with chest RT (64.8 Gy) and 2-year maintenance with cetuximab</td>
<td>24</td>
<td>91% total dose of RT and 18% maintenance with cetuximab</td>
<td>14 (8–17)</td>
<td>0</td>
<td>22.7% ≥ G3 non-haematological toxicity 14% G4 AE (1 pulmonary embolism, 2 hypomagnesaemia)</td>
</tr>
<tr>
<td>CALGB-30106 [52]</td>
<td>Stratums: Poor risk (PS 2 or weight loss ≥5%) Good risk (PS 0–1 or weight loss &lt;5%)</td>
<td>Induction with CBDCA, paclitaxel + gefitinib* ×2 cycles and then sequential RT plus: Gefitinib Weekl</td>
<td>21</td>
<td>NR</td>
<td>19 (9.9–28.4)</td>
<td>5%</td>
<td>During the induction with CT and gefitinib, two patients (one from each stratum) G5 febrile neutropenia and pneumonia TKI-RT group: 42.8% ≥ G3 neutropenia, 19% ≥ G3 oesophagitis, ≥ G3 pneumonitis 14.2% CTRT group: 38.4% ≥ G3 neutropenia, 31% ≥ G3 oesophagitis, ≥ G3 pneumonitis 15.4%</td>
</tr>
</tbody>
</table>

*Gefitinib was removed from induction when phase III trials showed no benefit of adding gefitinib to CT in advanced NSCLC. Gefitinib was administered as a maintenance therapy in both arms after completing the RT. The study was closed early due to results from SWOG S0023 which showed inferior survival for subjects who received adjuvant gefitinib after CTRT.

AE, adverse event; CALGB, Cancer and Leukemia Group B; CBDCA, carboplatin; COPD, chronic obstructive pulmonary disease; CTRT, chemo-radiotherapy; CT, chemotherapy; NCCTG, North Central Cancer Treatment Group; PS, performance status; SWOG, Southwestern Oncology Group; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
<10% of the patients had severe comorbidities such as cerebrovascular disease, arrhythmia or ischaemic heart disease. Furthermore, the control arm of radiotherapy alone is not considered standard in fit, selected elderly patients with stage III disease.

However, radical radiotherapy can be considered a reasonable treatment option in less selected elderly patients as suggested by a SEER-based analysis. This study included 10736 patients with unresected stage III NSCLC, older than 65 years and demonstrated that radiotherapy alone was associated with improved overall survival (HR = 0.76; 95% CI 0.74–0.79) after controlling for propensity scores [55]. Future studies should compare regimen similar to that of the experimental arm of JCOG 0301 to radiotherapy alone using optimal planning, delivery and verification techniques in a more vulnerable elderly population. A phase II randomized study design could provide insight into the tolerability of the experimental arm. If the experimental regimen was tolerable a follow-on randomized phase III trial would be necessary to show a benefit in overall survival. A validated geriatric assessment should be incorporated and used in patient selection, although it is still not clear which are the best criteria and tests to be used to optimally discriminate vulnerability from frailty [56].

As EGFR inhibitors result in milder toxicity than chemotherapy, poor-risk patients have been included in trials with those agents and the tolerability of tested drugs has been confirmed, but in terms of efficacy the results are inconclusive (50–53). It should be stressed that cetuximab when added to concurrent CTRT in a recently reported large phase III trial, RTOG 0617, failed to improve survival [57] and further research with this drug in unresectable stage III NSCLC seems unwarranted.

Clinical trials targeting poor-risk patients can be difficult to recruit to. There is a perception among physicians that survival for these patients is poor, and that the use of toxic combination of systemic therapy and radical radiotherapy is not justified. Furthermore, oncologists may not always have the necessary training and time to address potential multiple medical problems related to comorbidities [58]. Insufficient interest from the pharmaceutical industry may be another barrier [56].

Future studies should also consider that histological and genetic information has changed the therapeutic landscape of lung cancer [59, 60]. Incorporation of genomic information in the treatment of stage III NSCLC is a challenge for further research including in poor-risk patients [61].

In conclusion, there is an unmet need to develop tolerable combinations of systemic therapy with radiotherapy for this lung cancer population. These combinations should be tested in the context of well-designed clinical trials. The characterization of patients selected for those trials should include comorbidity measurement and when appropriate geriatric assessment.

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references
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Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†


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Background: Screening tools are proposed to identify those older cancer patients in need of geriatric assessment (GA) and multidisciplinary approach. We aimed to update the International Society of Geriatric Oncology (SIOG) 2005 recommendations on the use of screening tools.

Materials and methods: SIOG composed a task group to review, interpret and discuss evidence on the use of screening tools in older cancer patients. A systematic review was carried out and discussed by an expert panel, leading to a consensus statement on their use.

Results: Forty-four studies reporting on the use of 17 different screening tools in older cancer patients were identified. The tools most studied in older cancer patients are G8, Flemish version of the Triage Risk Screening Tool (fTRST) and Vulnerable Elders Survey-13 (VES-13). Across all studies, the highest sensitivity was observed for: G8, fTRST, Oncogeriatric screen, Study of Osteoporotic Fractures, Eastern Cooperative Oncology Group-Performance Status, Senior Adult Oncology Program (SAOP) 2 screening and Gerhematolim. In 11 direct comparisons for detecting problems on a full GA, the G8 was more or equally sensitive than other instruments in all six comparisons, whereas results were

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