Locally Advanced NSCLC and its management in the Elderly

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Topics covered

- Concurrent Chemoradiotherapy (conCRT) in elderly
- Radiotherapy for elderly
- Chemotherapy in elderly
  - Including adjuvant
- Prognostic and assessment tools
- **Not covering:** targeted therapy or surgery
Lung cancer and the elderly

Who is “elderly”?  

- >65, >70, >75?  
- NCCN clinical guidelines suggest 3 categories:  
  1) young old 65-75,  
  2) old 75-85,  
  3) >85 oldest old  
  (Hurria et al, J Natl Compr canc Netw 2012)

- 50% patients are >70yo at diagnosis  
- Large proportion of clinical practice and rising…
How are the elderly treated?

2 key SEER population-based database studies in LA NSCLC in >65yo.

• **Davidoff et al, JTO 2011**
  – 6000+ patients
  – **only 2/3rds received ANY treatment:**
  – Of these 45% combined modality Rx
  – **CT + RT improved survival** vs RT alone

• **Berry et al, JCO 2013**
  – 2004-7 almost 3000 >65yo.
  – **18% no Rx,**
  – Worse survival with increasing age, higher T stage, Charlson Comorbidity index, **No** treatment!
Trials and the elderly

• Elderly are under-represented in clinical trials (multifactorial reasons)

• Trials designed for elderly NSCLC demo
  – lower rates of adverse s/e
  – no difference in survival compared with elderly subsets in age-unspecified trials.

• Few pxs with LA NSCLC would meet age or PS restrictions for Con CRT let alone in context of trial entry
  (De Ruysscher et al, Ann Oncol 2009)
Radiotherapy in elderly


- Elderly benefit in same way as younger patients
- Christie data (260 px >80yo) MS 16.7mths 90/7 mortality 1.6%

- ConCRT, however, should be used with caution.

- Adjuvant RT not recommended for elderly given lack of benefit in general population.

EORTC Elderly task force Pallis et al, Ann Oncol 2013
Risks of radiotherapy in the elderly

- Signif risk factors for \textbf{radiation pneumonitis (RP)} $\geq$ G3 are:
  - Older age $\geq$70
  - Presence of co-morbidity

- Significantly increased risk of \textbf{vertebral fracture} with IMRT:
  - Increasing age
  - Increasing vertebral dose (Uyterlinde W. et al. Radiother Oncol 2016)
Concurrent Chemoradiotherapy

Standard of care for inoperable LA NSCLC
Auperin Meta-analysis JCO 2010

- ConCRT = absolute increase of 4.5% in 5YS vs sequential
  - Con CRT increases toxicity.
  - No age-based differences in survival seen (16% ≥70)

- Single institution retrospective studies (>yr 2000) demo elderly derive benefit from CMT.
JCOG trial (Atagi et al, Lancet Oncol 2012)

- ph 3 200 patients ≥ 70yo inoperable 3B NSCLC

ConCRT (60Gy + carbo 30mg/m2 daily x 5 days/wk for 20 days)
RT alone

<table>
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<tr>
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<th>ConCRT</th>
<th>RT alone</th>
<th>CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Median OS (mths)</td>
<td>22.4</td>
<td>16.9</td>
<td>0.47-0.98</td>
<td>0.0179</td>
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**Conclusion:**
- clear evidence of benefit for ConCRT in elderly
- BUT increased toxicity, so choose carefully
- **No** differences in G3-4 pneumonitis and late fibrosis.
North Central Cancer Treatment group
(Schild et al, Cancer 2007)

<table>
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<th>Cis/etop + RT</th>
<th>RT alone</th>
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<tr>
<td>Median survival (mths)</td>
<td>13.7</td>
<td>10.5</td>
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<tr>
<td>5YS</td>
<td>14.7%</td>
<td>5.4%</td>
<td>P=0.05</td>
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<tr>
<td>≥G3 toxicity</td>
<td>89.9</td>
<td>32.4</td>
<td>P&lt;0.01</td>
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Combination of 2 trials within CALGB
(Rocha et al, Cancer 2002)

- Cis/vin followed by RT vs conCRT
- Increased toxicity (≥3 neutropenia and renal toxicity)
- BUT age not a factor in survival or tumour response rate
A systemic review and meta-analysis.

- 400+ pxs
- CRT vs RT alone >70yo st 3 NSCLC
- OS favoured CRT (HR 0.66) so did PFS (HR 0.67)
- No signif difference in risk of death and G3+ pneumonitis between groups
- *Only haematogical toxicity increased*

**Conclusion**

- CRT tolerable in fit elderly and
- represents a reasonable Std of care.

Dawe DE et al, Lung cancer 2016
Advanced NSCLC in elderly

“In dog years, you would only be 7 years old. Chase some squirrels and see if it makes you feel younger.”
Issues with being “old”.

- Old age frequently associated with
  - several co-morbidities
  - Poor general condition
  - Physiological reduction in organ function

- This makes the elderly at greater risk of toxicity from chemotherapy and biological therapy
2 key ph 3 trials for chemo in elderly with advanced NSCLC

**ELVIS** (Gridelli c. Oncologist 2001)
- MS - SA vinorelbine 28wks vs 21wks BSC
- Toxicity worse in CT group **BUT** QOL better.

**MILES ph 3 study** (Gridelli C et al. J Natl Cancer Inst. 2003):
- Vin/gem vs SA vin vs SA gem (NB no platinum)
- Doublet (non-plat)↑ risk of death (HR1.17) & more toxic so **SA for unselected elderly on this basis**
Recent trials favouring doublet in selected Pxs

- **Ansari et al, Crit Rev Oncol Haematol 2011**
  - Ph 3 trial **Good PS 0-1 with 1135 pxs - 30% >70yo**
  - Gem/carbo vs gem/paclitaxel vs carbo/paclitaxel
  - OS comparable <70yo vs >70yo (~8mths) & tolerable.

- **Quoix et al, Lancet 2011**
  - Ph 3 451 pxs ≥ 79 yo **PS ≤2**
  - Carbo/pac vs SA vin or SA gem
  - MS with carbo/pac 10.3 vs 6.2 SA chemo (p < .0001)
  - Doublet myelosuppression and myasthenia but tolerable
Doublet favoured evidence continued

- **Qi et al 2012**
  - Doublet vs SA at first line = benefit with doublet

- + Age-based sub-analyses of other trials & review – similar benefits

- **Santos FN review article, 2016**
  - plat doublets vs non- plat doublets better survival (HR 0.76 95% CI 0.69-0.85) mod quality evidence
Recommendations for Chemotherapy in ADVANCED NSCLC in the elderly

- **Non-selected** Patients (EORTC Task force 2010/13)
  - S/A 3rd generation drugs (vinorelbine, gemcitabine, taxanes)
- **Selected** Patients
  - consider platinum-based combination CT

- Efficacy of plat-based CT is similar in FIT older and younger pxs
  - ASCO 2009- doublet chemo has an acceptable increase in toxicity for elderly patients
  - age alone should not be criteria of choice for best treatment
Adjuvant chemotherapy
Adjuvant chemotherapy

**Background:** LACE M/A and JBR10 suggest elderly benefit from adj CT, but under-represented in trials so reproducibility of results?

**2 key adjuvant trials:**

- **A Canadian pop-based study of adj CT (Cuffe et al, JCO 2012).**
  - 6300 px and 44% ≥70yo
  - 70% cis- based and 28% got carbo-based adj CT
  - Hospitalisation rates were similar across all age groups (~28%) across the age groups
  - Survival increased in all subgroups except ≥80yos
Key adj CT trials continued

- Veterans Administration Cancer Registry
  - >10,000 pxs (39% >70yo)
  - Of those getting adj CT, a smaller % of older pxs got cis-plat based (86.4% vs 91.8% p<0.001)
  - 3YS for elderly st 2 and 3 getting cis-based chemo (55%) vs carbo-based (42%) or no adj (35%) (Ganti et al, JCO 2013)
Conclusions for Adj CT

- Cis-based adj chemo is appropriate for selected healthy older patients.

- Despite receiving lower chemo total dose, elderly appear to derive same survival benefit.

- In >80yos, benefit of adj CT has NOT been established so use with extra caution.

- Carbo-based adj CT may have modest benefit, but no prospective trials to confirm. Caution with use.
Targeted agents (TAs)

• **Systematic rv and M/A: efficacy of TA in elderly with advanced NSCLC** (Chen et al, Oncol Targets Ther 2016)

  – 4000+ elderly from 17 RCT
  – Addition of TAs to 1\textsuperscript{st} line chemo vs chemo alone
    • signif increased PFS (HR 0.85, P<0.01)
    • tendency to increase OS (HR 0.92, P=0.064)
    • **Further trials needed**
Real case

- 79yo lady PS 1
- LUL adenocarcinoma T1a N2 M0. ALK and EGFR –ve.
- PMH: left breast Ca 1993 – Left WLE, ANC & breast RT
- Newly diagnosed of CCF (on scan), known AF, previous MI.
- Aspirin, Fruseamide 40mg od, Bisoprolol.
- Lives alone independently, supportive family, ex-smoker 65 pack year
Her management options:

• ConCRT
• Sequential CRT
  – If chemo: regimen/no. of drugs?
• Radical RT
• Palliative RT now or if symptomatic
• BSC
Her case

• Alternatives to chemo offered.

• Proceeded with dose reduced chemo:
  – gemcitabine (1000mg/m²) and carbo AUC 5
  – monitored closely.

• Consented for increased risk of clots and stroke as well as potential exacerbation of existing cardiac disease.
How did it go?

• G1 mucositis and fatigue
• Scan post C2 chemo – slight reduction (not PR) in LNs, stable primary.
• Admitted post C3 Day 10 with LRTI and diarrhoea – not neutropenic.
• C4 delayed by 1 week.
• Referred to me for radical RT.
• Post chemo CT scan- stable.
• Now PS 3 - profound fatigue 1 week post chemo.
Add a month to recover from chemo

- PS2 now at worst & improving
  - light housework jobs, getting meals, gaining weight, fatigue much better.

- Options: radical vs palliative radiotherapy
  - NB previous left breast cancer radiotherapy.

- Decided radical daily RT 50Gy/20 daily fractions over 4 weeks
  - PTV 336cm³ V20 29%
Tricky delivery of radiotherapy: a moving target!

- Progressive dyspnoea consistent with cardiac failure
- Pleural effusion threatening tumour coverage.
- Responded well to increased diuretics
- Now awaiting FU scan…
Approach to decision making in elderly with LA NSCLC

- Chronologic age alone is not reliable in estimating:
  - life expectancy,
  - functional reserve,
  - the risk of treatment complications.

- PS and comorbidity predict for M & M in NSCLC even after adjustment for age and stage
  
  (Maione et al, Ther Adv Med Oncol. 2010)
EORTC Elderly task force Lung Cancer 2013* & NCCN guidelines 2012**

Take into account:
• the estimated absolute benefit,
• life expectancy,
• treatment tolerance,
• cognition,
• Social support
• presence of comorbidities and
• patient preferences.

*Ann Oncol 2013, **Hurria et al, Natl Compr Canc Netw 2012
Comprehensive Geriatric Assessment (CGA)

- **CGA components**
  - comorbid conditions,
  - functional status,
  - geriatric syndromes, and
  - nutritional status

- Associated with the tolerance of cancer treatment and survival in elderly patients with cancer.

- Even with good PS, prevalence of geriatric syndromes is high eg cognitive impairment (70%) (Schulkes KJ et al. Lung Cancer 2016)

- Better baseline QOL and greater facility with ADLs is associated with improved survival (Maione et al, JCO 2005)
How to implement a practical GA

- CGA impractical for all.
- Initial simpler screening assessments can direct those at higher risk towards full CGA.

- Patient self-administered versions of GA now avail

- CARG (Cancer and aging research group) score (Hurria et al, JCO 2011).
  - Predicted for chemotherapy induced toxicity across tumour types and stages.
  - Good correlation of this score and adverse events in NSCLC elderly chemo pxs (Nie et al, J Geriat Oncol 2013).
Conclusion

• Selection is key
• Treat according to key guideline factors— not chronological age.
• Don’t under-treat because of age.
• Recruit to trials & design trials to prospectively evaluate.
• Lack of evidence in octogenarians