Combined modality treatment for N2 disease

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Overview

- Background
- The evidence base
  - Systemic treatment
  - Radiotherapy
- Future directions/clinical trials
Background

• 25-30% of NSCLC pts have stage III disease

• Few locally advanced NSCLC patients are candidates for surgery

• Survival is poor
  • stage IIIA  10-25% 5 year survival

• Scope for improving local and distant control
Radical treatment options for N2 disease

- Surgery
- Radiotherapy alone
- Sequential chemo-radiotherapy
- Concurrent chemo-radiotherapy
- Trimodality treatment
Radical treatment options for N2 disease

- Surgery
- Radiotherapy alone
- Sequential chemo-radiotherapy
- Concurrent chemo-radiotherapy
- Trimodality treatment
Sequential chemoradiotherapy

• BMJ metanalysis 1995:
  • hazard ratio of 0.87 in favour of combined treatment
  • 13% reduction in the risk of death
  • Absolute benefit of 4% at two years

• Heterogeneity in chemotherapy regimens and radiotherapy schedules used
Concurrent chemoradiotherapy

- Auperin metanalysis 2010:
  - Concurrent CTRT superior to sequential
  - HR 0.83 overall survival in favour of concurrent
  - 4.5% survival benefit at 5 years
  - Significantly higher oesophagitis rate (HR 4.9)
  - similar pneumonitis rate

Anne Aupérin et al. JCO 2010;28:2181-2190
Concurrent chemoradiotherapy

- **RTOG 9410**
  - Concurrent CTRT superior to sequential
  - 5 yr survival 16% v 10% (p=0.046)
  - Acute G3-5 toxicity higher with concurrent
  - Late toxic effects similar

_Walter J. Curran, Jr et al. JNCI J Natl Cancer Inst 2011;103:1452-1460_
Patient selection

- Performance status
  PS 0-1
- Co morbidities
- PET
  Encompassable within radical field
- Mediastinal staging
- Brain imaging
- Pulmonary function testing
  - FEV$_1$ > 40%
  - KCO >40%
- Age
Which chemotherapy?

- Platinum based chemo with 3\textsuperscript{rd} generation drugs
  - Taxol/Gemcitabine/Vinorelbine given at reduced doses
  - Cisplatin/Etoposide can be combined at full dose with RT

- ? Emerging role for Carboplatin/Paclitaxel

- No benefit of Pemetrexed in concurrent setting (PROCLAIM trial)

Senan, JCO 2016
More chemo

- Concurrent CTRT optimises local control but distant spread is still a major problem

- Further systemic-dose CT to optimise treatment of distant disease
Induction chemotherapy - CALGB 39801

- Randomised Ph III trial
- Induction chemo/CTRT v CTRT alone
### Consolidation chemotherapy - HOG 01-24

**Stage IIIAN2/IIIB**
- 203 pts
- Cisplatin 50mg/m²
  - D1,8,29,36
- Etoposide 50mg/m²
  - D1-5 and D29-33
- RT 59.4 Gy/6w

**Docetaxel 75 mg/m²/3 w x 3 cycles**

**Observation**

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<table>
<thead>
<tr>
<th>After randomisation</th>
<th>Docetaxel n=73</th>
<th>Observation n=74</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>11%</td>
<td>0%</td>
<td>0.003</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>9.6%</td>
<td>1.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Deaths attributed to RT</td>
<td>5.5%</td>
<td>0%</td>
<td>0.058</td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>28.8%</td>
<td>8.1%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>21.2</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>3 yr survival</td>
<td>27.1%</td>
<td>26.1%</td>
<td>0.88</td>
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</tbody>
</table>
Consolidation chemotherapy -KCSG-LU05-04

- Multicentre randomised Ph III trial
- CTRT alone v CTRT + Cis/Docetaxel consolidation
- n=437
Targeted agents/Immunotherapy

• No phase III evidence to support the use of TKI in the concurrent setting

• Role of consolidation immunotherapy being investigated in PACIFIC trial
**PACIFIC trial**

*Patients with unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation N = 702*

**Day 1** Max 42 days after the end of chemoradiation

**Arm 1**
- MEDI4376
- 10mg/kg Q2W for up to 12 months (MAX 26 doses)

**Arm 2**
- Placebo (matching placebo for infusion Q2W iv for up to 12 months (MAX 26 doses)

**Re-treatment for patients who have experienced disease control at end of 12 months treatment but progressed during follow-up**

MEDI4736 will commence treatment on Day 1 and continue on a Q2W schedule for a maximum of 12 months (26 doses) or until PD–IV administration

* Disease progression requires confirmation, treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression.
Radiotherapy planning

- RT commences D1 chemotherapy
  - RT planning scan done asap

- Motion management
  - 4D CT
  - Respiratory gating/Breath hold

- Advanced RT techniques
  - IMRT
  - IGRT
4D CT
Intensity Modulated Radiotherapy (IMRT)

- Improved conformity
- Avoidance of radiosensitive structures eg spinal cord
- Retreatments
- Large volumes
What RT?

• Sequential CTRT
  • 60-66Gy/30-33# OD
  • 55Gy/20# OD
  • 54Gy/36# TDS (CHART)

• Concurrent CTRT
  • 60-66 Gy in 30-33 fractions OD
More radiotherapy?

- Greater local control correlates with improved survival
- Modern RT techniques allow dose escalation
- Recent RTOG 0617 study
  - No defined role for dose escalation
RTOG 0617

- Higher dose arm:
  - Greater risk of locoregional failure
  - Poorer survival

![Local Progression Rate](image)

- **Local Progression Rate (%):**
  - Months since Randomization 0, 3, 6, 9, 12, 15, 18
  - Patients at Risk: Standard 213, High dose 206
  - Fail 65, Total 213, HR = 1.37 (0.99, 1.89), p = 0.0319

![Survival Rate](image)

- **Survival Rate (%):**
  - Months since Randomization 0, 3, 6, 9, 12, 15, 18
  - Patients at Risk: Standard 213, High dose 206
  - Dead 90, Total 213, HR = 1.56 (1.19, 2.06), p = 0.0007
Chemoradiotherapy – summary

- Gold standard: Concurrent platinum based CTRT
  - No consensus on chemo regimen
  - Modern RT techniques allow better sparing of normal tissue

- For patients unsuitable for concurrent treatment, sequential CTRT or radiotherapy alone

- No benefit to induction or consolidation chemotherapy

- No benefit to radiotherapy dose escalation with conventional fractionation
What combination of treatment is best for potentially resectable N2 disease?
EORTC 08941 – overall survival

Overall Logrank test: p=0.596

Intergroup 0139/RTOG 9309
Overall Survival by Treatment Arms

% Alive

Logrank p = 0.24
Hazard ratio = 0.87 (0.70, 1.10)

Dead/Total

CT/RT/S  145/202
CT/RT    155/194

Albain, Lancet. 2009 Aug 1;374(9687):379-86
Potentially resectable N2 disease – summary

• Trimodality treatment may have a role in selected operable cases

• No survival benefit to surgery over definitive CTRT
• Uncertain benefit of induction CTRT versus chemotherapy

• Importance of
  • Team working/MDT decision
  • Local surgical expertise (avoid pneumonectomies)
# Have we made progress in inoperable stage III NSCLC?

<table>
<thead>
<tr>
<th></th>
<th>Median survival (months)</th>
<th>2 yrs survival</th>
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<tbody>
<tr>
<td>RT</td>
<td>10</td>
<td>15%</td>
</tr>
<tr>
<td>CT → RT</td>
<td>14</td>
<td>30%</td>
</tr>
<tr>
<td>CTRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prePET era</td>
<td>17</td>
<td>35%</td>
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<tr>
<td>postPET era</td>
<td>24-26</td>
<td>Up to 60%</td>
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Future directions

- Individualised treatment
  - Personalised RT dose
  - ? Role of targeted agents

- Combinations with novel agents
  - Eg immunotherapy

- Proton therapy
ADSCaN
A Randomised Phase II study of Accelerated, Dose escalated, Sequential Chemo-radiotherapy in Non-Small Cell Lung Cancer

Histologically or cytologically confirmed stage III NSCLC fit for sequential treatment

Response or stable disease on CT assessment after 2 cycles of platinum based chemotherapy. Patients can receive 2-4 cycles in total.

Informed consent and screening procedures to be completed during last cycle of chemo

Centres can select to offer one or more of the following experimental regimens:

- **A** 55Gy in 20 fractions over 28 days (Control Arm)
- **B** CHART-ED: 54Gy in 36 fractions day 1-12 followed by 10.8 Gy in 6 fractions (days 15-17)
- **C** IDEAL Isotoxic radiotherapy 30 fractions, 5 weeks, dose individualised to a maximum dose to the oesophagus of 68 Gy
- **D** i-START: Isotoxic radiotherapy in 20 fractions over 4 weeks to a total dose of 55 – 63 Gy
- **E** Isotoxic IMRT: Isotoxic regime using IMRT in all patients, allowing for individualised dose escalation based on mean lung dose (maximum 20 Gy EQD2), spinal cord dose (maximum 50 Gy EQD2) and brachial plexus (maximum 66 Gy EQD2). The maximum total tumour dose (TTD) will be 79.2Gy in twice daily fractions of 1.8Gy delivered over 4 weeks
The Christie NHS Foundation Trust

T2-4 N0-3 M0

Primary tumor diameter > 4 cm

SUVmax > 5.0

Eligible for radical treatment (RT only, seq or conc)

Register

Dose Planning
Start dose 66 Gy in 24 fractions

<72 Gy Dose escalation not possible

radiotherapy to tolerance

> 72 Gy Dose escalation possible

RANDOMISED

RT
Homogeneous Boost (Arm A)

RT inhomogeneous Boost 50% SUVmax (Arm B)

Proceed with treatment plan for Arm A (boost entire primary tumour)
- If primary tumour dose < 72 Gy
  => patient treated up to this dose level (no randomization)
- If primary tumour dose ≥ 72 Gy
  ⇒ patient is randomized between Arm A and Arm B

Primary endpoint: LPFS at 1 year

PET boost- ARTFORCE

MLD 20 Gy
Med envelope and heart 76 Gy
Brachial Plexus 79 Gy
Spinal Cord 53 Gy
Oesophagus: V36 < 80%.
Patients with inoperable stage III NSCLC not suitable for concurrent chemoradiotherapy or stage IV patients with low metastatic disease burden

In the event of Dose Limiting Toxicities (DLT)

Dose level 1: n=3-6
Thoracic radiotherapy 60-66 Gy in 30-33#
With
Concurrent Pembrolizumab 200 mg q3w,
to start 2 weeks prior to RT
Maintenance Pembrolizumab for up to 12 months

Expanded cohort n=13
At RP2D
Maintenance Pembrolizumab for up to 12 months

Dose level -1: n=3-6
Thoracic radiotherapy 60-66 Gy in 30-33#
With
Concurrent Pembrolizumab 100 mg q3w,
to start 2 weeks prior to RT
Maintenance Pembrolizumab for up to 12 months
Take home messages

• Concurrent platinum based chemoradiotherapy remains gold standard for inoperable N2 disease

• No benefit to induction/consolidation chemo
• No benefit to dose escalation

• Trimodality treatment may be appropriate in selected operable cases

• Improved RT techniques may allow greater individualisation of treatment in the future
RTOG-EORTC randomised phase II study in stage III NSCLC with EGFR TK mutations or EML4-ALK fusion gene

Patients with EGFR TK or EML4-ALK fusion arrangement (done at a CLIA certified lab) will be enrolled

†Per treating physician’s discretion, a choice of the following chemotherapy regimens:
Cisplatin and etoposide every 4 weeks for 2 cycles
Paclitaxel and carboplatin weekly for 6 weeks followed by 2 cycles of consolidation
Pemetrexed 500 mg/m² and carboplatin AUC-5 every 3 weeks for a maximum of 4 cycles