Heuson Memorial Lecture
Lung Cancer
From the nihilism to some hope
The view point of a Radiation Oncologist
Van Houtte P
Institut Jules Bordet, Université Libre Bruxelles
PREVENTION : THE KEY MESSAGE

The mortality by lung ca is going down

But the production of cigarettes Worldwide is not decreasing!
Figure 4 – Age-adjusted 5-year survival from lung cancer in selected European countries among patients diagnosed 2000–2002 relative to that of the general population. Survival for the UK has been derived from estimates for England, Scotland, Wales and Northern Ireland and the average independently calculated. Data from EUROCare-4 study [www.eurocare.it].
Is it really so bad: the point of view of a radiation oncologist after 40 years treating lung cancer patients
A few cases

2009 NSCLC Large cell T4N2M0
Radiochemotherapy

2013 New nodule in left upper lobe
SBRT

2017 No evidence of disease
PS 0
Other stories

• 64 year old woman to-day
  2004  R breast Ca T2N0
    FEC taxotere mastectomy RT Aromasin
  2009  SCLC with 1 brain met (MRI)
    Chemotherapy chest and brain RT
  2011 adenoca R lower lobe wedge resection
  2015 local relapse : SBRT
  11/2016 new nodule : SBRT

• 76 year old man
  2012 stage IV adenocarcinoma  Carbo Pemetrexed
  7/2014 progression  Tarceva
  6/2015 progression  Carbo-Pemetrexed
  1/2017 progression  Nivolumab
Lung cancer: Negative view in ‘70
Our Middle Age

Oxford trial 1970-73

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<thead>
<tr>
<th>VA trial</th>
<th>1 Y S (%)</th>
<th>Median survival months</th>
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<tr>
<td>Radioth</td>
<td>22</td>
<td>5</td>
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<tr>
<td>Placebo</td>
<td>16</td>
<td>4</td>
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The tools available

Chest physician:
- Rigid bronchoscopy

Radiologists:
- Chest X-ray
- Tomography

Radiation oncologists:
- kV machines, Cobalt
- Non isocentric table
- Manual dosimetry, No IGRT

Medical oncologists:
- CTX, MTX, Procarbazine, Vinka, Doxo...
Postoperative Radiotherapy

Van Houtte et al
Int.J.Radiat 1980
Cobalt 60
No dosimetry except by hand one single plane
No CT but only a contour

Spinal cord bloc at 35 Gy!
But protection the mediastinal nodes!

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<th>Survival</th>
<th>Surgery</th>
<th>Postop RT</th>
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<tr>
<td>N1</td>
<td>1Y</td>
<td>71%</td>
<td>61%</td>
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<td>2Y</td>
<td>43%</td>
<td>43%</td>
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<td>N2</td>
<td>1Y</td>
<td>63%</td>
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<td>2Y</td>
<td>65%</td>
<td>43%</td>
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<td>3Y</td>
<td>21%</td>
<td>36%</td>
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MRC Trial
Brit.J.Ca 1996

This was the simulation film
The Renaissance 1980-2000 but

Radiotherapy: Linacs, CT & dosimetry from 2D to 3D
The dose-response relationship RTOG trial
Technological progress: exploring higher RT dose
Altered fractionation (CHART)

Chemotherapy: The Cisplatine story
Induction vs concurrent approach
Dillman (CALGB) & Schaake-Koning (EORTC) trials

The current dogma favoring the nihilistic approach
Local control is not an issue and an improvement will only be possible through a better systemic treatment leading to trials comparing chest RT to chemotherapy
DOSE RESPONSE RTOG TRIAL
Cancer 1980

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<tr>
<th>Schedule</th>
<th>Loc Rel</th>
<th>Med Surv Weeks</th>
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<tr>
<td>40 Gy/ 10 fr split</td>
<td>44</td>
<td>36</td>
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<tr>
<td>40 Gy/ 20 fr / 4 w</td>
<td>48</td>
<td>45</td>
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<td>50 Gy/ 25 fr / 5 w</td>
<td>38</td>
<td>41</td>
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<td>60 Gy/ 30 fr / 6 w</td>
<td>27</td>
<td>47</td>
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60 Gy in 6 weeks
The gold standard
Radiotherapy
Technical Evolution

2 D
3 D conformal rt
4 D (time)

Intensity modulated IMRT static or rotational
Image guided radiotherapy IGRT
Radiosurgery → SBRT/SAR

3DCRT   IMRT DVH   Radiosurgery
The Renaissance 1980-2000 but

**Radiotherapy**: Linacs, CT & dosimetry from 2D to 3D
- The dose-response relationship: RTOG trial
- Technological progress: exploring higher RT dose
- Altered fractionation (CHART)

**Chemotherapy**: The Cisplatine story
- Induction vs concurrent approach
- Dillman (CALGB) & Schaake-Koning (EORTC) trials

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Metaanalysis of ChemoRT

Sequential Chemo RT (1995)

Concurrent chemo RT (2006)

- Absolute benefit of CT-RT
  - 4% at 2 years
  - 2% at 5 years

- Sequential Chemo-RT
INDUCTION or CONCURRENT CHEMOTHERAPY
PATTERN of FAILURE
Two positive trials

IMPACT of INDUCTION CHEMOTHERAPY
Arriagada et al 1991

EORTC TRIAL  DDP & RT
Schaaeke-Koning et al

Less distant metastases
Better locoregional control
The modern era after 2000

- The key role of imaging: PET-CT
- The multimodal approach: from one to trimodality
- Concurrent chemo radiotherapy: the gold standard
- Maintenance therapies
- Chest Radiotherapy: the optimal schedule
- The introduction of SBRT for stage I disease
- Last but not least the role of surgery for stage III
RADIOCHEMOTHERAPY LUNG CA.
RT vs Sequential vs Concurrent CT-RT trials

Median survival

2 Y Survival

Arriagada
Dilman
Sause
Furuse
Curran
Fournel
Zatloukal

INSTITUT
JULES BORDET
INSTITUT

ULB
iris
CONCURRENT VS SEQUENTIAL CHEMORadiotherapy:
Auperin Metanalysis JCO 2010

Absolute benefit in OS with concomitant CT:
- At 2 years: 5.3%
- At 3 years: 5.7%
- At 5 years: 4.5%

Survival (%)

Time from randomisation (Years)

Locoreg. relapse

Risk of recurrence (%)

Time from randomisation (Years)
An invidual data metaanalysis of phase II trials on adjuvant or induction chemotherapy for Non Small Cell Lung Cancer treated with chemoradiotherapy


- Institut Jules Bordet, Bruxelles/BELGIUM,
- IRYCIS,Hospital University Ramon Y Cajal, Madrid/SPAIN
- University of Texas Southwestern Medical Center, Dallas/USA
- Institut de Cancerologie de la Loire, Saint Priest en Jarez/FR.
- Antwerp University Hospital, Edegem/BELGIUM
Absolutly : No difference
Do we need still the surgeons?

*Stage I with SBRT*

*Stage III with chemo RT*

G. Varela and J. Kuzdal
chairman of the ESTS

Medical oncologists
Bunn, Stahel

Happy radiation oncologists
SBRT Stage I operable patient   The debate

Pooled analysis of 2 randomized trial
Chang et al, Lancet Oncology 2015


65 Pts, Age: 50-91y  (median 79y)
38% died of other causes
Surgery or Radiotherapy for Stage III NSCLC
Results of Phase III trial

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>N Pat</th>
<th>R0 resection</th>
<th>Pathological CR</th>
<th>5 Y S</th>
<th>Local Progr.</th>
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<tr>
<td>Albain</td>
<td>RT+CT----S-- CT</td>
<td>202</td>
<td>71.3%</td>
<td>17.7%</td>
<td>27.2</td>
<td>10%</td>
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<tr>
<td></td>
<td>RT+CT----CT</td>
<td>194</td>
<td></td>
<td></td>
<td>20.3</td>
<td>22%</td>
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<tr>
<td>VanMeerbeeck</td>
<td>CT-----Surgery</td>
<td>167</td>
<td>50%</td>
<td>5%</td>
<td>15.7</td>
<td>45%</td>
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<tr>
<td></td>
<td>CT-----RT</td>
<td>165</td>
<td></td>
<td></td>
<td>14</td>
<td>62%</td>
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<tr>
<td>Eberhardt</td>
<td>CT—RT+CT--S</td>
<td>81</td>
<td>94%</td>
<td>33%</td>
<td>44%</td>
<td></td>
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<tr>
<td></td>
<td>CT----RT+CT</td>
<td>80</td>
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<td>40%</td>
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We need to identify for each patient the best approach!
Some great drawbacks

• Great results in stage IV were not a success in stage III
  Targeted therapies with cetuximab
  Pemetrexed

• Radiotherapy
  Higher radiation doses
  Underuse in modern practice
Positive results in stage IV did not translate in positive results for stage III

RT + DDP  
RT+DDP+Cet.

CETUXIMAB & RTOG trial

RADITUX TRIAL

PROCLAIM: Primary Endpoint, OS

\begin{tabular}{|l|c|c|}
\hline
Toxicity & RT + DDP & RT+DDP+Cet. \\
\hline
N patients & 51 & 51 \\
Gr 3 toxicity & 47 % & 71 % \\
Gr 3 pneumonitis & 0 % & 10 % \\
\hline
\end{tabular}

But no patient selection!
RTOG III trial

Bradley Lancet Oncology

2 Y survival 50%
More relapse after 74 Gy

2 Years locoregional relapse rate

60 Gy 30.7% 74 Gy 38.6%

But 60% of patients introduced by centre including less than 4 patients
Is IMRT safe for Stage III NSCLC
A subgroup analysis of RTOG 0617

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3D-CRT</th>
<th>IMRT</th>
<th>P-Value</th>
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<tr>
<td>Stage IIIB PTV</td>
<td>30 %</td>
<td>39 %</td>
<td>0.056</td>
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<tr>
<td>PTV:lung ratio</td>
<td>427 mL</td>
<td>486 mL</td>
<td>0.005</td>
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<tr>
<td>PTV:lung ratio</td>
<td>0.13</td>
<td>0.15</td>
<td>0.013</td>
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</table>

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<thead>
<tr>
<th>2 Y Outcome</th>
<th>OR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td>1.01 (0.8-1.28)</td>
<td>0.95</td>
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<tr>
<td>Progression free surv</td>
<td>1.12 (0.91-1.39)</td>
<td>0.28</td>
</tr>
<tr>
<td>Local control</td>
<td>0.91 (0.67-1.23)</td>
<td>0.54</td>
</tr>
<tr>
<td>Distant metastatic free</td>
<td>0.92 (0.71-1.19)</td>
<td>0.52</td>
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<table>
<thead>
<tr>
<th>Outcome</th>
<th>3D-CRT</th>
<th>IMRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ pneumonitis</td>
<td>8 %</td>
<td>3.5 %</td>
<td>0.0462</td>
</tr>
<tr>
<td>Heart V40</td>
<td>11.4 %</td>
<td>6.8 %</td>
<td>0.0026</td>
</tr>
<tr>
<td>Full consolidative chemo.</td>
<td>29 %</td>
<td>37 %</td>
<td>0.05</td>
</tr>
</tbody>
</table>

More advanced T with IMRT
Larger volume irradiated

No difference in outcome even for more advanced cases

V20 important prognostic factor and not V5

No difference in esophagitis, weight loss cardiovascular effects
Underuse of radiotherapy for lung cancer

Scotland 1995: radiotherapy was delivered to fewer than one third of patients
Southern region of Europe 2007:
  3051 patients diagnosed with lung ca
  610 were treated with radiation
  1383 as estimated from the literature
This is still the case worldwide and even in Belgium and not due to a lack of facilities!
The future: some hope & roads to be explored
2 Year survival move from < 15% to 50% (stage III)

Radiation Oncology
  Isotoxic radiation schedules
  Dose painting & metabolic data
  Using SBRT technique
  Hadrons: protons C Ions or...

A better multidisciplinary approach with individual based treatment

Immunomodulation
Oligometastatic concept

Be careful to the « learning process »
An abscopal response to RT & Ipilimumab

64 y old man adenoca stage IV lung ca
A) pemetrexed-carbopl maintenance pem
B) chest RT for progression
C) gemcitabine and vinorelbine for progression
D) SBRT on a liver lesion and ipilimumab
Free of disease one year later with a dramatic response on lung and bone lesions

Radiation combined with anti-PD-L1 upregulates MHC and FAS on tumour
The biological data to plan or adapt RT PET-boost trial Maastro-NKI

To adapt the dose distribution to the response or the metabolic activity
Protons & Lung Cancer

Better protection of OAR

<table>
<thead>
<tr>
<th>Proton RT</th>
<th>OAR</th>
<th>X-ray RT</th>
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<tbody>
<tr>
<td>13.3 Gy</td>
<td>Dmean Heart</td>
<td>33.5 Gy</td>
</tr>
<tr>
<td>11 Gy</td>
<td>Dmean Lung</td>
<td>17 Gy</td>
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NRG Oncology/RTOG 1308: Protons vs Photons

Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-III NSCLC

Current accrual = 88 / 560 patients
Oligometastatic disease & Local treatment
Gomez et al

Key patient inclusion criteria
- Histologically confirmed NSCLC
- Stage IV disease
- \( \leq 3 \) metastases
- No RECIST progression after FLST* (n=49)

Primary endpoint(s)
- PFS

Secondary endpoints
- OS, safety

Stratification
- Nodal status, EGFR/EML4-ALK status, response to FLST, CNS metastases, number of metastases

LCT† +/- ST (n=25) → PD

ST alone (n=24) → PD

Crossover to LCT allowed at progression

---

*\( \geq 4 \) cycles of platinum-doublet chemotherapy, \( \geq 3 \) months of erlotinib, afatinib or geftinib therapy if EGFR mutation or \( \geq 3 \) months of crizotinib therapy if EML4-ALK fusion; †LCT, local consolidative therapy (i.e. [chemo]radiation or surgical resection of all sites); ST, systemic therapy
Study closed early due to superiority

How to select the good from the bad one? The Lang stratification
Concurrent ChemoRT for Lung Ca
Patient selection, Treatment & The elderly

Age or Comorbidity
PS
Tumor extent stage III to-day is not the stage III of the past
Smoking issue

Chemoradiotherapy in elderly patients
A meta-analysis  Dawe D. Lung Ca 2016

De Ruysscher et al
Ann Oncol. 2009
NSC LUNG CANCER : CT & RT

The Learning Process

*RTOG trial 9106 & 9204*


<table>
<thead>
<tr>
<th>N patients per institution</th>
<th>4 patients or less</th>
<th>&gt; 4 patients</th>
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<tbody>
<tr>
<td>Median survival Months</td>
<td>13.4</td>
<td>20.5</td>
</tr>
<tr>
<td>2 Y S</td>
<td>20 %</td>
<td>45 %</td>
</tr>
<tr>
<td>3 Y S</td>
<td>13 %</td>
<td>31 %</td>
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*Concurrent radio-chemoth. with twice per day RT*
A concern for to-day and tomorrow

• Our goal is to provide to each individual patient access to modern management for his cancer

• Is it a reality and be still possible in the future

• Should we evolve from EBM to VBM
Radiation facilities worldwide

We are on the good side but we should still move forwards
A radiation oncologist should remain an oncologist first
ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

Ann Oncol 2016

EGFR-mutated non-small-cell lung cancer: formulary availability and out-of-pocket costs.

<table>
<thead>
<tr>
<th>Country</th>
<th>Erlotinib</th>
<th>Gefitinib</th>
<th>Afatinib</th>
<th>Crizotinib</th>
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National Health Expenditures Projections 2016-2025

From 17.8% in 2015 to 19.9% in 2025 PIB

Should we still be able to pay in the future for our medical care?
This was and is still a long road to hope

- Make it going on