Individual patient data meta-analysis in non-metastatic head & neck and lung cancers: the Gustave Roussy experience

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Outline

• **Background**: overview, place of the individual patient data (IPD) meta-analysis
• **Main results** from the IPD meta-analyses
• Interrelation between **trial and meta-analysis**, update of meta-analysis and future projects
• **Other results** obtained on IPD meta-analysis
• **Conclusion** and perspectives
Overview of Gustave Roussy meta-analysis team activities

- Since 1989 we have conducted meta-analyses mainly in non-metastatic:
  - Lung cancer:
    - Small cell [SCLC]
    - Non small cell [NSCLC]
  - Head & neck cancer:
    - Squamous carcinoma cell [HNSCC]
    - Nonkeratinizing nasopharynx carcinoma [NPC]
- Gathering individual patient data from more than 300 trials and 60,000 patients
We have studied the effects of radiotherapy alone or combined with chemotherapy. Organized 16 investigator conferences. This work needed > 40 person-years of work. 25 publications with impact factor > 15. These studies have led to designing new trials.
Place of individual patient data meta-analysis: Type of meta-analysis

- Most of the meta-analyses are based on summary data extracted from publication.
- Main risks of such meta-analyses are publication bias and reporting bias.
- Fewer meta-analyses are based on individual patient data (IPD) from the databases of the different trials.
- The IPD meta-analysis is the reference method, but it is more time consuming.
- Our group have used this approach in most cases, only IPD meta-analysis will be reported to-day.
Summary data meta-analysis

- They are useful if they are well performed
- A protocol should be prepared by a multidisciplinary team
- Trial search should be exhaustive: electronic databases (Pubmed, Embase ...), proceedings of meetings, trial registries
- Authors should be contacted in case of missing data
- Quality of the trials should be evaluated.
- Cochrane and PRISMA guidelines should be followed
- Hazard ratio (HR) should be used for survival data
Why individual patient data?

- **Include unpublished trials:** 16 out of 300 (4% of pts)
- **Update the follow-up,** 5 to 12 years depending on the meta-analysis, **to study long-term effect**
- **Check the quality of trials:** exclusion of 5 trials because of quality problems and sensitivity analyses according to quality
- **Perform intent-to-treat analysis:** > 80 % of the patients excluded from published analyses recovered, up to 4% of the analyzed patients
- **Study local vs. distant failure and cancer vs. non-cancer mortality**
- **Study interactions between treatment and co-variates such as age**
Quality of follow-up: Reverse Kaplan Meier curves*

Plateau = minimum follow-up

Events = Alive at last follow-up
Censoring = death

Duration of accrual

Reference
Experimental

*Control Clin Trials 1996;17:343
Reverse Kaplan Meier curves: absence of minimum follow-up and difference of follow-up between arms

Log-rank: p=0.045
Wilcoxon: p= 0.01

8-bis
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• Conclusion and perspectives
Treatments compared in lung and head & neck cancer

1. Radiotherapy Yes/No
2. Standard vs. modified fraction radiotherapy
3. Chemotherapy Yes/No (with systematic radiotherapy)
4. Chemotherapy 1 vs. chemotherapy 2
5. Concomitant vs. sequential chemo-radiotherapy
1. Radiotherapy Yes/No: Main results

- Thoracic radiotherapy (RT), added to chemotherapy in limited SCLC, improves 3-year overall survival by 5%\(^1\)
  - *ongoing meta-analysis on RT timing*
- Prophylactic Cranial Irradiation (PCI) for SCLC patient in complete response improves 3-year survival by 5%\(^2\)
  - *PCI dose trial in SCLC and PCI trials for NSCLC*
- Adjuvant thoracic RT using old techniques for NSCLC (MRC) decreases 5-year survival by 7%, with larger detriment in early stage and no effect in N2 pts\(^3\)
  - *Adjuvant thoracic RT using modern techniques in N2:Lung-ART trial*

\(^1\)Pignon et al, NEJM 1992;327:1618;
\(^2\)Auperin et al, NEJM 1999;341:476;
\(^3\)PORT, Lancet 1998;352:257
1. Radiotherapy Yes/No: Main results

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• Prophylactic Cranial Irradiation (PCI) for SCLC patient in complete response improves 3-year survival by 5%\(^2\)
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1. Radiotherapy Yes/No: Main results

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  ➔ ongoing meta-analysis on RT timing

• Prophylactic Cranial Irradiation (PCI) for SCLC patient in complete response improves 3-year survival by 5%\(^2\)
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• Adjuvant thoracic RT using old techniques for NSCLC (MRC) decreases 5-year survival by 7%, with larger detriment in early stage and no effect in N2 pts\(^3\)
  ➔ Adjuvant thoracic RT using modern techniques in N2: Lung-ART trial

\(^1\)Pignon et al, NEJM 1992;327:1618;
\(^2\)Auperin et al, NEJM 1999;341:476;
\(^3\)PORT, Lancet 1998;352:257
2. Modified (hyper-fractionated or accelerated) radiotherapy is better than standard radiotherapy

**Lung cancer**

**NSCLC**: locally advanced, modified RT improves survival by 3% at 5 years; HR=0.87 (p=0.009)

**SCLC**: modified RT improves survival by 5% at 5 years; HR=0.87 (p=0.08)

⇒ open question: which type of modified radiotherapy?

* Mauguen et al, JCO 2012;30:2788
2. Modified (hyper-fractionated or accelerated) radiotherapy is better than standard radiotherapy

**Head & neck squamous cell cancer**

Locally advanced H&NC: modified RT improves survival by 3% at 5 years with higher benefit for hyper-fractionated RT (8% at 5 years)\(^1,2\)

- **similar results when combined with chemotherapy or after surgery.**\(^2\)
- **is hyperfractionated RT + concomitant CT the best treatment?**

\(^1\) Bourhis et al. Lancet 2006;368:843
## Overall Survival

<table>
<thead>
<tr>
<th>No. Deaths / No. Patients</th>
<th>Experimental RT</th>
<th>Conventional RT</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
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<tbody>
<tr>
<td><strong>Hyperfractioned (HF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22791</td>
<td>126/180</td>
<td>135/176</td>
<td>0.83 [0.74;0.92]</td>
</tr>
<tr>
<td>RIO</td>
<td>41/52</td>
<td>47/51</td>
<td></td>
</tr>
<tr>
<td>PMH Toronto</td>
<td>152/172</td>
<td>151/164</td>
<td></td>
</tr>
<tr>
<td>RTOG 9003 HF</td>
<td>249/276</td>
<td>245/279</td>
<td></td>
</tr>
<tr>
<td>EORTC 22962</td>
<td>7/13</td>
<td>9/14</td>
<td></td>
</tr>
<tr>
<td>EORTC 22962 + CT</td>
<td>8/15</td>
<td>9/15</td>
<td></td>
</tr>
<tr>
<td>RTOG 9512</td>
<td>60/126</td>
<td>63/122</td>
<td></td>
</tr>
<tr>
<td>DAHANCA 9</td>
<td>6/41</td>
<td>5/36</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>649/875</td>
<td>664/857</td>
<td></td>
</tr>
<tr>
<td><strong>Moderately accelerated (MAc)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22843</td>
<td>20/27</td>
<td>21/26</td>
<td></td>
</tr>
<tr>
<td>EORTC 22851</td>
<td>171/257</td>
<td>164/255</td>
<td></td>
</tr>
<tr>
<td>BCCA 9113</td>
<td>36/41</td>
<td>33/41</td>
<td></td>
</tr>
<tr>
<td>MD Anderson</td>
<td>55/76</td>
<td>62/75</td>
<td></td>
</tr>
<tr>
<td>RTOG 9003 S</td>
<td>254/281</td>
<td>245/279</td>
<td></td>
</tr>
<tr>
<td>RTOG 9003 B</td>
<td>240/277</td>
<td>245/279</td>
<td></td>
</tr>
<tr>
<td>ORO 9301</td>
<td>50/65</td>
<td>47/63</td>
<td></td>
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<tr>
<td>DAHANCA 6&amp;7</td>
<td>580/755</td>
<td>568/730</td>
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<tr>
<td>CAIR</td>
<td>19/51</td>
<td>37/49</td>
<td></td>
</tr>
<tr>
<td>INRC-HN-10</td>
<td>61/113</td>
<td>59/113</td>
<td></td>
</tr>
<tr>
<td>KBN PO 79</td>
<td>42/196</td>
<td>41/199</td>
<td></td>
</tr>
<tr>
<td><strong>ARTSCAN</strong></td>
<td>223/375</td>
<td>222/375</td>
<td></td>
</tr>
<tr>
<td>IAEA-CRP-ACC</td>
<td>281/452</td>
<td>306/448</td>
<td></td>
</tr>
<tr>
<td>TMH 1114</td>
<td>34/68</td>
<td>31/66</td>
<td></td>
</tr>
<tr>
<td>GORTEC 9902</td>
<td>198/280</td>
<td>196/279</td>
<td></td>
</tr>
<tr>
<td>pCAIR</td>
<td>88/138</td>
<td>95/140</td>
<td></td>
</tr>
<tr>
<td>RTOG 0129</td>
<td>149/367</td>
<td>161/370</td>
<td></td>
</tr>
<tr>
<td>POPART</td>
<td>27/74</td>
<td>30/73</td>
<td></td>
</tr>
<tr>
<td>CONDOR</td>
<td>8/29</td>
<td>8/27</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>2536/3922</td>
<td>2571/3887</td>
<td></td>
</tr>
<tr>
<td><strong>Very accelerated (VAc)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 7913</td>
<td>91/106</td>
<td>87/104</td>
<td></td>
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<tr>
<td>CHART</td>
<td>376/552</td>
<td>238/366</td>
<td></td>
</tr>
<tr>
<td>CAIRO 1990</td>
<td>12/30</td>
<td>18/40</td>
<td></td>
</tr>
<tr>
<td>Vienna</td>
<td>62/78</td>
<td>68/81</td>
<td></td>
</tr>
<tr>
<td>TROG 9101</td>
<td>114/174</td>
<td>125/176</td>
<td></td>
</tr>
<tr>
<td>GORTEC 9402</td>
<td>118/137</td>
<td>114/131</td>
<td></td>
</tr>
<tr>
<td>CHARTWEL</td>
<td>21/57</td>
<td>20/57</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>794/1134</td>
<td>670/955</td>
<td></td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>3979/5931</td>
<td>3905/5699</td>
<td></td>
</tr>
</tbody>
</table>

### Test for heterogeneity
- **p = 0.12** ; **I² = 23%**

### Test for interaction
- **p = 0.05**

### Experimental RT effect
- **p = 0.003**

### Global absolute difference at 5 years [95% CI]
- **+3.1 [+1.2;+5.0]**
3. Chemotherapy added to radiotherapy improves overall survival

**NSCLC**\(^1\)

- Sequential (mostly induction) and concomitant chemotherapy (CT) both improve overall survival by 3% at 3 years

**Head & Neck Cancer**\(^2,3\)

- Adding CT to loco-regional treatment (mostly RT or surgery plus RT) improves overall survival by 4.5% and 6.3% at 5 years, in HNSCC and in NPC, respectively.

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\(^1\) Le Péchoux et al, JTO 2008;3(Suppl 1): S20;

\(^2\) Pignon et al, Rad Oncol 2009;92:4

\(^3\) Blanchard et al Lancet Oncol 2015: in press
# 3. Head & Neck Cancer: Overall survival

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+CT</td>
<td>3171 / 4824</td>
<td>-326.4</td>
<td>1587.7</td>
<td></td>
<td>0.81 [0.78;0.86]</td>
</tr>
<tr>
<td>RT</td>
<td>3389 / 4791</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>1877 / 2740</td>
<td>-40.0</td>
<td>900.7</td>
<td></td>
<td>0.96 [0.90;1.02]</td>
</tr>
<tr>
<td>RT</td>
<td>1813 / 2571</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>631 / 1244</td>
<td>17.9</td>
<td>317.4</td>
<td></td>
<td>1.06 [0.95;1.18]</td>
</tr>
<tr>
<td>RT</td>
<td>661 / 1323</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5679 / 8808</td>
<td>-348.5</td>
<td>2805.8</td>
<td></td>
<td>0.88 [0.85;0.92]</td>
</tr>
<tr>
<td>RT+CT</td>
<td>5863 / 8685</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction: $p < 0.0001$

LRT+CT effect: $p < 0.0001$

Pignon et al, Rad Oncol 2009;92:4
4. HNSCC: induction chemotherapy, adding taxane (T) to platinum + 5FU (PF)*

- 5 trials, 1,815 patients with 4.9 years median of follow-up
- Benefit on overall survival for taxane:
  HR of **0.79** (p=0.002) corresponding at **7.4%** at 5 years
- **Heterogeneity** (p=0.08; I²=51%): one trial with an HR of 1.14 when other trials an HR <0.75
- This trial had a significant **excess of early deaths** (within 120 days): HR of 2.53
- Protocol amended, inclusion G-CSF prophylaxis with TPF → decrease of early deaths and increase in OS in the TPF arm; HR for OS: **1.36** without G-CSF and **0.64** with G-CSF.

* Blanchard et al J Clin Oncol 2013;31:2854
4. HNSCC, TPF vs. PF: Mortality within 120 days post randomization

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Patients</th>
<th>O-E</th>
<th>Variance</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 1998</td>
<td>10/189, 13/193</td>
<td>-1.5</td>
<td>5.7</td>
<td>0.77 [0.34;1.75]</td>
</tr>
<tr>
<td>EORTC 24971</td>
<td>8/177, 20/181</td>
<td>-6.0</td>
<td>7.0</td>
<td>0.42 [0.20;0.89]</td>
</tr>
<tr>
<td>TAX 324</td>
<td>8/255, 10/246</td>
<td>-1.2</td>
<td>4.5</td>
<td>0.77 [0.31;1.95]</td>
</tr>
<tr>
<td>GORTEC 2000 -01</td>
<td>6/113, 5/107</td>
<td>0.4</td>
<td>2.7</td>
<td>1.14 [0.35;3.71]</td>
</tr>
<tr>
<td>TTCC 2002 before G-CSF</td>
<td>16/112, 3/117</td>
<td>7.0</td>
<td>4.7</td>
<td>4.34 [1.76 ; 10.7]</td>
</tr>
<tr>
<td>TTCC 2002 after G-CSF</td>
<td>2/43, 4/39</td>
<td>-1.2</td>
<td>1.5</td>
<td>0.46 [0.09 ; 2.27]</td>
</tr>
</tbody>
</table>

Total: 50/889, 55/883, -2.5, 26.2

Heterogeneity: p=0.05; I^2=70%
Disappears after exclusion of early trial phase

HR=2.53
5. Concomitant and sequential chemo-radiotherapy (CT-RT): direct and indirect information

The comparison of the hazard ratios from trials B and C provides an indirect comparison. Inconsistency = not the same results with direct and indirect comparison.
4. Concomitant chemotherapy is better than sequential/induction chemotherapy

\textbf{NSCLC}^{1,2}

- Indirect comparison (38 trials): HR = 0.86 for sequential CT and 0.88 for concomitant CT (NS); 0.88/0.86 = 1.02
- Direct comparison (6 trials; 1,265 pts): HR = 0.84 (p=0.004) for survival
- Inconsistent results may be explained by more intense CT in the concomitant arm for the direct comparison (more recent trials) than in the concomitant arm for the indirect comparison and change in RT modalities overtime

\textit{usefulness of combining induction and concomitant treatment (ongoing meta-analysis)}

\footnotesize
1 Le Pechoux et al, J Thorax Oncol 2008;3 (Suppl 1):S20;
2 Auperin et al, JCO 2010;28:2181
5. **NSCLC**: direct comparison: Overall survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>Conc CT + RT</th>
<th>Seq CT + RT</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 8831</td>
<td>45/46</td>
<td>39/45</td>
<td>1.12</td>
<td>[0.73;1.72]</td>
</tr>
<tr>
<td>WJLCG</td>
<td>131/156</td>
<td>142/158</td>
<td>0.78</td>
<td>[0.61;0.99]</td>
</tr>
<tr>
<td>RTOG 9410</td>
<td>180/204</td>
<td>189/203</td>
<td>0.80</td>
<td>[0.65;0.98]</td>
</tr>
<tr>
<td>GMMA Ankara 95</td>
<td>15/15</td>
<td>15/15</td>
<td>0.87</td>
<td>[0.41;1.82]</td>
</tr>
<tr>
<td>GLOT-GFPC NPC</td>
<td>87/102</td>
<td>96/103</td>
<td>0.80</td>
<td>[0.60;1.07]</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>63/80</td>
<td>66/78</td>
<td>0.98</td>
<td>[0.69;1.39]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>521/603</td>
<td>547/602</td>
<td><strong>0.84</strong></td>
<td>[0.74;0.95]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: p = 0.66

**Auperin et al, JCO 2010;28:2181**
5. Concomitant chemotherapy is better than sequential/induction chemotherapy

**Head & Neck Squamous Cell Cancer***

- Indirect comparison (70 trials): HR = 0.96 for induction CT and 0.81 for concomitant CT (p<0.0001) ; 0.81/0.96 = 0.84; if restricted to trials with 5FU-platin p=0.01
- Direct comparison (6 trials; 861 pts): HR = 0.90 (p=0.15) for survival and 0.81 (p=0.01) for progression-free survival

⇒ **superiority of concomitant CT still true with use of taxane as induction CT?**

* Pignon et al, Rad Oncol 2009;92:4*
Summary

• Thoracic and prophylactic cranial radiotherapy improves survival in limited SCLC

In both HNSCC and NSCLC,

• Modified fraction radiotherapy improves survival

• Concomitant chemo-radiotherapy improves survival compared to sequential/induction chemo-radiotherapy

• In NPC, chemotherapy, in particular concomitant (+/- adjuvant) chemotherapy, improves survival
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• Conclusion and perspectives
a. Interrelation between randomized trials and meta-analysis

**NSCLC:** Postoperative chemotherapy

- Initial *meta-analysis*\(^1\): HR of 0.87 (\(p=0.08\)) in a subset analysis in cisplatin combination ➔ several trials on cisplatin-based chemotherapy
- **IALT trial**\(^2\) (n=1,867 patients): HR of 0.86 (\(p<0.03\))
- Update of the *meta-analysis*\(^3\) (> 8,000 pts): HR of 0.87 (\(p<0.0000001\)) ➔ 4% benefit at 5 years

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\(^1\) NSCLC MA collaborative group. *Br Med J* 1995;311:899
\(^2\) IALT collaborative group *NEJM* 2004;350:351
\(^3\) NSCLC MA collaborative group. *Lancet* 2010;375:1267
Non-Small Cell Lung Cancer Post-operative Chemotherapy yes/no

<table>
<thead>
<tr>
<th>CT</th>
<th>(N^\circ) death/(N^\circ) patients</th>
<th>Hazard ratio</th>
<th>(P)-value</th>
<th>5-year survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents alkylants</td>
<td>1670/2145</td>
<td>1.15</td>
<td>0.005</td>
<td>-5 %</td>
</tr>
<tr>
<td>Other</td>
<td>338/918</td>
<td>0.89</td>
<td>0.30</td>
<td>4 %</td>
</tr>
<tr>
<td>Cisplatin combination</td>
<td>614/1398</td>
<td>0.87</td>
<td>0.08</td>
<td>5 %</td>
</tr>
</tbody>
</table>

Between CT heterogeneity: \(\chi^2_2 = p=0.004\)

Br Med J 1995;311:899
Interaction between randomized trials and meta-analysis

**SCLC**: prophylactic cranial irradiation in limited stage

- **Subset analysis** showed increasing effect on brain metastasis with increasing dose (test for trend \( p=0.02 \))\(^1\)
- But the **randomized trial** (PCI-99) comparing 2 doses (25 vs. 36 Gy) in 720 patients did **not confirm** this hypothesis → 25 Gy remains the standard\(^2\)

> Indirect comparison should be interpreted with caution and validated by direct comparison

\(^1\) Auperin et al, *NEJM* 1999;341:476;
\(^2\) Le Pechoux et al *Lancet Oncol* 2009;10:467
b. Why update individual patient data meta-analysis?

- Higher number of trials and patients
- Increased follow-up
- Analysis of other endpoints
- Increased power, in particular for subgroup analyses and analysis of infrequent events
- Validation of previous subset or subgroup analyses
- Inclusion of new comparisons, in particular direct comparison following indirect comparison (subset analysis)
## Head and neck meta-analyses

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Initial (n° trials/pts)</th>
<th>Update 1 (n° trials/pts)</th>
<th>Update 2 (n° trials/pts)</th>
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<tbody>
<tr>
<td></td>
<td>Publication</td>
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</tr>
<tr>
<td></td>
<td>(63,10 741)</td>
<td>(87, 16 485)</td>
<td>(102, 19 325)</td>
</tr>
<tr>
<td>MAC-NPC (CT, NPC)</td>
<td>&lt; 2002</td>
<td>2002-2010£,$$</td>
<td>initiated in 2016</td>
</tr>
<tr>
<td></td>
<td>(8, 1 753)</td>
<td>(19, 4 806)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red 2006</td>
<td>Lancet Oncol 2015</td>
<td></td>
</tr>
<tr>
<td>MARCH (RT, HNSCC)</td>
<td>1970-1998</td>
<td>1999-2011£,%</td>
<td>cf. final analysis finale et manuscript 2015</td>
</tr>
<tr>
<td></td>
<td>(15, 6 515)</td>
<td>(30, 11 140)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lancet 2006</td>
<td>ECCO 2013/ESTRO 2014</td>
<td></td>
</tr>
</tbody>
</table>

* MA on larynx preservation ; $ MA sequential vs. concomitant
£ Effect at 10 years, data on toxicity and compliance ;
% Postoperative trials eligible, MA standard radiotherapy (RT) + CT vs. modified fractionation RT
** JCO 2013 TPF vs. PF; $$ Trials of Timing 1 + Timing 2 eligible
Outline

• Background: overview, place of the patient data meta-analysis
• Main results from the IPD meta-analysis
• Interrelation between trial and meta-analysis, update of meta-analysis and future projects
• **Other results** obtained on IPD meta-analysis
• Conclusion and perspectives
Other results obtained with these individual patient data meta-analyses

a. Analysis of a network of trials
b. Study of the treatment effect according to age
c. Separate analysis of loco-regional and distant failure
d. Study of surrogate endpoints
e. Prognostic and predictive value of tumor markers
a. NPC: a network meta-analysis of 20 trials and around 5,000 patients

- In locally advanced disease, 2 treatments were superior to RT alone: Concomitant CT-RT (CRT), and CRT plus adjuvant CT (CRT-AC).
- superiority of CRT-AC on CRT is discussed and the place of induction CT plus CRT (IC-CRT) is unknown.
- In this setting with more than 2 treatments:
  - What is the best treatment?
  - Which two treatments should be compared in the next trial?

⇒ A network meta-analysis will allow the integration of all the direct and indirect comparisons available
Male: 74%  
< 50 years: 60%  
Stage III-IV: 90%  
WHO grade 2-3: 96%  
PS 0: 55%  
FU: 7.7 years

*a. NPC: Network meta-analysis*  

Presented by: 

Blanchard et al.  
*Rad Oncol 2015; 114 (Supp 1): 6*
a. NPC: Network meta-analysis

RT: Radiotherapy
IC: Induction chemotherapy (CT)
AC: Adjuvant CT
CRT: Concomitant CT-RT
a. NPC, network meta-analysis

Overall Survival: HRs (95% CI) vs. RT alone

Probability of being the best treatment

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>IC-RT</th>
<th>IC-CRT</th>
<th>CRT</th>
<th>CRT-AC</th>
<th>RT-AC</th>
<th>IC-RT-AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>1</td>
<td>0.93</td>
<td>0.82</td>
<td>0.78</td>
<td>0.65</td>
<td>1.01</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.76 1.12)</td>
<td>(0.63 1.04)</td>
<td>(0.65 0.93)</td>
<td>(0.56 0.75)</td>
<td>(0.75 1.32)</td>
<td>(0.58 1.29)</td>
</tr>
<tr>
<td>BEST</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>3%</td>
<td>84%</td>
<td>0%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Inconsistency* p = 0.42

- Same type of analysis with progression-free survival, locoregional control, distant control and cancer mortality

* Difference in results between direct and indirect comparisons
For almost all endpoints the best schedule contains **concomitant** chemotherapy (CRT)
Although pairwise HRs are not significant, CRT alone never ranked 1st whatever the endpoints studied
**More chemotherapy** (addition of induction or adjuvant CT) seems to provide an additional benefit compared to CRT
Need **to be confirmed** on direct comparison
What will be the place of **induction CT with taxane**?

* Blanchard et al. Rad Oncol 2015;114 (Supp 1): 6
b. Treatment effect modified by age

- In head & neck cancer, both in the meta-analysis of concomitant chemotherapy and in the meta-analysis of radiotherapy, a decreased treatment effect with increasing age was observed on overall survival.

- In SCLC a decreased effect of thoracic radiotherapy with age was also observed.
b. **Head & neck cancer**: Effect of concomitant chemotherapy according to age

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 or less</td>
<td>1 663 / 2 584</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>51-60</td>
<td>2 267 / 3 306</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>61-70</td>
<td>1 960 / 2 698</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>71 +</td>
<td>533 / 692</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Total</td>
<td>6 423 / 9 280</td>
<td></td>
<td>0.81</td>
</tr>
</tbody>
</table>

Test for trend: $p = 0.003$

Chemo effect $p < 0.0001$

*Pignon et al Rad Oncol 2009;92:4*
c. Separate analyses of local and distant failures

In both NSCLC and head & neck cancer:

• **Concomitant** chemotherapy decreases the risk of **local** failure
• **Induction** chemotherapy decreases the risk of **distant** failure
c. Head & neck cancer, local and distant failure by timing of chemotherapy

Concomitant Chemotherapy

- Local failure: Chemotherapy 60%, Control 51% (P<0.0001)
- Distant failure: Chemotherapy 19%, Control 17% (P=0.04)

Concomitant chemotherapy decreases the risk of local failure

_Pignon et al Rad Oncol 2009;92:4_
c. Head & neck cancer, local and distant failure by timing of chemotherapy

**Concomitant Chemotherapy**

- Local failure:
  - Chemotherapy: 60%
  - Control: 51%
  - P < 0.0001

- Distant failure:
  - Chemotherapy: 19%
  - Control: 17%
  - P = 0.04

**Induction Chemotherapy**

- Local failure:
  - Chemotherapy: 47%
  - Control: 46%
  - P = 0.43

- Distant failure:
  - Chemotherapy: 17%
  - Control: 13%
  - P = 0.001

**Concomitant chemotherapy decreases the risk of local failure**

**Induction chemotherapy decreases the risk of distant failure**

*Pignon et al Rad Oncol 2009;92:4*
d. Are loco-regional control (LRC) and progression-free survival (PFS) valid surrogate endpoints for overall survival?

**Methods:** correlation between surrogate endpoint and overall survival at the patient and trial level (Buyse et al)

**Head & neck cancer**

- PFS is a good surrogate **endpoint** in trials comparing RT modalities or addition of CT to RT, LRC may be an alternative choice in trials comparing RT modalities

**NSCLC**

- Locally advanced setting, results **similar** to head & neck cancer
- **Adjuvant** setting: **Disease-free survival** good surrogate of overall survival

---

d. Locally advanced NSCLC  **Trial level: Correlation between treatment effect on the surrogates and on the main endpoint for radiotherapy**

R=0.99

R=0.97

High correlations with overall survival for both progression-free survival and loco-regional control.
e. Analysis of prognostic and predictive value of tumor markers in NSCLC

- The LACE-Bio project includes 4 trials of adjuvant chemotherapy vs. none (IALT, ANITA, JBR10, CALGB) and around 1,500 patients with a tumor block.
- When a trial showed a tumor marker to have a significant prognostic and/or predictive value on overall survival (OS) or indicated a trend for such effects, the results were validated on the 3 other trials.
- Analysis adjusted on age, sex, type of surgery, performance status, stage, histology
- **Prognostic** = impact on OS in untreated patients
- **Predictive** = effect of chemotherapy compared to control on OS varies according to tumor markers
e. Validation of a tumor marker in NSCLC: β-tubulin

One trial (JBR.10, 265 patients) showed a significant prognostic and a borderline predictive effect of β-tubulin.

Validation in 3 other trials (1,149 patients):

- Deleterious effect of high β-tubulin on survival confirmed, HR of 1.42 and 1.27
- Predictive effect not confirmed:

<table>
<thead>
<tr>
<th>HR of chemo effect</th>
<th>JBR.10</th>
<th>Other trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low β-tubulin</td>
<td>1.13</td>
<td>1.03</td>
</tr>
<tr>
<td>High β-tubulin</td>
<td>0.58</td>
<td>0.83</td>
</tr>
<tr>
<td>p for interaction</td>
<td>0.08</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Reiman T et al Ann Oncol 2012;23:86
e. Validation of tumor markers in **NSCLC (LACE-Bio):**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Identified in</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1</td>
<td>IALT, ERCC1+: better prognosis (p=0.009) and ERCC1-: ↑CT effect (p=0.009)</td>
<td>Not prognostic, Not predictive</td>
</tr>
<tr>
<td>Lymphoid infiltration</td>
<td>IALT, Intense lymphoid infiltration: better prognosis (p=0.002)</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Mucin</td>
<td>CALGB, Mucin+: worse prognosis (p=0.002)</td>
<td>Prognostic (DFS only) Not predictive</td>
</tr>
<tr>
<td>β-tubulin</td>
<td>JBR10, High b-tubulin: trend for worse prognosis (p&lt;0.001) &amp; ↑ CT effect (p=0.08)</td>
<td>Prognostic Not predictive</td>
</tr>
<tr>
<td>FAS/FASL ratio (3 cat.)</td>
<td>IALT, trend for prognostic (0.02) &amp; predictive (0.03), but not linear</td>
<td>Not prognostic, Not predictive</td>
</tr>
<tr>
<td>P27</td>
<td>IALT, P27+: worse prognosis (p=0.04) &amp; ↑ CT effect (p=0.02)</td>
<td>Not prognostic, Not predictive</td>
</tr>
<tr>
<td>FASL</td>
<td>IALT, FASL↑ trend for predictive ↑ CT effect (p=0.06)</td>
<td>FASL↓ predictive ↑ chemo effect</td>
</tr>
<tr>
<td>BAX</td>
<td>IALT, BAX↑: trend for ↑ CT effect (p = 0.06)</td>
<td>Not prognostic, Not predictive</td>
</tr>
</tbody>
</table>

*Seymour et al Ann Oncol 2014; 25 (Suppl 4): abstract 167O*
e. LACE-Bio: discussion

- Markers with **highly** significant results are more likely to be validated
- Risk of **false positive** results with large number of analyses
- Numerous issues identified, including timing of section, Tissue Micro Arrays vs. slides, central lab or not, timing between the first analysis and its validation and batches of reagent.
- For **ERCC1**, prognostic and predictive values shown in IALT trial.\(^1\) Change in batches of antibody (old one not available anymore)\(^2\), no values not only in JBR10 and CALGB 9633 trials, but also in IALT with the new batches.
- Ongoing, search for new markers using **genomics** approach

\(^1\) Olaussen et al NEJM 2006;355:983  
\(^2\) Friboulet et al NEJM 2013;368:1101
ERCC1 in IALT trial

2006 analysis

Patients with ERCC1 negative tumor

Chemotherapy (105 deaths)

Control (113 deaths)

p=0.002

Patients with ERCC1 positive tumor

Chemotherapy (92 deaths)

Control (80 deaths)

p=0.40

p of interaction = 0.009
Patients with ERCC1 negative tumor

2006 analysis

Chemotherapy (105 deaths)

Control (113 deaths)

$p=0.002$

2013 analysis

Chemotherapy (35 deaths)

Control (35 deaths)

$p=0.53$

$p$ of interaction $= 0.009$

Patients with ERCC1 positive tumor

2006 analysis

Chemotherapy (92 deaths)

Control (80 deaths)

$p=0.40$

2013 analysis

Chemotherapy (118 deaths)

Control (114 deaths)

$p=0.79$

$p$ of interaction $= 0.53$
Conclusion

• Meta-analyses are only possible and interesting if there are good available trials.

• Trials demand hard work and are expensive, individual patient data meta-analyses make a good use of the accumulated data.
Perspectives

• Most of the meta-analyses are still based on summary data, and are useful only if well performed.
• Increasing access to individual patient data (IPD) ➔ increasing use of IPD meta-analysis.
• Network meta-analysis is a promising method still in its infancy, more work needed before generalizing its use in public health.
Perspectives

• Shift from diseases defined by histology to small entities defined by molecular abnormalities with increasing use of targeted therapy and decreasing number of patients enrolled in trials by disease/type of treatment.

• Shift to meta-analyses by molecular disease (from different organs), or by drug (toxicity)
Meta-analysis projects were supported mainly by grants from:
- Research Programs of the French Health Ministry and French National Cancer Institute
- European Commission
- French charities: Association against Cancer and National Cancer League
- Unrestricted Research grants from Sanofi-Aventis and Roche
Thank you to the patients and trialists, in particular Ola Brodin, Bengt Bergman, Freddi Lewin, Bjorn Zackrisson.
Back-up slides
4. HNSCC, TPF vs. PF: Overall and event-free survival

**Overall survival**

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR (95%CI)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 1998</td>
<td>0.70 [0.51 ; 0.97]</td>
<td></td>
</tr>
<tr>
<td>EORTC 24971</td>
<td>0.71 [0.56 ; 0.89]</td>
<td></td>
</tr>
<tr>
<td>TAX 324</td>
<td>0.74 [0.58 ; 0.94]</td>
<td></td>
</tr>
<tr>
<td>GORTEC 2000-001</td>
<td>0.75 [0.52 ; 1.09]</td>
<td></td>
</tr>
<tr>
<td>TTCC 2002</td>
<td>1.14 [0.86 ; 1.51]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.79 [0.70 ; 0.89]</strong></td>
<td><strong>0.72 [0.55 ; 0.95]</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** p=0.08

I²=51%

**Event-free survival**

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR (95%CI)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 1998</td>
<td>0.72 [0.55 ; 0.95]</td>
<td></td>
</tr>
<tr>
<td>EORTC 24971</td>
<td>0.71 [0.57 ; 0.89]</td>
<td></td>
</tr>
<tr>
<td>TAX 324</td>
<td>0.75 [0.60 ; 0.94]</td>
<td></td>
</tr>
<tr>
<td>GORTEC 2000-001</td>
<td>0.77 [0.54 ; 1.08]</td>
<td></td>
</tr>
<tr>
<td>TTCC 2002</td>
<td>1.00 [0.77 ; 1.31]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.78 [0.69 ; 0.87]</strong></td>
<td><strong>0.72 [0.55 ; 0.95]</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** p=0.35

I²=9%
4. HNSCC, TPF vs. PF: Mortality within 120 days post randomization

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>Tax-PF</th>
<th>PF</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 1998</td>
<td>10/189 13/193</td>
<td>10</td>
<td>13</td>
<td>-1.5</td>
<td>5.7</td>
<td>0.77</td>
<td>[0.34;1.75]</td>
</tr>
<tr>
<td>EORTC 24971</td>
<td>8/177 20/181</td>
<td>8</td>
<td>20</td>
<td>-6.0</td>
<td>7.0</td>
<td>0.42</td>
<td>[0.20;0.89]</td>
</tr>
<tr>
<td>TAX 324</td>
<td>8/255 10/246</td>
<td>8</td>
<td>10</td>
<td>-1.2</td>
<td>4.5</td>
<td>0.77</td>
<td>[0.30;1.93]</td>
</tr>
<tr>
<td>GORTEC 2000-01</td>
<td>6/113 5/107</td>
<td>6</td>
<td>5</td>
<td>0.3</td>
<td>2.7</td>
<td>1.14</td>
<td>[0.35;3.70]</td>
</tr>
<tr>
<td>TTCC 2002</td>
<td>18/155 7/156</td>
<td>18</td>
<td>7</td>
<td>5.8</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: 50/889 55/883 | -2.5 | 26.2 | 0.91 | [0.62;1.33] | p=0.62

Heterogeneity: p=0.03  
I²=64%
### b. SCLC: effect of radiotherapy according to age

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard Ratio</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 or less</td>
<td>487/561</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>55-59</td>
<td>417/472</td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>60-64</td>
<td>441/490</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>65-69</td>
<td>334/372</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>70 +</td>
<td>177/199</td>
<td></td>
<td>1.07</td>
</tr>
<tr>
<td>Total</td>
<td>1856/2094</td>
<td></td>
<td>0.84</td>
</tr>
</tbody>
</table>

Test for trend : $p = 0.01$

CT+RT better       | CT better       

CT+RT effect: $p = 0.0007$

*Pignon et al NEJM, 1992;327:1618*
Overall Survival

HR = 0.86 [0.76-0.98]  \( p < 0.03 \)

At risk
- 932  775  624  450  308  181
- 935  774  602  432  286  164

Years

Chemotherapy
Control

NEJM 2004;350:351
 Overall survival

HR: 0.87 (0.81-0.93), p<0.0000001

Absolute benefit at 5 yrs 4%, from 60% to 64%

NSCLC-MA: Surgery  vs Surgery + CT

Patients at Risk

<table>
<thead>
<tr>
<th>Survival time (in years)</th>
<th>Surg alone</th>
<th>Surg+chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4068</td>
<td>4079</td>
</tr>
<tr>
<td>1</td>
<td>3585</td>
<td>3607</td>
</tr>
<tr>
<td>2</td>
<td>3043</td>
<td>3074</td>
</tr>
<tr>
<td>3</td>
<td>2539</td>
<td>2584</td>
</tr>
<tr>
<td>4</td>
<td>2034</td>
<td>2137</td>
</tr>
<tr>
<td>5</td>
<td>1548</td>
<td>1665</td>
</tr>
<tr>
<td>6</td>
<td>779</td>
<td>835</td>
</tr>
<tr>
<td>7</td>
<td>358</td>
<td>389</td>
</tr>
<tr>
<td>8</td>
<td>103</td>
<td>108</td>
</tr>
</tbody>
</table>

Lancet 2010; 375:1267
c. Ongoing and future projects

Head and Neck Cancer

• **HNSCC**: Update of the meta-analysis (MA) of chemotherapy (CT) and update of the network
• **HNSCC**: Study of the prognostic and predictive value of HPV in the two meta-analyses (MARCH, MACH-NC)
• **HNSCC and NPC**: new update of the 3 MA, MA on targeted therapy, update of the two network MA.

Non-Small Cell Lung Cancer

• Ongoing meta-analyses on the addition of CT or targeted therapy to concomitant radiochemotherapy in locally advanced disease
a. Head & Neck SCC: analysis of a network of 98 trials, about 24,000 patients

- In locally advanced disease, 3 out of 5 treatments were superior to RT alone: Concomitant CT-RT, modified fraction RT and induction CT (5FU + platin) plus RT.

- Concomitant CT-RT was considered as the standard treatment and place of concomitant CT + modified RT is unknown.

- In this setting with more than 2 treatments:
  - What is the best treatment?
  - Which two treatments should be compared in the next trial?

⇒ A network meta-analysis will allow the integration of all the direct and indirect comparisons available
a. Head & Neck SCC: network of trials

Thick line = > 10 trials
Thin line = 5-10 trials
Dotted line = 1-2 trials

CT = Chemotherapy
IC = Induction CT
AC = Adjuvant CT
RT = Radiotherapy
CRT = Concomitant CT-RT
MF = Modified fractionation

Blanchard et al, J Clin Epidemiol 2011;64:985
a. Head & Neck SCC: network of trials

Results based on all direct and indirect comparisons

Probability to be the best treatment:

- **Concomitant CT + modified fractionation** RT = 95%
- **Concomitant CT-RT** = 5%

Diagram:

- CRT
- MF-RT
- HR=0.87
- HR=0.80
- HR=0.69
e. Study of chemotherapy compliance in SCLC*

- In some trials comparing early and/or short duration radiotherapy to late or standard duration radiotherapy, the compliance to chemotherapy is not the same in both arms.
- The benefit of early/short duration RT is restricted to the trials with good compliance to chemotherapy in both arms.

* De Ruysscher et al, Thorac Oncol 2011;6(Suppl. 6):S641