Cost-effectiveness of Particle Therapy

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PTCOG 49, Japan
Some facts…

• RT is a relatively cheap treatment modality (5% of costs of global oncology budget, advanced photon RT ~ 8000 euros)

• Particle therapy is about 2.4 times more expensive than most sophisticated RT with photons (Goitein & Jermann 2003)

• Investment costs PT facility about € 140 million

• Potential advantages PT regarding superior dose distributions are clear!

• However clinical efficacy PT not EVB proven yet…

• Once decided to build a PT facility it will take several years before first patients can be treated
Overview

• Cost
• Economic evaluation
• (Cost-)effectiveness PT
• Summary and conclusion
Costs

- **Construction (capital)**
  - project management, equipment, building, treatment infrastructure (CT, TPS etc.)

- **Operation costs (running cost)**
  - personnel, utilities, maintenance, business cost

- **Unit cost of treatment/cost per fraction**
  - depending on construction/operation costs and reimbursement system (agreements government/health insurances: can be highly variable between countries/regions)
Some factors of influence on costs:

- # patients/year
- # fractions/year
- # treatment rooms
- # operation time/day
- # operation days/week
- time per fraction
- reimbursement per treatment
- preparation time per patient
- Maintenance
- equipment (scanning beam, gantry, horizontal beam etc)
- treatment time
- irradiation time
- downtime
- required personnel
- repayment of loan
- etc
- …


Interestingly, investment in additional high costly equipments (i.e. carbon ions gantries, providing the technical feasibility) will lead to an increase of the mean treatment cost, but may improve the cost-effectiveness of the facility when increasing the proportion of patients with indications expected to benefit highly from the innovation.
Some results Cost model Etoile (Pommier et al)

Mean cost per patient and per session

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>« Ref»</th>
<th>Boost</th>
<th>Exclusive</th>
<th>hypofraction</th>
<th>Reduced session duration</th>
<th>1 beam/session</th>
<th>1 shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient (€)</td>
<td>21,000</td>
<td>19,805</td>
<td>26,122</td>
<td>17,287</td>
<td>17,033</td>
<td>13,114</td>
<td>33,194</td>
</tr>
<tr>
<td>Session (€)</td>
<td>1600</td>
<td>1650</td>
<td>1462</td>
<td>2055</td>
<td>1287</td>
<td>1018</td>
<td>2534</td>
</tr>
</tbody>
</table>

**Scenarios for the simulation:**
- « boost » vs. « exclusive » C ion therapy
- 13 vs. 10 mean # of sessions per patient
- mean session time duration: 30 vs. 20 min
- Mean # of beam per session: 2.3 vs 1
How further?

• A new treatment/technology is considered to be accepted as compared to standard treatment if:
  – Better survival rates
  – and/or a better QoL
  – Acceptable costs
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Health Technology Assessment

- Trade-off between costs and effectiveness
- To inform decisions regarding
  - Whether or not to adopt the new technology
  - Whether or not to perform additional research
- Cost control/management and efficiency
Economics: some basics

How societies meet their wants from limited resources

Three key questions:

– *What* should we produce?
  - *VALUE*

– *How* should we produce what is to be produced?
  - *EFFICIENCY*

– How to *distribute* what is to be produced between individual citizens?
  - *FAIRNESS*
What is efficiency?

1. Technical efficiency
   - do not waste resources

2. Allocative efficiency
   - produce products which people value most

3. Cost–effectiveness
   - produce each product at least cost
### Tool to assess efficiency: economic evaluation

<table>
<thead>
<tr>
<th>Are both costs (input) and effects (output) examined?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only effects</td>
<td>Only costs</td>
</tr>
<tr>
<td>Is there a comparison of two alternatives?</td>
<td>No</td>
<td>Outcome description</td>
</tr>
<tr>
<td></td>
<td>Efficacy or effectiveness</td>
<td>Cost analysis</td>
</tr>
</tbody>
</table>
## Types of full economic evaluation

<table>
<thead>
<tr>
<th>Method</th>
<th>Costs</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-minimisation analysis (CMA)</td>
<td>Monetary units (€)</td>
<td>No difference in effects</td>
</tr>
<tr>
<td>Cost-effectiveness analysis (CEA)</td>
<td>Monetary units (€)</td>
<td>Natural units (life years gained, point blood pressure, etc)</td>
</tr>
<tr>
<td>Cost-utility analysis (CUA)</td>
<td>Monetary units (€)</td>
<td>Utilities and Quality Adjusted Life Years (QALYs)</td>
</tr>
<tr>
<td>Cost –benefit analysis (CBA)</td>
<td>Monetary units (€)</td>
<td>Monetary units (€)</td>
</tr>
</tbody>
</table>
Quality Adjusted Life Year (QALY)

<table>
<thead>
<tr>
<th>Utility</th>
<th>Life years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>4</td>
</tr>
<tr>
<td>0.7</td>
<td>3</td>
</tr>
<tr>
<td>0.2</td>
<td>4</td>
</tr>
</tbody>
</table>

Total QALY: 6.5
(area under the curve)

4 * 0.9 = 3.6
3 * 0.7 = 2.1
4 * 0.2 = 0.8
Full economic evaluation:
Relevant costs and effects for each alternative (using the same methodology)

Incremental cost-effectiveness ratio: $(\text{Costs}_A - \text{Costs}_B)/(\text{Effects}_A - \text{Effects}_B)$

Choice

Cost A → Programme A → Effects A
Cost B → Programme B → Effects B

Difference in costs? $(\text{Costs}_A - \text{Costs}_B)$
Difference in effects? $(\text{Effects}_A - \text{Effects}_B)$
Incremental analysis

\[ \Delta \text{Costs} = \frac{56000}{8} - \frac{50000}{10} = 7000 - 5000 = 2000 \]

\[ \Delta \text{Effect} = \frac{56000}{8} - \frac{42000}{12} = 7000 - 3500 = 3500 \]
Cost-effective or not?

€5000/ QALY or LYG acceptable?

YES!!
Depending on benchmarked (varies between countries between 20.000-100.000 euros)

Ceiling-ratio of €50.000 is often used
Study design: two approaches

- **Trial based economic evaluation**
  - Use economic data collected alongside a single trial
  - Only right approach if the trial truly reflects the decision context

- **Model based economic evaluation**
  - Use a model as an analytical framework to synthesize evidence relevant to the decision problem from different sources
Different model based approaches

- Decision tree
- Discrete event simulation
- Markov model
Markov model

HEALTH STATES

T0
- Full health
- Illness
- Death

TRANSITIONS

T1
- Full health
- Illness
- Death

T2
- Full health
- Illness
- Death

CYCLETIME
Overview

- Cost
- Economic evaluation
- *(Cost-)effectiveness PT*
- Summary and conclusion
Systematic literature review*:

- Only 14 potential papers were retrieved
- 4 reported on cost-effectiveness 1-4


Some results....

• CUA based on Markov model for breast, prostate, H&N and medulloblastoma (Lundkvist et al, 2005):
  • Average cost QALY ≈ € 10,130
  • CEA skull base chordoma (Jäkel et al. 2007):
  • € 7692 per LYG (life year gained)

• Both studies high level of uncertainty: many assumptions, non-optimal methodology

CUA= cost-utility analysis
CEA=cost-effectiveness analysis
Conclusion review on cost-effectiveness PT

Cost-effectiveness:
- Only little evidence based on available data
- Lack of calculations of the cost per QALY
- No firm conclusion could be drawn

.... therefore recently several cost-effectiveness on PT studies were initiated for:
- Lung cancer
- Prostate cancer
- Head&Neck cancer
Example: NSCLC

Comparators:
1) Resection: meta-analysis
2) SBRT: N=179 refusal surgery (RS) out of 544 (4 studies)
   100 RS separately reported (1 study)
3) Proton: N=31 RS out of 126 (3 studies)
   results RS not separately reported
4) Carbon-ion:N=55 RS out of 210 (3 studies)
   results RS not separately reported

1) 3DRT: N>1000
2) SBRT: N>500
3) Proton: N=180 (5 studies)
4) Carbon-ion: N=210 (3 studies)

1) 3DRT: N>500
2) SBRT: N=12 out of 62 patients (2 studies)
   results stage II not separately reported
3) Proton: N=11 out of 86 patients (2 studies)
   results stage II not separately reported
4) Carbon-ion: N=0

1) Concurrent chemoradiation: meta-analysis
2) Proton: N=16 out of 86 patients (2 studies)
3) Proton + chemo: N=16 (abstract)
4) Carbon-ion: N=0
Research question

Which of the following treatment modalities is the most cost-effective for stage I inoperable non-small cell lung cancer (NSCLC)?

- Conventional radiotherapy (CRT)
- Stereotactic body radiotherapy (SBRT)
- Proton therapy
- Carbon-ion therapy
Method

- Systematic literature review and meta-analysis
- Cost-analysis
- Decision-analytic model (Markov)
  - Health care/ Societal perspective; cost-analysis of initial treatments
  - Total expected costs and outcome (QALYs) per patient 5 year period
  - Probabilistic sensitivity analysis
  - Additional sensitivity analysis only of recent studies
Model structure

Initial health state before treatment

- during treatment, no acute adverse events ≥ grade 3
- during treatment, pneumonitis ≥ grade 3
- during treatment, oesophagitis ≥ grade 3
- treatment-related death

• After treatment, alive without dyspnoea ≥ grade 3
• After treatment, alive with dyspnoea ≥ grade 3

Death
Results: Meta-analysis

- For stage I inoperable NSCLC
- 23 studies included
- Corrected for % of medically inoperable patients
- Pooled estimates for toxicity, disease specific survival and overall survival
## Model inputs: costs (2007 price level)

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>€ 8148</td>
<td>5996 - 10889</td>
</tr>
<tr>
<td>SBRT</td>
<td>€ 3259</td>
<td>1815 - 5881</td>
</tr>
<tr>
<td>Proton</td>
<td>€ 15473</td>
<td>11835 - 19673</td>
</tr>
<tr>
<td>Carbon-ion</td>
<td>€ 8774</td>
<td>4844 - 16602</td>
</tr>
<tr>
<td>Acute pneumonitis</td>
<td>€ 125</td>
<td>89 - 172</td>
</tr>
<tr>
<td>Acute oesophagitis</td>
<td>€ 1320</td>
<td>1124 - 1560</td>
</tr>
<tr>
<td>Irreversible dyspnoea</td>
<td>€ 1045</td>
<td>867 - 1254</td>
</tr>
<tr>
<td>Follow-up first cycle</td>
<td>€ 237</td>
<td>fixed, based on protocol and</td>
</tr>
<tr>
<td>second cycle / afterwards</td>
<td>€ 118 / 59</td>
<td>Dutch manual cost research</td>
</tr>
<tr>
<td>Death due to cancer</td>
<td>€ 21675</td>
<td>17969 - 25891</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>€ 15449</td>
<td>11753 - 19860</td>
</tr>
</tbody>
</table>
# Cost Analysis

**Operational model: base case**

<table>
<thead>
<tr>
<th></th>
<th>Combined protons + C-ions</th>
<th>Protons</th>
<th>Photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working days</td>
<td>5 days week</td>
<td>5 days week</td>
<td>5 days week</td>
</tr>
<tr>
<td>Quality assurance and calibration</td>
<td>06:00-08:00</td>
<td>06:00-08:00</td>
<td>06:00-08:00</td>
</tr>
<tr>
<td>Operating hours patient treatment</td>
<td>08:00-22:00</td>
<td>08:00-22:00</td>
<td>08:00-22:00</td>
</tr>
<tr>
<td>Contingency / Research</td>
<td>22:00-24:00 + Sat.</td>
<td>22:00-24:00 + Sat.</td>
<td>22:00-24:00 + Sat.</td>
</tr>
<tr>
<td>Hours per day available for patient treatment</td>
<td>14,0 h.</td>
<td>14,0 h.</td>
<td>14,0 h.</td>
</tr>
<tr>
<td>Days of operation p.a.</td>
<td>250 d.</td>
<td>250 d.</td>
<td>250 d.</td>
</tr>
<tr>
<td>Hours p.a. available for patient treatment</td>
<td>3,500 h.</td>
<td>3,500 h.</td>
<td>3,500 h.</td>
</tr>
<tr>
<td>Minutes p.a. available for patient treatment</td>
<td>210,000 min.</td>
<td>210,000 min.</td>
<td>210,000 min.</td>
</tr>
<tr>
<td>Average time per fraction (slot)</td>
<td>18 min.</td>
<td>18 min.</td>
<td>10 min.</td>
</tr>
<tr>
<td>Maximum fractions p.a. per treatment room</td>
<td>11,667 fra.</td>
<td>11,667 fra.</td>
<td>21,000 fra.</td>
</tr>
<tr>
<td>Chosen number of treatment rooms</td>
<td>3 rooms</td>
<td>3 rooms</td>
<td>2 rooms</td>
</tr>
<tr>
<td>Treatment room utilisation</td>
<td>98%</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment room availability</td>
<td>95%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Total number of fractions p.a. (realistic scenario)</td>
<td>32,585 fra.</td>
<td>33,614 fra.</td>
<td>41,160 fra.</td>
</tr>
<tr>
<td>Average number of fractions per patient</td>
<td>18 fra.</td>
<td>20 fra.</td>
<td>18 fra.</td>
</tr>
<tr>
<td>Total number of patients p.a.</td>
<td>1810</td>
<td>1681</td>
<td>2287</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Combined protons + C-ions</th>
<th>Protons</th>
<th>Photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital Cost</td>
<td>138,600,000 €</td>
<td>94,930,000 €</td>
<td>23,430,000 €</td>
</tr>
<tr>
<td>Assumed lifecycle in years</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Running Cost p.a.</td>
<td>32,138,027 €</td>
<td>21,800,383 €</td>
<td>8,800,850 €</td>
</tr>
<tr>
<td>Realistic Scenario: Total cost p.a.</td>
<td>36,758,027 €</td>
<td>24,964,716 €</td>
<td>9,581,850 €</td>
</tr>
<tr>
<td>Total cost per fraction</td>
<td>1,128,07 €</td>
<td>742,69 €</td>
<td>232,80 €</td>
</tr>
</tbody>
</table>
Results: costs for initial treatment per patient (inoperable stage I NSCLC)

- CRT: €0-€5,000 (35 fractions, 10 min/fraction)
- SBRT: €0-€5,000 (4 fractions, 40 min/fraction)
- Protons: €5,000-€15,000 (10 fractions, 30 min/fraction)
- C-ions: €5,000-€20,000 (4 fractions, 40 min/fraction)
Results: cost-effectiveness (all studies)

Exploring decision uncertainty and areas for future research. Cancer Treat Rev. 2010 Mar 17
Results: cost-effectiveness (all studies)

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Exploring decision uncertainty and areas for future research. Cancer Treat Rev. 2010 Mar 17
Results: cost-effectiveness (all studies)

C-ions slightly more effective and more expensive than SBRT: cost-effectiveness ratio €107,639 per extra QALY

Results: cost-effectiveness NSCLC stage I inoperable (excl studies <2005)

Exploring decision uncertainty and areas for future research. Cancer Treat Rev. 2010 Mar 17
Results: cost-effectiveness

Expected total costs per patient over 5 years

Expected QALYs per patient over 5 years

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Summary

- Cost–effectiveness is more than just look at cost issues
- Cost as well as effectiveness are taken into account
- At least 2 alternatives has to be compared
- Model based economic evaluations can give ‘quick’ recommendation for medical decision-making
What do we need NOW to prove EVB (cost-) effectiveness?

- More research, preferably with large N and follow-up at least 5 years
- Decision whether or not to build a particle facility is based on more indications
  - Examine cost-effectiveness for different NSCLC stages and other indications
- Model based economic evaluations
- With an adequate methodology
- Int. multidisciplinary project team, uniform databases!
- As much real data to decrease uncertainty
- Long term effects from broad health care perspective
Future perspective in (cost-)effectiveness of PT

- Improvement in equipment
- More hospital based facilities
- Number of treated patients will be increase
- Possibilities to perform high quality international multicentric research (in silico trials, prospective trials, RCT’s ??)
- Likely to expect clinical EVB evidence on efficacy in future…….
Current Clinical Evidence for Proton Therapy

Michael Brada, BSc, FRCP, FRCR,* Madelon Pijls-Johannesma, MSc, PhD,† and Dirk De Rysscher, MD, PhD*


The current lack of evidence for benefit of protons should provide a stimulus for continued research. Well designed in silico clinical trials using validated normal tissue complication probability-models are important to predict the magnitude of benefit for individual tumor sites but the future use of protons should be guided by clear evidence of benefit demonstrated in well-designed prospective studies, away from commercial influence, and this is likely to require international collaboration.