Costs, effectiveness and cost-effectiveness of hadron therapy

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2nd Workshop on Hadron Beam Therapy, Erice 2011
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 € 100-140 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
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
- .......
### 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><strong>3 rooms</strong></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 szenario)</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><strong>18 fra.</strong></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>

**Capital Cost**

<table>
<thead>
<tr>
<th></th>
<th>€</th>
<th>€</th>
<th>€</th>
</tr>
</thead>
<tbody>
<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 Szenario: Total cost p.a.</td>
<td>36,758,027 €</td>
<td>24,964,716 €</td>
<td>9,581,850 €</td>
</tr>
</tbody>
</table>

**Total cost per fraction**

<table>
<thead>
<tr>
<th></th>
<th>€</th>
<th>€</th>
<th>€</th>
</tr>
</thead>
<tbody>
<tr>
<td></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 (35 fractions, 10 min/fraction) €15,000
- SBRT (4 fractions, 40 min/fraction) €20,000
- Protons (10 fractions, 30 min/fraction) €0
- C-ions (4 fractions, 40 min/fraction) €5,000
The clinical efficacy of particle therapy as opposed to best available photon therapy (eg IMRT) is not proven (yet), mainly due to a lack of RCT’s and poor reporting of results.

Results literature search 12 databases
(Lodge et al 2007)

Number of relevant papers by topic, identified out of 5089 references retrieved by search strategy of the review

- Protons final results: 40 studies
- Ions final results: 22 studies

restrictions:
- < 20 patients
- FU < 2 years

563
140
54
10

neutron
proton
ion
economics
Results protons and ions per indication

Total number of patients included in studies per tumor site

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Protons</th>
<th>Ions</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;N</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Prostate</td>
<td>1642</td>
<td>96</td>
</tr>
<tr>
<td>Ocular</td>
<td>1343</td>
<td>73</td>
</tr>
<tr>
<td>Gastro-intest.</td>
<td>311</td>
<td>88</td>
</tr>
<tr>
<td>Lung</td>
<td>205</td>
<td>205</td>
</tr>
<tr>
<td>CNS</td>
<td>777</td>
<td>405</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>47</td>
<td>57</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Bladder</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>
Results protons and ions per indication

Lodge et al, 2007: total number of patients included in studies for H&N, prostate and lung
**Results protons and ions per indication**

Update 2010/2022: total number of patients included in studies for H&N, prostate and lung

- **H&N:**
  - Proton: 33 → 185
  - Ion: 37 → 333
- **Prostate:**
  - Proton: 1042 → 2075
  - Ion: 96 → 903
- **Lung:**
  - Proton: 88 → 203
  - Ion: 205 → 231
<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Protons result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head&amp;Neck</td>
<td>No firm conclusion</td>
</tr>
<tr>
<td>ACC (loc.adv.)</td>
<td>-</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>No firm conclusion</td>
</tr>
<tr>
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<td>No firm conclusion</td>
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<td>No firm conclusion</td>
</tr>
<tr>
<td>Bladder</td>
<td>No firm conclusion</td>
</tr>
<tr>
<td>Lung (non-small)</td>
<td>No firm conclusion</td>
</tr>
<tr>
<td>Prostate</td>
<td>Comparable to phot.</td>
</tr>
<tr>
<td>CNS</td>
<td>Comparable to phot.</td>
</tr>
<tr>
<td>Skull base chord.</td>
<td>Superior to photons 5y LC 63% vs 50%</td>
</tr>
<tr>
<td>Ocular</td>
<td>Superior to photons</td>
</tr>
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<td>Tumor location</td>
<td>Protons result</td>
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<td>Ocular</td>
<td>Superior to photons</td>
</tr>
</tbody>
</table>
Clinical evidence: Meta-analyses

- Systematic reviews
- Stratification per tumor site/stage/histology
- Correction for confounders e.g. % of medically inoperable patients
- Pooled estimates for toxicity, disease specific survival and overall survival

Examples:
- Inoperable stage I NSCLC (grutters et al 2010)
- H&N cancer: Oropharyngeal ca. and Mucosal Melanoma (Ramaekers et al, 2010)
Results: Oropharyngeal cancer (2y DFS)
Proton therapy vs IMRT

Slater 2005 (n=29)
Protons pooled*

Huang 2003 (n=41)
Chao (po) 2004 (n=43)
Chao 2004 (n=31)
Yao 2006 (n=66)
Garden 2007 (n=51)
Schoenfeld 2008 (n=64)
Rusthoven 2008 (n=32)
Eisbruch 2009 (n=67)
Daly 2010 (n=107)
IMO pooled

(I² = 49.9%)

Protons: 81% (66 – 96%)
IMRT: 87% (81 – 93%)
P = NS

* Consisted of only 1 study and therefore no pooled estimate is reported

□ = se retrieved from study, ■ = se calculated (proportion method), ◆ = se calculated (Peto method),
◆ = se calculated (Peto method assuming maximum % censoring reported in the particular analysis)
Results: Malignant Mucosal Melanomas (5y OS)
Carbon-ion therapy vs Conventional photon therapy

C-ion (N=157)
C-ions: 44% (32–56%)

CRT (N=696)
CRT: 25% (21–29%)
P = 0.007
Particle therapy: ongoing discussion

Proton beam therapy: Too expensive to become true?

On Equipoise and Emerging Technologies

Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Proton Therapy Should Be Tested in Randomized Trials

Protons and Parachutes

MAGICAL PROTONS?

Randomized controlled trials in health technology assessment: Overkill or overdue?

An Alternative View

Proton therapy is too expensive for the minimal potential improvements in outcome claimed

Personal View

A Patient’s Perspective on Randomized Clinical Trials for Proton Radiotherapy

The Potential Clinical Advantages of Charged Particle Radiotherapy using Protons or Light Ions
How to proceed?

• Trade-off between costs and effectiveness
  – Cost-effectiveness analysis
• To inform decisions regarding
  – Whether or not to adopt the new technology
  – Whether or not to perform additional research
Cost-effectiveness analysis

= The comparative analysis of alternative courses of action in both their costs and consequences
## Characteristics of cost-effectiveness analysis

<table>
<thead>
<tr>
<th></th>
<th>Only consequences</th>
<th>Only costs</th>
<th>Both costs &amp; consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comparison</td>
<td>Outcome description</td>
<td>Cost description</td>
<td>Cost-outcome description</td>
</tr>
<tr>
<td>Comparison</td>
<td>Efficacy / effectiveness evaluation</td>
<td>Cost analysis</td>
<td>Full cost-effectiveness analysis</td>
</tr>
</tbody>
</table>

Adapted from: Drummond et al. Methods for the economic evaluation of health care programmes, 2005
Cost-effectiveness analysis

- Incremental analysis
  - Incremental effect on health
    - $\text{Effectiveness} = \text{Effectiveness}_A - \text{Effectiveness}_B$
    - E.g. $\text{Effectiveness} = 4 \text{ life years} - 2 \text{ life years} = 2 \text{ life years}$
  - Incremental costs
    - $\text{Costs} = \text{Costs}_A - \text{Costs}_B$
    - E.g. $\text{Costs} = €20.000 - €4.000 = €16.000$
  - Incremental cost-effectiveness ratio
    - $\text{ICER} = \frac{\text{Costs}}{\text{Effectiveness}}$
    - E.g. $\text{ICER} = \frac{€16.000}{2 \text{ life years}} = €8.000 / \text{ life year gained}$
Cost-effectiveness particle therapy

Systematic literature review*:

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


Update 2011:
- Konski, 2007
- Grutters, 2010
- Mobaraki, 2010

Some results....

- Analysis based on decision model for breast, prostate, head and neck, and medulloblastoma (Lundkvist et al, 2005):
  - Average cost per quality adjusted life year
    \[ \approx € 10,130 \]

- Skull base chordoma (Jäkel et al, 2007):
  - € 7,692 per life year gained

- Both studies high level of uncertainty: many assumptions, suboptimal methodology
Conclusion review on cost-effectiveness

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

..... therefore cost-effectiveness studies were initiated for:
• Lung cancer
• Prostate cancer
• Head&Neck cancer
Example: lung cancer

- Cost-effectiveness of particle therapy in the treatment of lung cancer
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 review, meta-analysis (Grutters et al, R&O 2010)
- Cost-analysis (Peeters et al, R&O 2010)
- Decision-analytic model (Markov)
  - Health care perspective
  - Total expected costs and outcome (QALYs) per patient over a 5 year period
  - Probabilistic sensitivity analysis to examine existing uncertainty
  - Additional sensitivity analysis only of recent studies
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
Costs for initial treatment per patient

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

CRT less effective and more expensive than all other treatments.

Protons slightly less effective and more expensive than c-ions and SBRT.

C-ions slightly more effective and more expensive than SBRT:

Cost-effectiveness ratio €67,257 per extra QALY.
Results: cost-effectiveness (all studies)

high level of uncertainty!
Results: cost-effectiveness (excluding studies <2005)

Expected costs per patient over 5 years

- Protons cost €81,479 per QALY
- Carbon-ions cost €36,017 per QALY

Expected QALYs per patient over 5 years

SBRT
- Protons
- Carbon-ions
Conclusion

- Cost-effectiveness results highly uncertain / dependent on included studies
- For stage I inoperable NSCLC unable to conclude that particle therapy is cost-effective compared to SBRT
- More evidence needed to reduce uncertainty
  - Wait for new evidence? Sunk costs versus costs of delay
  - Evidence of toxicity (international particle therapy registry)
  - Particle therapy may be more beneficial in other indications
Summary

- Cost-effectiveness is more than just cost issues
- Cost as well as effectiveness are taken into account
- At least two alternatives have to be compared
- Model-based economic evaluations can give ‘quick’ recommendation for medical decision-making