Author's response to reviews

Title: A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy

Authors:

Valesca P Retel (v.retel@nki.nl)
Lisette van der Molen (l.vd.molen@nki.nl)
Frans JM Hilgers (f.hilgers@nki.nl)
Coen RN Rasch (c.rasch@nki.nl)
Annemiek AAMHJ l'Ortye (a.lortye@nki.nl)
Lotte MG Steuten (l.m.g.steuten@utwente.nl)
Wim H van Harten (w.v.harten@nki.nl)

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Author's response to reviews: see over
Reviewer's report

Title: A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy

Version: 1 Date: 6 June 2011

Reviewer: Kai Johannes K.J. Lorenz

Reviewer's report:
The authors conducted a cost effectiveness analyses in patients who underwent a cocomitant chemo-radiotherapy because of advanced head-and-neck cancer. A group of 53 patients with no further treatment was used as a control group, whereas 37 patients in the second group received a rehabilitation training with swallowing and mouse opening exercises. A cost effectiveness analyses was performed. I could be shown, that the rehabilitation training resulted in fewer hospital admissions and less tube dependency. The total coasts for both study arms were nearly equal. The rehabilitation training showed the highest probability of being cost-effective when compared to usual care.

The paper is well written and understandable, The topic is of a high interest to everybody dealing with cancer patients under rehabilatory aspects. The statistical methods are explained clearly.

In the discussion the limits of the study like various different effects of the rehabilitation program, the not compleatly comparable study groups are explained.

The conclusion is clearly defined, all important literature is cited. The figures are clear.

At all a very interesting manuscript, worthwhile to be published in the BMC

We would like to thank the reviewer for considering our study as interesting.
Reviewer: Keng Ho Pwee

Reviewer’s report:

1) This is a well-written report of an economic evaluation of an adjunctive intervention for a specific group of patients. I think the manuscript can be accepted for publication with just a few points of clarification required. These are listed below.

We would like to thank the reviewer for considering our study as interesting. The constructive comments were very helpful in improving the paper.

Minor essential revisions

2) The abstract should mention the perspective of the economic evaluation in the methods.

Answer to the reviewer:

This has been added.

Changes in the text, page 3:

This study presents cost-effectiveness analyses of a preventive (swallowing) exercise program (PREP) compared to usual care (UC) from a societal perspective.

3) In the conclusion of the abstract, replace ‘highest probability’ with ‘higher probability’ since it is a comparison between two states. This should also be done in the conclusion (pg 14).

Answer to the reviewer:

This has been changed.

4) Pg 5, Background - replace ‘contribute’ with ‘contribution’ in the last line of the first paragraph.

Answer to the reviewer:

This has been changed.

5) Pg 6, Case description - ‘... as and adjunct ...’ to change to ‘as an adjunct’.

Answer to the reviewer:

This has been changed.
6) Pg 7, Case description - it's mentioned that 'Since no significant differences in QoL and functional outcomes were found between the two arms, for the present cost-effectiveness study, both PREP arms were taken together.' That handles the effectiveness part, but what about costs? If the costs were also similar, that should be mentioned. If the costs were not similar, then was it reasonable to still combine the arms?

Answer to the reviewer:

This is correct, this has been changed in the text

Changes in the text, page 6:

*Since no significant differences in QoL, costs and functional outcomes were found between the two arms, for the present cost-effectiveness study both PREP arms were taken together.*

7) Pg 8, Health effects - The only statement on how quality of life was evaluated was 'The quality of life of patients treated with CCRT was examined by Ackerstaff et al, 2009'. While the details may be available in that paper, it would still be useful to the reader if a bit more detail on this (maybe an extra line or two) explaining the method could be included in this paper.

Answer to the reviewer:

This is correct, this has been changed in the text

Changes in text, page 7:

*For UC during treatment the QoL result of 7 weeks was incorporated (0.517), for UC after treatment, the QoL result of 12 months was taken (0.754).*

8) Pg 8, Health effects - same statement as above - the correct reference appears to be ref. no. 3 rather than 4. Might need to re-check all the reference numbering.

We checked the reference numbering

9) Table 3 - is the ICER 3167 Euros rather than 3197 Euros? Looks like a typographical error since 285 divided by 0.09 is 3166.6666 ...

Answer to the reviewer:

This is correct; the numbers might not add up to 100% because of rounding. We added this in the table caption, and the numbers with 4 decimals, so that one can calculate this.

Changes in text, Table 3:

*The numbers might not add up to 100% because of rounding; 284.8849/0.0891=3197.3614

10) Pg 10, Mean results - it would be useful to mention the base case ICER in the mean results.

Answer to the reviewer:

This has been added.

Changes in text, page 10:

*In comparison to UC, the PREP for advanced head and neck tumours costs € 3,197 per QALY gained and was found to be more effective and slightly more costly.*
11) Pg 10, Uncertainty analyses - it is not apparent to me how the sentence 'When focusing on quality adjusted survival, the PREP has the highest [should amend to 'higher'] probability of being cost-effective as long as the willingness to pay threshold for 1 additional QALY is at least €3,200 Euros/QALY (see Fig 1 and 2)' follows from Fig 1. and Fig 2. Please be more explicit in the text.

Answer to the reviewer:

Cost-effectiveness acceptability curves (CEACs) to show decision uncertainty are presented. CEACs show the probability that a pathway has the highest net monetary benefit, and thus is deemed cost-effective, for a range of Willingness to Pay (\(\lambda\)) values for one additional QALY, also referred as the ceiling ratio. This definition involves a Bayesian definition of probability i.e. the probability that the hypothesis ('PREP is cost-effective compared to UC') is true given the data. The two curves therefore always sum to 100% for one given value of \(\lambda\).

Changes in text:

Methods, page 7:

CEACs show the probability that a pathway has the highest net monetary benefit, and thus is deemed cost-effective, for a range of Willingness to Pay (\(\lambda\)) values for one additional QALY, also referred as the ceiling ratio. This definition involves a Bayesian definition of probability i.e. the probability that the hypothesis ('PREP is cost-effective compared to UC') is true given the data. The two curves therefore always sum to 100% for one given value of \(\lambda\).

Results, page 10:

When focusing on quality adjusted survival, the PREP has a higher probability of being cost-effective compared to UC, as long as the willingness to pay threshold for 1 additional QALY is at least €3,200/QALY (see Figure 1 and 2).

12) Fig 2. - I was not sure why there were two cost-effectiveness acceptability curves; I would have thought that there would be one curve based on the comparison between PREP and UC. However, I am not familiar with CEACs and I am recommending this part be reviewed by someone more adequately qualified.

Hopefully with the adjustments regarding point 11, the explanation of the two graphs is now better to understand.

13) Fig 3. - as a corollary to the above comment, I am similarly not sure about having separate curves for PREP and UC in this diagram, rather than one curve for each of the different situations.

Answer to the reviewer:

The reviewer is correct, this could be more explained. (We first decided to leave this out, for the overall clarity of the paper. We added now more explanation in the method section) Figure 3 shows the cost-effectiveness acceptability frontiers (CEAF) which shows the portion of competing CEACs that have the maximum expected value. We also present the findings as cost-effectiveness acceptability frontiers that illustrate the probability of any intervention being optimal compared to all its alternatives. The optimal intervention is defined as the one with the highest expected net health benefit. Cost-effectiveness frontiers also illustrate the crossover when one intervention is substituted by another as the one with the highest probability of being optimal, and therefore provide useful information for policy makers.
Changes in the text, page 8:

For various scenarios regarding costs and QALYs, we also present the findings as cost-effectiveness acceptability frontiers that illustrate the probability of any intervention being optimal compared to its alternative. The optimal intervention is defined as the one with the highest expected net health benefit. Each cost-effectiveness frontier also illustrates the potential crossover when one intervention is substituted by another as the one with the highest probability of being optimal, and therefore provides useful information for policy makers.

14) Pg 12, Discussion - The second paragraph notes that 'a quarter of the patients in the usual care cohort needed a feeding tube at 12 months, in contrast to only 3% in the PREP cohort. This suggests that patients in the UC group are more likely to suffer from aspiration rather than those in PREP, ...' However, Table 1 shows that the UC group had 8 tube dependent patients before CCRT compared to 0 in the PREP group. The UC group also had later stage patients compared to the PREP group. The discussion comments should be amended to take this into account.

Answer to the reviewer:

We agree that this distribution is a bit skewed; however, there is no significant difference between the patients with feeding substitutes versus tumour stage. We added more explanatory text in the discussion.

Changes in the text, page 12,13:

Another limitation of this cost-effective analysis is that the patient distribution in the two cohorts is not completely comparable. Although all patients had stage III or IV disease, the distribution according to stage (more stage IV in the UC group) and anatomical site (no oral cavity/oropharynx in the UC group) was somewhat different. Next to this, the chemotherapy type and scheme in both cohorts was identical except with respect to the application of radiotherapy. In the IV arm of the study of Ackerstaff et al., roughly one fourth of the patient population was treated with intensity-modulated radiotherapy (IMRT), whereas in all patients in the study of Van der Molen et al. IMRT was applied. These differences could have influenced the functional outcomes in the two cohorts. Exact data about these aspects unfortunately are not retrievable. But we are sufficiently confident, that in the study of Ackerstaff et al. most of the patients that were disease free at 1-year, indeed received IMRT.

15) Table 2 - ‘Succes rates’ is mispelled. Some of the abbreviations are also not spelled out at the bottom, while some are - would be good to be consistent. Utilities low, Utilities high and Costs: the rows should be continuous rather than divided.

Answer to the reviewer:

“Success rates” have been corrected, the abbreviations were added under the table and the utilities and costs in the table under sensitivity analyses were presented continuous.
Table 2: Input Parameters of base case and sensitivity analysis, including days of feeding substitutes, treatment success rates, aspiration probabilities, utilities and costs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SE</th>
<th>distribution</th>
<th>Source</th>
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<td>Days FS RB 2 months</td>
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<tr>
<td>Days FS RB 12 months</td>
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<td>4</td>
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<tr>
<td>Days FS UC 12 months</td>
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<td><strong>Success rates</strong></td>
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<td>CCRT</td>
<td>0.940$^b$</td>
<td>0.030</td>
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<td>5</td>
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PREP = preventive exercise program
UC = usual care
FS = feeding substitutes
NKI = Netherlands Cancer Institute
CCRT = concomitant chemo-radiotherapy
FS = Feeding substitutes
SE = Standard deviation
$^a$ calculated to monthly rate
$^b$ progression free survival probability of 50% over 5 years calculated to monthly survival rate
$^c$ recurrence rate from 'no cancer' to 'metastasis'