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# An economic model to assess the cost-benefit of BNCT

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## HIGHLIGHTS

- A model for assessing costs of introducing BNCT in patient treatments.
- Sensitivity analysis – one way of looking into the future.
- A tool for supporting decision making in choice of technology.

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## ABSTRACT

We have constructed a formal model on cost-benefit of new technology in health care, and apply it on boron neutron capture therapy (BNCT). We assume that the patient health benefit from getting cured in acute treatment is always higher than the patient utility resulting from any long term treatment or death. This assumption makes it possible to evaluate the monetary cost impacts of a new technology and relate these measures to the patient health benefit.



## 1. Introduction

The health care sector has reached a major crossroads in many Western countries. Particularly, advances in medical science, rising pressures from a growing elderly population and the discovery of previously unknown disease mechanisms bring with them new and more effective treatments causing rapidly increasing cost pressures. Hence a vast amount of Health Technology Assessment (HTA) in general and cost-benefit analyses in particular have been performed, and they are also a central issue in any discussions of future health care.

## 2. Measuring health benefits

The concept of Quality-Adjusted Life-Years (QALYs) has become the most commonly used method to measure health benefits in health economic evaluations (Blomqvist, 2002; Dranove, 2003; Baker et al., 2005; Dolan et al., 2005). For example, the National Institute for Clinical Excellence (NICE), in the UK, uses QALYs in cost-utility analyses of health technologies. The method has been compared with the basic Cost-Benefit Analysis (Bateman et al., 2003; Dolan et al., 2005; Phelps and Mushlin, 1991; Johannesson, 1995; Garber and Phelps, 1997; Bleichrodt and Quiggin, 1999; Dolan and Edlin, 2002).

The notion of a QALY itself has been critically evaluated, but the greatest concerns have been around the assumption of linearity of the model and the correctness of the social dimensions of a QALY. A QALY is sensitive to the valuation method used, such as time trade-off and standard gamble, as well as the study set-ups (*e.g.* Cook et al. (2001), Richardson et al. (1996), Bleichrodt and Johannesson (1997), Treadwell (1998), Treadwell et al. (2000), Bala et al. (1999), Unic et al. (1998), Sackett and Torrance (1978), McNeil et al. (1981), Miyamoto and Eraker (1988), Stalmeier et al. (1997) and Johannesson and Johansson (1997)). Moreover, a QALY has been claimed to introduce values into the monetary calculations in a manner that does not show robustness or which might not

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adequately reflect social preferences (see, *e.g.,* Blomqvist (2002), Harris (1991), Dolan (1998), Nord (1993), Ubel et al. (1999), Cookson and Dolan (1999), Ubel et al. (1999), Hadorn (1991), Shmueli (1999), Anand and Wailoo (2000), Choudhry et al. (1997), Olsen (2000), Rodriguez-Miguez and Pinto-Prades (2002), Ubel et al. (2001), Beresniak et al. (2010) and ECHOUTCOME (2013)). For a further discussion, see Dolan et al. (2005) and Blomqvist (2002), with references therein.

Willingness to pay (WTP) has more recently been used in conjunction with QALYs in assessing net benefits of medical interventions (Berg et al., 2007; Borgstrom et al., 2006; Deutsch et al., 2006; Fox et al., 2007; Hurley et al., 2007; Lyman et al., 2007; Quigley et al., 2008; Remak et al., 2005; Rubenstein and Inadomi, 2006; Rutten-van Molken et al., 2007; Steuten et al., 2007; Thompson Coon et al., 2007). However, critical concerns have been raised both concerning the validity of WTP for a QALY, and the use of QALYs *per se*. Empirical estimates of WTP for each QALY have yielded results ranging from 0.20 NOK (€0.03) to US$49,133 (€31,186) (Cunningham and Hunt, 2000; Blumenschein and Johannesson, 1998; Zethraeus, 1998; Bala et al., 1998; Olsen and Donaldson, 1998). Such a large range of values understandably casts doubt on the validity of this methodology. For further discussions on using WTP for QALY, see Baker et al. (2005) and Blomqvist (2002), with references therein.

## 3. A cost-benefit model for new technology

While there are many cost-benefit studies in the health economics literature, measures do not usually formally assess the social or economic optima of acute intervention versus long term treatment. To fill this gap we have developed a formal model that includes the entire treatment chain, and apply it on BNCT technology in brain tumour treatment.

The model can be used both for descriptive and normative analysis. We obtain predictions for the observed behaviour in the real world, and normative recommendations for the choice of technology. While current literature predicts hospitals to continue their current behaviour, normative analysis suggests that such behaviour may, in fact, be inefficient. This inefficiency is due to costs and benefits of the long term care.

In this article we introduce an innovative theoretical model with which a new technology can be applied to an acute intervention. This application, in turn, affects the number of patients requiring long term treatment. The aim of the formal theoretical model is to show how the patient health benefit and monetary costs obtained from the adoption of new technology in the acute-care intervention can be related to those of the long term treatment. For this article we define long term treatment as the need for prolonged use of medical products (such as pharmaceuticals and devices), medical services as well as required social services (such as home or institutional care) after the acute intervention.

Following the discussion by Buxton et al. (1997), we constructed a model that

1. is as simple as possible,
2. is as transparent as possible,
3. is possible to generalise to several setups,
4. offers an adequate comparison with current treatment(s),
5. respects the quality of the data in the model, especially helping the reader to distinguish between hard data (*e.g.* collected through controlled studies) and soft data (*e.g.* obtained from expert opinion), and
6. allows the assessment of robustness with appropriate sensitivity testing.

A description of the model and an example of applying it on thrombolytic therapy for stroke is downloadable from http://www.etla.fi/julkaisut/dp1037-fi/, and a free and non-proprietary version of the model transferred into a fully functional calculation engine at www.etla.fi/cost-benefit, to which home pages also further cases will be added. In this paper we will only show the input parameters and the end results of the formal modelling.

### 3.1. Input parameters

The formal model uses following inputs
Acute care and long term care
Technologies 0, 1 and 2 ($t_0$, $t_1$, $t_2$)
Respective prices for each technology ($p_0$, $p_1$, $p_2$)
Severity of disease: high or low severity ($h$, $l$)
Functional capacity of patient d
Probability of low severity after treatment $\tau_t = \text{Prob}(d = l|t)$
Number of patients ($n$)
total cost of applying technology $t$ to $n$ patients $np_t$
Fixed costs $F$
Treatment intensity ($q$)
Budget and budget share allocation ($\mu$B)
Slackness and Financial Surplus ($S$)
Cost functions for acute and long term treatments ($C$ and $c$)

Patients' utility or health benefit scores from having a low functional capacity ($u_l$, $u_l \geq 0$) or being only mildly ill ($u_h$, $u_h > u_l$) after acute-care intervention, and a benefit $v(q)$ of treatment intensity $q$ from the long term treatment.

*Assumption*: zero profit constraint[1]

*Acute intervention* refers to furnishing the initial treatment for patients.

### 3.2. Key results on efficient technology and treatment

A socially optimal technology and treatment intensity $(t^*, q^*)$ maximises the per-patient net benefit. Socially optimal treatment intensity equates the patient-level marginal benefit with marginal cost. Solving for the general model yields that a socially optimal acute-care intervention technology $t$ satisfies the condition

$$\tau_t u_h + (1-\tau_t)[u_l + v(q^*)] - p_t - (1-\tau_t)c(q^*) \geq \tau_s u_h + (1-\tau_s)[u_l + v(q^*)] - p_s - (1-\tau_s)c(q^*) \quad (3.1)$$

Modifying the inequality (3.2) we obtain

$$(\tau_t - \tau_s)\Delta u \geq p_t - p_s + (\tau_t - \tau_s)[V(q) - c(q^*)] \quad (3.2)$$

where $u_h - u_l = \Delta u$ and $v(q^*) = V(q)$. If technology $t$ is more effective than technology $s$, the condition (3.2) can be rewritten as

$$\Delta u - v(q^*) \geq \frac{p_t - p_s}{\tau_t - \tau_s} - c(q^*), \quad (3.3)$$

and, if technology $s$ is more effective than technology $t$, the condition (3.2) can be rewritten as:

$$\Delta u - V(q) \leq \frac{p_t - p_s}{\tau_t - \tau_s} - c(q^*). \quad (3.4)$$

[1] From an operational point of view, slackness should always be minimised as long as it incurs cost savings. In health care, there is a necessary conflict between redundancy (also called excess capacity) and operational efficiency: redundancy is desirable for public health reasons, such as potential widespread acts of terrorism, natural disasters and pandemics. If a provider unit is running optimally in an economic sense, however, it does not include redundancy. The model is designed to accommodate redundancy that can be included in a financial surplus $S$, but in this empirical case additional surplus is set at zero as it is already part of the costs derived from the hospitals' price lists.

Inequalities (3.3) and (3.4) are the key results of the model and can be explained as

Cost per cured patient $= \frac{p_t}{\tau_t} - c(q)$, where

- cost of one treated patient is divided by effectiveness; this results in how much one successful treatment costs, and
- long term treatment cost is subtracted from this cost, as a cured patient does not need long term treatment.

The result can also be negative, meaning that using the acute intervention actually saves money.

The left-hand sides of the inequalities (3.3) and (3.4) can be interpreted as willingness to pay for health improvement from $u_l$ to $u_h$.

## 4. Applying the model on boron neutron capture therapy

Glioblastoma multiforme has eluded efficient therapy, with the most effective treatment offering only a 15 month extension of life after diagnosis. (Andersen, 1978; Chin et al., 1981; Kristiansen et al., 1981; Lacroix et al., 2001; Stupp et al., 2009, 2005; Walker et al., 1978, 1980). In this section we define the Finnish Boron Neutron Capture Therapy (BNCT) project as *technology 2*. BNCT is an expensive radiation treatment with high startup and fixed costs (for a detailed explanation see (Joensuu et al., 2003) and references therein).[2]

### 4.1. Defining the parameters for glioblastoma treatments

The parameters for *glioblastoma multiforme* are collected in Table 1.

The regulator is the Hospital District of Helsinki and Uusimaa, HUS. However, there will still be only one BNCT treatment station in the foreseeable future, and as *glioblastomas* are rare, our implementation will cover entire Finland.

The acute intervention is provided by the Departments of Neurology, Neurosurgery and Oncology at HUCH, serving under HUS. The acute phase is here defined to include direct costs that are additional to normal treatment costs for patients suffering from *glioblastoma multiforme*.

The long term treatment is provided by HUCH and the regional hospitals of Helsinki and Uusimaa, all serving under HUS. In contrast to stroke, the majority of long term treatment is delivered during the first year from diagnosis.

The number of patients is approximately 150 per annum (Ohgaki and Kleihues, 2005).

Severity of illness at referral to the acute intervention provider is defined as glioblastoma with clear symptoms of disease and a Karnofsky score below 70; the Karnofsky score will be discussed in more detail below.

*Technology* 0, $t_0$, consists of prompt diagnosis, acute intervention, a neurosurgical operation and supportive care given initially at HUCH and later mainly at the regional hospitals. We define this technology as baseline treatment incurring no additional costs; thus $p_0 = 0$.

If the patient does not present with specific contraindications, she is usually offered radiation after the neurosurgical debulking. Concurrent temozololamide and radiotherapy followed by adjuvant temozololamide is the present established care with a more than doubling of 2-year survival rates compared to radiation only (Stupp et al., 2002, 2009, 2005; Yung et al., 2000). Moreover, a multitude of other treatment modalities are being developed and assessed, such as new operative techniques, advances in radiotherapy, new combinations of chemotherapy, biological response modifiers, and gene therapy (Anton et al., 2012).

We define *Technology 1* as consisting of: (1.) a neurosurgical operation with the aim of removing all malignant tissue, and (2.) a full series of traditional radiation therapy sessions, in addition to normal supportive procedures and therapy.

Of these two treatments, only the radiation therapy incurs additional cost when compared to technology 0. As the equipment is used mainly for the treatment of other, more frequently occurring, diseases, we do not accrue initial fixed costs for the introduction of technology 1; the fixed costs are adequately included in the DRG price for *glioblastoma multiforme*, and hence $p_1 = 2{,}420$ €/patient[3] (Neurology, 2005; Neurosurgery, 2005; Oncology knowledge centre Hospital District of Helsinki and Uusimaa HUS, 2005). As an intensified acute treatment leads to a longer survival time, we assume that the DRG price adequately reflects the true total additional costs induced by technology 1.

*Technology 2* encompasses: (1.) a normal neurosurgical operation, followed by (2.) BNCT-treatment.

The additional costs induced by technology 2 consist of allocated fixed and variable costs associated with BNCT therapy, less the price for giving a full series of conventional radiotherapy (which BNCT replaces). As several other brain cancer treatment modalities are being actively developed, especially accelerator-based neutron sources, we assume that the effective life cycle for nuclear reactor based BNCT is 10 years, after which the technology will become too obsolete to be competitive (Blue and Yanch, 2003; Kononov et al., 2004; Lee et al., 2004; Svensson and Moller, 2003). The first patient in Finland was treated on May 1999, and by May 2005 a total of 42 brain tumour patients received BNCT treatment (Kankaanranta, 2005, 2011c). Projecting a steadily rising patient stream, we for demonstration purposes assume 100 more patients would have been treated during the following four years. We additionally assume that the increasing patient stream brings about savings due to a streamlining of the procedures, which compensates for the impact of inflation on costs. Keeping the price for one treatment at the 2005 level, i.e., 20,000€, we obtain a price for technology 2: $p_2 = 890{,}120$€.[4]

**Table 1**
The parameters for glioblastoma multiforme.

| ***Glioblastoma Multiforme*** | | | | |
|---|---|---|---|---|
| Functional capacity | $d$ | $h$ (high) | $l$ (low) | |
| Obtained utility | v(q) | | | |
| *corresponding to Karnofsky* | | $\geq 70$ | $< 70$ | |
| Health care budget | B | 4.440 mill | | |
| | | 0 | $> 0$ | |
| Technology | $t$ | $t_0$ | $t_1$ | $t_2$ |
| Patients | N | 150 | 150 | 150 |
| Price of technology (total) | $p$ | 0 | 363,000 | 890,120 |
| probability of having a low severity of disease | $\tau$ | 0 | 0.082 | 0.123 |
| Average cost of treatment | c(q) | 27,182 | | |

[2] BNCT was originally developed solely for treating *glioblastoma mutliforme,* but later successfully developed to treat head and neck cancer. In this paper we use the data from the test treatments for *glioblastoma multiforme* in Finland as our example, as that was the original issue decision makers faced when considering the introduction of BNCT into Finland. In 2005 the glioblastoma treatments were at their peak, so we will use year 2005 as our reference point for costs.

[3] Corresponding to a total cost of $p_{1\text{tot}} = (2{,}420$€/patient*150 patients$) = 363{,}000$€.

[4] The cost for introducing technology 2 is $p_2 = (2420$€/patient*136 patients [treated conventionally]/year$) + 2{,}000{,}000$€/10 years$+ 20{,}000$€/patient*14.2 patients/year$= 329{,}120 + 200{,}000 + 280{,}000$€$= 890{,}120$€.

The health care budget B is, set regionally by respective political councils; however, in the case of rare diseases with interventions centralized to university hospitals, the budget is set by the respective university hospitals. As BNCT is given solely at HUCH, the decisions are made by a political council with representatives from all communities in Helsinki and Uusimaa that refers patients to HUS. We approximate the total budget for treatment of glioblastoma multiforme in Finland to be 4.440 million€ annually (City of Helsinki, 2005a, 2005b, 2005c; Neurological department Hospital District of Helsinki and Uusimaa HUS 2005; Neurology, 2005; Neurosurgery, 2005; Neurosurgical department Hospital District of Helsinki and Uusimaa HUS 2005; Oncology knowledge centre Hospital District of Helsinki and Uusimaa HUS, 2005).[5]

The share of budget allocation to acute intervention $B_a$ is also in brain tumour treatment set by HUS. However, in contrast to treatment of stroke, only the initial costs of introducing technology 1 were born by the acute intervention. The establishment of the BNCT treatment station was strongly supported by the National Technology Agency of Finland and therefore HUCH incurred no additional costs. Our model intends, however, to take as broad a view as possible, and thus we also include the fixed costs for technology 2 into the calculations.

The obtained utilities $u_l$ and $u_h$ are defined as the end-points of low and high functional capacity, corresponding to high and low severity of disease, respectively. The Karnofsky Performance Scale combines the degree of disease with a person's ability to care for self (Karnofsky et al., 1948). While it is widely used, it offers only a rather arbitrary assessment of severity of disease (Green, 1997; Murray et al., 1995; Slevin et al., 1988). However, since it has been commonly used in clinical trials concerning brain tumour treatment, we use it for the purpose of this study. Consequently, we define a Karnofsky score of $\geq 70$ (70=cares for self, unable to perform normal activity or to do active work) as demonstrating low severity of disease; high severity is defined as a Karnofsky score of $<70$.

The obtained health benefit is evaluated at one year after diagnosis as a function of the end-point and the probability $\tau_t$ of achieving that end-point.

At the end of the *acute intervention phase*, we define a patient with a Karnofsky score of $\geq 70$ as experiencing a positive health benefit from the treatment $u_h > 0$; even if the patient started with a score $>70$, the treatment can prevent deterioration. On the other hand, if the Karnofsky remains below 70, the health benefit: $u_l^l = 0$.

Surplus $S$ stems from an uneven allocation of resources, and thus S is preferably minimised. This assumption holds with all units in HUS.

The enhanced probability of having a high functional ability after basic treatment, *i.e.,* a Karnofsky score of $\geq 70$ at one year after diagnosis, is 0 for technology 0 ($\tau_0 = 0$), 0.082 for technology 1 ($\tau_1 = 0.082$) (Kristiansen et al., 1981; Laperriere et al., 2002).[6] For BNCT, the developers strived for an enhancement of $\tau$ by 50%,[7] yielding $\tau_2 = 0.123$ (Kallio et al., 1997).

We derived the average cost $c(q)$ of treating one Finnish glioblastoma patient with reference technology 0 ($p_0$) by combining several data sources.[8] The reference technology yields a total average cost 27,182€/patient.

### 4.2. Results

As indicated earlier, the utilisation of BNCT on glioblastoma-type brain cancer demonstrates a rather different setup for assessing the adoption of a new technology in health care. In *e.g.* thrombolytic therapy for stroke the key elements are an efficient treatment chain (availability) and marginal costs, whereas for *glioblastoma multiforme* the fixed costs and recovery rates prove to be critical.

In economic terms, BNCT seems to be the opposite of *e.g.* thrombolysis in stroke, where introduction of thrombolytic therapy induces a negative cost on healthcare – in other words, it saves money. For BNCT our model suggests that the health care payer decides to adopt the BNCT technology in acute intervention if the added value (or opportunity cost) of a successful acute treatment compared to optimal long term care exceeds 58,528€

$$\Delta u - v(q^*) \geq 58,528€ \tag{4.1}$$

Technology 2 does not offer any direct economic advantage, and thus the choice between technologies is uncertain. BNCT was originally developed for treating glioblastoma mutliforme; at present focus is particularly on treating severe forms of head and neck cancer (Kankaanranta et al., 2011b). In this paper we use the data from the treatments for glioblastoma multiforme in Finland as our example, since that data is available together with published full cost data for the preferred main treatment (radiation therapy) of the same period.

In retrospect, we are aware of the technology being adopted, but the not-for-profit treatment company went bankruptcy in 2012. However, a similar cost benefit analysis for BNCT treatment of head and neck cancer as well as a comparison with radiotherapy combined with temozololamide would be logical next steps of research.

### 4.3. Sensitivity analysis – one way of looking into the future

The introduction of technology 2 (BNCT) is associated with high startup costs. Typically they consist of building a treatment facility by remodelling an existent reactor or acquiring an accelerator based system; for the Finnish BNCT station the calculated initial investment was 2M€. Such costs could be recovered either by enhancing the patient base and thereby a higher number of treatments in a single unit, or by introducing a new technology which has higher direct health benefits and/or a lower variable cost.

A sensitivity analysis shows, however, that with the sunk costs that high, the cost-efficiency frontier for technology 2 does not break zero for any patient number (Fig. 1). As shown in Fig. 2, re-applying the model, while varying the recovery rate $\tau$, demonstrates that the costs of technology 2 quickly diminish with an increasing recovery rate. BNCT in Finland was developed further to treat malignant cancers of the head and neck region – indeed with even significantly higher recovery rates (Kankaanranta et al.,

[5] This budget consists of initial treatment costs of (2,400€+7,020€+2,420€)= 11,840/patient (diagnosis, initial treatment, neurosurgery and radiation therapy) and a three month late stage period totalling 16,200€, where the patient is again in need of intensified support and treatment.

[6] $\tau_1$ was derived by combining: (1.) Performance data on glioblastoma patients after operation and radiotherapy with or without chemotherapy, yielding an average 62% of patients not capable of caring for self at one year, and (2.) Risk ratio for 1-year mortality of post-operative radiotherapy versus no radiotherapy =0.81.

[7] The enhancement reflected anticipations of both a better survival for a subpopulation as well as a better quality of life as assessed by ability of caring for self.

[8] The DRG price 2,420€/patient reflects costs accrued from initial diagnosis and treatment (HUS 2005a). The initial CT-scan has to be complemented by an MR-

(*footnote continued*)
imaging and followed by neurosurgery, adding up to a total cost of 7,020€ (HUS 2005b). We exclude costs related to radiation therapy. With such treatment, the weighted average median survival of patients is 18 weeks, with an initial improvement phase, a long phase of deterioration and concomitantly an increasing need of care with occasional visits to an acute intervention unit (Chin et al. 1981). The supportive phase is about two thirds of the total survival time (Kristiansen et al. 1981), and thus we approximate the average price of later stage treatment to 17,762€ (City of Helsinki 2005a, 2005b, 2005c). The average treatment duration is 83 days and the daily cost 214€.

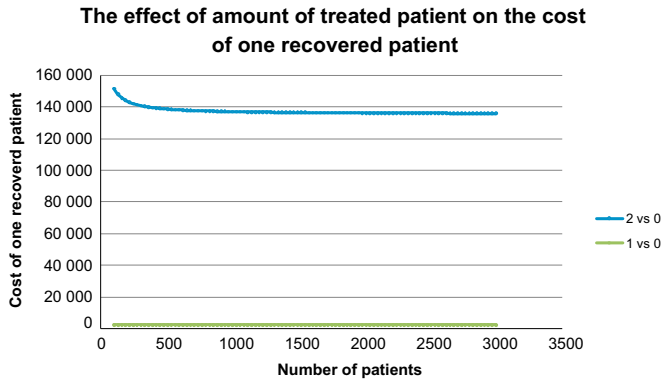


**Fig. 1.** The costs associated with one recovered patient as a function of the amount of treated patients for technologies 1 and 2 when the recovery rates are set at 0.082 and 0.123, respectively.

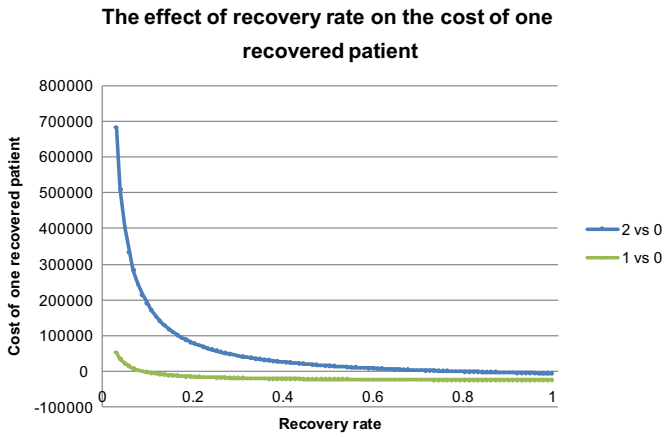


**Fig. 2.** The costs associated with one recovered patient as a function of the recovery rate associated with technologies 1 and 2. when the number of patients is set at 150 per annum.

2011a, 2007, 2011b; Savolainen, 2010).

Finally, the impact of varying the prices for technologies 1 and 2 is shown in Fig. 3. Since variable costs, by definition do not change with volume, Fig. 3 could be seen as reflecting differences in, *e.g.,* prices of available accelerator solutions and thereby differences in pricing of offered treatment.

The model suggests that technology 2 is not economically competitive with present recovery rates; however, it can be chosen on other grounds. Such arguments could be: an interest in the technology *per se*, a vision of a development of the technology to become more competitive, or a lower risk of death or dependency.

## 5. Conclusions and discussion

BNCT for *glioblastoma multiforme* presents a rare disease with a low probability of recovery, high sunk costs as well as acute treatment costs but relatively low long term treatment costs due to the rapidly aggressive progression of the disease. A new technology showing low effect but high initial costs calls for a larger population base that would only be possible with international cooperation. Yet, the rationale for adopting the technology must be found from other sources than pure economic reasoning.

The benefits from an adoption of new technology can be purely humanitarian, or they might involve economic impacts, typically secondary and indirect, that have not been taken into account in the conventional cost-benefit calculations. Examples of potential

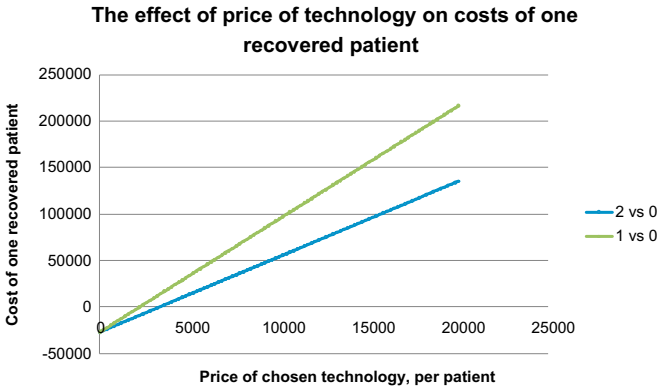


**Fig. 3.** The effects of technology pricing on the costs of one recovered patient when the recovery rates for technology 1 and 2 are set at 0.082 and 0.123, respectively, and the number of patients is set at 150 per annum.

benefits are

1. the non-monetary value of avoiding deaths *per se,*
2. the non-monetary value of an early recovery, leading to a better quality of life,
3. a preponderance of new technology *per se,*
4. spillover effects from supporting a novel technology (*e.g.* applications in other fields or further applications in the same field).

The above benefits are difficult to measure in monetary terms. The main benefit of the model is that it enables the comparison between the non-monetary health benefit and monetary cost-effectiveness. Although this presentation enables a direct valuation of distinctive policy decisions, it does not provide strict answers about whether the payer should adopt the new technology.

Developers of new technology can use this model to assess the impacts of their innovations, thereby supporting their [clinical] testing approval and pricing strategy. Similarly, the model functions as a means of transparent assessment and communication, for example between a company or research entity and the government agencies responsible for supporting, evaluating and implementing technological developments.

Finally, we need to recognise that any new technology can initially be regarded as overly expensive. But we also need to recognise, that almost by definition technologies develop and become not only cheaper but also more efficient. This indeed is very true also with BNCT: malignant glioma treatments were followed by more successful head and neck treatments, novel carriers are approaching clinical trials, and the era of accelerator based neutron beams has just begun. We encourage the use of our model's sensitivity analysis charts to analyse as well as communicate what happens, when parameters change.

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