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Cost-Effectiveness of Intraperitoneal Chemohyperthermia in the Treatment of Peritoneal Carcinomatosis from Colorectal Cancer

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ABSTRACT

Objectives: Our purpose was to assess the cost-effectiveness of intraperitoneal chemohyperthermia (IPCH) compared to palliative chemotherapy (STANDARD) against peritoneal carcinomatosis arising from colorectal cancer.

Methods: We performed a retrospective study of 96 patients whose peritoneal carcinomatosis had been diagnosed between January 1998 and December 2003 and treated either with IPCH or with palliative chemotherapy in French comprehensive cancer centers. Patients were followed up over a 3-year period. Effectiveness was measured by restricted mean survival at 3 years. The Bang and Tsiatis method was used to handle cost-censored data. The confidence limits of the mean cost per patient in each group and the mean incremental cost per life-year saved were computed using 1000 bootstrap replicates. We also computed an acceptability curve for the incremental cost-effectiveness ratio (ICER).

Results: We found that IPCH improved survival and was more costly than STANDARD treatment. Over a 3-year observation period, IPCH yielded an average survival gain of 8.3 months at the additional cost of €58,086 (95% confidence interval 35,893–112,839) per life-year saved.

Conclusion: The ICER of IPCH is acceptable given the severity and burden of peritoneal carcinomatosis for which there is no alternative curative treatment.

Keywords: cost-censored data, cost-effectiveness, intraperitoneal chemohyperthermia, peritoneal carcinomatosis from colorectal cancer, restricted mean survival.

Introduction

Peritoneal carcinomatosis (PC) is present in approximately 10% of colorectal cancer at initial diagnosis and in 25% of patients with recurrent disease [1]. PC is a very lethal condition. No curative treatment was available until oncology surgeons developed an innovative therapy in the 1990s combining complete cytoreductive surgery of all macroscopic/gross disease with hyperthermic chemotherapy. This procedure named intraperitoneal chemohyperthermia (IPCH, or intraperitoneal hyperthermic chemotherapy) was first developed by Sugarbaker [2]. Phase II studies suggested the efficacy of IPCH in terms of survival improvement [3–9]. A phase III randomized controlled trial published in 2003 [10] showed that IPCH halved the risk of death when compared to systemic chemotherapy (5-flurouracil-leucovorin followed by irinotecan) in PC of colorectal origin. In that study, the hazard ratio was 0.55 (95% confidence interval [CI] 0.321–0.951). Median survival with systemic chemotherapy was 12.6 months versus 22.3 months with IPCH. The completeness of cytoreductive surgery was the most important prognostic factor [11]. As IPCH is an innovative therapy, economic evaluations based on individual data collection are lacking. In a recent literature review from the UK Health Technology Assessment Agency [12], only one study evaluating the cost of IPCH in patients with pseudomyxoma peritonei was identified. The study was based on 25 cases treated in a US setting. Estimated treatment costs were €130,000 [13]. In a recent study [14], we assessed the cost of IPCH based on all procedures performed during a two-year period at our institution, whatever the origin of PC (mainly colorectal and pseudomyxoma peritonei). The mean cost of the hospital stay was €39,358 (SD €31,853). This procedure has not been added to the patient classification scheme under the new French Prospective Payment System and half its cost is reimbursed. In 2003, based on scientific evidence on the

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efficacy of IPCH, the French Ministry of Health decided to promote IPCH, by allocating financial support to selected surgical teams, and to assess its cost-effectiveness. It was not possible to perform a new randomized controlled trial [15] to assess the survival benefit, because the procedure had already demonstrated its efficacy in the 2003 trial [10]. We therefore used a retrospective comparison. Our objective was to assess the incremental cost-effectiveness ratio (ICER) of IPCH compared to palliative chemotherapy against PC of colorectal origin.

Patients and Methods

Study Design and Patient Selection

We performed a retrospective study on selected patients with colorectal PC treated either with IPCH or with palliative chemotherapy between January 1998 and December 2003 in six French comprehensive anticancer centers. The IPCH group consisted of all consecutive patients with colorectal PC having undergone IPCH in a single-institution, which was the French reference center for the technique. Forty-eight patients were identified. The control population consisted of comparable patients who had been treated in five comprehensive anticancer centers with standard chemotherapy combined or not with palliative surgery (STANDARD group). These patients did not benefit from IPCH because the technique was unavailable in these centers and because patients could not be referred to the reference center because of its limited treatment capacity. Patients were highly selected to ensure comparability with IPCH patients. The selection process was divided into two steps. During the first step, medical investigators selected from their records of all patients with colorectal PC diagnosed between January 1998 and December 2003 who had been treated with palliative chemotherapy and who met eligibility criteria. Patient eligibility was defined according to the six criteria deemed good prognostic factors for IPCH in the literature [15,16]: 1) a good general status (Eastern Cooperative Oncology Group Status 1–2); 2) age less than 65 years; 3) no extra-abdominal extension; 4) no evidence of bowel obstruction; 5) no tumor larger than 2 cm at computed tomography; 6) no rapid progression of PC under systemic chemotherapy. During the second step, the principal investigator double-checked the medical records of the potentially eligible patients provided by the centers (75 patients), by recontacting the investigators to ensure that the eligibility criteria had been applied homogeneously. Forty-eight patients were finally selected. During double-checking, the investigator was blinded to the detailed characteristics of the IPCH patients. The fact that there was exactly the same number in both groups was purely coincidental.

Cost Data

Cost computation focused on inpatient care. In each group, all PC-related hospital stays were recorded over a 3-year period since the diagnosis of PC. The reason for admission and the duration were recorded for each hospital stay. For chemotherapy-related stays, the drug and dose were also recorded. IPCH stays were valued using a microcosting approach. For each IPCH stay, the duration of the IPCH procedure, type and dose of IPCH agents (5-fluorouracil, irinotecan, and/or oxaliplatin), and the number of admissions days per ward type (intensive care and surgical ward) were recorded. Unit costs were extracted from the accounting data (year 2002) at the center where procedures had been performed: the cost of 1-hour use of the operating room, the cost of 1 mg of each chemotherapy agent, the cost of a bed day in a surgery unit, and the cost of a bed day in an intensive care unit. All other hospital stays in both groups were costed using the duration of hospital stay recorded in the study. According to the diagnosis-related group (DRG) in which the stay was classified, the duration of hospital stay was multiplied by the average cost per day of the given DRG, and derived from the 2004 French National Hospital Costs Survey (period 2001–2002). The full cost covers all expenditures related to a given stay: physician, nurses and other staff salaries, medication and medical devices, lab tests and other diagnostic procedures, depreciation of equipment and overheads. We proceeded in a different manner for chemotherapy stays. We excluded the medication costs from the average cost of the DRG, because we had a detailed record of the drugs used. We therefore valued the use of chemotherapy agents directly from data recorded in the study (type of agents and dose) and unit costs in our institution in 2005. The main unit costs used are summarized in Table 1.

Cost Analysis

Mean inpatient costs were assessed from the perspective of the payer for the whole study period. As the study was retrospective and concerned the 1998–2003 period, we did not collect data on workdays lost to avoid major memory biases for the earlier years. In addition, questioning families about deceased patients was likely to be highly unreliable and also unethical.

In the presence of cost-censored data, the mean of the costs observed is biased downwards because costs occurring after censoring are unknown. In the 90s, methods were proposed to deal with cost-censored data [17,18]. In each group, we used the partitioned estimator proposed by Bang and Tsiatis [18] to adjust for censoring of costs. The Bang and Tsiatis method consists in subdividing the study period into K intervals of time $(t_j,t_{j+1})_{1\leq j\leq K}$. For each interval, average costs are estimated as the sum of the costs M_{ij} observed

Table I Unit costs data (in €) and number of hospital stays in each group

	Unit cost	Number of stays	
		IPCH	STANDARD
IPCH stays (microcosting)		48	0
1 hour use of the operating room	394		
Mean cost of intraperitoneal chemotherapy drugs	3081		
Bed day in a surgery unit	431–642		
Bed day in an intensive care unit	1389		
Other hospital stays (costs per DRG)			
Chemotherapy		883	726
DRG for CT given in an inpatient setting (daily cost)*	448		
DRG for CT administered in an outpatient setting*	350		
Chemotherapy agents			
Range of costs per course for all agents	8–888		
Cost per course for Folfiri-Folfox regimens	332–343		
Surgery (IPCH excluded)		52	48
Daily cost for the three most frequent DRGs			
Rectum resection with associated comorbidities	650		
Digestive surgery with associated comorbidities	608		
Major surgery of the bowel or colon without comorbidities	567		
Palliative care and disease progression		34	103
DRG for palliative care	6067		
All hospital stays		1017	877

*Chemotherapy agents excluded.
CT, chemotherapy; DRG, diagnosis-related group; IPCH, intraperitoneal chemohyperthermia.

(IPCH procedure cost excluded) during this interval divided by the population size n. This "average" cost estimate is weighted by the probability $\hat{K}_j$ of not being censored at the beginning of the period calculated by the Kaplan–Meier method. This results in attributing costs for censored patients. The estimated average total cost for the study period is thus obtained by summing the costs across all intervals. The partitioned estimator is defined by:

$$\hat{\mu} = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{K}\frac{\Delta_i^j M_{ij}}{\hat{K}_j} \quad (1)$$

$\Delta_i^j = 1$ if the patient i is not censored at the beginning of the interval j. Our data were detailed enough to use a 1-month interval.

Survival Analysis

The effectiveness measure used was the number of years of life saved. As patients were still alive after 3 years of follow-up in both groups, we used the difference between restricted mean survivals at 3 years to evaluate the benefit of IPCH. Survival was estimated by the Kaplan–Meier method, which uses all available information including the observed survival time for censored data. To measure health benefits, economists use life expectancy, which is the mean survival μ defined by:

$$\mu = \int_0^\infty S(t)dt \quad (2)$$

where $S(t)$ is the Kaplan–Meier estimate of the survival probability.

The true mean survival is represented by the area under the Kaplan–Meier curve when all the patients were deceased. In the case of censored data, the reliability of $S(t)$ declines with t as the number of patients declines both as a result of deaths and censored observations. Therefore, the size of the CI of $S(t)$ increases as the number of patients at risk decreases. To deal with this difficulty, Irwin [19] suggested estimating the mean survival restricted to a suitably chosen time T^* called the point of restriction. The restricted mean survival μ_R is represented by the area under the curve up to T^* and is defined by:

$$\mu_R = \int_0^{T^*} S(t)dt \quad (3)$$

To determine the point of restriction T^*, Karrison [20] advised using the largest time point such that the standard error of the survival estimates $SE(S(t))$ at this point in each group is within 5% to 10%. He proposed using the following Peto et al. [21] formula to estimate the standard error:

$$SE(S(t)) = S(t)\sqrt{(1 - S(t))/n(t)} \quad (4)$$

where $n(t)$ is the number of patients at risk at t. Restricted mean survival was measured from the date of the diagnosis of PC until death or the date of the last follow-up in censored data or T^* for noncensored data. The difference between restricted mean survivals was tested with a two-sided log rank test.

Statistical and Sensitivity Analyses

We used Student's t-tests to compare continuous variables and chi-square tests to compare distributions of dichotomous variables. To handle uncertainty, we used a bias-corrected accelerated nonparametric bootstrap method [22] to estimate a 95% CI for mean costs in

Table 2 Patient characteristics at peritoneal carcinomatosis diagnosis

	IPCH ($n = 48$)	STANDARD ($n = 48$)	*P*
Females (%)	36	34	0.8
Mean age (year)	46	51	0.01
Site of cancer			0.8
Colon	40	41	
Rectum	8	7	
Initial pT staging			0.08
T1,T2	0	3	
T3	23	18	
T4	25	24	
Not reported	0	3	
Lymph node status			0.07
N+	34	31	
N–	14	12	
Not reported	0	5	
Tumor differentiation			0.02
Well	37	29	
Poor	11	12	
Not reported	0	7	
Extension of PC			0.07
Limited	27	26	
Extended	21	17	
Not reported	0	5	
CEA rate (ng/ml)			0.1
<30	33	40	
≥30	15	8	
Total number of lines of chemotherapy	102	110	0.52

CEA has a potential predictive value in PC arising from cancer.
CEA, carcinoembryonic antigen; IPCH, intraperitoneal chemohyperthermia; PC, peritoneal carcinomatosis.

each group and for the ICER and to compute a cost-effectiveness acceptability curve. The acceptability curve represents the probability that IPCH will be cost-effective for a wide range of threshold values. One thousand resamplings of the study population were performed. Although the retrospective group was selected through a thorough scrutiny of medical records, we still had to control for any residual selection bias. We performed a Cox regression analysis to predict the impact of patient characteristics on survival and to test the need to integrate significant variables in a sensitivity analysis.

Results

Demographic and clinical characteristics are presented in Table 2. All characteristics were comparable except age and tumor differentiation. IPCH patients were significantly younger. There was no difference in systemic chemotherapy, either in the type of agents used or in the number of lines administered in each group (102 vs. 110, $P = 0.52$). In the IPCH group, intraperitoneal chemotherapy was oxaliplatin in 30 patients and oxaliplatin combined with irinotecan in the remaining 18 patients. In both groups, three types of PC-related hospital stays were observed: surgery (IPCH or other type), chemotherapy, and palliative care (Table 1). In the STANDARD group, 877 hospital stays were recorded: 48 for surgery (36 at diagnosis of PC and 12 subsequent operations in those 36 patients), 726 for chemotherapy, and 103 for other reasons (mostly digestive DRGs and palliative care). For the remaining 12 patients who had not undergone palliative surgery, PC had been diagnosed either by imaging (8 patients) or at histological analysis (4 patients). In the IPCH group, 1017 hospital stays were recorded: 48 stays for IPCH, 52 for surgery (before or after IPCH), 883 for chemotherapy (before and after IPCH), and 34 for IPCH complications or disease progression. The mean number of admissions to hospital per patient was 21.2 (range: 1–50) in the IPCH group and 18.3 (range: 3–47) in the STANDARD group ($P = 0.17$). The cost of the hospital stay for IPCH was estimated at €33,659 (95% CI 30,571–36,747). On average, the IPCH procedure lasted 9 hours (range: 6–13) and its cost was estimated at €9098 (95% CI 8680–9516). The mean cost of IPCH drugs was €3081 (95% CI 2879–3284) and accounted for one-third of the cost of the procedure. On average, the duration of the hospital stay was 25 days, including 12 days in the intensive care unit. The cost of the stay in clinical wards was €24,561 (95% CI 21,426–27,696). Using Bang and Tsiatis' estimator, the total inpatient cost per patient over a 3-year period was estimated at €81,481 (95% CI 73,618–91,410) in the IPCH group and at €40,821 (95% CI 35,437–48,516) in the STANDARD group. Table 3 details the observed cost per type of hospital stay in both groups; these estimates have not been corrected for censoring. Figure 1 shows the distribution of costs observed in both groups (uncorrected for censoring). Three years after the diagnosis, median survival had not been attained in the IPCH group whereas it was 24.8 months in the STANDARD group ($P < 0.0001$, two-sided log rank test). The 3-year overall survival probability was 72% (95% CI 57–83%) for IPCH patients and 32% (95% CI 20–48%) for patients in the STANDARD group. The hazard ratio was 0.29 (95% CI 0.15–0.55) in favor of IPCH. At 3 years, the standard error of the survival estimate SE(S(t)) was 8% in the IPCH group and 9% in the STANDARD group. Thus, with this time point, Karrison's criterion was fulfilled. At 3 years, restricted mean survival was estimated at 31.7 months in the IPCH group and 23.4 months in the STANDARD group. Thus, IPCH

Table 3 Mean inpatient costs per patient (observed costs in €)

Type of hospital stay	IPCH ($n = 48$)	STANDARD ($n = 48$)
Hospital stay for IPCH	33,659 (10,635)	0
Hospital stays for chemotherapy	28,967 (16,807)	21,457 (13,515)
Hospital stays for other reasons	14,898 (15,224)	13,036 (14,986)
All hospital stays	77,524 (29,031)	34,493 (19,098)

Standard deviations are reported in parentheses.
IPCH, intraperitoneal chemohyperthermia.

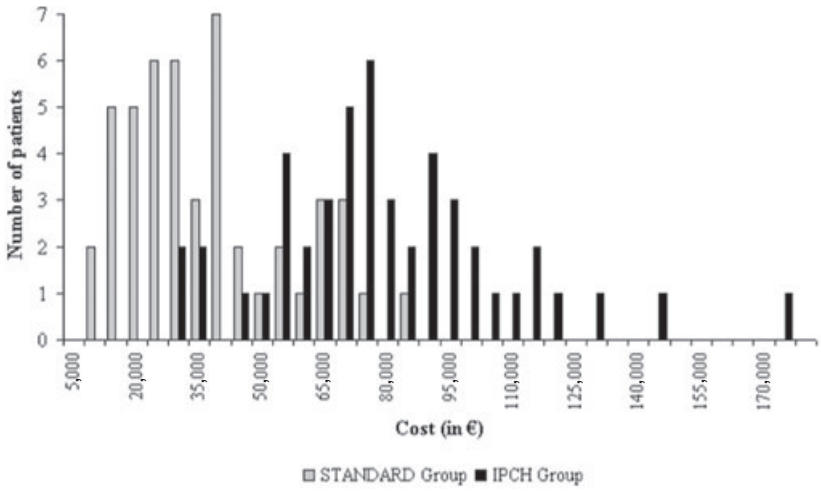

Figure 1 Distribution of total inpatient costs (observed costs). IPCH, intraperitoneal chemohyperthermia.

resulted in a mean survival gain of 8.3 months (or 0.7 years). Kaplan–Meier curves are shown in Figure 2. The cost per life-year saved was €58,086 (cf. Table 4). The CI for the ICER obtained by performing 1000 bootstrap replicates was 35,893–112,839. Figure 3 shows the costs and the effectiveness obtained for each bootstrapped sample. All cost-effectiveness values are located in the northeast quadrant meaning that IPCH improved survival at a higher cost. Seventy-five percent of ICERs were less than €70,000 per life-year saved (cf. Fig. 4). IPCH and the extent of carcinomatosis were the only prognostic factors singled out in the Cox regression analysis (adjusted hazard ratios were, respectively, 0.19 and 0.26). The extent of carcinomatosis was comparable in the two groups and was therefore not likely to influence the cost-effectiveness ratio.

Discussion

Our objective was to assess the cost-effectiveness of IPCH compared to standard treatment with palliative chemotherapy. We used retrospective data concerning 96 patients over a 3-year period after the diagnosis of PC. Although our study is the first to assess IPCH cost-effectiveness, some limitations must be mentioned. The major limitation is the question of confidence in survival results based on a nonrandomized study. Our study was not randomized because it would have been unethical to do so. IPCH was proposed as the last recourse for the cure of PC. The procedure has been performed for more than 10 years at the Institut Gustave Roussy (French reference center for the technique) even though its efficacy had not been proven in a randomized trial until 2003. Verwaal et al. did, however, demonstrate improved survival with IPCH in a controlled setting [10]. In our study, we attempted to address the selection bias. All consecutive patients with colorectal PC were included in the IPCH group. In the STANDARD group, patients were highly selected to ensure comparability with IPCH patients. Characteristics were similar except for age and tumor differentiation. Nevertheless, when we applied a Cox regression model to our data, it showed that the survival benefit was not sensitive to age and tumor differentiation. Finally, a potential selection bias in our study may be due to the identification of the patients. IPCH patients were identified through the IPCH procedure item whereas patients in the STANDARD group were identified through their diagnosis of PC. The fact that IPCH patients were selected through the IPCH item signifies that these patients had lived until the IPCH procedure. The median interval between the diagnosis of PC and IPCH was 9 months. This median interval could have led to an overestimation of survival in this group [23]. We checked that each IPCH patient was matched with a STANDARD patient on the following criterion: the time interval from diagnosis until death for a STANDARD patient was at least equal to the interval from the diagnosis to IPCH for the IPCH patient. This bias should therefore be minimized.

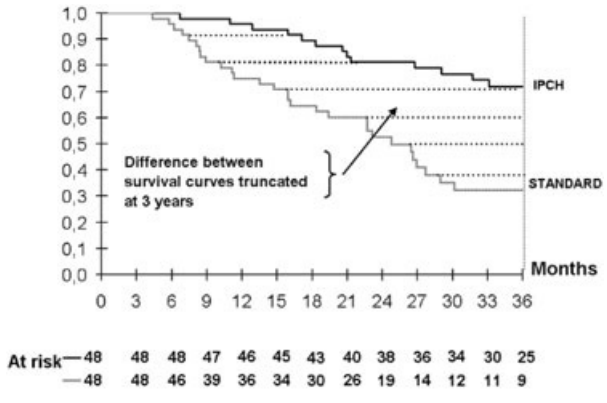

Figure 2 Overall survival in intraperitoneal chemohyperthermia (IPCH) and STANDARD groups.

Table 4 Cost-effectiveness results

	IPCH	STANDARD	Differential	ICER
Mean cost (in €)	81,481	40,821	40,660	
Mean cost (in €; IPCH stay excluded)	47,822	40,821	7,001	
Restricted mean survival (in years)	2.6	1.9	0.7	
Mean cost per life-year saved (in €)				58,086

ICER, incremental cost-effectiveness ratio; IPCH, intraperitoneal chemohyperthermia.

Potential biases in the method must also be underlined. First, restricted mean survival was used as an estimation of the treatment benefit. Although this measure appears to be conservative, it may underestimate the treatment benefit. Second, Bang and Tsiatis' method was used to handle cost-censored data. As there were more censored data in the STANDARD arm in the proportion of nondecreased patients, the ICER of IPCH was lower using Bang and Tsiatis' estimates. Third, our cost estimate omitted ambulatory costs as well as indirect costs. But it was difficult to collect these types of costs retrospectively. For ambulatory care, claims data from the Sickness Fund are only kept for an 18-month period, which excluded our study patients. Questioning families about the use of medical resources for events that happened 2 or more years ago was not reliable and particularly difficult for this lethal condition. We therefore focused our analysis on inpatient care for which information on costs was available. The severity of the condition implies that most outpatient and inpatient care was ensured by specialized institutions and in comparison, ambulatory care costs in doctors' offices can be assumed to be marginal. Finally, taking into account the impact on productivity of workdays lost may increase the ICER, since patients who had benefited from IPCH experienced more hospital admissions during the follow-up period than standard patients, but this needs to be corroborated by data.

Health economists are always faced with the issue of concluding whether or not a treatment strategy is cost-effective. We attempted to show that although IPCH is a resource intensive treatment (€33,659 [30,571–36,747]), the ICER €58,086 (35,893–112,839) is acceptable given the severity and the burden of PC. A widespread reference used to position the ICER result is the yearly cost of dialysis, which was recently estimated at €54,000 in France (Biomedical Agency website: http://www.agence-biomedecine.fr). We also selected three recent examples with proven high internal and external validity and whose disease severity is comparable to that of PC in terms of the prognosis: liver transplant versus no transplant, imatinib in unresectable metastatic gastrointestinal stromal tumors (GIST), and trastuzumab (including HER-2 testing) in metastatic breast cancer. In these studies, the ICERs were expressed as the cost per quality-adjusted life-year rather than as the cost per life-year saved. Nevertheless, some authors pointed out that quality adjusting does not substantially alter cost-effectiveness results [24,25]. The ICERs for liver transplant versus no transplant ranged between €31,000 and €70,000 [26]. In GIST [27], the ICER of imatinib compared to the best supportive care was estimated at between €75,000 and €146,000. The ICER of trastuzumab compared to standard chemotherapy (with no HER-2 testing) ranged from €103,000 to €120,000 depending on the combination of tests performed to establish the HER-2 status [28]. We conclude that IPCH is a cost-effective treatment in selected PC patients. Such a conclusion should have funding implications. In the French Prospective Payment System, no specific DRG exists for IPCH and the current tariff is far below the cost of the hospital stay for IPCH.

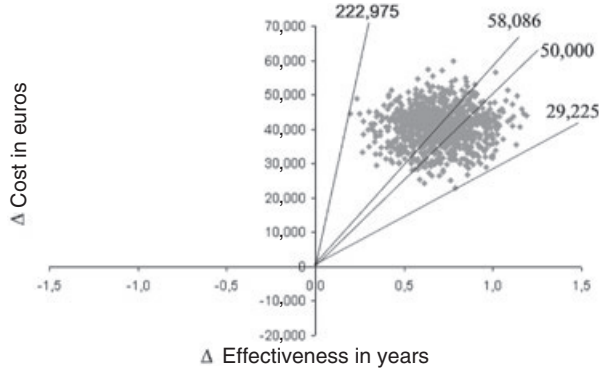

Figure 3 One thousand bootstrap replicates of the cost-effectiveness ratio.

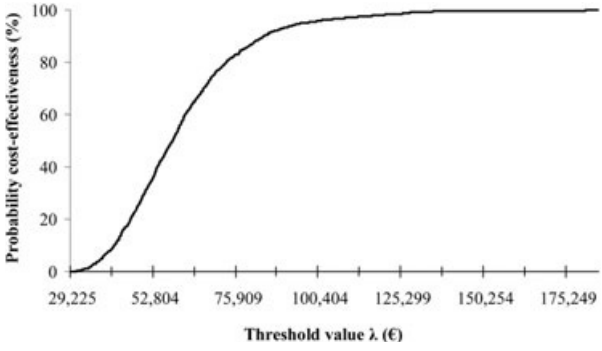

Figure 4 Cost-effectiveness acceptability curve.

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