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VALUE IN HEALTH

An Economic Evaluation of Cetuximab Combined with Radiotherapy for Patients with Locally Advanced Head and Neck Cancer in Belgium, France, Italy, Switzerland, and the United Kingdom

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[Correction added after online publication 28-May-2008: Table 6 caption has been updated]

ABSTRACT

Objectives: A phase III randomized trial that compared the combination of cetuximab and radiotherapy to radiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck provided a platform for a comprehensive economic evaluation. The study was conducted to estimate the cost-effectiveness of cetuximab in combination with radiotherapy compared to radiotherapy alone, for the treatment of locally advanced head and neck cancer in patients for whom chemoradiotherapy is inappropriate or intolerable.
Methods: Separate economic analyses were conducted for Belgium, France, Italy, Switzerland, and the United Kingdom. The economic model was based on individual patient data extracted from an international phase III trial. Country-specific costs of care from official sources were applied in each analysis. Clinical expert panels supplemented resource use estimates from the phase III trial and validated assumptions used to extrapolate costs and health outcomes beyond the follow-up of the phase III trial.
Results: In the base-case analysis, the incremental cost per quality-adjusted life-year for patients receiving radiotherapy in combination with cetuximab compared to radiotherapy alone among all countries was in the range of €7538 to €10,836. Sensitivity analysis showed the results to be robust.
Conclusion: This cost-effectiveness analysis indicated that the addition of cetuximab to high-dose radiotherapy offers a good value-for-money alternative to radiotherapy alone in the treatment of locally advanced head and neck cancer in five European countries.
Keywords: cetuximab, economic, head and neck cancer, models, quality-adjusted life-years, radiotherapy.

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is a group of malignant tumors primarily arising in the oral cavity, nasopharynx, pharynx, and larynx [1]. SCCHN is the sixth most common form of cancer worldwide representing approximately 5% of all cancers. A total of 500,000 new cases are diagnosed worldwide each year [2]. Tobacco and alcohol consumption are etiological factors involved in the onset of SCCHN, which commonly affects middle-aged or older men. Furthermore, patients with head and neck cancer are typically from lower-income groups and are often socially marginalized, and approximately half of the patients suffer numerous secondary health problems such as pulmonary, cardiovascular, hepatic, or neurological disorders [1,3].

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Chemotherapy with concurrent radiotherapy (CRT) presently is considered to be standard care for patients with good performance status [4]; however, survival gains with CRT are almost universally accompanied by severe, acute dose-limiting toxicities and, in some patients, a higher proportion of late toxicities [5]. Radiotherapy alone, especially through the delivery of altered fractionation, remains the principal treatment used in patients for whom CRT is contraindicated or cannot be tolerated [4–6].

The epidermal growth factor receptor (EGFR) is abnormally activated in patients with head and neck cancers. The cells of almost all such neoplasms express high levels of EGFR, a feature associated with a poor clinical outcome [7]. Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signaling sensitizes cells to the effects of radiation. Cetuximab (Erbitux), an IgG1 monoclonal antibody against EGFR, enhances the cytotoxic effects of radiation in SCCHN [8]. In a recent phase III randomized trial, the addition of cetuximab to high-dose radiotherapy (ERT) significantly increased duration of

locoregional disease control, progression-free and overall survival compared to high-dose radiotherapy alone among patients with locally advanced head and neck cancer treated with curative intent [9]. Notably, cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck. In the absence of a randomized trial between ERT and CRT, it remains unclear how these two regimens compare; however, it is reasonable for clinicians to consider the use of ERT in patients who are not good candidates for CRT or surgery [4].

Evidence of a new drug's safety and efficacy is no longer sufficient to ensure reimbursement for use in public markets. Increasingly, funding of new drugs is based on evidence of cost-effectiveness [10]. Many countries in Europe have introduced formal requirements and/or voluntary guidelines for economic evidence to be submitted as part of the pricing or reimbursement decision. These include, among others, Belgium, France, Italy, Switzerland, and the United Kingdom (including the Scottish Medicines Consortium and the National Institute for Health and Clinical Excellence).

The current literature evaluating the cost-effectiveness of interventions for patients with head and neck cancer is extremely scarce. A recent review could only identify publications that reported original cost data on diagnosis, treatment, and management. No economic evaluations have been published for cetuximab in locally advanced head and neck cancer [11]. The aim of this study was therefore to determine if ERT is cost-effective compared to radiotherapy in the treatment of locally advanced head and neck cancer. Separate analyses were conducted for five European countries: Belgium, France, Italy, Switzerland, and the United Kingdom.

Materials and Methods

Clinical Trial Design, Patient Population and Treatment

The economic evaluation was based on a phase III randomized trial that compared ERT to radiotherapy in patients with locally advanced SCCHN. Full details of this study have been published elsewhere [9]. Briefly, patients with stage III or IV, nonmetastatic, measurable SCC of the oropharynx, hypopharynx, or larynx were stratified by Karnofsky performance status (90–100 vs. 60–80), regional node involvement (positive vs. negative), tumor stage (T1–3 vs. T4), and radiation fractionation (concomitant boost vs. once daily vs. twice daily), and then randomized (1:1) to treatment with radiotherapy alone for 6 to 7 weeks (n = 213) or in combination with weekly administered cetuximab (n = 211).

In the ERT group, administration of intravenous cetuximab was initiated 1 week before radiotherapy at a loading dose of 400 mg/m^2 of body surface area over a period of 120 minutes, followed by weekly 60-minute infusions of 250 mg/m^2 for the duration of radiotherapy.

The primary end point was the duration of locoregional disease control; secondary end points were overall survival, progression-free survival, the response rate, safety, and quality of life. Routine assessments were performed weekly during radiotherapy, and disease assessments were performed at week 4 (except CT scans or magnetic resonance imaging) and week 8 after radiotherapy, every 4 months thereafter for 2 years; and then semiannually during years 3, 4, and 5. Acute toxic effects were assessed through the 8 weeks after treatment. Late radiation effects were assessed thereafter using the Radiation Therapy Oncology Group toxicity scales. Quality-of-life questionnaires were included in the study (the EORTC QLQ-C30, version 3.0 and the head and neck module QLQ-H & N35).

Economic Model Overview

The economic model provides cost-utility analyses undertaken from the perspective of the national health system of each country, or where not applicable, from the perspective of the major national payer in the relevant country. The time horizon of the model was patient lifetime (in the base case), which is appropriate when evaluating two interventions with different overall survival times. Costs and health outcomes were discounted to present value at 3.5%. The model was constructed at an individual patient level using the trial data set provided by Merck KGaA, Darmstadt, Germany. All study patients were included in the model for costs and outcomes (intention-to-treat analysis). Nevertheless, a few patients did not record any adverse events or treatment costs because of early withdrawal from the trial, and consequently some cost items were zero for these patients.

Health Outcomes in the Economic Evaluation

It is essential for economic evaluation to estimate mean—not median—survival times for each treatment group [12,13]. This involved an extrapolation of the survival curves beyond the follow-up time in the trial because the right tail of the survival distributions included censored observations.

Parametric survival models were used to impute censored survival times for progression-free and overall survival; otherwise, the known time-to-event data were used without any adjustment. The treatment goal for patients with newly diagnosed but unresectable disease is cure [6] and in this context it was deemed appropriate to fit a cure model [14]. Statistical analysis of the hazard functions for the progression-free survival and overall survival curves in the trial supported this decision. The STATA command "cur-

eregr" was used to estimate the proportion of patients who were "cured" and thus would never experience the event of interest (progression or death). The overall survival probability of cured patients was estimated from life tables together with an estimate of the proportional increase in mortality hazard for patients who have experienced locally advanced SCCHN, based on 10-year overall survival curves reported in a large meta-analysis [15]. For estimating the survival of non-cured patients, the goodness-of-fit of various models was assessed using the log-likelihood statistic and the results were similar across most of the models (Weibull, log-normal, logistic, gamma, and exponential). The log-normal model was chosen because it is appropriate for characterizing patterns of survival where the hazard is initially increasing, but then begins to decrease. The specific details of the cure model is not the central point of this article, so it is important to emphasize that two alternatives to the cure model were tested for the estimation of progression-free and overall survival times: first, an analysis limited to the period of follow-up in the trial; and second, a Weibull survival distribution. The results of these models are presented in the sensitivity analyses.

The model estimates quality-adjusted life-years (QALYs), life-years (LYs), and progression-free survival for each treatment group. The quality-of-life instruments in the trial (EORTC QLQ-C30, QLQ-H & N35) could not be used in cost-utility analysis because there is currently no preference-based scaling method to translate these data into an utility score where full health = 1 and dead = 0 [13,16]. Utility values for key health states were therefore estimated in a separate study where 50 oncology nurses in the United Kingdom evaluated quality of life using the EQ-5D for eight key health states (Table 1). Recruitment screening criteria identified nurses with experience of at least 2 years in medical oncology, seeing 11 patients or more with SCCHN in the last 3 months, with experience in treating patients with radiotherapy, chemotherapy, or chemoradiotherapy. The nurses were asked to complete the EQ-5D for each health state, which was described to them, such that their ratings reflected their judgement about a patient's health-related quality of life when experiencing each health state. Preference weights for the EQ-5D scoring function have been elicited using the time-trade-off technique on a random sample of 3395 members of the adult population in the United Kingdom [17], and therefore the scoring is representative of preferences of the general public.

Patient time was allocated among the first six health states (A–F, Table 1) according to adverse events recorded in the patient-level data set. Patients with more than one simultaneous adverse event were allocated to the health state associated with the worst quality of life. The average duration of each adverse event health state was calculated using the trial data set. The time in the acute treatment phase and the average duration of each health state event applied to the model for both treatment groups is presented in Table 1.

After the acute phase, the remainder of each patient's overall survival was allocated between the post-treatment health states according to their progression-free survival (health state J) and survival with progressive disease (health state K).

Resource Use

The patient-level data set provides the primary source of evidence regarding resource use in the model. Nevertheless, hospitalization in the trial was protocol-driven and therefore may not entirely be representative of local clinical practice. Furthermore, health-care resource use data collection was not an explicit part of the protocol and as a result information was not consistently collected in the trial. Where the data set did not provide adequate information about resource use, such as drug administration costs, local expert clinical opinion and published national reference costs were used. A panel of clinical experts was convened in each country to provide opinion about resource utilization representative of local practice. The clinicians provided individual written answers to a questionnaire,

Table 1 Model health states and utilities

Health state	Definition	Utility	Time (day)*
Acute phase health states			
A	General in-treatment—range of ≤grade 1 adverse events	0.659	n/a
B	As health state A plus grade 3 or 4 mucositis, stomatitis, and dysphagia	0.062	55.43
C	As health state A plus grade 2 mucositis, stomatitis, and dysphagia	0.608	34.46
D	As health state A plus grade 3 or 4 nausea and vomiting	0.108	13.14
E	As health state A plus grade 2 nausea and vomiting	0.573	29.82
F	As health state A plus grade 3 or 4 acne and rash	0.226	72.92
Postacute phase health states			
J	Post-treatment locoregional disease control	0.862	n/a
K	Post-treatment progressive or worsening disease	0.129	n/a

*An average time in adverse event health states B–F was calculated using patient-level data where a start and end date was known. Average time was then assigned to patients having the adverse event. Health state A took the remaining time in the acute phase after allocation of time to other health states. Time in health states J and K was available for each patient.

Table 2 Resource use categories and data sources

Resource	Primary data source
Radiotherapy treatment (type & days)	Pivotal trial data set
Study drug (vial usage)	Pivotal trial data set
Administration of therapy	Pivotal trial data set (frequency of administration); Expert panel (administration setting and schedule)
Treatment of adverse effects	Pivotal trial data set (frequency and duration of event); Expert panel (resource use)
Imaging	Expert panel
Routine monitoring	Expert panel
Procedures	Expert panel
Salvage/palliative care	Pivotal trial study report

and numerical estimates were then negotiated in open discussion until a consensus was reached. Table 2 presents the principal source of evidence for model variables.

Radiotherapy Treatment

The trial included three radiotherapy treatment regimens:

1. Once daily: 35 fractions, 5 fractions per week for 7 weeks (conventional regimen);
2. Twice daily: 60 to 64 fractions, 10 fractions per week for 6 to 6.5 weeks;
3. Concomitant boost: 42 fractions, 5 fractions per week for 3.5 weeks then 10 fractions per week for 2.5 weeks.

These latter schedules (2 and 3) were therefore two variants of altered fractionation regimens.

Costs consisted of radiotherapy set-up, daily radiotherapy, and administration. Members of expert clinical panels provided information about the local setting for radiotherapy administration (inpatient, day case, outpatient) while the patient-level data set provided information on the type and number of days of therapy received per patient.

Cetuximab Cost and Administration

The patient-level data set recorded the exact dose of cetuximab administered to each patient in the ERT group. Each dose was rounded up to the nearest vial size to account for wastage in the model. The cost of cetuximab in each country is shown in Table 3.

The cost of administration for patients in the ERT group was estimated by applying local clinical practice norms that dictated settings—inpatient, day admission, or outpatient—and using published national reference costs (Table 3). The cost of radiotherapy administration was added to cetuximab administration costs in the ERT group.

Treatment of Adverse Events

Consultation with experts sought to identify adverse events associated with the greatest cost significance and possible groupings of these events (Table 3). The patient-level data set provided incidence rates for the selected adverse events.

Published national reference costs for diagnosis-related groups of hospital admissions were used to establish costs for these adverse events on an episode basis. Members of the clinical expert panels estimated the probability of hospitalization for each adverse event. Table 3 presents the unit costs used for adverse event categories in each country analysis.

Patient Imaging and Routine Monitoring

The model includes imaging and routine-monitoring costs. The clinical expert panels provided estimates on the types of scans performed and their typical frequency, as well as information on the frequency of specialist visits, for patients in this population. Table 3 presents the unit costs for each type of scan and outpatient visit. Routine monitoring costs were applied for each patient according to survival duration. Costs incurred after the first year were discounted.

Salvage/Palliative Care

The model assumed that the pattern of care changed after patients moved into progressive disease. Information on rates of salvage surgery, secondary radiotherapy, and secondary systemic therapy was obtained from the trial. Expert opinion informed rates and use of palliative care nursing.

Unit costs were sourced for these items to estimate costs of salvage/palliative care and were applied in the model after disease progression of surviving patients (Table 3). The costs were discounted if that point occurred after the first year.

Percutaneous Endoscopic Gastrostomy

The economic model considers the cost of percutaneous endoscopic gastrostomy (PEG), which may be performed prophylactically on patients in this population. The clinical expert panels provided estimates of the frequency of PEG procedures. The cost of PEG in each country is presented in Table 3.

Addressing Uncertainty

In order to address uncertainty around the observed cost and effect values of the model cohort, stochastic and one-way sensitivity analyses were performed on the lifetime cost-utility analysis [18]. Individual patient cost and health outcomes estimates were sampled by applying a bootstrapping approach. A set of 2000 samples was obtained from the observed estimates in both the ERT and radiotherapy groups.

Sensitivity Analyses

One-way and scenario-based sensitivity analysis was also performed, where appropriate, on model variables (discount rate, radiotherapy administration cost, costs

Table 3 Unit costs by country (€, 2005/2006 values)

Parameter	Belgium	France	Italy	Switzerland	United Kingdom
Cetuximab 100 mg	199	209	199	200	203
Cetuximab administration: outpatient visit	118	424.17	21	468 (1st) 312 (latervisits)	266 (1st); 186 (latervisits)
PEG	1,733	126	n/a	n/a	1,118
Adverse events[†‡]					
Acne/rash grade 3	2,514	2,037	1,727	1,914	2,173
Acne/rash grade 4	2,514	3,995	1,727	1,914	2,173
Anaemia grade 3	3,507	378[§]	3,418	957	1,386
Anaemia grade 4	3,507	2,260	3,418	957	1,386
Dehydration grade 3 or 4	2,452	671	2,581	3,349	1,400
Febrile neutropenia grade 3 or 4	4,221	4,311	4,824	5,741	1,993
Fever/infection grade 3	4,001	277	5,983	4,784	3,288
Fever/infection grade 4	4,001	3,743	5,983	4,784	3,288
Mucositis/stomatitis/dysphagia grade 2	4,408	1,756	3,605	n/a	2,710
Mucositis/stomatitis/dysphagia grade 3	4,408	1,756	3,605	3,349	4,524
Mucositis/stomatitis/dysphagia grade 4	4,408	3,236	3,605	26,790[‖]	4,524
Nausea/vomiting grade 2	2,076	1,635	1,757	n/a	1,047
Nausea/vomiting grade 3	2,076	1,635	2,507	2,870	1,638
Nausea/vomiting grade 4	2,076	3,612	2,507	5,262	1,638
Thrombocytopenia grade 3	3,098	363*	4,824	1,914	1,993
Thrombocytopenia grade 4	3,098	6,580	4,824	1,914	1,993
Weight loss grade 3	3,198	1,981	n/a	10,046[‖]	2,264
Weight loss grade 4	3,198	3,697	n/a	10,046[‖]	2,264
Imaging					
CT scan	112.51	25.00	137.90	146	87
MRI scan	94.82	69.00	249.45	229	327
PET scan	324.84	0.00	n/a	403	1,304
X-rays	29.59	0.00	n/a	33	48
Palliative/salvage care					
Nurse (palliative)	54.63	37.70	n/a	35[¶]	639[#]
Nurse (oncology)	10.91	7.25	n/a	35[¶]	431[#]
Surgery: resection without severe complications	12,109	6,785	3,605	2,629	18,674
Cisplatin 50 mg	35	3	14	67	38

*Unit cost is €13 per 5 minutes. Assumed 180 minutes for initial loading dose, 120 minutes per infusion thereafter.
[†]With severity according to NCI CTC/RTOG toxicity grades.
[‡]For Switzerland, all adverse event costs were estimated using the average cost per diem of canton hospitals multiplied by average length of stay estimated by the local clinical expert panel for that adverse event.
[§]For France, the cost of anaemia grade 3 and thrombocytopenia grade 3 were day-case casemix codes.
[‖]For Switzerland, the high cost of mucositis/stomatitis/dysphagia grade 4 is due to an estimated inpatient length of stay of 28 days. Similarly, weight loss grades 3–4 had an estimated length of stay of 10.5 days.
[¶]For Switzerland, the hour rate for nursing care was estimated as the average tariff of a convenience sample of 10 cantons, assuming that typically 50% of real costs are covered by the taxpayer.
[#]For the United Kingdom, the costs of nursing care are per episode of community/outreach nursing care.
Unit cost sources: Belgium (Official tarifs Belgium, Cecodi, 2005, http://www.riziv.fgov.be/prices 2005, INAMI/RIZIF; Technische cel MKG-MFG data. Site: http//tct.fgov.be); France (T2A: casemix-based hospital financing system 2005); Italy (diagnosis-related groups); Switzerland (Bundesamt für Gesundheit, Spezialitätenliste, http://www.galinfo.net/sl/batchhtm/substance.htm; http://www.fmh.ch/tarif-browser/de/); United Kingdom (NHS reference costs [health-related groups]; MIMS March 2005).
Currency analysis: Unit cost values were provided in Euros except for Switzerland (CHF) and the United Kingdom (GBP). Exchange rate: CHF to Euros 0.628955; GBP to Euros 1.49022.
MRI, magnetic resonance imaging; PEG, percutaneous endoscopic gastrostomy; PET, positron emission tomography.

of adverse event treatment, acute health state utilities, duration of health states, and postacute health state utilities) and on different survival extrapolation methods [13,19] for all country analyses.

Results

Base-Case Analysis

Clinical. As reported previously [9], with a median follow-up of 54.0 months in the trial, the addition of cetuximab to radiotherapy prolonged the duration of locoregional control by almost 10 months compared to radiotherapy alone, with a median duration of 24.4 months versus 14.9 months ($P = 0.005$, 95% confidence interval [CI] 0.52–0.89, hazard ratio 0.68). The median survival time was 49.0 months among patients treated with combined therapy and 29.3 months among those who received radiotherapy alone ($P = 0.03$, 95% CI 0.57–0.97, hazard ratio 0.74), while the median progression-free survival was 17.1 months for ERT and 12.4 months for radiotherapy ($P = 0.006$, 95% CI 0.54–0.90, hazard ratio 0.70).

Economic. After extrapolation of the cure model's survival curves, ERT had an estimated overall survival advantage over radiotherapy of 12.7 months, or 0.92 years after discounting (discount rate applied 3.5% per annum, see Fig. 1, Table 4). In addition to this survival advantage, the model estimates that patients treated with ERT gain on average of 3.96 QALYs compared to 2.88 QALYs for those treated

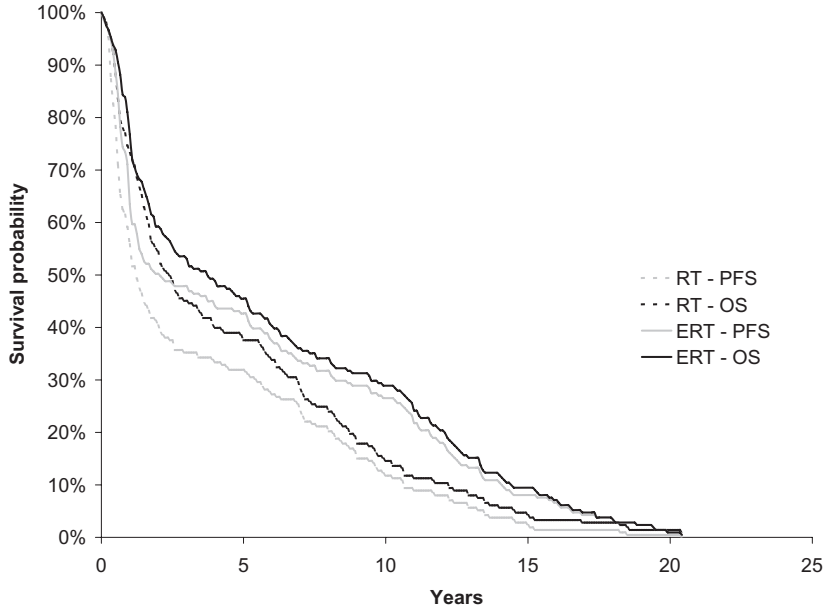

Figure 1 Cure model survival analysis (progression-free survival [PFS] and overall survival [OS]). ERT, cetuximab in combination with radiotherapy; RT, radiotherapy.

with radiotherapy. The health benefits of the two treatment groups in terms of QALYs, overall survival, and progression-free survival are summarized in Table 4.

Moreover, ERT is associated with an increased cost per patient. The expected cost values per patient for each country are presented in Table 5. The key driver of the cost difference is cetuximab acquisition, and subsequently, the administration cost. All other cost categories were comparable between treatment groups.

Most of the cost was incurred during the first 5 years of therapy. Imaging and routine-monitoring costs were accrued during the first 3 and 4 years, respectively. Palliative care was assumed to be administered from the point of disease progression.

Based on these estimated costs and outcomes, the incremental cost-effectiveness ratios (ICERs) were calculated for the five countries in focus. The additional costs per QALY gained ranged from €7000 to €11,000 (Table 6).

Addressing Uncertainty

The cost-effectiveness acceptability curves in Figure 2 present the probability that ERT is cost-effective compared to radiotherapy across different cost-effectiveness threshold values for all countries in focus. In all countries, 98% or more simulations produced a cost per incremental QALY of less than €30,000.

Table 4 Health outcomes results (discounting applied*)

	RT	ERT	Difference (95% CI†)
QALY	2.88	3.96	1.08 (0.42–1.80)
Overall survival (year)	4.18	5.10	0.92 (0.11–1.80)
Progression-free survival (year)	3.31	4.62	1.31 (0.53–2.15)

*Discounted at 3.5% per annum.
†95% Bias-corrected confidence interval (percentile method) based on 2000 bootstrap iterations.
ERT, cetuximab in combination with radiotherapy; QALY, quality-adjusted life-year; RT, radiotherapy.

Sensitivity Analysis

The results of the study were most sensitive to the choice of time horizon for the analysis (Table 7). The most conservative scenario assumes that the accrued survival benefit is immediately lost at the moment the trial ends and therefore considers only the period from the start of the study to the end of follow-up. This extreme analysis resulted in estimated mean overall survival times of 39.5 months and 34.9 months for ERT and radiotherapy, respectively, a difference of 4.6 months in favor of ERT, increasing the incremental costs per QALY up to €33,535.

Using the Weibull model instead of the cure model to extrapolate the survival curves beyond trial duration resulted in a small improvement of the cost-effectiveness ratio in favor of cetuximab and radiotherapy. This was due to an increased incremental QALY gain for cetuximab under the Weibull survival curves.

Substantial changes to the utility values for the post-acute treatment phase also had a significant impact on the ICER. Nonetheless, in all scenarios ERT still represents a cost-effective alternative to radiotherapy.

Discussion

The ERT significantly increased duration of locoregional disease control, progression-free survival, and overall survival compared to high-dose radiotherapy alone among patients with locally advanced head and

Table 5 Estimated costs by country (€)

	Belgium		France		Italy		Switzerland		United Kingdom	
	RT	ERT	RT	ERT	RT	ERT	RT	ERT	RT	ERT
Cetuximab	0	8,002	0	8,405	0	8,002	0	8,063	0	8,180
Radiotherapy	2,596	2,534	5,995	5,909	2,072	2,048	2,420	2,363	3,965	3,871
Administration	137	966	145	3,396	171	330	2,243	4,851	908	2,416
Adverse events	3,213	3,395	1,479	1,614	2,371	2,282	3,276	3,765	1,133	1,136
Imaging	1,022	1,187	454	475	787	823	444	458	437	437
Monitoring	253	275	197	215	238	244	553	574	2,417	2,766
Procedures	433	433	31	31	0	0	0	0	167	167
Palliative/salvage	1,741	1,846	1,072	1,019	519	561	615	620	1,685	1,603
Total	9,395	18,638	9,373	21,064	6,158	14,291	9,552	20,695	10,710	20,575
INCREMENT		9,244		11,691		8,133		11,143		9,865

ERT, cetuximab in combination with radiotherapy; RT, radiotherapy.

Table 6 Incremental cost-effectiveness ratios (€)

Analysis	Belgium	France	Italy	Switzerland	United Kingdom
Cost per QALY gained	8,568	10,836	7,538	10,328	9,144
Cost per LY gained	10,086	13,367	8,874	12,159	10,765
Cost per PFS year gained	7,041	8,907	6,195	8,489	7,515

1€ = 0.6289 CHF; 1€ = 0.671 GBP (November 2006).
LY, life-year; PFS, progression-free survival; QALY, quality-adjusted life-year.
[Correction added after online publication 28-May-2008: Table 6 caption has been updated].

neck cancer treated with curative intent [9]. The findings of the economic study presented here suggest that the use of cetuximab with radiotherapy is a cost-effective health-care intervention in the five countries studied for patients with locally advanced head and neck cancer who are not amenable to chemoradiotherapy. Despite the increase of total treatment costs through the addition of cetuximab to radiotherapy, the incremental costs per additional QALY range from €7538 (Italy) to €10,836 (France), which is far below commonly accepted cost-effectiveness thresholds in Europe [10]. Published estimates of a cost-effectiveness threshold for the United Kingdom [20,21] converted into Euros provide values of €30,000 to €45,000; this threshold range is higher than the estimated ICER for any country-specific analysis. Sensitivity analysis indicated the robustness of these results.

The objective of this economic evaluation was to estimate the cost-effectiveness of ERT compared to radiotherapy in the treatment of locally advanced head and neck cancer for those patients who presently are treated with radiotherapy alone. Chemoradio-

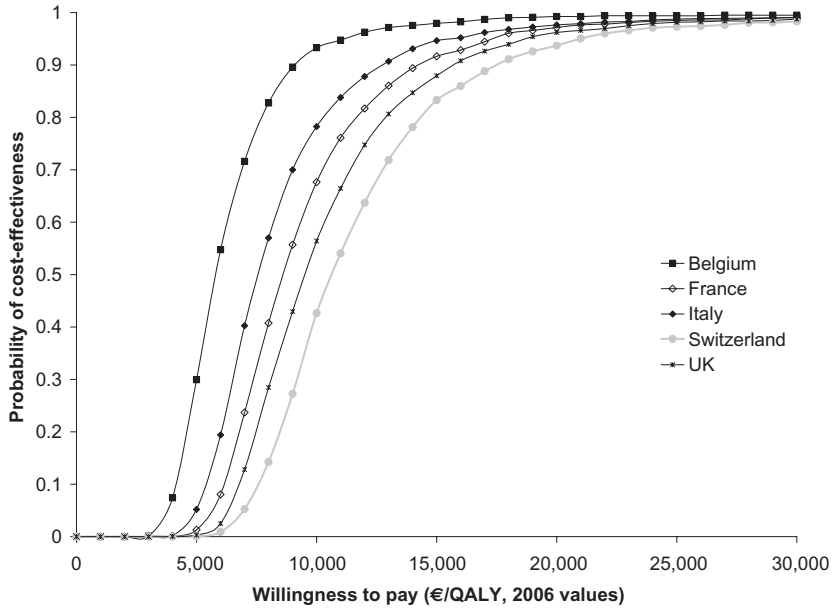

Figure 2 Cost-effectiveness acceptability curves. Curve shows the probability that a cetuximab in combination with radiotherapy is cost-effective versus radiotherapy alone for a range of decision-makers' maximum willingness to pay per quality-adjusted life-year (QALY).

Table 7 Sensitivity analysis on incremental cost per QALY gained (€)

Analysis	Belgium	France	Italy	Switzerland	United Kingdom
Base case	8,568	10,836	7,538	10,328	9,144
Extrapolation of survival					
Restricted means survival data*	26,731	33,535	23,740	32,440	28,729
Extrapolation using the Weibull distribution	7,970	10,394	6,959	9,524	8,407
Discounting					
0% discount rate (costs & benefits)	6,820	8,500	5,934	8,119	7,233
5% discount rate (costs & benefits)	9,393	11,925	8,297	11,373	10,050
Utility values					
Halve increment between locoregional control and progressive disease utility (HS J 0.679; HS K 0.312)	12,078	15,430	10,626	14,560	12,890
Administration cost for cetuximab					
Increased by 100%	9,406	13,849	7,685	12,706	10,537

*Analysis restricted to the study follow-up period.
HS, health state; QALY, quality-adjusted life-year.

therapy with cisplatin is the recommended standard of care for patients who can tolerate it [4–6]. This recommendation is not affected by the conclusions of our study: such a change to clinical practice normally would need a clinical trial directly comparing ERT to CRT. Nevertheless, our conclusion applies to the situation when CRT is inappropriate, such as when there are coexisting medical conditions in the light of chronic alcohol and tobacco use; contraindications to chemotherapy (e.g., renal failure, cardiac dysfunction, poor hearing, tinnitus, neuropathy); or in patients with poor performance status; and when there are other factors such as socioeconomic factors (e.g., low social support) and patient choice [5,9,22]. The trial that this economic evaluation is based on was not designed or statistically powered to assess specifically those subgroups of patients who may be inappropriate for CRT treatment. Nevertheless, in our opinion the use of the whole trial data set is justified because the clinical factors that lead to CRT being considered inappropriate are highly variable and these factors are not necessarily likely to modify the treatment benefit of ERT.

The economic model is conceptually simple. Costs are similar for both treatment groups, except for the additional cost of cetuximab, and the differences in health outcomes (progression-free survival and overall survival) were proven within the trial. The costs of managing the adverse effects of treatment in SCCHN are high [23,24]; however, cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck. Because the cost of cetuximab is the key driver of the cost difference between the treatment groups, it is useful that patient-level data were used to accurately estimate drug usage and costs.

Our analysis has several limitations. First, the imputation of censored progression-free and overall survival data is always subject of some uncertainty. Nevertheless, this should not be overstated, because sensitivity analyses show that the cost-effectiveness of cetuximab is robust to various methods of extrapolation, and in fact, the ICER for cetuximab is below common cost per QALY threshold even under the conservative situation of zero data imputation.

A second limitation is that utility data were not available directly from the trial. Therefore, it was necessary to estimate utilities based on a separate health state valuation study and a mapping exercise using patient-level data from the trial. Sensitivity analyses revealed that the economic model results were not sensitive to utility values based on adverse event status; however, they were somewhat sensitive to the use of extreme, albeit implausible, values for locoregional disease control and progressive disease.

A final concern is that some of the unit costs available for health economic evaluation varied substantially across the countries. Nevertheless, the absolute level of most unit costs does not differentially affect the treatment arms. The cost items that drive the difference between the treatment arms are the price of cetuximab and its administration costs.

In conclusion, the study shows that the addition of cetuximab to radiotherapy is a cost-effective treatment regimen in locally advanced head and neck cancer patients in Belgium, France, Italy, Switzerland, and the United Kingdom, who are not amenable to chemoradiotherapy, and for whom radiotherapy is the best option.

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