Cost–Utility Analysis of Short- Versus Long-Course Palliative Radiotherapy in Patients With Non–Small-Cell Lung Cancer

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Background: Radiotherapy can effectively palliate the symptoms of poor-prognosis patients with non–small-cell lung cancer. However, controversy remains about whether short-course or more protracted radiotherapy schedules provide better value for the money. We conducted a societal cost–utility analysis of a Dutch multicenter randomized trial with 1-year follow-up that compared the efficacy of radiotherapy schedules consisting of 10 fractions of 3 Gy (10 × 3 Gy) versus two fractions of 8 Gy (2 × 8 Gy) in 297 patients with inoperable stage IIIA/B or stage IV non–small-cell lung cancer. This trial found that the 10 × 3–Gy group had better survival than the 2 × 8–Gy group. Methods: Lifetime quality-adjusted life-years (QALYs) were estimated using the EuroQol questionnaire. Lifetime societal costs were estimated using a model estimated based on data from cost questionnaires filled out by a subset of patients (n = 56). Differences were analyzed statistically using twosided nonparametric bootstrapping. Results: Compared with the 2 × 8–Gy group, the 10 × 3–Gy group accrued statistically significantly more QALYs (20.0 versus 13.2 weeks; difference = 6.8 weeks, 95% confidence interval [CI] = 0.1 to 13.5 weeks, P = .05), which was mainly due to the statistically significantly better survival (38.1 versus 27.4 weeks; difference = 10.7 weeks, 95% CI = 0.9 to 20.6 weeks, P = .03) without a statistically significant difference with respect to the average valuation of health (P = .27). Total radiotherapy and radiotherapy-related costs were estimated at $5236 for the 10 × 3–Gy group and $2512 for the 2 × 8–Gy group (difference = $2724, 95% CI = $2501 to $2947, P < .001). The 39% increase in life expectancy in the 10 × 3–Gy group as compared with the 2 × 8–Gy group was associated with a 30% increase in survival-related nonradiotherapy costs ($11254 versus $8651, difference $2602, 95% CI = $357 to $5562, P = .09). The cost–utility ratio for the 10 × 3–Gy schedule versus the 2 × 8–Gy schedule was estimated at $40900 per QALY (95% CI = $19400 to $110000 per QALY). Conclusions: In these poor-prognosis non–small-cell lung cancer patients, the estimated cost–utility ratio for the palliative 10 × 3–Gy schedule was acceptable according to current economic standards. However, the additional costs for the protracted schedule were justified not by improved quality of life but by longer survival. [J Natl Cancer Inst 2006;98:1786–94]

In patients with non–small-cell lung cancer, palliative radiotherapy can effectively reduce chest pain and hemoptysis as well as dysphagia and dyspnea (1–3). Combined-modality treatment for patients with stage III disease and chemotherapy for patients with stage IV disease have resulted in improved quality of life and survival (4). However, these poor-prognosis patients are frequently too ill for these more intensive treatments (5). Moreover, even after palliative chemotherapy, locoregional treatment may eventually be required to control locoregional symptoms. Controversy remains about whether more protracted radiotherapy schedules provide better results than short-course schedules (6). To date, none of the randomized trials that have compared different radiotherapy schedules in non–small-cell lung cancer patients have shown a difference in palliation (7–10). The results of these trials with respect to survival have been inconclusive: two trials conducted in the early 1990s showed no difference (7,8), whereas two later trials (9,10) showed that patients who received the long-course radiotherapy schedules survived longer than those who received the short-course schedules, particularly patients with a good prognosis (9,10). To date, to our knowledge, no economic evaluations of these trials have been published.

The lack of an evidence-based consensus on the preferred palliative schedule for non–small-cell lung cancer patients with a poor prognosis led us to initiate a randomized trial in 1999 in The Netherlands (11). That trial included Dutch patients with stage IV disease or patients with stage IIIA/B disease who had experienced weight loss or had an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or worse. The patients were randomly assigned to receive radiotherapy in 10 fractions of 3 Gy (10 × 3 Gy) or in two fractions of 8 Gy (2 × 8 Gy). The trial showed no difference in average symptom control between groups during the first 9 months after the start of treatment. However, the patterns of symptom control over time did differ statistically significantly (P < .001), suggesting that the 10 × 3–Gy group had prolonged palliation with less worsening of symptoms than the 2 × 8–Gy group. In addition, 1-year survival was statistically significantly better in the 10 × 3–Gy group than in the 2 × 8–Gy group (19.6% versus 10.9%, P = .03). We therefore concluded that the 10 × 3–Gy schedule was preferred over the 2 × 8–Gy schedule for the palliative treatment of non–small-cell lung cancer patients with a poor prognosis. However, this conclusion did not take into account the difference in costs between the two treatment schedules: the protracted 10 × 3–Gy schedule results in
higher medical and patient costs and the gain in survival leads to continued costs. As a result, controversy has persisted about whether the better effectiveness of the 10 × 3–Gy schedule justified the additional costs.

To determine from a societal perspective which radiotherapy schedule provides better value for the money, we performed a full societal cost–utility analysis of the Dutch trial. We compared quality-adjusted life-years (QALYs), an overall measure of the patients’ quantity and quality of life, to the total costs to society, including the medical costs of radiotherapy as well as other health care costs and costs incurred by the patients during their remaining lifetime.

**Patients and Methods**

**Study Population**

A total of 303 patients from 13 of 21 Dutch radiotherapy centers entered the randomized trial from January 1, 1999, to May 31, 2002 (registered as trial ISRCTN04886579 at www.controlled-trials.com). The inclusion criteria for the randomized trial were cytologic or histologic confirmation of non–small-cell lung cancer; patients with stage IV disease [according to (12)] and patients with stage III A/B disease and either an ECOG performance score of 2 or worse or weight loss (defined as a decrease in total body weight of at least 5% during the 3 months before enrollment or of at least 10% during the 6 months before enrollment); at least some patient-reported burden due to the tumor on at least one of seven complaints: loss of appetite, dyspnea, chest pain, cough, hemoptysis, hoarseness, and dysphagia; and sufficient physical and mental fitness for study participation.

Patients were excluded if they had stage IV disease with an ECOG performance score of 2 or less and were eligible for chemotherapy, were undergoing chemotherapy, had previously undergone radiotherapy to the chest, had superior vena cava syndrome at presentation, or had been previously diagnosed with another malignant disease. Six patients who were initially characterized as eligible but subsequently found to have stage III disease with an ECOG performance score of 0 or 1 and no weight loss were later excluded. The remaining 297 patients were randomly assigned to the 10 × 3–Gy schedule (given in four or five fractions per week; n = 148) or the 2 × 8–Gy schedule (fractions given 1 week apart; n = 149).

Patients were followed for 1 year after randomization. The primary outcome measure of the study was a patient-assessed symptom score, which measured total disease burden with respect to seven symptoms: loss of appetite, dyspnea, chest pain, cough, hemoptysis, hoarseness, and dysphagia. Each symptom was rated on a 4-point scale that ranged from 1 (bothered not at all) to 4 (bothered very much). A total of 268 patients were needed for the primary outcome measure to obtain a power of 90% at a significance level of 5% to correctly conclude equivalence of the treatment arms (11). The study was approved by the Medical Ethics Committees of all participating institutions, and random assignment took place after the patients provided written informed consent.

**Assessment of Quality-Adjusted Life-Years**

The last systematic assessment of survival was performed in July 2002. At that time, 269 patients (91%) had died. By February 2004, 12 more patients (4%) were reported to have died, leaving 16 patients (5%) with unknown date of death (11 patients for the 10 × 3–Gy schedule and 5 patients for the 2 × 8–Gy schedule, P = .12). In the base-case analysis, we assumed that patients with unknown date of death had died in February 2004 and that their survival ranged from 21 to 60 months. This assumption likely underestimated the true survival times, especially for the group receiving the 10 × 3–Gy schedule, because that group contained more patients with unknown date of death.

Patients filled out at most 33 mailed questionnaires (at baseline before randomization, then every week for 12 weeks, and every other week for 40 weeks) containing questions about specific symptoms and about their quality of life, which was measured using the EuroQol (EQ-5D) classification system (13). The EQ-5D assesses general health status through five questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. We used the responses on the EQ-5D to calculate the EQ-5D utility (14). This utility reflects the valuation by the general public of the health states reported by the patients, ranging from 1.00 (optimal health), through 0.00 (as bad as death), to 0.594 (worse than death). In addition, patients directly evaluated their health on a 100-mm-long horizontal visual analog scale (VAS) that ranged from worst imaginable health (0.0) to perfect health (1.0). Because the VAS has repeatedly been found to render less favorable valuations of health than more valid (but also more complicated) utility measures (e.g., the time trade-off or the standard gamble methods), the reported VAS values were transformed using the power function TVAS = 1 − (1 − VAS)1.61 (15,16).

For each patient, QALYs were calculated as the area under the EQ-5D utility curve and were discounted at 3% per year. For most patients, utility measurements were not available for the entire lifetime: follow-up ended 1 year after randomization, and shortly before their deaths, patients tended to stop returning their questionnaires. During their lifetime, patients could on average have returned 17.3 EQ-5D questionnaires, of which on average 14.3 (83%) were actually obtained. Because the values of the missing utility measurements were likely to be worse than those of the available measurements, excluding the missing EQ-5D data or carrying forward the last measurement could lead to an overestimation of the utilities. For that reason, the missing EQ-5D utilities were imputed, using a decreasing first-degree rational curve from the last available measurement; the curve was estimated using the nonlinear regression module in SPSS 12.0.1 software (SPSS Inc, Chicago, IL) and the data shown in Fig. 3 as follows: imputed EQ-5D utility = constant × (1 + 50.1/remaining lifetime)−1, with remaining lifetime measured in days and the constant fitted to the patient’s last available EQ-5D utility. This utility model explained 23% of the variation in the data and provided extrapolated utility curves that were lower than those obtained by carrying forward the last available utility measurement but higher than those obtained by linear descent.

**Assessment of Costs**

For each patient, lifetime costs were estimated from a societal perspective. Estimated costs included the medical costs of radiotherapy, the nonmedical costs of radiotherapy (i.e., time and travel costs incurred by the patients), other medical costs (e.g., hospitalizations), health-related nonmedical costs (e.g., informal...
care), and survival-related costs (i.e., health care due to the length of the survival time) (17).

The medical costs of radiotherapy were estimated by using a previously published radiotherapy department model (18) in which the costs of different types of staff, equipment, material, housing, and overhead were obtained from three independent radiotherapy institutions and combined to represent a typical Dutch radiotherapy department. To estimate the costs of different radiotherapy schedules, we assigned each cost item to either of three allocation bases: treatments (for cost items that were independent of the treatment schedule), fractions (for cost items that were proportional to the number of fractions given), or Gy (for cost items that were proportional to the dose delivered). Thus, we estimated the unit costs to be $1898 per treatment, plus $109 per fraction, plus $9 per Gy, resulting in medical costs of $3260 and $2261 for the 10 × 3 Gy and the 2 × 8–Gy schedules, respectively. For other radiotherapy schedules and repeated radiotherapy, the actual schedules were used to estimate the costs. The average reported time spent per fraction was 126 minutes, and 68% of the patients reported that they had a travel companion. Time costs for patients and travel companions were valued at $11 per hour (19); the average time cost per fraction was estimated at $38. The means of transportation reported by patients to and from treatment were car (42%), taxi (50%), ambulance (6%), or walking (3%). The average travel distance was 20 km, and average travel costs were estimated at $65 per fraction.

Nonradiotherapy health care costs during the initial 12 weeks after randomization were estimated using patients’ responses to six biweekly mailed cost questionnaires. For practical reasons and to limit the burden to the patients, these questionnaires were sent to a subsample of the patients from the same three radiotherapy institutes that participated in the cost–price analysis “described above. Patients could refuse to fill out the cost questionnaires without being excluded from the effectiveness study. Of 113 consecutive patients, 56 (50%) consented. During their lifetime, patients could on average have returned 4.6 cost questionnaires, of which, on average, 3.3 (72%) were actually obtained. For missing cost measurements, the previous available measurement was carried forward. In the three-page, mostly closed-format cost questionnaires, patients reported all costs incurred by themselves and their families to treatment and other societal costs. Costs incurred by caregivers were valued at $11 per hour (19). Out-of-pocket expenses were valued as reported by the patients.

Lifetime nonradiotherapy health care costs were estimated for the entire sample, using a regression model and data obtained from the cost questionnaires. Using MLwiN 1.1 linear multilevel analysis software (Centre for Multilevel Modelling, University of Bristol, U.K.), which adjusted for repeated measures, we selected statistically significant predictors of total nonradiotherapy costs (stepwise selection with inclusion of variables with $P \leq 0.05$ and exclusion of variables with $P \geq 0.10$) from the following variables that were available throughout the remaining lifetime: time since randomization, time until date of death, age, sex, EQ-5D utility score, and VAS utility score. The analysis also included indicator variables for different costs during the initial 4 weeks after randomization in both randomization groups, to capture the costs related to the moment of randomization or to the initial radiotherapy.

Because most patients were retired or unemployed, differences in productivity costs between groups were assumed to be negligible (18). In a sensitivity analysis, we included consumption costs (24) at a rate of $43 per day, based on the average consumer expenditures for persons aged 65–74 years, excluding health care, insurance, and pension for 2003 (25).

Costs were discounted at 3%, updated to the price level of 2005 using the price index rate for the Dutch health care sector, and converted to US dollars using the July 2005 Dutch purchasing power parity index ($1 = $1.09).

Analysis

All analyses were performed on an intention-to-treat basis. For all outcome measures, differences between groups were tested using two-sided nonparametric bootstrapping (26) with 1000000 replications, and $P$ value of .05 or less was considered statistically significant. We report the corresponding symmetric 95% trimmed confidence intervals (CIs). Bootstrapping explicitly compares the means in both groups without making distributional assumptions, thus allowing for skewed distributed costs.

In the cost–utility analysis, the difference in lifetime QALYs between groups was compared to the difference in lifetime societal costs between groups. Whether a particular treatment is more cost effective than another treatment depends on the willingness to pay per QALY. We calculated the 95% confidence intervals for the cost–utility ratio (the difference in costs divided by the difference in QALYs) as those willingness-to-pay values for which the average net benefit (i.e., willingness to pay × QALYs – costs) in both randomization groups was not statistically significantly different (27). The net benefit approach avoids the problems associated with uninterpretable negative or infinite cost–utility ratios.

Statistical analysis represents only the uncertainty due to the random selection of the patient population and not the uncertainty due to modeling assumptions. We analyzed the latter using univariate sensitivity analyses for the assumed lifetime for patients with an unknown date of death (February 2004 versus 5 years after randomization), the utility measure (EQ-5D versus TVAS), and the included cost categories. The impact of assuming no survival difference was analyzed by multiplying each patient’s (quality-adjusted) survival time by a randomization group–specific factor, such that in both groups the average survival time matched the overall average survival time of 32.7 weeks.
RESULTS

Table 1 shows the baseline characteristics of the 297 patients included in the study. Baseline characteristics of the subsample of 56 patients who filled out the cost questionnaires did not differ statistically significantly from those of the rest of the sample (data not shown), except that the subsample contained more stage IV patients (59% versus 48%, \(P = .05\)) and more patients with squamous cell carcinoma (57% versus 42%, \(P = .04\)).

**Quality-Adjusted Life-Years**

The survival time was known for 95% of the patients. The solid lines in Fig. 1 show the survival curves for the two treatment groups, assuming that the remaining 5% of the patients died in February 2004. The corresponding life expectancy in the 10 × 3–Gy group was 39% longer than that in the 2 × 8–Gy group (38.1 versus 27.4 weeks; difference = 10.7 weeks, 95% CI = 0.9 to 20.6 weeks, \(P = .03\); Table 2).

Figure 2 shows the average valuation of health obtained from the EQ-5D as a function of the time since randomization. The average EQ-5D utility score improved slightly over time, because patients with worse scores were more likely to drop out of the sample because they died. Figure 3 shows the average EQ-5D utility measurements as a function of remaining lifetime. Toward the end of life, average EQ-5D utility markedly decreased, to values at or below zero. A total of 10% of all utility measurements were negative, indicating health states valued worse than death.

The average EQ-5D utility during the remaining lifetime was somewhat more favorable in the 10 × 3–Gy group than in the 2 × 8–Gy group, but the difference was not statistically significant (0.41 versus 0.37, \(P = .27\)). Quality-adjusted life expectancy (Table 2) was statistically significantly more favorable in the 10 × 3–Gy group than in the 2 × 8–Gy group (20.0 versus 13.2 weeks, difference = 6.8 weeks, 95% CI = 0.1 to 13.5 weeks, \(P = .05\)).

**Costs of Radiotherapy**

The average medical costs of the initial radiotherapy were estimated at $3120 for the 10 × 3–Gy group and $2173 for the 2 × 8–Gy group (Table 3). The actual radiotherapy schedule differed from the protocol-specified schedule for 35 patients (14% of the 10 × 3–Gy group versus 10% of the 2 × 8–Gy group, \(P = .28\)), mostly because of early stoppage of treatment. The difference between groups in total costs of the initial radiotherapy was estimated at $1668 ($4032 versus $2364, 95% CI = $1535 to $1801, \(P < .001\)); 57% of the estimated difference was medical costs, 15% was the patients’ time costs, and 28% was travel costs. The frequency of repeated radiotherapy was similar in both groups (5% in the 10 × 3–Gy group versus 6% in the 2 × 8–Gy group, \(P = .84\)), and the associated costs were nearly the same ($150 versus $148, respectively; \(P = .98\)). The total radiotherapy costs were estimated at $4182 for the 10 × 3–Gy group and $2512 for
the 2 × 8–Gy group (difference = $1670, 95% CI = $1459 to $1881, P < .001).

Societal Costs

Nonradiotherapy health care utilization and costs during the initial 12-week period after randomization, which were estimated from the cost questionnaires filled out by a subset of patients, showed no statistically significant differences between the randomization groups (Table 4). For both groups combined, approximately two-thirds of the estimated costs consisted of hospitalization costs.

Although the data from the cost questionnaires showed no difference between the randomization groups, they did provide an opportunity to construct a model to estimate the difference in survival-related costs between the groups. After we omitted non–statistically significant predictors (all with P ≥ .30), the multivariable regression model showed that costs were statistically significantly predicted by EQ-5D utility (P = .04) and were statistically significantly increased during the initial 4 weeks after randomization in the 10 × 3–Gy group (P = .001). These initially increased costs in the 10 × 3–Gy group were mainly due to hospitalizations and can be interpreted as radiotherapy-related costs because costs in the 2 × 8–Gy group were not statistically significantly increased during the initial 4 weeks after randomization (increased cost = $5, 95% CI = −$179 to $189, P = .96).

The model estimated the undiscounted weekly nonradiotherapy costs at $517, minus $395 times the EQ-5D utility, plus, in the 10 × 3–Gy group, $276 during the initial 4 weeks (after more than 4 weeks after randomization, the nonradiotherapy costs varied from $122 to $752 per week for patients in the worst possible health (i.e., $517 + [0.5940 × $395]).

When we applied the estimated cost model to all patients and included the radiotherapy-related costs incurred during the initial 4 weeks after randomization, this added $1054 to the costs for the 10 × 3–Gy group and $0 to the costs for the 2 × 8–Gy group (difference = $1054, 95% CI = $1025 to $1083, P < .001; Table 3). When combined with the costs of the initial and repeated radiotherapy, the total radiotherapy and radiotherapy-related costs

![Image](#)

**Fig. 2.** Average EuroQol (EQ-5D) utility score by randomization group, as a function of time since randomization. Solid and dashed curves show the average EQ-5D utility for patients randomly assigned to receive radiotherapy consisting of 10 fractions of 3 Gy (10 × 3 Gy) or two fractions of 8 Gy (2 × 8 Gy), respectively. The EQ-5D utility score reflects the valuation by the general public of the health states reported by the patients, ranging from 1.00 (optimal health), through 0.00 (as bad as death), to −0.594 (worse than death).

**Fig. 3.** Average EuroQol (EQ-5D) utility score by date of death. Solid and dashed curves show the average EQ-5D utility for patients randomly assigned to receive radiotherapy consisting of 10 fractions of 3 Gy (10 × 3 Gy) or two fractions of 8 Gy (2 × 8 Gy), respectively. The dotted curve shows the estimated utility model used to impute missing EQ-5D utilities from the last available measurement. The EQ-5D utility score reflects the valuation by the general public of the health states reported by the patients, ranging from 1.00 (optimal health), through 0.00 (as bad as death), to −0.594 (worse than death).

### Table 2. Quality-adjusted life expectancy*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>10 × 3 Gy (n = 148), average No. of weeks (95% CI)</th>
<th>2 × 8 Gy (n = 149), average No. of weeks (95% CI)</th>
<th>Difference (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>38.1 (29.7 to 46.5)</td>
<td>27.4 (20.9 to 33.8)</td>
<td>10.7 (0.9 to 0.6)</td>
<td>.03</td>
</tr>
<tr>
<td>QALYs</td>
<td>20.0 (14.0 to 25.9)</td>
<td>13.2 (8.8 to 17.5)</td>
<td>6.8 (0.1 to 13.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy‡</td>
<td>44.4 (33.0 to 55.9)</td>
<td>30.5 (21.6 to 39.3)</td>
<td>13.9 (0.6 to 7.3)</td>
<td>.04</td>
</tr>
<tr>
<td>QALYs‡</td>
<td>23.1 (15.4 to 30.8)</td>
<td>15.0 (9.1 to 20.9)</td>
<td>8.1 (−0.7 to 16.8)</td>
<td>.07</td>
</tr>
<tr>
<td>QALYs based on TVAS§</td>
<td>21.6 (15.6 to 27.5)</td>
<td>15.2 (10.4 to 19.9)</td>
<td>6.4 (−0.4 to 13.2)</td>
<td>.06</td>
</tr>
<tr>
<td>QALYs assuming equal survival</td>
<td></td>
<td>17.1 (12.0 to 22.3)</td>
<td>15.7 (10.6 to 20.9)</td>
<td>1.4 (−5.1 to 7.9)</td>
</tr>
</tbody>
</table>

* CI = confidence interval; QALYs = quality-adjusted life-years; TVAS = transformed visual analog scale.
† Double-sided nonparametric bootstrapping.
‡ The missing survival times (5% of patients) were set at 5 years, instead of at February 2004.
§ Visual analog scale ranging from worst imaginable health to perfect health (0.0–1.0), transformed using the power function TVAS = 1 − (1 − VAS)0.61.
∥ Assuming equal survival, by multiplying each patient’s (quality-adjusted) survival time by a randomization group–specific factor, such that in both groups the average survival time matched the overall average survival time of 32.7 weeks.
were estimated at $5236 for the 10 × 3–Gy group and $2512 for the 2 × 8–Gy group (difference = $2724, 95% CI = $2501 to $2947, P < .001). In addition, the 39% longer life expectancy in the 10 × 3–Gy group compared with the 2 × 8–Gy group was associated with a 30% increase in survival-related nonradiotherapy costs ($11 254 versus $8651, difference = $2602, 95% CI = $2501 to $5562, P = .09). When we finally accounted for all radiotherapy, radiotherapy-related, and survival-related costs, lifetime societal costs were estimated to be $5326 lower for the patients in the 2 × 8–Gy group than in the 10 × 3–Gy group (95% CI = $2327 to $8326, P < .001).

Cost–Utility Analysis

Having shown that the 10 × 3–Gy schedule provided statistically significantly more QALYs than the 2 × 8–Gy schedule (20.0 versus 13.2 weeks; P = .05) but at statistically significantly higher societal cost ($16 490 versus $11 164; P < .001), we carried out a cost–utility analysis to determine whether the additional QALYs provided by the 10 × 3–Gy schedule justified the additional cost. This determination depends on the relative value of QALYs compared with the relative value of money: for high willingness to pay per QALY the 10 × 3–Gy schedule was preferred, whereas for low willingness to pay the 2 × 8–Gy schedule was preferred. The cost–utility ratio for the 10 × 3–Gy schedule versus the 2 × 8–Gy schedule was estimated at $40 900 per QALY (95% CI = $19 400 to $1 900 000 per QALY). The upper limit of the 95% confidence interval was high because the difference in QALYs between the treatment groups was just barely statistically significant. For a willingness to pay of less than $19 400 per QALY, the short-course schedule was statistically significantly favored over the long-course schedule, and for a willingness to pay of greater than $1 900 000 per QALY, the preference was statistically significantly in favor of the long-course schedule (P ≤ .05).

Table 4. Average nonradiotherapy health care utilization and costs per patient during the first 12 weeks after randomization*

<table>
<thead>
<tr>
<th>Cost category</th>
<th>10 × 3 Gy (n = 31)</th>
<th>2 × 8 Gy (n = 25)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs of consultations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General practitioners</td>
<td>3.4</td>
<td>4.8</td>
<td>.72</td>
</tr>
<tr>
<td>Lung specialist</td>
<td>1.6</td>
<td>2.5</td>
<td>.25</td>
</tr>
<tr>
<td>Radiotherapist</td>
<td>1.2</td>
<td>1.1</td>
<td>.83</td>
</tr>
<tr>
<td>Other specialists</td>
<td>0.5</td>
<td>0.8</td>
<td>.63</td>
</tr>
<tr>
<td>Paramedical professionals</td>
<td>1.0</td>
<td>1.9</td>
<td>.48</td>
</tr>
<tr>
<td><strong>Other medical costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>39%</td>
<td>16%</td>
<td>.23</td>
</tr>
<tr>
<td>Analgesics</td>
<td>52%</td>
<td>56%</td>
<td>.16</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>13%</td>
<td>4%</td>
<td>.18</td>
</tr>
<tr>
<td>Other medication</td>
<td>68%</td>
<td>48%</td>
<td>.53</td>
</tr>
<tr>
<td>Home nursing care</td>
<td>4.1 h</td>
<td>0.6 h</td>
<td>.30</td>
</tr>
<tr>
<td>Paid domestic help</td>
<td>0.0 h</td>
<td>3.1 h</td>
<td>.22</td>
</tr>
<tr>
<td>Informal care</td>
<td>7.3 h</td>
<td>18 h</td>
<td>.19</td>
</tr>
<tr>
<td>Out-of-pocket expenses</td>
<td>3%</td>
<td>12%</td>
<td>.44</td>
</tr>
<tr>
<td><strong>Total nonradiotherapy costs</strong></td>
<td>—</td>
<td>3617 (928 to 6307)</td>
<td>2162 (2076 to 6401)</td>
</tr>
</tbody>
</table>

*Costs were only directly observed in a subset of patients; — = not applicable.
†Number of consultations, percentage of patients, or hours of care.
‡Average costs in US dollars at 2005 price level.
§Double-sided nonparametric bootstrapping, comparing the average costs in both groups.
||Totals differ from the calculated values because of rounding.
Sensitivity Analyses

We performed several sensitivity analyses to explore the impact of various assumptions on the results. The dotted curves in Fig. 1 show the survival curves for each group, assuming that the 5% patients for whom the date of death was not known had survived for 5 years. These curves are almost identical to the Kaplan–Meier survival curves previously published for the patients in these two study arms (11). Although only 5% of the patients had an unknown date of death, assuming longer survival times for these patients did have a considerable impact on outcome compared to the base-case analysis: the difference in life expectancy between the two groups increased from 10.7 to 13.9 weeks (95% CI = 0.6 to 27.3 weeks, \( P = 0.04 \)) and the difference in quality-adjusted life expectancy increased from 6.8 to 8.1 weeks (95% CI = −0.7 to 16.8 weeks, \( P = 0.07 \)) (Table 2). However, because the costs also increased with increasing life expectancy, the cost–utility ratio decreased, but by only 0.1%, from $40 900 per QALY to $40 800 per QALY (95% CI = $17 100 per QALY to \( \infty \)).

When we used the patients’ self-assessment of their health (i.e., via the TVAS) instead of society’s assessment (i.e., via the EQ-5D), the estimated QALYs for each group increased, but the difference in estimated QALYs between groups decreased by 6%, from 6.8 to 6.4 weeks (Table 2). Accordingly, the estimated cost–utility ratio increased by 6%, from $40 900 per QALY to $43 300 per QALY (95% CI = $23 000 per QALY to \( \infty \)).

In the base-case analysis, nonradiotherapy costs were estimated using a cost model that excluded the increased costs in the 2 × 8–Gy group during the initial 4 weeks after randomization because these costs were not statistically significantly increased. Inclusion of these costs produced a cost model in which the undiscounted weekly nonradiotherapy costs were estimated at $515, minus $393 times the EQ-5D utility, plus $276 (for the 10 × 3–Gy group) or $5 (for the 2 × 8–Gy group) during the initial 4 weeks after randomization. According to this model, the cost–utility ratio would decrease by only 0.7%, from $40 900 per QALY to $40 600 per QALY (95% CI = $19 200 to $18 900 per QALY).

All cost categories in the base-case analysis favored short-course radiotherapy. In contrast to the other sensitivity analyses, the extent to which the various cost categories were included in the analysis had a considerable impact on the cost–utility ratio. For example, excluding survival-related costs reduced the cost–utility ratio from $40 900 per QALY to $20 900 per QALY (95% CI = $15 600 to $133 000 per QALY), whereas including consumption costs at $43 per day increased the cost differences by $3078 and the cost–utility ratio to $64 500 per QALY (95% CI = $32 700 to $2 800 000 per QALY). Excluding all nonradiotherapy costs reduced the cost–utility ratio to $12 800 per QALY (95% CI = $6400 to $805 000 per QALY).

Excluding the observed survival difference between treatment groups from the analysis also had a considerable impact on the cost–utility ratio (Table 2). The difference in QALYs between groups decreased from 6.8 to 1.4 weeks (95% CI = −5.1 to 7.9 weeks) and the difference in total societal costs decreased from $5326 to $2162 (95% CI = −$814 to $5137), rendering a cost–utility ratio of $80 600 per QALY (95% CI unbounded).

DISCUSSION

With respect to palliative irradiation for poor-prognosis non–small-cell lung cancer patients, the long-course 10 × 3–Gy schedule has been shown to provide prolonged palliation and better survival than the short-course 2 × 8–Gy schedule (11). In the cost–utility analysis presented here, we examined the effectiveness of long-course versus short-course palliative irradiation in terms of quality-adjusted life expectancy, which captures both the length and the quality of life. We found that patients in the 10 × 3–Gy group had a quality of life that was more highly valued than the quality of life of patients in the 2 × 8–Gy group but that the difference was not statistically significant. However, when this difference in quality of life was combined with the statistically significant 10.7-week difference in life expectancy, the estimated 6.8-week difference in QALYs was statistically significant. The difference in lifetime societal costs was estimated at $5326, of which 31% were radiotherapy costs, 20% were other radiotherapy-related costs incurred during the initial 4 weeks after randomization, and 49% were costs due to the difference in life expectancy. The cost–utility ratio for the 10 × 3–Gy schedule versus the 2 × 8–Gy schedule was estimated at $40 900 per QALY. When this ratio is considered in light of the often-quoted cost acceptability threshold of $50 000 per QALY (28,29), we conclude that the 10 × 3–Gy schedule provides a better value for the money than the 2 × 8–Gy schedule. This conclusion has confirmed the consensus in The Netherlands that the 10 × 3–Gy schedule is the preferred standard treatment for non–small-cell lung cancer patients who have a poor prognosis.

The interpretation of the economic preference for long-course radiotherapy raises several important issues. First, it should not be concluded that long-course radiotherapy reduces costs. On the contrary, long-course radiotherapy was estimated to increase costs by $5326. Therefore, if a well-informed patient prefers the shorter schedule, there is no reason to impose the longer schedule. Second, if radiotherapy capacity is limited, it may be more efficient to treat several patients with short-course radiotherapy than to treat one patient with long-course radiotherapy. Third, treatment preference in settings other than that in our study may be influenced by differences in economic climates and treatment patterns.

The economic preference for long-course radiotherapy strongly hinges on the survival gain compared with short-course radiotherapy, without which the cost–utility ratio would increase to $80 600 per QALY (with unbounded 95% confidence interval). Although this ratio might still be considered acceptable (28,29), it would be based on an uncertain difference in quality of life. In our study, the survival gain for long-versus short-course radiotherapy was statistically significant, but this has not been a consistent finding in other studies. For example, in a Cochrane review of 10 randomized trials, Macbeth et al. (6) concluded that the evidence for a modest survival gain after higher-dose radiotherapy was only for patients who had a better performance status. Kramer et al. (11) compared and discussed these results in detail.

A matter of debate among health economists is to what extent future costs that are due to improved survival should be included in economic evaluations. A distinction can be made between costs that are related to the original health problem and costs that are unrelated. In our base-case analysis, we included both related and unrelated health care costs because the QALY measure we used also includes the health gain obtained from related and unrelated health care (17). It has been argued that only related health care costs should be included in economic evaluations because otherwise it would be inconsistent to exclude other unrelated costs. Therefore, we believe that our approach is appropriate.
future costs of subsistence (30). In a sensitivity analysis, excluding costs unrelated to radiotherapy reduced the cost–utility ratio from the base-case estimate of $40,900 per QALY to $20,900 per QALY, further confirming the preference for the 10 × 3–Gy schedule. Others have argued that all future health care costs as well as future productivity and consumption costs should be included (24). Generally, including all future costs would favor treatment of younger patients over older patients because the consumption costs of the younger patients would be compensated for by their future productivity. In a sensitivity analysis, assuming negligible productivity in both groups and including consumption costs increased the cost–utility ratio to $64,500 per QALY for the 10 × 3–Gy schedule, which does not seem excessive.

Another matter of debate among health economists is how health care costs are related to survival. Traditionally, economic models have described health care costs as increasing with age. More recently, however, it has been argued that costs are more closely associated with the time to death than with age (31,32). We found that neither age nor time to death was statistically significantly associated with cost but that the EQ-5D utility measure was. As a result and in line with the more recent view, costs increased toward death and the increase in life expectancy after long-course radiotherapy was associated with a less than proportional increase in costs. If our results for this terminally ill patient population are generalizable, then costs due to chronic diseases in which quality of life is determined by disease progression may be more strongly associated with age, whereas costs due to more acute conditions may be more strongly associated with time to death.

Our study has several potential limitations. First, and perhaps most important, because we had not anticipated a statistically significant difference in survival between the two treatment groups, we had to estimate the long-term costs related to the difference in survival from cost data obtained during the initial 12 weeks after randomization. The model we used identified short-term costs related to the initial radiotherapy that should not be extrapolated and was based on data with an observation period in which more than one-third of the patients had died. Nevertheless, the cost model may still not have been representative for long-term health care costs associated with living and dying. Second, we used the EQ-5D utility measure, which is frequently used in economic evaluations from a societal perspective but does not include quality-of-life domains that are specifically relevant for the valuation of end-of-life care (18,33). Unfortunately, no valuation instrument exists that incorporates such issues. Nevertheless, the distinct decrease in the EQ-5D utility that we observed toward the end of life suggests that this instrument is responsive to the changing health status of these patients, and our utility estimates were similar to results from another cost–utility analysis in terminally ill cancer patients (18). These and other issues were addressed in the sensitivity analyses, which rendered very stable estimates for the cost–utility ratio, suggesting that our results are robust.

In conclusion, including survival-related costs in our economic evaluation led to a higher cost–utility ratio for the 10 × 3–Gy schedule versus the 2 × 8–Gy schedule, but one that was still acceptable according to current economic standards. In our group of poor-prognosis non–small-cell lung cancer patients, the additional costs of the protracted radiotherapy schedule were justified by longer survival rather than by improved quality of life.

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NOTES

This study was funded by the Dutch Investigative Medicine Fund of the Health Insurance Executive Board, as study OG98/009. The study sponsor had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Dr Gijsbert W. P. M. Kramer died on May 6, 2006.

Manuscript received December 23, 2005; revised October 10, 2006; accepted October 30, 2006.

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Journal of the National Cancer Institute, Vol. 98, No. 24, December 20, 2006