Liver Resection for Breast Cancer Liver Metastases

A Cost-utility Analysis

Gaya Spolverato, MD,* Alessandro Vitale, MD, PhD,† Fabio Bagante, MD,* Roisin Connolly, MB, BCh,‡ and Timothy M. Pawlik, MD, MPH, PhD, FACS*

Objective: To estimate the cost-effectiveness of liver resection followed by adjuvant systemic therapy relative to systemic therapy alone for patients with breast cancer liver metastasis.

Background: Data on cost-effectiveness of liver resection for advanced breast cancer with liver metastasis are lacking.

Methods: A decision-analytic Markov model was constructed to evaluate the cost-effectiveness of liver resection followed by postoperative conventional systemic therapy (strategy A) versus conventional therapy alone (strategy B) versus newer targeted therapy alone (strategy C). The implications of using different chemotherapeutic regimens based on estrogen receptor and human epidermal growth factor receptor 2 status was also assessed. Outcomes included quality-adjusted life months (QALMs), incremental cost-effectiveness ratio, and net health benefit (NHB).

Results: NHB of strategy A was 10.9 QALMs compared with strategy B when letrozole was used as systemic therapy, whereas it was only 0.3 QALMs when docetaxel + trastuzumab was used as a systemic therapy. The addition of newer biological agents (strategy C) significantly decreased the cost-effectiveness of strategy B (conventional systemic therapy alone). The NHB of strategy A was 31.6 QALMs versus strategy C when palbociclib was included in strategy C; similarly, strategy A had a NHB of 13.8 QALMs versus strategy C when pertuzumab was included in strategy C. Monte-Carlo simulation demonstrated that the main factor influencing NHB of strategy A over strategy C was the cost of systemic therapy.

Conclusions: Liver resection in patients with breast cancer liver metastasis proved to be cost-effective when compared with systemic therapy alone, particularly in estrogen receptor-positive tumors or when newer agents were used.

Keywords: breast cancer liver metastasis, cost-effectiveness, hepatic resection, surgery

(*Ann Surg* 2017;265:792–799)

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women, accounting for 23% of the total cancer cases and 14% of cancer deaths.[1] The 5-year survival of patients diagnosed with breast cancer is strongly correlated with tumor stage. Specifically, 5-year survival of patients with localized breast cancer can be as high as 98.6% compared with 25.9% for patients with distant metastases.[2] Breast cancer tends to metastasize systemically, with nearly 30% of women initially diagnosed with early-stage disease ultimately developing metastatic lesions.[3] After lymph nodes and lung, the liver constitutes the third most frequent site of breast cancer metastases, with roughly 10% of metastases located in the liver.[4] In turn, isolated breast cancer liver metastases (BCLM) have been reported to occur in 5% to 25% of all women with breast cancer.[5] Whereas in the past, stage IV breast cancer was considered to be almost always incurable,[6] a remarkable evolution in systemic therapy has significantly improved progression-free and overall survival of patients with metastatic disease.[7–9]

The improvements in clinical outcomes have come, however, with an exceptional financial cost. Recent cost-effectiveness analyses have shown that new targeted therapies may not be cost-effective in the treatment of BCLM patients.[10,11] In fact, the use of targeted agents such as pertuzumab is associated with a cost of over $700,000 per quality-adjusted life years.[10,11] The combination of systemic therapy with aggressive local treatment may, however, improve survival in patients with resectable BCLM.[12] In fact, BCLM has become an increasingly accepted indication for hepatic resection in certain clinical settings.[13–20] Liver surgery may not only provide a survival benefit, but also decrease the need for repetitive cycles of cytotoxic chemotherapy, and also reduce the tumor burden potentially providing an immunologic benefit.[12] Although selected patients may benefit from liver resection (LR), use of hepatectomy for BCLM remains somewhat controversial.[21,22]

To date, no study has evaluated the cost-effectiveness of systemic chemotherapy alone versus LR plus systemic therapy for patients with resectable BCLM. Given the high potential cost associated with treating patients with breast cancer, data on the relative cost-benefit of surgery relative to systemic therapy alone for oligometastatic, resectable liver metastasis are important. Therefore, the objective of the current study was to use Markov modeling to estimate the net health benefit (NHB) and cost-effectiveness of systemic chemotherapy alone versus LR plus postoperative systemic chemotherapy for patients with BCLM.

METHODS

Definitions and Endpoints

The study focused on defining the NHB and cost-effectiveness of treating patients with BCLM with LR plus systemic therapy rather than systemic therapy alone (Fig. 1). We considered a base case scenario consisting of a 60-year-old woman with resectable BCLM as defined by Mariani et al: ≤4 hepatic metastases, stable disease or disease responding to chemotherapy and/or hormone therapy, performance status of 0 or 1, and the only allowable site of extrahepatic disease being stable bone metastasis.[20]

From the *Department of Surgery, Division of Surgical Oncology, The Johns Hopkins Hospital, Baltimore, MD; †Unità di Chirurgia Epatobiliare e Trapianto Epatico, Azienda Ospedaliera-Università di Padova, Padova, Italy; and ‡Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD.

GS and AV equally contributed to the manuscript.

Funding/support and conflicts of interest: none.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Reprints: Timothy M. Pawlik, MD, MPH, PhD, FACS, Professor of Surgery and Oncology, Chief, Division of Surgical Oncology, John L. Cameron Professor of Alimentary Surgery, Department of Surgery, Johns Hopkins Hospital, 600 N Wolfe Street, Blalock 688, Baltimore, MD 21287.
E-mail: tpawlik1@jhmi.edu.

ISSN: 0003-4932/16/26504-0792
DOI: 10.1097/SLA.0000000000001715

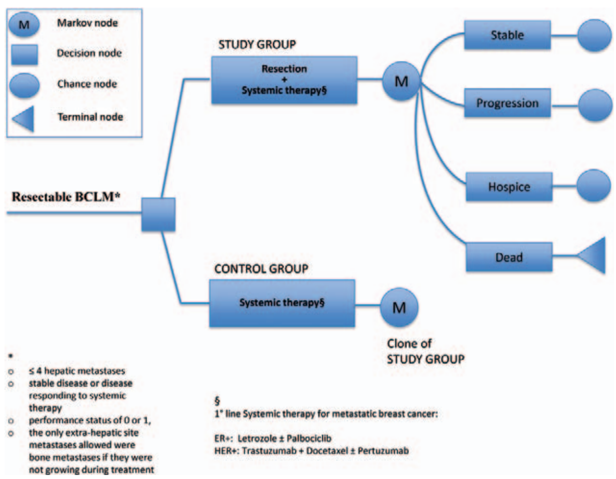

FIGURE 1. The event pathway: decision tree and states of health.

Given that there are no definitive cost-effectiveness studies that have assessed the efficacy of LR for BCLM, 2 main hypothetical subscenarios were considered. Scenario 1 compared LR as primary treatment (strategy A) followed by postoperative conventional systemic therapy (letrozole for hormone estrogen receptor-positive [ER+] patients; docetaxel + trastuzumab for human epidermal growth factor receptor 2 [HER2]-positive patients) versus conventional systemic therapy alone (strategy B). Scenario 2 compared LR as primary treatment (strategy A) followed by postoperative conventional systemic therapy versus newer systemic therapy alone (strategy C; letrozole + palbociclib for ER+ patients; docetaxel + trastuzumab + pertuzumab for HER2+ patients). Based on the accepted definition of resectable BCLM, all patients were considered to have stable disease during receipt of preoperative systemic therapy. As such, the cost and effect of preoperative systemic therapy was not considered in the model. Systemic therapy schemas were based on recent clinical trials maintenance dose.[8,9] Patients were hypothesized to continue with their regimens until progression or unmanageable toxicity.

The following endpoints were considered:

1. Survival benefit: The survival of each strategy was measured in terms of life-months. The survival benefit was defined as: strategy A survival—strategy B or C survival.
2. Incremental utility: The utility of each strategy was measured in terms of quality-adjusted survival and was expressed in quality-adjusted life-months. The incremental utility was defined as: strategy A utility—strategy B or C utility.
3. Incremental costs: Incremental costs were defined as: strategy A cost—strategy B or C cost.
4. Incremental cost-effectiveness ratio (ICER): ICER is the difference between the cost-utility of 2 competing strategies and was defined as follows: incremental costs/incremental utility.
5. NHB: The NHB of an alternative treatment was calculated using the formula employed by Stinnett and Mullahy[23]: NHB = sur-survival benefit − ICER/WTP, where WTP is the willingness to pay. WTP is a fundamental cost-effectiveness endpoint representing the accepted limit to the additional cost per unit of effectiveness gained that a rational decision-maker will accept to allocate resources efficiently among competing priorities. In the present study, following Durkee et al,[10] we assumed a WTP threshold of $100,000 per quality-adjusted life-years gained.

Decision-analytic Markov Model and Transition Probabilities

A decision-analytic Markov model was developed using TreeAge Pro 2013 software (TreeAge, Williamstown, MA). Data on costs and utilities were extracted from reports published in the established literature and then utilized in the Markov modeling to calculate survival benefit (quality-adjusted life months), incremental costs, ICER, and NHB.[8–10,20,24–26] Specifically, we used the model to perform a cost-effectiveness analysis of LR plus systemic therapy versus systemic therapy alone from the societal perspective. Based on the findings of Durkee et al,[10] the health states considered were as follows: stable disease, progressing disease, hospice, and dead (Fig. 1). The model followed patients monthly over their remaining lifetimes, tracking also toxicity rates. Patients in the stable disease state were treated with systemic therapy until progression, unmanageable toxicity, or death. Adverse events in the progressing disease state were not explicitly modeled, but were inherently accounted for assigned utilities and costs. After progression, patients were treated with the next-line regimen until hospice or death. Patients in hospice had marginally lower costs and higher utilities during the past several weeks of life than those who died before entering hospice.[26,27]

We inferred the cycle-specific transition probabilities from the CLEOPATRA and PALOMA-1 trials.[8,9,28] In particular, we used data from control arms of these trials (ie, conventional systemic therapy) as the baseline transition probabilities. Specific hazard ratios for LR (from Mariani et al[20]) or for newer therapies (from CLEOPATRA or PALOMA-1 trials[8,9,28]) were included in the model to modify stable-to-progression transition probabilities when required. We assumed that 61% of patients chose hospice in the last weeks of life, based on data from the Dartmouth Institute for Health Policy and Clinical Practice.[29] Age-specific mortality for other causes were based on life tables from the Centers for Disease Control.[30]

Annual rates or median values of survival and progression were transformed into monthly probabilities applying the declining exponential approximation of life-expectancy (DEALE) approach: $\mu = -1/t \times \ln(S)$. Transitional probabilities were varied within their relative 95% confidence intervals (CIs) assuming a triangular distribution.

Costs and Utilities

Costs were assessed from the perspective of the healthcare providers (Table 1). Rather than using estimated cost data such as those based on Medicare reimbursement data, we chose to use actual country-specific data.[31] Dosing calculations assumed a 70-kg patient with a 1.8-m^2 body surface area. Costs for second and third-line regimens were based on published data from the SEER and linked Medicare data, and the OptumInsight claims database.[27,32] Health state utilities were the same as those used in previously published cost-effectiveness analyses of systemic therapy for BCLM.[10,11] Minor toxicities were considered to be inherent to the metastatic cancer state and, therefore, were not explicitly modeled. Major toxicities were modeled with a 1-time disutility. Base-case estimates for all utilities extracted from the literature are detailed in Table 1. Ranges were assumed to be within 20% of the base-case values. The costs and the utilities were discounted at an annual rate of 3%. The cost-effectiveness analysis was performed based on the EVEREST guidelines.[33]

Sensitivity Analyses and Monte-Carlo Simulation

The correct calibration of the Markov model was confirmed in all the scenarios, to understand the impact of variable uncertainties on the model results and to estimate the confidence of the results.

TABLE 1. Base-case Value and Sensitivity Range Extracted From Literature for Transition Probabilities

Variables	Base-case Analysis	Range Tested	Source
Transition probabilities: triangular distribution			
Background (all-cause) mortality	Female age-specific	18–100	NA
Progression-free survival with letrozole (months)	10.2	5.7–12.6	9
Progression-free survival with docetaxel + trastuzumab, mo	12.4	10.2–15.0	8
Death unrelated to disease progression, %	5.2	3.0–10.0	8
Death due to disease progression, %	49.5	35.0–65.0	8
Hospice after progression, %	61	50–70	29
Median survival in hospice	1.5	1.0–2.0	24
Serious adverse events, %	29	20–60	8, 9
Unmanageable serious adverse event, %	5	3–7	8, 9
Pertuzumab-related hazard ratio	0.62	0.51–0.75	8
Palbociclib-related hazard ratio	0.49	0.32–0.75	9
Liver resection-related hazard ratio	0.33	0.20–0.53	20
Utilities: triangular distribution			
Stable state	0.65	0.50–0.80	10
Progressing state	0.29	0.16–0.41	10
Hospice state	0.48	—	26
Toll for major toxicity	−0.28	—	25
Cost per cycle: triangular distribution			
Liver resection ($) – 1-time cost	25,086	12,543–50,172	31
Docetaxel + trastuzumab ($) at stable state	5580	—	—
Docetaxel + trastuzumab + pertuzumab ($) at stable state	13,521	—	—
Letrozole ($) at stable state	543	—	—
Letrozole + palbociclib ($) at stable state	12,363	—	—
Progressing state	7652	268–24,088	10
Hospice state	2512	2136–2912	10
Toll for major toxicity – 1-time cost	2126	109–6368	10
Toll for death outside hospice – 1-time cost	3284	2773–3831	10
Time horizon, y	Life time	—	—

One-way sensitivity analysis was performed for all transition probabilities, costs, and utilities. A probabilistic sensitivity analysis, the Monte-Carlo simulation, was performed. A total of 10,000 BCLM patients for each therapeutic strategy (A vs B or C) were compared. Outcomes measured were quality-adjusted life-months, incremental costs, ICER, and NHB. Transitional probabilities were varied within their relative 95% CIs, whereas costs and utilities were varied within their plausible ranges, assuming a triangular distribution.

The impact of variables on the NHB distribution of 10,000 outcomes obtained from the Monte-Carlo simulation was determined using the multivariate standard least square regression method. Statistical significance was set at $P < 0.05$. The calculations were done with the JMP package version 9.0 (2010 SAS Institute Inc.) and TreeAge Pro version 2013 (1988–2013 TreeAge Software, Williamstown, MA). Documentation of our methods adhere to the recommendations of the Society for Medical Decision Making good research practices for model transparency and validation.[34]

RESULTS

Unadjusted Survival Analysis

Median survival of patients with ER + BCLM undergoing LR + letrozole was 58.3 months, compared with 36.5 months for patients receiving letrozole therapy alone, and 47.6 months for patients receiving letrozole + palbociclib (Supplemental Fig. A, http://links.lww.com/SLA/A994). Median survival of patients with HER2 + BCLM who received LR + docetaxel + trastuzumab trastuzumab was 63.8 versus 38.5 months for those receiving docetaxel + trastuzumab, and 54.6 months for patients receiving docetaxel + trastuzumab + pertuzumab (Supplemental Fig. B, http://links.lww.com/SLA/A994).

Base-case Analysis

In the base-case analysis, strategy A (LR plus postoperative chemotherapy) was initially compared with strategy B (systemic therapy alone) (Table 2). Two possible conventional systemic therapy regimens were considered: letrozole for ER+ tumors and docetaxel + trastuzumab for HER2+ tumors. The NHB of strategy A was 10.9 quality-adjusted life-months compared with strategy B when letrozole was used as the systemic therapy. In contrast, the NHB of strategy A was considerably less with only 0.3 quality-adjusted life-months compared with strategy B when docetaxel + trastuzumab was used as the systemic therapy. In ER+ patients, the ICER of strategy A compared with strategy B was $18,117/quality-adjusted life-years, whereas in HER2+ patients, the ICER of LR plus systemic therapy (strategy A) versus systemic therapy alone (strategy B) was $99,777/quality-adjusted life-years. Liver resection plus systemic therapy was largely cost-effective in patients with ER+ tumors treated with letrozole as systemic therapy, whereas it was only slightly cost-effective in HER2+ patients treated with docetaxel + trastuzumab as systemic therapy.

The addition of palbociclib and pertuzumab to systemic therapy resulted in an incremental utility of 5.5 (from 16.5 to 22.0) and 4.3 (from 17.8 to 22.1) quality-adjusted life-months, respectively, to the strategy A arm. Quality-adjusted survival gains were achieved at an incremental cost of $398,064 (from $245,648 to $643,712) for palbociclib and of $377,204 (from $332,199 to $709,403) for pertuzumab. Taken together, the addition of newer biological agents (strategy C) significantly decreased the cost-effectiveness of strategy B (systemic therapy alone). In fact, when we performed the second base-case analysis comparing strategy A versus strategy C (Table 3), LR was superior to both base case 3 (letrozole + palbociclib) and base case 4 (docetaxel + trastuzumab + pertuzumab). The NHB of strategy A was 31.6

TABLE 2. Incremental Cost-effectiveness Ratio and Net Health Benefit Comparing Hepatic Resection Followed by Conventional Systemic Postoperative Therapy and Conventional Systemic Therapy Alone at the Base Case

Various Costs		
Case 1	LR + letrozole	Letrozole
Resectable BCLM, ER+		
QALMs	29.9	16.5
Incremental QALMs gained	—	13.4
Lifetime cost (US $)	363,437	343,206
Incremental cost (US $)	—	20,231
ICER (US $/QALY)	—	18,117
WTP (US $)	—	100,000
Net health benefit (QALMs)	—	10.9
Is HR cost-effective?	—	Yes
Case 2	LR + TH	TH
Resectable BCLM, HER2+		
QALMs	33.3	17.8
Incremental QALMs gained	—	15.5
Lifetime cost (US $)	526,183	397,305
Incremental cost (US $)	—	128,878
ICER (US $/QALY)	—	99,777
WTP (US $)	—	100,000
Net health benefit (QALMs)	—	0.3
Is HR cost-effective?	—	Yes

HR indicates hepatic resection; QALMs, quality-adjusted life-months; QALY, quality-adjusted life-year; TH, docetaxel plus trastuzumab.

quality-adjusted life-months compared with strategy C when palbociclib was included in strategy C; similarly, strategy A had a NHB of 13.8 quality-adjusted life-months compared with strategy C when pertuzumab was included in the chemotherapy regimen. Moreover, in ER+ patients, the ICER of strategy A compared with strategy C was −$293,169/quality-adjusted life-years, whereas among HER2+ patients, the ICER of strategy A compared with strategy C was −$22,526/quality-adjusted life-years.

TABLE 3. Incremental Cost-effectiveness Ratio and Net Health Benefit Comparing Hepatic Resection Followed by Conventional Systemic Postoperative Therapy and Newer Systemic Therapy Combinations at the Base Case

Various Costs		
Case 3	LR + letrozole	Letrozole + palbociclib
Resectable BCLM, ER+		
QALMs	29.9	22.0
Incremental QALMs gained	—	7.9
Lifetime cost (US $)	363,437	556,440
Incremental cost (US $)	—	−193,003
ICER (US $/QALY)	—	−293,169
WTP (US $)	—	100,000
Net health benefit (QALMs)	—	31.6
Is HR cost-effective?	—	Yes
Case 4	LR + TH	PTH
Resectable BCLM, HER2+		
QALMs	33.3	22.1
Incremental QALMs gained	—	11.2
Lifetime cost (US $)	526,183	547,207
Incremental cost (US $)	—	−21,024
ICER (US $/QALY)	—	−22,526
WTP (US $)	—	100,000
Net health benefit (QALMs)	—	13.8
Is HR cost-effective?	—	Yes

HR indicates hepatic resection; PTH, docetaxel plus trastuzumab plus pertuzumab; QALMs, quality-adjusted life-months; QALY, quality-adjusted life-year; TH, docetaxel plus trastuzumab.

Monte-Carlo Simulation and Analysis of the Impact of Main Covariates on Net Health Benefit

When assessing the entire cohort, the acceptability curves in Figure 2A and B demonstrated that strategy A (LR plus postoperative chemotherapy) had a higher probability to be more cost-effective than strategy B, when a WTP above $12,000/quality-adjusted life-years (for letrozole) and $96,000/quality-adjusted life-years (for docetaxel and trastuzumab) was accepted. Conversely, the acceptability curves in Figure 2C and D demonstrated that strategy A completely dominated strategy C.

To obtain a more complete assessment of the relative benefit of LR plus postoperative chemotherapy (strategy A) versus conventional systemic chemotherapy alone (strategy B) or newer systemic chemotherapy (strategy C), a multivariable regression method was used to determine the impact of different model covariates on the NHB distribution of 10,000 outcomes obtained from the Monte-Carlo simulation. Specifically, the impact of a number of different factors on the NHB of patients with BCLM undergoing resection was assessed. These factors included all variables included in the model (Table 1): age, progression-free survival after conventional therapy, death without progression, death with progression, hospice after progression, serious adverse event, unmanageable serious adverse event, hazard of LR and newer systemic therapy, quality of life (QoL) of stable and progressive disease, costs of LR, costs of conventional and newer chemotherapy regimens, and costs associated with progressive disease and hospice. Of note, all the factors in the model had a significant impact on the NHB of LR for BCLM (all $P < 0.05$).

When LR + letrozole was compared with letrozole alone (Fig. 3A), the main factor influencing the NHB of strategy A over strategy B was the hazard ratios associated with LR, including type of surgery, resection margins, and postoperative complications. When LR + docetaxel + trastuzumab was compared with docetaxel + tras-trastuzumab alone (Fig. 3B), the main factor influencing the NHB of strategy A over strategy B was the cost of docetaxel + trastuzumab therapy. Similarly, when LR plus conventional chemotherapy was compared with newer chemotherapy regimens alone (Fig. 3C and D), the main factor influencing the NHB of strategy A over strategy C was the cost of newer therapies.

DISCUSSION

Although the cornerstone of the treatment of BCLM involves systemic therapy, there has been increasing interest in the use of hepatic resection to treat patients with breast cancer that has metastasized to the liver.[21] Specifically, with a better understanding of tumor biology and advancements in newer chemotherapeutic regimens, an increasing number of patients may be candidates for LR combined with systemic therapy. For example, Mariani et al[20] reported a case-matched control study in highly selected patients with stable BCLM and compared medical treatment alone versus surgery plus medical treatment. The authors noted that patients undergoing surgery plus systemic therapy had better survival compared with chemotherapy alone with a 3-year survival of 81% versus 51%, respectively ($P < 0.001$). In the present study, we expanded on this past work by evaluating and comparing the cost-effectiveness of 2 therapeutic approaches for patients with resectable BCLM: liver surgery plus systemic chemotherapy versus systemic chemotherapy alone. Using Markov modeling, we estimated the NHB and cost-effectiveness of LR plus systemic chemotherapy versus systemic chemotherapy alone for patients with BCLM.

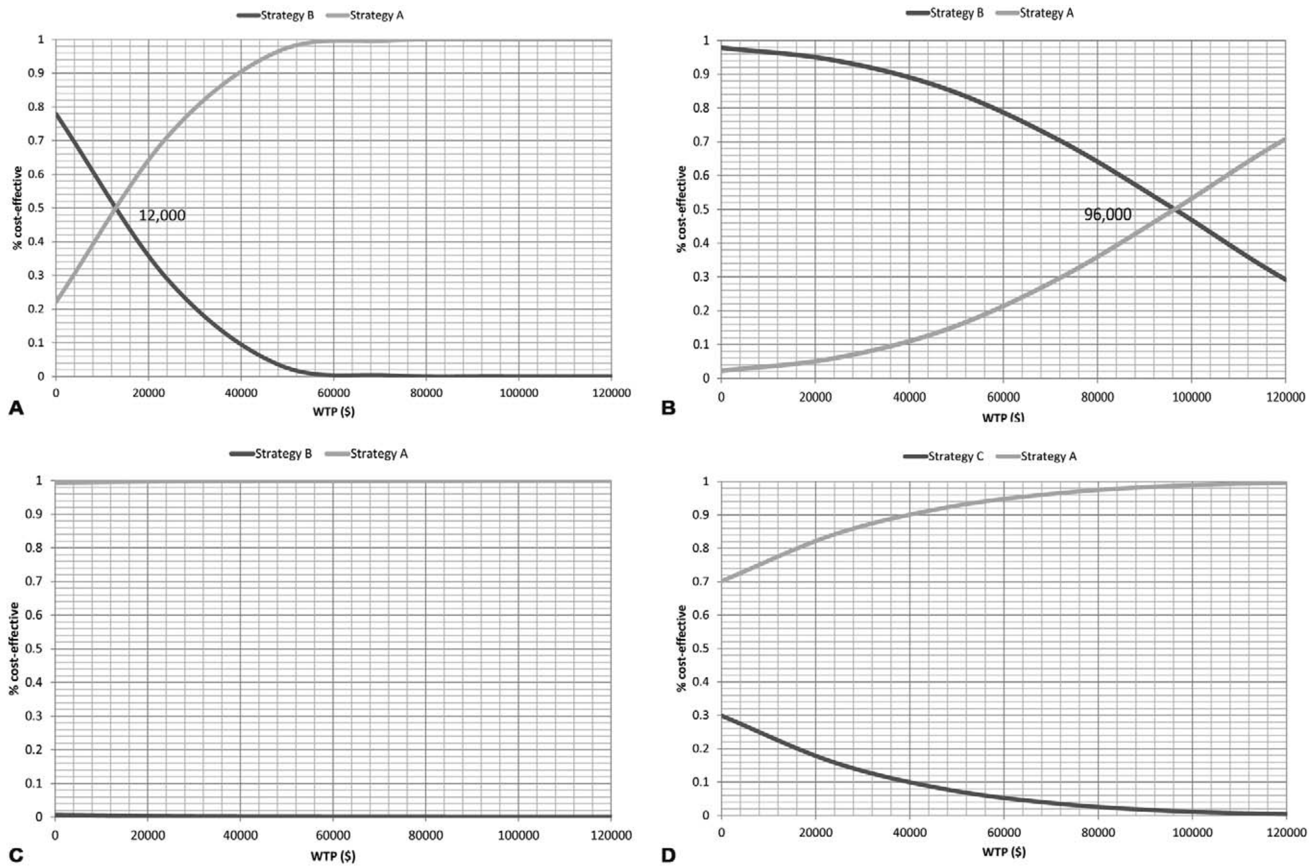

FIGURE 2. Cost-effectiveness acceptability curve of strategy A versus strategy B or C in patients with BCLM: liver resection (LR) + letrozole versus letrozole alone (A); LR + docetaxel + trastuzumab versus docetaxel + trastuzumab alone (B); LR + letrozole versus letrozole + palbociclib (C); LR + docetaxel + trastuzumab versus docetaxel + trastuzumab + pertuzumab (D).

The current study is important because it is the first report to examine the comparative cost-effectiveness of chemotherapy alone versus surgery plus chemotherapy for BCLM while accounting for different tumor-specific characteristics such as ER and HER2 status. In addition, we analyzed the implications of using different chemotherapeutic regimens based on ER and HER2 status. Of note, we report that LR plus systemic therapy was more cost-effective for patients with ER+ tumors than systemic therapy alone. For patients with HER2+ tumors, LR plus systemic chemotherapy had a cost-effectiveness that was comparable to systemic therapy alone. When compared with newer systemic chemotherapeutic agents, LR plus standard systemic chemotherapy was more cost-effective. The main factor influencing the cost-effectiveness of the different therapeutic options was the high cost of newer systemic agents.

The 2 main prognostic factors associated with patient survival after hepatectomy for BCLM are related to the biological behavior of the tumor.[18,35–37] In particular, the diagnosis of an ER-negative primary tumor (hazard ratio [HR] 3.3; 95% CI 1.4–8.2; $P = 0.009$) and preoperative disease progression (HR 3.8; 95% CI 1.6–9.2; $P = 0.003$) were both associated with a poor outcome after hepatic resection of BCLM.[17,18] In contrast, among patients with ER+ tumors who had stable or responsive disease on systemic therapy, surgical therapy was strongly associated with an improved survival compared with chemotherapy alone.[20] In the current study, in the first base-case analysis on ER+ patients, surgery combined with letrozole gave a NHB of 10.9 quality-adjusted life-months compared with chemotherapy alone.

These data would suggest that LR combined with letrozole for ER + BCLM is justified as the estimated survival benefit was about 1 year, which is the threshold previously proposed to justify an operative approach for patients with ER + resectable BCLM.[20] In contrast, LR plus chemotherapy was not as cost-effective for patients with HER2+ tumors. Specifically, the NHB of strategy A was only 0.3 quality-adjusted life-months compared with strategy B, when NHB + trastuzumab was used as a systemic therapy. In addition, the ICER of LR plus systemic therapy versus systemic therapy alone was $99,777/quality-adjusted life-years when a WTP of $100,000 was accepted. As such, a more conservative approach that does not include LR should be preferred in many patients with HER2+ tumors. Given that HER2+ patients demonstrate a high benefit from newer chemotherapeutical regimens, the relative benefit of adding surgery may be more modest. In addition to conventional chemotherapy agents, we then further compared surgery plus systemic therapy versus systemic therapy alone, considering drugs such as palbociclib and pertuzumab. Of note, in both base cases 3 and 4, when evaluating patients with ER+ and HER2+ tumors, strategy A was largely cost-effective compared with strategy C. In particular, the NHB of LR plus letrozole among ER+ patients was 31.6 quality-adjusted life-months compared with letrozole + palbociclib; similarly, the NHB of LR + docetaxel + trastuzumab among HER2+ patients was 13.8 quality-adjusted life-months compared with docetaxel + trastuzumab + pertuzumab. Due to the exceptionally high costs that did not correspond to a survival benefit in terms of quality-adjusted life-months gained, conventional chemotherapy

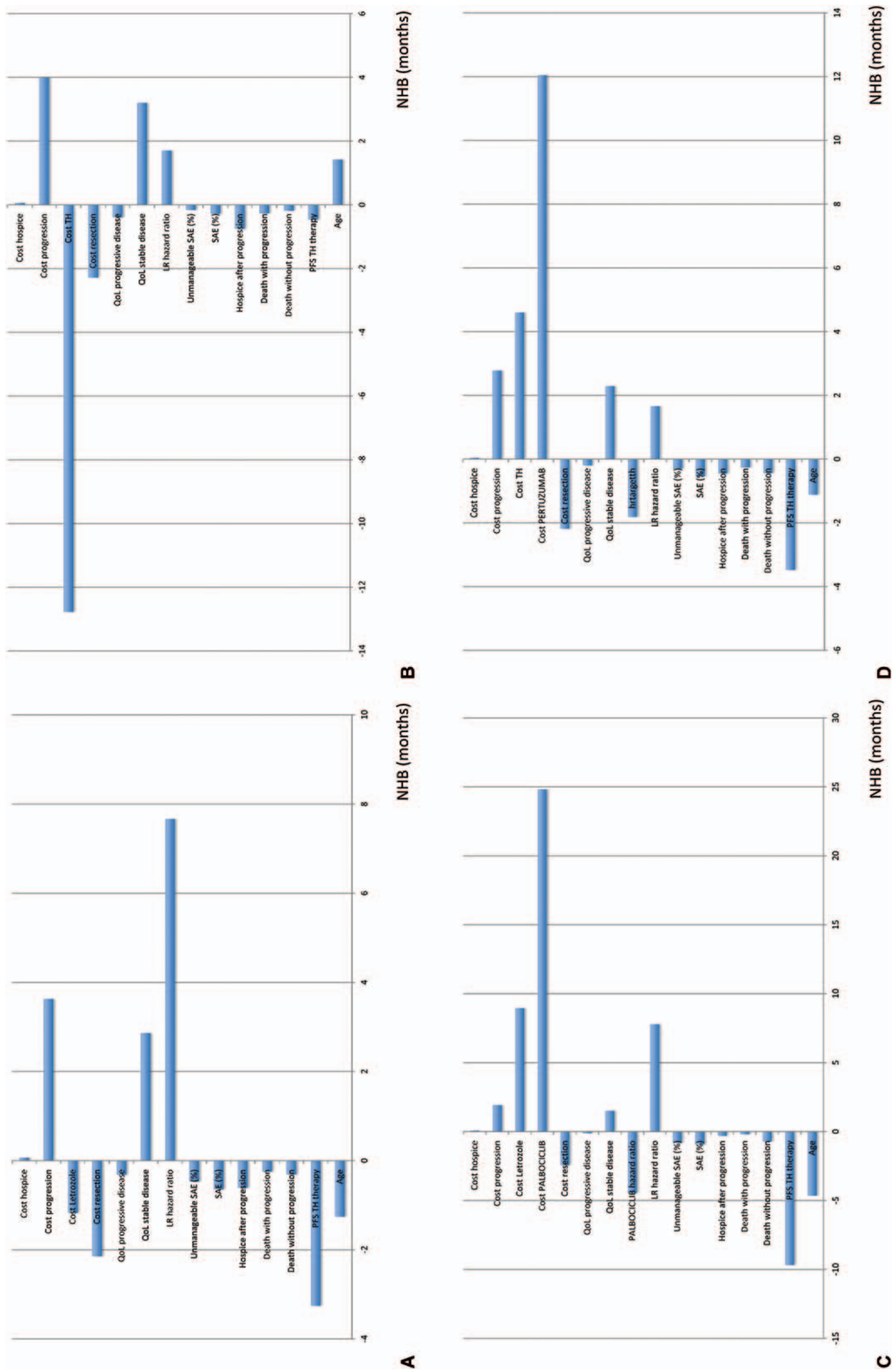

FIGURE 3. Multivariable analysis on the results of Monte-Carlo simulation showing the contribution of each covariate to the net health benefit of strategy A versus strategy B or C in patients with BCLM. LR + letrozole versus letrozole alone (A); LR + letrozole + docetaxel + trastuzumab versus docetaxel + trastuzumab alone (B); LR + letrozole versus letrozole + palbociclib (C); LR + docetaxel + trastuzumab + pertuzumab versus letrozole + docetaxel + trastuzumab versus docetaxel + trastuzumab + pertuzumab (D).

plus surgery is generally preferable to these new systemic biological agents in well-selected patients with BCLM.

The findings of the base-case analyses were confirmed by the Monte-Carlo simulation. Examining the entire cohort of 10,000 patients in the Monte-Carlo simulation, we found that LR was generally cost-effective compared with systemic therapy. Whereas strategy A was largely cost-effective compared with strategy B among patients with ER+ tumors, strategy A was only slightly cost-effective compared with strategy B for patients with HER2+ disease. These findings are likely related to the high cost of surgery when combined with both docetaxel and trastuzumab and due to the acceptable efficacy of standard systemic therapy alone in HER2+ patients. Indeed, strategy A had a higher probability to be more cost-effective than strategy B when a WTP above $12,000/quality-adjusted life-years (for letrozole) was accepted among patients with ER+ tumors. In contrast, strategy A had a higher probability to be more cost-effective than strategy B when a WTP of $96,000/quality-adjusted life-years (for docetaxel and trastuzumab) was accepted among patients with HER2+ tumors. Conversely, in both groups of patients who had ER+ and HER2+ tumors, strategy A completely dominated strategy C due to the excessive high cost of the biologic systemic treatments.

In addition to the cost-effective analyses, a multivariable analysis was performed to assess the impact that a wide array of different model covariates (ie. age, progression-free survival after conventional systemic therapy, QoL with stable and progressive disease, costs of LR, costs of systemic chemotherapy and biological therapies, costs of progressive disease and hospice, etc) had on the NHB distribution of 10,000 outcomes obtained from the Monte-Carlo simulation. Perhaps, as expected, the variable that impacted the most on strategy C was the cost of newer systemic therapy. In addition, the cost of docetaxel + trastuzumab impacted on the NHB of strategy A versus strategy B in HER2+ patients. In contrast, the NHB of strategy A when it consisted of LR + letrozole versus strategy B (only letrozole) was influenced the most by the surgery-related HR, corresponding to the type of surgery, resection margins, and postoperative complications.

The present study has several limitations. As with all the decision-making Markov models, it was necessary to use data from the literature in making assumptions regarding the transition probabilities. In particular, data on LR for BCLM were based on retrospective cohort studies and on a case-match analysis; conversely, data on systemic therapy were based on prospective randomized clinical trials. Whereas data to inform the model were derived from a mix of both retrospective and prospective studies, this approach to the incorporation of data from the literature was consistent with previous studies that have utilized Markov modeling.[38–42] In addition, we used data from randomized trials to evaluate the safety end efficacy of newer therapies for metastatic breast cancer (CLEOPATRA and PALOMA-1 trials). However, in these trials, there were no subgroup analyses for patients who had resectable BLCM. One possible criticism might be that resectable BCLM could have a better prognosis than the general population enrolled in these randomized clinical trials, but this is unlikely. The pricing of chemotherapy may vary by institution, regions of the country, or even among different countries. As such, accurate pricing can be difficult to obtain. The pricing used in the current study was based on established literature and was consistent with previous cost-analysis data on liver surgery and chemotherapy for breast cancer.[43] In addition, any differences in pricing estimates were likely to be nonsystematic. In turn, given that we focused on relative costs of conventional versus newer chemotherapy, any variations in cost estimates would not change the main findings of the current study.

In conclusion, data from the current study highlight the economic challenges of extending life for patients with BCLM. Liver resection plus conventional systemic therapy was more cost-effective for patients with ER+ tumors than systemic therapy alone. However, for patients with HER2+ tumors, LR plus systemic therapy that included trastuzumab had a cost-effectiveness that was comparable to conventional systemic therapy alone. Furthermore, the use of newer systemic chemotherapeutic agents such as palbociclib and pertuzumab for patients with resectable BCLM was not cost-effective. These data contribute to a broader discussion of value in health care. Although certain therapies may have a clinical effect, the cost-effectiveness of these agents may not justify their use compared with other therapies such as surgical resection and standard systemic chemotherapy. Although cost-effectiveness studies should not be viewed as definitive recommendations, these data do add to the broader discussion regarding how resources should be allocated resources to treat patients with cancer.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
2. http://seer.cancer.gov/statfacts/html/breast.html. Accessed September 1, 2015.
3. Redig AJ, McAllister SS. Breast cancer as a systemic disease: a view of metastasis. *J Intern Med*. 2013;274:113–126.
4. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. *Arch Pathol Lab Med*. 2008;132:931–939.
5. Caralt M, Bilbao I, Cortes J, et al. Hepatic resection for liver metastases as part of the ‘‘oncosurgical’’ treatment of metastatic breast cancer. *Ann Surg Oncol*. 2008;15:2804–2810.
6. Lermite E, Marzano E, Chereau E, et al. Surgical resection of liver metastases from breast cancer. *Surg Oncol*. 2010;19:e79–84.
7. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109–119.
8. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372:724–734.
9. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16:25–35.
10. Durkee BY, Qian Y, Pollom EL, et al. Cost-effectiveness of pertuzumab in human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2016;34:902–909. doi: 10.1200/JCO.2015.62.9105. Epub 2015 Sep 8.
11. Lopes G, Gluck S, Avancha K, et al. A cost effectiveness study of eribulin versus standard single-agent cytotoxic chemotherapy for women with previously treated metastatic breast cancer. *Breast Cancer Res Treat*. 2013;137:187–193.
12. Punglia RS, Morrow M, Winer EP, et al. Local therapy and survival in breast cancer. *N Engl J Med*. 2007;356:2399–2405.
13. Brunschwig A. Hepatic lobectomy for metastatic cancer. *Cancer*. 1963;16:277–282.
14. Foster JH. Survival after liver resection for secondary tumors. *Am J Surg*. 1978;135:389–394.
15. Elias D, Lasser P, Spielmann M, et al. Surgical and chemotherapeutic treatment of hepatic metastases from carcinoma of the breast. *Surg Gynecol Obstet*. 1991;172:461–464.
16. Polistina F, Costantin G, Febbraro A, et al. Aggressive treatment for hepatic metastases from breast cancer: results from a single center. *World J Surg*. 2013;37:1322–1332.
17. Adam R, Aloia T, Krissat J, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? *Ann Surg*. 2006;244:897–907 [discussion 907-8].
18. Abbott DE, Brouquet A, Mittendorf EA, et al. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. *Surgery*. 2012;151:710–716.
19. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg*. 2006;244:524–535.

20. Mariani P, Servois V, De Rycke Y, et al. Liver metastases from breast cancer: surgical resection or not? A case-matched control study in highly selected patients. *Eur J Surg Oncol*. 2013;39:1377–1383.
21. Chua TC, Saxena A, Liauw W, et al. Hepatic resection for metastatic breast cancer: a systematic review. *Eur J Cancer*. 2011;47:2282–2290.
22. Fitzgerald TL, Brinkley J, Banks S, et al. The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review. *Langenbecks Arch Surg*. 2014;399:989–1000.
23. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18:S68–80.
24. Younis T, Milch R, Abul-Khoudoud N, et al. Length of survival of patients with cancer in hospice: a retrospective analysis of patients treated at a major cancer center versus other practice settings. *J Palliat Med*. 2007;10:381–389.
25. Launois RJ, Reboul-Marty JM, Bonneterre J. [A medico-economic evaluation of second line chemotherapy in metastatic breast cancer: comparison between docetaxel, paclitaxel, and vinorelbine]. *Bull Cancer*. 1997;84: 709–721.
26. Casarett D, Fishman J, O'Dwyer PJ, et al. How should we design supportive cancer care? The patient's perspective. *J Clin Oncol*. 2008;26:1296–1301.
27. Chastek B, Harley C, Kallich J, et al. Health care costs for patients with cancer at the end of life. *J Oncol Pract*. 2012;8:75s–80s.
28. Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. *Clin Breast Cancer*. 2010;10:489–491.
29. http://www.dartmouthatlas.org. Accessed September 1, 2015.
30. Arias E. United States life tables, 2010. *Natl Vital Stat Rep*. 2014;63:1–63.
31. Spolverato G, Vitale A, Ejaz A, et al. The relative net health benefit of liver resection, ablation, and transplantation for early hepatocellular carcinoma. *World J Surg*. 2015;39:1474–1484.
32. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst*. 2011;103:117–128.
33. Siegel JE, Weinstein MC, Russell LB, et al. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276:1339–1341.
34. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. *Med Decis Making*. 2012;32:733–743.
35. Elias D, Maisonnette F, Druet-Cabanac M, et al. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. *Am J Surg*. 2003;185:158–164.
36. Bergenfeldt M, Jensen BV, Skjoldbye B, et al. Liver resection and local ablation of breast cancer liver metastases: a systematic review. *Eur J Surg Oncol*. 2011;37:549–557.
37. Martinez SR, Young SE, Giuliano AE, et al. The utility of estrogen receptor, progesterone receptor, and Her-2/neu status to predict survival in patients undergoing hepatic resection for breast cancer metastases. *Am J Surg*. 2006;191:281–283.
38. Ercolani G, Cucchetti A, Cescon M, et al. Effectiveness and cost-effectiveness of peri-operative versus post-operative chemotherapy for resectable colorectal liver metastases. *Eur J Cancer*. 2011;47:2291–2298.
39. Lim KC, Wang VW, Siddiqui FJ, et al. Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria. *Hepatology*. 2015;61:227–237.
40. Cillo U, Spolverato G, Vitale A, et al. Liver resection for advanced intrahepatic cholangiocarcinoma: a cost-utility analysis. *World J Surg*. 2015;39:2500–2509.
41. Spolverato G, Vitale A, Ejaz A, et al. Hepatic resection for disappearing liver metastasis: a cost-utility analysis. *J Gastrointest Surg*. 2015;19:1668–1675.
42. Vitale A, Volk ML, Pastorelli D, et al. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety. *Hepatology*. 2010;51:165–173.
43. Blank PR, Dedes KJ, Szucs TD. Cost effectiveness of cytotoxic and targeted therapy for metastatic breast cancer: a critical and systematic review. *Pharmacoeconomics*. 2010;28:629–647.