Title

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Journal

Journal of Neurological Surgery Part B Skull Base, 78(02)

ISSN

1526-8012

Authors

Zygourakis, Corinna C

Imber, Brandon S

Chen, Rebecca

et al.

Publication Date

2017-04-01

DOI

10.1055/s-0036-1592193

Peer reviewed

Cost-Effectiveness Analysis of Surgical versus Medical Treatment of Prolactinomas

Corinna C. Zygourakis[1,2] Brandon S. Imber[3] Rebecca Chen[1] Seunggu J. Han[1] Lewis Blevins[1] Annette Molinaro[1,4] James G. Kahn[5] Manish K. Aghi[1]

[1] Department of Neurological Surgery, University of California at San Francisco, San Francisco, California, United States
[2] Center for Healthcare Value, University of California at San Francisco, San Francisco, California, United States
[3] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, United States
[4] Department of Epidemiology and Statistics, University of California at San Francisco, San Francisco, California, United States
[5] Philip R. Lee Institute for Health Policy Studies, University of California at San Francisco, San Francisco, California, United States

Address for correspondence Corinna C. Zygourakis, MD, Department of Neurological Surgery, University of California at San Francisco, 505 Parnassus Ave., Room M779, San Francisco, CA 94143, United States (e-mail: corinna.zygourakis@ucsf.edu).

J Neurol Surg B 2017;78:125–131.

Abstract

Background Few studies address the cost of treating prolactinomas. We performed a cost-utility analysis of surgical versus medical treatment for prolactinomas.

Materials and Methods We determined total hospital costs for surgically and medically treated prolactinoma patients. Decision-tree analysis was performed to determine which treatment produced the highest quality-adjusted life years (QALYs). Outcome data were derived from published studies.

Results Average total costs for surgical patients were \$19,224 ($\pm$ 18,920). Average cost for the first year of bromocriptine or cabergoline treatment was \$3,935 and \$6,042, with \$2,622 and \$4,729 for each additional treatment year. For a patient diagnosed with prolactinoma at 40 years of age, surgery has the lowest lifetime cost (\$40,473), followed by bromocriptine (\$41,601) and cabergoline (\$70,696). Surgery also appears to generate high health state utility and thus more QALYs. In sensitivity analyses, surgery appears to be a cost-effective treatment option for prolactinomas across a range of ages, medical/surgical costs, and medical/surgical response rates, except when surgical cure rates are $\leq$ 30%.

Conclusion Our single institution analysis suggests that surgery may be a more cost-effective treatment for prolactinomas than medical management for a range of patient ages, costs, and response rates. Direct empirical comparison of QALYs for different treatment strategies is needed to confirm these findings.

Keywords
- pituitary tumor
- prolactinoma
- cost
- cost-effectiveness
- cost-utility analysis
- transsphenoidal surgery
- dopamine agonist

Introduction

Prolactin-secreting pituitary tumors (i.e., prolactinomas) are the most common endocrine-active pituitary adenomas, comprising 40% of pituitary tumors[1,2] and often presenting with hyperprolactinemia, hypopituitarism, vision problems, and/or headaches. Although dopamine agonists have become the standard first-line treatment modality for prolactinomas, a growing body of literature supports surgical resection as a primary treatment in certain circumstances, such as cystic tumors with

received
March 28, 2016
accepted
August 2, 2016
published online
September 27, 2016

DOI http://dx.doi.org/10.1055/s-0036-1592193.
ISSN 2193-6331.

intratumoral hemorrhage causing mass effect or apoplexy, pregnant patients, failure of dopamine agonist therapy, or patients with rapid visual loss.[1,3–7] Although frequently effective, pharmacological treatments for prolactinomas are long term, and potentially lifelong, in course. Moreover, dopamine agonists are associated with side effects, including gastrointestinal disturbances, headaches, and dizziness.[8] Studies report medical cure rates of 7 to 50%,[9,10] with a large meta-analysis showing that only 21% of patients are able to successfully come off dopamine agonists when their prolactin levels normalize.[11] In contrast, surgical resection can be immediately curative when successful. Surgical cure rates range from 10 to 80%, depending on multiple factors including prolactinoma size.[12,13]

Despite a large body of work regarding pituitary treatment efficacy, there is very little published about the cost of treating pituitary tumors.[14–17] Two studies on growth hormone producing pituitary tumors found that surgery is less expensive long term than either radiosurgery or medical therapies (pegvisomant and somatostatin analogs).[14,16] For prolactinomas, one article from the United Kingdom and another from China reported similar, but very slightly higher costs, for surgical versus medical treatment.[15,17] Importantly, both of these were cost comparison, rather than cost-effectiveness, studies.[15,17] Recently, a cost-effectiveness analysis of surgical versus medical treatment for microprolactinomas was published, using estimated Medicare costs.[18] Although single institution studies are subject to the practice tendencies of individual providers, it is important to determine actual costs of care, rather than estimated costs from Medicare reimbursements. The goal of our study was, therefore, to use our own hospital's cost data to perform a cost-utility analysis (CUA) for medical versus surgical treatment of prolactinoma patients.

Materials and Methods

Study Design

Our cost analysis is from the perspective of the payer. All costs are in U.S. dollars; averages are expressed as ± standard deviation. For surgical patients, we obtained cost data for patients undergoing transsphenoidal surgery for prolactinoma at the University of California, San Francisco, from 2010 to 2015. The goal was to capture the entire cost of care associated with the treatment of the prolactinoma, not just the index hospitalization. Total costs (including direct hospital and overhead costs from our financial accounting database) were, therefore, obtained for each separate patient encounter (i.e., hospitalization, office visit, etc.) and summed for each patient. We also added the cost of two serum prolactin checks, one magnetic resonance imaging (MRI), and one office visit × 3 years postoperatively to the cost of care for our surgical patients. Indirect costs (e.g., costs from lost labor productivity) were not included in our calculations.

For medical patients, we estimated the total annual cost of care based on our actual costs for MRIs, office visits, pituitary laboratories, and medication costs (specifically, both inpatient and outpatient medication costs). At our institution, the cost per 2.5 mg tablet of bromocriptine is $3, which is at the lower end of the range of average wholesale unit prices reported on REDBOOK online, which range from $2.2 for Paddock Laboratories generic (Allegan, Michigan, United States) to $6.7 for Validus Pharmaceuticals; Parlodel (Parsippany, New Jersey, United States). For cabergoline, our reported cost is $43 for the 0.5 mg tablet, which is at the high end of the published range ($19.5 for generic Actavis Pharma to $36.7 for Teva Pharmaceuticals [North Wales, Pennsylvania, United states]). Note that even cheaper medication prices than REDBOOK can be found at GoodRx (as low as $1.2 per 2.5 mg bromocriptine tablet and $13.2 per 0.5 mg cabergoline tablet), and we have accounted for this potential range in medication prices with our sensitivity analyses.

Medication costs are based on standard dosage (e.g., bromocriptine 2.5 mg BID, cabergoline 0.5 mg twice weekly) and can vary depending on the specific dosages required by each patient throughout the duration of their treatment. However, we have assumed these standard dosages to avoid extreme complexity in our model. All future costs were discounted at a 3% rate.

Cost Analysis

Our cost-effectiveness analysis adheres to the Consolidated Health Economic Evaluation Reporting Standards.[19] We created a decision-tree model in Microsoft Excel to analyze the cost-effectiveness of three treatment options (bromocriptine, cabergoline, and transsphenoidal surgery; see ►**Fig. 1**). The time horizon of the model is the entire patient's life expectancy. We created separate models for each decade of diagnosis (20–80 years old). Average life expectancies, rounded to the nearest year, contingent on current age were determined from Center for Disease Control (CDC) tables.[20]

Using this cost decision-tree model, we performed a CUA, using health state utility estimates from the literature.[21,22] For the medically treated patients, we obtained Short Form 36 (SF-36) scores for patients treated with bromocriptine and cabergoline.[21] We converted these into EQ-5D preference-based scores (on a scale of 0 to 1) using a published algorithm.[23] This generated health state utility estimates of 0.748 for patients taking bromocriptine and 0.882 for patients undergoing cabergoline therapy. For surgically treated patients, we obtained a health-utility score from a study using the 15D questionnaire, which like the SF-36 is a generic instrument for measuring health-related quality of life among adults.[22] This yielded a value of 0.941 for surgical patients.

Health state utilities were converted into quality-adjusted life years (QALYs) using the following Excel formula: net present value (NPV) (0.03, utility values) × (1 + 0.03)^0.5, where 0.03 represents our future discounting rate. Incremental cost-effectiveness ratios (ICER = Δ cost/Δ QALYs) were computed when appropriate. Finally, univariate sensitivity analyses were performed to evaluate the effect of several parameters (medical and surgical response rates, medical and surgical costs) on our model for patients diagnosed at 40 years of age.

Results

Total Costs of Treatment

We identified 108 patients with prolactinomas seen by neurosurgeons at our institution between 2010 and 2015.

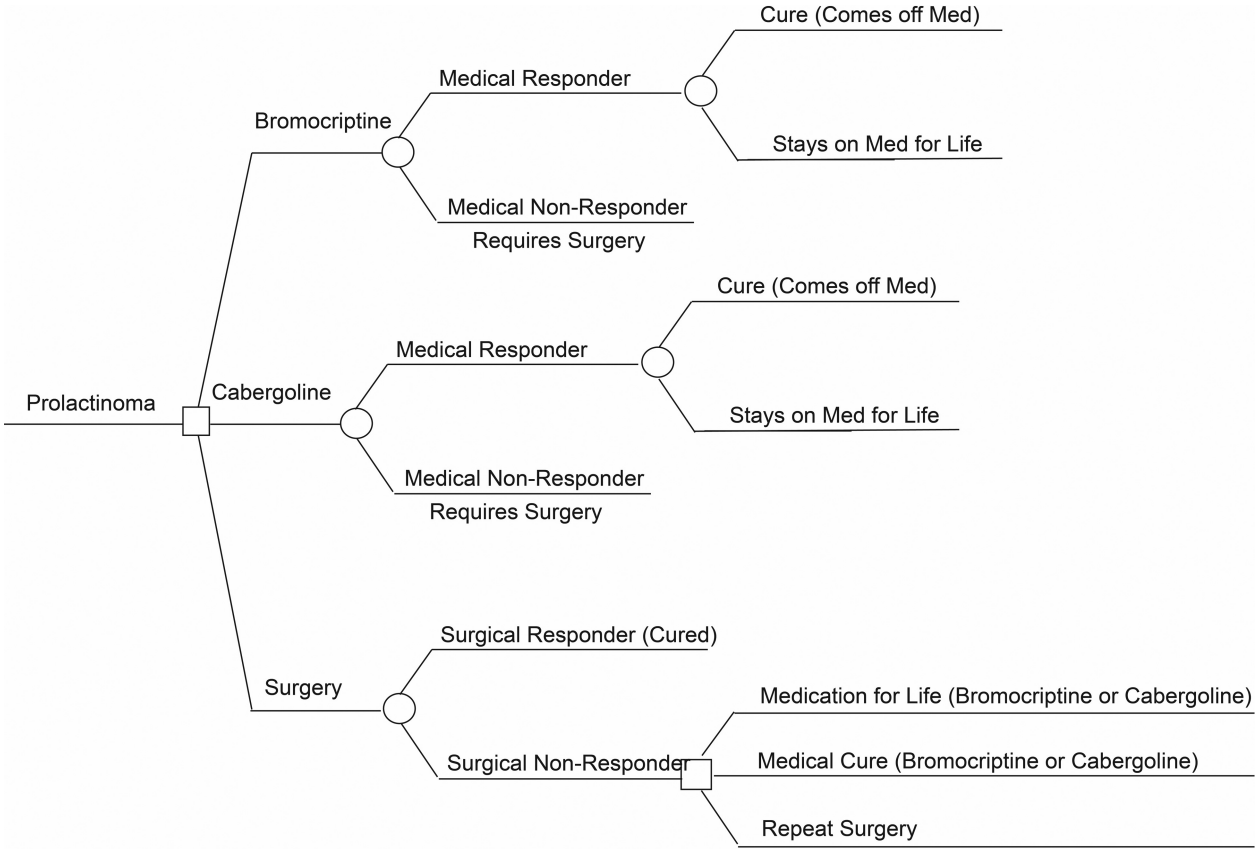

Fig. 1 Decision-tree model of prolactinoma treatment options. Squares indicate decision nodes, and circles are chance nodes.

All patients (surgical and medical) were followed by the same endocrinologist (L.B.). The average total cost for surgical patients is \$19,224 ($\pm$ 18,920) in the first year of treatment. Based on our cost estimate model, the average cost for our medically treated patients is \$3,935 for the first year of bromocriptine treatment and \$6,042 for the first year of cabergoline treatment (see ►**Table 1**). Our medical management algorithm is determined by our neuroendocrinologist (L.B.) as outlined in ►**Table 2**.

Cost-Effectiveness Analysis

►**Fig. 1** demonstrates our decision-tree model for the three basic treatment options for prolactinomas (bromocriptine, cabergoline, transsphenoidal surgery). Our baseline case assumes an 80% medical response rate and 60% surgical response rate, averaged from several studies in the literature.[24–28]

Table 1 Average total costs in the first year of treatment for prolactinoma patients

Treatment group	Average total costs in the first year
Surgery	\$19,224
Bromocriptine	\$3,935
Cabergoline	\$6,042

Note: See "Materials and Methods" section for details of how surgical costs are calculated and medical costs are estimated.

For patients diagnosed with a prolactinoma at 40 years of age, the overall lifetime cost is \$40,473 for surgical patients; \$41,601 for bromocriptine; and \$70,696 for cabergoline (see ►**Table 3**). Using available, if imperfect, health-utility data, our CUA analysis suggests that surgery may be dominant to both bromocriptine and cabergoline, as it appears to be cheaper and produce higher QALYs than both medical treatments (see ►**Table 3**). Note that if we simply compare cabergoline to bromocriptine therapy, we find an ICER = \$15,476, suggesting that although cabergoline is more expensive than bromocriptine therapy, it may produce better results (higher QALYs) and with a low ICER that is far below the usual cost-effectiveness threshold of \$150,000 (or three times our gross domestic product per capita) in the United States.

We find similar results for patients diagnosed with a prolactinoma at 20 and 30 years of age (see ►**Table 4**), where surgery appears dominant to both bromocriptine and cabergoline, meaning that surgery has a lower lifetime cost and may produce higher QALYs than medical treatment. For patients 50 through 80 years of age, surgery appears to remain dominant to cabergoline therapy. When comparing surgery to bromocriptine therapy, surgery may be slightly more expensive over the patient's lifespan but still appears to produce higher QALYs than bromocriptine treatment. As a result, the ICER for surgery versus bromocriptine appears

Table 2 Cost breakdown for medically treated prolactinoma patients

	Cost
First year	
Initial diagnosis—MRI	$437
Initial diagnosis—office visit	$139
Initial diagnosis—full pituitary hormone panel	$161
6/12 wk office visit	$139
6 wk serum prolactin	$15
12 wk serum prolactin	$15
6 mo MRI	$437
12 mo MRI	$437
1 y office visit	$139
Med cost bromocriptine/y[a]	$2,016
Med cost cabergoline/y[b]	$4,123
Total cost bromocriptine Tx in first year	$3,935
Total cost cabergoline Tx in first year	$6,042
Each additional year	
2 serum prolactin	$30
1 office visit	$139
1 MRI	$437
Med cost bromocriptine/y[a]	$2,016
Med cost cabergoline/y[b]	$4,123
Total cost bromocriptine Tx/y	$2,622
Total cost cabergoline Tx/y	$4,729

Abbreviation: MRI, magnetic resonance imaging.
[a]Bromocriptine cost/year is estimated based on assumption of standard bromocriptine dose 2.5 mg twice a day. Cost for each 2.5 mg tablet at our institution is $3.
[b]Cabergoline cost/year is estimated based on assumption of standard cabergoline dose 0.5 mg twice per week. Cost for each 0.5 mg tablet at our institution is $43.

very low, ranging from $599 for a 50-year-old patient to $10,411 for an 80-year-old patient (see ►**Table 4**). Similarly, when comparing only cabergoline to bromocriptine therapy, the ICER may remain very low across all age ranges, from $15,258 at 20 years of age to $15,597 at 80 years of age (not shown).

Table 4 Results of cost-utility analysis if patient is diagnosed with prolactinoma at different ages

Age at diagnosis (y)	ICER (surgery vs. bromocriptine)	ICER (surgery vs. cabergoline)
20	[a]Dominant	[a]Dominant
30	[a]Dominant	[a]Dominant
40	[a]Dominant	[a]Dominant
50	$599	[a]Dominant
60	$2,183	[a]Dominant
70	$4,678	[a]Dominant
80	$10,411	[a]Dominant

Abbreviation: ICER, incremental cost-effectiveness ratios.
[a]Dominant indicates that no ICER can be calculated because surgery is dominant to the alterative therapy, that is, it is both cheaper and has higher QALY.

Sensitivity Analysis

To assess the robustness of our results, we perform several univariate sensitivity analyses. We first vary the chance of response to bromocriptine, cabergoline, and surgical treatment from 0 to 100%. Our sensitivity analysis shows that surgery appears to remain cost-effective as compared with bromocriptine, even when the bromocriptine cure rate is as high as 100% (ICER for surgery vs. bromocriptine = $25,745 in this extreme case; see ►**Table 5**). Only when the bromocriptine response rate is 0% did we see a preference for the "medical treatment arm," but this is because all of the patients in this scenario undergo surgical resection (see ►**Table 5**).

Surgery appears to be more cost-effective than cabergoline, even when the cabergoline cure rate is 100%, although this ICER of $110,672 comes closer to the cost-effectiveness threshold (see ►**Table 5**). Only when the cabergoline response rate is 0% did we see a preference for the "medical treatment arm," but once again this is because 100% of the patients in this scenario undergo surgical resection (see ►**Table 5**).

Similarly, our results suggest that surgery may be cost-effective as compared with bromocriptine treatment at all ranges of surgical cure (0–100%), and compared with cabergoline at all ranges of surgical cure $\geq$ 30% (see ►**Table 5**). More specifically, cabergoline may produce higher QALYs than surgery and may become cost-effective

Table 3 Cost-utility model if patient is diagnosed with prolactinoma at 40 years of age

Treatment	Cost	ΔCost	QALYs	ΔQALYs	ICER
Surgery	$40,473		21.788		
Bromocriptine	$41,601	$1,128	19.57	− 2.218	[a]
Cabergoline	$70,696	$30,223	21.45	− 0.338	[a]

Abbreviations: ICER, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years.
Note: Total costs estimated over life expectancy of 40 additional years, with 3% future discounting.
[a]Surgery dominates both bromocriptine and cabergoline treatment, as it is cheaper and has higher QALY. Note that HUIs are derived from the literature, as described in "Materials and Methods" section.

Table 5 Sensitivity analysis for cost-utility model at 40 years of age, with each parameter varied independently

Parameter (base case value)	Surgery vs. bromocriptine			Surgery vs. cabergoline		
	ΔCost	ΔQALYs	ICER	ΔCost	ΔQALYs	ICER
Base case	− 1,128	2.21	[a]	− 30,222	0.34	[a]
Bromocriptine response (0.3,0.5,0.2)						
(1,0,0)	22,862	0.88	$25,745	− 30,222	0.34	[a]
(0,1,0)	− 21,104	4.0	[a]	− 30,222	0.34	[a]
(0,0,1)	13,590	− 0.2	[b]	− 30,222	0.34	[a]
Cabergoline response (0.3,0.5,0.2)						
(1,0,0)	− 1,128	2.21	[a]	9,739	0.1	$110,672
(0,1,0)	− 1,128	2.21	[a]	− 70,112	0.8	[a]
(0,0,1)	− 1,128	2.21	[a]	9,559	− 0.4	[b]
Surgical response (0.6)						
0.0	25,832	1.3	19,870	− 3,263	− 0.58	− 5,625
0.30	12,352	1.8	7,022	− 16,742	− 0.1	− 138,367
0.35	10,106	1.8	5,505	− 18,989	− 0.04	− 426,720
1.0	− 19,101	2.83	[a]	− 48,196	0.95	[a]

Abbreviations: ICER, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years.
Notes: A negative value for ΔCost indicates that surgery is less expensive than the medical alternative over the patient's lifespan; a positive value indicates that surgery is more expensive. A positive value for ΔQALY indicates that surgery produces a higher QALY that the medical alternative.
[a]Surgery is dominant to the medical therapy; therefore, no ICER can be calculated.
[b]Medical treatment is dominant to surgery; therefore, no ICER can be calculated.

(with ICER = $138,367) when the surgical cure rate is ≤ 30% (see ►**Table 5**).

Our conclusions remain the same (i.e., surgery is either dominant or cost-effective with a very low ICER) when we vary the cost of surgery, bromocriptine, and cabergoline ± 50% (see ►**Table 6**). Looking at even further extremes, for a patient diagnosed with a prolactinoma at 40 years of age, the lifetime cost of surgery must more than triple (from $40,473 to $121,396) in order for surgery to no longer appear cost-effective as compared with cabergoline (ICER > $150,000). Similarly, the surgical lifetime cost must increase more than nine times (from $40,473 to $374,301) in order for surgery to no longer appear cost-effective as compared with bromocriptine in our model. In addition,

Table 6 Sensitivity analysis for cost-utility model at 40 years of age

Parameter (base case value)	Surgery vs. bromocriptine			Surgery vs. cabergoline		
	ΔCost	ΔQALYs	ICER	ΔCost	ΔQALYs	ICER
Base case	− 1,128	2.21	[a]	− 30,222	0.34	[a]
Cost of surgery ($22,500/y)						
$11,250	− 11,460	2.21	[a]	− 40,555	0.34	[a]
$33,750	13,611	2.21	6,136	− 15,484	0.34	[a]
Cost of bromocriptine ($3,935 + 2,622/y)						
$1,968 + $1,311/y	14,878	2.21	6,707	− 32,959	0.34	[a]
$5,903 + 3,933/y	− 17,070	2.21	[a]	− 27,424	0.34	[a]
Cost of cabergoline ($6,042 + 4,729/y)						
$3,021 + $2,365/y	− 6,173	2.21	[a]	− 1,986	0.34	[a]
$9,063 + $7,094/y	3,920	2.21	1,767	− 58,471	0.34	[a]

Abbreviations: ICER, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years.
Note: Each cost parameter is varied independently ± 50%, and 3% future discounting is applied. Note that a negative value for ΔCost indicates that surgery is less expensive than the medical alternative over the patient's lifespan; a positive value indicates that surgery is more expensive. A positive value for ΔQALY indicates that surgery produces a higher QALY that the medical alternative.
[a]Surgery is dominant to the medical therapy; therefore, no ICER can be calculated.

given the higher QALYs produced by the surgical outcomes, the medical costs can decrease to $< 5\%$ of our calculated costs, and surgery still appears cost-effective in our model.

Finally, to test the potential effect of different sources for our health-utility measures, we performed another sensitivity analysis where we decreased our 15D measures by 0.50 (as the higher values of 15D could favor surgery in our model, as compared with the SF-36 values used for the medically treated patients). In this case, for a patient diagnosed with a prolactinoma at 40 years of age, we found that surgery remained the most cost-effective treatment option, as cabergoline's ICER was $>$ \$350,000. When we decreased our 15D measures by ≥ 0.75, surgery no longer remained the most cost-effective treatment option.

Discussion

Our study is one of the first CUAs for prolactinoma treatment in the United States. Despite higher upfront costs as compared with the British and Chinese studies,[15,17] our model suggests that surgery appears to be cost saving as compared with both types of medical treatment, bromocriptine and cabergoline, over the long term. In addition, even though cabergoline is more expensive than bromocriptine, it may be cost-effective, with a low ICER when compared with bromocriptine alone. Despite methodological differences, our findings are consistent with the only other U.S. cost-effectiveness analysis for prolactinomas,[18] lending further support to both studies' conclusions. Important distinctions between these two cost-effectiveness analyses are that we use our hospital's actual surgical costs for treating prolactinomas, rather than estimating costs from the very broad diagnosis-related groups 614/615 ("adrenal and pituitary procedures with or without comorbidities or major comorbidities"), which contain a heterogeneous group of procedures and are not limited to prolactinoma resections. As a result, our surgical costs are nearly double those reported by Jethwa et al[18]; therefore, our finding of surgical cost-effectiveness in this setting is even more convincing. In addition, we have derived our health state utilities from the published literature, rather than using estimates or assumptions.[18] For example, in our model, we assign surgical patients a health utilities index (HUI) of 0.941 (which incorporates the negative effect of even a successful surgery on one's quality of life[22]), rather than assuming a perfect HUI of 1 for surgically cured patients, as done in Jethwa et al's work.[18]

Our findings have potential implications for neurosurgical practice and for insurers. Although individual patients may have specific reasons for avoiding surgery (e.g., multiple medical comorbidities, surgical aversion), and not all tumors may be amenable to surgery, surgery may represent a cost-effective treatment for prolactinomas when feasible. Furthermore, although cabergoline is more expensive than bromocriptine, it produces higher QALYs and appears to be cost-effective at a very low threshold—an important fact that should be considered by insurers such as Medi-Cal that currently do not cover cabergoline for the treatment of prolactinomas.

A major strength of our study is that these conclusions hold, even across a wide range of ages (20–80 years) and a full range of medical response rates (0–100%). Only when the surgical cure rate falls to $\leq 30\%$ do we see a preference for cabergoline over surgical treatment. Thus, we would expect surgery to be the most cost-effective treatment option even at other institutions where the surgical cure rate for prolactinomas may be lower than 60% (which we used as our baseline because it represents the average in the literature). Similarly, based on this sensitivity analysis, surgery would remain cost-effective even if prolactinomas recurred at a rate of 20% after surgical cure, as has been suggested in the literature.[13]

Our conclusions also hold across a wide range of medical and surgical costs. We appreciate that patients may get their medications filled at various locations and under different insurance plans, and wholesale drug prices for bromocriptine and cabergoline vary considerably and may change in the future. Because our sensitivity analysis shows that surgery may remain cost-effective even when medication costs are less than 5% of our estimated costs, we do not expect our results to change significantly with future variations in drug costs or with alternative sources of cheaper drugs, such as GoodRx. The results of this sensitivity analysis also indicate that surgery may remain a cost-effective option even if the MRI frequency of medically treated patients is reduced significantly, and/or they stop needing medical treatment after menopause. Another sensitivity analysis shows that surgical costs may increase up to ninefold while still remaining cost-effective, allowing for surgical complications that may be very costly.

There are several limitations of this study. An important limitation is the reliance for the CUA on health state utility values from two separate studies, in different patient populations, and using different measures of health state utility.[8,22] Although evidence suggests that these measures are correlated,[29] it is possible that the higher utility value for surgical patients is an artifact of methodological issues. We have performed a sensitivity analysis to assess the impact of this issue; however, in the future, these utilities should be measured in one study population, to confirm or revise comparisons across treatment options. In addition, as a tertiary care neurosurgical department in which a neuroendocrinologist works alongside neurosurgeons, referral patterns could create a bias toward our center treating this disease surgically more frequently than typical providers. However, the frequency with which surgery or medicine is chosen shouldn't impact the cost of these treatments. In addition, we did not analyze the cost of the morbidities of surgery or medical treatment, with the former having quantifiable costs and the latter having potential quality of life costs. A prospective trial would be the only way to truly address that limitation.

Future work in this area should seek to directly measure health-related quality of life outcomes in both medical and surgical prolactinoma patients from one cohort, as there are currently no published studies that do this. We should also consider multistaged treatments (e.g., subtotal surgical resection, followed by treatment of residual tumor with medication or radiation), as well as medical and surgical complications, which were not included in our model to avoid extraordinary

complexity. Note, however, that given the robustness of our conclusions in multiple sensitivity analyses, we would expect surgery to remain a cost-effective treatment for prolactinomas despite the potential for costly surgical complications.

Conclusion

In summary, we report the average first-year cost for surgically treated prolactinomas ($19,224) versus $3,395 for the first year of bromocriptine treatment and $6,042 for cabergoline. Our CUA suggests that for a patient diagnosed with a prolactinoma at 40 years of age, surgery has the lowest lifetime cost ($40,473) followed by bromocriptine ($41,601) and cabergoline ($70,696). Surgery appears to dominate both types of medical therapies in that it is both cheaper and produces higher QALYs, if past studies on health state utility are correct in ranking surgical outcomes higher. In our sensitivity analyses, surgery may remain the most cost-effective treatment option for prolactinomas across a wide range of ages (20–80 years), medical/surgical costs ($\pm$ 50%), and medical/surgical response rates, except when surgical cure rates are $\leq$ 30%. This is one of the first cost-effectiveness analyses for prolactinomas using an institution's actual cost data published in the United States.

Acknowledgments

C.C.Z. is funded by a grant from the UCSF Center for Healthcare Value. B.S.I. was supported by UCSF-CTSI Grant Number TL1 TR000144.

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