Carpal Tunnel Syndrome Management in Breast Cancer Survivors at Risk for Lymphedema: A Markov Model

Helene Retrouvey, M.D.C.M.
Murray Krahn, M.D., M.Sc.
Heather L. Baltzer, M.Sc., M.D.

Toronto, Ontario, Canada

Background: Breast cancer survivors that have undergone axillary lymph node dissection have an increased risk of developing same-side upper extremity lymphedema. Patients with carpal tunnel syndrome in the ipsilateral limb may not receive appropriate surgical therapy (carpal tunnel release) because of concerns that it may trigger or worsen lymphedema.
Methods: A state transition cohort model was used to evaluate the treatment options for breast cancer survivors at risk of upper extremity lymphedema presenting with carpal tunnel syndrome. The model reflected three treatment strategies: (1) early surgical intervention, (2) delayed surgical intervention, or (3) nonsurgical management. Both life-years and quality-adjusted life-years were modeled over a 30-year time horizon.
Results: Over a 30-year time horizon, the preferred strategy was delayed surgery, which resulted in 21.41 quality-adjusted life-years. Early surgery and nonsurgical management yielded 20.42 and 21.06 quality-adjusted life-years, respectively. The model was robust and was not sensitive to variation in any of the parameters within the clinically plausible ranges.
Conclusions: Based on this decision analytic model, the optimal choice for breast cancer survivors with mild carpal tunnel syndrome who are at risk for lymphedema would be delaying surgery until severe symptoms develop. This strategy balances the potential increased risk of lymphedema following carpal tunnel release with the decreased long-term risk of severe carpal tunnel syndrome. The model comprehensively assesses a controversial area in the breast cancer and hand surgery literature to inform decision-making for patients and clinicians. (*Plast. Reconstr. Surg.* 141: 689e, 2018.)

Breast cancer survivors that have undergone axillary lymph node dissection have an increased risk of developing same-side upper extremity lymphedema.[1] Based on anecdotal evidence, breast cancer survivors are often advised that any procedure—even one as minor as blood pressure measurement—performed on the side of the breast cancer will trigger the development of lymphedema.[2,3]

In the context of breast cancer survivors, the safety of elective hand surgery on the same side as the axillary lymph node dissection is controversial because of concerns of developing de novo upper extremity lymphedema. Patients who have undergone breast cancer treatment (i.e., axillary lymph node dissection) and who need elective hand surgery for carpal tunnel syndrome may be dissuaded from the procedure because of the perceived risk of developing lymphedema. These patients may be forced to continue living with the symptoms and disability related to their hand abnormality.[2,3]

Previous reports regarding breast cancer survivors that require elective hand surgery are mainly small retrospective cohort studies, which have demonstrated a minimal risk of developing lymphedema with hand surgery following axillary lymph node dissection.[4–6] A recent, larger retrospective cohort study reported that the incidence

From the Division of Plastic and Reconstructive Surgery, University of Toronto; and the Toronto Health Economics and Technology Assessment Collaborative, Toronto General Hospital.
Received for publication September 13, 2017; accepted November 21, 2017.
Presented at Gallie Day, in Toronto, Ontario, Canada, April 28, 2017.

DOI: 10.1097/PRS.0000000000004318

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

of post–elective hand surgery lymphedema was 3.8 percent in breast cancer survivors that had previously undergone axillary lymph node dissection or sentinel lymph node biopsy.[6]

The problem faced by both the patient and the clinician is the decision to proceed with a carpal tunnel release if the patient does not respond to nonsurgical management. Carpal tunnel release may increase the risk of developing lymphedema; however, if carpal tunnel syndrome is left untreated, it can progress in severity, causing significant limitations and decreasing quality of life. Decision analysis is an appropriate method to address this controversial question, as this will allow weighing the advantages and disadvantages of performing carpal tunnel release (i.e., improved quality of life by relieving carpal tunnel syndrome symptoms versus increased risk of lymphedema) or continuing with nonsurgical management (i.e., decreased risk of lymphedema, but continued impact on quality of life from carpal tunnel syndrome). The primary objective of this study was to model this controversial question using decision analysis.

PATIENTS AND METHODS

Model

This study conforms with the Declaration of Helsinki. A clinical decision analysis model was used to evaluate the treatment options for breast cancer survivors at risk for upper extremity lymphedema presenting with carpal tunnel syndrome using TreeAgePro Software (TreeAge Software, Inc., Williamstown, Mass.). We developed a state transition cohort model with a cycle length of 3 months.

Our base case was a 55-year-old woman 1 year after completion of breast cancer treatment, including axillary lymph node dissection, presenting with same-side mild carpal tunnel syndrome nonresponsive to a standard 3-month course of nonsurgical management (e.g., night splinting). Three treatment strategies were included: (1) early surgical intervention, (2) delayed surgical intervention, or (3) continued nonsurgical management (Fig. 1). The early surgical intervention strategy directed patients to carpal tunnel release under local anesthesia, without the use of a tourniquet at presentation (during the first cycle). After the early carpal tunnel release, patients could either improve (no carpal tunnel syndrome) or have persistent symptoms (mild carpal tunnel syndrome). Patients with no carpal tunnel syndrome could have a recurrence to mild carpal tunnel syndrome, and patients with mild carpal tunnel syndrome could progress to severe carpal tunnel syndrome. The delayed surgical intervention strategy initiated with nonsurgical intervention for mild carpal tunnel syndrome. Patients could then either improve (no carpal tunnel syndrome), remain the same (mild carpal tunnel syndrome), or experience progression of their symptoms (severe carpal tunnel syndrome). Patients with progression from mild to severe carpal tunnel syndrome underwent surgery under local anesthesia, without the use of a tourniquet (i.e., they transitioned to the carpal tunnel release health state). Patients who improved or remained the same continued with nonsurgical management. The nonsurgical strategy did not allow patients to transition to carpal tunnel release. Patients could either improve with conservative therapy (mild carpal tunnel syndrome to no carpal tunnel syndrome), remain the same (mild carpal tunnel syndrome), or progress to severe carpal tunnel syndrome.

All three strategies included the possibility of developing lymphedema, with an increased risk of this condition following carpal tunnel

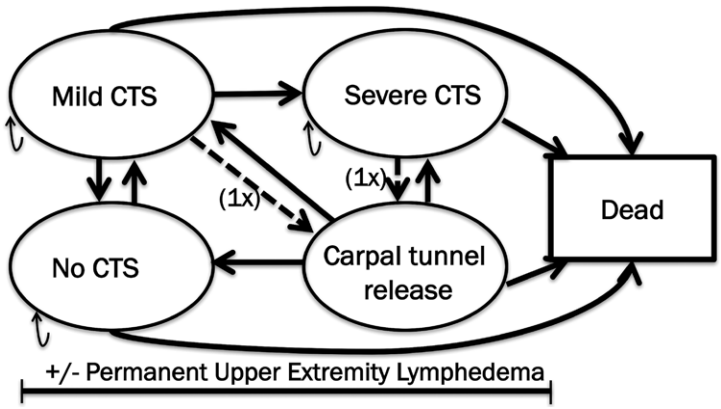

Fig. 1. Model structure. *CTS*, carpal tunnel syndrome.

release. Surgery could occur only once in the early and delayed surgery strategies. We assumed that patients with recurrent carpal tunnel syndrome following carpal tunnel release would not undergo another operation.

Patients cycled between health states every 3 months to account for the natural progression of the disease and response to therapy. The model had 120 cycles (30 years), which translated to a nearly lifetime time horizon for a 55-year-old woman (life expectancy, 85 years).[7] A lifetime horizon was chosen to weigh the risks and the benefits of each strategy, specifically, the risk of developing lymphedema in this high-risk population versus the benefits of improvement of carpal tunnel syndrome symptoms (Fig. 1).

Assumptions

Several assumptions were made in the design of this model. First, patients who developed severe carpal tunnel syndrome did not improve spontaneously with the early surgery and nonsurgical strategies. With the delayed surgical strategy, patients underwent only one operation to treat severe carpal tunnel syndrome. Second, carpal tunnel release was treated as a health state. During the carpal tunnel release cycle, patients experienced a disutility, which included both the adverse effects of surgery and the complications that some patients experienced. We did not explicitly model complications. Third, carpal tunnel release was performed under local anesthesia, without the use of a tourniquet. As our patient population included breast cancer patients, the use of a tourniquet was a relative contraindication; as such, all carpal tunnel release procedures in our model were performed under local anesthesia using a combination of lidocaine and epinephrine. Fourth, all patients in the model were at risk of lymphedema. Nonsurgical patients had a baseline probability of lymphedema of 20 percent, whereas surgical patients had an additional risk of 4 percent.[1,6] This probability remained static over time. Fifth, lymphedema was a permanent health state. Lastly, upper extremity lymphedema was treated as a disutility, and its disutility was subtracted from the utility of carpal tunnel syndrome if present.

Baseline Probabilities and Utilities

A thorough review of the literature was conducted to establish baseline utility values and baseline probabilities of health state transition for different treatment strategies and the associated risk of recurrence and lymphedema. Health state utility values were adapted from previously published literature (Table 1).[8–20] Of note, the disutility of surgery was evaluated to be −0.20 and applied for one cycle.[8]

Analysis

We evaluated the validity of the model structure and base outputs by presenting it to several experts in the field of hand surgery and plastic surgery. The internal validity of the model was tested using extensive univariate sensitivity analysis and input of null or extreme values.[21,22] The external validity of the model was not assessed, as all available data were included in the model and could therefore not be used for comparison with model outputs.

Base Case

Once validated, the model was run to determine the strategy that generated the greatest

Table 1. Summary of Data Included in the Model

Health State Utilities	Value	Range	Reference
Post–carpal tunnel release disutility	−0.20	−0.15 to −0.23	Li et al., 2015[8]
Resolution of carpal tunnel syndrome	0.97	0.95–1	Thoma et al., 2006[10]
Mild carpal tunnel syndrome	0.81	0.77–0.84	Marti et al., 2016[11]
Severe carpal tunnel syndrome	0.69	0.56–0.82	Li et al., 2015[8]; Atroshi et al., 2007[12]
Upper extremity lymphedema	0.80	0.76–0.85	Cheville et al., 2010[13]
Effectiveness			
Effectiveness of nonsurgical management	0.50	0.32–0.54	Gerritsen et al., 2002[14]; Muhlau et al., 1984[16]
Effectiveness of CTR	0.90	0.81–0.97	Thoma et al., 2006[10]
Probabilities			
Probability of recurrence after successful conservative treatment	45.8%	35–55%	Weng et al., 2016[18]
Probability of progressing from mild to severe CTS after conservative management	20%	10–23%	Resende et al., 2003[17]; Burton et al., 2016[19]
Probability of recurrence of CTS after CTR	25%	14–32%	Rodrigues et al., 2006[20]
Probability of progressing from mild to severe CTS after CTR	2.2%	0–12%	Kern et al., 1993[9]; Rodrigues et al., 2006[20]
Probability of lymphedema baseline	20%	14.9–29.8%	DiSipio et al., 2013[1]
Probability of lymphedema after CTR	24%	20–28%	Baltzer et al., 2017[6]

CTS, carpal tunnel syndrome; CTR, carpal tunnel release.

number of life-years and quality-adjusted life-years. Discounted (3 percent) and nondiscounted outcomes were evaluated. The validity of our model was also evaluated using deterministic one-way sensitivity analyses to test the key assumptions and model parameters. Sensitivity analyses assessed all model variables, including the probability of recurrence and immediate failure, and utility values. One-way and two-way sensitivity analyses were performed. One-way sensitivity analysis allowed for determination of the preferred strategy when modifying the value of each of the variables in the model. Two-way sensitivity analysis allowed for evaluation of the preferred strategy when concomitantly modifying the value of two variables. Scenario analysis was performed to assess optimal treatments for different populations.

RESULTS

Base Case Analysis

Our base-case, a 55-year-old female breast cancer survivor presenting with 3 months of mild carpal tunnel syndrome with increased risk for developing upper extremity lymphedema secondary to axillary lymph node dissection, was analyzed using both life-years and quality-adjusted life-years. The model demonstrated that all three strategies generated the same number of life-years, specifically, 29.40 years without discounting and 19.57 years with 3 percent discounting (Table 2). This finding was expected, as the mortality risk was the same across all strategies.

When effects of treatment on quality of life were included, delaying carpal tunnel release emerged as the preferred choice. Delayed surgery led to a total of 21.41 quality-adjusted life-years, compared to 21.06 and 20.42 quality-adjusted life-years for nonsurgical treatment and early surgery, respectively. With 3 percent discounting, delayed carpal tunnel release leads to 14.56 quality-adjusted life-years, compared with 14.34 and 13.99 for nonsurgical treatment and early surgery, respectively (Table 2). The difference between delayed carpal tunnel release and nonsurgical treatment (0.35 quality-adjusted life-year) is neither very small nor very large, and almost certainly clinically significant.[23]

One-Way Sensitivity Analysis

One-way sensitivity analysis was performed on all variables in the model using clinically plausible ranges. Figure 2 illustrates the overall estimate variation in quality-adjusted life-months when one-way sensitivity analysis was performed on all variables within clinically plausible ranges. The utility of lymphedema and the baseline risk of developing lymphedema were the parameters that introduced the most variability into the model; however, the threshold analysis for each parameter demonstrated that the model was not sensitive to variation of any parameter within the clinically relevant range (Fig. 2 and Table 3). The preferred strategy remained delayed surgery despite variation in baseline probabilities and utilities (Fig. 2). Thresholds approached but did not fall within a clinically relevant range for two model parameters: (1) decreasing the effectiveness of nonsurgical management below 0.269 resulted in early surgery as the preferred option; (2) decreasing the probability of recurrence of carpal tunnel syndrome after surgery to below 11.2 percent resulted in early surgery as the preferred option (Table 3).

Two-Way Sensitivity Analysis

Two-way sensitivity analyses were performed for the two parameters that produced the most variability on one-way sensitivity analysis. The utility of lymphedema varied between 0 and 1 and the baseline probability of lymphedema varied between 0 and 100 percent (Fig. 3). The base case (utility of lymphedema = 0.8; probability of lymphedema = 20 percent) is shown with a dotted line; this case favors delayed surgery. With decreasing both the utility of lymphedema and the baseline probability of lymphedema, nonsurgical intervention becomes the preferred strategy. Increasing the baseline probability of lymphedema and keeping the lower utilities of lymphedema, early surgery is favored (Fig. 3).

Table 2. Model Outputs

	Without Discounting		With 3% Discounting	
Strategy	**Life Expectancy (yr)**	**QALYs**	**Life Expectancy (yr)**	**QALYs**
Nonsurgical management	29.40	21.06	19.57	14.34
Early surgery	29.40	20.42	19.57	13.99
Delayed surgery	29.40	21.41	19.57	14.56

QALYs, quality-adjusted life-years.

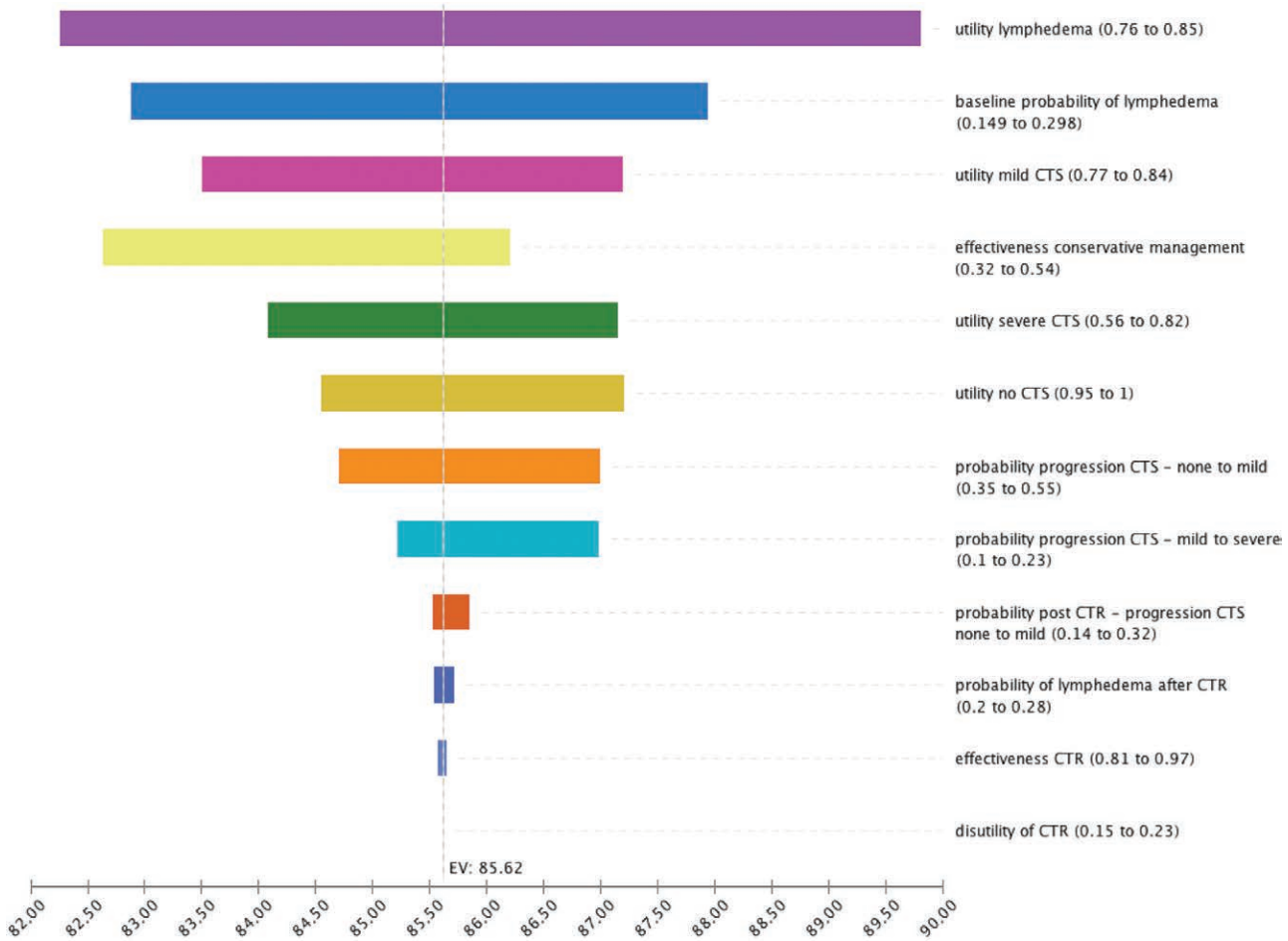

Fig. 2. One-way sensitivity analysis of all variables in clinically plausible ranges illustrated using a Tornado diagram. *CTS*, carpal tunnel syndrome; *CTR*, carpal tunnel release.

Table 3. Thresholds of Model Parameters

Parameter	Base Case	Range	Threshold
Utility resolution CTS	0.97	0.95–1	0.813
Utility mild CTS	0.81	0.77–0.84	1. 0.59 2. 0.92
Utility severe CTS	0.69	0.56–0.82	1. 0.30 2. 0.84
Effectiveness of nonsurgical management	0.50	0.32–0.54	1. 0.27 2. 1
Probability of recurrence of CTS after CTR	0.25	0.14–0.32	0.11
Probability of progressing from mild to severe CTS after conservative management	0.20	0.1–0.23	0.53
Probability of lymphedema baseline	0.20	0.15–0.30	0.38
Probability of lymphedema after CTR	0.24	0.20–0.28	0.13

CTS, carpal tunnel syndrome; CTR, carpal tunnel release.

Scenario Analysis

Scenario analysis was performed to assess the impact of decreased effectiveness of nonsurgical management with prolonged duration of carpal tunnel syndrome symptoms. This scenario tested the assumption that prolonged use of nonsurgical interventions decreases its effectiveness (Table 4). For the base case (effectiveness of nonsurgical management = 0.5), delayed surgery was the preferred strategy. In scenario 1, in a patient presenting with 2 years of carpal tunnel syndrome symptoms treated conservatively (effectiveness of nonsurgical management = 0.3), delayed surgery was still favored; however, in scenario 2, with

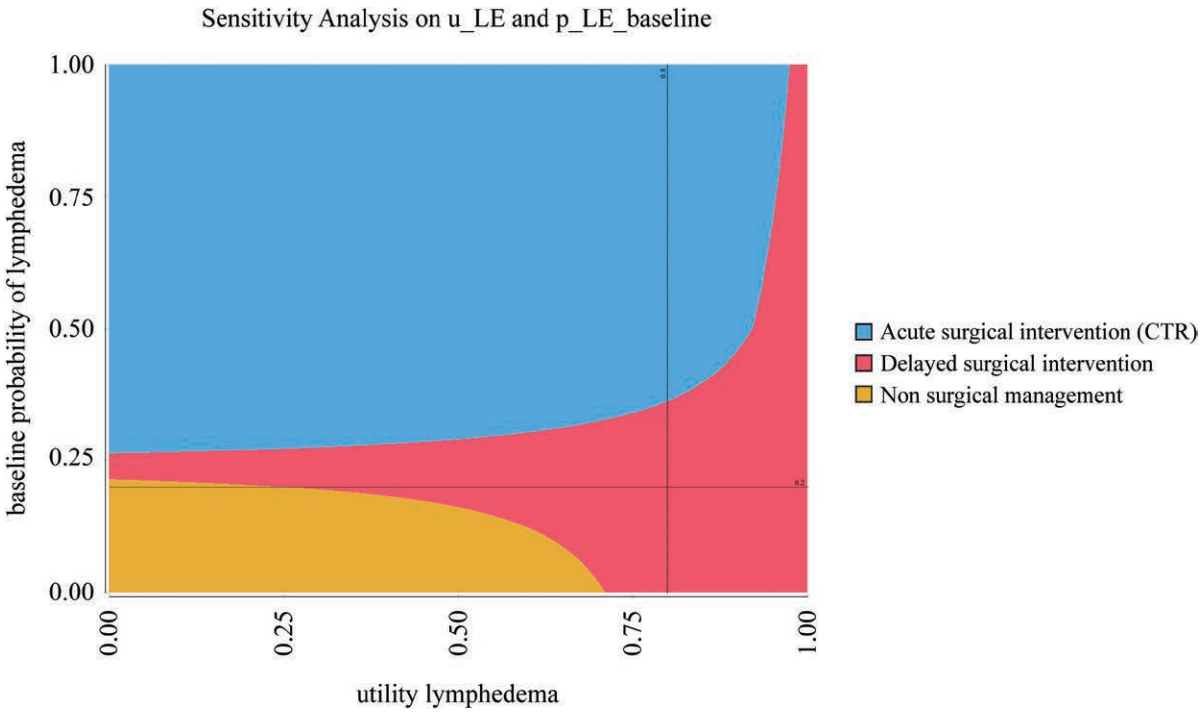

Fig. 3. Two-way sensitivity analysis for utility of lymphedema versus baseline probability of lymphedema. *CTR*, carpal tunnel release; *u_LE*, utility of lymphedema; *p_LE*, probability of lymphedema.

Table 4. Scenario Analysis of Three Cases*

	Scenario 1	Scenario 2	Scenario 2
Strategy	**QALYs**	**QALYs**	**QALYs**
Nonsurgical	21.06	20.00	18.65
Early surgery	20.42	20.41	20.42
Delayed surgery	21.41	20.57	19.55

QALYs, quality-adjusted life-years.
*Scenario 1 (base case), a 55-yr-old woman, 1 yr after breast cancer surgery, 3 mo of mild carpal tunnel syndrome, effectiveness of conservative management = 0.50; scenario 2, a 55-yr-old woman, 1 yr after breast cancer surgery, 2 yr after mild carpal tunnel syndrome, effectiveness of conservative management = 0.30; and scenario 3, a 55-yr-old woman, 1 yr after breast cancer surgery, 5 yr after mild carpal tunnel syndrome, effectiveness of conservative management = 0.10.

5 preceding years of symptoms (effectiveness of nonsurgical management = 0.1), early surgery became the favored strategy.

DISCUSSION

This study used a decision analytic state-transition model to project outcomes for a hypothetical cohort of breast cancer survivors with both carpal tunnel syndrome and a risk for upper extremity lymphedema. Using the defined base case parameters, delaying carpal tunnel release until the patient developed worsening symptoms (severe carpal tunnel syndrome) was the preferred strategy.

Current recommendations for lymphedema prevention are to refrain from any procedure (e.g., blood pressure measurement or hand surgery) on the extremity with a history of axillary lymph node dissection for breast cancer treatment. These recommendations are based on case reports.[24,25] This area of controversy has recently generated interest, with three retrospective cohort studies demonstrating no increased risk of lymphedema after hand surgery among patients that had previously undergone axillary lymph node dissection.[4–6,26] These studies suggest that carpal tunnel release following axillary lymph node dissection is safe with respect to the risk of lymphedema, but are limited in making firm conclusions because of the limitations associated with the retrospective nature and small sample sizes. Despite emerging evidence from these studies, preventative measures for lymphedema are still enforced. Our study is the first to use decision analysis to address this problem. The integration of multiple clinical sources of data and the explicit representation of the effects of treatment on quality of life for this patient population provide a more comprehensive approach to evaluating optimal treatment strategies in this difficult clinical area.

Delaying carpal tunnel release until severe carpal tunnel syndrome was always the preferred strategy in this model. The model was not sensitive to parameter changes within the clinically relevant ranges, indicating its robustness. Threshold

analysis supported the strength of the model but identified a parameter (i.e., effectiveness of nonsurgical management) whose threshold approached clinically plausible values. Decreased effectiveness of nonsurgical management makes early surgery the preferred strategy. This can be explained by the fact that this reduces the proportion of the hypothetical cohort that would experience resolution of symptoms with nonsurgical management, and increases the proportion that would progress to severe carpal tunnel syndrome (with an increased risk of lymphedema). With a larger population experiencing the low utility of severe carpal tunnel syndrome, early surgery is favored, as the utility of lymphedema is greater than severe carpal tunnel syndrome. Populations represented by a lower effectiveness of nonsurgical interventions are patients that have failed to improve for a certain period despite nonoperative management, as seen in our scenario analysis. Although the natural history of resolution of carpal tunnel syndrome symptoms with prolonged nonsurgical management has not been well described, it is reasonable to assume that prolonged ineffective nonsurgical management has a decreasing effectiveness with time. To better address this question, future studies outlining the natural history of nonsurgical management are needed.

The one-way sensitivity analyses revealed that two variables, utility of lymphedema and baseline probability of lymphedema, introduced the most variability into the model. Variation in the utility of lymphedema is an important consideration, as our model does not reflect mild versus severe lymphedema. The only reported upper extremity lymphedema utility in the literature was 0.80.[13] As there are no studies on the utility values of mild versus severe lymphedema, and no studies on the probabilities of mild versus severe lymphedema in breast cancer patients over time and after hand surgery, it is not possible to know how the model would change if lymphedema was divided into two severities. Studies are therefore needed to better understand these variables to increase the accuracy of future models.

The two-way sensitivity analysis modeled changes in the baseline probability of lymphedema versus the utility of lymphedema. This was performed, as the baseline risk of lymphedema was static in our model but is thought to decrease with time after completion of breast cancer treatment.[1] This analysis demonstrated that, with a lower baseline probability of lymphedema and a lower utility of lymphedema, nonsurgical management would be preferred. With a lower baseline probability of lymphedema and a stable to higher utility of lymphedema, delayed surgery was preferred. This can be explained by the fact that as lymphedema (which is more likely after surgery) becomes a less desirable health state, and as the probability of lymphedema after carpal tunnel release remains stable, the impact of developing this condition after surgery significantly lowers quality-adjusted life-years and therefore favors nonsurgical strategies. Despite these findings, the values at which nonsurgical intervention is favored are well outside the clinically plausible ranges, demonstrating the model robustness and its conclusion that delayed surgery is the favored strategy.

Several limitations in this model need to be considered. First, the outputs of the model depend on data available from the published literature. With limited published utility values and probabilities for specific health state transitions, data included in our model originated from a limited number of small cohort studies. To account for this, sensitivity analysis was performed on all variables using a range of clinically plausible values. Within this range, no thresholds were reached. Furthermore, this study highlighted gaps in the literature and put forward suggestions for further research. Second, our model does not account for the increased mortality rate of patients because of their history of breast cancer. As the risk of death is equal in all arms, this limitation does affect our preferred decision. This was confirmed by one-way analysis on life expectancy. Third, the risk of lymphedema and the effectiveness of conservative management did not change with time in our model. We anticipate that both likely decrease with time, although this has not been previously described. To model for these possible variations over time, sensitivity and scenario analyses were performed. With a decrease in the probability of lymphedema within clinically plausible values, delayed surgery remained the favored option. With a decrease in the effectiveness of conservative management, early surgery was favored.

This clinical decision analysis model supports delayed carpal tunnel release in breast cancer survivors. Although this model can be further improved by increased knowledge and understanding of the probabilities and utilities of the different health states, our current model demonstrated a solid conclusion that was robust with changes in all model parameters. The overall conclusion that breast cancer survivors with mild carpal tunnel syndrome should not undergo hand surgery until they demonstrate more severe symptoms is a novel

addition to the literature and provides guidance to the clinician faced with a difficult decision. Delayed surgery produced the best outcome through balancing the risk of lymphedema following surgery, the benefit of allowing patients with mild carpal tunnel syndrome to improve without surgery, and directing the increased risk of lymphedema only to patients with severe carpal tunnel syndrome. Currently, patients are advised by health care providers to avoid elective hand surgery, even if there is a benefit to function and quality of life. Our expectation is that our results will augment the existing literature on this topic and provide useful guidance to clinicians and patients regarding the optimal strategy (surgical versus nonsurgical management) and timing of surgery based on severity of carpal tunnel syndrome.

Heather L. Baltzer, M.Sc., M.D.
Division of Plastic and Reconstructive Surgery
University of Toronto
399 Bathurst Street
East Wing, 2nd Floor, Room 422
Toronto, Ontario M5T 2S8, Canada
heather.baltzer@uhn.ca

ACKNOWLEDGMENT

We would like to thank Beate Sander, Ph.D., for help with the conception of the decision model.

REFERENCES

1. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol.* 2013;14:500–515.
2. Mann T, Hammert WC. Upper extremity surgery after lymph node dissection. *J Hand Surg Am.* 2011;36:1684–1686.
3. Habbu R, Adams JE. Role of elective hand surgery and tourniquet use in patients with prior breast cancer treatment. *J Hand Surg Am.* 2011;36:1537–1539; quiz 1540.
4. Dawson WJ, Elenz DR, Winchester DP, Feldman JL. Elective hand surgery in the breast cancer patient with prior ipsilateral axillary dissection. *Ann Surg Oncol.* 1995;2:132–137.
5. Hershko DD, Stahl S. Safety of elective hand surgery following axillary lymph node dissection for breast cancer. *Breast J.* 2007;13:287–290.
6. Baltzer HL, Harvey J, Fox PM, Moran SL. De novo upper extremity lymphedema after elective hand surgery in breast cancer survivors. *Ann Plast Surg.* 2017;79:24–27.
7. Statistics Canada. Deaths and age-standardized mortality rate 2017. Available at: http://www.statcan.gc.ca. Accessed July 21, 2017.
8. Li YK, Alolabi N, Kaur MN, Thoma A. A systematic review of utilities in hand surgery literature. *J Hand Surg Am.* 2015;40:997–1005.
9. Kern BC, Brock M, Rudolph KH, Logemann H. The recurrent carpal tunnel syndrome. *Zentralbl Neurochir.* 1993;54:80–83.
10. Thoma A, Wong VH, Sprague S, Duku E. A cost-utility analysis of open and endoscopic carpal tunnel release. *Can J Plast Surg.* 2006;14:15–20.
11. Marti C, Hensler S, Herren DB, Niedermann K, Marks M. Measurement properties of the EuroQoL EQ-5D-5L to assess quality of life in patients undergoing carpal tunnel release. *J Hand Surg Eur Vol.* 2016;41:957–962.
12. Atroshi I, Gummesson C, McCabe SJ, Ornstein E. The SF-6D health utility index in carpal tunnel syndrome. *J Hand Surg Eur Vol.* 2007;32:198–202.
13. Cheville AL, Almoza M, Courmier JN, Basford JR. A prospective cohort study defining utilities using time trade-offs and the Euroqol-5D to assess the impact of cancer-related lymphedema. *Cancer* 2010;116:3722–3731.
14. Gerritsen AA, de Vet HC, Scholten RJ, Bertelsmann FW, de Krom MC, Bouter LM. Splinting vs surgery in the treatment of carpal tunnel syndrome: A randomized controlled trial. *JAMA* 2002;288:1245–1251.
15. Gerritsen AA, Korthals-de Bos IB, Laboyrie PM, de Vet HC, Scholten RJ, Bouter LM. Splinting for carpal tunnel syndrome: Prognostic indicators of success. *J Neurol Neurosurg Psychiatry* 2003;74:1342–1344.
16. Mühlau G, Both R, Kunath H. Carpal tunnel syndrome: Course and prognosis. *J Neurol.* 1984;231:83–86.
17. Resende LA, Tahara A, Fonseca RG, Sardenberg T. The natural history of carpal tunnel syndrome: A study of 20 hands evaluated 4 to 9 years after initial diagnosis. *Electromyogr Clin Neurophysiol.* 2003;43:301–304.
18. Weng C, Dong H, Chu H, Lu Z. Clinical and electrophysiological evaluation of neutral wrist nocturnal splinting in patients with carpal tunnel syndrome. *J Phys Ther Sci.* 2016;28:2274–2278.
19. Burton CL, Chesterton LS, Chen Y, van der Windt DA. Clinical course and prognostic factors in conservatively managed carpal tunnel syndrome: A systematic review. *Arch Phys Med Rehabil.* 2016;97:836–852.e1.
20. Rodrigues R, Shin A. Treatment options for recurrent carpal tunnel syndrome: Local flaps. *Tech Orthop.* 2006;21:61–74.
21. Guyatt G, Drummond M, Feeny D, et al. Guidelines for the clinical and economic evaluation of health care technologies. *Soc Sci Med.* 1986;22:393–408.
22. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada. Available at: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed January 8, 2017.
23. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions: Standardizing data on outcomes. *N Engl J Med.* 1998;339:380–386.
24. Donachy JE, Christian EL. Physical therapy intervention following surgical treatment of carpal tunnel syndrome in an individual with a history of postmastectomy lymphedema. *Phys Ther.* 2002;82:1009–1016.
25. Smith WK, Giddins GE. Lymphoedema and hand surgery. *J Hand Surg Br.* 1999;24:138.
26. Assmus H, Staub F. Postmastectomy lymphedema and carpal tunnel syndrome: Surgical considerations and advice for patients (in German). *Handchir Mikrochir Plast Chir.* 2004;36:237–240.