

Cost-effectiveness analysis of whole-mount pathology processing for patients with early breast cancer undergoing breast conservation

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ABSTRACT

Background Obtaining accurate histopathologic detail for breast lumpectomy specimens is challenging because of sampling and loss of three-dimensional conformational features with conventional processing. The whole-mount (WM) technique is a novel method of serial pathologic sectioning designed to optimize cross-sectional visualization of resected specimens and determination of margin status.

Methods Using a Markov chain cohort simulation cost-effectiveness model, we compared conventional processing with WM technique for breast lumpectomies. Cost-effectiveness was evaluated from the perspective of the Canadian health care system and compared using incremental cost-effectiveness ratios (ICERs) for cost per quality-adjusted life-year (QALY) over a 10-year time horizon. Deterministic and probabilistic sensitivity analyses were performed to test the robustness of the model with willingness-to-pay (WTP) thresholds of \$0–\$100,000. Costs are reported in adjusted 2014 Canadian dollars, discounted at a rate of 3%.

Results Compared with conventional processing, WM processing is more costly (\$19,989 vs. \$18,427) but generates 0.03 more QALYs over 10 years. The ICER is \$45,414, indicating that this additional amount is required for each additional QALY obtained. The model was robust to all variance in parameters, with the prevalence of positive margins accounting for most of the model's variability.

Conclusions After a WTP threshold of \$45,414, WM processing becomes cost-effective and ultimately generates fewer recurrences and marginally more QALYs over time. Excellent baseline outcomes for the current treatment of breast cancer mean that incremental differences in survival are small. However, the overall benefit of the WM technique should be considered in the context of achieving improved accuracy and not just enhancements in clinical effectiveness.

Key Words Breast cancer, pathology, cost-effectiveness

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INTRODUCTION

Contemporary breast cancer management commonly involves the surgical resection of breast tumours with curative intent. With the routine use of screening mammography, breast cancers are increasingly identified at an early stage, in which small tumour size permits lumpectomy with preservation of the remaining breast parenchyma^{1–3}. The extent of surgical excision is guided by tumour dimensions as inferred from preoperative imaging. However, beyond the detection of gross disease, microscopic assessment with post-surgical histopathologic processing of the lumpectomy specimen is critical

to determining the probability that *in situ* or invasive disease of clinical significance could remain in the breast.

Pathologists systematically assess the breast lumpectomy at the cut surgical margin for viable tumour cells, known as a positive margin. Awareness of positive margin status, a known predictor of local relapse^{4,5}, allows for accurate counselling of the patient about the potential value of additional surgery for disease clearance and an estimation of the probability of cancer recurrence.

Conventional histopathologic processing of breast specimens has several limitations. *Ex vivo* specimen handling is limited by the inherent flaccid scaffolding of fatty tissue and the accompanying difficulty in maintaining

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three-dimensional shape and orientation^{6,7}. Furthermore, lumpectomy specimens are representatively sampled in 10–40 small slides, thereby characterizing only 0.007%–0.02% of the entire volume of resected tissue⁸. Under-sampling of disease can affect the accurate determination of tumour size and the presence and extent of positive margins^{9,10}.

Whole-mount (wm) processing is a pathology technique established to serially section breast lumpectomy specimens in their entirety while preserving three-dimensional conformation and orientation and allowing for a more precise assessment of the relative relationship between tumours and margins. Compared with standard processing, the wm method allows for an evaluation of 30 times more tissue⁸. The fresh specimen is suspended in a gel to reduce tissue collapse and distortion, and then serially sectioned into uniform 4-mm slices suitable for processing, staining, and interpretation^{8,11}. The method has been refined and demonstrates preservation of cellular morphology, reduction in specimen shrinkage, compatibility with standard breast cancer immunohistochemistry, and superiority to standard processing with respect to evaluating specimen orientation and volumetric extent of disease^{12–15}. Furthermore, the wm process is the backbone for slide digitization and three-dimensional reconstructive imaging, thus providing unparalleled interpretation of the entire resected specimen.

The adoption of wm processing has several advantages, but also creates several possible downstream issues. The widespread use of wm technique is expected, as greater volumes of tissue are analyzed, to result in more positive margins being reported. The increase in such reports would, in turn, have short- and long-term consequences. More operations for disease clearance will occur and place strain on an already overburdened health care system. However, a short-term rise in operative intervention might ultimately be balanced by improved rates of disease recurrence and survival, although the time to that potential equilibrium is as yet unknown. Furthermore, the relative patient value stemming from more upfront treatment in the form of possible margin re-excision compared with appropriate treatment at the time of recurrence is unknown. Achieving an understanding of those trade-offs is critical.

The goal of the present work was therefore to generate a cost-effectiveness analysis comparing wm serial sectioning of breast lumpectomy specimens with standard pathologic processing over a 10-year horizon.

METHODS

Model Structure

To make the comparison of interest, we constructed a Markov chain cohort simulation model (Figure 1). First, the sensitivity and specificity of positive margin detection were compared for the wm and conventional techniques, and then the consequences of repeated surgery for positive margins was modelled. Sensitivity and specificity values for wm were defined based on a “positive margin” being the presence of tumour cells 0.1 mm or less from the cut edge¹⁶, with sensitivity analyses (discussed later in this section).

After completion of primary surgical therapy, patients proceed to any one or some combination of adjuvant chemotherapy, trastuzumab therapy, radiation therapy, and endocrine therapy at rates described in the literature. Patients were then placed under surveillance and entered into the Markov model. A Markov model was appropriate for this scenario because it incorporates ongoing risks (for example, cancer recurrence and death) throughout the time horizon and allows for the use of sensitivity analyses to assess variation in key parameters.

The 10-year time horizon for our analysis reflects the median time to local recurrence after breast-conserving surgery in early breast cancer (54 months⁵) and the fact that endocrine therapy is typically applied over a 5- to 10-year period. A cycle length of 1 year was chosen, because 12 months is the common interval for recall clinical examinations and surveillance mammography.

The analysis was conducted using the TreeAge Pro 2014 software application (TreeAge Software, Williamstown, MA, U.S.A.).

Base Case, Markov States, State Transitions, and Probabilities

The base case was a 61-year-old woman undergoing breast-conserving surgery for a stage I cancer¹⁷. After completion of primary treatment (surgery with or without chemotherapy, radiation, and endocrine therapy), all patients entered the Markov model in the Surveillance, No Recurrence state. Five additional Markov states were available after the first cycle: Local Recurrence, Metastatic Recurrence, Death, Surveillance After Local Recurrence, and Best Supportive Care. State transitions could occur at each cycle, based on probabilities extracted from the literature, where available (Table 1). Probabilities were calculated based on reported event rates, using $p = 1 - e^{-rt}$, where p is the probability for a 1-year period, r is the annual rate of an event, t is time in years, and e is the natural logarithm. Patients in the Death and Best Supportive Care states remained in those states to the end of the time horizon.

To build a robust and clinically appropriate model, these key assumptions were made:

- If patients initially underwent breast-conserving surgery, they underwent mastectomy at the time of recurrence.
- Patients in the Metastatic Recurrence or Best Supportive Care states did not undergo surgery, and the former group received chemotherapy.
- Only 1 local recurrence was modelled within the time horizon.
- Patients with tumours overexpressing HER2 (the human epidermal growth factor 2) received trastuzumab alone, because accurate costs for pertuzumab, trastuzumab emtansine, and combination therapy were not yet available in the province of Ontario.
- Prophylactic surgery, reconstructive surgery, neoadjuvant therapy, and clinical trials were not included.

Costs

Costs were calculated from the perspective of the Canadian health care system, recognizing that this universal

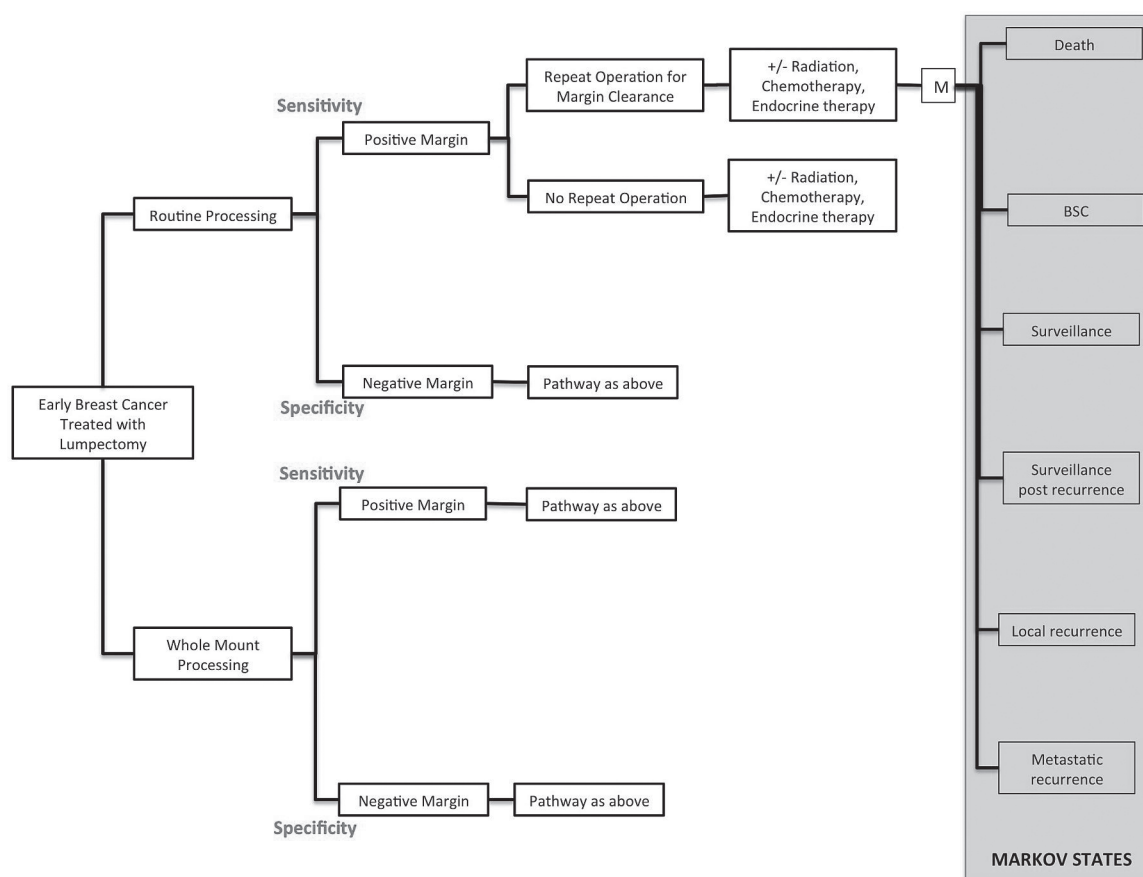


FIGURE 1 Schematic of Markov cohort model for the assessment of whole-mount compared with conventional processing of breast lumpectomy specimens. M = start of Markov model; BSC = best supportive care.

government-funded system pays for hospital-based procedures, in-hospital drugs, and compensation of health care providers. All costs were inflated to 2014 Canadian dollars, adjusted based on the Canadian consumer price index, health care component. Costs are discounted at 3% for future expenditures.

The Ontario Schedule of Benefits for Physician Services (2015 version)²⁷ was used to estimate physician costs associated with pathology and delivery of surgery, chemotherapy, and radiation (Table II). Fixed capital costs for equipment purchase, installation, safety assurance, and maintenance contracts were not included, because those costs are borne across all disease sites requiring pathology processing. Costs for processing in both the wm and conventional arms included costs related to materials and quality control procedures, and the hourly rates for pathology assistants and medical laboratory technologists (based on union-controlled 2014 institutional rates). No costs were assigned to fixation and processing times that do not involve human labour. Times (hours) required for wm and conventional processing were derived from institutional estimates by Sunnybrook Health Sciences Centre based on currently accepted protocols⁸ and 59 completed wm lumpectomy cases, for which research ethics board approval was obtained.

At the start of each 1-year cycle, the costs of screening mammography are incurred. Once a recurrence or metastatic disease is diagnosed, costs of unilateral ultrasonography, core biopsy, and staging with computed tomography imaging (chest, abdomen, pelvis) and bone scan are included.

Costs for surgery include physician and hospital-related costs. The hospital-related costs were obtained from the Ontario Case Costing Initiative, with sensitivity analysis ranges that included costs for potential postoperative infection. A mean estimate was used in the base case, with sensitivity analyses reflecting various surgical procedures (for example, mastectomy with sentinel lymph node biopsy vs. axillary lymph node dissection) and quoted provincial hospital variation. Surgical costs were counted once, within the cycle in which they occurred.

Costs for radiation are based on a 50-Gy regimen in 25 fractions without boost and include costs for physician oversight and radiation therapist time for administration. Chemotherapy costs in the base case are reported as averages for first-, second-, and third-line regimens used in the province of Ontario²⁹, and costs for trastuzumab include costs for a loading dose (8 mg/kg) and a maintenance dose (6 mg/kg) every 3 weeks for 1 year for a 70-kg woman. The trastuzumab regimen also includes costs for

TABLE I Parameter estimates for base case and tested sensitivity ranges

Parameter	Base-case probability	Sensitivity range tested	Reference
<i>Labour for pathology processing</i>			
Whole-mount processing (hours)			Based on 59 clinical cases ^a
Gel embedding and slicing	1.09	0.68–2.5	
Sampling	0	0	
Processing (microwave)	1.375	0.75–2	
Embedding	3.47	0.76–6.18	
Microtomy	15.4	1.68–29.09	
Staining	2.475	0.46–4.49	
Pathologist interpretation	1.46	1.06–2	
TOTAL hours	26.36	5.39–46.26	
TOTAL slides processed (<i>n</i>)	14.5	8–35	
Conventional processing (hours)			Based on reporting by 5 pathologists over 3 months ^a
Embedding and slicing	0.27	0.27	
Sampling	4.085	2–6.17	
Processing (regular)	0.425	0.15–0.55	
Embedding	2.335	1–3.67	
Microtomy	2.335	1–3.67	
Staining	0.414	0.25–0.58	
Pathologist interpretation	1.8	1.08–4	
TOTAL hours	11.664	5.75–18.91	
TOTAL slides processed (<i>n</i>)	28	12–44	
<i>Clinical parameters</i>			
Sensitivity for positive margin			
Routine processing	0.57	0.50–0.80	Clarke <i>et al.</i> , 2015 ¹⁶
Whole-mount processing	0.95	0.75–0.99	Clarke <i>et al.</i> , 2015 ¹⁶
Specificity for positive margin			
Routine processing	0.98	0.75–0.99	Clarke <i>et al.</i> , 2015 ¹⁶
Whole-mount processing	0.81	0.60–0.95	Clarke <i>et al.</i> , 2015 ¹⁶
Prevalence of margin positivity post lumpectomy	0.219	0.103–0.309	Houssami <i>et al.</i> , 2014 ⁵
Probability of re-excision given a positive margin	0.859	0.737–0.935	McCahill <i>et al.</i> , 2012 ¹⁸
With a positive margin ^b , probability of ...			
Local recurrence	0.0122		Houssami <i>et al.</i> , 2014 ⁵
Metastatic disease	0.0231		Goldstein <i>et al.</i> , 2003 ¹⁹
With a negative margin ^a , probability of			
Local recurrence	0.00699		Houssami <i>et al.</i> , 2014 ⁵
Metastatic disease	0.00830		Goldstein <i>et al.</i> , 2003 ¹⁹
Probability of			
Operable disease at time of recurrence	0.9		Expert opinion ^c
Choosing mastectomy after recurrence	0.9		Expert opinion ^c
Radiation after breast conservation	0.9		Dunnwald <i>et al.</i> , 2007 ²¹
Chemotherapy after breast conservation	0.256	0.183–0.38	Houssami <i>et al.</i> , 2014 ⁵
Trastuzumab	0.2	0.15–0.30	Slamon <i>et al.</i> , 1987 ²⁰
Endocrine therapy	0.6	0.5–0.75	Dunnwald <i>et al.</i> , 2007 ²¹
Complication with mastectomy	0.038		Vitug and Newman, 2007 ²²
Death with metastatic disease ^a	0.144		Edge <i>et al.</i> , 2009 ²³

TABLE I Continued

Parameter	Base-case probability	Sensitivity range tested	Reference
Probability of death from other causes at age			Statistics Canada, 2013 ²⁴
61 Years	0.00257		
62 Years	0.00280		
63 Years	0.00307		
64 Years	0.00336		
65 Years	0.00368		
66 Years	0.00403		
67 Years	0.00442		
68 Years	0.00485		
69 Years	0.00533		
70 Years	0.00586		
71 Years	0.00645		
Utilities			
Event-free on surveillance	0.98		
Local recurrence	0.75	0.60–0.80	Earle <i>et al.</i> , 2000 ²⁵ ,
Metastatic disease	0.65	0.25–0.80	Hedden <i>et al.</i> , 2012 ²⁶
Best supportive care	0.25	0.10–0.50	

^a Cases processed and analyzed at Sunnybrook Health Sciences Centre, Toronto, ON.

^b Probability calculated as $1 - e^{-(\text{rate} \times \text{time})}$, annual.

^c Generated by multidisciplinary physicians at a tertiary cancer centre with expertise in breast oncology.

administration of concurrent paclitaxel and for cardiac monitoring²⁶. Endocrine therapy costs are weighted based on the relative proportions of patients in the Ontario Drug Benefit program (patients > 65 years of age) undergoing treatment with either tamoxifen or an aromatase inhibitor. The latter is costed using letrozole for a 5- to 10-year period³⁰.

Outcomes

Outcomes are represented as quality-adjusted life years (QALYs), incorporating utilities for 4 unique states: well with no recurrence, metastatic disease on chemotherapy, local recurrence, and best supportive care (Table I)^{25,26,32}. Utilities reflect known adjustments for a given state of health and were multiplied by the length of time in each state. Those values were subsequently totalled to create the final number of QALYs³³. Cost effectiveness is quantified by the incremental cost-effectiveness ratio (ICER)—that is, the incremental cost per additional QALY gained or lost.

Sensitivity Analyses

Our model contains two major sources of uncertainty: uncertainty in the input clinical parameters, and uncertainty in the model calculations. Sensitivity analyses addressed both of those issues.

One-way and multiway deterministic sensitivity analyses were completed to address uncertainty in input clinical parameters over the ranges shown in Tables I and II, as derived from the literature and institutional experience with pathology techniques. To address model uncertainty, stochastic probability-based sensitivity analyses and Monte Carlo simulation with 10,000 trials were

performed to generate sampling distributions associated with the calculation of costs and outcomes. Distributions for each strategy were combined to form net monetary benefit distributions over a range of willingness-to-pay (WTP) thresholds. Net monetary benefit [calculated as (effectiveness $\times$ WTP) – cost], which is less statistically unstable when small changes in effectiveness are observed and distributions are nonparametric, was used to facilitate the transparent comparison of interventions³⁴. Net monetary benefit distributions generated from simulation analyses were then plotted in a cost-effectiveness acceptability curve to graphically represent the probability of each strategy being cost-effective at each WTP threshold between \$0 and \$100,000^{35,36}.

RESULTS

The average per-case cost of WM processing for breast lumpectomy specimens is greater than that for conventional processing (\$19,988 vs. \$18,427), and WM processing incurs 19% more operations after initial treatment (including a possible margin re-excision or mastectomy) is complete. However, over a 10-year time horizon, WM processing generates 0.03 more QALYs. The resulting ICER indicates that each additional QALY resulting from the use of WM processing costs the health care system \$45,414 (Table III). At the completion of 10 cycles, 85.6% of patients were alive with no recurrence, 4.3% had metastatic disease, and 3.7% had died.

Deterministic one-way sensitivity analyses demonstrated the robustness of the model and its preferred

TABLE II Costs in Canadian dollars for pathology processing and clinical variables for base case and tested sensitivity range

Parameter	Base case cost	Sensitivity range tested	Source
Pathology processing			
Whole-mount processing			
Embedding and slicing	216.00	89.36–342.63	Institutional costs ^a
Microtomy	149.33	29.15–269.51	
Slide staining	31.28	13.26–49.30	
Pathology assistant labour ^b	249.27	91.98–406.56	
Lab technician labour ^b	750.12	89.88–1410.36	
Quality control slides	29.27	7.32–51.21	
Conventional processing			
Embedding and slicing	119.98	88.79–151.16	Institutional costs ^a
Microtomy	77.33	43.70–110.96	
Slide staining	29.65	19.10–40.191	
Pathology assistant labour ^b	295.68	143.64–447.72	
Lab technician labour ^b	115.50	52.50–178.50	
Quality control slides	7.32	—	
Clinical costs			
Breast re-excision operative costs	5521.31	5521.31–7956.98 ^c	Ontario Case Costing Initiative, OHIP ²⁷
Complication of breast surgery	308.09 ^d		Vitug and Newman, 2007 ²² , Platt <i>et al.</i> , 1993 ²⁸
Pathologist reading	103.20		OHIP ²⁷
Surveillance visit	79.85		OHIP ²⁷
Screening bilateral mammography	64.15		OHIP ²⁷
CT imaging of chest, abdomen, pelvis	249.05		OHIP ²⁷
Bone scan	166.50		OHIP ²⁷
Diagnostic bilateral mammography and unilateral ultrasonography	104.25		OHIP ²⁷
Radiation (50 Gy, 2 Gy/fraction)	5,014.05 ^e		Earle <i>et al.</i> , 2000 ²⁵
Chemotherapy, adjuvant (per course)	7,376.10 ^f		Mittmann <i>et al.</i> , 2014 ²⁹
Herceptin (8 cycles), includes paclitaxel chemotherapy and visits (per course)	29,709		ODB Formulary ³⁰
Endocrine therapy (annual)			
Tamoxifen	383.40		ODB Formulary ³⁰
Letrozole	822.40		ODB Formulary ³⁰
Chemotherapy (metastatic)	10,349.59 ^g		Mittmann <i>et al.</i> , 2014 ²⁹
Best supportive care			
Continuing phase of care (annual)	1,288.82 ^g		Yabroff <i>et al.</i> , 2008 ³¹
Last year of life	31,334.06 ^g		

^a Generated from cases processed and analyzed at Sunnybrook Health Sciences Centre, Toronto, ON.^b Using an hourly rate of \$42.^c Includes cost of mastectomy as a possible second procedure, with or without axillary lymph node dissection if initial surgery demonstrates positive nodes, plus 7 units and up to 3 hours of anesthesia time.^d Includes infection treated with 14 days cephalexin, fine-needle aspiration, and 3 additional visits to the surgeon.^e Per course, 50 Gy in 25 fractions at \$188.38/fraction, inflated to 2014 dollars.^f Average cost of first-, second-, and third-generation regimens, per course, inflated to 2014 dollars.^g Average annual cost, inflated to 2014 dollars.

OHIP = Ontario Health Insurance Plan; ODB = Ontario Drug Benefit.

TABLE III Cost-effectiveness in all patients, 10-year time horizon

Processing type	Cost	95% CI	Life years	95% CI	QALYs	95% CI	Cost difference	QALY difference	ICER
Whole-mount	\$19,988	\$18,813 to \$20,942	8.88	8.82 to 8.92	8.51	8.42 to 8.58	—	—	—
Conventional	\$18,427	\$17,321 to \$19,384	8.87	8.81 to 8.91	8.48	8.39 to 8.56	1461	0.03	45,413

CI = confidence interval; QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio [(cost 2 – cost 1) / (effect 2 – effect 1)].

treatment strategies for all tested values and showed the most sensitivity to changes in the positive margin prevalence. As indicated in Figure 2, a lower prevalence of positive margins increases the ICER to a tested maximum of \$100,607 at a prevalence of 10.3%.

Probabilistic sensitivity analyses using Monte Carlo simulation generated a cost-effectiveness acceptability curve in which WM is the preferred strategy at a WTP threshold exceeding \$45,414 (Figure 3).

DISCUSSION

The present cost-effectiveness analysis, which followed patients for a 10-year period, generated average per-case costs that were higher for patients whose lumpectomies were processed initially with the WM technique (compared with conventional techniques). A modest 0.03 increase in QALYs in the WM group arose from the significantly higher sensitivity of the WM technique to detect positive margins and a consequent downstream reduction in local and systemic recurrences. However, given that recurrence rates with conventional processing of breast lumpectomies are already low at baseline, any incremental difference generated solely from the WM technique ultimately result in small changes in overall life-years and in QALYs.

But changes in clinical cost-effectiveness are accompanied by the associated benefits of adopting the WM technique, including a comprehensive three-dimensional assessment of the lumpectomy specimen and the more accurate correlation of tumours to their respective margins. Obtaining those details is truly novel, because conventional processing can miss or misrepresent those relationships because of extensive tissue processing and sampling. Accurate margin assessment could help to guide more informed use of adjuvant therapies such as chemotherapy and radiation. Additive to the present cost-effectiveness study is an anticipated improvement in time efficiency experienced by breast pathologists; that effect will be reported separately in work forthcoming from our research team.

When interpreting the present analysis, it is important to reflect on the definition of a “positive margin,” because that definition has been extensively debated. The literature is replete with several reported definitions of positivity after lumpectomy, with thresholds ranging anywhere from 1 cm to no-tumour-on-ink. In a recent comprehensive meta-analysis and multi-organizational consensus statement^{5,37}, experts stated that the critical threshold for declaring margin positivity is no-tumour-on-ink, because achieving wider margins did not, in the modern era, reliably lead to better clinical outcomes. Given that statement, fewer re-operations for positive margins—based on margin width

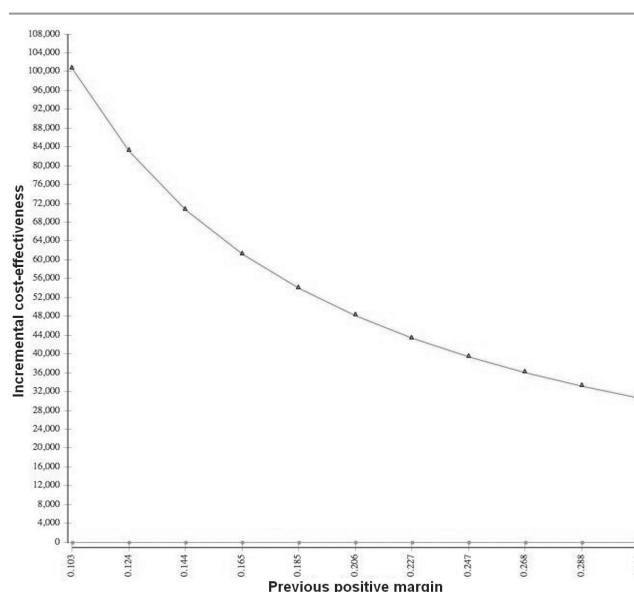


FIGURE 2 One-way sensitivity analysis demonstrating the change in incremental cost effectiveness with variation in positive margin prevalence. Closed circles = routine processing; closed triangles = whole-mount processing.

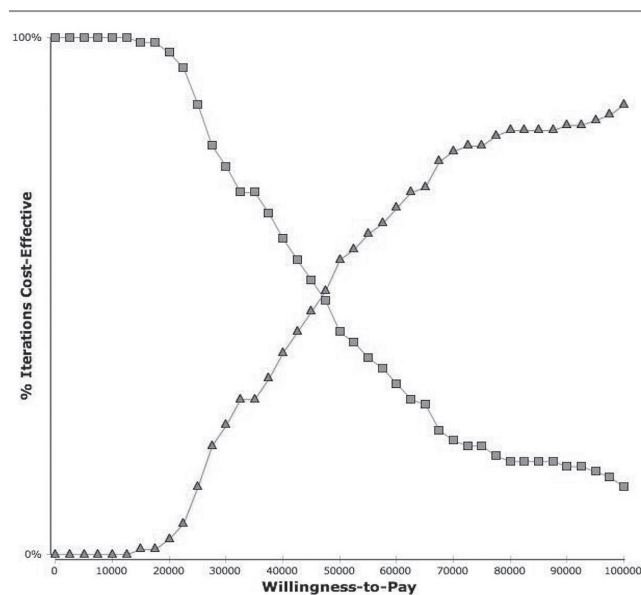


FIGURE 3 Cost effectiveness acceptability curve of the dominant strategy based on willingness-to-pay (WTP) values of CA\$0–CA\$100,000, demonstrating cost-effectiveness of whole-mount processing at a WTP exceeding \$45,413. Closed squares = routine processing; closed triangles = whole-mount processing.

alone—are anticipated to take place in future, although the precise clinical consequences of widespread change in practice remain to be seen. The quoted sensitivity and specificity ranges for WM processing in the present analysis reflect a threshold of 0.1 mm as a practical implementation of no-tumour-on-ink. However, to ensure model robustness, tested sensitivity ranges for the prevalence of positive margins reflect variations in clinical interpretation.

The challenge of interpreting the present cost-effectiveness analysis comes in contextualizing the ICER within the landscape of the cost that hospital administrators and health policy advisors are willing to pay for interventions for the care of breast cancer patients. In essence, an ICER of \$45,414 indirectly represents an investment in secondary prevention, whereby the attempt to identify positive margins as accurately as possible averts a subsequent breast cancer recurrence. Studies in breast cancer care demonstrate that patients with metastatic breast cancer are willing to spend between US\$1,458 and US\$3,894 annually to avoid the adverse effects of chemotherapy-based cancer treatments³⁸. Current WTP estimates for prevention programs in breast cancer range from US\$9,860 per life-year saved for chemoprevention in high-risk patients, to US\$21,577 per life-year saved for mammography every 2 years for women 40–49 years of age, to US\$137,922 per life-year saved for chemoprevention for all breast patients³⁹. The ICER of \$45,414 in the present study therefore does not seem inconsistent with the costs for other strategies considered for harm reduction in breast cancer.

Evidence also indicates that cost-effectiveness thresholds for the adoption of health care interventions might differ based on the payment structure of the relevant health care system. In the United Kingdom, £20,000–£30,000 per QALY has been accepted as the threshold to adopt new health care technology, with the U.S. threshold being US\$50,000–US\$100,000⁴⁰. However, those thresholds are not based on scientific evidence, have not adapted to inflation over time, and have been criticized for being too low^{41,42}. Furthermore, in prevention studies, WTP estimates have been found to decline approximately 1.5% per year of latency (time from risk exposure to onset of cancer)⁴³.

In Canada, Laupacis *et al.*⁴⁴ described a schema whereby an ICER of less than CA\$20,000 per QALY (equivalent to CA\$29,857 in 2014 Canadian dollars) constituted strong evidence for adoption and appropriate utilization of an intervention, and thresholds of CA\$20,000–CA\$100,000 and more than CA\$100,000 (\$148,287 in 2014 Canadian dollars) constituted moderate and weak evidence respectively. In a recent international appraisal to assess the value of an additional QALY in Japan, Korea, Taiwan, the United States, the United Kingdom, and Australia, WTP thresholds were found to vary widely, being £23,000 per QALY in the United Kingdom and US\$62,000 in the United States⁴⁰. Interestingly, a relationship was detected between WTP threshold and the proportion of private expenditure on health, whereby populations with a higher proportion of market-driven investment in health care were willing to pay more per QALY for a new intervention⁴⁰, even after adjustment for variations in intrinsic national wealth. Clearly, determinations of estimated WTP are context-specific and require consideration of the burden of disease, the scope of the population affected,

and the fluidity of the budget. Estimates below \$100,000 appear to be reasonable for consideration, but each decision requires thoughtful deliberation by all parties involved.

Our cost-effectiveness analysis has limitations. The sensitivity and specificity values for the WM process were based on data from a single institution and are difficult to report with certainty, because WM is assumed to be the most accurate—the “gold standard.” However, sensitivity analyses using variations in those values within clinically plausible ranges showed that the overall results of the model were robust.

CONCLUSIONS

Adoption of routine WM processing for breast lumpectomy specimens from patients with early breast cancer requires an investment of \$45,414 for each additional QALY gained. In addition, implementation of the method could require capital investment for equipment (for example, a slicing machine for large slides) and training of pathology assistants and medical laboratory technologists. Those expenditures are significant. Given the fixed or shrinking health care budgets in the current economic climate, such an investment will require disinvestment in another theoretically less efficacious intervention. To mitigate large-scale swings in cost, gradual adoption of the WM method might be envisioned, or implementation of a hybrid model of handling in which patients at higher perceived risk for close or positive margins (for example, multifocal disease, large areas of mammographic calcifications, known ductal carcinoma *in situ*) might best be treated with WM, because they are most at risk for under-identification of positive margins and consequently might benefit most from the “prevention” aspect of this novel technique.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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