Journal of Cancer Policy 9 (2016) 1–7

Contents lists available at ScienceDirect

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jcpo

The cost of accuracy: A budget impact analysis of whole-mount histopathology processing for patients with breast cancer undergoing breast conservation☆

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ARTICLE INFO

Article history:
Received 3 April 2016
Accepted 23 July 2016
Available online 25 July 2016

Keywords:
Breast cancer
Lumpectomy
Pathology
Economics
Accuracy

ABSTRACT

Background: Obtaining precise histopathologic detail for breast lumpectomy specimens is challenging due to extensive sampling and loss of 3-dimensional conformation with conventional methods. Whole-mount (WM) technique is a method of serial pathologic sectioning designed to maximize cross-sectional visualization, and enhance evaluation of margin status.
Methods: A decision analytic model was used to create a budget impact analysis comparing costs and outcomes for conventional processing and WM technique for breast lumpectomy specimens. Outcomes included additional operations, time required for processing and pathology interpretation, and the number of slides produced. Cost trade-offs were compared using incremental cost-effectiveness ratios, and a 3-year cost forecast was generated to estimate institutional expenditures required for variable adoption of the WM process. Deterministic and probabilistic sensitivity analyses were performed. Costs are reported in Canadian dollars and are 2014 appraisals.
Results: WM technique has a higher mean cost per patient ($3218) compared to conventional processing ($1414) and generates 19% more operations due to detection of positive margins. The number of pathology slides produced and pathologist hours required for interpretation were reduced with WM technique. WM costs an additional $9495 per extra operation completed but is forecasted to save approximately 1200 pathologist work hours over 3 years. The model was robust to tested ranges and most sensitive to changes in positive margin prevalence.
Conclusion: The initiation of routine WM processing for breast lumpectomy specimens is costly. However, favourable tradeoffs in diagnostic accuracy and histopathologic efficiency underpin the need to deliberately consider the adoption of WM technique.

1. Introduction

Current breast cancer management frequently involves the surgical resection of breast tumours with curative intent. With the routine use of screening mammography, breast cancers are increasingly identified at early stages, where modest tumour size permits lumpectomy, which removes the known cancer while preserving the remaining breast parenchyma [1–3]. The extent of surgical excision is guided by known tumour dimensions interpreted from pre-operative 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 may be remaining in the breast. Pathologists systematically assess the breast lumpectomy for viable tumour cells located at the cut surgical margin, known as a positive margin. Awareness of margin status, a known predictor of local relapse [4,5], equips surgeons with ammunition to accurately guide patients on the potential value of additional operations for disease clearance and the associated probability of cancer recurrence.

☆ This manuscript was presented as a poster presentation at the ***American Society of Breast Surgeons*** Annual Meeting, Dallas Texas, 2016.

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http://dx.doi.org/10.1016/j.jcpo.2016.07.002
2213-5383/

Conventional histopathologic processing of breast specimens has several limitations. First, *ex vivo* specimen handling is limited by the fatty tissue's inherent flaccid scaffolding and the accompanying difficulty in maintaining 3-dimensional shape and orientation. Furthermore, lumpectomy specimens are representatively sampled in 10–40 small slides, thereby characterizing only 0.007–0.02% of the entire area of resected tissue [6]. Undersampling of disease may impair the accurate determination of tumour size, and the presence of positive margins [7,8]. Finally, the ability to relate positive specimen margins spatially within a patient's remaining *in vivo* breast lumpectomy cavity is clinically challenging based on the small, discontinuous pieces of tissue seen on slides. Re-operation for margin re-excision, therefore, is an imprecise science.

Whole-mount (WM) processing is a pathologic technique established to serially section breast lumpectomy specimens in their entirety while preserving 3-dimensional conformation and orientation, and allowing assessment of the relative relationship between tumour(s) and margins. This method allows the evaluation of 30 times more tissue than standard processing [6]. The fresh specimen is suspended in a gel to drastically reduce tissue collapse and distortion, and then serially sliced into uniform 4 mm slices suitable for processing, staining, and interpretation [6,9]. This methodology has been refined and demonstrates cellular morphologic preservation, 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 [10–13]. Furthermore, the WM process is the backbone for slide digitization and 3-dimensional reconstructive imaging. The technique has been largely automated and therefore also has the potential to reduce the number of hours required for manual processing by pathology technicians and assistants [10].

The adoption of WM processing clearly has several purported advantages. However, while it may reduce the total number of labour hours required for processing, widespread use of WM technique is expected to generate more patients with reported positive margins, as greater volumes of tissue are analyzed. The clinical consequences of recognizing more positive margins are yet unknown, but at minimum, will generate more operations in the short-term. In the cost-constrained healthcare environment, maintaining a holistic and balanced picture of these tradeoffs is critical.

Budget impact analyses (BIAs) are a relatively new form of economic evaluation specifically aimed at evaluating the fiscal impact and sustainability of adopting new interventions in the short to medium term ($\leq$3 year) setting. As a complementary adjunct to traditional cost-effectiveness analyses, the formalized framework of BIAs includes the generation of short-term, context-specific, undiscounted comparisons of alternative versus standard scenarios. Biases include tradeoffs in effectiveness between compared situations within the context of available resources and known market dynamics [14–17]. The overall purpose is to provide simple, targeted, realistic counsel for local policy-makers and budget administrators. The goal of this project is therefore to generate a budget impact analysis of WM serial sectioning of breast lumpectomy specimens compared to standard pathologic processing from the perspective of a single-payer health care system.

2. Methodology

2.1. Analytic framework

A simulated decision analytic model was constructed to assess the budgetary impact of adopting WM serial sectioning of breast lumpectomy specimens compared with conventional processing technique (Fig. 1). Specifically, the sensitivity and specificity of positive margin detection were compared between the two techniques and the consequence of additional operations for disease clearance were modeled. Budgetary impact was calculated as net costs from pathologic processing and resultant surgical procedural costs. Several measures of effectiveness were evaluated, as these costs were thought to be critical condition-related trade-offs to the use of WM processing.

The time horizon for this analysis ends at the completion of first repeated operation, as required. This BIA is meant to compare costs associated specifically with short-term adoption of the WM technique and therefore, ongoing costs related to monitoring and changes in recurrence/survival are not included.

Analysis was done using TreeAge Pro 2013 (TreeAge Software, Inc. Williamstown, MA).

2.2. Probabilities

Probabilities used in the base case analysis and sensitivity analyses were extracted from the literature where possible (Table 1A). Times (hours) required for WM and conventional processing were derived from institutional estimates from Sunnybrook Health Sciences Centre based on currently accepted protocols [6] and 59 completed cases, vetted by the institutional review board. Sensitivity and specificity values for WM are defined based on "positive" margins practically defined as tumour cells $\leq$0.1 mm from the cut edge [18].

2.3. Costs

Costs were calculated from the perspective of the Canadian health care system, recognizing that the universal government-funded organization provides subsidy for the conduct of hospital-based procedures and compensation of health care providers. All costs are 2014 valuations, quoted in Canadian dollars, adjusted based on the Canadian consumer price index, healthcare component.

The Ontario Schedule of Benefits (2015 version) was used for physician costs associated with pathology and surgery (Table 1B). Fixed capital costs for equipment purchase, installation, safety assurance, and service contracts were not included, as these costs are distributed across all disease sites requiring pathology processing. Costs for pathology processing in both the WM and conventional arms include costs related to materials and quality control, as well as hourly rates for pathology assistants and medical laboratory technicians based on union-controlled 2014 rates. No cost is assigned to fixation/processing times where human labour is not involved.

Costs for surgery include physician and hospital-related costs. The latter were obtained from the Ontario Case Costing Initiative breast re-excision values [19], with sensitivity analysis ranges including costs for potential post-operative infection, completion mastectomy with or without sentinel lymph node biopsy or axillary lymph node dissection. A mean estimate was used in the base case, with sensitivity analysis reflecting different surgical procedures, as well as quoted provincial hospital variation. Costs are undiscounted, as recommended in reporting guidelines for BIAs for short-term evaluations [14,16].

2.4. Outcomes

Four key outcome measures are reported in this analysis: (a) proportion with repeat/additional operations (only one allowed in this model per patient), (b) total number of hours required for tissue processing, (c) total number of pathologist hours required for interpretation (including additional operations), and (d) total number of slides processed. Clinical tradeoffs are reported as short-term cost