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Original Article

Omission of Breast Radiotherapy in Low-risk Luminal A Breast Cancer: Impact on Health Care Costs

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Abstract

Aims: The economic burden of cancer care is substantial, including steep increases in costs for breast cancer management. There is mounting evidence that women age ≥ 60 years with grade I/II T1N0 luminal A (ER/PR+, HER2− and Ki67 ≤ 13%) breast cancer have such low local recurrence rates that adjuvant breast radiotherapy might offer limited value. We aimed to determine the total savings to a publicly funded health care system should omission of radiotherapy become standard of care for these patients.

Materials and methods: The number of women aged ≥ 60 years who received adjuvant radiotherapy for T1N0 ER+ HER2− breast cancer in Ontario was obtained from the provincial cancer agency. The cost of adjuvant breast radiotherapy was estimated through activity-based costing from a public payer perspective. The total saving was calculated by multiplying the estimated number of luminal A cases that received radiotherapy by the cost of radiotherapy minus Ki-67 testing.

Results: In 2010, 748 women age ≥ 60 years underwent surgery for pT1N0 ER+ HER2− breast cancer; 539 (72%) underwent adjuvant radiotherapy, of whom 329 were estimated to be grade I/II luminal A subtype. The cost of adjuvant breast radiotherapy per case was estimated at $6135.85; the cost of Ki-67 at $114.71. This translated into an annual saving of about $2.0million if radiotherapy was omitted for all low-risk luminal A breast cancer patients in Ontario and $5.1million across Canada.

Conclusion: There will be significant savings to the health care system should omission of radiotherapy become standard practice for women with low-risk luminal A breast cancer.

Key words: Breast cancer; cost savings; Ki-67; luminal A; omission; radiotherapy

Introduction

The economic burden of cancer care is substantial [1]. Breast cancer is the most common malignancy affecting women worldwide [2]. The financial resources required for breast cancer management have been soaring, primarily due to the increasing utilisation and costs of chemotherapy and radiotherapy [3].

Adjuvant breast radiotherapy after breast-conserving surgery (BCS) reduces local recurrence, resulting in long-term survival similar to that of mastectomy [4]. Currently, most women with early stage breast cancer are treated with radiotherapy after BCS; however, the majority will not recur even without radiotherapy [5]. Breast radiotherapy causes inconvenience for the patient, requiring daily treatments, is

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not without side-effects and has an associated cost of delivery.

Previous randomised studies failed to identify women at very low risk of local recurrence after BCS alone (without radiotherapy) based on clinicopathologic factors, although older women with smaller oestrogen receptor-positive (ER+) tumours experienced a lower risk of local recurrence [6–8]. The most recent UK PRIME II trial that randomised women age $\geq$ 65 years with hormone receptor-positive, node-negative breast cancer ($\leq$ 3 cm) after BCS and endocrine treatment to radiotherapy versus observation concluded that adjuvant endocrine treatment alone is a reasonable therapeutic option for some women, based on the low local recurrence risks of the overall study population (4.1% no radiotherapy versus 1.3% radiotherapy) [9]. These trials included all patients with early stage breast cancer independent of molecular subtyping, which only became evident after the era of gene expression and next-generation sequencing studies [10]. The distinct molecular subtypes with varying prognosis and treatment response can also be estimated using immunohistochemical (IHC) surrogates: ER, progesterone receptor (PR), HER2, CK5/6, EGFR and Ki-67 [11,12]. The favourable biology of luminal A subtype has been well established [13], but its potential predictive value for radiotherapy response has never been explored until recently. Tumours from the Toronto/British Columbia trial [7], a randomised trial of tamoxifen ± radiotherapy in node-negative breast cancer patients age $\geq$ 50 years were recently subtyped using IHC. This study showed that patients with luminal A tumours (ER/PR+, HER2− and Ki-67 $\leq$ 13%) [11] had the lowest local recurrence rate [14]. When molecular subtyping was combined with clinicopathological features, women over age 60 years with T1 grade I/II luminal A tumours experienced a 10 year local recurrence rate of 1.3% with tamoxifen alone versus 5.0% with tamoxifen plus radiotherapy ($P = 0.3$) [14]. Thus, these patients had such a favourable prognosis that they could be spared the inconvenience and side-effects of radiotherapy. This observation is being validated in a prospective cohort study evaluating the risk of local recurrence after BCS and endocrine therapy in women age $\geq$ 60 years with T1 grade I/II luminal A breast cancer (LUMINA NCT01791829).

Given that women age $\geq$ 60 years with T1N0, grade I/II luminal A tumours have such a favourable prognosis, and breast radiotherapy might offer minimal benefit, omission of radiotherapy would spare these women side-effects and achieve significant cost savings. The main objective of this current study was to estimate the total savings to a publicly funded health care system should omission of radiotherapy in these patients become standard of care.

Materials and Methods

This study received approval from the Review Ethics Board at University Health Network. The main cost analysis was conducted from the perspective of a public payer, the Ontario Ministry of Health and Long-Term Care. The estimated cost savings from the omission of radiotherapy in luminal A breast cancers was calculated using the following equation:

$$\$\ \text{totalsavings} = n \times (\$\ \text{radiotherapycost} - \$\ \text{Ki} - 67\text{cost})$$

where n = estimated number of patients age $\geq$ 60 years with low-risk luminal A breast cancer being treated with adjuvant radiotherapy; radiotherapy cost = estimated cost of adjuvant radiotherapy; and Ki-67 cost = estimated cost of routine Ki-67 IHC testing.

Estimated Number of Patients with Low-risk Luminal A Breast Cancer (n)

The number of patients with luminal A breast cancer was calculated using data collected by Cancer Care Ontario (CCO), the provincial cancer agency. Patients with newly diagnosed breast cancer in 2010 and 2011 were identified from the Ontario Cancer Registry [15], the population-based registry for Canada's largest province. The number of patients age $\geq$ 60 years with pT1N0, ER+ and HER2− breast cancer was determined from collaborative staging data [16]. The proportion of patients who underwent radiotherapy, as reported by the cancer centres to CCO was ascertained. We estimated that 61% of these patients would have had grade I/II luminal A tumour, based on data from the Toronto/British Columbia trial [14], where 157 of 258 pT1N0, ER+ HER2− tumours in women age $\geq$ 60 years were of grade I/II luminal A subtype.

Costs

All costs were expressed in 2014 Canadian dollars. Costs obtained from earlier years were adjusted using the health and personal care component in the Canadian Consumer Price Index. The cost of adjuvant radiotherapy for breast cancer was estimated using an updated activity-based costing model for radiotherapy (Supplementary Table S1) [17]. In this model, the costs of equipment (capital, specialised construction, maintenance), personnel and immobilisation costs were allocated to five major activities of radiotherapy: consultation; computed tomography simulation; dosimetry; physics quality assurance; treatment preparation and delivery. In the base case analysis, the cost of a course of standard 16-fraction adjuvant breast cancer radiotherapy regimen [18] was estimated for the Princess Margaret Cancer Centre, one of the largest single-institution radiotherapy programmes in Canada, delivering more than 10 000 radiotherapy courses each year. As all adjuvant breast radiotherapy cases at the Princess Margaret Cancer Centre were treated with intensity-modulated radiotherapy (IMRT), the costing for this technique was used.

Costs and the expected lifespan of equipment were obtained from the Capital Planning Department at CCO; operating cost estimates were supplemented by financial information from the Radiation Medicine Program at the Princess Margaret Cancer Centre. Maintenance costs were assumed to be 10% of the acquisition cost. The equipment cost per activity was estimated using cost per unit time or per patient, based on operating hours and the total number

of external beam radiotherapy (EBRT) courses delivered at the centre. Physician costs included physician fee and base funding from the Ontario Ministry of Health and Long-Term Care; staff salaries were derived from the Capital Planning department at CCO, Princess Margaret Cancer Centre and collective agreements from radiation therapists in Ontario. The personnel costs included 24% benefits plus 6 weeks of vacation and statutory holidays. The average time for simulation, planning, physics quality assurance, pre-treatment preparation and treatment delivery were estimated via a survey of radiation therapists, medical physicists and radiation oncologists, and via records of actual time per activity spent at the Princess Margaret Cancer Centre. The cost for each activity was calculated by multiplying the activity time required by the unit costs of equipment and/or personnel. The costs for radiotherapy also included overhead costs, estimated from the annual financial budget of the Princess Margaret Cancer Centre allocated to the Radiation Program, divided by the number of courses delivered in 2013.

Cost of Ki-67 Testing

The cost of Ki-67 IHC testing was estimated based on a previous study from the University Health Network Laboratory Medicine Program [19].

Sensitivity Analyses

All parameters were varied separately in a one-way and a selected two-way sensitivity analysis. The cost of radiotherapy has been shown to be a function of facility size and hours of operation, where the cost of radiotherapy per patient in a facility treating 400 patients per year is about 50% more than one treating 1600 patients per year [20]. The smallest centre in Ontario treats about 400–450 patients per year. The costs of radiotherapy and Ki-67 testing are expected to be much higher elsewhere in Ontario than in an academic centre used in the base case; hence, the costs for radiotherapy and Ki-67 were varied by +30% and −10%. Three-dimensional conformal radiotherapy (3D CRT) is less costly than IMRT due to the lower dosimetry fee for radiation oncologists for 3D CRTs. In a sensitivity analysis, we assumed 97.5% cases used IMRT and 2.5% cases used 3D CRT, based on the IMRT utilisation rate in Ontario for 2013. The IMRT utilisation rate for adjuvant breast radiotherapy is expected to increase with time. The proportion of luminal A subtype was varied by ±10%. For the worst case scenario (i.e. most conservative estimate), the consultation cost was also excluded (assuming patients will still see radiation oncologists for discussion of their management).

Results

In 2010, 8922 cases of breast cancer were diagnosed in Ontario, among which 748 women age ≥ 60 years underwent surgery for pT1N0 ER+ HER2− breast cancer and 539 (72%) received adjuvant radiotherapy (Figure 1). The corresponding data for 2011 were 773 and 556 (72%), respectively. Based on the observations from the Toronto/British Columbia trial [14], we estimated that 61% of these patients had grade I/II luminal A tumour: 329 in 2010 and 339 in 2011 (average 334).

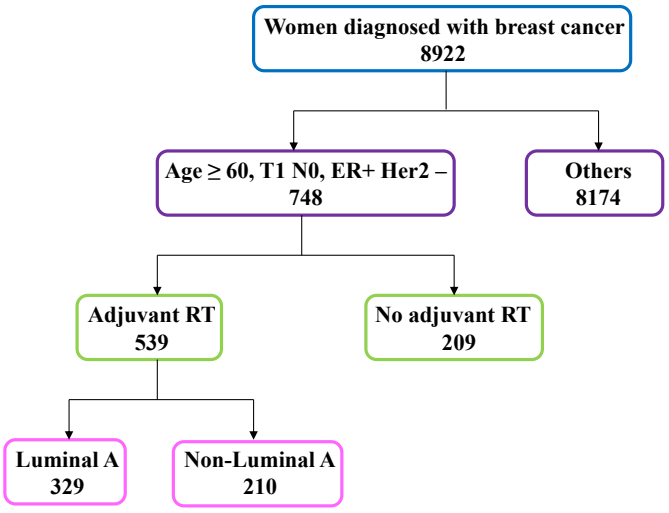

Fig 1. Estimated number of women age ≥ 60 years diagnosed with T1N0 luminal A breast cancer and treated with adjuvant radiotherapy in 2010 in Ontario.

Using activity-based costing, the estimated cost of adjuvant breast IMRT is $6135.85 per case in a large academic centre within a publicly funded health care system and $6004.85 for 3D CRT (Table 1). The cost of Ki-67 testing was estimated at $80.30 per case ($40 for IHC testing [19] and $40.30 for physician fee). Given that about 70% of T1N0 grade I/II ER+ HER2− breast cancer in women age ≥ 60 years are luminal A tumours (157/224 in Toronto/British Columbia trial) [14], the identification of each luminal A case via Ki-67 testing would cost $114.71 ($80.30/0.70).

Table 1
Cost per case of breast radiotherapy from the Ontario Ministry of Health and Long-Term Care perspective

Activity	Intensity-Modulated Radiotherapy	3-Dimensional Conformal Radiotherapy
Consultation	$ 254.13	$ 254.13
CT Simulation	$ 187.56	$ 187.56
Dosimetry	$ 1,655.44	$ 1,524.44
Physics Quality Assurance	$ 153.31	$ 153.31
Treatment Preparation & Delivery Review Visits	$ 2,232.32 $ 324.65	$ 2,232.32 $ 324.65
Overhead*	$ 1,328.44	$ 1,328.44
Total cost	**$ 6,135.85**	**$ 6,004.85**

* Overhead include costs associated with hospital administration, security, building services, laundry, medical records, social work, clerical radiotherapy, utilities, clerical (hospital registration), and housekeeping.

Therefore, the net savings for omitting IMRT for each case of low-risk luminal A breast cancer would be $6021.14.

The proportion of adjuvant radiotherapy cases post-BCS treated with IMRT in Ontario has been consistently above 90% (CCO target) and steadily increasing since June 2011. In 2012, 96.6% of the breast tangent patients were treated using IMRT; in 2013, 97.5% of cases were treated as such. Assuming that all cases will be treated with IMRT, this translates into total savings of $2.0 million per year if radiotherapy was omitted for all low-risk luminal A breast cancer patients in Ontario. Given that 39% of new breast cancer cases in Canada were diagnosed in Ontario [21], and assuming similar costs and proportion of luminal A breast cancer in each province, the estimated annual cost savings for Canada would be about $5.1 million.

Sensitivity Analysis

The results of the sensitivity analyses (Table 2) indicated that the cost of breast radiotherapy was the main driver of total savings to the publicly funded health care system. If the proportion of luminal A breast cancer, radiotherapy cost and IMRT utilisation rate all decreased, and the cost of Ki-67 testing increased (worst case scenario), then the total savings would decrease slightly to $1.5 million per year. If the costs of radiotherapy and the proportion of luminal A breast cancer both increased and Ki-67 testing cost decreased, then the potential annual savings would increase to $2.9 million per annum for the Ontario health care system and $7.4 million across Canada.

Discussion

The best approach to reducing the cost, inconvenience and morbidity of breast radiotherapy is to develop an effective biomarker that could identify women at such low risk of local recurrence after BCS such that breast radiotherapy could be safely omitted. This study showed that the approach of combining clinicopathological factors with IHC subtyping to identify women with lowest-risk luminal A breast cancer and the omission of radiotherapy for these patients would result in significant health care savings in a publicly funded system. Our findings were robust across a reasonable range of input.

The cost of breast cancer management has risen drastically due to changes in standard management, increased sophistication in radiation delivery techniques (e.g. IMRT) and inflation. For example, use of adjuvant chemotherapy for women age $\geq$ 45 years with breast cancer in Ontario rose from 27% in 1997 to 44% in 2007; associated with a seven-fold increase in cost [3]. Likewise, radiotherapy use also increased from 44% to 66% during the same time period, with a tripling in cost [3]. Similar trends have been reported for the USA [22].

A recent US study showed that EBRT is cost-effective for women age $\geq$ 70 years with pT1N0, ER+ breast cancer [$44 600 per quality adjusted life year (QALY)], but not IMRT (> $100 000 per QALY) [23]. As expected, EBRT became substantially less cost-effective for women with shorter life expectancies; this analysis was based primarily on results from the CALGB C9343 trial [8] and was not limited to the luminal A subtype.

The cost of radiotherapy varies across the world; we also explored the potential savings in the USA and UK should omission of radiotherapy in low-risk luminal A breast cancer become standard of care. The number of patients age $\geq$ 60 years diagnosed with T1N0 low-risk luminal A breast cancer in the USA each year was estimated using data from the SEER registries, which cover about 28% of the US population. In 2010, 7194 patients aged $\geq$ 60 years underwent BCS for T1N0 grade I/II ER+ HER2− breast cancer, and 5202 (72%) received EBRT. The corresponding figures in 2011 were 8112 and 5741 (71%), respectively. Of these, we

Table 2
Sensitivity Analyses

Scenario	Description	% luminal A subtype	Breast IMRT cost	IMRT utilization	3D CRT cost	Ki-67 cost*	Potential total savings in Ontario (million dollars)
Base case		61%	$6,135.85	100%	NA	$80.30	**$ 2.0**
1a	10% lower prevalence of luminal A	55%					**$ 1.8**
1b	10% higher prevalence of luminal A	67%					**$ 2.2**
2a	30% higher cost of RT for lower volume center		$7,976.61				**$ 2.6**
2b	10% lower cost of RT		$5,522.27				**$ 1.8**
3	97.5% IMRT cases instead of 100%			97.5%	$6,004.85		**$ 2.0**
4a	30% higher cost of Ki-67 testing					$104.39	**$ 2.0**
4b	10% lower cost of Ki-67 testing					$72.27	**$ 2.0**
5	30% higher cost of RT and 30% higher cost of testing		$7,976.61			$104.39	**$ 2.6**
6	Worst case	55%	$5,293.55	97.5%	$5,175.65	$104.39	**$ 1.5**
7	Best case	67%	$7,976.61			$72.27	**$ 2.9**

IMRT: intensity-modulated radiotherapy; 3D CRT: 3-dimensional conformal radiotherapy.
Empty cells imply the same estimates as in the base case.
* Total Ki-67 cost = Ki-67 cost listed / % luminal A subtype.

estimated that 70% [14] were luminal A tumours: 3641 in 2010 and 4019 in 2011 (average 3830). The mean cost per case to Medicare from a payer perspective was $16 154 for EBRT; $24 767 for IMRT; $24 791 for brachytherapy; and $132 for Ki-67 testing [23,24]. According to a SEER–Medicare study, 12.6% of patients with breast cancer who received adjuvant radiotherapy were treated with IMRT, and 9% with brachytherapy in 2007 [25]; another study using the National Cancer Data Base showed a similar proportion of IMRT use (~11%) from 2009–2011 [26]. Assuming that the treatment pattern in SEER regions is representative of the entire US population, the annual cost savings to the US would be about US$243 million if patients were treated with standard fractionation of 50 Gy in 25 fractions [3830 × (0.784 EBRT × $16 154/EBRT + 0.126 IMRT × $24 767/IMRT + 0.09 brachytherapy × $24 791/brachytherapy − $132/0.7)/0.28]. A recent National Cancer Data Base study showed that the proportion of patients with early stage breast cancer treated with hypofractionation is rising: 18.3% in 2010 and 22.8% in 2011 [27]. If 25% of the patients are treated with hypofractionation, the annual cost savings to the USA would be about US$145 million [3830 × (0.784 EBRT × $8512/hypofractionated EBRT [28] + 0.126 IMRT × $14 853/hypofractionated IMRT [28] + 0.09 brachytherapy × $24 791/brachytherapy − $132/0.7)/0.28].

In the UK, there were on average 29 136 new breast cancer cases diagnosed per year in women age ≥ 60 years between 2009 and 2011 [29]. From this, it is estimated that 41.8% (12 179) were stage I [30]; 86% (10 473) received adjuvant radiotherapy [31]; and 50% of the stage I ER/HER2 unknown (5236) were of luminal A subtype [14]. The UK PRIME trial that randomised patients age ≥ 65 years with T0-2, N0-1 breast cancer treated by BCS and endocrine therapy to adjuvant radiotherapy versus no radiotherapy reported a mean 2004 radiotherapy cost of £2846 per patient (adjusted to 2014 pounds sterling using the UK Consumer Price Index for health) [32]. This cost was estimated for 3D CRT; the proportion of breast cancer patients treated with IMRT or intraoperative radiotherapy is currently unknown in the UK. A 2008 UK survey reported that only 18.8% of radical breast radiotherapy cases were treated with IMRT [33]. The estimated cost for Ki-67 testing was £112 per case [34]; hence, the estimated saving in the UK per year could be over £14 million [5236 × (2846–112/0.5)].

The economic savings estimate in our study was limited to that of the health care system perspective and did not include other potential costs to the patient or society. A recent study from Quebec reported an average out-of-pocket expense of $445 for patients with breast cancer to access adjuvant radiotherapy [35]. A US study documented that 25% of breast cancer survivors experienced financial decline at least partly attributed to breast cancer treatment (not limited to radiotherapy cost alone) [36]. The costs associated with lost or impaired ability to work was not included in this study, although only a minority of women age ≥ 60 years would be in the work force. We also did not account for costs associated with the management of acute and late toxicities of breast radiotherapy as serious side-effects from breast radiotherapy are uncommon; previous cost-effectiveness studies pertaining to breast radiotherapy also did not include such costs [23,37,38]. Although hypofractionation (16 fractions) has been widely adopted in most parts of Canada following the publication of the Ontario Clinical Oncology Group trial [18], about 15–25% of women with early stage breast cancer may still be treated with standard fractionation (25 fractions) [39]. Hence, for all of these above reasons, the costs that we have estimated from the health care system perspective might well be conservative.

The base case analysis in this study was intentionally built upon a large academic centre in Canada to avoid overestimating the potential savings. A previous study has shown that the cost of radiotherapy is significantly lower in a larger facility treating more patients than a smaller one [20]. Indeed, sensitivity analyses showed that the main driver of total savings to the publicly funded health care system was the cost of breast radiotherapy.

This study used a simple costing analysis; we did not use a Markov model with utilities because the expected difference in local recurrence rate associated with omission of radiotherapy in patients with luminal A tumours, and in utilities, would be negligible. The UK PRIME trial observed no difference in overall quality of life or utility scores between the breast radiotherapy versus no radiotherapy arm from baseline up to 5 years [32,38].

A Canadian study from 1997 identified that 54% of interviewed patients were willing to forego radiotherapy if the quoted 5 year recurrence risk was the same or close to that with radiotherapy [40]. The willingness to forego therapy was influenced by maximal acceptable waiting time, employment status and tumour size. Given the accumulating evidence on the low risk of local recurrence in women with luminal A breast cancer, further research on patients' attitudes towards omission of radiotherapy is warranted.

An international reproducibility study found substantial variability in Ki-67 scoring on centrally stained tissue microarray slides [41]. However, after calibrating to a common scoring method via a web-based tool, high inter-laboratory reproducibility in Ki-67 scoring was achieved [42]. Ki-67 is less expensive than commercial tests such as Oncotype DX and Prosigna (up to about US$4000), which are being used in some ongoing studies in the USA. The potential cost savings of omitting radiotherapy would be substantially decreased if these tests were used. Hence, further research on strategies to reduce inter-observer variability in Ki-67 scoring is also warranted.

Conclusions

This current cost analysis showed substantial savings to a publicly funded health care system should the omission of radiotherapy become standard of care for women age ≥ 60 years with T1N0 grade I/II ER+ HER2− luminal A breast cancer. The ongoing LUMINA study is anticipated to validate the low risk of local recurrence in these patients. Hence, this

advancement in personalised radiotherapy is expected to achieve significant benefit for both women with early breast cancer and the health care system.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clon.2016.04.003.

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