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Original Article

Lives and Economic Loss in Brazil due to Lack of Radiotherapy Access in Cervical Cancer: A Cost-Effectiveness Analysis

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Abstract

Aims: Among all malignancies, the use of radiotherapy incurs the highest survival benefit within cervical cancers. Radiotherapy, however, remains underutilised for cervical cancers within the Brazilian public health system (BPHS). The objective of this study was to estimate the potential health and monetary benefits for universal access to radiotherapy and chemoradiotherapy (CRT) for untreated cervical cancer patients in the BPHS.

Materials and methods: Using 2016 data on Brazilian cervical cancer incidence and availability of radiotherapy/CRT in the BPHS, the number of cancer deaths due to radiotherapy/CRT underutilisation was estimated. The incremental effectiveness was calculated by life-year gain. The indirect costs from mortality-related productivity loss (MRPL) were estimated based on life expectancy, wage and labour force participation rate. MRPL was compared with direct medical costs after being adjusted to 2016 US dollars. This study was conducted from the payer's perspective; both costs and effectiveness were discounted at a rate of 3%. The incremental cost-effectiveness ratio (ICER) was calculated to determine the cost-effectiveness of radiotherapy for cervical cancer in Brazil. One-way sensitivity analyses were carried out to assess the robustness of the model.

Results: The total number of life-years lost due to lack of universal access to radiotherapy and CRT per year were 27 199 and 31 627, respectively. The annual cost to match the radiotherapy gap was $10.5 million, with an additional cost of $3 million to close the CRT gap. The mean years of potential life lost per death was 20.5. The cost per life saved was $7942 for radiotherapy alone (ICER $388/life-year) and $8774 for CRT (ICER $429/life-year). MRPL due to shortage of radiotherapy and CRT were $59 million and $69 million, respectively.

Conclusion: Providing universal access to radiotherapy/CRT for cervical cancer patients in the BPHS is highly cost-effective and should be prioritised as an impactful public health initiative.

Key words: Brazil; cervical cancer; cost-effectiveness analysis; radiotherapy access

Introduction

Although cervical cancer is highly treatable in its early stages, it continues to be a lethal disease in developing countries. In Brazil, incident cases total over 16 000 annually and account for over 5800 deaths per year [1]. Most cervical cancers occur in women with low socio-economic status and who rely on the Brazilian public health system (BPHS) for health care. Previously, our group estimated that nearly half of patients with cervical cancer in the BPHS do not have access to radiotherapy treatment, leading to over 1300 cervical cancer-related deaths within a 5-year period [2].

Although effective interventions, such as screening strategies, are well established, in some low- and middle-income countries like Brazil they are not broadly carried out [3] and, therefore, cancer diagnoses are commonly made when the primary tumour is clinically evident. Also, cervical cancers tend to affect women early in life and, thus, a higher number of years of potential life lost (YPLL) and significant financial burden from deaths caused by cervical cancer could be averted. Given the increasing recognition of

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the concept of value-based cancer care and the fact that radiotherapy has an undisputable role in the treatment of cervical cancer, the purpose of this study was to estimate the YPLL and the financial deficit associated with the underutilisation of radiotherapy/chemoradiotherapy (CRT) within the cervical cancer population in the BPHS.

Materials and Methods

The methodology of this study was in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline reported by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) task force group [4]. It was based on the estimated number of cervical cancer cases not receiving radiotherapy in the BPHS for the year 2016 [2].

Model Construction

Cervical cancer incidence, mortality, treatment indication, medical costs and national census data were extracted from the published literature and used in this model (Table 1). These parameters were used to develop a model to evaluate the cost-effectiveness of providing universal radiotherapy/CRT access to women with cervical cancer in comparison with the current availability in the BPHS. All costs were adjusted to 2016 US dollars. Costs and life-years were discounted at a standard rate of 3% with half-cycle correction applied. The model schema is illustrated in Figure 1. The model and graphs were constructed and analysed using Microsoft Excel 2013.

Life-year Gain

Life-year gain was conceptually equivalent to YPLL due to untreated cervical cancer in the model. YPLL adjusted by age group was calculated based on life expectancy, Brazilian cervical cancer incidence and the number of cancer deaths due to lack of radiotherapy/CRT access were estimated as previously described [2]. The source data for estimating the clinical effectiveness of radiotherapy/CRT were from a systematic review by Hanna *et al.* [10] and a 5-year period was chosen based on the assumption that untreated cervical cancer is fatal or at least incapacitating within 5 years [14].

$$ICER = \frac{Incremental\ cost}{Incremental\ effectiveness} = \frac{Incremental\ direct\ medical\ cost}{Life\ year\ gain}$$

Life year gain [a,d]
=Life expectancy [a,d] ** No. of lives saved* [a]

Incremental direct medical cost[a,b, c]
= RT/CRT cost [b,c] ** (Incidence* [a] ** P* $_{patients\ in\ BPHS\ requiring\ RT}$ ** P* $_{RT/CRT\ shortfall}$[a])

Mortality-related productivity loss [a,b, c, d]
= PVFLE [a,b, c, d,e] ** No. of lives saved* [a]

Fig 1. Model scheme. ICER, incremental cost-effectiveness ratio; RT, radiotherapy; CRT, chemoradiotherapy; *P*, proportion; BPHS, Brazilian public health system; PVFLE, present value of future lifetime earnings; a, age adjusted; b, inflation adjusted; c, currency adjusted; d, discounting applied, with half-cycle correction; e, return to work adjusted.

Table 1
Model parameters: baseline value, range, source

	Value	Minimum	Maximum	Range	Reference
Inflation	–	–	–	±10%	[5]
Currency conversion June 2016 (USD-BRL)	3.49	3.19	4.05		[6]
Cervix cancer incidence in Brazil (2016)	16340	14706	17974	±10%	[7]
Proportion of patients in BPHS (2016)	0.751	0.713	0.789	±5%	[8]
Radiotherapy cost in BRL (2016)	8768	7014	10522	±20%	[9]
Chemotherapy cost in BRL (2016)	2600	2080	3120	±20%	[9]
Proportion of unmet radiotherapy needs (2015)	0.466	0.366	0.566	±10%	[2]
Proportion of radiotherapy treatment with indication for concurrent chemotherapy	0.96	0.86	1.00	±10%	[10]
Potential life saved with universal radiotherapy access	1328	1063	1594	±20%	[2]
Additional potential life saved with universal chemoradiotherapy access	216	173	260	±20%	[2]
Discount rate	3%	0%	6%	0–6%	–
Annual wage (2010)	Age dependent			±20%	[11]
Life expectancy (2015)	Age dependent			±5%	[11]
Labour force participation rate (2016)	Age dependent			±10%	[12]
Proportion of women return to work	0.84	0.64	1.00	±20%	[13]

BPHS, Brazil public health system; BRL, Brazilian Real; USD, US dollar.

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Direct Medical Cost

The direct medical cost to account for radiotherapy/CRT needs was calculated for 2016 from a payer's perspective. The number of new cases with unmet radiotherapy/CRT needs was estimated based on the incidence of cervical cancer, the proportion of patients in the public system and the proportion of new cases not receiving appropriate treatment. We assumed that the proportion of unmet CRT need was equal across all age groups, as the source data for access to medical care were not stratified by age. Radiotherapy costs for the treatment of cervical cancer were obtained from the BPHS reimbursement fee schedule for four fractions of two-dimensional brachytherapy and 30 fractions of four-field conformal external beam radiation therapy [9]. To calculate the total CRT cost, the cost of five cycles of cisplatin was added to the radiotherapy cost.

Mortality-related Productivity Loss

The indirect costs as represented by mortality-related productivity loss (MRPL) were estimated through the age-adjusted present value of future lifetime earnings for paid work, which were calculated from life expectancy, wage and labour force participation rates based on the method described by Menzin *et al.* [15]. The proportion of women who were able to return to work after 5 years was estimated from previous work by Nakamura *et al.* [13].

Incremental Cost-effectiveness Ratio

To calculate the incremental cost-effectiveness ratio (ICER), incremental costs were attributed to the direct medical cost of the radiotherapy/CRT shortfall, whereas incremental effectiveness was evaluated from the associated life-years gained through universal radiotherapy/CRT availability.

Sensitivity Analysis

Deterministic one-way sensitivity analyses were carried out to evaluate the overall robustness of the model as well as the influence of various model parameters on the ICER. The sensitivity analysis ranges were determined based on the property of each variable and the quality of the source data. Variables from the census data or direct measurement were set between 5 and 10%. Estimated values from research studies were set in the range of 10–20%. All variables on cost were varied by 20% above or below their baseline value. The willingness-to-pay threshold was not pre-specified, but discussed in the context of World Health Organization standard and opportunity cost [16].

Results

Based on a previous estimation that 4197 of the 12 271 cervical cancer patients in the BPHS did not receive radiation treatment in 2016, the incremental annual cost for universal radiotherapy and CRT coverage would be $10.5 million and $13.6 million, respectively.

The total YPLL due to a lack of radiotherapy or CRT were 27 199 and 31 627, respectively. The mean YPLL per patient was 20.5 years. This translates to a cost per life saved of $7942 for radiotherapy and $8774 for CRT. The ICER for providing universal access to radiotherapy was $388 per life-year saved (Figure 2). The ICER for providing universal access to CRT was $429/life-year and $678/life-year when compared with current baseline coverage and universal access to radiotherapy, respectively (Figure 2).

The total age-adjusted MRPL due to the lack of radiotherapy was $59.4 million and was $69.0 million for CRT access. The annual cost to meet the radiotherapy or CRT

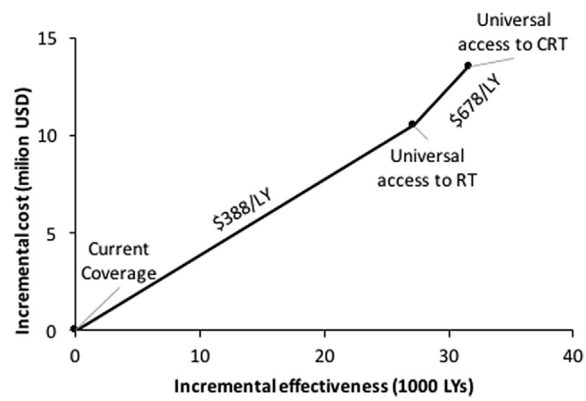

Fig 2. Incremental direct medical cost of providing universal access to RT and CRT for cervical cancer versus incremental life-year gain in the Brazilian Public Health System. Abbreviation: USD, the United States Dollar; LY, life-year; RT, radiotherapy; CRT, chemo-radiotherapy. All costs were adjusted to 2016 USD.

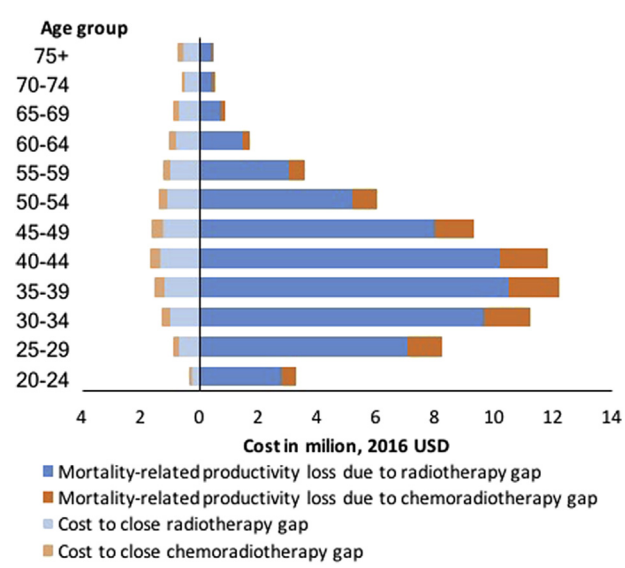

Fig 3. Mortality-related productivity loss per age group versus direct costs to close treatment gap in the Brazilian Public Health System. Abbreviation: USD, the United States Dollar. All costs were adjusted to 2016 USD.

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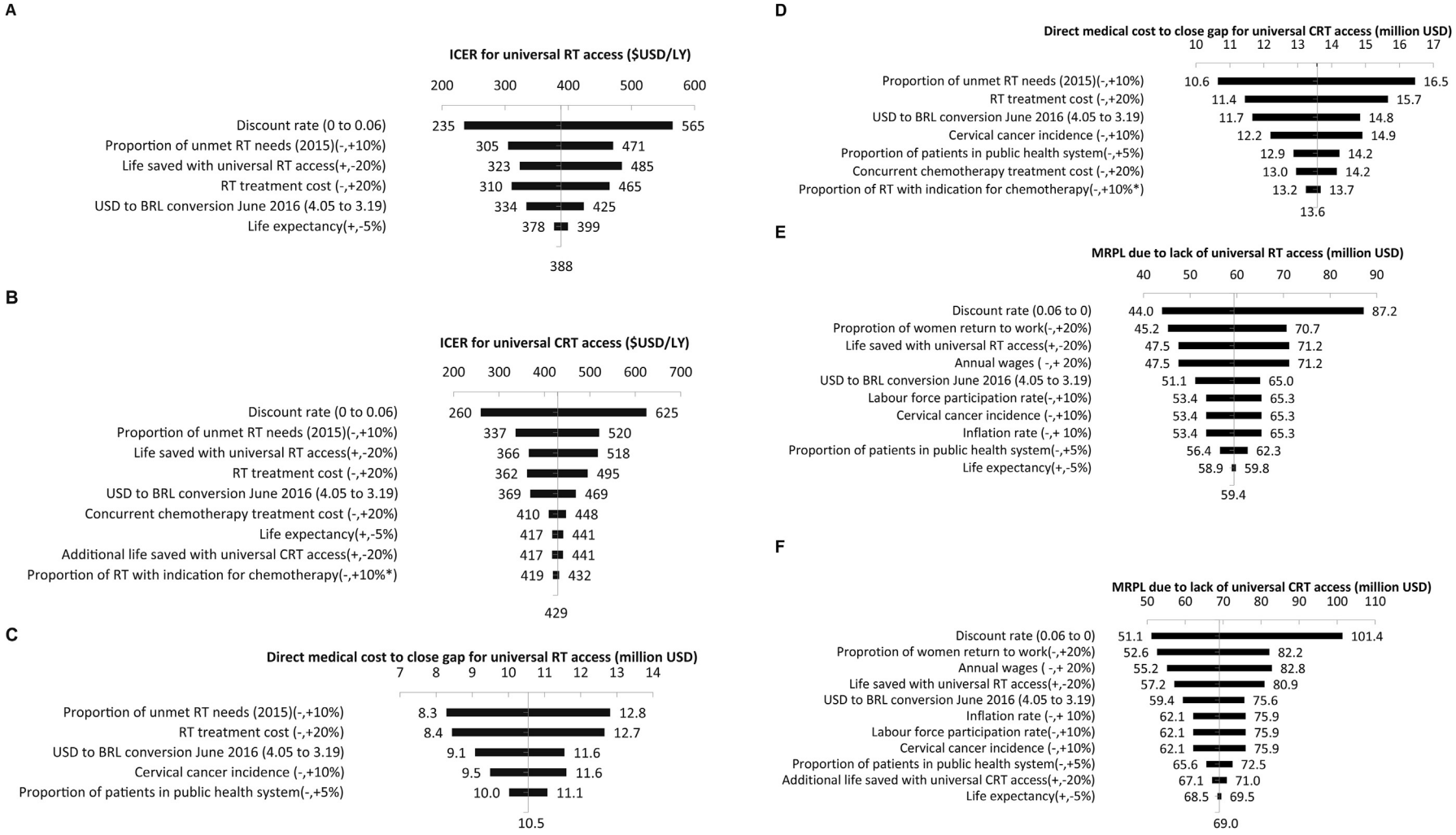

Fig 4. One-way sensitivity analysis by tornado plot. All costs were adjusted to 2016 USD. * maximal proportion = 100%. Abbreviation: ICER, incremental cost-effectiveness ratio; MRPL, mortality related productivity loss; RT, radiotherapy; CRT: chemo-radiotherapy; USD, the United States Dollar; BRL, Brazilian Real.

underutilisation in the BPHS versus losses in productivity associated with early deaths due to lack of treatment is shown in Figure 3. When considering both MRPL and direct medical costs, the net financial loss for the Brazilian population was estimated to be $48.9 million or $55.4 million due to a shortage of radiotherapy and CRT, respectively.

Sensitivity analyses for the variables used in this study are shown in Figure 4. The ICERs for providing universal radiotherapy and CRT were most sensitive to the discount rate used and ranged from $235/life-years to $565/life-years and $260/life-years to $625/life-years, respectively. The direct medical cost for universal radiotherapy/CRT access was most sensitive to the proportion of unmet radiotherapy needs. The MRPL due to a lack of universal radiotherapy/CRT access was most sensitive to the discount rate.

Discussion

In this model-based study, we found that the lack of universal availability of radiotherapy and CRT within the BPHS for cervical cancer patients has a profound effect on the estimated YPLL for an otherwise cost-effective treatment. These findings are particularly striking, as no definitive measure to substantially increase radiotherapy capacity in the BPHS has been seriously pursued, according to recent media reports [17]. Moreover, the findings of this study indicate that the lack of treatment for cervical cancer patients would cost the BPHS much more than the actual treatment expenditure, as a significant financial loss is associated with early deaths.

The lack of radiotherapy access in low- and middle-income countries is a reality that has a significant negative effect on survival for the cervical cancer population [18]. Previously, our group estimated that about 40% of the preventable cancer deaths in the BPHS were due to a radiotherapy shortage for cervical cancers [2]. The significant impact of radiotherapy in this population is further accentuated by the detection of cervical cancer at later stages in the BPHS than in many other countries, which is a reflection on an inefficient screening programme [3] and the lack of prompt access to treatment once a diagnosis is confirmed. Moreover, other therapeutic options, such as surgery, have a small role in the treatment of locally advanced cancers. Finally, a narrow curative window is seen for patients at this stage, as tumours rapidly progress to a non-curable scenario if left untreated [19].

A willingness-to-pay threshold is defined by the World Health Organization [20] as an estimate of what a health care system is willing to pay for a certain health benefit based on cost-effectiveness ratios. In this study, an extremely low cost-per-life-saved of less than $9000 and a cost-per-year-life-saved less than $500 for either radiotherapy or CRT is justified within the BPHS [21]. Also, as cervical cancer affects women early in life, early death in our model translated to an average of over 20 YPLL. This is congruent with findings of a Surveillance, Epidemiology, and End Results Program (SEER) study, whereby, cervical cancer was the third highest contributor to YPLL in the USA, after childhood and germ cell cancers [22].

Despite the shortcomings of the lack of universal access to radiotherapy for cervical cancer in Brazil, other current measures, such as human papillomavirus (HPV) vaccination, are expected to have an important impact on reducing cervical cancer incidence and therefore morbidity and mortality burden. These vaccines have proven efficacy in preventing human infection by high-risk HPV infection and in decreasing HPV-associated cancers in the future [23]. The Brazilian government has launched a programme to make these vaccines available to girls younger than 15 years old and to 11–14-year-old boys. However, this programme is far from achieving universal coverage [24]. Also, measures including prompt diagnosis as well as easy access to treatment persist as obstacles, even if improvements in the widespread adoption of HPV vaccination is achieved, particularly as multiple generations of women have already been infected by HPV.

Brazil is an upper middle-income country according to the World Bank [25] and therefore cost-utility analyses are of great importance. In this setting, our results indicate a significant financial deficit due to early deaths and MRPL associated with radiotherapy shortage in the BPHS, with about $50 million annually lost due to this shortage of radiotherapy access. Moreover, the average projected value of life (economical gain) was found to be higher than the cervical cancer treatment cost for all age groups below the age of 65 years, indicating the affordability of this treatment. In light of the radiotherapy and CRT cost-effectiveness findings described herein, we would propose that there is an urgent need to prioritise radiotherapy expansion for cervical cancer within the BPHS.

The findings of the present study are limited by assumptions inherent in any model-based prediction. The model purposefully assumes idealised conditions of adoption to determine the potential benefit of universal access. Regardless, additional benefits of improved infrastructure for the availability of radiotherapy can reasonably be assumed, as radiotherapy is a guideline-based treatment of other prevalent, highly fatal cancers, including lung and head and neck cancers, among others. In this context, the ongoing Brazilian radiotherapy expansion programme could represent a partial solution for closing this treatment gap. However, its implementation is slower than expected, with eight units (from 80–100 initially expected) currently in operation [17]. Moreover, the programme is only anticipated to increase a percentage of the treatment capacity, even if it is fully successful, due to aging and the need to replace current units in operation.

We acknowledge other limitations of this study that need to be discussed. First, the costs and benefits associated with three-dimensional brachytherapy were not taken into account. This advancement in treatment is associated with improved outcomes and may possibly further increase the estimated benefit of radiotherapy, in terms of lives saved [26]. Moreover, a few assumptions were made in this

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study's methodological design. The productivity value for life estimate was estimated based on the annual average wage from 2010 adjusted by the inflation rate and life expectancy in 2015. Lives potentially lost due to a lack of radiotherapy previously published by our group did not take into account the benefits associated with adjuvant radiation post-surgery in cervical cancer patients with a high relapse risk. Finally, the cost to meet the (chemo) radiotherapy cervical cancer gap was calculated without consideration to the infrastructure associated with an expansion of radiotherapy demands.

Conclusion

In this model-based study, we found that radiotherapy and CRT shortage within the BPHS had significant financial and survival implications. As these strategies seem to be highly cost-effective, efforts to increase the availability of high-quality radiotherapy are paramount in order to minimise future missed opportunities in the management of this disease in Brazil.

Conflict of Interest

A.V. Louie has received honoraria from Varian Medical Systems and Astra Zeneca. His research is supported by the Ontario Association of Radiation Oncology Clinician Scientist Program.

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