Cost-effectiveness of Post-Mastectomy Radiotherapy (PMRT) for breast cancer in India: An economic modelling study

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Summary

Background The role of post-mastectomy radiotherapy (PMRT) for breast cancer is controversial when 3-or-less lymph nodes are metastatic. Apart from local control, survival and toxicity, cost also plays an important role in decision-making.

Methods A Markov model was designed to assess cost, health outcomes and cost-effectiveness of different radiotherapy techniques for management of PMRT patients. Thirty-nine scenarios were modelled based on type of radiotherapy, laterality, pathologic nodal burden, and dose fractionation. We considered a societal perspective, lifetime horizon and a 3% discount rate. The data on quality of life (QoL) was derived using the cancer database on cost and QoL. Published data on cost of services delivered in India were used.

Findings Post-mastectomy radiotherapy results in incremental quality adjusted life years (QALYs) that ranged from −0.1 to 0.38 across different scenarios. The change in cost ranged from estimated median savings of USD 62 (95% confidence intervals: −168 to −47) to incurring an incremental cost of USD 728 (650−811) across different levels of nodal burden, breast laterality and dose fractionation. For women with node-negative disease, disease-specific systemic therapy remains to be the preferred strategy. For women with node-positive disease, two-dimensional radiotherapy (2DRT) with hypofractionation is the most cost-effective strategy. However, a CT based planning is preferred when maximum heart distance (MHD) >1cm, irregular chest wall contour and inter-field separation >18cm.

Interpretation PMRT is cost-effective for all node-positive patients. With similar toxicity and effectiveness profile compared with conventional fractionation, moderate hypofractionation significantly reduces the cost of treatment and should be the standard of care. Conventional techniques for PMRT are cost-effective over newer modalities which provide minimal additional benefit, at high cost.

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Keywords: Postmastectomy radiotherapy (PMRT); Breast cancer radiotherapy; Radiation toxicity; Economic evaluation; Hypofractionation

Introduction

Breast cancer is the most common cancer among women in India, with 162,468 new cases diagnosed in 2018 and, accounts for 27% of all cancers in women. This number is predicted to double by the year 2025.[1] Most patients with breast cancer present at a locally advanced stage.[2] Modified radical mastectomy is the commonly performed surgery for patients with breast

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Research in context

Evidence before this study

We conducted a PubMed search using the following search string: "((((((((((((((((((((((cost-effectiveness) OR (cost-utility)) OR (economic evaluation)) AND (radiotherapy)) OR (radiation)) OR (2DRT)) OR (two-dimensional radiotherapy)) OR (3D-CRT)) OR (3 dimensional conformal radiotherapy)) OR (IMRT)) OR (Intensity modulated radiotherapy)) AND (hypofractionation)) OR (conventional fractionation)) AND (lymph node subgroups)) AND (breast cancer)) AND (postmastectomy)) OR (post-mastectomy radiotherapy)) AND (radiotherapy side-effects)) AND (long-term toxicity with radiotherapy)) OR (PMRT)". No filter in terms of the time-period, language, or study design was applied. The initial search yielded 643 results, of which 632 were eliminated based on screening the title and/or abstract. The remaining 11 papers were reviewed in detail based on which 5 records that assessed the cost-effectiveness of postmastectomy radiotherapy (PMRT) were selected. Among these, 3 studies assessed the cost-effectiveness of two-dimensional radiotherapy (2DRT) in comparison to no radiotherapy, however, neither of these studies differentiated based on nodal subgroups or accounted for radiotherapy-related toxicities. One study used lymph node stratification but did not analyse the cost and health outcomes of modern radiotherapy techniques or hypofractionated regimens which are now the new standard of care. Further, none of these studies accounted for long-term radiation toxicities like secondary cancers and cardiac mortality. Another recent model-based analysis compared the newer radiation techniques for incidence of late toxicities; however, they did not account for variation in nodal status as well as the side of the breast involved. Importantly, we could not identify any study conducted on the Indian population.

Added value of this study

We present a comprehensive analysis wherein 39 scenarios were modelled to assess the cost-effectiveness of PMRT. The study accounts for the impact of modern radiotherapy techniques on the long-term occurrence of secondary cancers and cardiotoxicity post-radiotherapy among women with different lymph node involvement status. We also examined the impact of radiotherapy depending on the laterality of the breast involved. Finally, we evaluate the scenarios of standard fractionation and hypofractionation for different combinations of radiotherapy techniques, nodal status, and laterality of breast.

Implications of all the available evidence

Current evidence indicates that adjuvant radiotherapy remains cost-effective for all node-positive postmastectomy patients, who receive systemic therapy. In the Indian population, both three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) were not found to be cost-effective compared to 2DRT. This signifies that radiation doses to the heart, lung or contralateral breast do not cause significant long-term morbidity or mortality, and cost of modern radiotherapy techniques outweighs the cost of management of long-term radiation adverse effects. Chest wall irradiation continues to be the essential target while which regional nodes to irradiate, remains a topic of debate. Long-term survival data from recent trials with use of systemic therapy including taxanes, anthracyclines, HER2-targeted therapies and hormone therapy with aromatase inhibitors will provide more evidence about the effectiveness of radiotherapy in patients with 1–3 positive lymph nodes.

cancer in India, in view of advanced stage at presentation and limited resources in terms of surgical expertise, pathology, radiology and radiotherapy.[3]

Postmastectomy radiation therapy (PMRT) is widely accepted in patients with four or more positive lymph nodes, where PMRT decreases both locoregional recurrence (LRR) and breast cancer mortality.[4] However, for patients with 1–3 metastatic lymph nodes and node-negative disease with high-risk features, the use of PMRT is widely debated.[5] Newer trials with more effective systemic therapy have shown <10% loco-regional recurrence (LRR) in the subgroup of 1–3 lymph node positive patients.[6] PMRT is associated with incidental irradiation of lungs, heart and contralateral breast and this may further influence treatment decisions; cardiotoxicity is of specific concern especially with left-sided tumours.[7] These adverse effects reduce with modern radiotherapy techniques like three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT). Further, hypofractionated radiotherapy is also considered to be a safe and effective regimen for breast cancer patients and reduces the cost of treatment as well.[8] The conflicting data on indications of PMRT with added cost of modern radiotherapy techniques merit a cost-effectiveness analysis for use of PMRT.

There is limited evidence on the cost-effectiveness of PMRT. Most studies have neither used long-term survival data nor considered the subgroups according to the number of lymph nodes involved.[9–11] A study which used the lymph node stratification did not analyse the cost of modern radiotherapy techniques or hypofractionated regimens, which are now the new standard of care.[12] Further, none of these studies accounted for the long-term radiation toxicities like secondary cancers and cardiac mortality.[9–12] A recent model-based analysis compared the newer radiation techniques for incidence of late toxicities, however, the authors did not account for variation in nodal status as well as the laterality of breast involved.[13] Most importantly, all these studies represent high or upper middle income countries and thus there is a need to generate such evidence for low-and-middle income countries like India as well. In the present analysis, we evaluate the cost-effectiveness of PMRT based on the type of radiation technique, i.e., 2-dimensional radiotherapy (2-DRT), 3D-CRT and IMRT; extent of lymph node involvement; incidence of late radiation hazards; left or right sided tumours; and finally evaluated the scenarios of standard fractionation and hypofractionation for all the possible combinations.

Methods

Overview of analysis and scenarios

The present study was designed to compare the cost, health outcomes and cost-effectiveness between different radiotherapy techniques, i.e., 2-DRT, 3D-CRT and IMRT as well as avoidance of radiotherapy for the management of patients with breast cancer after mastectomy. 2-DRT in the context of breast cancer is defined as X-ray simulator-based planning which follows the skin marking using conventional portals based on anatomical landmarks. The dose-volume constraints are met by considering a central lung distance (CLD) <2.5–3 cm and maximum heart distance (MHD) <1 cm. Patients not meeting the above criterion or with interfield separation of >18 cm, irregular chest wall contour or requiring regional node irradiation (RNI) with hypofractionation are referred for CT based planning. Treatment is executed using tangential beams for chest wall by 4–6 MV photons using breast board. Additional supraclavicular, axillary, internal mammary portals may be added as required with an ideal matching technique.[14]

The analysis was undertaken for three sub-groups as per pathologic nodal status: Node-negative disease; 1–3 positive lymph nodes and four or more positive lymph nodes. Each subgroup was further analysed based on whether radiation was delivered to the left or the right breast because of possible cardiac toxicity. In addition, each radiation technique was also assessed in terms of dosage administered in different durations. Two scenarios were considered for the same: 50 Gray (Gy) in 25 fractions delivered over 5 weeks, and 42.5 Gy in 16 fractions delivered over three weeks. Overall, with these combinations, we analysed 39 scenarios based on the type of radiotherapy (including no radiotherapy), laterality of disease, pathologic nodal status, and dose fractionation.

Model structure

We estimate the lifetime costs and consequences in a hypothetical cohort of 50-year-old Indian women who have undergone mastectomy. The Markov model allows us to estimate costs and utilities using a hypothetical cohort when individual patient-level data are not available. The movement of patients from one stage to another and for the development of toxicities has been based on the annual transition probabilities available from published literature. A disaggregated societal perspective was chosen to incorporate both the health system costs and direct out-of-pocket (OOP) expenditure. Indirect costs due to productivity losses were not included in the analysis. Health outcomes were valued in terms of life years (LY) and quality-adjusted life years (QALY). Both the future costs and consequences were discounted at a rate of 3%.[15,16] The cycle length of the model was assumed to be annual. The cost-effectiveness of each radiation technique, in comparison to the previous best in terms of effectiveness, was assessed using the incremental cost-effectiveness ratio (ICER).

We modelled 7 Markov health states which included: disease-free, loco-regional recurrence, distant metastasis, late toxicities (post-radiotherapy), death from breast cancer as well as from late toxicities and all-cause mortality. As per the model, a patient who is disease-free, can develop LRR or metastasis or could have late side-effects. A patient with LRR could further progress and develop distant metastases. Moreover, a person with LRR or distant metastases could also develop late side-effects or vice versa. We made several assumptions (listed below) based on published data. Every subsequent year, 10% of those new patients who developed LRR were assumed to revert back to being disease-free.[17] The rate of developing metastasis from LRR was assumed to be three times that of developing metastasis from a disease-free state.[17,18] Three types of late toxicities were modelled: cardiotoxicity, lung cancer and contralateral breast cancer. The incidence of contralateral breast cancer was assumed to occur six years after the delivery of radiotherapy, while the occurrence of lung and cardiac events were assumed to appear 11 years post-radiotherapy.[3,7] A patient was assumed to die of breast cancer only if she had distant metastases. Death could also occur due to any of the toxicities, besides risk of all-cause mortality from unrelated illness.

Clinical parameters and utility values

The probability of progression i.e., into LRR or metastasis, as per the nodal status, was assessed from the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis (Supplementary file: Table S1).[4] Due to lack of strong evidence suggesting significant difference in the effectiveness between the three radiotherapy techniques i.e. 2-DRT, 3D-CRT and IMRT, we assumed a similar rate of LRR and metastasis with each of these techniques.[20] The data for incidence of toxicities following 2-DRT was obtained from studies that had a follow-up period of over 15 years.[3,7,19] Further, as literature pertaining to long-term toxicities following 3D-CRT and IMRT is very scarce, we used evidence from dosimetry studies which provide mean organ dose delivered to contralateral breast, lung and heart with 3D-CRT and IMRT.[21] The mean organ dose was then used to calculate the corresponding incidence of organ toxicity using evidence from literature.[7,19,22] Finally, we assumed that there would be no difference in the incidence of toxicities following radiotherapy whether delivered with conventional fractionation (50Gy in 25 fractions) or moderate hypofractionation (42.5Gy in 16 fractions).[8]

We used the estimates from an Indian study that had reported long-term breast cancer survival rates to estimate probability of dying from primary or contralateral breast cancer.[23] The mortality for lung cancer and cardiotoxicity was assessed from published evidence.[7,19] All-cause age-specific mortality rates were assessed from Indian sample registration survey (SRS) life-tables for women.[24]

Primary data being collected as part of the study to develop cancer database of cost and quality of life (CaDCQoL) were analysed to estimate the utility scores.[25] Data on 843 patients with breast cancer recruited from six cancer hospitals in India, who were interviewed using EQ-5D instrument comprising of the EQ-5D-5L descriptive system and EQ-VAS were analysed to estimate utility score for patients with LRR and metastasis. For quality of life (QOL) of patients who were disease-free, we used the gradient reported in published literature between LRR and the disease-free state, to patients with LRR in our dataset.[12] For lung cancer and cardiotoxicity, utility scores as available from the published Indian literature were used (Supplementary file: Table S1).

Costing

We included both health system cost and patient level OOP payments for radiotherapy, management of recurrence, complications, and follow-up costs. The health system cost of radiotherapy included the initial cost of out-patient department (OPD) consultation, baseline diagnostics, followed by planning and delivery of radiotherapy. OOP payments constituted expenses incurred on transport, boarding/lodging, food, etc., during the course of radiotherapy (Supplementary file: Table S2). The cost of OPD consultation, planning and delivery cost (per session) with the 3 radiotherapy techniques was assessed from a previous study undertaken in a large tertiary-care public sector hospital in north India.[26] The estimates for OOP expenditure, separately for each of the three modalities, have been obtained from the primary data collected under the CaDCQoL study.[25]

The cost of managing patients in LRR or a metastatic health state included the cost of OPD consultation, routine diagnostic/radiologic tests and the cost of therapeutic procedures in the form of surgery, radiotherapy, chemotherapy or hormone therapy. The data on proportion of patients requiring either or a combination of therapeutic interventions was as per the Indian Council of Medical Research (ICMR) cancer registry.[27] The cost of management of acute and late toxicities following radiotherapy was as per the standard treatment guidelines (STG).[28] Specifically, for the management of each of the late toxicities, i.e., lung cancer, cardiotoxicity and contralateral breast cancer, the treatment cost included the cost of medical management, surgery, radiation, chemotherapy or a combination of these therapeutic interventions (based on information from STGs). In addition to the costs associated with radiotherapy and treatment of its recurrence/toxicities, the annual cost of management and follow-up for patients was also incorporated. This included the annual OPD consultation cost, cost of diagnostics, hormone therapy for patients in the DFS/LRR state and cost of palliative/supportive care for patients in metastatic state.

The unit costs of diagnostic and therapeutic procedures were obtained from the locally published studies.[17] Wherever, such data was not available, the public procurement rates listed under the various state medical service corporations[29–31] or the provider payment rates of the national insurance schemes (AB PM-JAY and CGHS) were utilized.[32] All the costs reported in the study pertain to the year 2021 and are reported in United States Dollar (US$) as per conversion rate for year 2021 i.e., 1 US $ = 72.16 Indian Rupees.[33] The cost estimates that were assessed from previous studies were inflated to the year 2021 using GDP deflators.

Sensitivity analysis

We undertook a probabilistic sensitivity analysis (PSA) to account for the impact of joint parameter uncertainty. Using Monte Carlo method results were simulated 1000 times and median estimates along with 2.5th and 97.5th percentile were estimated. A one-time per-capita Gross Domestic Product (GDP) value for India of INR145,679 (USD 1962) for the year 2020–21 was used as the threshold for cost-effectiveness.[16] This implies that interventions which incur an incremental cost of less than INR145,679 (USD 1962) per QALY gained will be considered cost-effective.

Different studies report varied estimates of mean and maximum doses delivered to heart with 3D-CRT and IMRT, where, maximum heart dose is more with 3D-CRT when compared to IMRT and mean heart dose delivered is more with IMRT compared to 3D-CRT.[34,35] Since, the organ dose directly translates into the incidence of late toxicity which develops with each radiotherapy technique and given the uncertainty reported in literature, a scenario analysis was done to examine the impact on cost-effectiveness when using maximum doses.

Secondly, the studies which reported on long-term effectiveness of PMRT were initiated during the early 2000s, following which there has been substantial improvement in systemic treatment including chemotherapy, targeted therapy and hormone therapy. As a result, it could be argued that additional improvements with radiotherapy following current, more effective systemic therapy could be less than what has been observed in the published studies. In order to test the same, we undertook a scenario wherein we computed ICER values at various levels of reduced effectiveness of radiotherapy (in terms of LRR) in comparison to disease specific systemic therapy which includes chemotherapy/ hormone therapy or HER2 targeted therapy.

Thirdly, recently published studies suggest that there has been a shift in the mean age of presentation of breast cancer which is ten years earlier than the western population.[36] Therefore, we assumed the mean age of presentation as 50 years. However, in view of the prevailing debate that some cases present around 40–45 years of age, we did a scenario analysis to run our model with the mean age of presentation as 40 years.

We have also filled out the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) Statement for our analysis and reported in the Supplementary File as Table S6.[37]

Role of funding source

The funding to collect primary data for the study was provided by Department of Health Research, Ministry of Health and Family Welfare, New Delhi, wide letter number F. No. T.11011/02/2017-HR/3100291. The funders had no role in the design, data collection, analysis, and interpretation, or preparation of this manuscript.

Results

The absolute and incremental outcomes along with the results of cost-effectiveness have been summarised below as the median values along with their 95% confidence intervals.

Absolute outcomes

The absolute number of QALYs lived by a patient who had mastectomy for left-sided breast cancer varied from 7.46 (6.42–8.19) to 11.48 (9.87 –12.53) and incurred a lifetime cost ranging from USD 856 (790–924) to USD 3021 (2793–3298) depending upon the nodal status as well as the type of radiotherapy received (Table 1). Similarly, a woman following mastectomy for right-sided breast cancer lived a total of 7.46 (6.52–8.18) to 11.46 (10.03–12.43) QALYs at a lifetime cost of USD 855 (790–923) to 3020 (2785–3274) based on the nodal status and the type of radiotherapy treatment (Table 1).

Incremental outcomes

Use of 2DRT when compared to no radiotherapy for the management of a patient with left breast cancer results in a gain of 0.23 (0.07–0.39) and 0.19 (0.10–0.27) QALYs for N1-3 and N4+ nodal subgroups respectively. For the same scenario, treating the patients with 1-3+ nodes results in cost saving of USD 62 (-168–47) whereas it an additional USD 213 (137–286) incurred for N4+ subgroup when compared to no radiotherapy (Supplementary file: Table S3). Similarly, for patients with left sided breast cancer treated with 3D-CRT in comparison to 2DRT, results in incremental gains of 0.09 (0.04–0.14) and 0.04 (0.02–0.07) QALYs for N1-3 and N4+ nodal subgroups respectively. Overall, for both N1-3 and N4+ subgroups in this scenario, additional costs are incurred in the range of USD 464 to 821 (Supplementary File: Table S3). Further, for a patient following mastectomy of right breast, different radiotherapy techniques yield incremental outcomes which were similar to those reported for the left breast (Supplementary File: Table S3).

Cost-effectiveness

Among women with node negative disease, no radiotherapy/disease specific systemic therapy (including chemotherapy/hormone therapy or HER2 targeted therapy) had lesser costs and higher health benefits than some of the other radiotherapeutic scenarios (Tables 2 and 3). As a result, alternate radiotherapeutic scenarios are excluded from treatment options and systemic therapy alone was the most efficient strategy, at a threshold of one-time GDP per capita. Similarly, for women in the node status of N1-3 and N4+ with either left or right breast, a 5-week conventional regimen of 2DRT and 3D-CRT, as well as both 3 and 5-week regimens of IMRT, were dominated by the hypofractionated regimen of 2DRT and 3D-CRT. However, at a threshold of GDP per capita, 2DRT is the most preferred strategy and results in cost savings.

Further, cost-effectiveness acceptability curves shows that there is 100% and 99% probability of hypofractioned 2-DRT to be cost-effective as compared to no radiotherapy for women in either N1-3 and N4+ positive nodal status respectively (Supplementary file: Figure S1-4). We also did a price sensitivity analysis to assess the optimal cost for delivering 3D-CRT wherein it becomes cost-effective. We estimated that cost of planning and delivering 3D-CRT needs to be brought down by at least 50% to make it cost-effective (Supplementary File: Figure S7) (Figure 1).

We also found that even if the reduction in the 10-year locoregional recurrence risk with radiotherapy, among breast cancer patients 1–3 lymph nodes positive and patients with 4 or more lymph nodes positive is 40% and 60% less respectively than what has been reported in the efficacy trial,[4] PMRT remains a cost-

		50Gy in 25 fractions over 5 weeks			42.5Gy in 16 fractions over 3 weeks		
Node status		**Life Years (95% CI)**	**QALYs (95% CI)**	**Cost (95% CI) In USD**	**Life Years (95% CI)**	**QALYs (95% CI)**	**Cost (95% CI)In USD**
LEFT BREAST							
N0	**IMRT**	13.22 (12.95–13.5)	11.36 (9.89–12.34)	2573 (2366–2824)	13.22 (12.95–13.5)	11.36 (9.89–12.34)	2102 (1941–2274)
	3D-CRT	13.33 (13.04–13.6)	11.46 (9.99–12.43)	2221 (2049–2414)	13.33 (13.04–13.6)	11.46 (9.99–12.43)	1862 (1722–2010)
	2DRT	13.21 (12.94–13.48)	11.34 (9.83–12.32)	1583 (1481–1691)	13.21 (12.94–13.48)	11.34 (9.83–12.32)	1367 (1281–1451)
	No RT	13.34 (13.05–13.63)	11.48 (9.87–12.53)	856 (790–924)	13.34 (13.05–13.63)	11.48 (9.87–12.53)	856 (790–924)
N1-3	**IMRT**	12.15 (11.78– 12.49)	10.4 (9.11–11.29)	2736 (2522– 3002)	12.15 (11.78–12.49)	10.4 (9.11–11.29)	2259 (2093–2438)
	3D-CRT	12.24 (11.86–12.58)	10.47 (9.16–11.36)	2384 (2209– 2578)	12.24 (11.86–12.58)	10.47 (9.16–11.36)	2023 (1889–2177)
	2DRT	12.14 (11.81– 12.48)	10.37 (9.04– 11.29)	1741 (1635–1853)	12.14 (11.81–12.48)	10.37 (9.04–11.29)	1525 (1433–1617)
	No RT	11.95 (11.58– 12.31)	10.16 (8.86–10.98)	1585 (1472–1708)	11.95 (11.58–12.31)	10.16 (8.86– 10.98)	1585 (1472–1708)
N4+	**IMRT**	9.05 (8.62–9.53)	7.66 (6.69– 8.37)	3021 (2793– 3298)	9.05 (8.62– 9.53)	7.66 (6.69–8.37)	2545 (2376–2736)
	3D-CRT	9.09 (8.66– 9.58)	7.69 (6.72– 8.41)	2673 (2482–2873)	9.09 (8.66– 9.58)	7.69 (6.72–8.41)	2314 (2163– 2479)
	2DRT	9.06 (8.59–9.54)	7.64 (6.64–8.37)	2024 (1907– 2158)	9.06 (8.59–9.54)	7.64 (6.64–8.37)	1806 (1704–1914)
	No RT	8.88 (8.43–9.34)	7.46 (6.42–8.19)	1596 (1492–1704)	8.88 (8.43–9.34)	7.46 (6.42–8.19)	1596 (1492–1704)
RIGHT BREAST							
N0	**IMRT**	13.23 (12.93–13.5)	11.36 (9.97–12.32)	2575 (2339–2825)	13.23 (12.93–13.5)	11.36 (9.97–12.32)	2105 (1938–2286)
	3D-CRT	13.33 (13.04–13.6)	11.46 (10.03–12.43)	2216 (2039–2410)	13.33 (13.04–13.6)	11.46 (10.03–12.43)	1861 (1722– 2016)
	2DRT	13.21 (12.93– 13.47)	11.34 (9.91–12.34)	1583 (1478–1699)	13.21 (12.93–13.47)	11.34 (9.91–12.34)	1364 (1286–1452)
	No RT	13.34 (13.05– 13.63)	11.48 (9.87–12.53)	856 (790–924)	13.34 (13.05–13.63)	11.48 (9.87–12.53)	856 (790–924)
N1-3	**IMRT**	12.14 (11.78–12.48)	10.39 (9.06–11.29)	2733 (2508– 2987)	12.14 (11.78–12.48)	10.39 (9.06–11.29)	2264 (2092–2451)
	3D-CRT	12.22 (11.84–12.56)	10.46 (9.14–11.37)	2379 (2194– 2561)	12.22 (11.84–12.56)	10.46 (9.14–11.37)	2024 (1879–2170)
	2DRT	12.13 (11.78–12.5)	10.38 (9.04–11.33)	1741 (1635– 1858)	12.13 (11.78–12.5)	10.38 (9.04–11.33)	1523 (1437–1618)
	No RT	11.95 (11.58–12.31)	10.16 (8.86–10.98)	1585 (1472– 1708)	11.95 (11.58–12.31)	10.16 (8.86–10.98)	1585 (1472–1708)
N4+	**IMRT**	9.05 (8.6–9.52)	7.64 (6.67–8.45)	3020 (2785–3274)	9.05 (8.6–9.52)	7.64 (6.67–8.45)	2551 (2377–2743)
	3D-CRT	9.09 (8.63– 9.55)	7.67 (6.7–8.49)	2665 (2474–2869)	9.09 (8.63–9.55)	7.67 (6.7–8.49)	2312 (2152–2479)
	2DRT	9.07 (8.59–9.52)	7.66 (6.73–8.41)	2022 (1903–2158)	9.07 (8.59–9.52)	7.66 (6.73–8.41)	1805 (1705–1915)
	No RT	8.88 (8.43– 9.34)	7.46 (6.42–8.19)	1596 (1492–1704)	8.88 (8.43–9.34)	7.46 (6.42–8.19)	1596 (1492–1704)

***Table 1*: Lifetime health outcomes gained and costs incurred with each radiotherapy technique and with no radiation therapy.**
RT: Radiotherapy, 2DRT: Two-dimensional radiotherapy, 3D-CRT: Three-dimensional conformal radiotherapy, IMRT: Intensity modulated radiotherapy, N0: Node negative disease, N1-3: One to three positive nodes, N4+: Four or more positive nodes, QALY: Quality adjusted life years, CI: Confidence Interval.

	Left Breast					Right Breast				
Node status	Intervention	Costs	QALYs	ICER (USD)		Intervention	Costs	QALYs	ICER (USD)	
N0	No radiotherapy	855	11.38		ND	No radiotherapy	855	11.38		ND
	2-DRT (3 weeks)	1365	11.26		D	2-DRT (3 weeks)	1364	11.26		D
	2-DRT (5 weeks)	1585	11.26		D	2-DRT (5 weeks)	1584	11.26		D
	3D-CRT (3 weeks)	1863	11.37		D	3D-CRT (3 weeks)	1862	11.37		D
	IMRT (3 weeks)	2104	11.27		D	IMRT (3 weeks)	2103	11.28		D
	3D-CRT (5 weeks)	2219	11.37		D	3D-CRT (5 weeks)	2218	11.37		D
	IMRT (5 weeks)	2583	11.27		D	IMRT (5 weeks)	2582	11.28		D
N1-3	2-DRT (3 weeks)	1523	10.30		ND	2-DRT (3 weeks)	1522	10.30		ND
	3D-CRT (3 weeks)	2025	10.39	5630	ND	3D-CRT (3 weeks)	2024	10.39	5628	ND
	No radiotherapy	1586	10.07		D	No radiotherapy	1586	10.07		D
	2-DRT (5 weeks)	1743	10.30		D	2-DRT (5 weeks)	1742	10.30		D
	IMRT (3 weeks)	2264	10.32		D	IMRT (3 weeks)	2263	10.32		D
	3D-CRT (5 weeks)	2381	10.39		D	3D-CRT (5 weeks)	2381	10.39		D
	IMRT (5 weeks)	2743	10.32		D	IMRT (5 weeks)	2742	10.32		D
N4+	No radiotherapy	1590	7.41		ND	No radiotherapy	1590	7.41		ND
	2-DRT (3 weeks)	1803	7.60	1133	ND	2-DRT (3 weeks)	1803	7.60	1127	ND
	3D-CRT (3 weeks)	2312	7.64	12,170	ND	3D-CRT (3 weeks)	2311	7.64	12,168	ND
	2-DRT (5 weeks)	2023	7.60		D	2-DRT (5 weeks)	2023	7.60		D
	IMRT (3 weeks)	2549	7.60		D	IMRT (3 weeks)	2548	7.60		D
	3D-CRT (5 weeks)	2669	7.64		D	3D-CRT (5 weeks)	2668	7.64		D
	IMRT (5 weeks)	3028	7.60		D	IMRT (5 weeks)	3027	7.60		D

***Table 2*: Cost-effectiveness of radiotherapy techniques.**
Note: All costs in US Dollars.
The figures reported in Table 2 do not exactly match those reported in Table 1. This is because Table 1 presents the result of probabilistic sensitivity analysis (PSA) whereas Table 2 represents the results of dominance analysis which is based on the deterministic results. However, the figures reported in Table 2 fall within the confidence interval generated by PSA presented in Table 1.
RT: Radiotherapy, 2DRT: Two-dimensional radiotherapy, 3D-CRT: Three-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, N0: Node negative disease, N1-3: One to three positive nodes, N4+: Four or more positive nodes, QALY: Quality adjusted life years, ICER: Incremental cost-effectiveness ratios, D: Dominated, ND: Non-Dominated.

	Left Breast		Right Breast	
	50Gy in 25 fractions over 5 weeks	42.5Gy in 16 fractions over 3 weeks	50Gy in 25 fractions over 5 weeks	42.5Gy in 16 fractions over 3 weeks
Node status: N0				
IMRT Vs 3D-CRT[a]	−3822 (−10,411 −534)	−2527 (−6791 −512)	−3895 (−10,736 −910)	−2573 (−7577 −493)
3D-CRT Vs 2DRT	5829 (3307 − 12,577)	4485 (2612−9184)	5857 (3372−12,531)	4524 (2583−9363)
2DRT Vs No RT[b]	−6023 (−11,684 −3901)	−4143 (−7436 −2761)	−6086 (−10,867 −4082)	−4282 (−8070 −2713)
Node status: N1-3				
IMRT Vs 3D-CRT[a]	−4654 (−12,148 −628)	−3085 (−8354 −593)	−4773 (−13,354 −1055)	−3115 (−9142 −569)
3D-CRT Vs 2DRT	7193 (4114−15,229)	5558 (3256−11,359)	7173 (4127−15,389)	5620 (3221−11,664)
2DRT Vs No RT	664 (112−2208)	−259 (−1190 −260)	651 (89−2507)	−267 (−1175 −202)
Node status: N4+				
IMRT Vs 3D-CRT[a]	−9721 (−25,593 −1310)	−6473 (−16,522 −1196)	−10,059 (−28,708 −2234)	−6597 (−19,739 −1155)
3D-CRT Vs 2DRT	15,502 (8719−32,370)	11,947 (6938−25,034)	15,675 (9130−33,563)	12,062 (6972−24,569)
2DRT Vs No RT	2317 (1403−4235)	1121 (565−2385)	2302 (1381−4433)	1144 (539−2447)

***Table 3*: Incremental costs per quality-adjusted life year gained (QALY) for different radiotherapy techniques (in USD).**
[a] The negative sign in the incremental cost-effectiveness ratio (ICER) values imply that giving 3D-CRT provides more benefits (QALYs) than IMRT, i.e, the net incremental gains are negative when IMRT is compared over 3D-CRT. However, IMRT costs more than 3D-CRT.
[b] The negative sign in the incremental cost-effectiveness ratio (ICER) values imply that giving No radiotherapy yields more QALYs that 2DRT for N0 subgroup, i.e, the net incremental gains are negative when 2DRT is compared over No radiotherapy.
RT: Radiotherapy, 2DRT: Two-dimensional radiotherapy, 3D-CRT: Three-dimensional conformal radiotherapy, IMRT: Intensity modulated radiotherapy, N0: Node negative disease, N1-3: One to three positive nodes, N4+: Four or more positive nodes, QALY: Quality adjusted life years.

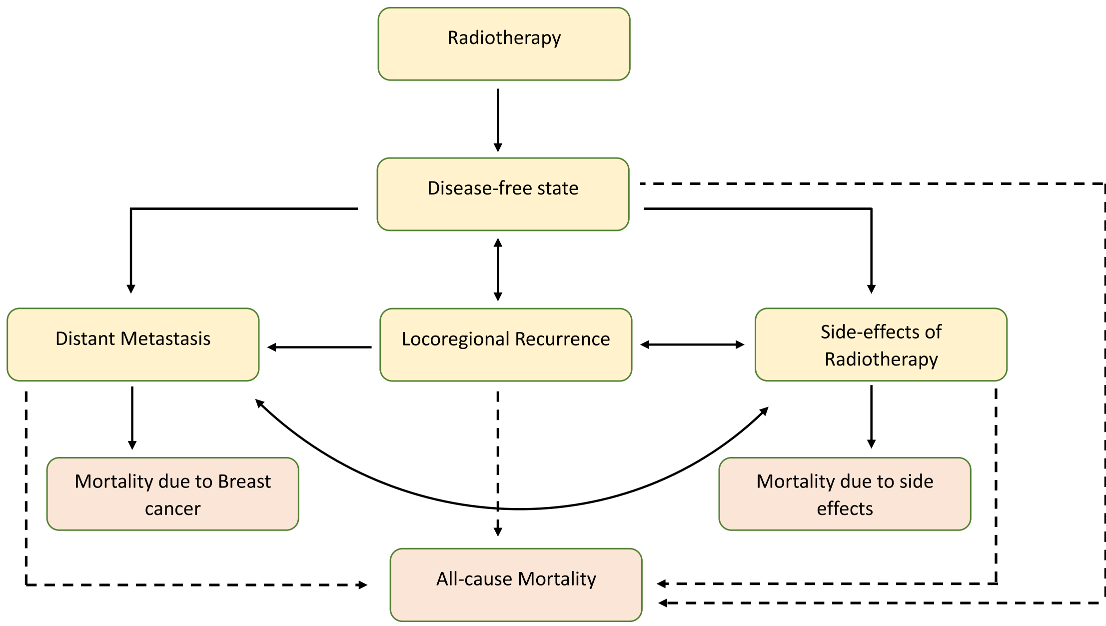

Figure 1. Markov state transition model for breast cancer.

effective option for treatment. Secondly, even when using incidence of heart toxicity corresponding to maximum heart dose instead of mean dose delivered with 3D-CRT and IMRT, there is no change in the results of cost-effectiveness, i.e., 3D-CRT yields better outcomes in lesser costs when compared with IMRT.

Thirdly, even when using the mean age of presentation of breast cancer as 40 years instead of 50 years, the lifetime incidence of developing cardiac toxicity increases from 1.65% to 2.51% with 2DRT and from 1.59% to 2.44% with 3D-CRT. Similarly, the lifetime incidence of developing lung cancer increases from 1.37% to 2.18% with 2DRT and from 0.88% to 1.34% with 3D-CRT. However, the findings of the analysis do not report any change in the direction of results and PMRT remains cost-effective in node-positive patients, rather, the cost savings increase for N1-3 group and N4+ group.

Model validation

We estimated that women with node-negative disease have a 10-year survival of 73%. Similarly, those with 1−3 positive lymph nodes and 4 or more positive lymph nodes have a 10-year survival of 65% and 42% respectively. Our findings are consistent with stage-specific survival data from Indian population which report an overall 10-year estimated survival of 75% for stage I, 55% for stage II, 35% for stage III, and 5% for stage IV patients. The survival curves have been reported in supplementary file: Figure S5. Secondly, our model findings are consistent with the findings of the EBCTCG 2005 report, which reports that for every 4.7 locoregional recurrences averted by radiation, one breast cancer mortality is prevented at 15 years.[38]

Discussion

Overall, we found that postmastectomy radiotherapy is cost-effective in patients with node-positive breast cancer. Among the different techniques, both 2-DRT and 3D-CRT are the preferred strategies for treatment given over a duration of 3 weeks (42.5 Gy in 16 fractions), however, 2DRT was the most cost-effective option given a threshold of GDP per capita. However, the use of 3D-CRT is the preferred approach when MHD >1 cm, CLD > 2.5-3 cm, inter-field separation >18 cm, irregular chest wall contours and hypofractionation schedules requiring RNI. For node-negative disease, disease-specific systemic therapy which may include chemotherapy/ hormone therapy or HER2-targeted therapy, remains the preferred strategy over radiotherapy.

We used the EBCTCG meta-analysis findings to value consequences in our model-based analysis. However, there are certain limitations of this meta-analysis. Firstly, it includes relatively old trials when systemic therapy was inadequate and less effective. Drugs like anthracyclines, taxanes, HER2-targeted therapy, aromatase inhibitors were not used. Similarly, axillary dissection and histopathology reporting probably may not match current standards. The staging system has also undergone many changes since then. Hence the benefits shown by PMRT may not be as high in the current scenario with more effective systemic therapy, which decreases both LRR and systemic metastasis. To test this model assumption, we lowered the effectiveness of PMRT in our sensitivity analysis. Even if we reduce our base assumption of reduction in risk of LRR following radiotherapy by 40% and 60% among those with patients with 1–3 nodes positive and 4-or-more nodes positive respectively, PMRT remains to be cost-effective. This implies that our findings are robust to the uncertainties in nature of evidence available.

According to our model, there is an incremental gain in the range of 0.16–0.39 QALYs per woman with node-positive breast cancer. These findings are like other studies which demonstrate a QALY gain ranging from 0.19 to 0.76.[10,12,13,39] In terms of ICER, our findings are consistent with other studies in different settings. Wan et al. reports that PMRT for patients with 1–3 node involvement is cost-effective in China, however, uncertainty of PMRT being cost-effective are relatively greater for patients with pN4+.[12] Xie and colleagues report that PMRT with advanced techniques like IMRT are cost-effective at a willingness to pay of $100,000, however, none of the advanced radiotherapy techniques are cost-effective at $50,000.[13] Similar to findings of this study, our model also reports that IMRT is not cost-effective at our threshold of USD 1962.

Five-year breast cancer-specific survival for locally advanced disease is 78–90%.[40] In these patients with long survival, PMRT is associated with cardiotoxicity, as well as secondary malignancy in the lung and contralateral breast. In a study by Darby et al. rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy (95% confidence interval, 2.9 to 14.5).[19] According to the study, for a 50 year woman with no prior cardiac risk factors, a mean dose of 3 Gy to the heart, increased her absolute risk of a cardiac event by 0.9% and death from ischemic heart disease (IHD) by 0.5% before the age of 80 years.

With modern radiotherapy planning and targets, most studies report that the heart receives 1–5 Gy (majority receiving less than 3Gy), hence it is unlikely that radiation will significantly contribute to cardiotoxicity.[7] Also, it remains unclear whether the mean or maximum heart dose is to be considered more appropriate to assess the impact of radiation on cardiac events. In our model, the lifetime risk of developing cardiotoxicity at mean dose with 1–3 positive nodes receiving treatment with 2-DRT is 1.65%, which is marginally reduced to 1.59% with 3D-CRT. Considering the maximum dose delivered, the lifetime incidence of cardiac toxicity is 1.52% with 3D-CRT and 1.48% with IMRT.

Secondly, PMRT causes a marginally increased risk of lung cancer due to the incidental lung irradiation. For a 50-year-old non-smoker, a 5Gy whole lung dose would increase lung cancer mortality before the age of 80 years by 0.3%, while for smokers this increase in lung cancer mortality will be 4.4%.[7] In our analysis, only 1 in 1000 women with 1–3 positive lymph nodes was estimated to develop lung cancer, whereas, there is an overall reduction of 9.7% in mortality due to breast cancer with PMRT. Hence, the health benefits of PMRT outweigh the risk of developing long-term complications like lung cancer.

Thirdly, various studies have shown that the risk of contralateral breast cancer with and without radiation is around 5%. The contralateral breast cancer rate at 10 year was 5.4% for mastectomy only and 5.1% in the mastectomy plus radiotherapy group.[3] We also estimated a very similar lifetime risk of developing contralateral breast cancer to be 4.52% and 5.24% in the mastectomy only and mastectomy plus radiotherapy group respectively.

2D and 3D conformal radiation are the most commonly used radiation techniques in India. IMRT is considered when heart or lung volume constraints are not met, especially for a left sided tumour.[34] All these modern radiotherapy techniques come at an added cost. In our analysis, though both 3D-CRT and IMRT generate additional QALYs when compared to 2DRT, however they were not found to be cost-effective when compared to 2D radiation therapy, for both left sided and right sided breast tumours. The incremental cost of gaining one QALY with IMRT is 19 times the GDP per capital of India, which is the threshold for considering an intervention as cost-effective. Hence, it is not considered as real value for money.

We acknowledge that CT based planning has entirely changed the breast cancer treatment practices.[28] However, resource-constrained settings such as India, treatment with 2-DRT is practiced widely. Currently, India has a total of approximately 545 teletherapy machines, of which 33% are telecobalt units, while the rest are medical accelerators. Further, of the 90 simulators available, 36% are X-ray simulators, and the rest are CT simulators.[41] The dose constraints for this 2D planning by X-ray based simulators are met by assessing the CLD and MHD.

Provision of advanced radiotherapy techniques for all cancer patients would need significant additional resources to be incurred on infrastructure, human resource, equipment and others. As a result, decisions for public financing of cancer care will require priority setting based on explicit criteria. Three important criteria listed by the Indian Government for consideration of health care interventions for public financing include – value for money, extent to which these reduce out-of-pocket expenditure, and finally their impact on improving equity of healthcare utilization.[42,43] Our conclusions for recommendations of therapy are based on the efficiency argument, i.e. the incremental cost per unit gain in health consequences, and whether it represents a value for money.

However, we do acknowledge the clinical effectiveness of CT based planning. The use of 3D-CRT should be the preferred approach when MHD >1 cm, irregular chest wall contour and inter-field separation >18 cm. In addition, in practice for patients with CLD >2.5–3 cm and RNI using hypofractionation, CT based planning should be preferred. These clinical decision rules are also currently practiced and have been recommended by the National Cancer Grid (NCG) guidelines in India.[41,44]

Hypofractionation has been extensively used and established as the standard of care after breast conservative surgery.[45] However, its use for PMRT has been limited. A recent meta-analysis showed that hypofractionated radiotherapy (39–48.3 Gy over 13–17 fractions) for PMRT has high control rates in terms of local control rate and survival and is associated with low acute and late toxicity, comparable to conventional fractionation (50 Gy over 25 fractions).(9) Hypofractionation for breast cancer has also been reported to reduce the cost of treatment by 31.7% and 33% in the United States and Asia respectively.[46,47] In our analysis, PMRT for 1–3 lymph node subgroup becomes cost saving when hypofractionation is used, while it becomes even more cost-effective for the 4-or-more lymph node positive subgroup.

Our study has several strengths – firstly, we present a comprehensive analysis on PMRT which factors in several variables including nodal burden, laterality of the breast involved, duration and dose of radiation therapy, as well as different techniques of radiotherapy. Secondly, most studies conducted in the same domain analyse the outcomes of breast cancer for a 15-year time horizon.[10,12,13] We have used a lifetime horizon, which appears to be more suitable given the longer survival seen in patients with breast cancer. Thirdly, most of the previous studies have considered only direct medical costs of treatment. Given the repetitive nature of treatment, it is important to account for direct non-medical costs as well. In our country, the care for cancer treatments is available at sentinel facilities and thus provision of such care is not too decentralised. Therefore, such expenditures related to travel, food and accommodation contribute significantly to the total cost of care. It is also reported that, direct non-medical expenditures account for more than 60% of the total direct expenditure on cancer radiotherapy in India.[48] Finally, the data on out of pocket expenditure and QOL of different states of breast cancer was assessed from India's national database–CaDCQoL, making our conclusions more reliable.[25]

A potential limitation of our study is that we did not consider other risk factors like tumour size, lympho-vascular invasion, margin status, receptor status and age when evaluating the benefit of PMRT. This is especially important for the node-negative and 1–3 lymph node positive subgroups. However, there is no robust data available for these scenarios at present and future prospective trials will bring more clarity to this group with heterogeneous practice. Secondly, the valuation of the health system cost was based on the costing in public sector hospital. We acknowledge that the costs may vary significantly in private sector hospitals, as there is significant heterogeneity in private sector. However, we believe that the cost of oncology services may differ little between public and private sector as these are specialized services with adherence to set guidelines. Moreover, the prices for health benefit packages under India's large national insurance scheme are also set considering the costs determined in public sector tertiary care hospitals.[49]

Conclusion

In light of current evidence, adjuvant radiotherapy remains a cost-effective modality for all node-positive patients with breast cancer after mastectomy. In resource-limited settings like India, it is not feasible to treat high volumes of patients using the 3D technique in public set up. However, a practical approach is to consider 3D-CRT for limited indications in patients where ideal constraints cannot be met with 2DRT. Long-term survival data from recent trials with the use of systemic therapy including taxanes, anthracyclines, HER2-targeted therapies and hormone therapy with aromatase inhibitors will provide more evidence about the effectiveness and cost-effectiveness of radiotherapy in patients with 1–3 metastatic lymph nodes which could be used to update this analysis.

Contributors

Conception of study design: NG, SP. Acquisition of data: NG, YC, ASC. Development of model: YC, ASC, SP. Interpretation of results: NG, SP, CSP, YC, ASC. Writing first draft of manuscript: YC, NG, ASC. Critical inputs for revision of the manuscript: CSP, SP. NG and YC contributed equally to this work.

Data sharing statement

All the information pertaining to the article has been given in the main text and supplementary files.

Declaration of interests

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lansea.2022.100043.

References

1 Latest statistics of breast cancer in India 2020 | breast cancer India. Breastcancerindia.net. 2021. Available from: https://www.breastcancerindia.net/statistics/latest_statistics_breast_cancer_india.html. [cited 22 July 2021].
2 Ramani PA, Niharika VS, Lakhsmi BK, Jahnavi S, Reddy GV. Incidence of locally advanced breast cancer in women presenting to a tertiary care center. *Int Surg J*. 2019;6(10):3626–3631.
3 Yadav BS, Sharma SC, Patel FD, Ghoshal S, Kapoor RK. Second primary in the contralateral breast after treatment of breast cancer. *Radiother Oncol*. 2008;86:171–176.
4 McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet (London, England)*. 2014;383(9935).
5 Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves locoregional control and survival for selected patients with locally advanced breast cancertreated with neoadjuvant chemotherapy and mastectomy. *L Clin Oncol*. 2004;22:4691–4699.
6 Zeidan YH, Habib JG, Ameye L, et al. Postmastectomy radiation therapy in women with T1-T2 tumors and 1 to 3 positive lymph nodes: analysis of the breast international group 02-98 trial. *Int J Radiat Oncol Biol Phys*. 2018;101(2):316–324.
7 Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol*. 2017;35(15):1641.
8 Liu L, Yang Y, Guo Q, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. *Radiat Oncol*. 2020;15(1):1–5.
9 Dunscombe P, Samant R, Roberts G. A cost outcome analysis of adjuvant postmastectomy locoregional radiotherapy in premenopausal node positive breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2000;48(4):977–982.
10 Lee JH, Glick HA, Hayman JA, Solin LJ. Decision analytic model and cost effectiveness evaluation of paostmastectomy radiation therapy in high risk premenopausal breast cancer patients. *J Clin Oncol*. 2002;20(11):2713–2725. https://doi.org/10.1200/JCO.2002.07.008.
11 Marks LB, Hardenbergh PH, Winer ET, Prosnitz LR. Assessing the cost effectiveness of postmastectomy radiation therapy. *Int J Radiat Oncol Biol Phys*. 1999;44(1):91–98.
12 Wan X, Peng L, Ma J, Chen G, Li Y. Subgroup economic evaluation of radiotherapy for breast cancer after mastectomy. *Clin Ther*. 2015;37(11):2515–2526.
13 Xie Y, Guo B, Zhang R. Cost-effectiveness analysis of advanced radiotherapy techniques for post-mastectomy breast cancer patients. *Cost Eff Res Alloc*. 2020;18(1):1–7.
14 Kong FM, Klein EE, Bradley JD, et al. The impact of central lung distance, maximal heart distance, and radiation technique on the volumetric dose of the lung and heart for intact breast radiation. *Int J Radiat Oncol Biol Phys*. 2002;54(3):963–971.
15 Tan-Torres Edejer T, Baltussen R, Adam T. *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*. Geneva: World Health Organization; 2003.
16 Department of Health Research. *Health Technology Assessment in India*. New Delhi: Ministry of Health & Family Welfare, Government of India; 2018.
17 Gupta N, Verma RK, Gupta S, Prinja S. Cost effectiveness of trastuzumab for management of breast cancer in India. *JCO Global Oncol*. 2020;6:205–216.
18 Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five national surgical adjuvant breast and bowel project node-positive adjuvant breast cancer trials. *J Clin Oncol*. 2006;24(13):2028–2037.
19 Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987–998.
20 Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol*. 2013;31(36):4488–4495.
21 Aras S, İkizceli T, Aktan M. Dosimetric comparison of three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy techniques (IMRT) with radiotherapy dose simulations for left-sided mastectomy patients. *Eur J Breast Health*. 2019;15(2):85.
22 Boice Jr JD, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med*. 1992;326(12):781–785.
23 Agarwal G, Ramakant P. Breast cancer care in India: the current scenario and the challenges for the future. *Breast Care*. 2008;3(1):21–27.
24 Office of the Registrar General & Census Commissioner India: SRS Statistical Report 2015. Available from: http://www.censusindia.gov.in/vital_statistics/SRS_Reports_2015.html.
25 Prinja S, Dixit J, Gupta N, et al. Development of National Cancer Database for Cost and Quality of Life (CaDCQoL) in India: a protocol. *BMJ Open*. 2021;11(7):e048513.
26 Chauhan AS, Prinja S, Ghoshal S, Verma R, Oinam AS. Cost of treatment for head and neck cancer in India. *PLoS One*. 2018;13(1):e0191132.
27 National centre for disease informatics and research: consolidated report of hospital based cancer registries 2007−2011. Available from: https://icmr.nic.in/sites/default/files/reports/Preliminary_Pages_0.pdf. [cited 13 August 2021].
28 National comprehensive cancer network: NCCN clinical practice guidelines in oncology 2019. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. [cited 13 August 2021].
29 Tamil Nadu Medical Services, Government of Tamil Nadu: essential drug list. Available from: https://www.tnmsc.tn.gov.in/user_pages/drugtender.php?drugcat=T18028.
30 Bureau of Pharma PSUs of India (BPPI), Government of India. Janaushadhi.gov.in. 2021. Available from: http://janaushadhi.gov.in/ProductList.aspx. [cited 22 June 2021].
31 Rajasthan Medical Service Corporation. Drugs, surgical and sutures. Rmsc.health.rajasthan.gov.in. 2021. Available from: http://www.rmsc.health.rajasthan.gov.in/content/raj/medical/rajasthan-medical-services-corporation-ltd-/en/Approved-Rate-Lists/DrugsRC.html#. [cited 22 June 2021].
32 India M. CGHS rate list - CGHS: Central Government Health Scheme. Cghs.gov.in. 2021. Available from: https://cghs.gov.in/index1.php?lang=1&level=3&sublinkid=5948&lid=3881. [cited 22 June 2021].
33 USD to INR | Convert 1 US Dollar to Indian Rupees | Xe. Xe.com. 2021 Available from: https://www.xe.com/currencyconverter/convert/?Amount=1&From=USD&To=INR. [cited 23 June 2021].
34 Aras S, İkizceli T, Aktan M. Dosimetric comparison of three-dimensional Conformal Radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy Techniques (IMRT) with radiotherapy dose simulations for left-sided mastectomy patients. *Eur J Breast Health*. 2019;15(2):85–89.
35 Xie X, Ouyang S, Wang H, et al. Dosimetric comparison of left-sided whole breast irradiation with 3D-CRT, IP-IMRT and hybrid IMRT. *Oncol Rep*. 2014;31(5):2195–2205.
36 Bhattacharyya GS, Doval DC, Desai CJ, Chaturvedi H, Sharma S, Somashekhar SP. Overview of breast cancer and implications of overtreatment of early-stage breast cancer: an Indian perspective. *JCO Global Oncol*. 2020;6:789–798.
37 Stevens GA, Alkema L, Black RE, et al. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. *PLoS Med*. 2016;13(6):e1002056.
38 Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366(9503):2087–2106.
39 Yang J, Qi SN, Fang H, et al. Cost-effectiveness of postmastectomy hypofractionated radiation therapy vs conventional fractionated radiation therapy for high-risk breast cancer. *Breast*. 2021;58:72–79.
40 Park JH, Anderson WF, Gail MH. Improvements in US breast cancer survival and proportion explained by tumor size and estrogen-receptor status. *J Clin Oncol*. 2015;33(26):2870–2876.
41 Munshi A, Ganesh T, Mohanti BK. Radiotherapy in India: history, current scenario and proposed solutions. *Indian J Cancer*. 2019;56(4):359.
42 Prinja S, Downey LE, Gauba VK, Swaminathan S. Health technology assessment for policy making in India: current scenario and way forward. *PharmacoEconomics-Open*. 2018;2(1):1–3.

43 National Health Authority. *Provider Payments and Price Setting under Ayushman Bharat Pradhan Mantri Jan Arogya Yojana Scheme (Pm-Jay) in India: Improving Efficiency, Acceptability, Quality & Sustainability*. New Delhi: National Health Authority; 2022: p. 51. Available from: https://pmjay.gov.in/sites/default/files/2022-03/AB%20PM-JAY%20Price%20Consultation%20Paper_25.03.2022. pdf.

44 Tata Memorial Centre. *NCG GUIDELINES- 2019 Breast Cancer Management Guidelines*. Mumbai: National Cancer Grid; 2022. Available from: https://tmc.gov.in/ncg/docs/pdf/NCG_Guidelines_ %202019/NCG%20Guidelines%20for%20Breast%20Cancer-2019. pdf.

45 Kim KS, Shin KH, Choi N, Lee SW. Hypofractionated whole breast irradiation: new standard in early breast cancer after breast-conserving surgery. *Radiat Oncol J*. 2016;34(2):81.

46 Greenup RA, Camp MS, Taghian AG, et al. Cost comparison of radiation treatment options after lumpectomy for breast cancer[J]. *Ann Surg Oncol*. 2012;19(10):3275–3281. https://doi.org/10.1245/s10434-012-2546-5.

47 Karasawa K, Kunogi H, Hirai T, et al. Comparison of hypofractionated and conventionally fractionated whole-breast irradiation for early breast cancer patients: a single-institute study of 1,098 patients[J]. *Breast Cancer*. 2014;21(4):402–408. https://doi.org/10.1007/s12282-012-0406-6.

48 Chauhan AS, Prinja S, Ghoshal S, Verma R. Economic burden of head and neck cancer treatment in North India. Asian Pacific journal of cancer prevention. *APJCP*. 2019;20(2):403.

49 Prinja S, Singh MP, Rajsekar K, et al. Translating research to policy: setting provider payment rates for strategic purchasing under India's national publicly financed health insurance scheme. *Appl Health Econ Health Policy*. 2021;19(3):353–370.