review articles

Can the Adoption of Hypofractionation Guidelines Expand Global Radiotherapy Access? An Analysis for Breast and Prostate Radiotherapy

Omoruyi Credit Irabor, MBBS, MPH[1,2]; William Swanson, MS[1,3]; Fiza Shaukat, BS[4]; Johanna Wirtz[1,5]; Abba Aji Mallum, MD[6]; Twalib Ngoma, MD[7]; Ahmed Elzawawy, MD[8]; Paul Nguyen, MD[2]; Luca Incrocci, MD, PhD[9]; and Wilfred Ngwa, PhD[1,2,3]

abstract

PURPOSE The limited radiotherapy resources for global cancer control have resulted in increased interest in developing time- and cost-saving innovations to expand access to those resources. Hypofractionated regimens could minimize cost and increase access for limited-resource countries. In this investigation, we estimated the percentage cost-savings per radiotherapy course and increased radiotherapy access in African countries after adopting hypofractionation for breast and prostate radiotherapy. For perspective, results were compared with high-income countries.

METHODS The cost and course of breast and prostate radiotherapy for conventional and hypofractionated regimens in low-resource facilities were calculated using the Radiotherapy Cost Estimator tool developed by the International Atomic Energy Agency (IAEA) and then compared with another activity-based costing model. The potential maximum cost savings in each country over 7 years for breast and prostate radiotherapy were then estimated using cancer incidence data from the Global Cancer Observatory database with use rates applied. The increase in radiotherapy access was estimated by current national capacities from the IAEA directory.

RESULTS The estimated cost per course of conventional and hypofractionated regimens were US$2,232 and $1,339 for breast treatment, and $3,389 and $1,699 for prostate treatment, respectively. The projected potential maximum cost savings with full hypofractionation implementation were $1.1 billion and $606 million for breast and prostate treatment, respectively. The projected increase of radiotherapy access due to implementing hypofractionation varied between +0.3% to 25% and +0.4% to 36.0% for breast and prostate treatments, respectively.

CONCLUSION This investigation demonstrates that adopting hypofractionated regimens as standard treatment of breast and prostate cancers can result in substantial savings and increase radiotherapy access in developing countries. Given reduced delivery cost and treatment times, we anticipate a substantial increase in radiotherapy access with additional innovations that will allow progressive hypofractionation without compromising quality.

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INTRODUCTION

Breast and prostate cancer are two of the three most common cancers worldwide, each respectively accounting for 11.6% and 7.1% of all cancers in 2018.[1] An analysis of global cancer databases between 1990 and 2016 shows breast cancer as the most common cancer among women in 131 countries and the most common cause of cancer deaths in 112 countries.[2] Prostate cancer was the cancer with the highest incidence for men in 92 countries and the leading cause of cancer deaths for men in 48 countries.[2] The disability adjusted life-years (DALY) and mortality rates from these diagnosed cancers substantially vary across countries and within each country, depending on the degree of the country's economic development.[1]

Resources for planning and implementing evidence-based cancer control programs are not available in most low- and middle-income countries (LMICs).[1] Thus, although breast and prostate cancer incidence increases with higher income levels at all ages, women and men in the poorest countries bear a relatively higher burden of its DALY and deaths.[3,4] The standard management approach for both cancers depends on the tumor grade and risk stratification. In either case, more than half of patients with breast or prostate cancer in LMICs require either curative or palliative radiation therapy (RT).[5,6] The standard treatment approach for early breast cancer in LMICs includes whole-breast irradiation with an additional boost to the tumor site usually delivered after treatment planning, with, minimally, a two-dimensional imaging system.[7] For prostate

Author affiliations and support information (if applicable) appear at the end of this article.

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cancer, the American Urological Association (AUA) guidelines offer active surveillance; radical prostatectomy, with or without pelvic lymphadenectomy; external beam radiotherapy (EBRT); and interstitial RT or brachytherapy for clinically localized disease (ie, T1, T2).[8]

Applying hypofractionated radiotherapy (HRT) requires appropriate equipment, quality assurance, a well-trained staff, and other support systems for RT. Unfortunately, the limited RT resource remains a challenging aspect of cancer management in Africa, where 29 of 54 countries have no RT unit.[9] In countries with RT units, the prohibitive upfront and operational costs of the RT facility often translate in a high cost per treatment course for patients and national financial burden for cancer. The pressure on limited resources and daily cost of traveling also cause a delay in commencement of treatment, interruptions, and low adherence rates to treatment schedules.

Considering these challenges, expanding access requires time- and cost-saving innovations. The development of HRT regimens is an example of such an innovation. Hypofractionation (HF) is the delivery of larger doses of radiation per treatment fraction to complete the full course of treatment over a shorter period compared with the conventional fractionation (CF). HF has been touted as an RT technique with potential to reduce the cost per course relative to CF treatment of various cancers.[10] HF, which demonstrates superior or noninferior outcomes to the CF, could save treatment time and increase the treatment capacity of an LMIC RT facility. Consequently, changes in scheduling fractions accounted for the second largest contribution of cost-effective studies in the field of RT for the past decade.[10]

Multiple prospective and retrospective studies on HF schedule for whole-breast RT (WBRT) reported similar rates of local control, cosmetic outcomes, and concerning morbidities when compared with the CF schedule.[11,12] Several clinics already implement HF schedules as standard treatment of appropriate patient groups, because data suggest prescribing the dose across additional fractions are unnecessary for operable breast cancer.[13] Prospective trials comparing various HF and CF schedules for localized prostate cancer also demonstrated noninferior outcomes for HF schemes.[14] Unfortunately, the clinical evidence often does not translate in the adoption of HF regimens, because managerial factors play a major role in the diffusion of therapeutic strategies.[15] For global health, cost containment and changes in treatment access are often critical factors in adopting new clinical techniques and innovation.

In this study, we estimated the 7-year (2019 to 2025) cost savings and potential increase in RT access that would occur in African countries after a global adoption of an evidence-based HF scheme over the CF technique for the irradiation of early breast cancer and localized prostate cancer with curative intent. The results are compared with those of high-income countries (HICs) in North America and Europe.

METHOD

Estimating the Cost of Breast and Prostate RT

The financial implication of breast and prostate RT for each African country was calculated and projected over 7 years (2019 to 2025), using the methods described in the following paragraphs.

Cancer Burden Projection

Annual cancer incidence for each country was linearly interpolated from the 2018 updated Global Cancer Observatory (GLOBOCAN) database, an online database developed by the International Association of Cancer Registries.[16] The GLOBOCAN online tool permits projections regarding future cancer burden over time[16] The number of new cancer cases, "I," in the 7-year time frame is reported as "I2019-2025."

Clinical Use

Using an optimal RT utilization (RTU) rate of 87% for breast and 58% for prostate cancer cases, we projected the future demand for breast and prostate between 2019 and 2025 for each country. The RTU rate for any cancer is the proportion of the patients with cancer for whom RT is indicated.[17] RTUs of 87% for breast cancer and 58% for prostate cancer are based on expert opinion and epidemiologic evidence-based estimation.[5,6,17]

Treatment Cost

The departmental cost of an RT course in an LMIC facility can be calculated using the Radiotherapy Cost Estimator model developed by the IAEA.[18] The cost per RT course for a single linear accelerator (LINAC) facility model, $F = [Cp + Op] / Q$, is determined by three components: (1) the upfront capital costs (Cp) of setting up the facility and equipment (infrastructure amortized over 30 years and three sequentially installed LINACs each amortized over 10 years); (2) the annual operations cost (Op), which includes staff salaries, quality assurance, and maintenance; and (3) the annual LINAC productivity in number of delivered treatment courses, Q.[19]

The cost per LINAC RT course varies with several adjustable parameters that determine each cost component. These parameters include the personnel salaries, daily machine working time, departmental size, treatment complexities, and mean number of fractions delivered by the RT unit. We used parameters similar in value to that used by the Global Task Force on Radiotherapy (GTFR)[5] and other recent studies.[20,21] However, we varied each cost component by 10% to obtain a confidence range. The annual capacity of a LINAC machine was estimated at 9,700 fractions[22] if on a 10-hour workday schedule, excluding weekends. At this capacity, a LINAC could deliver anywhere from 300 to 800 courses of RT per year, depending on fractionation schedule length.[22] The number of patients a LINAC machine can safely treat in a year was computed for selected CF and HF protocols for breast and prostate RT. The number of patients treatable per protocol was then input on productivity parameters to estimate the cost of RT for each protocol (Fig 1). Costs are presented in US dollars.

Model Comparison

To provide additional perspective on the results, a fractionation schedule cost analysis was performed using a previously published activity-based costing model based on IAEA calculations by Van Dyk et al.[21] The base-case scenario in that model was a 100% use of two multienergy LINACs with multileaf collimators, electronic portal imaging devices, on-board cone-beam computed tomography (CT), and other resources.[21] This includes personnel salaries and working hours; consumable resources, scaled to fit the needs of activity and complexity; and the cost of facility construction and maintenance.[21] The study determined costs for 15 and 25 fraction courses in HICs and low-income countries (LICs) averaging over many scenarios with varying department size, operating hours, and treatment planning technique.[21] The effective cost per fraction and overhead cost were determined by the difference in costs for those course schedules. These costs per fraction were used to determine the cost reduction of performing HF for the prostate and breast cases of our investigation. Linearly interpolating the GLOBOCAN incident projections and applying the RTU, we estimated the national cost savings for several HICs and LICs from 2019 through 2025 with the proposed HF scheduling implemented.

Estimating Potential National Cost Savings With Adoption of Evidence-Based HF Guidelines

The potential cost saved by each country in adopting the HF over CF schedule is the cost saving per patient multiplied by all patients who are expected to receive RT within the specified period. This is computed as: $(I2019\text{-}2025 \times RTU \times FCF) - (I2019\text{-}2025 \times RTU \times FHF)$, where FCF and FHF are the estimated cost per RT course for the CF and HF treatment protocols, respectively (Fig 1).

All CF and HF protocols are for curative intent. CF schemes for WBRT range from 1.8-2.0 Gy per fraction for a total dose of 45 to 50 Gy in 25 to 28 daily fractions with or without a subsequent radiation boost to the tumor bed.[23-25] In this study, we used 25 fractions of 1.8 to 2.0 Gy per fraction because this was the most commonly used CF scheme in the recent studies from Nigeria.[26] Standard RT for prostate cancer with EBRT typically involves 38 to 45 treatment fractions of 1.8 to 2.0 Gy per treatment for 8 to 9 weeks. In this study, we used a CF prostate RT scheme of 78·0 Gy (39 fractions of 2.0 Gy, five fractions per week).[27]

The breast and prostate CF schemes used in this study were clinically compared with HF schemes.[23-25,28] Our WBRT HF scheme was based on the 2018 American Society for Radiation Oncology (ASTRO) guideline.[29] The 2018 ASTRO WBRT guideline was developed by the ASTRO Guidelines Subcommittee after evaluating new evidence and conducting a systematic literature review of existing WBRT

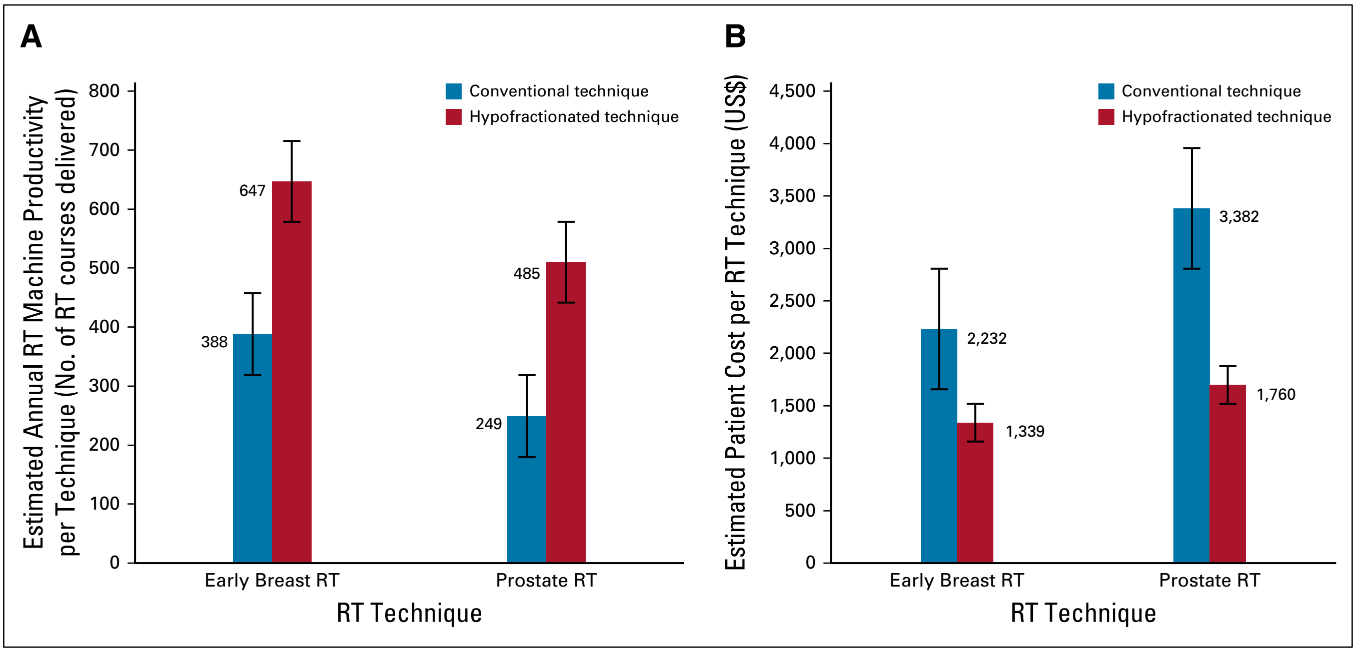

FIG 1. Bar graphs of (A) the estimated annual output of a department with a single linear accelerator, assuming the machine was used solely to deliver the specified radiation therapy (RT) technique; and (B) the estimated differences in cost with changes in RT fractions.

guidelines.[29] The preferred scheme for women with invasive breast cancer receiving WBRT is an HF dose of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.[29] We selected the lower fraction scheme of 40 Gy in 15 fractions because RT cost was mostly contained by the reduction in fractions.[30] The same approach was applied for prostate RT. We obtained the optimum HF scheme for EBRT of localized prostate cancer from the 2018 evidence- based consensus published by ASTRO, AUA, and ASCO.[27] Suggested optimum regimens for moderate prostate RT HF include the schedules used with the largest number of patients in randomized clinical trials: 60 Gy delivered in 20 fractions of 3 Gy over 4 weeks or 70 Gy delivered in 28 fractions of 2.5 Gy over 5.5 weeks.[27] These moderate HF doses can be offered as an alternative to CF regardless of cancer risk group, patient age, comorbidity, anatomy, or baseline urinary function. The consensus could not determine one regimen to be superior to the other, because they have not been compared in clinical trials.[27] In this study, we used the lower fraction scheme of 20 fractions for best possible cost minimization. It is noted that the cost of treatment preparation does not necessarily increase with the complexity of fractionated RT.[30] Although the treatment preparation and the consumption of resources increase with growing complexity, the increase is negligible because this activity is generally performed once at the start of the treatment.[30-32]

Estimating Potential Changes in RT Access With HF

The projected national cost savings obtained from the models is applicable only at full RT access for all breast and prostate cancer RT indications. However, many African countries do not have full RT access for patients with cancer, and few with installed facilities have suboptimal access. Thus, we obtained the number of EBRT units in each African country from the IAEA directory of RT[9] to estimate the current percent coverage in each country, which quantifies the number of patients currently receiving treatment. We estimated cost savings on the basis of the current treatment output and projected the potential increase in treatment access with adopting the optimum HF schemes over CF protocols. The percent coverage is based on IAEA recommendation of one megavolt machine per 250,000 population.[19]

RESULTS

Whole-Breast Irradiation

The GLOBOCAN database estimates a total of 168,690 new cases of breast cancers in Africa for 2018. This report is based on incidence of breast cancer across the continent, which ranged from 27 per 100,000 women in central Africa to 39 per 100,000 women in southern Africa in 2012.[33] With an increasing population, the number of new breast cancer cases reported annually in Africa is projected to be 210,219 by 2025 (a 24% increase). Compared with the rest of the world, Africa is projected to report the highest percentage increase for breast cancer from 2018 to 2025. The percent increase is projected to vary for each region in Africa, from as high as 28.7% in eastern Africa to as low as 19% in southern Africa. Middle Africa is expected to experience a 26.9% increase within this period. At the current evidence-based RTU rates, there will be a demand for 824,625 courses of WBRT for all countries combined within the time frame. The demand is projected to be lowest in São Tome and highest in Nigeria, where nearly 180,000 women will require breast irradiation between 2019 and 2025. The base-case cost per course of CF WBRT using the stipulated parameters is $2,232 (range, $2,009-$2,455), whereas that of the HF schedule is $1,339 (range, $1,205-$1,473; Fig 1). Our computed costs are close in value to the cost of 25 fraction courses and 15 fraction courses recently estimated by Van Dyk et al.[21]

The difference in cost between the CF and HF regimens translates to a 40% reduction in departmental cost of delivering WBRT per patient for departments adopting the HF protocol rather than the CF protocol. The combined cost of delivering CF WBRT for the 7 years across the continent is $2.7 billion. However, a universal adoption of the ASTRO HF WBRT guideline will reduce the national cost by a progressive amount each year, totaling $1.1 billion for all RT indications between 2019 and 2025 (Fig 2). The cost savings will be $170 million in the upper-middle–income countries, $598 million in the LMICs, and $339 million in the LICs (Table 1). The treatment time and cost saved by adoption of the ASTRO HF protocol is also expected to increase the treatment capacity of RT centers across Africa. The percentage increase in RT access resulting from implementing the HF WBRT regimen would range from a 0.3% increase in Ethiopia to a 25.4% increase in Libya. Patients in low-population countries and countries with already established RT programs will experience the highest increase in breast RT access.

Prostate RT

The pooled prostate cancer incidence in Africa is approximately 22.0 per 100,000 population, varying from 10.6 and 7.0 per 100,000, in Northern Africa to average rates of 34.3 and 22.1 per 100,000 in sub-Saharan Africa.[34] Our analyses for African countries using the GLOBOCAN online projection tools estimated 643,601 new prostate cancer cases for the continent between 2019 and 2025. The base cost per course of a standard regimen of 39 fractions would be $3,382, whereas the HF regimen of 20 fractions would cost $1,760, representing a 48% cost reduction with HF. There will be a demand for 373,289 courses of prostate EBRT, which will cost approximately $1.3 billion to deliver at the CF scheme within the same period. However, a full implementation of the ASTRO/ASCO/AUA HF regimen for localized prostate cancer is expected to reduce this cost by approximately $606 million (Table 1). The HF regimen would also

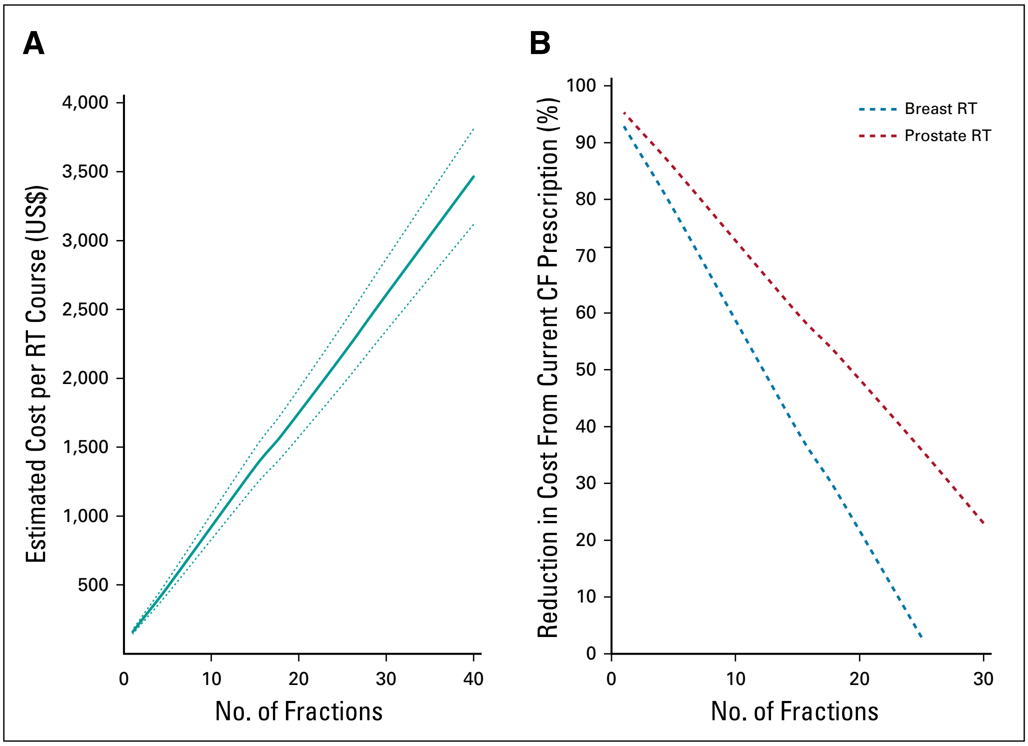

FIG 2. Graphs of (A) estimated cost of a radiation therapy (RT) course per number of fractions delivered; and (B) estimated percent reduction in cost with changes in number of fractions for breast and prostate RT. CF, conventional fractionation.

expand access to RT for men with prostate cancer in each country. An increment in accessibility ranging from 0.3% in Ethiopia to 36.0% in Libya is projected.

Calculations Using the Van Dyk et al Model

Based on the Van Dyk et al model,[21] implementing the HF treatment scheduling would result in a $1,850 (30%) and $3,515 (40%) cost reduction, respectively, for breast and prostate cancer in HICs and a $810 (40%) and $1,539 (49%) cost reduction, respectively, for breast and prostate cancer in LICs (Fig 3). The HIC fraction and overhead costs were $185/fraction and $1,545, respectively; and the LIC fraction and overhead costs were $375 per fraction and $81, respectively (Fig 4).

We projected the cost reduction of HF to the HIC and LIC cumulative patient loads over the next 6 years and compared that with our IAEA-based model estimates (Table 2). Our cost comparison with the Van Dyk et al model[21] projects similar national savings, between 75% and 99% agreement with two outliers, with our calculated estimations. It also demonstrates that HICs would have significantly more cost reduction over the projected time.

DISCUSSION

The GTFR estimated the nominal cost of scaling up RT for demand between 2015 and 2035 as $26.6 billion in LICs, $62.6 billion in LMICs, and $94.8 billion in upper-middle–income countries, which amounts to $184.0 billion across all LMICs[5] This study shows prospects for decreasing this cost and increasing RT access for cancer management in LMICs through the adoption of lower fractionation schemes as the new prescription standard.

Our findings corroborate results of multiple studies in the developed world that have demonstrated HF to minimize the cost per patient in the delivery of breast and prostate RT.[10,30,35,36] National cost savings in this study are conservative because some patient-related costs are not factored in, including patient transport to the hospital and time off work for treatment. The potential impact of HF schemes in expanding global RT access have become pertinent, considering the lower fraction schemes and doses also proffer an equivalent local control, superior toxicity profile, and noninferior late effects compared with CF prescription. HF schemes also realize other goals of high-quality care, including patient centeredness, timeliness, efficiency, and equity.[37,38] Given that shorter courses of RT reduce the capital and operational investment needed to scale radiation oncology in LMICs, we anticipate an improvement in RT access with additional innovations that would allow for progressive HF until there are capabilities and techniques to deliver a single fraction without compromising the benchmarks of quality for RT delivery. We have depicted in Figure 2 these possible changes in treatment cost and percent reduction in cost from the CF prescription with each HF scheme.

TABLE 1. Potential National Cost Savings and Increase in Radiotherapy Access with Adoption of Evidence-Based Hypofractionated Schemes

Country	2019 National RT Access (%)	Breast Cancer (2019-2025)			Prostate Cancer (2019-2025)		
		Projected National Cost for Full Access to Breast RT at CF (US$ million)	Projected National Cost Savings With HF Breast RT (US$ million)	Potential Increase in RT Access With HF (%)	Projected National Cost for Full Access to Prostate RT at CF (US$ million)	Projected National Cost Savings With HF Prostate RT (US$ million)	Potential Increase in RT Access With HF (%)
Upper-middle–income countries							
Algeria	9.4	180	71.2	6.9	420	20	9.8
Botswana	10.5	2.8	1.1	7.8	1.1	0.5	11.1
Libya	34.2	110	4.6	25.4	4.9	2.3	36
Mauritius	19.7	9.5	3.8	14.6	2.8	1.4	20.6
Namibia	18.9	5.1	2	14	3.2	1.5	19.9
South Africa	29.3	210	85.2	21.7	190	90.2	30.7
Equatorial Guinea	0	2.1	0.9	NA	1.4	0.7	NA
Gabon	11.9	2.8	1.1	8.8	2.9	1.4	12.4
Lower- and middle-income countries							
Angola	1.6	360	14.5	1.2	33	1.6	1.7
Cape Verde	0	0.7	0.3	NA	1.3	0.6	NA
Cameroon	2	530	21.1	1.5	34	16	2.1
Republic of Congo	0	6.4	40.4	NA	8.1	43.6	NA
Djibouti	0	2.7	1.1	NA	0.3	0.2	NA
Côte d'Ivoire	0	430	17.2	NA	38	18.1	NA
Réunion	0.4	5.4	2.2	0.3	6.6	3.1	0.4
Egypt	17.8	360	142.8	13.2	49	23.3	18.7
Ghana	2.5	73	29.4	1.8	33	15.8	2.6
Kenya	3.8	100	40.8	2.8	47	22.3	4
Lesotho	0	2.2	0.9	NA	1.8	0.8	NA
Mauritania	5.4	6.6	2.7	4	3.3	1.6	5.6
Morocco	17.1	150	60.5	12.6	66	31.5	17.9
Nigeria	1.2	420	167.4	0.9	200	96.7	1.3
São Tomé and Principe	0	0.2	0.08	NA	0.2	0.1	NA
Sudan	0	91	36.3	NA	15	7.1	NA
Swaziland (Eswatini)	0	1.2	0.5	NA	1.2	0.6	NA
Tunisia	23.3	34	13.5	17.3	13	6	24.5
Zambia	1.4	15	6.1	1	19	9	1.4

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TABLE 1. Potential National Cost Savings and Increase in Radiotherapy Access with Adoption of Evidence-Based Hypofractionated Schemes (Continued)

		Breast Cancer (2019-2025)			Prostate Cancer (2019-2025)		
Country	**2019 National RT Access (%)**	**Projected National Cost for Full Access to Breast RT at CF (US$ million)**	**Projected National Cost Savings With HF Breast RT (US$ million)**	**Potential Increase in RT Access With HF (%)**	**Projected National Cost for Full Access to Prostate RT at CF (US$ million)**	**Projected National Cost Savings With HF Prostate RT (US$ million)**	**Potential Increase in RT Access With HF (%)**
Low-income countries							
Benin	0	25	9.9	NA	21	10	NA
Burundi	0	11	4.2	NA	12	5.8	NA
Burkina Faso	0	24	9.4	NA	11	5.2	NA
Central African Republic	0	8.5	3.4	NA	4.8	2.3	NA
Chad	0	27	10.9	NA	9	4.3	NA
Comoros	0	0.7	0.3	NA	0.8	0.4	NA
Congo, Democratic Republic of	0	180	40.4	NA	91	43.6	NA
Ethiopia	0.5	250	100	0.3	26	12.6	0.5
Eritrea		12	4.8	NA	1.4	0.7	NA
Guinea	0	1	3.9	NA	14	6.7	NA
Guinea- Bissau	0	2.7	1.1	NA	1.2	0.6	NA
Liberia	5	6.7	2.7	3.7	5.8	2.8	5.3
Madagascar	1.9	22	8.8	1.4	28	13.5	1.9
Malawi	0	20	8.2	NA	7.9	3.8	NA
Mali	1.3	29	11.5	0.9	8.1	3.9	1.3
Mozambique	0.8	22	8.8	0.6	26	12.3	0.8
Niger	1.1	27	10.7	0.8	2.8	1.4	1.1
Rwanda	0	19	7.4	NA	12	5.7	NA
Senegal	4.5	29	11.5	3.3	15	7	4.7
Sierra Leone	0	16	6.6	NA	5.9	2.8	NA
Somalia	0	30	12	NA	6	2.9	NA
South Sudan	5.7	23	9	4.2	11	5.3	5.9
Tanzania	1.6	50	20.2	1.2	68	32.7	1.7
Republic of Gambia	0	0.8	0.3	NA	0.5	0.2	NA
Togo	0	12	4.8	NA	4.9	2.3	NA
Uganda	1.1	40	16	0.8	33	15.8	1.1
Zimbabwe	1.4	31	12.5	1	19	9.1	4.6
Total		2,671	1,107		1,262	606	

Abbreviations: CF, conventional fractionation; HF, hypofractionation; NA, not applicable; RT, radiation therapy.

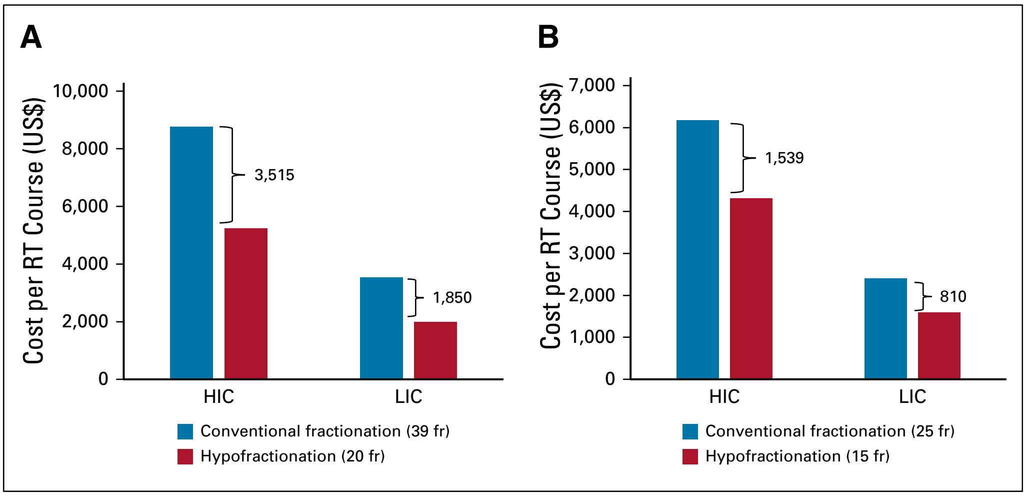

FIG 3. Bar graphs of (A) a comparison of the cost reduction per radiation therapy (RT) course for prostate cancer using hypofractionation (HF) instead of conventional fractionation (CF) in high-income countries (HICs) and low-income countries (LICs) calculated by the Van Dyk et al model[21]; and (B) a comparison of the cost reduction per RT course for breast cancer using HF instead of CF in HICs and LICs calculated by the Van Dyk et al model.[21] fr, fraction.

The calculations were performed assuming all patients who received RT were eligible for HF scheduling. It is important that patients are selected for treatment modalities that produce the best clinical outcome. In the United States, 62% of breast cancer cases and 90% of prostate cancer cases are localized disease at detection.[39,40] Assuming these HF-eligible case rates are the same globally, this would decrease the total cost-savings estimates. It is likely that HF-eligible cases would also fall in the same group prescribed RT by the RTU; however, this is not guaranteed. Additional investigation of HF-eligible cases in tandem with RTU determination is necessary to provide accurate estimation of an "effective" RTU for HF treatment. LMICs can greatly benefit from downstaging intervention to improve early cancer detection such that those cases would more likely be eligible for HF.[41] Increasing the HF eligibility of cases would increase the patient load for HF scheduling and increase the cost reduction in that clinic, where otherwise those patients would be treated with CF scheduling.

Calculations based on the Van Dyk et al model[21] included some assumptions. The model was developed by averaging

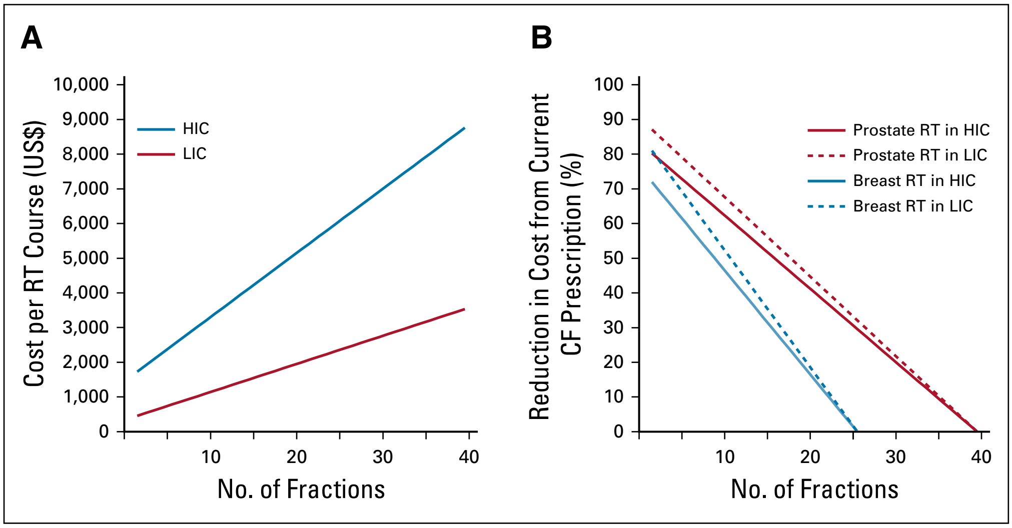

FIG 4. Graphs of (A) the estimated cost of an radiation therapy (RT) course per number of fractions delivered for high-income countries (HICs) and low-income countries (LICs) calculated by the Van Dyk et al model[21]; and (B) the estimated percent reduction in cost with changes in number of fractions for breast and prostate RT for HICs and LICs calculated by the Van Dyk et al model.[2] CF, conventional fractionation.

TABLE 2. Potential National Cost Savings With Adoption of Evidence-Based Hypofractionated Schemes Calculated using the Van Dyk et al Model[21]

	Breast Cancer (2019-2025)	Prostate Cancer (2019-2025)
Country	**Projected National Cost Savings With HF Breast RT (US$ million)**	**Projected National Cost Savings With HF Prostate RT (US$ million)**
High-income countries		
Canada	340.2	340.1
France	652.4	990.8
Germany	825.3	953.1
Japan	746.3	1055.7
Spain	383.4	497.2
Sweden	93.7	159.6
United Kingdom	650.5	866.4
United States	2,790.8	3,309.3
Upper-middle–income countries		
Algeria	65.4	19
Botswana	1	0.5
Equatorial Guinea	0.7	0.6
Gabon	1	1.3
Libya	4.2	2.2
Mauritius	3.5	1.3
Namibia	1.8	1.5
South Africa	76.9	85.6
Lower- and middle-income countries		
Angola	12.5	15.1
Cabo Verde	0.3	0.6
Cameroon	18.5	15.6
Republic of Congo	2.2	3.7
Côte d'Ivoire	14.9	17.2
Djibouti	1	0.2
Egypt	127.7	22.2
Réunion	2	3
Ghana	26.2	15
Kenya	35.2	21.2
Lesotho	0.8	0.8
Mauritania	2.3	1.5
Morocco	55.3	29.9
Nigeria	146.4	91.8
São Tomé and Principe	0.1	0.1
Sudan	31.9	6.8
Swaziland (Eswatini)	0.4	0.5
Tunisia	12.4	5.8
Zambia	5.1	8.6

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all cancer sites together, defining an average treatment cost independent of cancer site.[21] Accounting for different treatment modalities and clinical activity based on the cancer site would yield a site-dependent cost per fraction and overhead cost. In addition, these calculations assume the cost per fraction scales linearly with the number of fractions in the treatment with a constant overhead cost per course. If fewer fractions are delivered, more patients can be treated in the same time for CF treatments, increasing the overhead activity for quality assurance and treatment planning. Additional personnel and other resources may be necessary to accommodate a larger patient load. With these assumptions in mind, the calculations from the Van Dyk et al model[21] yield comparable values within 25% of our model with two outliers, Angola and Republic of Congo. Variations are likely due to differences in model resource parameters, including available clinical equipment and personnel salaries.

Technical requirements for implementing HF techniques include image guidance and treatment planning requirements. The acceptable image guidance could include ultrasound and cone-beam CT. Image-guided RT with three to four implanted gold fiducials are typically used.[42] CT-based treatment planning with magnetic resonance imaging fusion allows for accurate volume delineation. Volumetric modulated arc therapy (VMAT) or intensity-modulated RT (IMRT) are the ideals for treatment delivery.[42] Position verification before every fraction with electronic kilovoltage or megavoltage portal imaging or x-ray volumetric imaging ensures accurate delivery.[42] A reasonable option, whether VMAT or IMRT techniques are available, is modified forward planning with the field-in-field technique or three-dimensional conformal therapy with higher energies. In resource-constrained settings, setup verification with daily, online, electronic portal imaging and bony setup correction remains feasible with the addition of appropriate planning target volumes.[42] This is not suitable for the weekly high-dose-per- fraction regimens but is well suited to the 19- to 20-fraction schedules and has been adopted in some centers in Africa.

The education of technical personnel and staff is necessary for successful implementation of HF techniques in low-resource countries. Considering LMICs with 30% increased treatment accessibility by applying these high-efficiency techniques, this is a major accomplishment, because only 5% of patients with cancer in sub-Saharan LMICs have access to RT.[43] For LMICs that have less increase in accessibility, implementing HF can be supplemented with the development of more RT clinics with expert faculty trained to deliver HF and other innovative treatment strategies.[43,44] Technical training and quality assurance can be supported through web-based systems, including teleconferencing with partner institutions in HICs.[42,44] Our goal is to initiate a win-win scenario incentivizing collaboration to innovate new evidence-based treatments, advancing cancer management as

TABLE 2. Potential National Cost Savings With Adoption of Evidence-Based Hypofractionated Schemes Calculated using the Van Dyk et al Model[21] (Continued)

Country	Breast Cancer (2019-2025) Projected National Cost Savings With HF Breast RT (US$ million)	Prostate Cancer (2019-2025) Projected National Cost Savings With HF Prostate RT (US$ million)
Low-income countries		
Benin	8.6	9.5
Burkina Faso	8.1	4.9
Burundi	3.6	5.5
Central African Republic	2.9	2.2
Chad	9.4	4.1
Comoros	0.2	0.4
Democratic Republic of Congo	34.8	41.4
Eritrea	4.2	0.6
Ethiopia	87.3	12
Guinea	3.4	6.4
Guinea-Bissau	0.9	0.6
Liberia	2.3	2.6
Madagascar	7.6	12.8
Malawi	7	3.6
Mali	9.9	3.7
Mozambique	7.7	11.7
Niger	9.1	1.3
Rwanda	6.5	5.4
Senegal	10	6.6
Sierra Leone	5.8	2.7
Somalia	10.3	2.7
South Sudan	7.9	5
United Republic of Tanzania	17.4	31
Republic of Gambia	0.3	0.2
Togo	4.2	2.2
Uganda	13.5	15
Zimbabwe	10.8	8.7

a whole.[43-45] We currently have collaboration in providing educational resources through the Global Oncology University, including training for conventional treatment strategies and evidence-based innovations.[44,45]

Innovations leading to the efficacy and safety of moderate HF schemes delivery will make RT affordable to millions. At the moment, extreme fractionation (< 5 fractions) studies have reported low incidence of adverse effects, and single-fraction, high-dose rate (HDR) brachytherapy has been effectively demonstrated in small clinical studies for localized prostate cancer.[46] Single-fraction prostate EBRT can be planned with a stereotactic approach while respecting HDR brachytherapy constraints and can possibly be planned and delivered in a single day.[47] Single-fraction RT delivered pre- and intraoperatively have also shown some feasibility for selected patients with breast cancer.[47-50] An ongoing trial (ClinicalTrials.gov identifier: NCT02482376) extends the findings to a larger cohort of subjects. In this study, women with biopsy-proven ductal carcinoma in situ or invasive carcinoma will be treated with 21 Gy as a single fraction delivered preoperatively and followed for response. Low-cost nanotechnologies that could enable the delivery of extreme and single HF with minimal adverse effects have been developed but are yet to be clinically tried. These innovations include the smart RT biomaterials for RT delivery.[51] Smart biomaterials include next-generation fiducial markers, brachytherapy spacers, and balloon applicators, designed to respond to stimulus and perform additional desirable functions like controlled delivery of therapy-enhancing payloads directly into the tumor subvolume while minimizing normal tissue toxicities.[51] Smart biomaterials are inexpensive and could potentially allow for the safe delivery of extreme HF and single-fraction RT.[51] These biomaterials could also allow for combining RT with immunotherapy or chemotherapy.[51] These innovative approaches, if developed and translated clinically, could yield important benefits in access to RT.

In conclusion, our analysis shows that adopting hypofractionated RT schedules for breast and prostate cancers can save billions of dollars in HICs as well as LICs. In addition, the reduced treatment times would improve patient convenience, which, in curative approaches, but especially in palliative situations, hold great advantage for the patient. The shorter treatment time per patient also allows more patients to receive treatment in the same period. Therefore, by adopting hypofractionated regimens, we anticipate a substantial increase in RT access in developing countries. Additional investigations in cost-effective treatment options without quality compromises, such as progressive HF and combination therapies, are greatly needed.

AFFILIATIONS

[1]Dana Farber Cancer Institute, Boston, MA
[2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[3]University of Massachusetts Lowell, Lowell, MA
[4]Boston University, Boston, MA
[5]Ulm University, Ulm, Germany
[6]National Hospital, Bloemfontein, South Africa
[7]Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
[8]Suez Canal University, Ismailia, Egypt
[9]Erasmus MC, Rotterdam, The Netherlands

CORRESPONDING AUTHOR

William Swanson, MS, Dana-Farber Cancer Institute, 4 Blackfan Cir, HIM 347, Boston, MA 02115; e-mail: William_Swanson@dfci.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Omoruyi Credit Irabor, William Swanson, Fiza Shaukat, Twalib Ngoma, Ahmed Elzawawy, Luca Incrocci, Wilfred Ngwa
Provision of study material or patients: Omoruyi Credit Irabor, Abba Mallum
Collection and assembly of data: Omoruyi Credit Irabor, William Swanson, Fiza Shaukat, Johanna Wirtz, Twalib Ngoma, Luca Incrocci
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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