HEALTH SERVICES RESEARCH

Hypofractionation in Breast Cancer Radiotherapy Across World Bank Income Groups: Results of an International Survey

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PURPOSE Hypofractionated breast radiotherapy has been found to be equivalent to conventional fractionation in many clinical trials. Using data from the European Society for Radiotherapy and Oncology Global Impact of Radiotherapy in Oncology survey, we identified preferences for hypofractionation in breast cancer across World Bank income groups and the perceived facilitators and barriers to its use.

MATERIALS AND METHODS An international, electronic survey was administered to radiation oncologists from 2018 to 2019. Demographics, practice characteristics, preferred hypofractionation regimen for specific breast cancer scenarios, and facilitators and barriers to hypofractionation were reported and stratified by World Bank income groups. Variables associated with hypofractionation were assessed using multivariate logistic regression models.

RESULTS One thousand four hundred thirty-four physicians responded: 890 (62%) from high-income countries (HICs), 361 (25%) from upper-middle–income countries (UMICs), 183 (13%) from low- and lower-middle–income countries (LLMICs). Hypofractionation was preferred most frequently in node-negative disease after breast-conserving surgery, with the strongest preference reported in HICs (78% from HICs, 54% from UMICs, and 51% from LLMICs, $P < .001$). Hypofractionation for node-positive disease postmastectomy was more frequently preferred in LLMICs (28% from HICs, 15% from UMICs, and 35% from LLMICs, $P < .001$). Curative doses of 2.1 to < 2.5 Gy in 15-16 fractions were most frequently reported, with limited preference for ultra-hypofractionation, but significant variability in palliative dosing. In adjusted analyses, UMICs were significantly less likely than LLMICs to prefer hypofractionation across all curative clinical scenarios, whereas respondents with > 1 million population catchments and with intensity-modulated radiotherapy were more likely to prefer hypofractionation. The most frequently cited facilitators and barriers were published evidence and fear of late toxicity, respectively.

CONCLUSION Preference for hypofractionation varied for curative indications, with greater acceptance in earlier-stage disease in HICs and in later-stage disease in LLMICs. Targeted educational interventions and greater inclusivity in radiation oncology clinical trials may support greater uptake.

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ASSOCIATED CONTENT

Data Supplement

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

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INTRODUCTION

Breast cancer is the most common cancer worldwide, with the most rapid increases in incidence occurring in low- and middle-income countries (LMICs).[1] Radiotherapy is an essential component of breast cancer treatment, but large global disparities in access have limited the extent to which women can benefit.[2,3] Although these disparities are most pronounced in LMICs, they are also present in more well-resourced regions such as Europe.[4] Hypofractionation, in which larger doses per day are delivered over shorter periods of time, has been identified as an important mechanism for improving access and reducing the cost of treatment without compromising outcomes,[3] yet there is limited understanding of its adoption in the treatment of breast cancer across different resource settings and the factors affecting its use.

The use of moderate hypofractionation for breast cancer radiotherapy has been well established in the adjuvant setting on the basis of several large randomized trials.[5-8] More recently, the FAST and Fast-Forward trials have established the noninferiority of ultra-hypofractionation regimens involving five fractions for early-stage disease after breast-conserving surgery (BCS)[9,10] and openly accruing trials are evaluating this regimen for node-positive disease.[11] In the palliative setting, hypofractionation has been used to provide both effective symptom control and maintain quality of

CONTEXT

Key Objective

To what extent do radiation oncologists prefer hypofractionated radiotherapy for breast cancer and what are the barriers and facilitators to its use across different resource settings?

Knowledge Generated

Hypofractionation was widely accepted for palliation, but there was significant variability for adjuvant curative indications, with concerns of worse toxicity and insufficient data limiting adoption. Stronger preference for hypofractionation was observed in early-stage disease among high-income respondents and in postmastectomy or node-positive disease among low- and middle-income country respondents.

Relevance

Addressing barriers to hypofractionation, including ultra-hypofractionated regimens, is an important mechanism for increasing access to radiotherapy around the world and improving the quality of care delivered.

life.[12] Economic analyses in different settings have also demonstrated the cost-effectiveness of these shortened fractionation schedules.[13]

Despite the strong evidence base for hypofractionation in breast cancer, evidence on its real-world use has been mixed. In 2020, the European Society for Radiotherapy and Oncology's Global Impact of Radiotherapy in Oncology (ESTRO-GIRO) initiative published an international survey of hypofractionation across several disease sites.[14] Findings from the survey identified significant variation in the preference for hypofractionation across indications and regions, but the extent to which practice patterns differed between low- and lower–middle-income countries (LLMICs), upper-middle–income countries (UMICs), and high-income countries (HICs) and the factors affecting its use in breast cancer were not explored. Understanding the perspectives of practitioners on hypofractionation in the treatment of breast cancer in different resource settings is essential to promote the translation of evidence into practice. In the present study, we report on findings from the ESTRO-GIRO survey to describe the preferences for breast cancer hypofractionation among radiation oncologists across World Bank income group regions and the facilitators and barriers to its use.

MATERIALS AND METHODS

The ESTRO-GIRO initiative administered an anonymous, electronic survey using the SurveyMonkey platform to radiation oncologists from January 2018 to January 2019 through the ESTRO membership database and liaisons of several national and regional professional radiation oncology societies globally. Before administration, the survey was pilot tested by radiation oncologists representing four different countries, with representation from HICs and LMICs. This ensured that the questions and response options were comprehensive and clearly articulated and that respondent burden was minimized. The survey was iteratively revised and considered validated when no further revisions were suggested and subsequently translated into English, Spanish, Japanese, and Mandarin. Complete details on the survey design have been described previously.[14]

Data on physician demographics and clinical practice characteristics were collected. Demographic characteristics of respondents included age, sex, country of current practice, and country of training. Clinical practice characteristics included scope of practice (university affiliation, public, private, and public-private partnership), population size of practice catchment area ($<$ 10,000, 10,000-50,000, 50,000-100,000, 100,000-500,000, 500,000-1,000,000, and $>$ 1,000,000), and available radiotherapy technology (intensity-modulated radiotherapy [IMRT], three-dimensional [3D] conformal radiotherapy, computed tomography–based 3D planning, and two-dimensional [2D planning]).

Respondents who treated at least one breast cancer case per month were invited to respond to a series of questions on hypofractionation in breast cancer management (Data Supplement). Respondents were presented with five different clinical scenarios on radiotherapy for breast cancer and asked to specify whether they preferred hypofractionation ($\geq$ 2.1 Gy per fraction), conventional fractionation (1.8-2.0 Gy per fraction), or both. Those who selected both were asked to specify the proportion of patients for whom hypofractionation was preferred. Those who selected hypofractionation were asked to specify the dose per fraction and the number of fractions used. The clinical scenarios included the following: (1) node-negative disease after BCS, (2) node-negative disease after mastectomy, (3) node-positive disease after BCS, (4) node-positive disease after mastectomy, and (5) palliative symptom control. Respondents were asked to indicate the justifications and barriers that supported their decision.

Descriptive statistics were reported as counts and proportions. Analyses were reported for the full sample and were stratified by World Bank income groups on the basis of respondents' country of practice. The 2019 World Bank income group and regional classification system were used

for this analysis.[15] The association between justifications and barriers to hypofractionation and income group was assessed using the Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to determine the factors predictive of hypofractionation by clinical scenario. All results from these models are presented as odds ratios with 95% CIs. The covariates included all demographic and practice characteristics of respondents collated in the survey. For this analysis, a hypofractionation user was defined as a respondent who preferred hypofractionation or both in ≥ 75% of their patients.[14]

A P value of $< .05$ was considered statistically significant, and all statistical tests were two-sided. All analyses were conducted using the R statistical environment, version 3.5.2 (R Foundation for Statistical Computing). The study received institutional review board exemption.

RESULTS

A total of 2,316 radiation oncologists completed the survey, of which 1,928 respondents treated at least one breast cancer case per month. Of the respondents who treated breast cancer, 494 did not respond to the breast-specific survey questions. The final sample size was 1,434 (breast practitioner survey response rate 74%), of which 890 respondents (62%) were from HICs, 361 (25%) from UMICs, and 183 (13%) from LLMICs. Because of the distribution method, an overall survey response rate could not be estimated. Most respondents reported access to linear accelerators (94%) and advanced radiotherapy planning techniques such as IMRT (87%). Full sample characteristics are shown in Table 1; characteristics of the excluded respondents are shown in the Data Supplement.

Utilization of hypofractionation for each clinical scenario by income group region is shown in Figure 1. After BCS for node-negative disease, respondents in HICs were significantly more likely to report hypofractionation as their preferred fractionation compared with UMICs and LLMICs (75% from HICs, 52% from UMICs, and 48% from LLMIC; $P < .001$). There was greater preference for hypofractionation by physicians in LLMICs after mastectomy for node-positive disease than in HICs or UMICs (26% in HICs, 14% in UMICs, and 31% in LLMICs; $P < .001$). There was high overall utilization of hypofractionation for palliation (92% in HICs, 83% in UMICs, and 82% in LLMIC; Fig 1).

In the curative clinical scenarios, the most frequently preferred fraction dose was between 2.1 and < 2.5 Gy, which corresponded with 15 or 16 fractions (Fig 2). No respondents reported use of ultra-hypofractionation schedules (eg, five fractions). More heterogeneity was observed in the palliative dose regimens, with doses between 3 and < 4.0 Gy being the most frequently preferred by 46% of respondents.

The results of the multivariable logistic regression analyses are presented in Table 2; univariable regression analyses are shown in the Data Supplement. Compared with

TABLE 1. Characteristics of Respondents

Characteristic	N = 1,434, No. (%)
Sex	
Female	564 (39)
Male	870 (61)
Age, years	
45	742 (52)
45-54	375 (26)
55	317 (22)
Years in practice	
5	417 (29)
6-10	275 (19)
11-20	358 (25)
20	384 (27)
Region	
Europe	766 (53)
Asia-Pacific	284 (20)
Africa	36 (3)
Latin America	199 (14)
North America	75 (5)
Middle East	74 (5)
World Bank income group	
LLMICs	183 (13)
UMICs	361 (25)
HICs	890 (62)
University affiliation	
No	642 (45)
Yes	792 (55)
Public	
No	842 (59)
Yes	592 (41)
Private	
No	1,037 (72)
Yes	397 (28)
Public-private partnership	
No	1,261 (88)
Yes	173 (12)
Catchment area	
100,000	246 (17)
100,000-500,000	422 (29)
500,000-1,000,000	274 (19)
1,000,000	492 (34)
Cobalt 60 machine	
No	1,259 (88)
Yes	175 (12)
Intensity-modulated radiotherapy	
No	192 (13)

(Continued on following page)

TABLE 1. Characteristics of Respondents (Continued)

Characteristic	N = 1,434, No. (%)
Yes	1,242 (87)
Linear accelerator	
No	79 (6)
Yes	1,355 (94)
3D conformal radiotherapy	
No	118 (8)
Yes	1,316 (92)
CT-based 3D planning	
No	108 (8)
Yes	1,326 (92)
2D planning	
No	871 (61)
Yes	563 (39)

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; CT, computed tomography; HICs, High-income countries; LLMICs, low- and lower-middle–income countries; UMICs, upper-middle–income countries.

respondents in LLMICs, those in UMICs were significantly less likely to prefer hypofractionation across all curative scenarios, with no significant differences in the palliative setting. Regionally, respondents in Asia-Pacific were significantly less likely to hypofractionate across curative scenarios, compared with respondents in Europe, with no differences in palliation. Respondents from North America were significantly more likely to hypofractionate for scenario 1, with no significant differences across other clinical scenarios. By contrast, those in the Middle East were significantly more likely to hypofractionate after mastectomy (scenarios 3 and 4) and for palliation. Respondents in large catchment areas and those with IMRT availability were significantly more likely to hypofractionate, with no significant differences among those using 2D planning.

Respondents were asked to report their perceived justifications and barriers to hypofractionation, which was stratified by the World Bank income group (Table 3). Published evidence was the most cited facilitator for hypofractionation overall but was cited more frequently in HICs (94%) compared with UMICs (81%) and LLMICs (79%; $P < .001$). Reimbursement was reported by only 5%, with no significant differences between income groups. Patient and provider preference, acceptance among peers, and convenience were more prominent in HICs than in other income groups ($P < .001$). Lack of long-term data and concerns about both acute and late toxicities were commonly reported barriers to hypofractionation and were reported more frequently in UMICs compared with other income groups (Table 3).

DISCUSSION

In this large, international survey of hypofractionation, with a specific focus on breast cancer radiotherapy, hypofractionation was widely accepted for palliation, but significant differences were observed in its acceptability across adjuvant curative indications and across resource settings, with significantly lower reported use in UMICs. Preference for hypofractionation was lower in the setting of chest wall or node-positive radiation, where concerns about worse acute and late toxicities and perceptions of insufficient long-term data limited adoption.

The highest rates of hypofractionation were observed in early-stage disease after BCS, but 25% of respondents from HICs and half of the respondents from UMICs and LLMICs still preferred conventional fractionation. Respondents with IMRT had 2.68 greater odds of using hypofractionation (95% CI, 1.81 to 3.99; $P < .001$), with similar findings observed across all scenarios. In the postmastectomy setting, respondents from UMICs were significantly less likely to prefer hypofractionation, compared with respondents from LLMICs or HICs. These findings are consistent with another European survey, which found that overall rates of postmastectomy hypofractionated radiation were approximately 30% and that its use was less common in Eastern Europe,[16] where the majority of European UMICs are located.

In our adjusted analyses, respondents from Asia-Pacific were significantly less likely than European respondents to hypofractionate overall, but significantly higher reported preferences were observed in the Middle East postmastectomy, with no significant differences between Africa and Latin America. This may reflect the heterogeneity of the regions, which include countries across a wide range of gross national incomes with differing resource constraints and practice patterns. Although variation in worldwide radiotherapy availability has been found to correspond to regional income level, previous work has demonstrated large variations in gross national incomes per capita for different countries in each of the geographic regions.[17]

Notably, respondents from LLMICs were the most likely to prefer hypofractionation in the node-positive setting. Because of advanced stage at presentation and the high rates of mastectomy in LLMICs, these scenarios are most commonly encountered by those respondents in routine practice.[1,18-21] The moderate hypofractionation study by Wang et al[8] included a small proportion of node-positive patients, and the results of currently open trials for node-positive patients may improve overall acceptability of hypofractionation for node-positive disease over time.[11] Furthermore, in the DCBG HYPO trial, 42% of patients received chemotherapy, with no increase in toxicity, providing further support for hypofractionation in high-risk patients.[22]

Published evidence was the most cited facilitator of hypofractionation adoption across all income groups. Many of the practice changing trials for hypofractionation[5-7] were conducted in patients after BCS, and many had node-negative disease. The well-established evidence base in

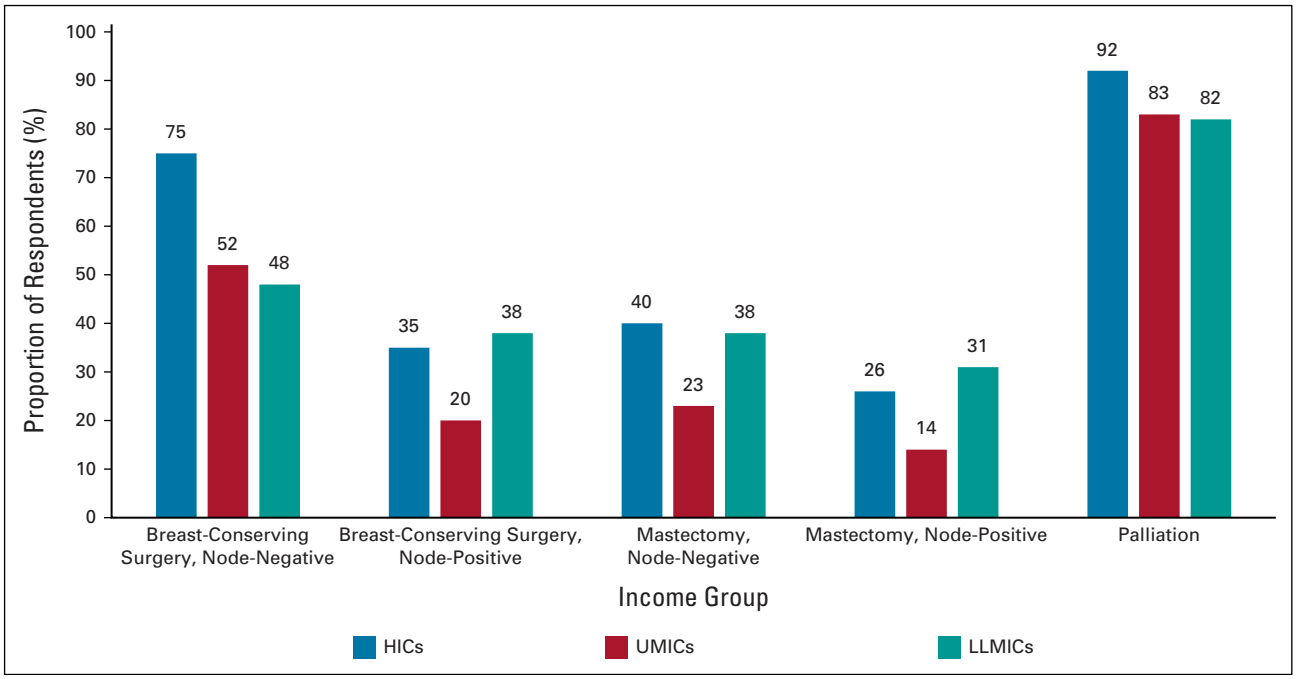

FIG 1. Hypofractionation refers to respondents who selected hypofractionation as their preferred fractionation scheme overall or in >75% of patients. All comparisons are statistically significant with $P < .001$. HICs, high-income countries; LLMICs, low- and lower-middle income countries; UMICs, upper middle-income countries.

low-risk disease is reflected in the higher overall preference for hypofractionation reported by survey respondents in this scenario. However, the differences between income groups and regions, as observed in BCS node-negative, where there was a 50% higher preference for hypofractionation in HICs compared with UMICs and LLMICs, may also reflect the fact that most trials for this clinical scenario were conducted in Europe and North America in HICs. A randomized controlled trial of moderate hypofractionation published by Wang et al[8] in China, where uptake of hypofractionation was reported to be as low as 12%, may help to improve evidence diffusion in that region. Radiotherapy research seldom originates from LLMICs,[23] and there are limited opportunities for clinicians from these regions to conduct studies in their practice settings with patients who are more representative of those they encounter in routine practice. The Cervical Cancer Research Network (Gynecologic Cancer Intergroup) has been making great advances in this area by promoting clinical trial participation and initiation in low-resource settings. This model could also be applied in breast cancer care.[24]

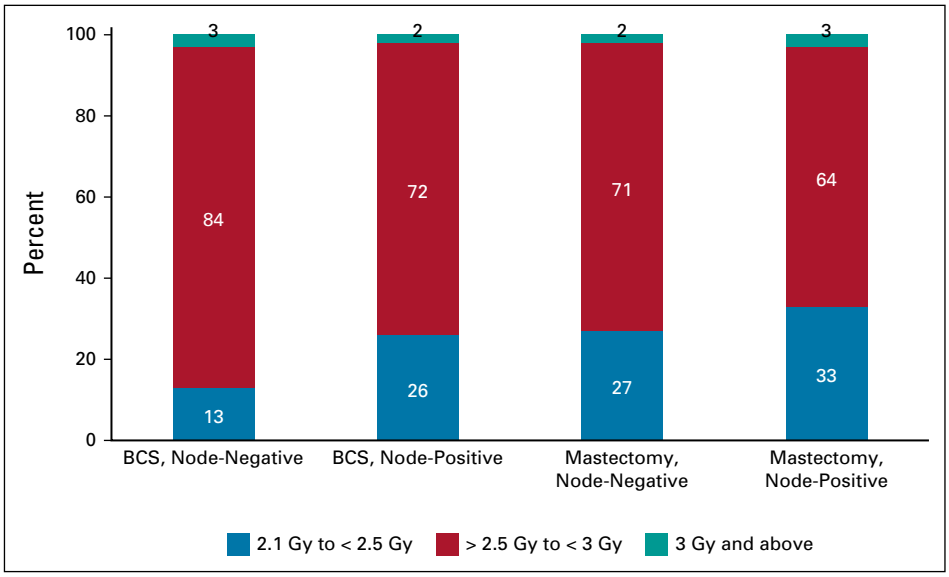

FIG 2. Preferred hypofractionation dose per fraction by clinical scenario. BCS, breast-conserving surgery.

TABLE 2. Multivariate Logistic Regression Analysis of Hypofractionation Use by Clinical Scenario

	BCS, Node-Negative		BCS, Node-Positive		Mast, Node-Negative		Mast, Node-Positive		Palliative	
Covariate	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Sex										
Female	Reference		Reference		Reference		Reference		Reference	
Male	1.11 (0.85 to 1.44)	.46	1.30 (1.01 to 1.69)	**.044**	1.08 (0.84 to 1.39)	.53	1.13 (0.86 to 1.50)	.38	1.17 (0.81 to 1.69)	.4
Years in practice		.13		**.030**		.31		.14		**.033**
5	Reference		Reference		Reference		Reference		Reference	
6-10	0.74 (0.51 to 1.09)	.13	1.34 (0.94 to 1.91)	.10	1.09 (0.77 to 1.55)	.63	1.19 (0.81 to 1.74)	.39	0.69 (0.41 to 1.15)	.16
11-20	0.61 (0.39 to 0.93)	**.022**	0.91 (0.60 to 1.38)	.65	0.84 (0.55 to 1.27)	.41	0.93 (0.59 to 1.47)	.77	0.76 (0.41 to 1.41)	.39
20	0.62 (0.35 to 1.10)	.10	0.61 (0.35 to 1.07)	**.086**	0.65 (0.37 to 1.12)	.12	0.6 (0.33 to 1.11)	.10	0.47 (0.21 to 1.07)	.073
Income group		**.001**		**.001**		**.001**		**.001**		**.001**
LLMICs	Reference		Reference		Reference		Reference		Reference	
UMICs	0.49 (0.30 to 0.79)	**.003**	0.29 (0.17 to 0.49)	**.001**	0.37 (0.22 to 0.63)	**.001**	0.32 (0.18 to 0.58)	**.001**	0.75 (0.4 to 1.38)	.58
HICs	1.49 (0.91 to 2.45)	.11	0.70 (0.41 to 1.18)	.18	0.89 (0.52 to 1.51)	.66	0.79 (0.44 to 1.42)	.43	2.24 (1.16 to 4.33)	**.017**
Region		**.001**		**.001**		**.001**		**.001**		**.001**
Europe	Reference		Reference		Reference		Reference	**.001**	Reference	
Asia-Pacific	0.45 (0.31 to 0.64)	**.001**	0.54 (0.36 to 0.81)	**.003**	0.46 (0.31 to 0.68)	**.001**	0.37 (0.23 to 0.59)	**.001**	0.57 (0.35 to 0.92)	.023
Africa	0.44 (0.18 to 1.08)	.075	0.66 (0.25 to 1.74)	.40	1.64 (0.68 to 4)	.27	1.50 (0.59 to 3.82)	.4	1.16 (0.39 to 3.42)	.79
Latin America	1.60 (1.03 to 2.49)	.052	0.89 (0.55 to 1.44)	.63	1.03 (0.64 to 1.66)	.89	0.77 (0.45 to 1.32)	.33	1.52 (0.83 to 2.79)	.18
North America	9.59 (2.31 to 39.87)	**.002**	0.76 (0.45 to 1.29)	.31	1.07 (0.64 to 1.76	.80	0.69 (0.39 to 1.23)	.21	1.48 (0.44 to 4.94)	.53
Middle East	1.19 (0.64 to 2.18)	.58	1.81 (1 to 3.28)	.051	3.26 (1.77 to 6.01)	**.001**	1.90 (1.02 to 3.53)	**.042**	3 (0.99 to 9.12)	.052
Catchment area		.38		**.001**		.11		**.017**		.46
100,000	Reference		Reference		Reference		Reference		Reference	
100,000-500,000	1.03 (0.7 to 1.51)	.89	1.27 (0.86 to 1.89)	.23	1.15 (0.79 to 1.67)	.47	1.13 (0.73 to 1.73)	.49	1.31 (0.77 to 2.23)	.32
500,000-1 million	1.27 (0.84 to 1.93)	.26	1.68 (1.10 to 2.57)	**.015**	1.19 (0.79 to 1.80)	.40	1.27 (0.8 to 2.02)	.3	1.46 (0.82 to 2.60)	.20
1 million	1.29 (0.88 to 1.88)	.19	2.02 (1.37 to 2.98)	**.001**	1.52 (1.05 to 2.21)	**.028**	1.78 (1.18 to 2.71)	**.006**	1.49 (0.90 to 2.48)	.12
IMRT										
No	Reference		Reference		Reference		Reference		Reference	
Yes	2.68 (1.81 to 3.99)	**.001**	2.81 (1.70 to 4.67)	**.001**	3.12 (1.87 to 5.23)	**.001**	2.32 (1.34 to 4.03)	**.003**	2.04 (1.25 to 3.34)	**.005**
2D planning										
No	Reference		Reference		Reference		Reference		Reference	
Yes	0.96 (0.73 to 1.26)	.78	1.02 (0.79 to 1.34)	.86	1.28 (0.99 to 1.66)	.060	1.36 (1.02 to 1.81)	.034	1.18 (0.80 to 1.75)	.4

NOTE. Age, access to linear accelerator, 3D conformal radiotherapy, University Affiliation, Cobalt 60 machine, and computed tomography–based 3D planning had no significant impact on the use of hypofractionation. *P* values in bold indicate statistical significance ($P < .05$).

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; BCS, breast-conserving surgery; HICs, high-income countries; IMRT, intensity-modulated radiation therapy; LLMICs, low- and lower-middle–income countries; Mast, mastectomy; OR, odds ratio; UMICs, upper-middle–income countries.

TABLE 3. Facilitators and Barriers to Hypofractionation

Facilitators and Barriers	Full Sample (N = 1,434), No. (%)	HICs (n = 890), No. (%)	UMICs (n = 361), No. (%)	LLMICs (n = 183), No. (%)	*P*
Facilitators					
Regimen supported by published evidence	1,273 (89)	836 (94)	293 (81)	144 (79)	.001
Equivalent local control	1,183 (82)	786 (88)	274 (76)	123 (67)	.001
Equivalent toxicities	1,050 (73)	714 (80)	225 (62)	111 (61)	.001
More optimal use of machine time	851 (59)	535 (60)	202 (56)	114 (62)	.27
More economically efficient use of resources	671 (47)	432 (49)	139 (39)	100 (55)	.001
Better reimbursement	68 (5)	37 (4)	22 (6)	9 (5)	.32
Prior clinical experience	482 (34)	311 (35)	99 (27)	72 (39)	.007
Personal preference from prior clinical experience	721 (50)	481 (54)	167 (46)	73 (40)	.001
Generally accepted treatment strategy among peers	521 (36)	396 (44)	74 (20)	51 (28)	.001
Patient preference	501 (35)	367 (41)	97 (27)	37 (20)	.001
Patient convenience	1,016 (71)	671 (75)	234 (65)	111 (61)	.001
Barriers					
Not enough long-term data available for hypofractionation	365 (25)	215 (24)	111 (31)	39 (21)	.026
Fear of inferior local control	123 (9)	47 (5)	58 (16)	18 (10)	.001
Fear of worse acute toxicity	240 (17)	119 (13)	88 (24)	33 (18)	.001
Fear of worse late toxicity	420 (29)	257 (29)	124 (34)	39 (21)	
Lack of advanced technology for hypofractionation	92 (6)	27 (3)	40 (11)	25 (14)	.001
Insufficient reimbursement	119 (8)	62 (7)	47 (13)	10 (5)	.002
Personal preference prior clinical experience	187 (13)	94 (11)	69 (19)	24 (13)	.001
Treatment strategy not generally accepted among peers	143 (10)	80 (9)	40 (11)	23 (13)	.23
Patient preference	169 (12)	115 (13)	38 (11)	16 (9)	.22

Abbreviations: HICs, high-income countries; LLMICs, low- and lower-middle–income countries; UMICs, upper-middle–income countries.

Peer acceptance was cited as a facilitator for hypofractionation by 35% of respondents although it was reported by twice as many respondents from HICs as LLMICs and UMICs. In many HICs, peer acceptance and the building of consensus around hypofractionation have been promoted within practice groups through the implementation of clinical protocols that indicate a preference for hypofractionation[25] and by implementing utilization management strategies such as peer review or payer restrictions.[26] A US study on payer restriction, in which claims for conventional radiotherapy were not reimbursed for patients eligible for hypofractionation, was associated with both direct and spillover increases in the use of hypofractionated radiotherapy.[26] In Europe, a study by Prades et al[25] in the Public Health Service in Spain found that utilization of hypofractionation for breast cancer ranged between 9% and 75% in 2015 and that factors such as endorsement of hypofractionation by department heads and the inclusion of hypofractionation in clinical protocols as a preferred regimen strongly influenced uptake. In LLMICs, and particularly in Africa, there are often fewer radiation oncologists in the country with reduced opportunities for peer audit and review.[27] Initiatives such as the International Atomic Energy Agency's regional virtual tumor board projects through their Regional Cooperative Agreements have attempted to address this barrier.[28] Patient preference was also more commonly cited in HICs than in UMICs or LLMICs, which may reflect cultural differences in the nature of the patient-provider relationship and the lack of decisional aids to support patients undergoing adjuvant radiotherapy and can help to facilitate shared decision making.[29,30]

Reimbursement was cited as a barrier to hypofractionation by only a minority of respondents although no in-depth evaluation of the health system reimbursement methods was conducted in this survey. In Europe, for example, most radiotherapy reimbursement systems are still fee-for-service–based and fractionation-driven, which may pose an important hurdle on the adoption of hypofractionated treatment schemes.[31] A survey of an international group of

radiation oncologists from 13 countries reported that adoption of moderately hypofractionated radiotherapy for breast cancer would result in a financial loss of up to 40%, depending on the provider and setting.[32] Recognizing the important recent trend toward ultra-hypofractionated radiotherapy in breast cancer, as in other common tumor types such as prostate, recommendations have been made to develop reimbursement systems supporting this evolution, such as episode-based payment models.[33] A large proportion of respondents in the present survey identified hypofractionation as a mechanism for promoting more efficient use of resources. Whether hypofractionation ultimately lowers health system costs depends on whether excess capacity created by hypofractionation can be repurposed toward other patients.[34]

Less than 1% of physicians used ultra-hypofractionation in the curative setting although the survey was distributed before COVID-19 pandemic and the publication of the Fast-Forward Trial, which demonstrated the noninferiority at 5 years of 40 Gy in 15 fractions and 26 Gy in five fractions in early-stage breast cancer after BCS.[9] The Fast-Forward publication coincided with the first wave of the COVID-19 pandemic, which catalyzed adoption of this regimen. Several international guidelines published by professional societies, experts, and institutions further promoted the adoption of hypofractionation, including one-week regimens, to minimize viral exposure through reduced hospital visits.[35-41] In that regard, ESTRO recently published recommendations for the adoption of ultra-hypofractionation (five fractions) for non-nodal breast or chest wall (without reconstruction) radiotherapy either as standard of care or within a randomized trial or prospective cohort.[42]

Limitations of this study include possible selection bias as the survey was administered by convenience sampling through professional society membership databases, which may lead to over- or under-representation of groups from specific regions or income levels. Furthermore, 25% of the respondents who indicated that they treated breast cancer did not respond to the breast scenario questions and were therefore excluded from the analysis. Since a higher proportion of these excluded respondents were from LMICs, this may also bias the results. This survey-based study also measured reported preferences, which was not correlated with utilization. To encourage a high completion rate, it was not possible to address all nuances of hypofractionation use in the clinical scenarios surveyed. Although provider comfort with hypofractionation might have evolved during the COVID-19 pandemic and with the publication of new trials such as FAST-Forward,[9] these results provide important global benchmark data. These data will facilitate evaluation of the impact of recent consensus statements published by ESTRO and the American Society of Radiation Oncology and African expert groups on breast hypofractionation.[42-44] Similarly, the use of conventional fractionation for early-stage breast cancer was included in the recent publications of Indian and African Choosing Wisely guidelines, which reflect consensus statements on low-value clinical practices that should be avoided.[44-47]

In conclusion, the study demonstrated significant variability in the preference of hypofractionation in breast cancer across World Bank income groups for curative indications, with a lack of long-term evidence cited as the most common barrier to uptake. Targeted interventions tailored to different resource settings, such as through ESTRO, the Federation of Asian Organisations of Radiation Oncologists, Southeast Asia Radiation Oncology group, and African Organisation of Research and Training in Cancer, may be necessary to increase evidence-based adoption of hypofractionation for breast cancer. Inclusivity in multi-institutional radiation oncology clinical trials by supporting the accreditation of centers from diverse income groups may further promote knowledge diffusion and guideline implementation.

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DISCLAIMER

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