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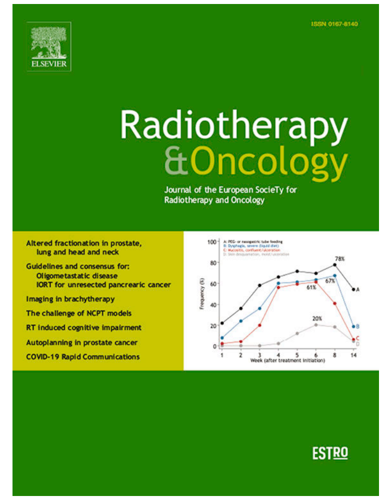

Original Article

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Hypofractionated radiotherapy in the real-world setting: An international ESTRO-GIRO survey

Danielle Rodin MD[1,2], Bouchra Tawk MD[3,4], Osama Mohamad MD[5], Surbhi Grover MD[6,7], Fabio Y. Moraes MD[8], Mei Ling Yap MBBS[9,10], Eduardo Zubizarreta MD[11], Yolande Lievens PhD[12]

[1]Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[2]Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada
[3] German Cancer Research Consortium, Core Site Heidelberg, German Cancer Research Center, Heidelberg, Germany
[4] Division of Molecular and Translational Radiation Oncology, Department of Radiation Oncology, Heidelberg Faculty of Medicine and Heidelberg University Hospital, Heidelberg, Germany
[5]Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas, United States
[6]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania, United States
[7]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States
[8]Department of Oncology, Division of Radiation Oncology, Queen's University, Kingston, ON, Canada
[9]Collaboration for Cancer Outcomes, Research and Evaluation (CCORE), Ingham Institute, UNSW Sydney, Liverpool, NSW, Australia
[10]Liverpool and Macarthur Cancer Therapy Centres, Western Sydney University, NSW, Australia
[11]International Atomic Energy Agency, Vienna, Austria
[12]Ghent University Hospital and Ghent University, Ghent, Belgium

Corresponding Author:
Danielle Rodin, MD MPH FRCPC
Radiation Medicine Program, Princess Margaret Cancer Centre
700 University Ave, Room 7-611
Toronto, ON
M5G 1Z5

ABSTRACT

BACKGROUND AND PURPOSE: Multiple large trials have established the non-inferiority of hypofractionated radiotherapy compared to conventional fractionation. This study will determine real-world hypofractionation adoption across different geographic regions for breast, prostate, cervical cancer, and bone metastases, and identify barriers and facilitators to its use.

MATERIALS AND METHODS: An anonymous, electronic survey was distributed from January 2018 through January 2019 to radiation oncologists through the ESTRO-GIRO initiative. Predictors of hypofractionation were identified in univariable and multivariable regression analyses.

RESULTS: 2,316 radiation oncologists responded. Hypofractionation was preferred in node-negative breast cancer following lumpectomy (82·2% vs. 46·7% for node-positive; $p<0.001$), and in low- and intermediate-risk prostate cancer (57·5% and 54·5%, respectively, versus 41·2% for high-risk ($p<0.001$)). Hypofractionation was used in 32·3% of cervix cases in Africa, but <10% in other regions ($p<0.001$). For palliative indications, hypofractionation was preferred by the majority of respondents. Lack of long-term data and concerns about local control and toxicity were the most commonly cited barriers. In adjusted analyses, hypofractionation was least common for curative indications amongst low- and lower-middle-income countries, Asia-Pacific, female respondents, small catchment areas, and in centres without access to intensity modulated radiotherapy.

CONCLUSION: Significant variation was observed in hypofractionation across curative indications and between regions, with greater concordance in palliation. Using inadequate fractionation schedules may impede the delivery of affordable and accessible radiotherapy. Greater regionally-targeted and disease-specific education on evidence-based fractionation

schedules is needed to improve utilization, along with best-case examples addressing practice barriers and supporting policy reform.

INTRODUCTION

Many clinical trials have established the equivalence of conventionally fractionated and hypofractionated radiotherapy in terms of tumour control and long-term toxicity.[1-7] In the curative setting of breast and prostate cancer, both among the most common cancers and often requiring radiotherapy[8,9], a strong body of evidence supporting hypofractionation has informed professional society guidelines.[10-12] Within prostate cancer, three non-inferiority trials with over 30,000 combined patient-years of follow-up found that moderate hypofractionation was non-inferior to conventionally fractionated treatment for 5-year biochemical or clinical failure.[5-7] In breast cancer, large Canadian and United Kingdom trials have shown no difference between conventional and hypofractionated treatment in local recurrence, overall survival, or cosmetic outcome at 10 years.[1,4] Most recently, the FAST-Forward trial established the non-inferiority of a 5-fraction regimen for breast radiotherapy, as compared to 15-fractions.[13]

Hypofractionation is especially relevant in the palliative setting to alleviate symptoms of advanced disease. Over the last 20 years, there have been 9 trials of over 4,000 patients with bone metastases, which found no differences in pain relief or medication requirements between single fraction and multi-fraction radiotherapy regimens.[14] This is especially relevant in low- and middle-income countries (LMICs), where availability of machines is limited and the presentation of patients with disease is often delayed.[9,15] Adopting hypofractionation has also been found to be the most efficient treatment option by reducing treatment time and reducing costs associated with daily treatment.[16] Shorter treatment courses also liberates machine time, thereby improving access to radiotherapy for a greater number of patients. Moreover, since the onset of COVID-19, delivering shorter radiotherapy courses has also been advocated to mitigate the risk of infection to patients and healthcare workers by decreasing the time patients spend in hospitals.[17-19]

Despite the evidence base for hypofractionation, the extent to which this knowledge is accepted amongst oncologists and translated into clinical practice at a global level remains unknown. The European Society for Radiotherapy and Oncology's Global Impact of Radiotherapy in Oncology (ESTRO-GIRO) initiative, which has a mandate to drive evidence-based policy solutions to improve access to radiotherapy, launched an international patterns-of-care study to determine the extent of hypofractionation adoption in breast cancer, prostate cancer, cervical cancer, and bone metastases. Although the evidence on hypofractionation in cervical cancer is more limited, this cancer site was included due to its high burden in resource-constrained settings.[20] The objective of this study was to identify the clinical circumstances in which hypofractionation is used and to identify the barriers and facilitators to hypofractionation across different geographic regions and resource settings.

MATERIALS AND METHODS

Participants

Radiation oncologists who had completed their training were invited to participate. The survey was disseminated from January 2018 to January 2019 through the membership database of ESTRO and through the liaisons of several national and regional professional societies globally (see Appendix p9 for a list of professional societies engaged in survey distribution).

Survey Design

An anonymous, electronic survey of hypofractionation practice patterns was developed using SurveyMonkey software, which could be answered only once from any single device (Appendix p1-8). The survey was designed to take 10 to 15 minutes to complete and consisted of 5 sections with a total of 28 questions. The first section focused on demographics, clinical experience, and available technology within respondents' departments. The other four sections focused on clinical scenarios related to breast, prostate and cervical cancer, and bone metastases. For each disease site, only respondents who indicated that they treated at least one patient per month were subsequently surveyed on their practice patterns.

Multiple clinical scenarios were presented per disease site, asking for: (1) the use of conventional fractionation [≤2 Gray (Gy) per fraction], hypofractionation (>2Gy per fraction), or both; (2) the proportion of hypofractionated cases if "both" was selected; and (3) the preferred hypofractionated dose and fractionation. Respondents using hypofractionation were asked to justify their selection from a series of possible options, with the opportunity to indicate a free-text answer. Respondents not using hypofractionation were similarly asked about barriers to its use.

The questionnaire was written and initially assessed by 3 investigators (DR, OM, YL) from two different countries and was translated from English to Spanish, Japanese, and Mandarin. A panel of 4 radiation oncologists (SG, MLY, EZ, FYM) from 4 other countries pilot-tested the survey to establish face and content validity, ease of understanding, and completion time. The survey was revised based on the panel's comments, who reviewed the survey again after each round of revisions. The survey was considered validated when the panel offered no further revisions. No incentives were provided for participation. This study received institutional review board exemption.

Statistical Analysis

Descriptive statistics were reported as proportions, medians, and ranges for categorical variables and as means with standard deviations (SD) for continuous variables. Continuous variables were compared using the *t* test and categorical variables were compared using the Chi-square or Fisher's exact test. Analyses were stratified by the following geographic regions based on the World Bank classification system: (1) North America, (2) Latin America and the Caribbean ("Latin America"), (3) Europe and Central Asia ("Europe"), (4) Middle East and North Africa ("Middle East"), (5) Sub-Saharan Africa ("Africa"), and (6) South Asia, and East Asia and Pacific ("Asia-Pacific") .[21] Justifications and barriers were analyzed by geographic region and disease site and were grouped into the following categories: clinical evidence, economic and resource impact, professional culture, and patient considerations. Free-text responses were brief and not mandatory and were therefore not analyzed.

Univariable and multivariable logistic regression analyses measured the association between hypofractionation use and respondent characteristics using odds ratios (OR) and 95% confidence intervals. All factors significant or associated with hypofractionation ($p \leq 0.10$) were entered into two distinct multivariable models for curative and palliative indications, respectively. Palliative indications included palliative symptom control for breast, prostate, and cervical cancer, as well as bone metastases. Hypofractionation use was defined as a dichotomous variable and included respondents who preferred hypofractionation for >75% of their patients within each disease site and in >50% of clinical scenarios overall, stratified by curative versus palliative indications. This definition was applied to evaluate respondents who expressed a consistent preference for hypofractionation in the majority of patients. The distribution of responses to the proportion of patients who hypofractionate is presented for each clinical scenario in the Appendix (p17-19). Independent variables evaluated in the univariable model included: sex, age, years in practice, region and World Bank income group, university-affiliation, size of patient catchment area, and available technology. All analyses were conducted using R (version 3.6.1), using 2-sided statistical testing at the 0.05 significance level.

RESULTS

A total of 2,316 radiation oncologists responded to the survey (see Appendix p9-15 for country representation). Overall, 40.1% of respondents were female, 58.1% were affiliated with a university, with the majority using linear accelerators (93.3%), CT-based 3D-planning (90.9%) and IMRT (85.0%) (Table 1). Over half of the total sample (54.3%) were from Europe; 36.3% were from LMICs.

Responses for each clinical scenario are reported by region in Figure 1 (Appendix p16). Hypofractionation was preferred by 82.2% in the node-negative setting following lumpectomy, with the highest proportion of hypofractionation users in Europe (88·5%) and North America (97.3%); the lowest in Africa (40.0%) ($p<0.001$). Hypofractionation was significantly reduced post-mastectomy, with the highest utilization in the Middle East (70.4%) and the lowest in Latin

America and Asia-Pacific (38.5% and 36.2%, respectively; p=0.002). Similar findings were observed for node-positive disease. In prostate cancer, the highest hypofractionation utilization rates were in low- and intermediate-risk disease at 57.5% and 54.5%, respectively, compared to 41.9% in high-risk disease and 23.6% when pelvic nodes were treated. The highest rates were in North America (94.3% low-risk, 87.8% intermediate-risk), and the lowest were in the Middle East (31.5% for low- and intermediate-risk) and Africa (18.8% for low-risk, 22.6% for intermediate-risk) (p<0.001).

Fewer than 10% of respondents outside of Africa favoured hypofractionation for locally advanced cervical cancer, compared with 32.3% in Africa (p<0.001). By contrast, 84.3% of respondents favoured hypofractionation for palliative symptom control, ranging from 76.5% in the Middle East to 96.7% in North America (p=0.04). High rates of hypofractionation for palliation of breast and prostate cancer were similarly reported. For bone metastases, ≥85% of respondents preferred hypofractionation in all scenarios, with a difference of 10% or less between regions.

Barriers and justifications for hypofractionation are presented in Figures 2 and 3, respectively. Across disease sites, clinical evidence (75.8%) and equivalence in local control (71.7%) were most frequently cited as their justification for hypofractionation. Reimbursement was the least frequently cited (5.4%), but resource optimization for improved machine availability and lower cost were reported by over half of respondents (66.7% and 52.2%, respectively). Those who reported barriers to hypofractionation most frequently cited lack of long-term data (35.0%) and concerns about acute and late toxicity (30.3% and 36.4%, respectively). Lack of technology was cited by only 14.0% overall, but varied across sites, being reported in 8.4% of respondents treating breast cancer and 23.2% of those treating prostate cancer. In the regional analysis, technology was most frequently cited as a barrier in the Middle East and Latin America (22.7% and 24.2%, respectively), but in only 3.2% of respondents in North America. Reimbursement was reported as a barrier by 15.1% and 14.3% of Latin American and Asia-Pacific respondents, respectively, but by ≤8.1% elsewhere.

Predictors of hypofractionation are presented in Table 2. For curative indications, univariable regression identified practice in North America or in a high-income country, university affiliation, large catchment area (>1 million population), and use of IMRT as significantly associated with hypofractionation. Respondents who practiced in Asia-Pacific or Latin America, in a LMIC, and those who used Cobalt-60 were significantly less likely to use hypofractionation. On multivariable regression, however, only practice in Asia-Pacific and in a low- or lower-middle-income country remained significantly associated with decreased hypofractionation use; IMRT remained associated with increased hypofractionation. Further, women were 25% less likely to use hypofractionation.

For palliative indications, univariable analysis similarly revealed that practice in Asia-Pacific and Latin America, practice in low- and lower-middle-income countries, and use of Cobalt-60 were associated with decreased hypofractionation use; in addition, age>55 was associated with decreased use. Use of IMRT, as well as use of a linear accelerator and 3D-conformal therapy, and practice in a catchment area >100,000 were associated with increased hypofractionation use. On multivariable regression, only age>55 remained associated with decreased use and practice in catchment areas of >1 million population remained associated with increased use.

DISCUSSION

This international study on hypofractionation is the first to measure practice patterns across geographic regions, demonstrating significant variability in the adoption of hypofractionation across curative indications and much greater use and concordance in the palliative setting. Although over half of respondents cited resource optimization as a justification for hypofractionation, respondents in low- and lower-middle-income countries were significantly less likely to hypofractionate than their peers in high-income countries. These findings are especially relevant in the context of the ongoing COVID-19 pandemic in which minimizing infection risk to patients and staff and preservation of hospital resources have become important drivers of clinical and health-system decision-making.

In North America, almost all respondents reported using hypofractionation for early-stage breast cancer following lumpectomy. This contrasts sharply from an earlier US study that reported hypofractionation in 13·6% of patients in 2009-2010.[22] In 2013, the American Society of Radiation Oncology included conventional fractionation for early-stage breast cancer in its Choosing Wisely list of low-value interventions.[23,24] Findings from the present survey suggest changing attitudes, although over half (61%) of North American respondents in this study were Canadian. A 2015 Canadian study found that 75% of patients with ductal carcinoma in-situ or early-stage breast cancer received hypofractionated treatment post-lumpectomy and 40% post-mastectomy. This compares to 50% in our survey who reported using hypofractionated chest wall radiotherapy.[25] Similar trends of increasing breast hypofractionation have also been reported in other countries, including Australia and Spain.[26,27]

The recently-published FAST-Forward trial reported the 5-year results of randomising older women with low-risk disease to either moderate hypofractionation (40Gy in 15 fractions) or ultra-hypofractionated radiotherapy (26-27Gy in 5 fractions over 1 week).[13] Both regimens demonstrated equivalent disease control, with no difference in normal tissue effects between 26Gy and 40Gy. Although questions remain unanswered, including late effects beyond 5 years,[28] this trial has already been endorsed as a standard-of-care regimen by an international panel of experts during COVID-19[18] and has indeed been adopted by several centres and jurisdictions.[17] In our study, concern about late toxicity was the most commonly cited barrier to hypofractionation in breast cancer, which raises the question about whether FAST-Forward and other accelerated and ultra-hypofractionated regimens will continue to be adopted post-pandemic. Further, patient preference was most commonly cited as a barrier to hypofractionation in breast cancer. In that regard, prior studies in other disease sites have found that, when patients are presented with the available evidence, many express a preference for more fractionated schedules.[29]

With the exception of Africa, prostate hypofractionation was used up to two-thirds less frequently in patients who had pelvic irradiation compared to patients with low-risk disease. This is in keeping with published guidelines[10], as the clinical trials did not include pelvic lymph node treatment. However, there was also a significant drop in hypofractionation for patients with high-risk disease, and concerns about toxicity were noted as a barrier by a significant proportion of respondents. While the evidence is strongest in low- and intermediate-risk, there is evidence supporting hypofractionation in high-risk groups. The CHHiP trial did not find a significant interaction between treatment effect and risk group (p=0.17).[6] Further, the HYPRO study, which enrolled predominantly high-risk patients, did not find evidence of significant heterogeneity across subgroups (p=0.95).[30] In Africa, however, acceptance of prostate hypofractionation overall was low overall, but increased for high-risk and pelvic lymph node indications, raising concerns about knowledge gaps. Meanwhile, consensus guidelines for radiation during COVID-19 have recommended hypofractionation for localized disease and moderate hypofractionation postprostatectomy.[19] Even in the absence of image-guidance, moderate 20-fraction hypofractionation was recommended.

Hypofractionation in cervical cancer is less well studied than in other disease areas and over half of respondents reported the lack of long-term data as a barrier to hypofractionation. Recently, the Cervix Cancer Research Network , founded by the Gynecologic Cancer Intergroup to increase patient access – especially in LMICs – to high-quality clinical trials[20], launched two phase II trials. These chemoradiation trials randomize patients to conventionally fractionated (50Gy or 45 Gy in 25 fractions) or hypofractionated treatment (40Gy in 16 fractions), followed by definitive radical hysterectomy in one trial and brachytherapy in the other.[20] If these studies demonstrate similar efficacy and toxicity profiles, hypofractionation use may increase patient access to radiotherapy and limit patients' time away from home.

Although 86% of respondents overall did not perceive technology as a barrier, use of IMRT was one of the strongest predictors of hypofractionation use in curative disease, while technology was most frequently cited in prostate cancer (23.2%) as a barrier to hypofractionation. Although modern trials have failed to establish an improved toxicity profile in prostate cancer patients treated with hypofractionation and modulated treatment techniques,[10,31] trials using conventionally fractionated regimens with IMRT have been associated with a greater than 50% reduction in toxicity.[6] This suggests that treatment quality, including margin reduction with appropriate image-guidance, and modulated treatment with lower hot spots on organs at risk, may be more significant factors than fractionation schedule.[6]

In 2015, the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) published an investment framework, demonstrating the health and economic benefits of scaling up radiotherapy in LMICs.[9] This framework was modelled using the mean number of fractions per treatment course needed for each indication and tumour type, favouring the lower number of fractions when two regimens were of equal efficacy. The findings of this survey, however, suggest that some of the lowest uptake of curative hypofractionation are in regions with significant issues in access. Achieving the results produced by the GTFRCC, and delivering affordable and accessible radiotherapy, will require greater adherence to evidence-based guidelines of practice.

Given the large body of high-level evidence in support of hypofractionation for bone metastases, it is reassuring to note such a high degree of acceptance, although the proportion using single-fraction versus multi-fraction radiotherapy was not analysed. Reimbursement was infrequently cited as a barrier to hypofractionation, but the reimbursement system was not evaluated. In an earlier European study, fee-for-service reimbursement predicted for lower uptake of hypofractionation in uncomplicated bone metastases.[32] A recent reimbursement survey conducted by the ESTRO-HERO (Health Economics in Radiation Oncology) project found that all but 5 of the 25 responding European countries reported lower reimbursement for hypofractionation compared with conventional fractionation.[33] While some countries support specific techniques for ultra-hypofractionation (such as stereotactic body radiotherapy) with additional reimbursement, there are still financial disincentives to adopt shorter fractionation schedules. Applying provider payment models that link reimbursement with performance, which are already used by several countries for specialist care to incentivize adherence to evidence-based practice[34], could provide an opportunity to move away from fee-per-fraction and increase hypofractionation use.

This study must be considered in the context of its strengths and limitations. The survey was administered through professional society membership databases in order to survey a large sample of international radiation oncologists. As a result, however, sample size could not be accurately estimated, and selection bias may be present. Further, survey responses were not correlated with actual utilization and there may be incomplete adjustment or unknown confounders in the multivariable regression analysis. This study's generalizability to other disease sites such as head and neck or lung cancer, where hypofractionation is also being applied, is unclear. Further, while translating evidence into clinical practice and changing well-entrenched habits is complex and time-intensive, further research is needed to identify the most effective means of promoting knowledge translation.[35]

In conclusion, this international survey of hypofractionation identified progress in adoption and concordance of hypofractionation for palliative indications, but significant variability across curative clinical indications and between geographic regions and income groups. These findings underscore the need to develop more effective clinical decision-support and targeted clinician and patient education to address knowledge gaps, entrenched practices, and patient expectations, with a focus on low- and lower-middle-income countries. Improving global adoption of hypofractionation is an important step toward increasing availability, access, and affordability of treatment.

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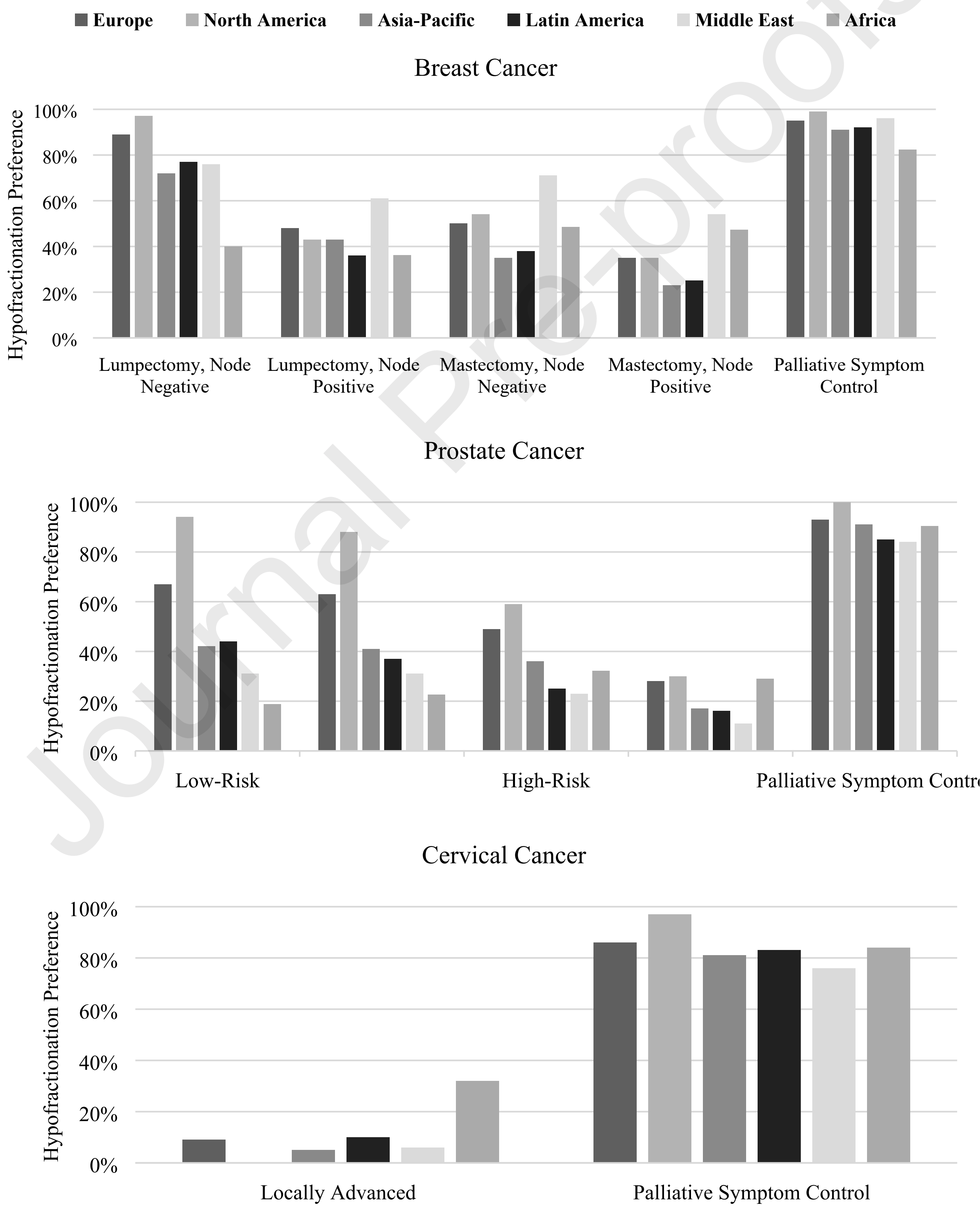
Figure 1. Hypofractionation practices by region and disease site



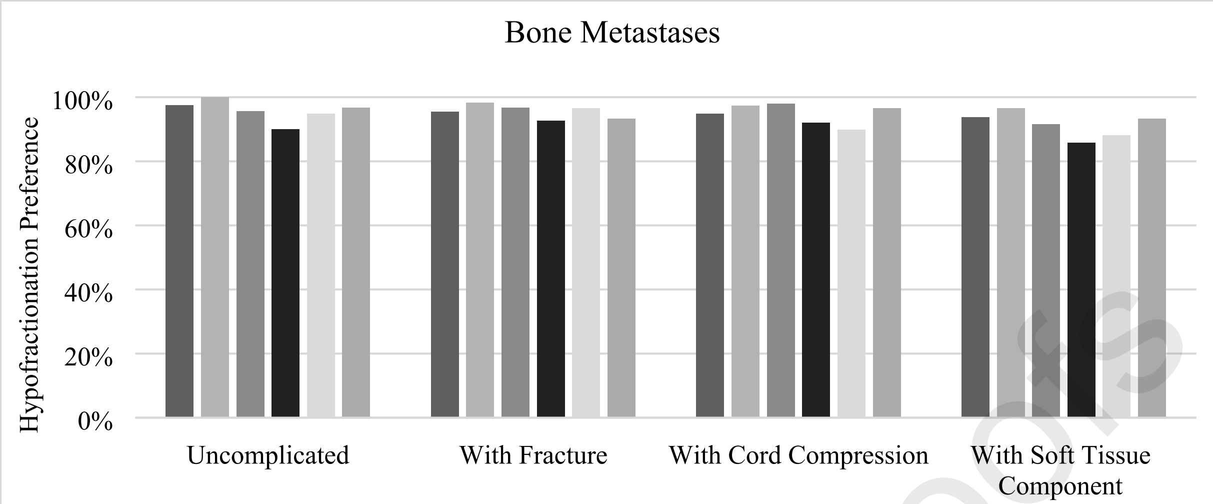


Figure 1. Justifications for and barriers to hypofractionation by disease site

	Breast Cancer		Prostate Cancer		Cervical Canc
Justifications	**N=755**	**No (%)**	**N=642**	**No (%)**	**N=36**
Clinical Evidence	Evidence	559 (74·0%)	Evidence	527 (82·1%)	Evidence
	Equivalent local control	511 (67·7%)	Equivalent local control	560 (87·2%)	Equivalent local contro
	Equivalent toxicity	474 (62·8%)	Equivalent toxicity	461 (71·8%)	Equivalent toxicity
Economic and Resource Impact	Resource optimization: machine	441 (58·4%)	Resource optimization: machine	455 (70·9%)	Resource optimization:
	Resource optimization: expense	377 (49·9%)	Resource optimization: expense	362 (56·4%)	Resource optimization:
	Reimbursement	24 (3·2%)	Reimbursement	30 (4·7%)	Reimbursement
Professional Culture	Prior clinical experience	275 (36·4%)	Prior clinical experience	250 (38·9%)	Prior clinical experienc
	Personal preference	329 (43·6%)	Personal preference	295 (46·0%)	Personal preference
	Peer-accepted	289 (38·3%)	Peer-accepted	239 (37·2%)	Peer-accepted
Patient Considerations	Patient preference	222 (29·4%)	Patient preference	250 (38·9%)	Patient preference
	Patient convenience	487 (64·5%)	Patient convenience	435 (67·8%)	Patient convenience
Barriers	**N=858**	**No (%)**	**N=703**	**No (%)**	**N=888**
Clinical evidence	Lack of long-term data	299 (34·8%)	Lack of long-term data	250 (35·6%)	Lack of long-term data
	Inferior local control	99 (11·5%)	Inferior local control	122 (17·4%)	Inferior local control
	Acute toxicity	176 (20·5%)	Acute toxicity	259 (36·8%)	Acute toxicity
	Late toxicity	300 (35·0%)	Late toxicity	318 (45·2%)	Late toxicity

Economic and Resource Impact	Technology	72 (8·4%)	Technology	163 (23·2%)	Technology
	Reimbursement	109 (12·7%)	Reimbursement	72 (10·2%)	Reimbursement
Professional Culture	Personal preference	157 (18·3%)	Personal preference	130 (18·5%)	Personal preference
	Peer preference	112 (13·1%)	Peer preference	100 (14·2%)	Peer preference
Patient Considerations	Patient preference	119 (13·9%)	Patient preference	40 (5·7%)	Patient preference

* The values reported for all disease sites reflect the average value of responses for each disease site.

Figure 3. Justifications and barriers for hypofractionation by geographic location

	Europe		**Asia Pacific**		**Africa**		**Latin Americ**
Justifications	**N=1654**	**No (%)**	**N=464**	**No (%)**	**N=63**	**No (%)**	**N=332**
Clinical Evidence	Equivalent local control	1441 (87·1%)	Equivalent local control	384 (82·8%)	Equivalent local control	38 (60·3%)	Equivalent lo control
	Equivalent toxicity	1170 (70·7%)	Equivalent toxicity	309 (66·6%)	Equivalent toxicity	30 (47·6%)	Equivalent toxicity
	Evidence	1528 (92·4%)	Evidence	382 (82·3%)	Evidence	52 (82·5%)	Evidence
Economic and Resource Impact	Resource optimization: machine	1126 (68·1%)	Resource optimization: machine	264 (56·9%)	Resource optimization: machine	42 (66·7%)	Resource optimization: machine
	Resource optimization: expense	869 (52·5%)	Resource optimization: expense	226 (48·7%)	Resource optimization: expense	40 (63·5%)	Resource optimization: expense
	Reimbursement	76 (4·6%)	Reimbursement	38 (8·2%)	Reimbursement	2 (3·2%)	Reimburseme
Professional Culture	Prior clinical experience	688 (41·6%)	Prior clinical experience	200 (43·1%)	Prior clinical experience	30 (47·6%)	Prior clinical experience
	Personal preference	870 (52·5%)	Personal preference	196 (42·2%)	Personal preference	16 (25·4%)	Personal preference
	Peer-accepted	749 (45·3%)	Peer-accepted	208 (44·8%)	Peer-accepted	29 (46·0%)	Peer-accepted
Patient Considerations	Patient preference	581 (35·1%)	Patient preference	153 (33·0%)	Patient preference	13 (20·6%)	Patient preference
	Patient convenience	1176 (71·1%)	Patient convenience	311 (67·0%)	Patient convenience	36 (57·1%)	Patient convenience
Barriers	**N=1265**	**No (%)**	**N=551**	**No (%)**	**N=72**	**No (%)**	**N=413**

Clinical Evidence	Lack of long-term data	516 (40·8%)	Lack of long-term data	243 (44·1%)	Lack of long-term data	13 (18·1%)	Lack of long-term data
	Inferior local control	214 (16·9%)	Inferior local control	123 (22·3%)	Inferior local control	16 (22·2%)	Inferior local control
	Acute toxicity	410 (32·4%)	Acute toxicity	204 (37·0%)	Acute toxicity	21 (29·2%)	Acute toxicity
	Late toxicity	588 (46·5%)	Late toxicity	230 (41·7%)	Late toxicity	22 (30·6%)	Late toxicity
Economic and Resource Impact	Technology	144 (11·4%)	Technology	87 (15·8%)	Technology	14 (19·4%)	Technology
	Reimbursement	103 (8·1%)	Reimbursement	83 (15·1%)	Reimbursement	0 (0·0%)	Reimburseme
Professional Culture	Personal preference	218 (17·2%)	Personal preference	104 (18·9%)	Personal preference	19 (26·4%)	Personal preference
	Peer preference	173 (13·7%)	Peer preference	100 (18·1%)	Peer preference	14 (19·4%)	Peer preferen
Patient Considerations	Patient preference	91 (7·2%)	Patient preference	72 (13·1%)	Patient preference	5 (6·9%)	Patient preference

Table 2. Characteristics of Respondents

	Number (%)							
	Europe (N=1259)	**Asia-Pacific (N=438)**	**Africa (N=64)**	**Latin America (N=285)**	**North America (N=145)**	**Middle East (N=125)**	**Total (N=2316)**	**P-value**
Female	625 (49·6%)	127 (29·0%)	20 (31·3%)	78 (27·4%)	43 (29·7%)	36 (28·8%)	929 (40·1%)	<0·001
Age								
18-34	246 (19·5%)	107 (24·4%)	9 (14·1%)	55 (19·3%)	27 (18·6%)	35 (28·0%)	479 (20·7%)	
35-44	383 (30·4%)	150 (34·2%)	21 (32·8%)	112 (39·3%)	44 (30·3%)	46 (36·8%)	756 (32·6%)	
45-54	361 (28·7%)	103 (23·5%)	18 (28·1%)	54 (18·9%)	36 (24·8%)	33 (26·4%)	605 (26·1%)	
>55	269 (21·4%)	78 (17·8%)	16 (25·0%)	64 (22·5%)	38 (26·2%)	11 (8·8%)	476 (20·6%)	<0·001
Years in practice								
<5	410 (32·6%)	104 (23·7%)	19 (29·7%)	73 (25·6%)	44 (30·3%)	44 (35·2%)	694 (30·0%)	
6-10	227 (18·0%)	106 (24·2%)	16 (25·0%)	61 (21·4%)	29 (20·0%)	26 (20·8%)	465 (20·1%)	
11-20	311	113	16	85	29	29	583	0·032

	(24·7%)	(25·8%)	(25·0%)	(29·8%)	(20·0%)	(23·2%)	(25·2%)	
>20	311 (24·7%)	115 (26·3%)	13 (20·3%)	66 (23·2%)	43 (29·7%)	26 (20·8%)	574 (24·2%)	
Income group								
Low	0 (0·0%)	8 (1·8%)	11 (17·2%)	0 (0·0%)	0 (0·0%)	6 (4·8%)	25 (1·1%)	
Lower-Middle	20 (1·6%)	190 (43·4%)	31 (48·4%)	14 (4·9%)	0 (0·0%)	54 (43·2%)	309 (13·3%)	
Upper-Middle	172 (13·7%)	40 (9·1%)	22 (34·4%)	235 (82·5%)	0 (0·0%)	38 (30·4%)	507 (21·9%)	
High	1067 (84·7%)	200 (45·7%)	0 (0·0%)	36 (12·6%)	145 (100·0%)	27 (21·6%)	1475 (63·7%)	<0·001
Region of training								
North America	12 (1·0%)	3 (0·7%)	1 (1·6%)	14 (4·9%)	129 (89·0%)	17 (13·6%)	176 (7·6%)	
Latin America	3 (0·2%)	0 (0·0%)	1 (1·6%)	246 (86·3%)	1 (0·7%)	2 (1·6%)	253 (10·9%)	
Asia-Pacific	5 (0·4%)	417 (95·2%)	2 (3·1%)	4 (1·4%)	3 (2·1%)	5 (4·0%)	436 (18·8%)	
Europe	1233 (97·9%)	16 (3·7%)	12 (18·8%)	21 (7·4%)	9 (6·2%)	22 (17·6%)	1313 (56·7%)	
Middle East	6 (0·5%)	1 (0·2%)	3 (4·7%)	0 (0·0%)	2 (1·4%)	76 (60·8%)	88 (3·8%)	
Africa	0 (0%)	1 (0·2%)	45 (70·3%)	0 (0·0%)	1 (0·7%)	3 (2·4%)	50 (2·2%)	<0·001
University affiliation	822 (65·3%)	196 (44·7%)	31 (48·4%)	103 (36·1%)	123 (84·8%)	70 (56·0%)	1345 (58·1%)	<0·001
Scope of practice*								
Public	521 (41·4%)	169 (38·6%)	25 (39·1%)	124 (43·5%)	26 (17·9%)	62 (49·6%)	927 (40·0%)	
Private	171 (13·6%)	157 (35·8%)	19 (29·7%)	171 (60·0%)	19 (13·1%)	31 (24·8%)	568 (24·5%)	
Public-Private	92 (7·3%)	38 (8·7%)	10 (15·6%)	77 (27·0%)	4 (2·8%)	14 (11·2%)	235 (10·0%)	<0·001
Catchment population								

<100,000	531 (42·2%)	187 (42·7%)	14 (21·9%)	73 (25·6%)	9 (6·2%)	41 (32·8%)	855 (36·0%)	
100,000-500,000	83 (6·6%)	24 (5·5%)	4 (6·3%)	18 (6·3%)	27 (18·6%)	6 (4·8%)	162 (7·0%)	
500,000-1,000,000	285 (22·6%)	73 (16·7%)	5 (7·8%)	39 (13·7%)	30 (20·7%)	14 (11·2%)	446 (19·3%)	
>1,000,000	360 (28·6%)	154 (35·2%)	41 (64·1%)	155 (54·4%)	79 (54·5%)	64 (51·2%)	853 (36·8%)	<0·001
Available technology*								
Cobalt-60	83 (6·6%)	102 (23·3%)	24 (37·5%)	48 (16·8%)	11 (7·6%)	39 (31·2%)	307 (13·3%)	<0·001
Linear Accelerator	1212 (96·3%)	379 (86·5%)	46 (71·9%)	266 (93·3%)	145 (100·0%)	112 (89·6%)	2160 (93·3%)	<0·001
2D-planning	431 (34·2%)	213 (48·6%)	36 (56·3%)	124 (43·5%)	76 (52·4%)	63 (50·4%)	943 (40·7%)	<0·001
CT-based 3D-planning	1169 (92·9%)	402 (91·8%)	37 (57·8%)	255 (89·5%)	141 (97·2%)	102 (81·6%)	2106 (90·9%)	<0·001
3D-conformal therapy	1171 (93·0%)	378 (86·3%)	38 (59·4%)	261 (91·6%)	138 (95·2%)	102 (81·6%)	2088 (90·2%)	<0·001
IMRT	1141 (90·6%)	367 (83·8%)	16 (25·0%)	221 (77·5%)	143 (98·6%)	80 (64·0%)	1968 (85·0%)	<0·001

*Responses were not mutually exclusive.
Abbreviations: 2D-planning, two-dimensional planning; CT-based 3D-planning, computed tomography three-dimensional planning; 3D-conformal therapy, three-dimensional conformal therapy; IMRT, intensity-modulated radiation therapy.

Table 2. Univariable and Multivariable Logistic Regression Analysis of Provider Characteristics Associated with Hypofractionation Use

	Curative (N=1,550)					
	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-val
Sex						
Male	..	..	..			..
Female	0.84	(0.68-1.03)	0·09	0.75	(0.6-0.95)	**0.01**

Age (years)						
<45	..	..	..	..	..	..
45-54	1.11	(0.87-1.41)	0·39	1.07	(0.75-1.52)	0.8
>55	0.78	(0.60-1.01)	0·06	0.77	(0.48-1.26)	0.7
Years in Practice						
<5	..	..	..	..	..	..
6-10	1.01	(0.75-1.36)	0.93	1.03	(0.75-1.52)	0.8
10-20	1.03	(0.79-1.35)	0.82	1.00	(0.69-1.46)	0.9
>20	0.77	(0.59-1.01)	0.06	0.75	(0.45-1.24)	0.2
Region of Practice						
Europe	..	..	..	..	..	..
Asia-Pacific	0.46	(0.35-0.61)	**< 0.001**	0.47	(0.33-0.65)	**<0.0**
Africa	0.53	(0.26-1.08)	0.08	1.02	(0.44-2.31)	0.9
Latin America	0.44	(0.31-0.61)	**< 0.001**	0.74	(0.48-1.13)	0.1
North America	2.18	(1.42-3.36)	**0.003**	1.64	(0.99-2.73)	0.0
Middle East	1.19	(0.73-1.92)	0.49	1.39	(0.80-2.41)	0.2
Income Group						
High	..	..	..	..	..	..
Upper-Middle	0.38	(0.29-0.50)	**<0.001**	0.69	(0.45-1.07)	0.1
Low and Lower-Middle	0.54	(0.40-0.73)	**<0.001**	0.37	(0.26-0.52)	**<0.0**
University Affiliation						
No	..	..	..	..	..	..
Yes	1.46	(1.19-1.79)	**<0.001**	1.14	(0.90-1.42)	0.2
Catchment Area						
<100.000	..	..	..	..	..	..
100.000-500.000	1.15	(0.83-1.58)	0.40	0.93	(0.66-1.31)	0.6
500·000-1·000·000	1.55	(1.1-2.19)	0.01	1.35	(0.93-1.97)	0.1
>1·000·000	1.46	(1.07-1.98)	**0.02**	1.64	(1.17-2.31)	**0.00**
Available Technology$^{\alpha}$						
Cobalt-60	0.68	(0.49-0.94)	**0.02**	1.16	(0.78-1.73)	0.4
IMRT	2.37	(1.71-3.27)	**<0.001**	1.99	(1.36-2.91)	**<0.0**
Linear Accelerator	1.16	(0.74-1.82)	0.52			
3D-conformal therapy	1.12	(0.78-1.61)	0.55			
CT-based 3D-planning	1·16	(0.79-1.72)	0.45			
2-D planning	0.99	(0.8-1.21)	0.91			

Notes: A hypofractionation user was defined as a provider who preferred hypofractionation for >75% of their p
significant at p≤0.05 are displayed in bold font. Practice setting (private, public, or mixed) was not included in t
$^{\alpha}$The reference category for each variable under available technology was "no/no access".
Abbreviations: OR, Odds ratio; CI, confidence interval; IMRT, intensity-modulated radiation therapy.

HIGHLIGHTS

- Conventional and hypofractionated radiotherapy are equivalent in many disease sites
- Less hypofractionation in low- and lower-middle income countries and Asia-Pacific
- Lack of long-term data, inferior local control, and toxicity cited as barriers
- Significant global variation in use of hypofractionation for curative indications
- Accepted for palliation of breast, prostate, cervical cancer, and bone metastases

Appendix

A. SURVEY

A survey of the practice patterns of radiation oncologists in breast cancer, prostate cancer, cervical cancer and bone metastasis

Thank you for agreeing to take part in this study. This questionnaire surveys the practice patterns of radiation oncologists in the treatment of breast cancer, prostate cancer, cervical cancer and bone metastases.

This survey is sponsored by the ESTRO-GIRO (Global Impact of Radiotherapy in Oncology) partnership.

Instructions:

1. This study is voluntary and you can skip any questions you do not want to answer.
2. All information will be kept confidential and will be used only for academic research purposes.

For any questions or comments, please contact Gabriella Axelsson at: gaxelsson@estro.org

Thank you for your participation.

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY

SECTION 1: DEMOGRAPHICS

1- Age (Drop-down menu in SurveyMonkey):

2- Sex *Choose an item.*

3- Country of current practice (Drop-down menu in SurveyMonkey):

4- Country of training (Drop-down menu in SurveyMonkey):

5- Number of years in practice since completion of training: Choose an item.

6- Scope of practice (choose all that apply):
☐ University-affiliated hospital
☐ Public
☐ Private
☐ Public-private partnership
☐ Other, please specify *Click here to enter text.*

7- Estimated population size of your practice catchment area (choose one):
☐<10,000
☐10,000 – 50,000
☐50,000 – 100,000
☐100,000 – 500,000
☐500,000 – 1,000,000
☐>1,000,000

8- Do you have access to (choose all that apply):
☐Cobalt-60 machine
☐ MV Linac
☐ 2D-planning
☐ CT-based 3D-planning
☐ 3D-conformal therapy
☐ Intensity modulated radiotherapy (IMRT)
☐ Stereotactic body radiotherapy (SBRT)
☐ kV imaging
☐ MV imaging
☐ Cone beam CT (CBCT) imaging
☐ High-Dose Rate (HDR) Brachytherapy
☐ Low-Dose Rate (LDR) Brachytherapy
☐ Pulsed-Dose Rate (PDR) Brachytherapy

SECTION 2. BREAST CANCER

1- What is the approximate number of breast cases you see per month? *Choose an item* (<5, 6-10 times, 11-20, 21-50 cases, >50 cases)

2- What is the approximate number of breast cases in your department per month? *Choose an item.*

Assuming the decision has been made to proceed with radiotherapy for the following patients, which of the following treatment options do you **preferably recommend** to your breast cancer patients?

Clinical Scenario		**Preferred fractionation schedule (conventional vs hypofractionation vs both)**	**If both is selected, % of patients for whom you use hypofractionation**	**Hypofractionation regimen used**
After breast conserving surgery	Node Negative	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
	Node Positive	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
After Mastectomy	Node Negative	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
	Node Positive	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
Palliative symptom control		Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.

Notes: The dropdown menu for preferred fractionation schedule allowed respondents to select from one of the following options: 1) conventional fractionation (1.8-2.0 Gy/fx); 2) hypofractionation (≥2.1 Gy/fx); 3) both. The dropdown option for

3- If you offer hypofractionation, which of the following rationales support your choice (choose all that apply):

Evidence Base

☐ Regimen supported by published evidence
☐ Equivalent local control compared to conventional fractionation
☐ Equivalent toxicities compared to conventional fractionation

Practical Reasons

☐ More optimal use of resources (liberate machine time to increase access for patients)
☐ More optimal use of resources (liberate machine time to allow other complex treatments)
☐ More convenient to patients (less travels / less time away from home)

Economic Reasons

☐ More efficient use of resources (less expensive treatment strategy)
☐ Better reimbursement

Preferences
☐ Personal preference/prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient preference

☐ None of the above

4- If you do not offer hypofractionation, why not? (choose all that apply)

Evidence Base
☐ Not enough long-term data available for hypofractionation
☐ Fear of inferior local control
☐ Fear of worse acute toxicity
☐ Fear of worse late toxicity

Practical Reasons
☐ Lack of advanced technology to allow hypofractionation

Economic Reasons
☐ Insufficient reimbursement

Preferences
☐ Personal preference/prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient Preference
☐ None of the above

SECTION 3. PROSTATE CANCER

1- What is the approximate number of prostate cases you see per month? *Choose an item.*(<5, 6-10 times, 11-20, 21-50 cases, >50 cases)

2- What is the approximate number of prostate cases in your department per month? *Choose an item.*

Assuming the decision has been made to proceed with radiotherapy for the following patients, which of the following treatment options do you **preferably recommend** to your prostate cancer patients?

Clinical Scenario	Preferred fractionation schedule (conventional vs hypofractionation vs both)	If both is selected, % of patients for whom you use hypofractionation	Hypofractionation regimen used
Low risk prostate cancer (≤T2a, Gleason ≤ 6, PSA <10 ng/ml)	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.

Intermediate risk prostate cancer (T2b to 2c, Gleason ≤ 6, and PSA ≤ 20 ng/mL or T1 to 2, Gleason = 7, and PSA ≤ 20 ng/mL)	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
High risk prostate cancer (T3 or Gleason 8-10 or PSA >20 ng/mL)	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
Prostate cancer requiring pelvic irradiation	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
Palliative symptom control	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.

3- If you offer hypofractionation, which of the following rationales support your choice (choose all that apply):

Evidence Base
☐ Regimen supported by published evidence
☐ Equivalent local control compared to conventional fractionation
☐ Equivalent toxicities compared to conventional fractionation

Practical Reasons
☐ More optimal use of resources (liberate machine time to increase access for patients)
☐ More optimal use of resources (liberate machine time to allow other complex treatments)
☐ More convenient to patients (less travel/less time away from home)

Economic Reasons
☐ More efficient use of resources (less expensive treatment strategy)
☐ Better reimbursement

Preferences
☐ Personal preference/prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient preference

☐ None of the above

4- If you do not offer hypofractionation, why not? (choose all that apply)

Evidence Base
☐ Not enough long-term data available for hypofractionation
☐ Fear of inferior local control
☐ Fear of worse acute toxicity
☐ Fear of worse late toxicity

Practical Reasons
☐ Lack of advanced treatment modalities to allow hypofractionation

Economic Reasons

☐ Insufficient reimbursement

Preferences
☐ Personal preference/ prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient Preference

☐ None of the above

SECTION 4. CERVICAL CANCER

5- What is the approximate number of cervical cancer cases you see per month? *Choose an item.*(<5, 6-10 times, 11-20, 21-50 cases, >50 cases)

6- What is the approximate number of cervical cancer cases in your department per month? *Choose an item.*

7- Assuming the decision has been made to proceed with radiotherapy (with concurrent chemotherapy and brachytherapy boost), which of the following treatment options do you **preferably recommend** to your non-metastatic cervical cancer patients?

Clinical Scenario	**Preferred fractionation schedule (conventional vs hypofractionation vs both)**	**If both is selected, % of patients for whom you use hypofractionation**	**Hypofractionation regimen used**
Locally advanced cervical cancer	Choose an item.	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.

8- If you offer hypofractionation, which of the following rationales support your choice (choose all that apply):

Evidence Base
☐ Regimen supported by published evidence
☐ Equivalent local control compared to conventional fractionation
☐ Equivalent toxicities compared to conventional fractionation

Practical Reasons
☐ More optimal use of resources (liberate machine time to increase access for patients)
☐ More optimal use of resources (liberate machine time to allow other complex treatments)
☐ More convenient to patients (less travel/less time away from home)

Economic Reasons
☐ More efficient use of resources (less expensive treatment strategy)
☐ Better reimbursement

Preferences
☐ Personal preference/prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient preference

☐ None of the above

9- If you do not offer hypofractionation, why not? (choose all that apply)

Evidence Base
☐ Not enough long-term data available for hypofractionation
☐ Fear of inferior local control
☐ Fear of worse acute toxicity
☐ Fear of worse late toxicity

Practical Reasons
☐ Lack of advanced treatment modalities to allow hypofractionation

Economic Reasons
☐ Insufficient reimbursement

Preferences
☐ Personal preference/ prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient Preference

☐ None of the above

SECTION 5. BONE METASTASIS

1- What is the approximate number of bone metastases cases you see per month? *Choose an item.*(<5, 6-10 times, 11-20, 21-50 cases, >50 cases)

2- What is the approximate number of bone metastasis cases in your department per month? *Choose an item.*

3- Assuming the decision has been made to proceed with radiotherapy for the following patients with bone metastasis, which of the following treatment options do you **preferably recommend**:

Clinical Scenario	**Preferred fractionation schedule (conventional vs hypofractionation vs both)**	**If both is selected, % of patients for whom you use hypofractionation**	**Hypofractionation regimen used**
Uncomplicated bone metastasis (no fracture, no cord compression)	***Choose an item.***	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
Bone metastasis with fracture	***Choose an item.***	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.
Bone metastasis with cord compression	***Choose an item.***	Choose an item.	Total dose Click here to enter text.

			Fraction number Choose an item.
Bone metastasis with important soft tissue component	***Choose an item.***	Choose an item.	Total dose Click here to enter text. Fraction number Choose an item.

4- If you offer hypofractionation, which of the following rationales support your choice (choose all that apply):

Evidence Base
☐ Regimen supported by published literature
☐ Equivalent pain control compared to conventional fractionation
☐ Equivalent toxicities compared to conventional fractionation
☐ Poor Performance status
☐ Expected poor prognosis of patient

Practical Reasons
☐ More optimal use of resources (liberate machine time to increase access for patients)
☐ More optimal use of resources (liberate machine time to allow other complex treatments)
☐ More convenient to patients (less travel/less time away from home)

Economic Reasons
☐ More efficient use of resources (less expensive treatment strategy)
☐ Better reimbursement

Preferences
☐ Personal preference/prior clinical experience
☐ Generally accepted treatment strategy among peers
☐ Patient preference

☐ None of the above

5- If you do not offer hypofractionation, why not? (choose all that apply)

Evidence Base

☐ Not enough long-term data available for hypofractionation
☐ Fear of inferior local and pain control
☐ Fear of worse acute toxicity
☐ Fear of worse late toxicity

Practical Reasons
☐ Lack of advanced treatment modalities to allow hypofractionation

Economic Reasons
☐ Insufficient reimbursement

Preferences
☐ Personal preference/prior clinical experience
☐ Generally accepted treatment strategy among peers

☐ Patient Preference

☐ None of the above

B. COUNTRY REPRESENTATION

The survey was disseminated through the membership databases and liasons of the following national and regional professional societies: the European Society for Radiotherapy and Oncology (ESTRO), the Canadian Association of Radiation Oncology (CARO), the Royal Australian and New Zealand College of Radiologists (RANZCR), the Federation of Asian Organizations for Radiation Oncology (FARO), the Japanese Society for Radiation Oncology (JASTRO), the Latin American Radiation Oncology Association (ALATRO), the Indian College of Radiation Oncology (AROI), the Indonesian Radiation Oncology Society (IROS), and the African Organization for Research and Training (AORTIC) radiation oncology membership. The survey was also administered to other international radiation oncologists through professional contacts of the International Atomic Energy Agency (IAEA) and snowball sampling of the study investigators.

eTable 1. Number of respondents by country of practice

COUNTRY	NO.
Europe	
Italy	151
United Kingdom of Great Britain and Northern Ireland	142
Spain	123
Germany	98
Denmark	66
Poland	57
Belgium	55
Portugal	54
Turkey	52
Netherlands	46
France	45
Romania	42
Switzerland	32
Greece	28
Austria	24
Sweden	23
Russian Federation	20
Norway	16
Israel	15
Slovakia	15
Hungary	14
Serbia	13

Georgia	12
Slovenia	12
Czech Republic	11
Ireland	11
Bulgaria	9
Croatia	9
Kazakhstan	9
Macedonia	9
Finland	7
Estonia	6
Albania	5
Bosnia and Herzegovina	5
Belarus	4
Ukraine	4
Azerbaijan	2
Lithuania	2
Montenegro	2
Uzbekistan	2
Andorra	1
Cyprus	1
Iceland	1
Kyrgyzstan	1
Latvia	1
Republic of Moldova	1
Asia-Pacific	
Japan	163
India	113
Indonesia	34
Australia	29
Philippines	22
China	15
Thailand	15
Bangladesh	10
Malaysia	10
Nepal	8
Myanmar	4
New Zealand	3
Republic of Korea	3
Sri Lanka	3
Singapore	2
Vietnam	2
Cambodia	1

Papua New Guinea	1
North America	
Canada	89
United States of America	57
Africa	
Nigeria	17
South Africa	15
Kenya	5
Ghana	4
Namibia	4
United republic of Tanzania	4
Angola	3
Botswana	3
Uganda	2
Zimbabwe	2
Cameroon	1
Ethiopia	1
Madagascar	1
Mauritania	1
Senegal	1
Latin America	
Brazil	134
Mexico	49
Chile	17
Colombia	15
Venezuela (Bolivarian Republic of)	15
Argentina	8
Peru	7
Dominican Republic	6
Uruguay	5
Bolivia (Plurinational State of)	4
El Salvador	4
Costa Rica	3
Ecuador	3
Honduras	3
Nicaragua	3
Barbados	2
Paraguay	2
Trinidad and Tobago	2
Antigua and Barbuda	1
Bermuda	1
Cuba	1

Guyana	1
Middle East	
Saudi Arabia	19
Pakistan	18
Iraq	14
Egypt	10
Morocco	10
Tunisia	9
Jordan	8
Lebanon	8
Sudan	7
Afghanistan	4
Qatar	4
Algeria	3
Iran (Islamic Republic of)	3
Bahrain	2
United Arab Emirates	2
Libya	2
Syrian Arab Republic	1
Yemen	1

eTable 2. Number of respondents by country of training

COUNTRY	NO.
Europe	
Italy	162
United Kingdom of Great Britain and Northern Ireland	145
Spain	136
Germany	109
Denmark	68
France	68
Poland	66
Belgium	57
Turkey	57
Portugal	55
Netherlands	50
Romania	43
Greece	27
Switzerland	26
Austria	22
Sweden	22
Russian Federation	19
Serbia	16
Hungary	15
Ireland	15
Slovakia	14
Norway	13
Czech Republic	12
Slovenia	12
Israel	11
Croatia	10
Kazakhstan	9
Macedonia	9
Bulgaria	6
Estonia	6
Finland	6
Belarus	4
Bosnia and Herzegovina	4
Albania	3
Georgia	3
Lithuania	3
Ukraine	3
Azerbaijan	2

Republic of Moldova	2
Andorra	1
Kyrgyzstan	1
Uzbekistan	1
APAC	
Japan	162
India	132
Indonesia	32
Australia	27
Philippines	23
Thailand	17
China	15
Malaysia	6
Myanmar	4
Nepal	4
Bangladesh	3
Republic of Korea	3
New Zealand	2
Singapore	2
Sri Lanka	2
Bhutan	1
Vietnam	1
North America	
Canada	89
United States of America	87
Africa	
South Africa	27
Nigeria	14
Zimbabwe	5
Ghana	3
Kenya	1
Latin America	
Brazil	135
Mexico	42
Venezuela (Bolivarian Republic of)	17
Argentina	15
Chile	12
Colombia	10
Peru	9
Uruguay	5
Cuba	4

Barbados	1
Costa Rica	1
Ecuador	1
Honduras	1
Middle East	
Egypt	19
Pakistan	18
Iraq	10
Jordan	9
Morocco	7
Sudan	4
Tunisia	4
Algeria	4
Afghanistan	3
Iran (Islamic Republic of)	3
Lebanon	3
Saudi Arabia	1
Syrian Arab Republic	1
Bahrain	1
State of Palestine	1

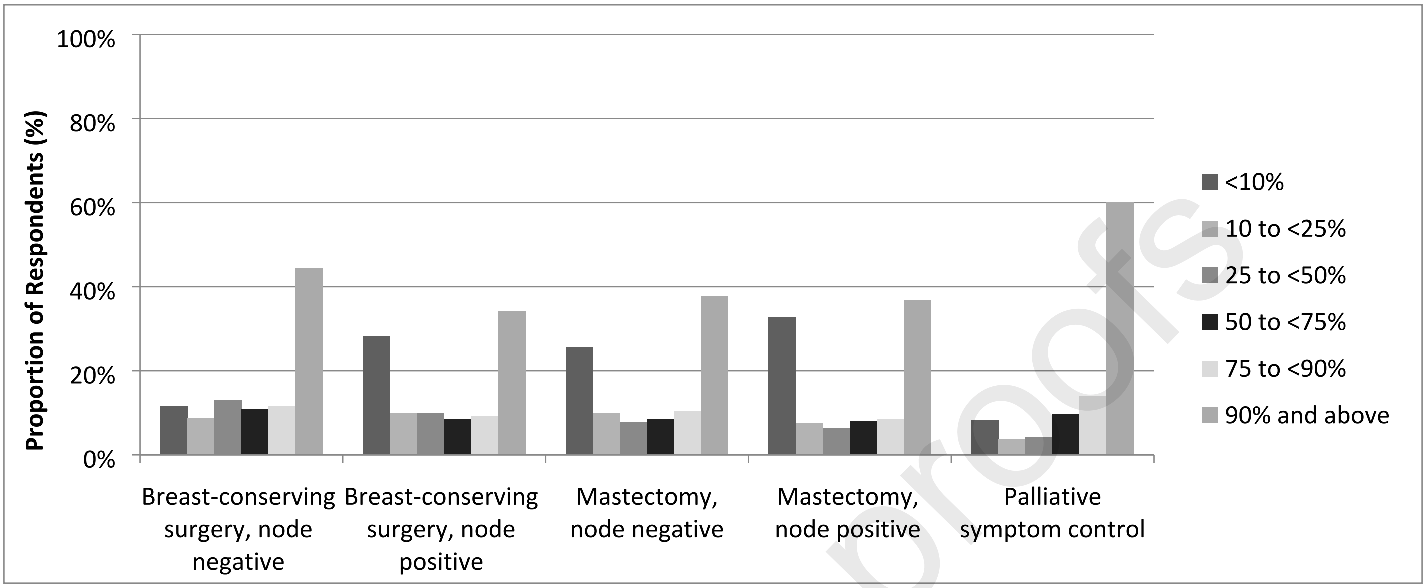
C. HYPOFRACTIONATION PREFERENCES

eTable 3. Hypofractionation preference by geographic region and disease site

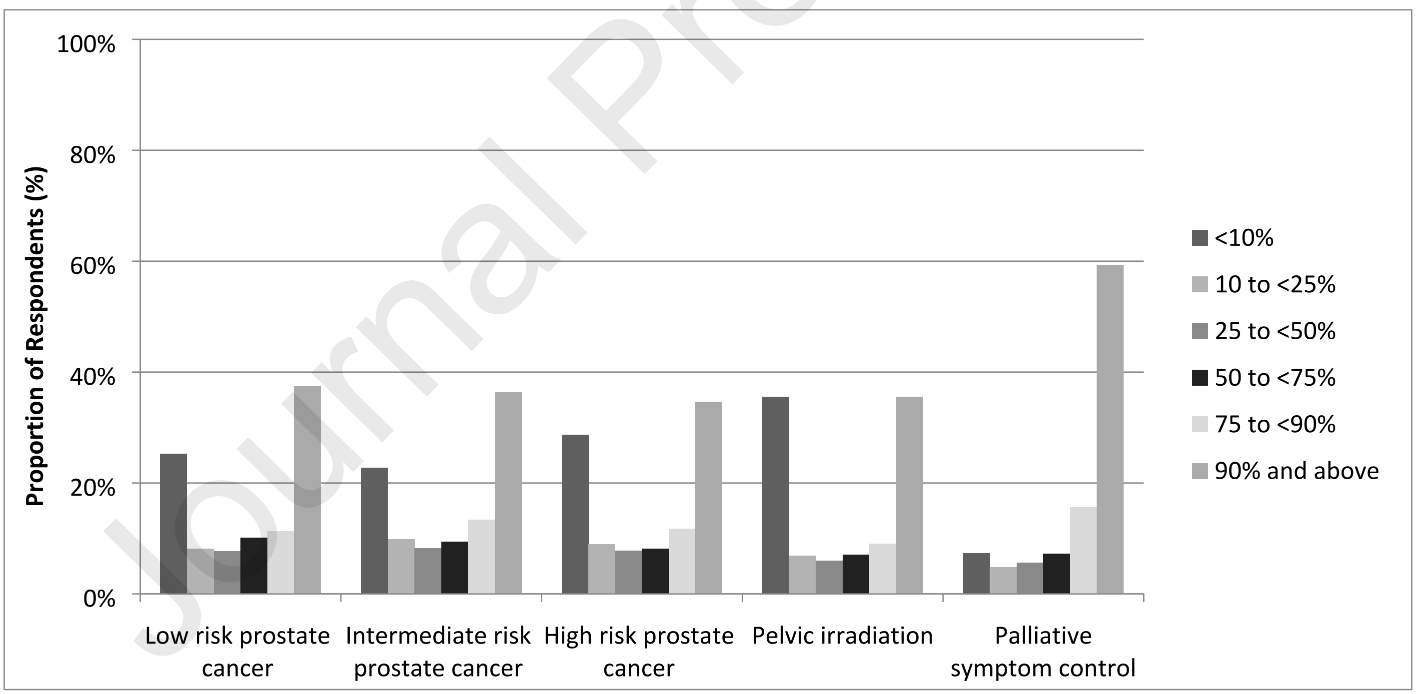
	Europe	North America	Asia-Pacific	Latin America	Middle East	Africa	Total	p-value
Breast								
Lumpectomy, Node Negative	89%	97%	72%	77%	76%	40%	82%	<0.001
Lumpectomy, Node Positive	48%	43%	43%	36%	61%	36%	46%	<0.002
Mastectomy, Node Negative	50%	54%	35%	38%	71%	49%	47%	$<10^{-8}$
Mastectomy, Node Positive	35%	35%	23%	25%	54%	47%	32%	<0.001
Palliative Symptom Control	95%	99%	91%	92%	96%	82%	94%	<0.001
Prostate								
Low-Risk	67%	94%	42%	44%	31%	19%	57%	<0.001
Intermediate-Risk	63%	88%	41%	37%	31%	23%	54%	<0.001
High-Risk	49%	59%	36%	25%	23%	32%	42%	<0.001
Pelvic Irradiation	28%	30%	17%	16%	11%	29%	24%	<0.001
Palliative Symptom Control	93%	100%	91%	85%	84%	90%	92%	<0.001
Cervix								
Locally Advanced	9%	0%	5%	10%	6%	32%	9%	<0.001
Palliative Symptom Control	86%	97%	81%	83%	76%	84%	84%	<0.038
Bone Metastases								
Uncomplicated	98%	100%	96%	90%	95%	97%	96%	<0.000039
With Fracture	96%	98%	97%	93%	97%	93%	96%	<0.1649
With Cord Compression	95%	97%	98%	92%	90%	97%	95%	<0.008001
With Soft Tissue Component	94%	97%	92%	86%	88%	93%	92%	<0.001575

eTable 4. Proportion of respondents for whom hypofractionation is preferred by disease site

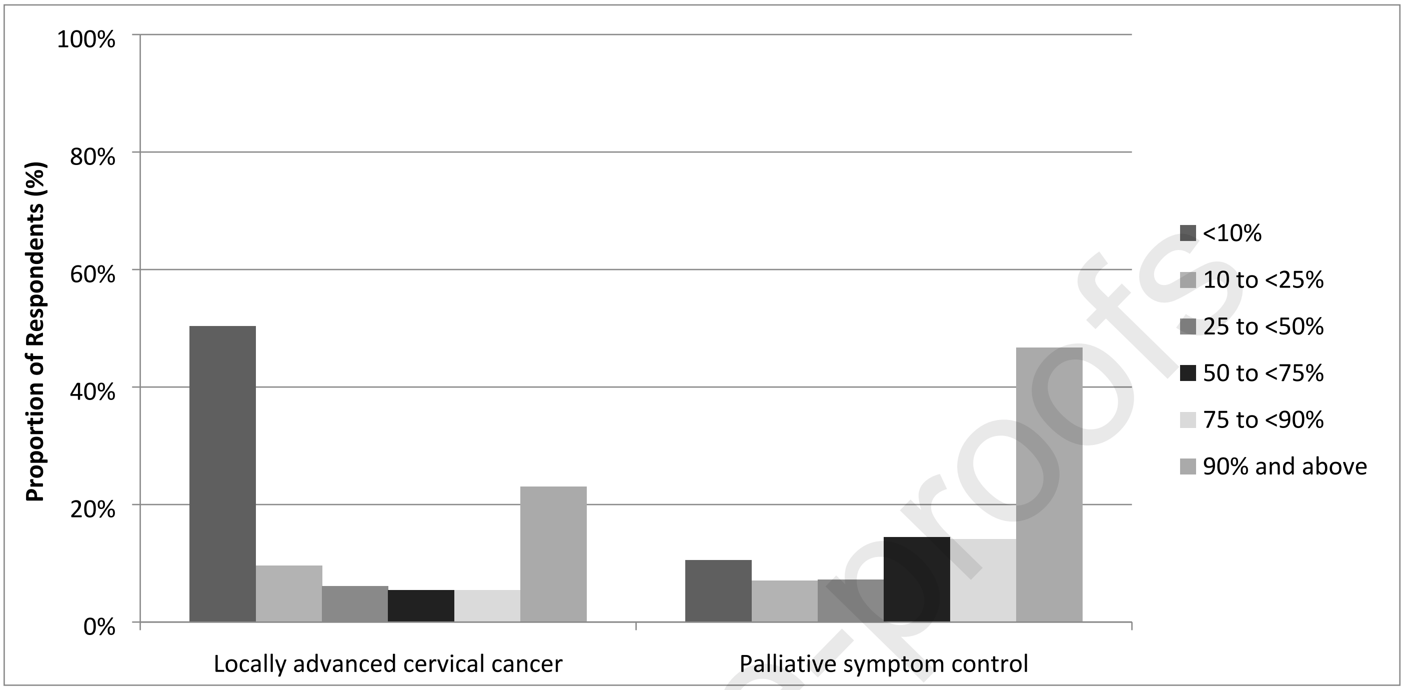
A. Breast



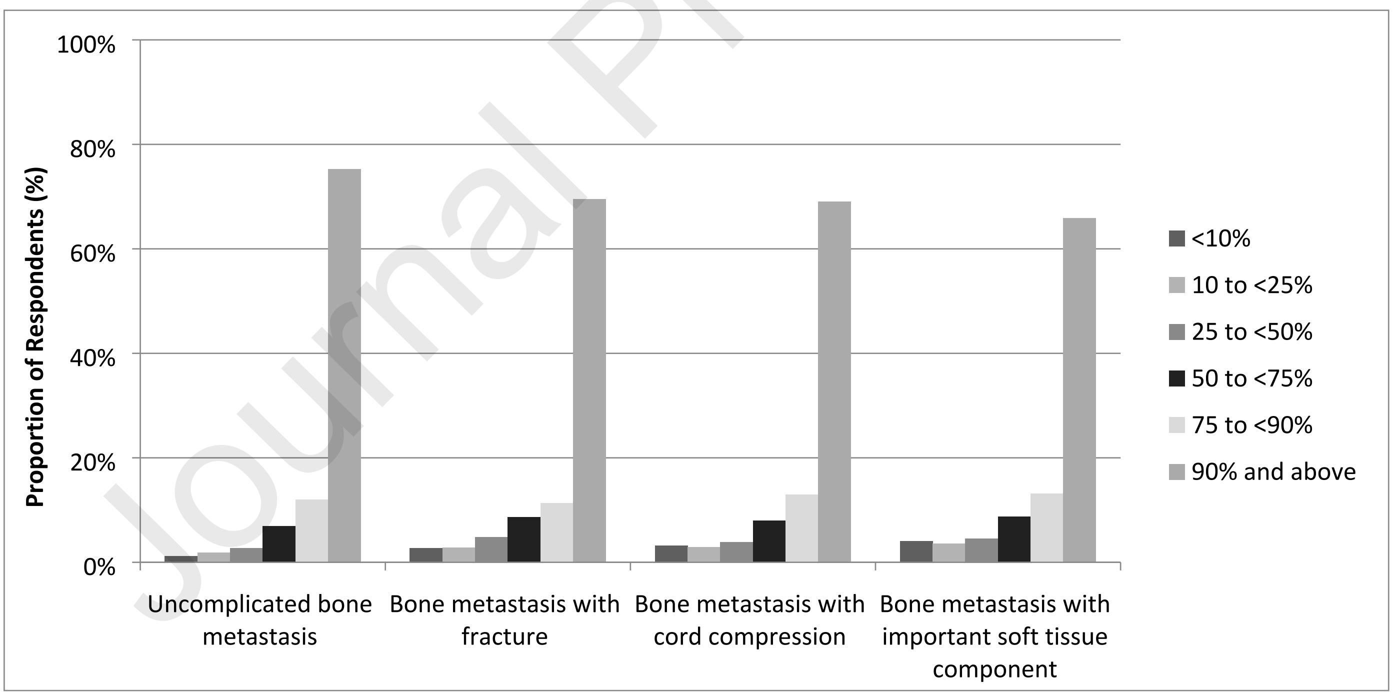
B. Prostate



C. Cervix

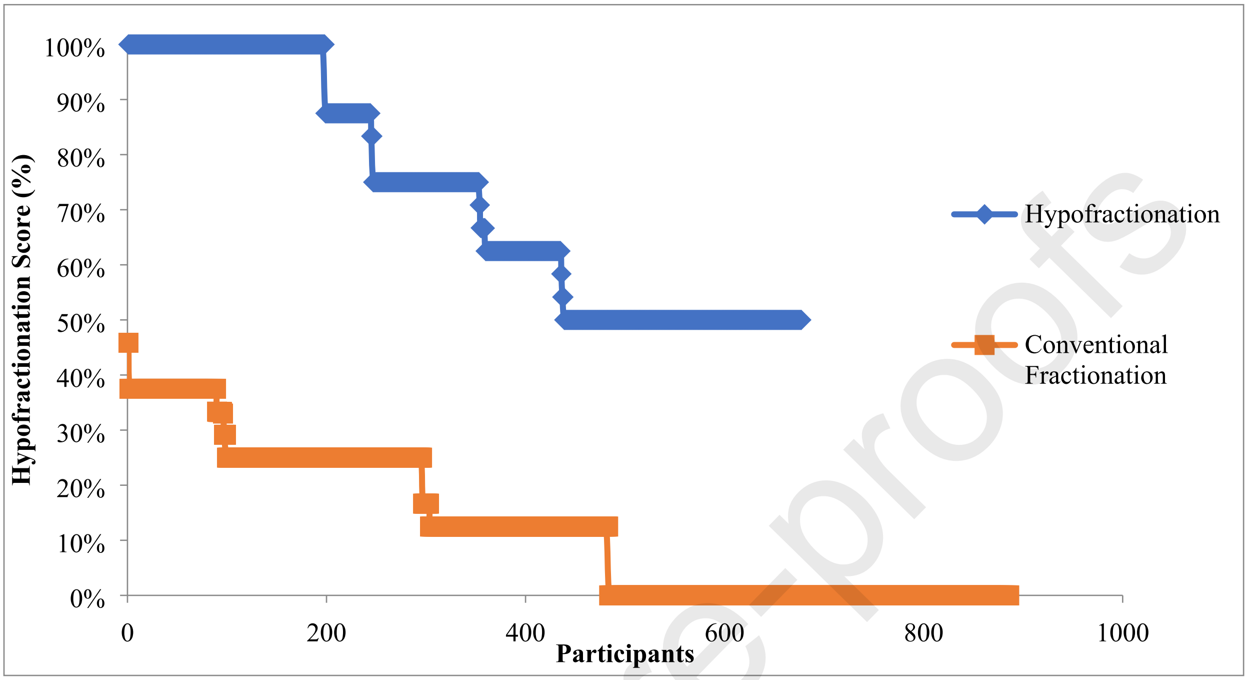


D. Bone Metastases



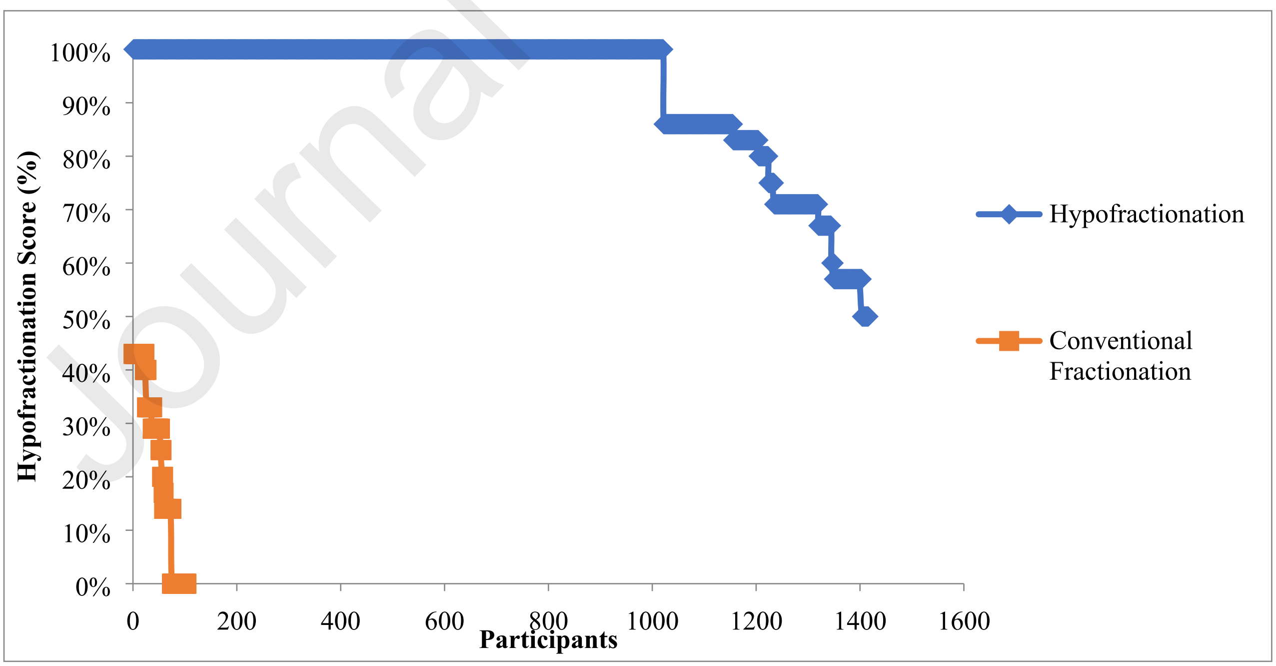
eTable 5. Global Hypofractionation Preferences

Curative



Notes: A hypofractionation user was defined in the multivariate analysis as a respondent who indicated a preference for hypofractionation in ≥75% of patients in a given scenario and in ≥50% of scenarios. Respondents' average hypofractionation preference across scenarios was determined and is plotted around the 50% cut-off point.

E. **Palliative**



Notes: A hypofractionation user was defined in the multivariate analysis as a respondent who indicated a preference for hypofractionation in ≥75% of patients in a given scenario and in ≥50% of scenarios. Respondents' average hypofractionation preference across scenarios was determined and is plotted around the 50% cut-off point.