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Original Article

Hypofractionated radiation therapy for breast cancer: Preferences amongst radiation oncologists in Europe – Results from an international survey

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ABSTRACT

Background and purpose: We aimed to assess the prescription preference about hypofractionated radiation therapy (HFRT) for breast cancer (BC) patients amongst radiation oncologists (ROs) practicing in Europe and to identify restraints on HFRT utilisation.

Materials and methods: An online survey was circulated amongst ROs in Europe through personal, RO and BC societies' networks, from October 2019 to March 2020. The statistical analyses included descriptive statistics, chi-squared testing, and logistic regression analysis.

Results: We received 412 responses from 44 countries. HFRT was chosen as the preferred schedule for whole breast irradiation (WBI) by 54.7% and for WBI with regional nodes irradiation (RNI) by 28.7% of the responding ROs. In the case of postmastectomy RT with or without reconstruction, HFRT was preferred by 21.1% and 29.6%, respectively. Overall, 69.2% of the responding ROs selected at least one factor influencing the decision to utilise HFRT, the most frequent of which included age (51.4%), RNI (46.9%), internal mammary lymph nodes irradiation (39.7%), BC stage (33.5%) and implant-based breast reconstruction (31.6%). ROs working in academic centres (odds ratio, (OR), 1.7; 95% confidence interval, (CI); 1.1–2.6, $p = 0.019$), practicing in Western Europe (OR, 4.2; 95%CI; 2.7–6.6, $p < 0.0005$) and/or dedicating >50% of clinical time to BC patients (OR, 2.5; 95%CI; 1.5–4.2, $p = 0.001$) more likely preferred HFRT.

Conclusion: Although HFRT is recognised as a new standard, its implementation in routine RT clinical practice across Europe varies for numerous reasons. Better dissemination of evidence-based recommendations is advised to improve the level of awareness about this clinical indication.

Breast cancer (BC) is the most common cancer in women [1], and post-operative radiation therapy (RT) is a fundamental part of treatment after either conservative surgery or mastectomy [2–4]. BC ranks as the first amongst all cancer types with respect to the absolute numbers of RT indications needed in the forthcoming years in more than half of the European countries [5]. Furthermore, it has been estimated that the number of RT courses for BC patients in Europe will increase on average by 10.1% from 2012 to 2025 [5].

Conventionally fractionated radiation therapy (CFRT), delivering 45–50 Gy in 1.8–2.0 Gy daily fractions for 5 days per week over 5–7 weeks, was empirically introduced into the clinics aiming to eradicate sub-clinical disease while efficiently sparing healthy tissues. CFRT was the schedule employed in early pivotal trials, comparing breast-conserving therapy to mastectomy [6,7], paving the way for CFRT to become a standard approach for BC post-operative RT for many years.

After the publication of long-term results of randomised controlled trials (RCTs) comparing safety and effectiveness of hypofractionated RT (HFRT) delivered in three weeks, vs CFRT, HFRT in node-negative BC has been increasingly implemented [8–12]. Starting in 2008, numerous national and international guidelines recommended hypofractionated (HF) whole breast irradiation (WBI) as the new standard. HFRT was primarily suggested for selected patients with BC [13,14] with subsequent extension to all patients requiring WBI [15–17].

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In certain countries, shortened fractionation schedules have been implemented not only for WBI but also for nearly every indication, including regional nodal irradiation (RNI) and postmastectomy radiation therapy (PMRT). Cost-effectiveness [18], limited resources [19], excessively long RT waiting lists [20], and patients' convenience prioritisation [18] were all stated as the most common factors behind HFRT utilisation. Another important argument for the use of HFRT is that 40 Gy in 15 fractions, even assuming α/β of 1.5 Gy, is biologically milder or, at worst, isoeffective for healthy tissues compared to CFRT [21]. Moreover, using modern RT treatment planning, allowing for homogeneous dose distribution, hot spots contributing to the so called "double-trouble" or "triple-trouble" effects may be consistently avoided [18,21,22]. Marta GN et al. provides a detailed overview on the use of moderately hypofractionated post-operative RT for patients with BC in clinical practice, focusing on factors influencing clinical decision making [23].

Considering the evidence on the advantages of HFRT and assuming there might be variations regarding its implementation in clinical practice, we set up an online survey to assess the current patterns of practice and to identify factors that influence the decision-making process with respect to fractionation for BC patients in Europe.

Materials and methods

An anonymous, 38-question electronic survey was distributed to ROs practicing in Europe (World Health Organization definition of Europe) through personal contacts, European Society of Breast Cancer Specialists (EUSOMA) and RT national societies' networks from October 2019 to March 2020. The survey was created with the 1KA survey platform [24] and covered different topics in RT practice for early BC (see Appendix 1). Questions were designed on a multi-choice frame, allowing for multiple responses as well as free-text replies. In the present study, we report on the different aspects of fractionation use in post-operative BC RT. Participating ROs were also geographically allocated according to classifications in DIrectory of RAdiotherapy Centres (DIRAC) as follows: Western Europe (WE), Eastern Europe and Northern Asia (EENA) and Middle East (ME) [25].

The statistical analyses included descriptive statistics and chi-squared testing. Binary multivariate logistic regression analysis was also performed to recognise factors related with the preferred use of the HFRT schedule. All tests were two-sided, and a statistic level of significance was set to p values <0.05. Statistical analyses were carried out using IBM SPSS Statistics software version 26 (statistical package for the Social Sciences Statistical Software; SPSS Inc., IBM corporation, Armonk, NY, USA). Figures were created using mapchart.net and Microsoft® Excel® for Office 365 version 1812 (Microsoft Corporation, One Microsoft Way Redmond, WA, USA).

Results

We received 412 valid responses (277 totally and 139 partially completed questionnaires) from 44 countries. In total, the survey reached 1525 ROs, which results in a 27% response rate. The estimated percentage of responding ROs from each country ranged from 0.6% to 33.3% (Appendix B). About half of the respondents (50.6%) were working in an academic environment, and most of them (73.7%) were older than 35 years. The vast majority of respondents (80.3%) were experienced ROs who had worked in the RT field for ≥5 years and treated ≥10 patients with BC per month (53.9%). Compared with ROs from academic practice, ROs from non-academic practice were less likely to work in the RT field for >10 years (29.7 vs. 27.2, p = 0.012). Except for this aspect, the two groups were well balanced (Table 1). In WE countries, 54.2% of ROs were practicing in academic centres, compared to 46.4% in EENA-ME countries (p = 0.440). A detailed analysis of the survey's response rates is presented in Appendix B.

The proportion of participating ROs preferring HFRT as their first choice in four different clinical settings ranged from 0% to 100%. ROs from seven countries (Albania, Belgium, Iceland, Ireland, Malta, the Netherlands, and the United Kingdom) consistently selected HFRT as a favoured fractionation schedule irrespective of the clinical setting (Fig. 1). Overall, in the case of WBI, 54.7% of the 371 responding ROs preferred HFRT. The use of both schedules (HFRT and CFRT) was declared by 28.0%, while CFRT was preferred by 17.3% (Fig. 2).

For WBI with RNI, HFRT was preferred by 28.7% of respondents. In the case of patients receiving PMRT with or without reconstruction, HFRT was chosen by 21.1% and 29.6%, respectively. In contrast, CFRT was preferred by 17.3%, 55.1%, 54.3% and 72.5% of the responding ROs for patients receiving WBI, WBI with RNI, or PMRT without or with reconstruction, respectively (Appendix C).

ROs from academic centres were more likely than those working in non-academic practice to favour HFRT as their first choice: 61.6% vs. 47.5% (p = 0.006) in case of WBI, 40.4% vs. 22.6% (p = 0.008) in case of WBI with RNI, and 28.5% vs. 14.9% (p = 0.008) for patients with reconstructed breasts receiving PMRT. However, for the patients without reconstruction, there was no statistically significant difference in choosing HFRT schedule (37.6% vs. 25.5%; p = 0.099). In multivariate analysis, working in an academic centre (odds ratio, (OR), 1.7; 95% confidence interval, (CI), 1.1–2.6, p = 0.019) and dedicating ≥50% of clinical time to BC patients (OR 2.5, 95% CI 1.5–4.2, p = 0.001) were found to be significantly associated with the choice of HFRT as the preferred schedule in case of WBI. The distribution of the favoured fractionation schedule considering different clinical settings and type of practice (academic vs. non-academic) is presented in Fig. 3.

Participating ROs practicing in WE were more likely to prefer HFRT for WBI (OR, 4.2; 95% CI; 2.7–6.6, p < 0.0005), WBI with RNI (OR, 2.4, 95% CI 1.5–3.9, p < 0.0005), PMRT without reconstructed breast (OR, 2.6, 95% CI; 1.6–4.2, p < 0.0005), or PMRT with reconstructed breast (OR, 3.2; 95% CI; 1.8–5.5, p < 0.0005) compared to ROs practicing in EENA-ME countries.

When adding a boost dose to the primary tumour bed, 46.0% of all respondents would offer a CFRT boost, while 37.3% would offer a HFRT boost (i.e., 3–4 daily fractions of 2.5–3.0 Gy). Sequential boost was preferred by 38.4% and simultaneous integrated boost (SIB) by 30.8% of the participating physicians, respectively. ROs practicing in WE were more likely to select HFRT boost schedule (58.3% vs. 41.7%, p = 0.015) and SIB (64.0% vs. 36.0%, p < 0.0005) compared to ROs practicing in EENA-ME. The use of SIB, CFRT or HFRT boost did not differ with respect to the type of practice or dedicated clinical time to patients with BC.

Factors influencing ROs' decisions to recommend HFRT schedules are detailed in Table 2, and the ROs' views on contraindications of HFRT, both for academic and non-academic practice, are presented in Table 3. Overall, 69.2% ROs selected at least one of the factors mentioned in the survey as drivers of their decisions, and 58.7% ROs considered at least one of the suggested options as an absolute contraindication to use HFRT schedules.

ROs dedicating ≥50% of their clinical time to patients with BC were less likely to have been influenced in their decisions to choose HFRT schedules by the age of the patient (12.3% vs. 39.2%, p = 0.007), BC stage (6.7% vs 26.6%, p = 0.003) or breast size (5.9% vs. 21.8%; p = 0.021) and were less concerned about HFRT schedules with respect to the dose to OARs (5.3% vs. 21.8%; p = 0.007) or by any of the factors mentioned in the survey (8.7% vs. 10.6%,

Table 1
Respondents' demographics.

Characteristics		All respondents		Academic practice		Non-academic practice		*p* value
		N	%	*N*	%*	*N*	%*	
Age group (*N* = 400) (years)	<35	105	26.0	56	13.9	49	12.1	0.263
	35–45	122	30.2	68	16.8	54	13.4	
	46–60	147	36.3	64	15.8	83	20.5	
	61–7	26	6.4	17	4.2	9	2.2	
Years in practice (*N* = 401)	<5	79	19.7	44	11.0	35	8.7	0.012
	5–10	94	23.4	43	10.7	51	12.7	
	11–20	103	25.7	60	15.0	43	10.7	
	>20	125	31.2	59	14.7	66	16.5	
N of patients with BC treated per month (*N* = 393)	<5	39	9.9	21	5.3	18	4.6	0.308
	5–10	134	34.1	59	15.0	75	19.1	
	11–20	114	29.0	65	16.5	49	12.5	
	>20	98	24.9	50	12.7	48	12.2	
N of ROs treating BC patients in participant's place of work (*N* = 389)	<5	142	36.5	63	16.2	79	20.3	0.060
	≥5	247	63.5	134	34.3	113	29.0	
% of clinical time, dedicated to BC (*N* = 386)	<25%	115	29.3	60	15.5	55	14.2	0.618
	25–50%	159	41.2	80	20.7	79	20.5	
	51–75%	61	15.8	30	7.8	31	8.0	
	>75%	51	13.2	21	5.4	30	7.8	

Abbreviations: Abbreviations: *N* = Number of the respondents, BC = Breast cancer, RO = Radiation oncologist, % = Percentage of respondents within the column

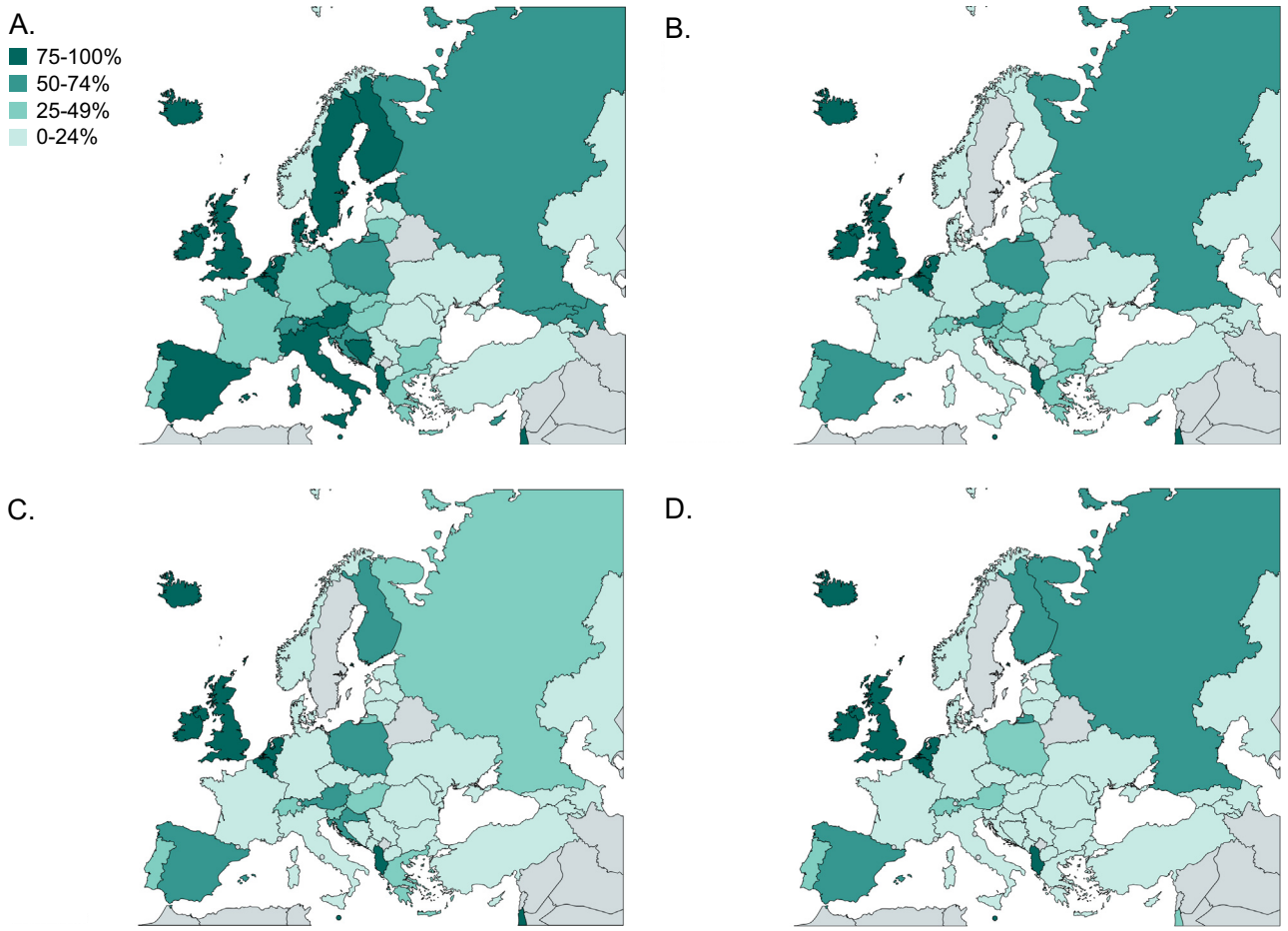

Fig. 1. The proportion of participating radiation oncologists preferring hypofractionated fractionated schedule as their first choice in four different clinical settings. (A) Whole breast irradiation; (B) whole breast and regional nodes irradiation; (C) postmastectomy radiation therapy without reconstruction; (D) postmastectomy radiation therapy with reconstruction.

p = 0.003), compared to ROs who dedicated <50% of their time to patients with BC. Similarly, age of the patient (1.7% vs. 9.0%; p = 0.044), BC stage (0.6% vs. 9.0%, p = 0.001), breast laterality (0% vs. 3.8%, p = 0.015), tumour grade (0% vs. 3.8%; p = 0.015), dose to OARs during HFRT schedule (3.2% vs. 13.7%, p = 0.035) or none of the factors (16.0% vs. 24.8%, p = 0.004) were less likely considered as absolute contraindications by physicians dedicating ≥50% of their time to patients with BC.

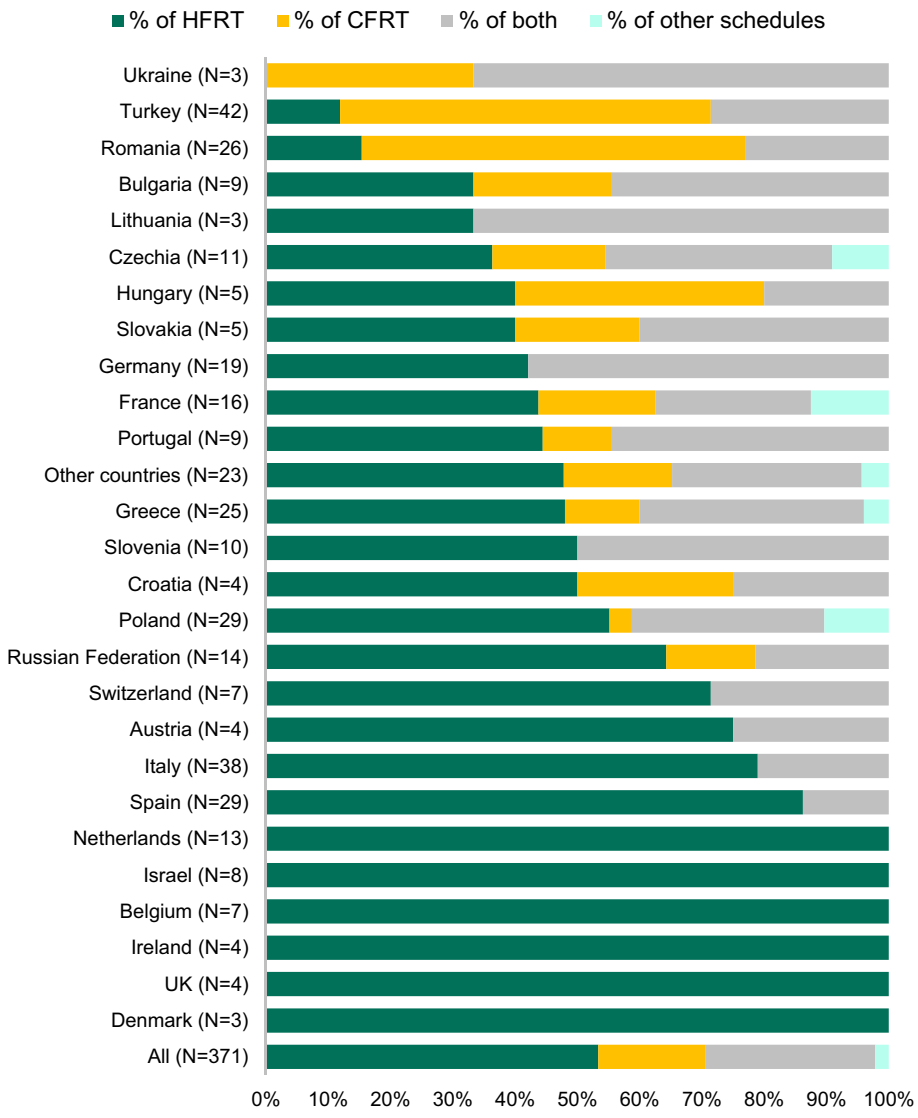

Fig. 2. Participating radiation oncologists and their fractionation preference for patients receiving whole breast radiation therapy. Only countries with ≥3 participating radiation oncologists are shown in this figure. Other schedules listed by radiation oncologists included 17× 2.5 Gy, 20× 2.5 Gy and 15× 2.8 Gy (4 fractions per week). *Abbreviations*: HFRT = Hypofractionated radiation therapy, CFRT = Conventionally fractionated radiation therapy, *N* = Number of the respondents from each country, UK = The United Kingdom.

Factors influencing the clinical decision-making process with respect to HFRT use differed by geographical location. ROs from WE, as compared to ROs from EENA-ME countries, less frequently reported the influence on their decisions by the age of the patient, BC stage and grade, breast laterality, surgical margins, dose to OARs and financial reimbursements (Appendix D).

Discussion

With this study, we assessed the current European ROs' preferences and views regarding the use of HFRT schedules in the setting of post-operative RT in BC. Herein we report on a considerable disparity regarding HFRT utilisation preference across different clinical settings. In our survey, the overall preference for HF-WBI by the responding ROs was 54.7% and ranged from 0% (9 countries) to 100 % (13 countries). Overall, ≥30% of the responding ROs acknowledged the decision to utilise HFRT in clinical practice to be affected by at least one of these factors: patient's age, the need for RNI, internal mammary lymph node chain RT, BC stage and RT following implant-based breast reconstruction. However, HFRT was consistently selected as a favoured fractionation schedule irrespective of the clinical setting in seven countries (Albania, Belgium, Iceland, Ireland, Malta, the Netherlands, and the United Kingdom).

Other researchers have also described the infrequent use of HF-WBI and various concerns regarding higher daily fractionation dose, even after the publication of key clinical studies. The reported HF-WBI utilisation rates vary across the globe, from 34.5% to 95%, [20,26–29], reflecting geographical and also time variations, and the most common regimes are 40.05–42.56 Gy, delivered in 15–16 fractions [27–29]. Younger age [27–30], breast laterality [28,30], breast volume [30], radiation plan (in)homogeneity [27], receipt of adjuvant chemotherapy [27,28,30], BC stage [27] and triple-negative biology [28] were all reported to lead to lower HF-WBI utilisation. The use of HFRT schedules is likewise not universally adopted in patients with BC who require PMRT or RNI due to concerns regarding acute and late toxicities, especially with respect to lymphedema, shoulder symptoms and peripheral neuropathy [29,31]. In our study, we have identified factors limiting HF-WBI utilisation in the routine clinical practice that ≥20% of

the responding ROs addressed: breast size, the impact of higher dose per fraction on the dose to OARs and treatment plan inhomogeneity. HFRT is reportedly underutilised in large-sized breast BC patients [32], although with modern RT planning, there is no reason to withhold HFRT in women with large breasts, higher body mass index or longer central axis separation [33–35]. Nevertheless, large breast volume *per se* seems to be a risk factor for acute or late adverse events, independently of dose inhomogeneity, treatment planning technique or fractionation schedule used [34,36]. Recently, long-term data from the randomized phase III trial DBCG HYPO evaluating HFRT versus CFRT in patients with early BC or ductal carcinoma in situ were reported. The trial also included 188 (10.1%) patients with triple negative BC and 155 (8.4%) patients with human epidermal growth factor (HER2) positive BC, both molecular subtypes having relatively high recurrence risk. At 3-year follow up, the cosmetic outcome was at least equal for 40 Gy compared with 50 Gy RT schedule, irrespective to systemic therapies (taxane-based chemotherapy, trastuzumab, and letrozole), breast size (clinical target volume; ≤ volume > 600 cm^3), smoking status (never/prior vs. current) or RT boost (yes vs. no). At 9 years of follow up the overall survival was 93.4% in both fractionation groups, and the locoregional control was almost equal (97% for HFRT vs. 96.7% for CFRT) [37]. Fractionation sensitivity according to different BC molecular subtypes was also addressed in a large population-based cohort with prospectively collected outcomes (rates of local recurrence) and long-term follow-up. No significant interaction was found between BC molecular subtype and fractionation regimen [38].

HFRT schedules seem to be as safe as CFRT with respect to cardiac toxicity. The linear quadratic model indicates that 40 Gy in 15 fractions and 42.5 Gy in 16 fractions both spare the heart when compared to CFRT schedule, assuming that the late cardiac effects

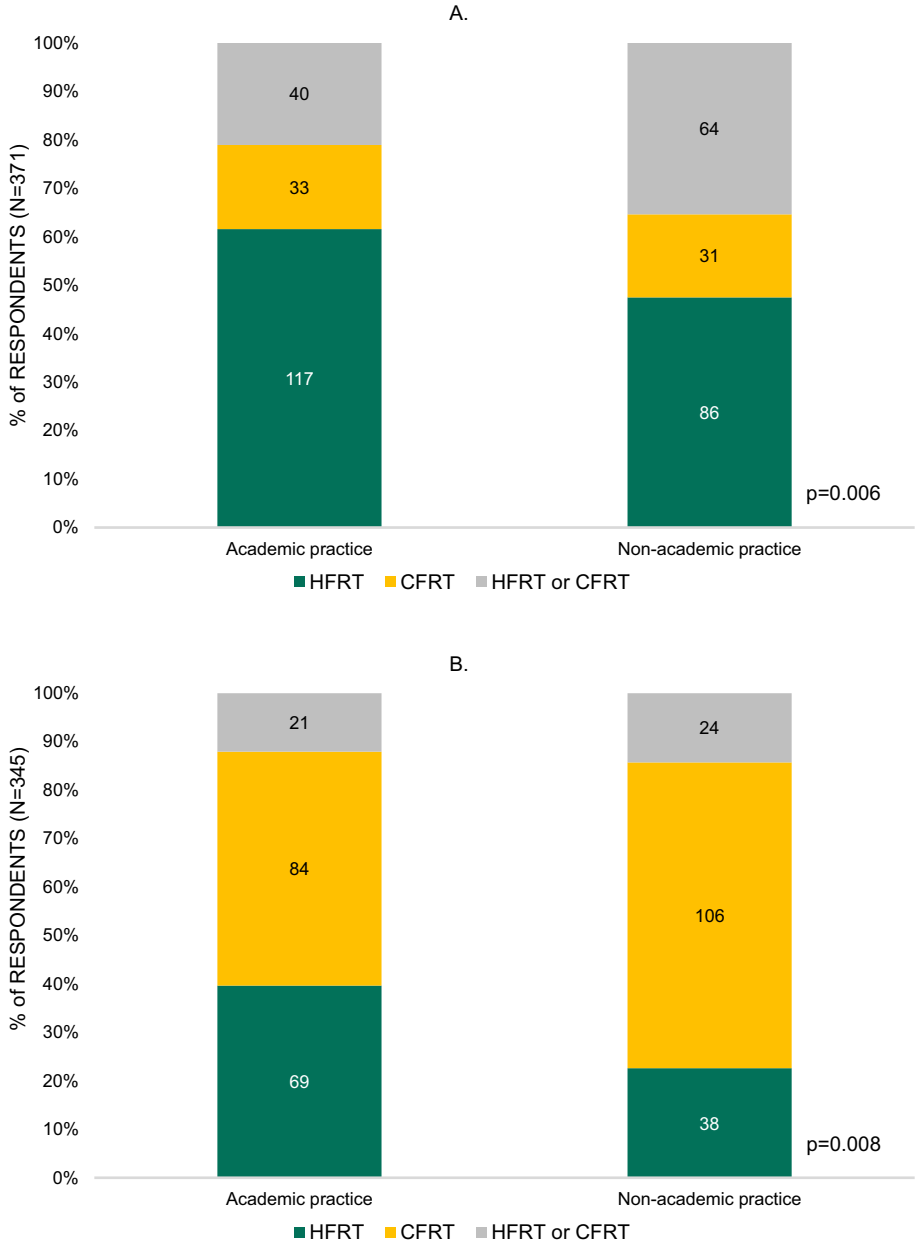

Fig. 3. The preferable use of fractionation schedules in academic vs. non-academic practice. (A) Whole breast irradiation; (B) Whole breast and regional nodes irradiation; (C) postmastectomy radiation therapy without reconstruction; (D) postmastectomy radiation therapy with reconstruction. *Abbreviations*: HFRT = Hypofractionated radiation therapy, CFRT = Conventionally fractionated radiation therapy, *N* = Number of the respondents.

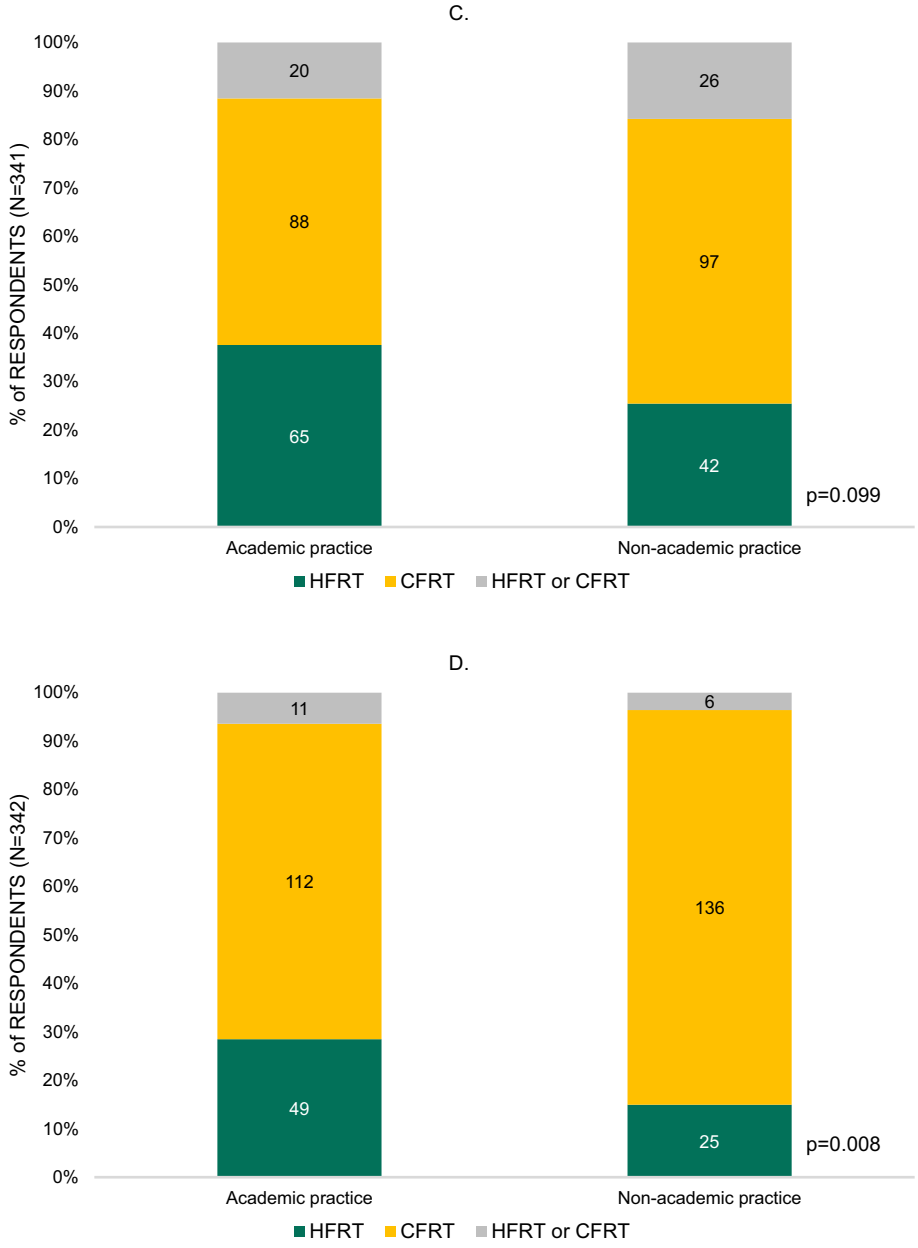

Fig. 3 (*continued*)

are not sensitive to overall treatment time and as long as $\alpha/\beta \geq 1.5$ Gy [39]. In addition, clinical studies demonstrated that HFRT schedule is not significantly associated with post-radiation cardiac toxicity, compared to CFRT [9,40,41]. However, regardless of the fractionation schedule used, cardiac-sparing techniques are advised in clinical practice whenever possible to avoid unnecessary dose to the heart and other OARs.

Although the use of HFRT is scientifically grounded in terms of efficacy and safety with level I evidence, scientific debate continues about generalising RCTs' results for those patients' subgroups that were underrepresented in clinical trials. Only about 25% of patients in Standardisation of Breast Trials (START) and Canadian trials were younger than 50 years, less than 25% of patients received adjuvant chemotherapy, about one-third had node-positive disease, less patients had tumour stage ≥T2, few had mastectomies (15%) and a smaller proportion (<15%) received RNI [8–10,42]. In addition, patients requiring comprehensive nodal irradiation, as well as patients with flap- or implant-based breast reconstruction, were not included in pivotal trials [8–10,42,43]. However, a subgroup analysis of START trials – though numbers were small in some groups – found no suggestion for a harmful effect of 40 Gy schedule in terms of higher risk of local–regional relapse or normal tissue effects with respect to patient age, breast size, tumour grade, axillary node status, type of surgery, adjuvant chemotherapy, tumour bed boost and RNI [40,44]. Recent prospective and retrospective data also added to the evidence that there are no identifiable reasons to avoid HFRT in patients with BC who require PMRT or RNI [43,45]. Wang et al. prospectively evaluated CFRT and HFRT (43.5 Gy in 15 fractions) in patients with high-risk BC following mastectomy and reported similar 5-year recurrence rates and no significant differences in acute or late toxicities, including skin, lung, heart toxicities, lymphedema and shoulder dysfunction, except for fewer grade 3 acute skin toxicities in the HFRT group [43]. This study was nevertheless criticised for using outdated

Table 2
Factors, influencing the decision of radiation oncologists to recommend hypofractionated schedule.

Factor	All respondents		Academic practice		Non-academic practice		*p* value
	N	%	*N*	%	*N*	%	
N of respondents	358	100	174	48.6	184	51.4	
At least one selected factor*	285	69.2	136	73.9	149	85.6	0.006
Age	184	51.4	78	44.8	106	57.6	<0.0005
Regional nodal irradiation	168	46.9	85	48.9	83	45.1	0.775
IM lymph node chain RT	142	39.7	74	42.5	68	36.9	0.826
BC stage	120	33.5	68	39.1	52	28.3	0.030
Implant-based breast reconstruction	113	31.6	61	35.1	52	28.3	0.506
Breast size	100	27.9	47	27.0	53	28.8	0.300
Dose to organs at risk	97	27.1	43	24.7	54	29.3	0.103
Flap-based breast reconstruction	82	22.9	43	24.7	39	21.2	0.830
Dose inhomogeneity	72	20.1	33	18.9	39	21.2	0.291
None of the factors	69	19.3	44	25.3	25	13.6	0.022
BC grade	57	15.9	27	15.5	30	16.3	0.507
Surgical margins	56	15.6	27	15.5	29	15.7	0.604
Treated side (left vs. right)	55	15.4	21	12.1	34	18.5	0.033
BC molecular subtype	42	11.7	19	10.9	23	12.5	0.395
Financial issues/Reimbursement	33	9.2	10	5.7	23	12.5	0.011
Use of “high tangents”	23	6.4	12	6.9	11	5.9	0.939

Abbreviations: N = Number, BC = Breast cancer, IM = Internal mammary, RT = Radiation therapy, % = Percentage of respondents within the column.
* Other factors listed by responding ROs included re-irradiation, patient preference, receipt of adjuvant chemotherapy, connective tissue disease and radiotherapy waiting list.

Table 3
Absolute contraindications for the use of hypofractionated schedule as reported by responding radiation oncologists.

Factor	All respondents		Academic practice		Non-academic practice		*p* value
	N	%	*N*	%	*N*	%	
N of respondents	344	100	176	51.1	168	48.8	
At least one selected factor*	202	58.7	97	55.1	105	62.5	0.164
None of the factors	141	41.0	78	44.3	63	37.5	0.199
IM lymph node chain RT	82	23.8	41	23.3	41	24.4	0.809
Regional nodal irradiation	76	22.1	37	21.0	39	23.2	0.624
Implant-based breast reconstruction	70	20.3	38	21.6	32	19.0	0.558
Dose to organs at risk	58	16.9	20	11.4	38	22.6	0.005
Flap-based breast reconstruction	51	14.8	26	14.8	25	14.9	0.977
Breast size	38	11.0	17	9.6	21	12.5	0.401
Age	37	10.8	14	7.9	23	13.7	0.086
Dose inhomogeneity	37	10.8	12	6.8	25	14.9	0.016
BC stage	33	9.6	15	8.5	18	10.7	0.490
Surgical margins	24	7.0	11	6.3	13	7.7	0.588
Treated side (left vs. right)	13	3.8	2	1.1	11	6.5	0.009
BC grade	13	3.8	7	3.9	6	3.6	0.844
BC molecular subtype	5	1.5	1	0.6	4	2.4	0.160
Financial issues/Reimbursement	12	3.5	4	2.3	8	4.8	0.208
Use of “high tangents”	3	0.9	1	0.6	2	1.2	0.535

Abbreviations: N = Number, BC = Breast cancer, IM = Internal mammary, RT = Radiation therapy, % = Percentage of respondents within the column.
* Other factors listed by responding radiation oncologists included neoadjuvant radiation therapy, connective tissue disease, bilateral breast cancer radiation therapy, receipt of adjuvant chemotherapy and re-irradiation.

two-dimensional RT techniques and an unconventional HFRT schedule, partially inadequate systemic therapy, the single-centre set-up and for reporting high locoregional recurrence rates. However, the main statement was about the redundancy of that study and thereby the lack of a need for more data before generally introducing HFRT [22].

Clinical management factors and financial issues also influence the inconsistent use of HFRT implementation. Healthcare environment, the strength of HFRT recommendations in institutional protocols, implementation of the clinical pathway or active advocacy for the shorter fractionation schedules, access to peer review, continuing medical education and existence of BC-dedicated ROs were all demonstrated as important factors in implementing new evidence-based recommendations [30,46–48]. Similar patterns were reflected in our survey, as HF-WBI was more often preferred by ROs who worked in academic environments and dedicated ≥50% of their clinical time to patients with BC, thus demonstrating the importance of working context and professional experience. In addition, ROs from academic centres considered fewer factors when deciding to use HFRT schedule. In our study, financial issues were taken into account by 9% of the responding ROs and were more often well thought out by non-academic physicians and by ROs practicing in EENA-ME countries. Factors that influence care-related expenses are complex and associated with the available technology and reimbursement policies. Lievens et al. reviewed the publicly founded RT services in Europe and showed the substantial variance in the coverage scope, which is also dependent on the fractionation schedule. The authors advocated the need to discuss new reimbursement strategies with policymakers, combining the flexibility with incentives to improve productivity and

quality, thus allowing radiation oncology services to follow evidence-based treatment [49]. Economic studies confirm that HFRT is more cost-effective than CFRT [26,50]. Still, pan-Asian guidelines recommend the use of HF-WBI, depending on the local reimbursement practices and equipment availability [17].

Further research, testing higher doses per fraction (>2.0 Gy) is ongoing. The results of two phase III trials, the UK IMPORT HIGH and the RTOG 1005, are eagerly awaited to show if dose escalation by three-dimensional conformal RT or intensity modulated concomitant boost after breast-conserving surgery could reduce RT side effects whilst preserving or even increasing cancer cure in women who have higher than average local recurrence risk [51,52]. Also, the recruitment of patients in phase III clinical studies, to assess both safety and efficacy of HFRT after mastectomy with or without reconstruction and/or for the patients after breast conserving surgery in the need of RNI, is under way (ClinicalTrials.gov identification numbers: NCT03127995/HYPOG-01, NCT02384733/The SKAGEN trial 1, NCT03414970, NCT03422003/FABREC, NCT03730922/DBCG RT Recon, and NCT03414970/RT CHARM).

The limitations of the surveys, in general, are also applicable to this study. Although the survey responses provide some insight into current HFRT practice for patients with BC in Europe, the responding ROs are self-selected and due to response bias the results should not be perceived to be representative for the whole radiation oncology community. However, as not every practicing European RO treats patients with BC, the representativity of the responses to our survey may be much superior as estimated in Appendix B. Finally, although we noticed low survey participation rates from ROs practicing in some WE countries, such as United Kingdom, Belgium, Denmark, Ireland, and The Netherlands, we assume it to be very unlikely that the observed ≈100% HFRT preference rates in virtually every clinical setting in those countries would considerably change with a higher participation rate. The interpretation of the survey's results from those underrepresented countries, where HFRT is routinely practiced and recommended by national guidelines, would be less troublesome when compared to some other countries with a low survey's response rates that have a less-centralised guideline-based approach [53,54]. With the results of the FAST-Forward trial [55,56], a huge challenge lies ahead – to introduce extreme HFRT of 26 Gy in 5 daily fractions – because roughly half of the RO community has not yet transitioned from CFRT to moderate HFRT, based on evidence dating from more than 10 years ago. Again, the same countries seem to be leading here [57].

To our knowledge, this is the first survey to evaluate current RT practice for patients with BC among ROs across Europe, with a focus on fractionation schedule choice and hesitations regarding the prescription of HFRT schedules. We have identified hesitations with HFRT use in certain clinical situations for which high-level clinical evidence is currently missing. Collected data could help to generate further research studies by focusing on barriers that preclude HFRT implementation.

The survey's results show a considerable variation across Europe in the HFRT schedule utilisation preference for patients with BC. Although international guidelines support the use of HF-WBI as a new standard, a considerable proportion of responding ROs in our study favour CFRT over HFRT schedules. We have identified hesitations on HFRT utilisation in certain clinical situations for which current evidence is less robust, such as in the setting of PMRT or RNI. Nevertheless, European-level variations imply opportunities in improving cancer care by enhancing knowledge transitions between academic and non-academic centres and among different geographic regions.

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Data sharing statement

The data that support the findings of this study are available on request from the corresponding author, IR. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.10.008.

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