Hypofractionated Postoperative Radiation Therapy for Breast Cancer – Do we Need More Evidence or Adapted Reimbursement Policies?

Monica-Emilia Chirilă¹, Ivica Ratosa^{2,3}, Gustavo Nader Marta^{4,5}, Philip Poortmans^{6,7}

¹ Amethyst Radiotherapy Centre, Cluj-Napoca, Romania

² Division of Radiation Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

³ Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

⁴ Department of Radiation Oncology - Hospital Sírio-Libanês, Sao Paulo, Brazil

⁵ Latin American Cooperative Oncology Group, Brazil

⁶ Department of Radiation Oncology, Iridium Netwerk, Wilrijk-Antwerp, Belgium

⁷ University of Antwerp, Faculty of Medicine and Health Sciences, Wilrijk-Antwerp, Belgium

Corresponding Author: Monica-Emilia Chirilă **e-mail:** monica.emilia.chirila@gmail.com

Abstract

More than 10 years ago, two pivotal trials, the Ontario Clinical Oncology Group trial and START B trial, firmly established that hypofractionated radiation therapy (RT) of 40–42.5 Gy in 15–16 fractions over 3 weeks after breast conserving surgery or mastectomy results in similar rates of local recurrence and normal tissue effects. This led to a new standard for postoperative whole breast and chest wall RT. Further trials confirmed these findings and show that hypofractionated RT can also be applied for other indications, including regional nodal RT and for ductal carcinoma in situ (DCIS). More recently, a so-called ultra-fractionation trial demonstrated that 26 Gy in 5 fractions over 1 week was non-inferior to 40 Gy, in 15 fractions in 3 weeks for local recurrence at 6 years and that late effects were similar between fractionation schedules being a treatment option for most patients with early breast cancer. Several countries and departments are now adopting hypofractionated schedules as a new standard for breast, chest wall or partial breast RT. In addition to the improvement in convenience and reduction in resources required, hypofractionated RT offers important benefits with respect to acute and late toxicity that can improve the quality of life of patients receiving breast RT.

Keywords: *breast cancer, radiotherapy, radiation therapy, fractionation.*

1. Background

Postoperative radiation therapy (RT) for breast cancer reduces the locoregional relapse rate and increases survival rates, as has been shown in systematic reviews and meta-analyses of prospective trials [1].

Conventionally fractionated (CF) whole breast RT (WBRT) (50–50.4 Gy/ 25–28 fractions over 5–6 weeks) was based on the assumption that it maximizes tumour control while minimizing normal-tissue injury, and it was used for decades as gold-standard. Early studies of hypofractionation (HF) in breast cancer caused high rates of late side-effects, due to inaccuracies of the radiobiological models, dose calculation, and treatment delivery [2].

Clinical data

Moderately hypofractionated RT

More recent studies, starting with the 90s, implemented moderately hypofractionated whole breast radiation therapy (HF-WBRT), in which the radiobiological equivalence was achieved by using fractions (fr) of less than 3 Gy and a lower total dose. Nine randomized phase III trials, including more than 12,000 patients with breast cancer reported encouraging results regarding the efficacy and safety of HF. Six of them included only patients with breast-conserving surgery, one was designed exclusively for post-mastectomy RT, and two studies included both these categories of patients [3–10].

The Royal Marsden Hospital and Gloucestershire Oncology Centre study

included 1,410 patients who had T1–3 N0–1 M0 breast cancer with a maximum of one involved node and who were at least 50 years old. Based on the higher and lower estimated α/β ratio, the calculated dose schedules to be isoeffective with 50 Gy/25 fr were 39 Gy/13 fr and 42.9 Gy/13 fr, respectively. The local recurrence rate at 10 years was 12.1%, 14.8%, and 9.6%, respectively, with no significant difference when comparing either of the CF-WBRT groups with the HF-WBRT group. The side effects were limited in all groups, but the 42.9 Gy/13 fr was shown to have a higher effect on normal tissues when compared to 50 Gy/25 fr [6]. This was the reason for which in the UK START A the dose was reduced to 41.6 Gy/13 fr. The other arms received the previously tested dose of 39 Gy/13 fr and the CF-WBRT of 50 Gy/25 fr, respectively. From a total of 2,236 patients included in this study, 336 (15%) underwent mastectomy, and had similar inclusion criteria, regarding the staging. At 10-year follow-up, there was no significant difference in loco-regional relapse between the 3 arms (it was 5.6% in the 41.6 Gy HF group, 8.1% in the 39 Gy HF group, and 6.7% in the CF group, respectively). Long term side-effects were significantly reduced for 39 Gy as compared to the patients treated with 50 Gy, but there were no significant differences between patients who received 50 Gy and 41.6 Gy.

The UK START B trial included patients having the same stage as UK START A, both conservative and radical surgery, and had only two arms: the CF and 40.05 in 15 daily

fractions, delivered over 3 weeks. Some of the patients had a boost of 10 Gy in 5 fr. Like in the UK START A trial, the loco-regional recurrence did not significantly differ between the two arms (5.5% for CF and 4.3% for the 40.05 Gy HF group), and this time, the HF group had an even lower percentage for some of the normal tissue effects such as breast edema, telangiectasia, and breast shrinkage, while the others did not differ. The START trials showed that the α/β ratio for both breast cancer and late reacting normal tissues appears similar, which would not translate to any advantage in using conventional, 2 Gy per fraction schedules [3,7].

Another trial that included patients with breast cancer who received WBRT after breast-conserving surgery, was the Ontario Clinical Oncology Group trial. It randomized 1,234 women, stage T1–2 N0 M0, who received either CF-WBRT 50 Gy/25 fr, either HF-WBRT 42.56 Gy/16 fr. At 10 years, there was no significant difference in local relapse (6.7% vs 6.2%), overall survival (84.4% vs 84.6%), or cosmetic outcome, which was good or excellent for 71.3% and 69.8%, respectively [8].

The MD Anderson Cancer Center Trial included 287 patients, with stage 0-II breast cancer, after breast-conserving surgery, receiving the same fractionation schedules as the Ontario Clinical Oncology Group trial (50 Gy/25 fr vs 42.56 Gy/16 fr). The patients in the CF-WBRT group received a boost of 10–14 Gy (in 5 or 7 fractions, respectively), and those in the HF-WBRT group received 10–

12.5 Gy (in 4 or 5 fractions, respectively). Significantly higher acute side effects (hyperpigmentation, breast pain, acute dermatitis, fatigue, and pruritus) were reported in the CF-WBRT group than in the HF-WBRT group. Grade 2 or higher acute side effects and the 3-year poor cosmetic outcomes were much less frequent in the HF-WBRT group [9].

More advanced breast cases (stages pT3–4 pN2–3), treated with mastectomy, were included in the Beijing trial. This time, the supraclavicular and level 3 lymph nodes were irradiated along with the chest wall, using either CF schedule (50 Gy/25 fr), either HF schedule (43.5 Gy/15 fr). The trial randomized 820 patients, having local control as the primary endpoint. The 5 year follow-up results for loco-regional relapse were similar between the two groups (8.1% vs 8.3%). Grade 3 acute skin toxicity was significantly lower in the HF group, and no other acute or late toxicities differed between the two arms [11].

Data from three clinical trials, including patients with early breast cancer or ductal carcinoma in situ (DCIS) were published in 2020 and are reassuring: there was no difference in the local recurrence rates between CF-WBRT and HF-WBRT arms with or without tumor bed-boost [4,5,10]. In the BIG 3-07/TROG 07.01 trial, investigators found improved local recurrence rates with the addition of tumor bed boost for patients with non-low risk DCIS, irrespective of the fractionation schedule [10]. Overall, there were no significant differences in the rates of

acute or late tissue effects in the CF-WBRT compared to HF-WBRT groups, except that some of the acute toxicities were even less frequent in the HF-WBRT group [4,5].

Ultra-fractionation

FAST Forward trial (Phase III, non-inferiority) tested 40 Gy/15 fr in 3 weeks vs 27 Gy/5 fr in one week vs 26 Gy/5 fr in one week. It included 4,096 patients, either breast conservation or mastectomy being eligible. After a median follow-up of 71.5 months, the local recurrence at 5 years was non-inferior for the 1-week schedules and the normal tissue effect was not worse for the 26 Gy schedule compared to the 40 Gy schedule [12,13].

Ten-year results from the FAST Trial (CRUKE/04/015; Phase III), evaluating 50 Gy/25 fr vs once-weekly 5-fr schedules (30 Gy/ 5fr or 28.5 Gy/5 fr), delivered to the whole breast for patients with stage pT1–2 pN0 breast cancer demonstrated higher risks for normal tissue effects when 50 Gy/25 fr was compared to 30 Gy/5 fr. On the other hand, there was no difference in the rates for any moderate or marked physician-assessed side effects, including breast-shrinkage, induration, teleangiectasia, edema, comparing conventional 50 Gy/25 fr vs 28.5/5 fr Gy once-weekly schedule [14].

A summary of the studies discussed above, can be found in Table 1.

2. Radiobiology

The breast cancer HF schedules are supported also from the radiobiological point of view, by the equivalent doses calculated using a broad range of α/β values for normal tissue and breast cancer. The reduced total dose of 40 Gy/ 15 fractions leads to a relative sparing of normal tissues, which even increases proportionally for lower dose levels. On the basis of an α/β value of 2.7 Gy (from the START trials), the 40 Gy/15 fr schedule is isoeffective to 45.7 Gy in 2.0 Gy – equivalents [14]. The non-inferior local control can be explained by the effect that shortened overall treatment time has on tumour cell proliferation. The START trialists estimated that between 3 and 5 weeks of treatment, 0.6 Gy per calendar day could be lost [15]. In the FAST trial, change in photographic breast appearance gave an unadjusted α/β estimate of 2.7 Gy (1.5 to 3.9) and physician-assessed normal tissue effects gave an unadjusted α/β estimate from 1.6 Gy (breast induration) to 3.1 Gy (telangiectasia). Using an α/β of 2.7 Gy, the isoeffect doses expressed in 2.0-Gy equivalents for 30 Gy and 28.5 Gy in 5 fractions were approximately 56 Gy and 51 Gy, respectively, and the once-weekly 5-fraction schedule (28 Gy total dose, 95% confidence interval, CI, 26–30) was estimated to be isoeffective with 50 Gy/25 fr [14]. The α/β estimates from FAST are compatible with the START-A trial analysis, which generated estimates around 3–4 Gy for late normal tissue effects in the breast [7].

Table 1. Randomized controlled trials on Moderate Hypofractionation and Ultra-Hypofractionation in postoperative Radiation therapy for Breast Cancer

	Number of patients	Years	Inclusion Criteria	Median follow- up - years (range)	Type of surgery N (%)		Chemotherapy N (%)	Endocrine therapy N (%)	Chemotherapy and endocrine therapy N (%)	Boost N (%)	Regional nodal irradiation N (%)
					Breast- conserving surgery	Mastectomy					
<i>Moderate Hypofractionation</i>											
RMH/GOC611	1410	1986–1998	T1-3 N01 M0	9.7 (7.8–11.8)	1410 (100)	0	196 (14)	918 (65.1)	156 (11.1)	1051 (75)	290 (21)
START A	2236	1998–2002	T1–3 N0–1 M0	9.3 (8.0–10.0)	1900 (85)	336 (15)	793 (35)	1210 (54.1)	548 (24.5)	1152 (61)	318 (14)
START B	2215	1999–2001	T1–3 N0–1 M0	9.9 (7.5–10.1)	2038 (92)	177 (8)	491 (22)	1592 (71.9)	336 (15.2)	875 (43)	161 (7)
OCOG514	1234	1993–1996	T1–2 N0 M0	12.0*	1234 (100)	0	136 (11)	516 (41.8)	NA	0	0
Beijing Trial	820	2008–2016	T3–T4 N2–3 M0	4.9 (3.7–6.8)	0	820 (100)	820 (100)	620 (75.6)	NA	0	820 (100)
DBCG HYPO	1882	2009–2014	pTis–T2 N0– N1(mic) M0	7.3*	1882 (100)	0	668 (36)	560 (29.7)*	NA	426 (23)	0
NCT01413269	729	2010–2015	T1–2 N0–2a M0	6.1*	729 (100)	0	477 (65)	238 (32.7)	358 (49.1)	732 (99.7)	28 (3.9)
BIG 3-07/TROG 07.01	1608	2007–2014	pTis N0 M0	6.6*	1608 (100)	0	0	225 (14)	0	803 (50)	0
<i>Ultra-Hypofractionation</i>											
FAST (CRUKE/ 04/015)	915	2004–2007	pT1–2 N0 M0	3.1	915 (100)	0	0	809 (88.4)	0	0	0
FAST- Forward	4096	2011–2014	pT1–3 N0–1 M0	6	3832 (93.6)	264 (6.4)	1447 (35.3)	3512 (96.2)	NA	1011 (24.7)	0**

RMH/GOC = Royal Marsden Hospital/Gloucestershire Oncology Centre; OCOG = Ontario Clinical Oncology Group; START = Standardization of Breast Radiotherapy Trial; DBCG = Danish Breast Cancer Group; * The information was not available in the original publication; ** Lower axilla included in standard tangential fields to breast/chest wall irradiation was allowed; NA = data not available; ¥ = At least 29% of all patients included in the study received endocrine therapy; in the original publication endocrine data were reported only for the Denmark cohort, within the Denmark cohort 560/1489 (37.6%) patients received endocrine therapy.

In the FAST FORWARD Trial, the unadjusted α/β value estimate for any moderate/marked physician-assessed normal tissue effect was 1.7 Gy (95% CI 1.2–2.3), for the photographic endpoint was 1.8 Gy (95% CI 1.1–2.4) and for patient reported change in breast appearance was 2.3 Gy (95% CI 1.8–2.9), resulting in EQD₂ – equivalents estimate of 46.1–47.1 Gy for 40 Gy/15 fr, 48.2–51.6 Gy for 27 Gy/5 fr and 48.3–45.2 Gy for 26 Gy/5 fr [12].

3. Discussion points

The HF schedules are not uniformly implemented, and many clinicians still prefer to

use CF, although the evidence, regarding the efficacy and safety of the moderately hypofractionated schedules is accumulating. The reasons could be related to concerns regarding possible late side-effects on patients who were underrepresented in most of the trials, or reimbursement-related issues [16,17].

At the 2019 St Gallen/Vienna conference, there was no clear consensus between the panelists regarding hypofractionation [18], but the recently updated ESMO guidelines recommend moderate HF for routine postoperative RT of breast cancer. Careful monitoring of patients not fitting into the inclusion criteria of the published studies treated with HF was recommended [19].

3.1. Chest wall and regional lymph nodes

One of the categories in which some of the doctors seem to be reluctant to prescribe HF schedules is represented by the patients who were previously treated with modified radical mastectomy and lymph node dissection.

The results of the United States National Cancer Database study demonstrated that between 2004 and 2014 the use of HF post-mastectomy RT of the chest wall (with or without the regional lymph nodes) represented 1.1% of all patients. For this category of patients who were treated with mastectomy, the European survey reported HF preference ranged from 0% (in Slovakia, Ukraine, and Lithuania) to 100% (in Netherlands, Belgium, UK, and Ireland). Overall, it was used by 37.6% practicing in academic hospitals and by 25.4% from those from non-academic clinics or departments [16].

The START A and B trials included 14.7% (n=864) patients who received lymphatic radiation, and 8.5% (n=513) who underwent mastectomy. There were no statistically significant differences in the cumulative local recurrence rates after mastectomy or breast-conserving surgery, irrespective of being evaluated by patients or physicians [7]. The Beijing trial reported similar results, in patients with higher stage breast cancer and treated with 3DCRT [11]. In the recent second trial from China, evaluating WBRT with (small proportion, 3–4%) or without nodal irradiation, the authors demonstrated that HF-WBRT, followed by

the HF-boost had a similar local recurrence rate without increased rates of acute or late toxicity, compared to CF-WBRT [5].

The toxicity related to fractionation to the regional nodal areas is not considered as a reason of concern for several other types of cancer. For example, locally advanced head and neck cancer patients are treated with high biological equivalent doses of radiation (60–70 Gy), even concomitant with chemotherapy, the fractionation schedules being independent of the anatomical subsite [20].

An additional concern was raised when HF RT was used before or after breast reconstruction was done, using implants or autologous tissue. Although there is no extensive data on this topic, a phase II prospective trial including 69 stage II-III breast cancer patients should be mentioned. The patients were treated with mastectomy and postoperative HF RT (36.63 Gy over 11 days) to the chest wall and the regional lymph nodes, followed by an optional boost to the mastectomy scar of 13.32 Gy in 4 fractions [21]. Temporary expanders or implants were used for breast reconstruction in 41 patients. The relapse-free survival rate was 89.2% for all patients after 3 years of follow-up. The expanders were removed due to infection in 3 of the patients before RT. The rate of additional surgical correction was 8%, and 24% for the implant failure. Similar complication rates were observed after conventional RT in patients with breast-reconstruction [22]. Since most breast-related radiation toxicities (skin retraction,

fibrosis, and breast shrinkage) seem to be less frequent and less severe in patients who were treated with HF RT, we can expect that a homogenous dose distribution provided by moderate HF to have outcomes at least as good as CF. The ESTRO-ACROP guidelines allow reducing the irradiated volume by limiting the target to the zones at risk, which is expected to lower the side effects, too [23]. Reduced toxicity by delivery of HF RT with methods that improve the homogeneity of dose distribution (IMRT/VMAT) is currently being investigated for patients with the reconstructed chest wall.

3.2. Boost fractionation

Even if most patients in the HF clinical trials used a CF boost of 5–8 fractions of 2 Gy, there are teams from the UK, the Netherlands, and Italy that have many years of experience with HF boost schedules leading to good results [24].

Tumor bed boost (n=388) vs no boost (n=389) following HF-WBRT in patients with non-low risk DCIS was investigated in the BIG 3-07/TROG 07.01 trial. For the whole group of investigated patients (n=1,608), including patients who received CF-WBRT with or without boost, the 5-year local recurrence rates were 3% in the boost group and 7% in the non-boost group [10]. However, cosmetic status was worse with tumor bed boost than with no boost across all time points – at the end of treatment and were persisting at 24 months. In addition, CF-WBRT was associated with worse body

image than HF-WBRT at the end of treatment [25].

The feasibility of the utilization of the sequential tumor bed boost in the setting of ultra-hypofractionated schedules was demonstrated in the FAST FORWARD trial, where a sequential tumor bed boost was allowed for the patients under 40 years of age and for those aged 40–49 years and adverse tumor characteristics (grade 3 tumors with or without lymphovascular space invasion). Sequential tumor bed boost dose, delivered in 10 Gy/ 5 fr (76–81%) and 16 Gy/8 fr (19–23.4%), was received by about 25% of patients in each of the three treatment arms [12].

The simultaneously integrated boost (SIB) can be implemented by adding several fractions (5, mostly) and without increasing the maximum fraction size. Postoperative RT with SIB has a potential to further shorten the treatment time without compromising clinical outcomes and is under intensive clinical investigation. The IMPORT High trial included more than 2,600 patients and integrated the boost while maintaining a constant number of fractions. The HF SIB is safe in terms of 3-year toxicity and correlated adverse effects with increasing dose, but not with fraction size [26]. An analysis of the tumour factors that might be predictive of response to HF RT did not find a correlation with tumour grade, molecular subtype, and hypoxia, suggesting that patients of all grades and molecular subtypes may benefit from these protracted schedules [27].

A small, multicenter single arm prospective phase II study from Germany

included 149 patients with breast cancer, receiving 40 Gy/16 fr to the whole breast and 48 Gy/16 fr to the tumor bed demonstrated encouraging results in terms of acute toxicity. Acute skin reaction grade ≥ 2 occurred in 14.7% (95% CI 9.8-21.4) of patients [28].

In the HYPOSIB randomized trial (ARO 2013-05, NCT02474641, phase III, multicentric, non-inferiority), comparing standard postoperative WBRT (50.4 Gy/28 fr plus sequential boost 10–16 Gy/5-8 fr) and HF-WBRT with a SIB (40 Gy/16 fr to the whole breast and 48/16 fr to the tumor bed), 2,324 patients with breast cancer were recruited from 2015 to 2019 [29]. Preliminary safety data, with a median follow-up of 28 months demonstrated a comparable number of all adverse events (1741 vs 1657) and severe adverse events (80 vs 72) in both arms. Maximal rates of grade ≥ 2 acute skin reactions were 23.9% (week 6) and 15.8% (week 4) for the control and experimental arm, respectively [30].

The UK IMPORT HIGH trial (CRUK/06/003, randomised, multi-centre, phase III trial) compared 40 Gy/15 fr plus 16 Gy/8 fr sequential boost, to other 2 arms. Both arms had 36 Gy/15 fr to the whole breast and 40 Gy to the partial breast. Test Group 1 received 48 Gy/15 fr SIB and Test Group 2 received 53 Gy/15 fr SIB on the tumour bed. The study included early stage breast cancer with a higher risk of local relapse and the treatment was delivered by IMRT. Preliminary results reported data acquired from 2,617 women with a median

age of 49 years. At 3 years, rates of moderate/marked adverse events were similar between the groups receiving IMRT sequential and concomitant boost, respectively [26].

Additional research, evaluating higher doses per fraction (> 2.0 Gy) is underway. The final results of the three phase III trials, including the UK IMPORT HIGH trial, the RTOG 1005 (NCT01349322) and the SKAGEN trial 1 (NCT02384733), are excitedly awaited to show if dose escalation by modern treatment planning using either 3DCRT-SIB or IMRT/VMAT-SIB could improve overall treatment results [31,32].

The results of the IMRT-MC2 Trial (Phase III, noninferiority, n=502), evaluating CF 3DCRT (50.4 Gy/28 fr) with sequential boost (16 Gy/8 fr) vs conventionally fractionated IMRT-SIB (50.4 Gy/28 fr, SIB 64.4 Gy/28 fr) are also adding to the evidence of the efficacy and safety of the integrated tumor dose approach. At 2-years, both treatment arms demonstrated excellent local control and equivalent objective or subjective cosmetic assessment [33].

3.3. Late effects on the organs at risk and the added toxicity of chemotherapy

Some clinicians express their doubts regarding a possible underestimation of late toxicities on lung, heart, and nervous tissue, because of the long necessary follow-up. It should be mentioned that the only patient who received RT to the breast and supraclavicular fossa area developed a mild plexopathy in the START trials had a

suspected genetic disorder. Using α/β ratios of 3 Gy and 1.5 Gy, the 40 Gy in 15 fractions (START B trial) HF regimen is estimated at an equivalent EQD₂ Gy biological dose of 45.42 Gy and 47.72 Gy to the brachial plexus [34].

Other radiation oncologists are pointing out that only a limited number of patients enrolled in the HF clinical trials received chemotherapy (i.e., 11%, 35%, and 22% of patients in the Ontario Clinical Oncology Group, START A, and START B trials, respectively) [7]. However, the MD Anderson trial and Beijing trial (with the temporary reserve of a relatively short follow-up), reported satisfactory toxicity results in patients receiving standard chemotherapy, including anthracycline and taxane- or anthracycline-based regimens [9,11]. Similarly, in an aforementioned study by Wang et al., the receipt of current-era chemotherapy was evenly distributed in the CF-WBRT arm (up to 64% patients) and in the HF-WBRT arm (up to 66% patients). Of the 477 patients, 350 (73.4%) received chemotherapy followed by radiotherapy, and 127 (26.6%) received radiotherapy followed by chemotherapy [5]. Regarding the rates of ischemic heart disease and lung fibrosis, they are very low (<2%), and the dose received by these organs at risk is expected to get even lower in the context of the wider availability of high conformal techniques and image-guided RT [35,36].

4. Technical considerations

Dose inhomogeneity can determine certain regions to receive a higher dose, which leads to the "double trouble" of both higher dose per fraction and higher total dose. In the case of HF, the equivalent dose in 2 Gy fractions is higher relative to CF, this situation being referred to as "triple trouble" [37]. This effect should not be present in the current HF schedules for hotspots up to 107%, thanks to the moderately increased fraction size in the context of a consistent decrease in total dose [3].

The impact of dose inhomogeneity was retrospectively evaluated on 390 datasets from patients included in the FAST Forward trial. The risk of change in breast appearance at 2 years follow-up did not differ in the 40 Gy control arm and the HF schedules (26 and 27 Gy, respectively, in 5 fr) after adjusting for breast size and surgical deficit [38].

Except for the obvious improvements in RT technological aspects related to planning and delivery, other essential factors are the accuracy in defining target volumes as recommended by cooperative groups or societies [23] and the accuracy of daily set-up and positioning.

5. Economic considerations

Treatment protocols that involve fewer fractions decrease the caseload at radiation therapy units and free up resources for more patients, reducing the waiting time. It also decreases indirect costs associated with

outpatient's daily traveling and also the productivity loss for those who still work during treatment [39].

On the other hand, many of the reimbursement systems are based on payment/fraction. The financial impact of using HF for breast cancer was recently analyzed by an international consortium, taking in account data from 13 countries (Denmark, France, Italy, the Netherlands, Spain, UK; Canada, USA, Brazil, Australia, Israel, Taiwan). In 77% of the participant countries, a financial loss would occur by applying the HF schedule. In 60% of situations when a revenue loss would occur, it would be 30-40% per patient. Since patients with breast cancer represent about a quarter of the patients treated in most radiation oncology departments, this economic impact cannot be neglected [40]. In the EBCC Manifesto, a calculation was presented for 1 single example, showing that the introduction of moderate HF, combined with restricting the indications for a boost to the primary tumour bed, are financially not viable for any radiation oncology department under these circumstances [41].

6. General discussion

Despite the high supporting evidence and the significant financial benefits, HF RT for breast cancer has not been generally adopted in many countries. One of the reasons is probably related to a reluctance to apply it for certain patient groups.

Almost 70% of the radiation oncologists who participated in the European survey

mentioned at least one factor that they take into account when deciding on choosing HF over CF for breast cancer. The age of the patient was important for more than half of the respondents, followed by the necessity of regional nodal irradiation, (especially the internal mammary node chain) breast cancer stage, implant-based reconstruction, dose to organs at risk, breast laterality, surgical margins, dose to OARs, flap-based reconstruction and dose inhomogeneity. All these elements were considered as decision-influencing by at least 20% of the respondents. Breast cancer grade, surgical margins, breast laterality, molecular subtype, financial issues, and use of "high tangents" were important only for few radiation oncologists (up to 15.9%)

Participants practicing in Western European Countries or Academic hospitals, and those dedicating more than 50% of their time to treating breast cancer patients, were significantly less influenced in their acceptance of HF RT by these factors [16].

More information on this topic will be brought by the current ongoing trials (e.g., NCT02690636, NCT02700386, NCT02958774, NCT03127995) and will eventually answer the existent doubts of more reluctant radiation oncologists. However, even then and in the context of solid scientific data, the reimbursement systems have to be adapted, so the clinicians will not have to deal with the hard decision of prescribing a treatment that they know it is effective, safe, and logistically convenient, being aware at the same time

that they are causing severe financial losses to the department.

In general, health policy decision-makers and funders do not have sufficient clinical insights and knowledge to guide more adapted reimbursement policies, and possibly do not realize that a proactive approach can provide strong incentives for the clinical practice. Unfortunately, too often, the reimbursement practices are not aligned with treatment guidelines, varying significantly between countries, regions, and even institutions.

Even if a perfect overlapping of the treatment costs and treatment reimbursement cannot be achieved, adapting the policies according to the complexity of the treatment and not on the number of fractions, will improve the access to quality healthcare. Especially in the countries with limited resources, this effect is even more visible, by also decreasing the waiting time for the treatment initiation [42].

This topic is gaining more visibility by the official position of experts and professional organizations and patient advocates representatives, pleading for better use of the existent funding [41].

Abbreviations

RT – radiation therapy

DCIS – ductal carcinoma in situ

CF – Conventionally fractionated

WBRT – whole breast RT

HF – hypofractionation

HF-WBRT – hypofractionated whole breast radiation therapy

EBCC – European Breast Cancer Confere

7. Conclusions

Moderate hypofractionated postoperative radiation therapy for breast cancer is supported by current evidence and is safe and effective, irrespective of patient-, tumour- and treatment-related factors. More recent evidence even strongly supports the use of ultra-hypofractionated postoperative breast radiation therapy, 26 Gy delivered in 5 fractions in 1 week or 28.5 Gy in 5 fractions over 5 weeks. These could be considered as an alternative schedule for whole breast, chest wall and PBI, with similar rates of local control normal tissue toxicity. There is currently a significant variation between countries in implementing it and the reasons are both subjective and objective, but the pandemic helped convincing its use to limit the viral transmission risks. The personal reluctance of some radiation oncologists to prescribe HF schedules for certain patients can arise from insufficient information and reimbursement policies that do not encourage their implementation

Statements:

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