Radiotherapy and Oncology 156 (2021) 239–243

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Short Communication

Three large trials on radiotherapy for early breast cancer: What did we learn?

L.J. Boersma *, L.H.P. Murrer

Maastricht University Medical Centre+, Dept. of Radiation Oncology (Maastro), GROW School for Oncology and Developmental Biology, Maastricht, the Netherlands

Recently, the results of three large trials ($N > 1500$ patients per trial) were published, with data on cancer outcome and morbidity in early breast cancer patients, investigating a variety of modern de-escalating strategies: i.e. the DBCG Hypo trial with a moderate hypofractionation (mHypo) scheme of 15 fractions/3 weeks [1], the ultra-hypofractionation (uHypo) regimen of the FAST Forward (FF) trial [2], i.e. 5 fractions/1 week, and finally the TARGIT-A trial [3], with a single 20 Gy intra-operative (IORT) fraction applied with 50 kV, combined with an additional series of external beam radiation therapy to the whole breast (WBRT) if considered necessary (Table 1 for an overview of the 3 studies). All trials reported on their results after a follow-up of at least 5 years. It is wonderful to realize that the local recurrence rates in early breast cancer have become that low, that research can be aimed at treatment de-escalation, instead of burdening our patients with more intensive treatment to improve local control rates.

The FF and DBCG Hypo trials nicely fit in the de-escalating strategies aiming to reduce the number of fractions: they investigated whether "normofractionation" (i.e. 2 Gy per fraction) can safely be replaced by mHypo (2.67 Gy per fraction) to uHypo (>5 Gy per fraction). The TARGIT-A trial combined application of a single fraction with an extreme form of partial breast irradiation (PBI). The TARGIT-A trial came with remarkable results, i.e. the IORT-arm, in combination with WBRT in selected cases, yielded a low 5-years recurrence rate of 2.11% (vs. 0.95% after standard WBRT), a good cosmetic outcome, and remarkably, in less deaths unrelated to breast cancer compared with the standard WBRT arm [3]. Especially the last finding raises questions, since breast cancer specific survival and overall survival were similar to the WBRT group. In addition, this difference was not found in the TARGIT delayed trial, where the IORT was delivered at median 37 days after lumpectomy. This reassuring finding supports the hypothesis that the higher incidence of deaths unrelated to breast cancer in the WBRT arm of the TARGIT-A is just a spurious finding [4]. Much has already been said about the TARGIT-A results. Many radiation oncologists have criticized the coverage of the target volume, since the 50 kV device only delivers 7 Gy to 1 cm [3], whilst the consensus paper on target volume delineation for PBI reports that the target volume should be at least 2 cm around the tumour bed [5]. Several others calculated that the observed local recurrence in the IORT-TARGIT arm, corresponds very well with no radiotherapy at all, supporting the thought that the 7 Gy to 1 cm depth does not have any preventive effect on local recurrence [4,6]. Consequently, on our strive for de-escalation, it seems more promising to focus on hypofractionation strategies such as from the UK and DBCG group.

Moderate hypofractionation

The UK group has been investigating the feasibility of hypofractionation in a beautiful set of consecutive trials: they showed in the START trials that mHypo yields similar local control rates and similar, or even less normal tissue toxicity as compared to normofractionation [7]. At the same time, a similar trial was performed in Ontario [8], and found identical results. Nevertheless, since hypofractionation in the early days had caused substantial late normal tissue toxicity [9], mHypo was not yet widely adopted. Therefore, the Danish group set up an additional similar trial comparing 15×2.67 Gy vs 25×2 Gy [1]. They recently published their first results, and showed that the 3-year breast induration with the mHypo scheme was similar to or even less than the 25×2 Gy [1], thereby confirming the START B trial and the Ontario trial. In addition, with 7-year f-up, the local recurrence rates were very low, and similar to the 25×2 Gy.

For whole breast/chestwall radiotherapy for invasive cancer, it can be concluded that ample level 1 evidence is available for mHypo [1,7,8,10], and consequently several guidelines state that mHypo can be considered standard of care in this situation, independent of age, breast cancer subtype [11] or margins [e.g. [12], www.oncoline.nl].

For DCIS and regional nodal irradiation (RNI) however, the evidence is however somewhat weaker: most trials did not include DCIS at all, and the DBCG Hypo only included 246 patients with DCIS [1]. Consequently, the results of TROG trial (NCT00470236) are eagerly awaited. In the TROG trial patients treated with BCT for DCIS are randomized twice: first between normofractionation and mHypo, and second between a boost and no boost to the tumour bed. Radiotherapy departments could choose whether they wanted to participate to both randomisations or only one. The trial aimed to include 1608 patients and results are expected in 2024.

Data for mHypo in RNI are currently accumulating. In a small subgroup analysis of the START trial, RNI already seemed to be safe

* Corresponding author at: Dr Tanslaan 12, 6229 ET Maastricht, The Netherlands.
E-mail address: liesbeth.boersma@maastro.nl (L.J. Boersma).

https://doi.org/10.1016/j.radonc.2020.12.018

Table 1
Overview of the 3 recently published studies.

	Fast Forward	DBCG Hypo	Targit-A
Primary endpoint	5 yr IBTR	3 yr Gr2-3 breast induration	5 yr IBTR
Number of hospitals	97	8	32
Recruitment period	2011–2014	2009–2014	2000–2012
Inclusion criteria	> 18 yr, pT1–3, pN0–1, M0 *Median size: 1.6 cm; <2% pT3; 80% pN0; 40% high risk (<50 yr or G3)*	> 40 yr, pT1-2pN0-1mi Invasive BC or DCIS for which BCS. *82% T1, 20% G3, 80% pN0*	> 45 yr, < 3.5 cm, cN0-N1 BC. *90% < 50 yr, 84% pT1, 20% G3, 78% pN0*
Systemic treatment	> 95% endocrine treatment ~ 25% chemotherapy	75% any systemic treatment	80% endocrine treatment 20% chemotherapy
Fractionation schedules	40 Gy/15 fx/3 weeks vs 27 Gy/5 fx/1 week vs 26/5 fx/1 week	50 Gy/25 fx/5 weeks vs 40 Gy/15 fx/3 weeks	IORT 20 Gy +/- EBRT (3–6 weeks) vs EBRT (3–6 weeks) only 20% received IORT and EBRT
Boost	25% yes: 10–16 Gy/5–8 fx, indication by physician	23% yes, boost of 10 Gy	Allowed, not clear which percentage and which dose
Target Volume	Whole Breast/Chestwall No RNI in case of pN1	Whole Breast	Tumor cavity vs Whole Breast
Specifications of dose distributions	PTV: V95% > 95% PTV: V105% < 5% PTV: V107% <2% Dmax < 110%	Dose was usually prescribed to a **mean volume.** The dose distribution was required to be 95%-107% (50 Gy) and 95%-105% (40 Gy)	IORT: 5–7 Gy at 1 cm depth; EBRT: not given
N - randomisation	4096:1371 vs1 367 vs 1368 *Stratification by RT centre and risk group (high [age < 50 years or grade 3] vs low [age ≥ 50 years and grade 1 or 2]).*	1854 (246 DCIS): 937 vs 917 *Randomisation was stratified by institution, use of chemotherapy (yes vs no), use of RT boost (yes vs no), and breast size measured by primary clinical target volume of the breast (CTVp_breast; <> 600 mL).*	2298:1140 IORT + 20% also EBRT vs 1158 : EBRT only
Local recurrence rate	5 yr IBTR: 2.1% vs 1.7%, vs 1.4%	Median f-up 7.26 yrs. Number LRR: 19/814 vs 14/794	5 yr IBTR: 2.11% vs 0.95%
Overall survival (OS)	5 yr OS: 93% for the whole group	9 yr OS: 93.4% both groups	Median f-up 8.6 yr: 110 vs 131 deaths
Normal tissue effects (NTE)	5 yr moderate/marked NTE: 9.9%, 15.4%, 11.9%	3 yr induration: 11.8% vs 9% 5 yr induration: 13% vs 11%	Not reported in this paper
Cosmetic outcome	Photographs 2 yr mild or marked change: 8.5%, 15.6%, 10.8%	5 yr Patient-rated favorable outcome: 75% vs 80%	Not reported in this paper; earlier papers reporting on small subsets < 10% of patients) suggest at least similar cosmesis of TARGIT-A vs EBRT

IBTR: ipsilateral breast tumour recurrence; IORT: intraoperative radiotherapy; EBTR: external beam radiotherapy; RNI: Regional Nodal

Table 2
Overview of variation in EQD2 for de Fast (28.5 Gy/5 fx), FF (26 Gy/5 fx), START (40 Gy/15 fx) and normofractionation schedules (50 Gy/25 fx). **2A** The worst and best case scenario per scheme was defined by calculating the lowest and highest relative therapeutic ratio (i.e. EQD2 tumour/EQD2 normal tissue) for the lowest and higherst limit of the 95% CI for the α/β ratio, and for the time-factor/without application of a time-factor at all. In addition, the relative therapeutic ratio was determined for all schemes for the average estimates of the α/β ratios and time factors. The time factor is applied as additional effect in Gy per day with respect to the 25 × 2 Gy in 35 days. For this calculation the overall treatment time for the FF 26 Gy scheme was considered to be 7 days, for the FAST scheme to be 28 days, and for the START scheme 21 days. See also Fig. 1. **2B** Lower and upper limits of the 95% confidence intervals for α/β ratios [2] and the time factors for tumour and normal tissue [176], applied to calculate the relative therapeutic ratio for Table 2A.

Table 2A

	Applied α/β ratio (Gy) for tumour/ normal tissue	Applied timefactor (Gy/day) tumour/ normal tissue	EQD2 tumour	EQD2 normal tissue	Relative therapeutic ratio
Normofractionation	independent	independent	50 Gy	50 Gy	1
FF - average α/β ratio	3.7/1.7	0.6/0.14	57.4 Gy	52.4 Gy	1.10
Fast- average α/β ratio	3.7/1.7	0.6/0.14	51.2 Gy	58 Gy	0.88
START- average α/β ratio	3.7/1.7	0.6/0.14	53.2 Gy	49.3 Gy	1.08
FF – worst case – no timefactor	7.1/1.2	No time factor	35.1 Gy	52.0 Gy	0.68
Fast - worst case – no timefactor	7.1/1.2	No time factor	40.1 Gy	61.5 Gy	0.65
START-worst case- no timefactor	7.1/1.2	No time factor	43.0 Gy	48.4 Gy	0.89
FF - worst case	7.1/1.2	No time factor/0.34	35.1 Gy	61.5 Gy	0.57
Fast – worst case	7.1/1.2	No time factor/0.34	40.1 Gy	63.8 Gy	0.63
START – worst case	7.1/1.2	No time factor/0.34	43.0 Gy	53.2 Gy	0.81
FF – best case	0.3/2.3	1.18/-0.09	95.2 Gy	42.8 Gy	2.22
Fast – best case	0.3/2.3	1.18/-0.09	82.6 Gy	52.4 Gy	1.58
START – best case	0.3/2.3	1.18/-0.09	68.2 Gy	45.0 Gy	1.52

Table 2B

	Tumour	Normal Tissue				
	Average estimate	Lower limit of 95% CI interval	Upper limit of 95% CI interval	Average estimate	Lower limit of 95% CI interval	Upper limit of 95% CI interval
α/β ratio	3.7 Gy	0.3 Gy	7.1 Gy	1.7 Gy	1.2 Gy	2.3 Gy
Time factor	0.6 Gy/day	0.10 Gy/day	−0.09 Gy/day	0.14 Gy	1.18 Gy/day	0.34 Gy/day

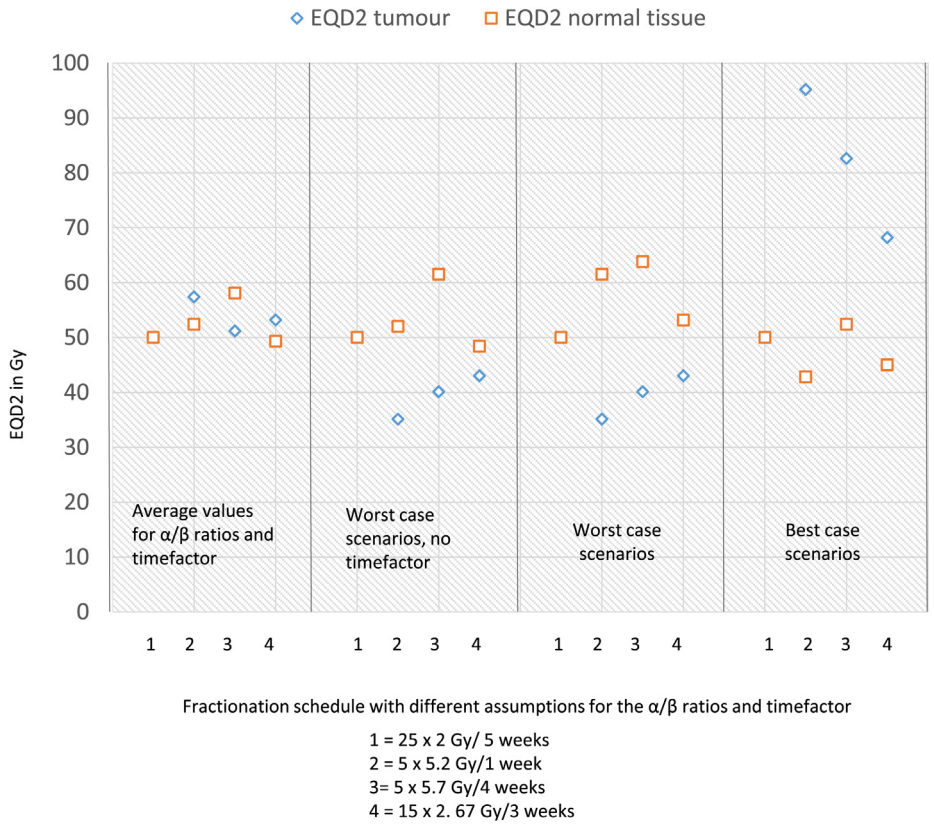

Fig. 1. Fractionation schedule with different assumptions for the α/β ratios and timefactor.

with respect to normal tissue toxicity [13]. The recently published RCT from Wang et al [10] confirmed this finding and found that it was also safe from an oncological point of view. Based on these data and the progress made in treatment planning, such that hot spots due to overlap of radiation fields resulting in "double-trouble" or "triple-trouble" effects can be prevented, mHypo for RNI is currently being applied in several countries. A recent survey showed however that 23% of respondents still considered RNI a contraindication [14]. Several trials are currently ongoing to provide additional level 1 evidence for the safety of hypofractionation for RNI (France (NCT03127995), the USA (NCT02700386, NCT02958774), Denmark (NCT02384733), and Egypt (NCT02690636)) with a total number of patients of to be included of >4000 patients.

Ultra-hypofractionation

Although mHypo is now widely accepted, uHypo has been less accepted until recently. The FF trial included >4000 pT1–3, pN0–1, M0 breast cancer patients, and randomized between 40 Gy/15 fx/3 weeks, 27 Gy/5 fx/1 week or 26 Gy/5 fx/1 week. With a relatively short follow-up of 5 years it was found that the tumour control was similar between the three treatment arms, with possibly even somewhat (not significant) higher tumour control in the uHypo arms compared to the mHypo arm. The findings for normal tissue effects (NTE) showed significantly worse NTE for the 27 Gy schedule compared to the mHypo arm, and similar or (not significant) slightly worse for the 26 Gy arm compared to the mHypo arm. During the first weeks of the COVID-19 crisis, the results of the 26 Gy FF-schedule were considered however sufficiently solid, to advise that uHypo should be considered to reduce the risk of COVID-infection as a result of frequent radiotherapy contacts, especially in vulnerable patients [15]. Brunt et al [2] mentioned that they do not expect much change in the FF results after 10 years, since the 10 year results of both START and FAST schemes were similar to the 5 year results. Nevertheless, as stated by Offersen et al [1,16], we should remain cautious, since the 26 Gy arm of the FF scheme could mean a reduction in EQD2 from 44.7 Gy to 40.6 Gy (-9.2%) if the α/β ratio for tumour is 3.7 Gy. In their calculations they did not take into account a time factor [16], whereas Haviland et al [17] did find a time factor of 0.6 Gy per day (95% CI 0.10–1.18 Gy per day) for tumour tissue, and of 0.14 Gy per day for normal tissue (95% CI −0.09–0.34 Gy per day). If this time-factor is taken into account, the 26 Gy FF scheme has an EQD2 of 57.4 Gy for tumour, and of 52.4 Gy for normal tissue, assuming an α/β ratio of 3.7 Gy for tumour and of 1.7 Gy for NTE [2] (Table 2 and Fig. 1).

Moderate or ultra-hypofractionation?

Assuming that the α/β ratio is in reality close to the estimation of the FF trial, and the time factor comes close to the estimation from the START Trials, i.e. 0.6 Gy for tumour and 0.14 Gy for normal tissue [17], both the mHypo and the uHypo schemes would be at least equivalent or even more effective with regard to tumour control; the Fast (5x 5.7 Gy, one fraction per week [18]) and FF would then be somewhat worse for NTE, whereas the START would be equivalent.

Since the estimation of the α/β ratios and the time factors have some uncertainties, it is not trivial to predict which fractionation scheme will be the optimal scheme: if the tumour and normal tissue α/β ratios would be at the lower limits of the 95% confidence intervals, the α/β ratio for tumour would be lower than for normal tissue (0.3 Gy vs 1.2 Gy), which then would obviously favour the uHypo schedules. If, in addition, the time factor would appear to be at the higher limit of the 95% CI, then the EQD2 of the uHypo schedules would even be alarmingly high: for the FF and Fast scheme it would be 95.2 Gy and 82.6 Gy for tumour respectively, and 61.5 Gy and 63.8 Gy for normal tissue. Fortunately, the clinical evidence shows that this cannot be the case. Nevertheless, it illustrates that the uncertainties in α/β ratios and in the value of the time factor have the largest impact on the uHypo schemes, whereas the impact on the EQD2 of the mHypo schemes is limited (68.1 Gy and 63.8 Gy for tumour and normal tissue, respectively) (Table 2 and Fig. 1). Consequently, whereas uHypo in combination with a short overall treatment time potentially offers the highest benefits, it also yields the highest risks. This is reflected in the wide range of therapeutic ratios observed, which is 0.57–2.22 in FF as compared to 0.81–1.52 in mHypo (Table 2 and Fig. 1). The results of the FF trial however, suggest that it is a safe approach. Nevertheless, confirmation of these results in an independent similar trial would be welcome. Until such a similar trial is available, one should either choose to implement the FF scheme with careful prospective monitoring of the results, or choose for the mHypo scheme, that can currently be considered as conventional fractionation [19].

In conclusion, the currently extreme low risks on local recurrence in early breast cancer, challenges the radiotherapy community to develop new de-escalation strategies, which should be tailored towards individual risks, e.g. based on biomarkers. One of the de-escalating strategies is to reduce the number of fractions, which is supported by a currently accumulating number of data on hypofractionation. mHypo can now be considered standard for local radiotherapy for invasive breast cancer and probably also for RNI and for local radiotherapy of DCIS; uHypo is very promising for local radiotherapy for invasive breast cancer, but should be investigated further, especially for RNI and DCIS.

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.

References

[1] Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Danish breast cancer group radiation therapy committee. hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: The DBCG HYPO trial. J Clin Oncol 2020. https://doi.org/10.1200/JCO.20.01363. JCO2001363.

[2] Brunt MA, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. FAST-Forward Trial Management Group Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613–26.

[3] Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ 2020;19(370):. https://doi.org/10.1136/bmj.m2836m2836.

[4] Bentzen S. No apparent effect of 50kV intra-operative radiation therapy on loco-regional control after lumpectomy for early breast cancer. Response to Vaidya et al BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2836.

[5] Major T, Gutiérrez C, Guix B, van Limbergen E, Strnad V, Polgár C. Breast, Cancer Working Group of GEC-ESTRO. Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol 2016;118:199–204.

[6] Sasieni PD, Sawyer EJ. Intraoperative radiotherapy for early breast cancer - insufficient evidence to change practice. Nat Rev Clin Oncol 2020;17 (12):723–4.

[7] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94.

[8] Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362(6):513–20.

[9] Overgaard M, Bentzen SM, Christensen JJ, Madsen EH. The value of the NSD formula in equation of acute and late radiation complications in normal tissue following 2 and 5 fractions per week in breast cancer patients treated with postmastectomy irradiation. Radiother Oncol 1987;9:1–11.
[10] Wang S-L, Fang H, Song Y-W, Wang W-H, Hu C, Liu Y-P, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019;20:352–60.
[11] Lalani N, Voduc KD, Jimenez RB, Levasseur N, Gondara L, Speers C, et al. Breast cancer molecular subtype as a predictor of radiotherapy fractionation sensitivity. Int J Radiat Oncol Biol Phys 2020. S0360–3016(20)34133-X.
[12] Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018;8(3):145–52.
[13] Haviland JS, Mannino M, Griffin C, Porta N, Sydenham M, Bliss JM, et al. START Trialists' Group Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018;126(1):155–62.
[14] Ratosa I, Chirilă ME, Steinacher M, Kozma E, Vojtíšek R, Franco P, et al. Hypofractionated radiation therapy for breast cancer: preferences amongst radiation oncologists in europe – results from an international Survey. Radiother Oncol 2021;155:17–26. https://doi.org/10.1016/j.radonc.2020.10.008.
[15] Coles CE, Aristei C, Bliss J, Boersma L, Brunt AM, Chatterjee S, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. Clin Oncol (R Coll Radiol) 2020;32(5):279–81.
[16] Offersen BV and Overgaard J. Breast cancer fractionation. Letter to the editor, Lancet 2020.
[17] Haviland JS, Bentzen SM, Bliss JM, Yarnold JR. START Trial Management Group Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. Radiother Oncol 2016;121(3):420–3.
[18] Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020;38:3261–72.
[19] Ling DC, Vargo JA, Beriwal S. Fractionation in and changed in patient care. Breast, Prostate, and Rectal Cancer: Should 5-5-5 be a new standard of care?. Int J Radiation Oncol Biol Phys 2020;108(2):390–3.