



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

FRACTIONATION AND CHANGES IN PATIENT CARE

Breast, Prostate, and Rectal Cancer: Should 5-5-5 Be a New Standard of Care?

Diane C. Ling, MD, John A. Vargo, MD, and Sushil Beriwal, MD, MBA

Department of Radiation Oncology, UPMC Hillman Cancer Center, Magee Women's Hospital, Pittsburgh, Pennsylvania

Received Apr 22, 2020. Accepted for publication Jun 21, 2020.



Introduction

The COVID-19 pandemic brought unprecedented changes to the world as we know it. In an attempt to balance the risks of exposure and spread in the face of national shut-downs, evidence-based guidelines were published encouraging the use of 5-fraction regimens of radiation therapy for the most common disease sites, including breast, prostate, and rectal cancer.¹⁻⁵ Before the COVID-19 pandemic, adoption rates of hypofractionation for any disease site remained lower in the United States than in other countries such as the United Kingdom and Canada.⁶⁻⁸ The source of variability in use of hypofractionation was largely not a function of patient characteristics, but rather at the level of the practice and provider, who did not feel comfortable with hypofractionation for multiple reasons. This did not change with the publication of randomized trials or guidelines.⁹⁻¹¹ It appears that the COVID-19 pandemic may provide the impetus for evidence-based adoption of hypofractionation as physicians increase their comfort level with and see the practical benefits of shorter regimens with their own experience during the crisis. This may lead to a change in fractionation for breast, prostate, and rectal cancer including adoption of 5-5-5 for patients suitable for 5 fractions of radiation therapy.

Breast Cancer

Before COVID-19, published guidelines and randomized trials supported shorter courses for whole (15-20 fractions) or partial breast (10 fractions) radiation therapy in early-stage node-negative breast cancers; however, guidelines stopped short of encouraging the shortest 5-fraction regimens.¹²⁻¹⁴ Recently, for whole breast irradiation, 10-year follow-up from the UK FAST trial with 992 patients showed no difference in cancer control or toxicity for 28.5 Gy in 5 weekly fractions compared with conventional fractionation,¹⁵ and 5-year results from FAST-FORWARD showed noninferiority of 26 Gy in 5 daily fractions to 40 Gy in 15 fractions with respect to ipsilateral breast recurrence.¹⁶ In addition, 10-year results of an Italian randomized trial showed equivalent oncologic outcomes and less toxicity with 30 Gy in 5-fraction partial breast radiation therapy compared with conventionally fractionated whole breast radiation therapy.¹⁷

Consistent with the evidence, COVID-19 breast radiation therapy guidelines have recommended 30 Gy in 5-fraction partial breast or 26 Gy in 5-fraction whole breast radiation therapy as the preferred standard in suitable patients.¹⁻³ Post-COVID, new standard nomenclature should refer to 15 to 16 fractions of 2.66 to 2.67 Gy per fraction as

Corresponding author: Sushil Beriwal, MD, MBA; E-mail: beriwal@upmc.edu

Disclosures: J.V. reports personal fees from Elsevier and being the clinical pathways director for lymphoma. S.B. reports consultancy for Varian and being the Via oncology medical director.

“conventional fractionation” and be considered standard of care for all patients after breast-conserving surgery. Five fractions at 5.2 to 6.0 Gy per fraction should be referred to as the new “hypofractionation” and should be used for suitable patients.

Rectal Cancer

Preoperative short-course RT (25 Gy in 5 fractions) and long-course chemoradiation (45-50.4 Gy at 1.8-2 Gy per fraction) are both recommended options for locally advanced, resectable rectal cancer. These 2 approaches have been compared in randomized phase 3 trials, showing similar local control (at least in upper and midrectal cancer) and overall survival, less acute toxicity with short course, and similar late effects.¹⁸⁻²¹ Recent studies have included 5-fraction short-course RT as part of total neoadjuvant therapy and shown comparable pathologic complete response rates to long course, with no increase in surgical complications.²²⁻²⁴ Despite the equipoise in randomized trials, before COVID-19, 2020 National Comprehensive Cancer Network clinical practice guidelines supported long-course chemoradiation as the preferred option for T3 and node-positive T1-2 patients, stating that 5-fraction short-course radiation “can also be considered for patients with stage T3 rectal cancer.”²⁵

This lukewarm endorsement of short-course radiation as a second option, despite strong evidence supporting its use, contrasts with recently published European COVID-19 guidelines for rectal cancer, which flips the order of preference to favor 5-fraction short-course RT in most patients who require radiation, with the possible exception of advanced disease.⁴ Memorial Sloan Kettering Cancer Center has gone a step further to mandate 5-fraction RT for all localized rectal cancers until the pandemic passes.²⁶ Yet, even in a postpandemic world, for appropriate patients with resectable upper to midrectal cancers, short-course radiation can be a new standard of care and preferred option in many cases, given that it is oncologically noninferior to long-course radiation and has potentially less acute toxicity, as backed by multiple randomized trials, and imposes a smaller burden on both health care systems and patients.

Prostate Cancer

Before COVID-19, the 2018 American Society for Radiation Oncology (ASTRO) guidelines stated there is “moderate”-quality evidence to support 5-fraction stereotactic body radiation therapy (SBRT) for low-risk prostate cancer and “low”-quality evidence to support it for intermediate or high risk.²⁷ There was a conditional recommendation to offer SBRT for low-risk patients, and high-risk patients were not recommended to be treated with SBRT outside of a clinical trial or multi-institutional registry; for intermediate-risk patients, treatment on a clinical trial was strongly recommended. These guidelines do not take into

account newer data in support of SBRT published since then, reflective of the fact that clinical guideline updates often lag behind the available evidence.¹¹

Two recent meta-analyses including several thousand men treated with definitive prostate SBRT for low-, intermediate-, or high-risk prostate cancer showed excellent long-term disease control with 5- to 7-year follow-up and a favorable toxicity profile with late grade ≥ 3 toxicities on the order of 1% to 2%.^{28,29} The HYPO-RT-PC randomized phase 3 trial has demonstrated noninferiority of ultrahypofractionated RT to conventional fractionation in a cohort of mostly intermediate-risk patients with regard to biochemical control, with a slight increase in patient-reported acute gastrointestinal and genitourinary symptoms (likely because of use of 3-dimensional conformal technique and larger planning target volume margins), but no difference in late toxicities at 5 years.³⁰ Likewise, early results of the PACE B trial showed similar toxicity between SBRT and conventional fractionation arms.³¹

It is unlikely that biochemical control or morbidities would dramatically change with further follow-up of prospective studies. Moreover, concern for increased morbidity with ultrahypofractionation can be mitigated with the addition of modern techniques such as image guidance and hydrogel spacer. On the basis of the increasing data in support of SBRT use across risk groups, the National Comprehensive Cancer Network guidelines were updated in early 2020 to list 5-fraction SBRT as an appropriate regimen for all risk groups of localized prostate cancer, from very low risk to very high risk.³² COVID-19 prostate radiation therapy guidelines support 5- to 7-fraction SBRT, exhorting that “the shortest fractionation schedule should be adopted that has evidence of safety and efficacy.”⁵ Whether the increasing use of such regimens in the COVID-19 era will continue afterward remains to be seen, but substantive evidence already supports the safety and efficacy of 5-fraction SBRT in localized prostate cancer, as final results from PACE-B are eagerly awaited.

Conclusions

The COVID-19 pandemic has imposed sweeping and potentially long-lasting changes on the world. As we work to rebuild and return to a new normalcy, it is imperative that radiation oncologists continue the evidence-based adoption of shorter courses of radiation therapy brought to attention by COVID-19. The evidence behind hypofractionated regimens recommended in various COVID-19 guidelines includes large, randomized prospective trials with thousands of patients published before the COVID-19 era. These shorter courses are patient-friendly, associated with less financial toxicity, equally efficacious, and similar to or less morbid than prolonged schedules. Older concerns regarding hypofractionation were driven by 2-dimensional planning limitations, which are now mitigated by conformal or inverse planning, use of hydrogel spacer,

heart-sparing techniques such as deep inspiration breath-hold, and daily image guidance.

Unfortunately, one factor potentially limiting widespread acceptance of shorter regimens is the economic model in the US health care system, which does not reward nonstereotactic 5-fraction treatment. Therefore, physicians may be disincentivized to adopt 5-fraction regimens for breast and rectal cancer in particular, whereas enthusiasm for prostate SBRT may be greater. On the other hand, the opposite is true in some countries outside the United States with universal health care, where 5-fraction breast and rectal cancer regimens may already be standard in light of the support from randomized trials. Some of this discrepancy in practice pattern between the United States and other countries may be mitigated by the upcoming Alternate Payment Model, wherein there is fixed-rate reimbursement irrespective of treatment technique, fraction number, or fraction size. Nevertheless, regardless of health care model, ultimately practice patterns should reflect what is best for the patient.

A global pandemic should not be requisite for us to continue evidence-based hypofractionated regimens. We propose redefining the terms used to describe fractionation based on our improved understanding, to encourage greater adoption of shorter courses. To that end, we propose that “standard fractionation” include treatments with 15 to 28 fractions of ≥ 2.5 Gy. The term “hypofractionation” could be used for schedules that are currently referred to as “extreme hypofractionation,” such as the 5-5-5 regimens discussed herein for breast, prostate, and rectal cancer.

References

- Braunstein LZ, Gillespie EF, Hong L, et al. Breast radiotherapy under COVID-19 pandemic resource constraints—Approaches to defer or shorten treatment from a comprehensive cancer center in the United States [e-pub ahead of print]. *Adv Radiat Oncol*. <https://doi.org/10.1016/j.adro.2020.03.013>. Accessed July 1, 2020.
- Simcock R, Thomas TV, Estes C, et al. COVID-19: Global radiation oncology’s targeted response for pandemic preparedness. *Clin Transl Radiat Oncol* 2020;22:55-68.
- Coles CE, Aristei C, Bliss J, et al. International guidelines on radiation therapy for breast cancer during COVID-19 pandemic. *Clin Oncol* 2020;32:279-281.
- Marijnjen CAM, Peters FP, Rodel C, et al. International expert consensus statement regarding radiotherapy treatment options for rectal cancer during the COVID 19 pandemic. *Radiother Oncol* 2020;148:213-215.
- Zaorsky NG, Yu JB, McBride SM, et al. Prostate cancer radiotherapy recommendations in response to COVID-19 [e-pub ahead of print]. *Adv Radiat Oncol*. <https://doi.org/10.1016/j.adro.2020.03.010>. Accessed July 1, 2020.
- Bekelman JE, Sylwestrzak G, Barron J. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA* 2014;312:2542.
- Stokes WA, Kavanagh BD, Raben D, et al. Implementation of hypofractionated prostate radiation therapy in the United States: A National Cancer Database analysis. *Pract Radiat Oncol* 2017;7:270-278.
- Haque W, Verma V, Butler EB, et al. Trends and disparities in the utilization of hypofractionated neoadjuvant radiation therapy for rectal cancer in the United States. *J Gastrointest Oncol* 2018;9:601-609.
- Jagsi R, Griffith KA, Heimburger D, et al. Choosing wisely? Patterns and correlates of the use of hypofractionated whole-breast radiation therapy in the state of Michigan. *Int J Radiat Oncol Biol Phys* 2014;90:1010-1016.
- Jagsi R, Falchuk AD, Hendrix LH, et al. Adoption of hypofractionated radiation therapy for breast cancer after publication of randomized trials. *Int J Radiat Oncol Biol Phys* 2014;90:1001-1009.
- Rodríguez-Lopéz JL, Ling DC, Heron DE, et al. Lag time between evidence and guidelines: Can clinical pathways bridge the gap? *J Oncol Pract* 2019;15:e195-e201.
- Gradishar WJ, Anderson BO, Abraham J, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2020;18:452-478.
- Smith BD, Bellon JD, Biltzblau R, et al. Radiation therapy for the whole breast: Executive summary of the American Society for Radiation Oncology (ASTRO) evidence-based guidelines. *Pract Radiat Oncol* 2018;8:145-152.
- Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 2017;7:73-79.
- Brunt AM, Haviland J, Sydenham M, et al. FAST phase III RCT of radiotherapy hypofractionation for treatment of early breast cancer: 10-year results (CRUKE/04/015). *Int J Radiat Oncol Biol Phys* 2018;102:1603-1604.
- Brunt AM, Haviland JS, Wheatley DA, et al. 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;395:1613-1626.
- Meattini I, Saieva C, Lucidi S, et al. Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer: 10-year follow up results of the APBI IMRT Florence randomized phase 3 trial. Paper presented at: 2019 San Antonio Breast Cancer Symposium. December 10-14, 2019; San Antonio, TX.
- Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93:1215-1223.
- Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012;30:3827-3833.
- Ansari N, Solomon MJ, Fisher RJ, et al. Acute adverse events and postoperative complications in a randomized trial of preoperative short-course radiotherapy versus long-course chemoradiotherapy for T3 adenocarcinoma of the rectum: Trans-Tasman Radiation Oncology Group trial (TROC 01.04). *Ann Surg* 2017;265:882-888.
- Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): A multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol* 2017;18:336-346.
- Chapman W, Kim H, Bauer P, et al. Total neoadjuvant therapy with short course radiation compared to concurrent chemoradiation in rectal cancer. Paper presented at: 2019 Gastrointestinal Cancers Symposium. January 17-19, 2019; San Francisco, CA.
- Myerson RJ, Tan B, Hunt S, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. *Int J Radiat Oncol Biol Phys* 2014;88:829-836.
- Bujko K, Nasierowska-Guttmejer A, Wyrwicz L, et al. Neoadjuvant treatment for unresectable rectal cancer: An interim analysis of a multicentre randomized study. *Radiother Oncol* 2013;107:171-177.
- Rectal cancer, version 2.2020, NCCN clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed April 22, 2020.

26. Romesser P, Wu AJ, Cercek A, et al. Management of locally advanced rectal cancer during the COVID-19 pandemic: A necessary paradigm change at Memorial Sloan Kettering Cancer Center [e-pub ahead of print]. *Adv Radiat Oncol*. <https://doi.org/10.1016/j.adro.2020.04.011>. Accessed July 1, 2020.
27. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: Executive summary of an ASTRO, ASCO, and AUA evidence-based guideline. *Pract Radiat Oncol* 2018;8:354-360.
28. Kishan AU, Dang A, Katz AJ, et al. Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. *JAMA Netw Open* 2019;2:e188006.
29. Jackson WC, Silva J, Hartman HE, et al. Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol Biol Phys* 2019;104:778-789.
30. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* 2019;394:385-395.
31. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): Acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol* 2019;20:1531-1543.
32. Prostate cancer, version 1.2020, NCCN clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed April 22, 2020.