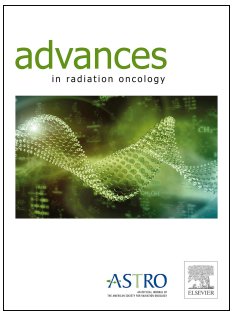

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Breast radiotherapy under COVID-19 pandemic resource constraints -- approaches to defer or shorten treatment from a Comprehensive Cancer Center in the United States

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Abstract

Introduction:
Breast radiotherapy accounts for a significant proportion of patient volume in contemporary radiation oncology practice. In the setting of anticipated resource constraints and widespread community infection with SARS-CoV-2 during the COVID-19 pandemic, measures for balancing both infectious and oncologic risk among patients and providers must be carefully considered. Here, we present evidence-based guidelines for omitting or abbreviating breast cancer radiotherapy, where appropriate, in an effort to mitigate risk to patients and optimize resource utilization.

Methods:
Multidisciplinary breast cancer experts at a high-volume comprehensive cancer center convened contingency planning meetings over the early days of the COVID-19 pandemic to review the relevant literature and establish recommendations for the application of hypofractionated and abbreviated breast radiation regimens.

Results:
Substantial evidence exists to support omitting radiation among certain favorable risk subgroups of breast cancer patients and for abbreviating or accelerating regimens among others. For those who require either whole-breast or post-mastectomy radiation, with or without coverage of the regional lymph nodes, a growing body of literature supports various hypofractionated approaches that appear safe and effective.

Conclusion:
In the setting of a public health emergency with the potential to strain critical healthcare resources and place patients at infection risk, the parsimonious application of breast radiotherapy may alleviate a significant clinical burden without compromising long term oncologic outcomes. The judicious and personalized use of immature study data may be warranted in the setting of a competing mortality risk from this widespread pandemic.

Introduction:
Breast radiotherapy (RT) is a curative component of treatment for many breast cancer presentations, albeit with limited locoregional benefit for certain patients and no survival implications for others (e.g. DCIS).[1] In the setting of the COVID-19 pandemic in which community infection represents a mortal risk, the anticipated benefit of breast RT in certain settings must be carefully weighed against infectious risk.

Whereas breast cancer represents the most common non-cutaneous malignancy in the United States, limiting the overall use and duration of breast RT under conditions of extreme resource constraints is prudent and may significantly alleviate institutional burdens. Guidance from the US Centers for Disease Control and World Health Organization advise limiting the sorts of person-to-person interactions that are likely to occur in clinical spaces among patients and healthcare staff during prolonged daily fractionation regimens. In addition, healthcare resources in many settings may need to be repurposed for pandemic management such that limiting utilization is of renewed importance.

Therefore, abbreviated fractionation regimens with nascent feasibility literature, as presented below, should be more strongly considered than under typically-conservative practice conditions.

Methods:
A team of radiation oncologists that specialize in breast cancer management at our comprehensive cancer center convened multi-disciplinary and cross-institutional contingency planning meetings over the early days of the COVID-19 pandemic to review the relevant literature and establish recommendations for the safe application of hypofractionated and abbreviated radiation regimens. The literature was reviewed with an emphasis on randomized controlled trial and level one evidence, followed by prospective observational studies, systematic reviews and meta-analyses.

Suggested considerations:

Omission of RT:
In general, the omission of radiotherapy among those who are eligible should be prioritized. These subgroups of low-risk patients have been studied in landmark trials demonstrating a moderate local control benefit of RT without improvement in already-excellent disease-specific survival outcomes.

- *Ductal carcinoma in situ:* Prospective observational studies[2] and randomized controlled trials[3] have reproducibly demonstrated a lack of survival benefit for RT among favorable DCIS presentations. It is, therefore, advisable to forego RT for those with mammographically-detected lesions <2.5cm in size, of low- or intermediate-grade, with adequate >=2mm resection margins.[4] Caution is warranted if foregoing RT in patients under 40 years of age.[5,6]
- *Invasive disease:* The omission of RT is preferred among those age 70 years and older who have estrogen-receptor positive (ER+) tumors that are <=3cm in size with no involved nodes (pT1-2N0M0), negative resection margins (i.e. "no tumor on ink"[7]), and who are eligible to receive endocrine therapy.[8] A large study with limited follow-up suggests lowering this threshold to 65 years of age is also safe.[9] For patients younger than 65 years of age, ongoing studies demonstrate equipoise with regard to those who have biomarker-low disease that otherwise fits the above clinicopathologic parameters, but no mature data exist in this domain[10–12].

Delaying RT:
Uncertainty surrounding the current public health emergency has made predictions about future resource allocation particularly challenging. Estimates of population-level relief range from weeks to over one-year.[13,14] In the interest of alleviating current workload and resource constraints, evidence exists to support delaying RT among certain populations, as follows:

- *Ductal carcinoma in situ*: In patients requiring RT for DCIS, radiation can be safely delayed up to 12 weeks following breast conserving surgery.[15]
- *Invasive disease*: Patients with early-stage, node-negative, ER+ breast cancer can safely begin radiotherapy 8-12 weeks after breast conserving surgery without compromising disease control or survival, with several large studies showing that a delay up to 20 weeks may be safe in an appropriate subset.[16,17] There is limited evidence to guide the interval from chemotherapy to RT, and most trials initiate RT 4-6 weeks following chemotherapy. Extrapolation from the surgical literature above suggests that an interval of up to 12 weeks from chemotherapy to RT may be reasonable.

For patients with ER+ breast cancers, either DCIS or invasive, who may otherwise experience a delay or interruption in treatment, we support the prompt initiation of endocrine therapy among those eligible. There is no evidence to suggest inferior local control or survival with concurrent hormonal therapy and radiation, including both tamoxifen[18,19] and aromatase inhibitors.[20]

Though subtle differences in breast edema, fibrosis/cosmesis, and lung toxicity have been reported, the overall evidence is mixed and should not limit use of concurrent therapy.[21]

Accelerated partial breast irradiation (APBI):
A large body of literature, including several landmark prospective trials, has established the safety and efficacy of APBI among appropriately selected patients. This paradigm is based on the historical observation that most recurrences occur proximate to the tumor cavity, such that treatment of the tumor bed with a margin has now been shown to confer outcomes similar to whole-breast RT in select settings. Moreover, utilization of a smaller target volume allows for acceleration of the overall regimen from 3-6 weeks down to 1-2 weeks - a critical gain under resource constrained circumstances. Additional benefits may include reduced acute toxicity as evidenced by ten-year follow-up of the Florence regimen (30Gy in 5 fractions, administered every-other-day).[22]

Various techniques and fractionation regimens are available for partial breast radiation. The use of brachytherapy is discouraged in the setting of strain on hospital resources, also yielding increased opportunities for exposure and infection. Accelerated external beam PBI regimens using 3D-CRT now have a large body of evidence supporting their use, with 38.5Gy in 10 fractions delivered twice-daily as a well-studied scheme. In one report, cosmesis appeared to score worse with this regimen[23], while in the seminal US study, this appeared to be less of a concern.[24] Other well-established options for APBI include 40Gy in 10 fractions daily using 3D-CRT[25,26], and 30Gy in 5 fractions every-other-day using IMRT[22] (daily fractionation appears well-tolerated; personal correspondence). Meanwhile, 40Gy in 15 daily fractions to the partial breast is also an effective regimen, though is more prolonged than the other APBI options.[27]

ASTRO consensus guidelines[28] and UK[29] have identified a population for which there is reasonable agreement regarding suitability of APBI: patients 50 years of age or older with screen-detected invasive disease that is <=2cm in size, ER+ and node negative, or DCIS that is low/intermediate grade and <=2.5cm in size. Of note, NSABP-B39 also included 800 patients with ER- breast cancer who exhibited excellent local control, suggesting that APBI may be reasonable among this group.

Whole-breast RT and hypofractionated regimens:
Among patients who require whole-breast RT without nodal treatment, hypofractionation is the preferred standard of care in the United States[30,31]. To that end, a number of fractionation schemes are well-supported by randomized trials including: 42.56Gy in 16 fractions[32] and 40Gy in 15 fractions[33]. Data is emerging for more extreme hypofractionation supporting 28.5Gy in 5 once-weekly fractions[34], as well as a more accelerated daily regimen of 26Gy in 5 daily fractions.[35] Though long-term local recurrence data have not yet resulted for FAST Forward, 3-year normal tissue toxicity appears equivalent to the well-tolerated three-week fractionation scheme. While various concerns have slowed widespread adoption of shorter regimens for whole-breast radiation, a number of prospective phase II, single arm and retrospective series

have demonstrated efficacy and safety among groups that were previously thought to be of particular concern including: high grade tumors[36], DCIS[37], young age[38] or triple-negative breast cancer.[36]

Post-mastectomy and/or Regional Nodal Irradiation (RNI):
Analyses of the two landmark studies, MA.20 and EORTC 22922, reproducibly demonstrated that RNI reduces distant recurrence risk and significantly improves disease-free-survival, even among those with a limited axillary disease burden.[39,40] As a result, an increasing number of patients have become eligible to receive comprehensive RNI following breast conservation or PMRT. Unfortunately, hypofractionated nodal irradiation has yet to see widespread adoption in the United States, although a nascent literature does suggest it is safe to employ 40 Gy in 15 daily fractions targeting the breast/chest wall and regional nodes (presuming the supraclavicular hotspot is below 105%; otherwise 39Gy in 15 fractions is preferred)[33,41–43] , with ongoing studies utilizing this regimen in a randomized fashion to suggest true clinical equipoise (RT-CHARM: NCT03414970; FABREC: NCT03422103). The UK FAST FORWARD trial includes a 5-fraction lymphatic RT cohort, but this is not yet considered safe outside of a trial or in the setting of palliation.

Boost to the tumor bed:
Boost radiotherapy has more limited applications in emergency settings.

- *Ductal carcinoma in situ*: The largest study to date evaluating the benefit of a boost in the setting of DCIS found a <2% local control benefit following whole breast radiation.[44] Given the absence of a survival benefit, boost can be omitted in resource-constrained settings, as was standard on RTOG 9804.[3] However, as above, caution is warranted among those younger than 40 years of ages in whom boost was shown to improve local control by 10% at 72 months.[45]
- *Invasive disease:* Following whole breast radiation, a tumor bed boost should be considered only in the presence of significant local recurrence risk factors: ≤60 years of age, high grade tumors, or inadequate margins.[46]

A standard boost after hypofractionated whole breast radiation involves 4-6 fractions, although evidence suggests that a simultaneous integrated boost may be similarly safe and effective.[47,48] In the setting of ultra-hypofractionation with 5-fraction regimens, it is reasonable to consider a single 5.2Gy dose to the tumor bed (personal correspondence), although this fractional boost dose remains to be reported beyond the brachytherapy literature.[49]

For patients receiving whole breast and nodal irradiation, a simultaneous integrated boost (SIB) can reduce treatment visits. This can be achieved with IMRT or VMAT, but is also possible with a supplemental electron field delivered with each 3D-CRT fraction.

Patient prioritization:

Under extreme circumstances, it may be necessary to prioritize which breast cancer patients can receive radiotherapy services. Prioritization of patients for whom RT is anticipated to provide a survival benefit is paramount. Based on available evidence and nascent clinical judgement, we have defined tiers of elevated priority (see **Table 2**). Of note, prioritization within each tier is left to the treating physicians' discretion based on patient age, comorbidities, risk of exposure and predicted benefit of RT.

Discussion:
As governments restrict public movement to limit continued spread of the SARS-CoV-2 pandemic, radiation oncologists must now make an unprecedented calculus on behalf of our patients: the mortal risk of presenting for treatment and being exposed to infection, versus the benefit of radiotherapy itself. It therefore behooves us to consider 1) omitting radiotherapy when appropriate, 2) delaying radiation while initiating endocrine therapy in low-risk patients with ER+ breast cancer, and 3) rapidly adopting accelerated schemes when possible in a concerted effort to protect our communities and conserve scarce healthcare resources.

Table 1. Hypofractionated or accelerated breast radiotherapy regimens.

TARGET	**Total dose / # of fractions**	**Technique/ Contours**	**Dose Constraints** (for shortest regimen only)	**Notes**
Partial breast	30Gy/5 every other day (preferred) or daily (acceptable) 40Gy/10 daily	**IMRT/VMAT** (preferred) **3DCRT** GTV (clips*) to PTV ~2cm (1.5cm to CTV with 5mm PTV margin)	30Gy in 5 fractions: Dmax <110% V105%(31.5Gy)<5% of breast volume Ipsi breast-PTV V15Gy<50% Contra breast Dmax <1Gy Lung (ipsi) V10Gy<20% Lung (contra) V5Gy<10%	Florence PBI trial[22] http://econtour.org/cases/47 MSK prospective[25,26] http://econtour.org/cases/108 *Clips strongly preferred for targeting and daily setup *Daily kv match to clips vs CBCT match to seroma
Whole breast	26Gy/5 daily +/- 5.2Gyx1 boost 40Gy/15 daily 42.4Gy/16 daily	**3DCRT** For left-sided, DIBH (preferred) and/or heart block	26Gy in 5 fractions: Dmax <110% V107% <2% of breast volume V105% <5% of breast volume Lung V8Gy <15% (<17% acceptable) Heart V7Gy <5%, V1.5Gy <30%	UK FAST Forward[35] http://econtour.org/cases/117
Post-mastectomy (PMRT)	42.56Gy/16	**3DCRT or IMRT**	42.56Gy in 16 fractions: Dmax<115% V107% <10cc of PTV Contra breast V3Gy<10% (preferred), V5Gy<10% (acceptable) Lung V18Gy≤35% (≤40% acceptable) Heart mean≤3Gy (preferred), ≤5Gy (acceptable) Heart V22.5Gy<10% (Left-sided), V22.5Gy<2% (Right-sided)	RTCHARM (NCT03414970) http://econtour.org/cases/110
Breast and regional nodal irradiation (RNI)	42.56Gy/16 with SIB to tumor bed 48Gy/16 (3Gy/fx) 40Gy/15 with SIB** to tumor bed 48Gy/15 (3.2Gy/fx)	**3DCRT or IMRT** 3DCRT SIB involves a separate electron plan delivered after photon plan Seroma/clips 7-10mm for CTV, then another 5-7mm for PTV. NOTE: expansions can be smaller for SIB.	(see PMRT constraints)	UK START B[33] and extrapolation from RTOG 1005[50] **SIB: EQD2 57Gy for a/b 3

For illustrative case presentations and guidance in contouring and planning the various regimens described above including target volumes, organs at risk, and relevant expansions, please visit http://econtour.org/hypofrac. Online cases also include dosimetric guidance and the dose constraints used in various supportive protocols.

Table 2. Prioritization of radiation for breast cancer based on treatment indication.

Tier 1 (high priority for breast RT)	• Inflammatory breast cancer
	• Residual node positivity after NAC
	• 4 or more positive nodes (N2)
	• Recurrent disease
	• Node-positive TNBC
	• Extensive LVI
Tier 2 (intermediate priority for breast RT)	• ER+ with 1-3 positive nodes (N1a)
	• Path N0 after NAC
	• LVI (NOS)
	• Node negative TNBC
Tier 3 (low priority for breast RT)	• Early-stage ER+ breast cancer (esp older)
	• DCIS
	• Otherwise not meeting criteria for Tiers 1-2

Abbreviations: Neoadjuvant chemotherapy (NAC), triple negative breast cancer (TNBC), lymphovascular invasion (LVI).

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Table 1. Hypofractionated or accelerated breast radiotherapy regimens.

TARGET	**Total dose / # of fractions**	**Technique/ Contours**	**Dose Constraints** (for shortest regimen only)	**Notes**
Partial breast	30Gy/5 every other day (preferred) or daily (acceptable) 40Gy/10 daily	**IMRT/VMAT** (preferred) **3DCRT** GTV (clips*) to PTV ~2cm (1.5cm to CTV with 5mm PTV margin)	30Gy in 5 fractions: Dmax <110% V105%(31.5Gy)<5% of breast volume Ipsi breast-PTV V15Gy<50% Contra breast Dmax <1Gy Lung (ipsi) V10Gy<20% Lung (contra) V5Gy<10%	Florence PBI trial[22] http://econtour.org/cases/47 MSK prospective[25,26] http://econtour.org/cases/108 *Clips strongly preferred for targeting and daily setup *Daily kv match to clips vs CBCT match to seroma
Whole breast	26Gy/5 daily +/- 5.2Gyx1 boost 40Gy/15 daily 42.4Gy/16 daily	**3DCRT** For left-sided, DIBH (preferred) and/or heart block	26Gy in 5 fractions: Dmax <110% V107% <2% of breast volume V105% <5% of breast volume Lung V8Gy <15% (<17% acceptable) Heart V7Gy <5%, V1.5Gy <30%	UK FAST Forward[35] http://econtour.org/cases/117
Post-mastectomy (PMRT)	42.56Gy/16	**3DCRT or IMRT**	42.56Gy in 16 fractions: Dmax<115% V107% <10cc of PTV Contra breast V3Gy<10% (preferred), V5Gy<10% (acceptable) Lung V18Gy≤35% (≤40% acceptable) Heart mean≤3Gy (preferred), ≤5Gy (acceptable) Heart V22.5Gy<10% (Left-sided), V22.5Gy<2% (Right-sided)	RTCHARM (NCT03414970) http://econtour.org/cases/110
Breast and regional nodal irradiation (RNI)	42.56Gy/16 with SIB to tumor bed 48Gy/16 (3Gy/fx) 40Gy/15 with SIB** to tumor bed 48Gy/15 (3.2Gy/fx)	**3DCRT or IMRT** 3DCRT SIB involves a separate electron plan delivered after photon plan Seroma/clips 7-10mm for CTV, then another 5-7mm for PTV. NOTE: expansions can be smaller for SIB.	(see PMRT constraints)	UK START B[33] and extrapolation from RTOG 1005[50] **SIB: EQD2 57Gy for a/b 3

For illustrative case presentations and guidance in contouring and planning the various regimens described above including target volumes, organs at risk, and relevant expansions, please visit http://econtour.org/hypofrac. Online cases also include dosimetric guidance and the dose constraints used in various supportive protocols.

Table 2. Prioritization of radiation for breast cancer based on treatment indication.

Tier 1 (high priority for breast RT)	• Inflammatory breast cancer
	• Residual node positivity after NAC
	• 4 or more positive nodes (N2)
	• Recurrent disease
	• Node-positive TNBC
	• Extensive LVI
Tier 2 (intermediate priority for breast RT)	• ER+ with 1-3 positive nodes (N1a)
	• Path N0 after NAC
	• LVI (NOS)
	• Node negative TNBC
Tier 3 (low priority for breast RT)	• Early-stage ER+ breast cancer (esp older)
	• DCIS
	• Otherwise not meeting criteria for Tiers 1-2

Abbreviations: Neoadjuvant chemotherapy (NAC), triple negative breast cancer (TNBC), lymphovascular invasion (LVI).