Article:
Thomson, DJ, Yom, SS, Saeed, H et al. (20 more authors) (2020) Radiation Fractionation Schedules Published During the COVID-19 Pandemic: A Systematic Review of the Quality of Evidence and Recommendations for Future Development. International Journal of Radiation: Oncology - Biology - Physics, 108 (2). pp. 379-389. ISSN 0360-3016

https://doi.org/10.1016/j.ijrobp.2020.06.054

Radiation Fractionation Schedules Recommended During the COVID-19 Pandemic: A Systematic Review of the Quality of Evidence and Considerations for Future Development

David J. Thomson, MA, MD, FRCR,*[1] Sue S. Yom, MD, PhD, MAS,*[2] Hina Saeed, MD,*[3] Issam El Naqa, PhD,**[4] Leslie Ballas, MD,[5] Soren M. Bentzen, PhD, DMSc[6] Samuel T. Chao, MD,[7] Ananya Choudhury, MA, PhD, MRCP, FRCR,[8] Charlotte E. Coles, MD, MRCP, FRCR, PhD,[9] Laura Dover, MD,[10] B. Ashleigh Guadagnolo, MD, MPH,[11] Matthias Guckenberger, MD,[12] Peter Hoskin, MD, FRCR[13] Salma K. Jabbour, MD,[14] Matthew S. Katz, MD,[15] Somnath Mukherjee, MD, FRCP,[16] Agata Rembielak, MD, PhD,[17] David Sebag-Montefiore, MD, FRCR,[18] David J. Sher, MD, MPH,[19] Stephanie A. Terezakis, MD,[20] Toms V. Thomas, MD,[21] Jennifer Vogel, MD,[22] Christopher Estes, MD[23]

* co-first author
** statistical author

Affiliations
1. Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, and the Division of Cancer Sciences, University of Manchester, Manchester, UK
2. Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA
3. Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA
4. Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA
5. Department of Radiation Oncology, University of Southern California, Los Angeles, CA, USA
6. Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
7. Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, USA
8. University of Manchester and Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK
9. Department of Oncology, University of Cambridge, Cambridge, UK
10. Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
11. University of Texas - M. D. Anderson Cancer Center, Houston, TX, USA
12. Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
13. Mount Vernon Cancer Centre, Northwood and University of Manchester, Manchester, UK
14. Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA
15. Department of Radiation Medicine, Lowell General Hospital, Lowell, MA, USA
16. Department of Oncology, Oxford University, Oxford, UK
17. Department of Clinical Oncology, The Christie NHS Foundation Trust and University of Manchester, Manchester, UK
18. Leeds Institute of Medical Research, University of Leeds, Leeds, UK.
19. Department of Radiation Oncology, University of Texas – Southwestern, Dallas, TX, USA
20. Department of Radiation Oncology, University of Minnesota, Minneapolis, MN, USA
21. Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA

22. Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, MD, USA
23. Mercy Hospital, Springfield, MO, USA

Conflicts of Interest:
Drs. Ballas, Bentzen, Coles, Dover, Guadagnolo, Hoskin, Mukherjee, Rembielak, Saeed, Sebag-Montefiore, Sher, Terezakis, Thomas, Thomson, and Vogel report nothing to disclose;
Dr. Chao reports personal fees from Varian Medical Systems, outside the submitted work;
Dr. Choudhury reports grants from National Institute of Health Research, Manchester Biomedical Research Centre, Cancer Research, UK, Medical Research Council, UK, Prostate Cancer, UK, and Bayer, UK, personal fees from Janssen Pharmaceutical, non-financial support from ASCO, and grants and non-financial support from Elekta AB, outside the submitted work;
Dr. El Naqa reports grants from National Institutes of Health, Endectra LLC, and Resero AI LLC, outside the submitted work;
Dr. Estes reports other from Novocure, outside the submitted work;
Dr. Guckenberger reports grants from Varian and AstraZeneca and personal fees from AstraZeneca, outside the submitted work;
Dr. Katz owns common stock in Dr. Reddy's Laboratories, Healthcare Services Group, Mazor Robotics, and U.S. Physical Therapy;
Dr. Jabbour reports grants, personal fees and non-financial support from Merck & Co, outside the submitted work;
Dr. Yom reports grants from Genentech, Bristol-Myers Squibb, Merck, and BioMimetix, and personal fees from Springer and UpToDate, outside the submitted work.

Statistical author:
Issam El Naqa, PhD
Department of Radiation Oncology
University of Michigan
1500 E Medical Center Dr,
Ann Arbor, MI 48109
Tel: 734-934-4290
Email: ielnaqa@med.umich.edu

Corresponding author:
Sue S. Yom, MD, PhD, MAS
University of California, San Francisco
Department of Radiation Oncology
1825 4th Street, Suite L1101
San Francisco, CA 94143
Tel: (415) 353-7175
Email: sue.yom@ucsf.edu

Funding: No funding was paid to the authors or their institutions for this work. AC, DJT and PH are supported by NIHR Manchester Biomedical Centre. CEC is supported by NIHR Cambridge Biomedical Centre. DJT is supported by a grant from The Taylor Family Foundation/Cancer Research UK. SM is partly supported by NIHR Oxford Biomedical Centre.

Acknowledgments: None.

Data sharing statement: All data generated and analyzed during this study are included in this published article (and its supplementary information files).

Radiation Fractionation Schedules Recommended During the COVID-19 Pandemic: A Systematic Review of the Quality of Evidence and Considerations for Future Development

Abstract

Introduction

Numerous publications during the COVID-19 pandemic recommended the use of hypofractionated radiotherapy. This project assessed aggregate changes in the quality of the evidence supporting these schedules, to establish a comprehensive evidence base for future reference and highlight aspects for future study.

Methods and Materials

Based on a systematic review of published recommendations related to dose-fractionation during the COVID-19 pandemic, twenty expert panellists assigned to fourteen disease groups named and graded the highest-quality of evidence schedule(s) used routinely for each condition and also graded all COVID-era recommended schedules. The ASTRO quality of evidence criteria were used to rank the schedules. Process-related statistics and changes in distributions of quality ratings of the highest-rated versus recommended COVID-19-era schedules were described by disease groups and for specific clinical scenarios.

Results

From January to May 2020 there were 54 relevant publications, including a total of 233 recommended COVID-19-adapted dose-fractionations. For site-specific curative and palliative schedules, there was a significant shift in the publishing record from established higher-quality evidence to lower-quality evidence and expert opinions for the recommended schedules ($p = 0.022$ and $p < 0.001$, respectively). For curative-intent schedules, the distribution of quality scores was essentially reversed (51.4% high-quality 'pre-COVID' versus 49.3% supported only by expert opinion 'in-COVID), although there was variation in the magnitude of shifts between disease sites and among specific indications.

Conclusions

A large number of publications recommended hypofractionated radiotherapy schedules across all major disease sites during the COVID-19 pandemic, which were supported by a lower quality of evidence than the highest-quality routinely used dose-fractionation schedules. This work provides an evidence-based assessment of these potentially practice-changing recommendations and informs individualized decision-making and counselling of patients. These data would also support radiotherapy practices in the event of second waves or surges of the pandemic in new regions of the world.

Introduction

The coronavirus (SARS-CoV-2) outbreak was first reported in December 2019 and named COVID-19 by the World Health Organization in February 2020.(1) By June 2020, there were an estimated 400,000 deaths worldwide, with approximately one-third of these in the United States and United Kingdom.(2) As the COVID-19 pandemic expanded and matured, the pace of scientific investigation and publication related to the coronavirus and its effects also exponentially increased. In the spring of 2020 at the peak of the pandemic, the number of SARS-CoV-2-related research publications had an estimated doubling time of less than 14 days.(3) This acceleration was distinct from patterns of publication during the outbreak of severe acute respiratory syndrome (SARS) in Asia in 2003, when only a small fraction of related articles were published during the time of the actual epidemic.(4) This historic shift likely reflects: (i) the rapid worldwide spread of the COVID-19 pandemic with a devastating global effect stimulating urgent actions in every nation, (ii) a contemporary research, publishing, and social media infrastructure allowing for extremely rapid production and dissemination of information, and (iii) the unprecedented open access of academic journals, societies, institutes, and companies, as demonstrated by the nearly 100 such entities which pledged to make coronavirus-related research freely available for the duration of the pandemic.(5)

Due to restrictions on services within radiotherapy departments and the need to minimize the exposure of patients at risk of severe infection from SARS-CoV-2 in heavily affected regions, numerous expert groups, professional societies, and other institutions very early on proposed serious consideration of delay or alteration of regular radiation schedules.(6, 7) In the face of a need for immediate action, these recommendations were limited by a number of sizeable uncertainties, including: (i) difficulty predicting the future prevalence of SARS-CoV-2 and the impact of the pandemic at a local or regional level, including over a prolonged course of fractionated radiotherapy, (ii) variation in the nature of resource constraints, and the need for prioritization between disease sites and hospital departments, and (iii) limited data to personalize treatment decisions based on an individual patient's risk from exposure to SARS-CoV-2 infection, as preliminary information only became available after the peak of the pandemic.(8)

Practice recommendations included the deferral of treatments for those at presumed lowest risk of cancer progression (e.g., slowly growing cancers, or select cases of adjuvant radiotherapy) or where potentially reasonable alternatives (e.g., extended duration of neoadjuvant hormone therapy) could be used for a limited period as a temporizing measure. Many suggested the use of hypofractionated radiotherapy schedules (those that are shorter overall but give a larger dose per fraction) to reduce patient exposures and optimize use of limited resources. These recommendations were frequently based on a theory of "shorter is better." While for some radiotherapeutic indications, published trials have demonstrated that hypofractionation is a standard of care,(9) data supporting hypofractionation are not available for all sites and/or radiotherapy indications. Therefore, shorter courses were sometimes recommended to truncate treatment courses for indications where data were lacking, perhaps with allowances that compromises were needed in the face of unavoidable circumstances.

Whether the rapid pace of information exchange, facilitated by social media outlets, professional society dissemination, and markedly accelerated peer review and publication processes,(10) has resulted in a lower quality of research or practice recommendations is unknown.(11, 12) From the scientific perspective, expressions of editorial concern about duplicate reporting and high-profile retractions have raised increasing doubt about the reproducibility and durability of parts of the COVID-era research production.(13-16) However, the selection of a radiotherapy dose-fractionation schedule is fundamental to high-quality cancer care, and the particular body of COVID-era recommendations for hypofractionation may stand as one of the enduring creations of the pandemic having a lasting effect. This project was aimed at an assessment of the quality of the treatment recommendations produced on the topic of hypofractionation during the COVID-19 era, directed at multiple objectives: first, to establish and disseminate an evidence base around this phenomenon for future reference; second, to comment on aggregate changes in the quality of evidence of these recommendations either positive or negative between and within disease groupings, and third, to highlight aspects of changes in quality requiring further, considered study, post-COVID.

Methods and Materials

Literature Search

With the intention of identifying all recommendations related to fractionation published during the early COVID-19 pandemic, a literature search was conducted in PubMed/MEDLINE for the terms “COVID” and “radiotherapy” to retrieve all relevant English-language articles appearing through June 1, 2020 (Literature Search and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, Supplemental Appendix). An initial screening of titles and abstracts identified candidate publications and excluded duplicates or those which were clearly irrelevant (CE, HS).

Brachytherapy and proton therapy recommendations were excluded due to their extremely limited appearance in this scientific literature and the lack of alteration from non-pandemic guidelines. The remaining publications were fully reviewed to identify any containing a recommendation of a specific schedule of radiation fractionation for a cancer or benign tumor condition (CE, HS, TT, SY), including treatments with palliative intent. This project did not address recommendations related to delay or omission of radiation therapy or adjustment of aspects of multidisciplinary care. Articles containing recommendations related to logistics of radiation therapy operations or COVID crisis management were excluded.

In addition, a manual search for articles in press which had not yet been indexed in PubMed/MEDLINE included the following radiation oncology-specific journals: Int*ernational Journal of Radiation Oncology, Biology, Physics*; *Radiotherapy and Oncology*; *Practical Radiation Oncology*; *Advances in Radiation Oncology*; and *Clinical Oncology*. Articles found to be in press were added if they contained fractionation recommendations and had not been captured by the initial search (CE, SY).

Finally, the websites of national or international organizations were searched for practice statements or other resources which included any unique COVID-specific fractionation recommendations. These organizations included: Royal College of Radiologists UK, National Institute for Health and Care Excellence, Royal Australian and New Zealand College of Radiologists, American Society for Radiation Oncology, European Society for Radiotherapy and Oncology, National Comprehensive Cancer Network, American Society of Clinical Oncology, International Lymphoma Radiation Oncology Group, and European Society for Pediatric Oncology. If a fractionation schedule was found in a document that had not previously been captured in the literature search, the publication was added to the search and the schedule was added to the list of regimens (CE, SY).

From this study set, all of the fractionation recommendations that had been recommended in any of these publications were recorded, noting the number of publications in which each schedule had been mentioned and the references pertinent to each fractionation.

Rating Procedures

An international team was assembled including 20 disease site experts, of whom one to three were assigned to each disease group. Experts assigned to each group were asked to provide routinely used fractionation schedule(s) considered to be at the highest level of evidence for each specific condition in question and to provide references justifying their designation (Table, Supplemental Appendix).

The selected experts graded the quality of the evidence using the American Society of Radiation Oncology (ASTRO) classification.(17) The ASTRO scale defines four levels of quality of evidence: high, moderate, low, and expert opinion. To be designated high-quality, the fractionation schedule had to be supported by at least two or more well-conducted and highly generalizable randomized clinical trials or meta-analyses of such trials. Specifically for this project, a rating of high quality required intentional comparison of the attributes of that schedule's fractionation question as a randomization versus another fractionation schedule (e.g., if the schedule had just been incidentally used in one of the arms of the trial, the study was classified as observational, hence automatically reducing the quality level of the evidence supporting that schedule).

Experts named and graded the highest-quality schedule or schedules known to be routinely used for the specific clinical condition and also graded all of the alternative or proposed fractionation schedules that had been recommended for that clinical condition in publications identified from the COVID-era literature search. Experts first rated each of the fractionation schedules in isolation but then convened by assigned disease sites to determine a consensus quality score for the evidence supporting each fractionation schedule (Table, Supplemental Appendix). Each disease group also had the option of nominating schedules they deemed most worthy of further development or dissemination.

Statistical Analyses

Descriptive statistics were used for process metrics related to the number of participants, numbers of publications and recommendations evaluated, and the quality of evidence scores. Contingency tables with chi-square tests were used to evaluate the distribution of the quality of evidence of the highest-rated schedules compared to that of the COVID-era schedules. Analysis of variance (ANOVA) methods were used to determine differences between disease groups.

Scatter regression plots were used to visualize the overall changes in quality from the highest-quality schedules for specific clinical scenarios to the quality of evidence of the alternative schedules proposed in the pandemic-era literature. The ASTRO quality scores were converted to a linear scale with units of 1, and regression lines were based on plotted shifts for each disease group. A diagonal slope of 1 represented no change in the quality of evidence from 'pre-COVID' to 'in-COVID.' Pooled t-tests were used to measure differences of regression slopes from 1.

The shifts in the quality of evidence from 'pre-COVID' to the highest-ranked 'in-COVID' site-specific recommendations were compared. The disease sites with less shift were compared against those with greater changes in quality using the adjusted chi-square test. DIfferences between disease sites were further compared using a weighted shift based on the 'pre-COVID' evidence quality and the levels of evidentiary shift to the 'in-COVID' ranking, with significance determined by the adjusted chi-square test. The weights were assigned according to a progressive hierarchy of the shifts: high to opinion, high to low, high to moderate, moderate to opinion, moderate to low, and low to opinion - receiving a numerical value from 6 to 1, respectively. Top-weighted shifts were compared to low-weighted shifts around the median. Significance for all tests was assessed at a p-value <0.05.

This study was granted exempt status (#20-30633) by the Institutional Review Board at the University of California, San Francisco.

Results

Literature Search

The literature search was conducted without a start date with a last run on June 1, 2020. The search retrieved a total of 238 articles, and by consecutive month from February to May 2020 there were 2, 16, 89, and 110 articles appearing in the literature, with another 21 already pre-indexed for June. Of these, 36 were reviewed and found to be relevant to radiotherapy dose-fractionation, and an additional 18 publications were found by manual searches, including one article in press and 17 practice recommendations or related resources issued by the National Comprehensive Cancer Network, the Royal College of Radiologists and the Royal Australian and New Zealand College of Radiologists. In total, 54 selected publications were included as the evidence base for this systematic review. All radiotherapy dose-fractionation schedules recommended in these publications are provided in the Supplemental Appendix (Table).

Systematic Review of 'Pre-COVID' and 'In-COVID' Evidence Quality

Twenty panelists divided into 14 disease groups named the schedules with the highest level of evidence for each clinical indication and rated the quality of evidence supporting 233 recommended COVID-19-adapted dose-fractionation schedules. The 14 disease sites and the respective number of COVID-19-adapted fractionation schedules (curative+palliative) were: breast (28+3), central nervous system (CNS) (13+5), cutaneous (inclusive of melanoma (3+4) and non-melanoma (11+3)), lung (22+8), upper gastrointestinal (UGI (14, 8)), lower gastrointestinal (LGI (6+3)), genitourinary (GU) (15+3), gynecology (1+6), head and neck (11+7), hematologic (0+8), lymphoma (10+5), pediatrics (19+0), general palliative (0+11), and sarcoma (6+0). Aggregated quality ratings were generally grouped as disease site-specific curative, disease-site specific palliative, general palliative (e.g. for bone metastases), and curative-intent cutaneous radiotherapy schedules (because skin cancer treatments often involve superficial orthovoltage or electron techniques, and there is frequent routine use of hypofractionation). The individual panelists' scores and the disease group's consensus scores for each of the dose-fractionation schedules are catalogued in the Supplemental Appendix (Table).

For site-specific curative and palliative schedules, there was a significant shift in the publishing record from established higher-quality evidence schedules to lower-quality evidence and opinions for schedules recommended in the COVID era (Figures 1a and 1b, $p=0.022$ and $p<0.001$, respectively). For curative-intent schedules, the overall distribution of quality scores was essentially reversed; 51.4% of the highest rated evidence schedules were high-quality versus 4.8% of COVID-era recommended schedules, and 49.3% of the recommended COVID-era schedules were at the level of opinion versus 5.6% of the highest-quality of evidence schedules (Table 1). Cutaneous curative-intent radiotherapy was an outlier, as schedules commonly used prior to the COVID era were all already at a low-quality evidence level, with pandemic recommendations consistently ranked even further downward to the level of opinion (Figure 1, Supplemental Appendix). While this shift was significant due to the consistent pattern ($p=0.008$), it was attributable to the pre-existing low quality of evidence rather than indicative of a major shift in quality. Conversely, for the general palliative schedules, there was high-quality evidence supporting the use of hypofractionated radiotherapy as standard, with 5/11 schedules rated as high-quality, including the use of a single fraction for spinal cord compression and bone metastases. As these schedules were already hypofractionated prior to the COVID era, there was no impetus for alteration and the quality level was unchanged (Figure 2, Supplemental Appendix, $p=0.09$).

For most disease groups, high-quality evidence supported the routine use of conventionally fractionated radiotherapy. There was moderate-to-low quality evidence supporting conventionally fractionated regimens for some gastrointestinal indications, such as borderline or inoperable pancreas cancers (25-30 x 2 Gy, moderate-quality evidence) or pre-operative esophageal cancer (28 x 1.8 Gy, moderate-quality evidence) and anal cancer if treated without concurrent chemotherapy (28-30 x 1.8 Gy, low-quality evidence). On the other hand, there was high-quality evidence supporting hypofractionated schedules for specific indications such as intact prostate (20 x 3 Gy),(18) adjuvant breast (e.g., 15-16 x 2.67-2.66 Gy),(19, 20) preoperative rectal (5 x 5 Gy),(21-24) and T1 larynx (28 x 2.25 Gy) cancers,(25) and glioblastoma in older or less fit patients (15 x 2.67 Gy).(26, 27) Lastly, for some disease groups, there was lower-level evidence supporting hypofractionated treatments, including stereotactic body radiation

therapy (SBRT) in a single fraction for peripheral T1-2 non-small cell lung cancer (NSCLC) (moderate-quality evidence),(28) 20 x 2.75 Gy for organ preservation in bladder cancer (moderate-quality evidence),(29, 30) and various fractionations (e.g. 10 x 4 Gy, 15 x 3.33 Gy, 20 x 2.75 Gy) for cutaneous cancers (low-quality evidence).

The overall shifts in the quality of evidence between the highest-rated fractionation schedules and the COVID-era recommended schedules were organized in scatter plots by disease groups (Figure 3, Supplemental Appendix). These shifts were further mapped by disease groups in forest plots demonstrating the range of experts' quality rankings for each of the COVID-era schedules (Figure 4, Supplemental Appendix). The overall differences in shifts across disease groups were found to be not significant across the curative-intent disease groupings ($p=0.422$) but were significant for the disease-specific palliative groupings ($p=0.005$). However, the difference between curative-intent disease groupings with shifts of ≤1 (lower and upper GI, renal) from those with shifts >1 was significant ($p = 0.001$).

In scatter regression plots, the diagonal with a slope of 1 represented no change in the evidence level from 'pre-COVID' to 'in-COVID' and was visually compared against the regression slope for each disease group (Figures 5 and 6, Supplemental Appendix). All plot points for curative-intent schedules fell below the diagonal confirming a universal shift to a lower quality of evidence (p-value <0.01) (Figure 2a). Sarcoma, CNS, and pediatrics showed the most negative slopes, but relatively reduced slopes were seen for upper GI, lung, lower GI, GU, breast, and head and neck. Results for site-specific palliative schedules were mixed but all were located on or inferior to the diagonal with lung and head and neck sloping negatively (Figure 2b).

For some disease groups, the recommendation to use shorter than routinely applied fractionated schedules was underpinned by high- to moderate-quality evidence, including those for adjuvant whole breast (e.g., 5 x 5.2 Gy),(31) intact prostate (e.g., 7 x 6.1 Gy or SBRT at 5 x 7.25-8.0 Gy),(32, 33) salvage prostate (20 x 2.625 Gy),(34) and NSCLC (20 x 2.75 Gy).(35) For others, the shift was from high- to low-quality evidence (e.g., head and neck cancer: 20 x 2.75 Gy (36, 37) or 30 x 2.17 Gy(38); limited-stage small cell lung cancer (SCLC): 15-16 x 2.67-2.81 Gy (39, 40) or from high-quality evidence to expert opinion (e.g., glioblastoma, grade III glioma, or low-grade glioma: 15 x 2.67 Gy).

Because there was a non-linear relationship between the integral change in the quality of evidence and the potential significance of the evidentiary shift (e.g., high to moderate versus low to opinion or high to low versus moderate to opinion), we also assessed disease sites by weighted shifts based on the highest-quality schedule's score and the number of levels of shift separating it from the in-COVID recommendation (Figures 7 and 8, Supplemental Appendix). For curative radiotherapy, there was heterogeneity in the highest levels of evidence within disease group sites (e.g., pre-operative rectal versus anal cancer) or indications (e.g., adjuvant whole breast versus adjuvant breast boost or head and neck definitive versus head and neck post-operative), and between the groups there was variation in the magnitude and weight of the shifts to the COVID-era quality of evidence. Less impact was seen for disease groups already with a lower quality of evidence for their highest-ranked schedules (e.g., upper

and lower gastrointestinal) or those which experienced minimal change (e.g. pediatrics), and more for those with a pre-existing higher quality of evidence that resulted in larger decreases towards the COVID-era quality of evidence (e.g., lymphoma, GU, CNS, HN, breast). The distribution of weighted shifts falling below the median value of 3 (Gyn, Hematologic, Lower GI, Pediatrics, Renal, Upper GI) versus those above was significant ($p<0.00001$). For disease site-specific palliative schedules, the change associated with the COVID-era schedules was less, because of the lower quality of pre-existing evidence. Exceptions to this generalization were genitourinary (bladder) and CNS, where there were notable COVID-era reductions in quality for site-specific palliative recommendations due to the pre-existing high-quality evidence for palliative schedules.

Due to the heterogeneity of the surveyed curative-intent scenarios, we also assessed disease-specific shifts in evidence quality by comparing the highest-quality 'pre-COVID' schedules to the highest-rated and most frequently recommended (between 1 to 10 recommendations; Figure 9, Supplemental Appendix) COVID-era hypofractionated schedules for a specific cancer condition ('best versus best') (Figure 3). This analysis was not meant to designate preferred or endorsed schedules (as the intent was not to conflate frequency of recommendation with quality of evidence), but to test for differences in evidence shifts that might separate the most commonly recommended schedules. There were no differences among weighted shifts overall for these chosen specific indications, but distribution of the indications having weighted shifts above and below 3 was significant ($p<0.0001$). It was apparent that for some indications, such as limited-stage SCLC, locally advanced head and neck cancer, glioblastoma, and lymphoma, there were substantial declines in the quality of the evidence in the COVID era. On the other hand, for adjuvant whole breast or intact prostate cancer treatments, there was pre-existing high-quality evidence supporting 3-4 week schedules (which are routinely used in some parts of the world) and moderate-quality evidence for 1 week schedules, such that the shifts from the highest-quality schedules to COVID-era schedules were minimal.

Among some groups, panelists demarcated certain schedules as worthy of further development or dissemination if not already part of the standard of care (Table, Supplemental Appendix). Numerous fractionation schedules were deemed highly acceptable in the treatment of breast cancer (e.g. 15 x 2.67 Gy for various scenarios or 5 x 5.2 Gy postoperatively). Other schedules pertained to specific groups, such as older or less fit patients (e.g. 15 x 2.67 Gy for glioblastoma and 8 x 5 Gy for definitive skin cancer therapy). Some groups noted a need for testing of hypofractionation in combination with chemotherapy (e.g. 20 x 2.75 Gy for definitive-intent head and neck and NSCLC treatments). While some disease groups declined to nominate specific schedules, participants expressed universal sentiment that evidence-based assessment should be the basis of any such process.

Discussion

To safeguard treatment capacity from staff shortages and mitigate the risk of patient infection by SARS-CoV-2 from daily hospital attendances, a large number of publications early on in the COVID-19 pandemic recommended consideration of hypofractionated radiotherapy under the premise "shorter is better."(7, 41) The unpredictable nature of the pandemic, and the prolonged course of most

radiotherapy treatments, meant that these schedules were often proposed in advance of an actual critical resource constraint or surge in SARS-CoV-2 community prevalence. Early in the pandemic, the potential impacts on cancer care could not be predicted given the lack of evidence guiding any formalized risk assessment. This systematic review was aimed at a large-scale evaluation of this phenomenon, assessing across all disease groups the shifts in the quality of evidence for these 'in-COVID' recommended schedules compared with those defined by experts to be in routine use in the 'pre-COVID' era which were supported by the highest quality of evidence. A schedule at the highest quality of evidence was considered to be the most objective reference point that would be independent of the variation and subjectivity incurred in defining a 'standard of care', which did not clearly exist for some specific disease indications.

Over the course of just a few months during the early and peak pandemic, there were 54 published articles from the radiotherapy community specifically recommending the use of hypofractionation during COVID-19. The high number of articles and speed to publication were notable, which resulted from a perception of an urgent need to support radiation oncologists, many of whom may have been unfamiliar with the use of such schedules or the evidence supporting them, particularly in an international context. The resulting body of literature as summarized in this paper advocated for a range of dose-fractionation schedules from the worldwide radiotherapy community, but the range of the evidence base for these recommendations varied widely from randomized trials to opinion. As these publications constitute a major scholarly response of the radiotherapy community to the COVID-19 pandemic, it is important to critically evaluate this literature in light of the consistently stronger evidence that has long supported historically accepted conventional regimens.

For some disease sites such as head and neck cancer and high-grade glioma, there were large shifts from high- to low-quality evidence or expert opinion, which was acknowledged in published consensus statements, leading to advice in most cases to maintain standard practices except where impossible due to severely reduced resources. (42, 43) For pediatric cancers, where the mitigation of late effects is a priority, there was only low-quality evidence or opinion supporting the use of hypofractionated radiotherapy. This was reflected in a practice recommendation to continue standard treatments, reserving isoeffective hypofractionated radiotherapy for selected poor-prognosis patients for whom radiotherapy could not be safely deferred.(44)

For other situations, including adjuvant whole breast and intact prostate treatments, there was pre-existing high-quality evidence to support the recommended use of moderate hypofractionation over three and four weeks respectively, and moderate evidence to support further shortening over one week. In the setting of resource constraints, such recommendations have the potential for greatest impact as these are high-volume cancers. For example, adjuvant whole or partial breast radiotherapy may account for approximately 30% of all delivered fractions within a radiotherapy department,(45, 46) and the use of 15-16(20, 47) or five fractions(31, 48, 49) instead of 25 fractions would reduce the overall demand for delivered fractions by an estimated 10-25%.

Within disease sites there was some variation in the quality of evidence across specific clinical scenarios, partly influenced by restricted access to operating rooms or rationing of surgical resources during the pandemic, resulting in the need for alternative treatments as a temporizing measure prior to surgery (e.g., preoperative whole breast radiotherapy where there is no option for preoperative systemic therapy, low-quality evidence).(50-52) In some cases there was variation within the same disease-specific indication, where there were recommended hypofractionated schedules supported by higher- or lower-quality evidence. Examples of such situations and the schedules with lower-quality evidence or expert opinion included: adjuvant partial breast (4.0 Gy x 10 fractions, expert opinion)(53) (7.0-8.8 Gy x 5 alternating daily fractions for radiotherapy alone, expert opinion; 3.0 Gy x 18 fractions, expert opinion),(42, 54) non-small cell lung cancer (2.5 Gy x 20 fractions for sequential chemo-radiotherapy, expert opinion)(55) and intact prostate cancer (2.7 Gy x 26 fractions, low-quality evidence)(56, 57).

This systematic evaluation of hypofractionated schedules by standardized quality of evidence ratings informs comparisons between treatments and provides evidence-based assessment of potentially practice-changing recommendations. The project's compilation of all recommended fractionation schedules from the early and peak pandemic will serve as a useful reference. At a time of constrained resources and on a policy-making level, evidence-based assessment benefits prioritization decisions between and within disease sites, and for the practitioner it supports individual treatment discussions and informed consent processes with patients. In a situation of adequate resources but risk mitigation, decision-making processes for an individual patient would likely require a more deliberative conversation than might be possible in a situation of resource inadequacy. Furthermore, in some cases, quality ratings may support hypofractionated regimens over current standards.

A potential learning from the COVID-19 pandemic is to coordinate and integrate responses from the radiotherapy community to provide rationalization and harmonization of recommendations. In this respect, there are numerous limitations to this particular work: the literature search had to be stopped before the pandemic had truly ceased and was limited only to English-language publications, and the schedules were rated by a relatively small number of disease specialists using only one system from ASTRO. In addition, the COVID-era literature itself may be incomplete and not represent a true catalogue of all of the best hypofractionated regimens, and the level of peer review may have been less or zero, especially for emergently issued practice statements and editorials. In this project, analyses were mostly in aggregate without focus on the nuances of specific disease conditions.

A lesser emphasis of this work was to consider which of the suggested dose-fractionation schedules might be worthy of further study or dissemination. It is important to recognize that while the COVID-era schedules were generally concerned with shortening treatment time while maintaining similar levels of local tumor control (isoeffectiveness), future studies might also be concerned with dose-intensification or isotoxicity. The COVID-era literature is not exhaustive of all schedules under investigation; there are ongoing trials evaluating the use of hypofractionated schedules to address resource constraints(48) and for patient convenience.(49) Some disease group panelists opted not to select particular schedules for further study, but all commented on the importance of systematic evaluation of the outcomes of patients treated in the COVID-19 pandemic, to inform clinical practice and the design of future research.

It is unclear to what extent the international oncology community has actually implemented practice-changing recommendations based on lower levels of evidence. It is also unknown whether individual oncologic or toxicity outcomes were sacrificed for purposes of risk mitigation or to manage constrained resources. The real-world application of hypofractionated schedules during the pandemic and any impact on patient outcomes will be a subject of future work. Examples of such initiatives include the National Cancer Research Institute's COVID RT radiotherapy registry in the United Kingdom,(58) the COVID-19 & Cancer Consortium (CCC19) registry, and the American Society of Clinical Oncology's Survey on COVID-19 in Oncology Registry, supported by ASTRO in the United States. (59) We should harness the tangible observed benefits of collaboration and rapid research outputs to streamline and accelerate innovation. There may be novel opportunities to learn from patients treated with non-standard dose fractionations during the COVID-19 pandemic, either to discard certain fractionation practices or to inform future rational clinical trial designs. These data would also support radiotherapy practices in the event of second waves or surges of the pandemic in new regions of the world.

References

1. Naming the coronavirus disease (COVID-19) and the virus that causes it 2020 [06/01/2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
2. Coronavirus disease (COVID-19) Situation Report – 137 2020 [06/05/2020]. Available from: https://www.who.int/docs/default-source/sri-lanka-documents/20200605-covid-19-sitrep-137.pdf?sfvrsn=a13df572_2
3. COVID-19 Primer 2020 [Available from: https://covid19primer.com/dashboard.
4. Xing W, Hejblum G, Leung GM, Valleron A-J. Anatomy of the epidemiological literature on the 2003 SARS outbreaks in Hong Kong and Toronto: a time-stratified review. PLoS medicine. 2010;7(5):e1000272-e.
5. Yasinski E. Journals Open Access to Coronavirus Resources 02/13/2020 [Available from: https://www.the-scientist.com/news-opinion/journals-open-access-to-coronavirus-resources--67105.
6. Filippi AR, Russi E, Magrini SM, Corvò R. Letter from Italy: First practical indications for radiation therapy departments during COVID-19 outbreak. Int J Radiat Oncol Biol Phys. 2020.
7. Achard V, Tsoutsou P, Zilli T. Radiotherapy in the time of the Coronavirus pandemic: when less is better. Int J Radiat Oncol Biol Phys. 2020.
8. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020;10(6):783-91.
9. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016;17(8):1047-60.
10. COVID-19 Rapid Communications 2020 [Available from: https://www.sciencedirect.com/journal/radiotherapy-and-oncology/special-issue/1086W2WWCC6.
11. Jackie Flynn M. Science Has an Ugly, Complicated Dark Side. And the Coronavirus Is Bringing It Out. 2020 2020/04/28/.
12. Dagens A, Sigfrid L, Cai E, Lipworth S, Cheung V, Harris E, et al. Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic: rapid review. Bmj. 2020;369:m1936.
13. Mehra MR DS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. . N Engl J Med. 2020.
14. Mehra MR RF, Patel AN. . Retraction - Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis The Lancet. 2020.
15. Bauchner H, Golub RM, Zylke J. Editorial Concern—Possible Reporting of the Same Patients With COVID-19 in Different Reports. JAMA. 2020;323(13):1256.
16. Tingley K. Coronavirus Is Forcing Medical Research to Speed Up. New York Times. 2020 2020/04/16/;Sect. Sunday Magazine.
17. Patton; C, Bradfield L. ASTRO Clinical Practice Guideline Methodology Guide. 2019.
18. Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. J Clin Oncol. 2017;35(17):1884-90.

19. Start Trialists G, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet (London, England). 2008;371(9618):1098-107.
20. 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.
21. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. 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(10):1215-23.
22. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, 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(31):3827-33.
23. Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C, 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(3):336-46.
24. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016;27(5):834-42.
25. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): Results of prospective randomized study of radiation fraction size and overall treatment time. International Journal of Radiation Oncology, Biology, Physics. 2006;64(1):77-82.
26. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol. 2004;22(9):1583-8.
27. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol. 2012;13(9):916-26.
28. Singh AK, Gomez-Suescun JA, Stephans KL, Bogart JA, Hermann GM, Tian L, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. International Journal of Radiation Oncology, Biology, Physics. 2019;105(4):752-9.
29. Hall E, Hussain SA, Porta N, Crundwell M, Jenkins P, Rawlings CL, et al. BC2001 long-term outcomes: A phase III randomized trial of chemoradiotherapy versus radiotherapy (RT) alone and standard RT versus reduced high-dose volume RT in muscle-invasive bladder cancer. Journal of Clinical Oncology. 2017;35(6_suppl):280-.
30. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med. 2012;366(16):1477-88.
31. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, 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. The Lancet. 2020.

32. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, 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. The Lancet. 2019;394(10196):385-95.
33. Jackson WC, Silva J, Hartman HE, Dess RT, Kishan AU, Beeler WH, 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(4):778-89.
34. Chin S, Fatimilehin A, Walshaw R, Argarwal A, Mistry H, Elliott T, et al. Ten-Year Outcomes of Moderately Hypofractionated Salvage Postprostatectomy Radiation Therapy and External Validation of a Contemporary Multivariable Nomogram for Biochemical Failure. International Journal of Radiation Oncology*Biology*Physics. 2020;107(2):288-96.
35. Maguire J, Khan I, McMenemin R, O'Rourke N, McNee S, Kelly V, et al. SOCCAR: A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III Non-Small Cell Lung Cancer and good performance status. European Journal of Cancer. 2014;50(17):2939-49.
36. Tobias JS, Monson K, Gupta N, Macdougall H, Glaholm J, Hutchison I, et al. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. The Lancet Oncology. 2010;11(1):66-74.
37. Benghiat H, Sanghera P, Cashmore J, Hodson J, Mehanna H, Simmons R, et al. Four Week Hypofractionated Accelerated Intensity Modulated Radiotherapy and Synchronous Carboplatin or Cetuximab in Biologically Staged Oropharyngeal Carcinoma. Cancer and Clinical Oncology. 2014;3(2).
38. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. The Lancet Oncology. 2011;12(2):127-36.
39. Turgeon GA, Souhami L, Kopek N, Hirsh V, Ofiara L, Faria SL. Thoracic irradiation in 3weeks for limited-stage small cell lung cancer: Is twice a day fractionation really needed? Cancer/Radiothérapie. 2017;21(2):89-98.
40. Sculier JP, Lafitte JJ, Efremidis A, Florin MC, Lecomte J, Berchier MC, et al. A phase III randomised study of concomitant induction radiochemotherapy testing two modalities of radiosensitisation by cisplatin (standard versus daily) for limited small-cell lung cancer. Annals of Oncology. 2008;19(10):1691-7.
41. Simcock R, Thomas TV, Estes C, Filippi AR, Katz MA, Pereira IJ, et al. COVID-19: Global radiation oncology's targeted response for pandemic preparedness. Clin Transl Radiat Oncol. 2020;22:55-68.
42. David J. Thomson M, MD, FRCR, David Palma M, PhD, Matthias Guckenberger M, Panagiotis Balermpas M, Jonathan J. Beitler M, MBA, Pierre Blanchard M, et al. Practice Recommendations for Risk-Adapted Head and Neck Cancer Radiation Therapy During the COVID-19 Pandemic: An ASTRO-ESTRO Consensus Statement. Int J Radiat Oncol Biol Phys. 2020;In Press.
43. Bernhardt D, Wick W, Weiss SE, Sahgal A, Lo SS, Suh JH, et al. Neuro-oncology management during the COVID-19 pandemic with a focus on WHO grades III and IV gliomas. Neuro-Oncology. 2020.
44. Janssens GO, Mandeville HC, Timmermann B, Maduro JH, Alapetite C, Padovani L, et al. A rapid review of evidence and recommendations from the SIOPE radiation oncology working group to help

mitigate for reduced paediatric radiotherapy capacity during the COVID-19 pandemic or other crises. Radiother Oncol. 2020;148:216-22.

45. Al-Rashdan A, Roumeliotis M, Quirk S, Grendarova P, Phan T, Cao J, et al. Adapting Radiation Therapy Treatments for Patients with Breast Cancer During the COVID-19 Pandemic: Hypo-Fractionation and Accelerated Partial Breast Irradiation to Address World Health Organization Recommendations. Adv Radiat Oncol. 2020.

46. 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.

47. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. 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(11):1086-94.

48. Whelan TJ, Julian JA, Berrang TS, Kim DH, Germain I, Nichol AM, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet. 2019;394(10215):2165-72.

49. Vicini FA, Cecchini RS, White JR, Arthur DW, Julian TB, Rabinovitch RA, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet. 2019;394(10215):2155-64.

50. Lightowlers SV, Boersma LJ, Fourquet A, Kirova YM, Offersen BV, Poortmans P, et al. Preoperative breast radiation therapy: Indications and perspectives. Eur J Cancer. 2017;82:184-92.

51. Neoadjuvant Chemotherapy Followed by Preoperative Radiotherapy in High-risk Breast Cancer: a Prospective, International Randomised Multicentre-phase III Trial
Bethesda (MD): National Library of Medicine (US).2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT04261244.

52. Pre- Versus Postoperative Accelerated Partial Breast Irradiation in Early Stage Breast Cancer Patients Bethesda (MD): National Library of Medicine (US)2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT02913729).

53. Braunstein LZ, Gillespie EF, Hong L, Xu A, Bakhoum SF, Cuaron J, 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. Adv Radiat Oncol. 2020.

54. Parashar B, Chen WC, Herman JM, Potters L. Disease Site-Specific Guidelines for Curative Radiation Treatment During 'Limited Surgery' and 'Hospital Avoidance': A Radiation Oncology Perspective From the Epicenter of COVID-19 Pandemic. Cureus. 2020;12(5):e8190.

55. Rathod S, Dubey A, Bashir B, Sivananthan G, Leylek A, Chowdhury A, et al. Bracing for impact with new 4R's in the COVID-19 pandemic - A provincial thoracic radiation oncology consensus. Radiother Oncol. 2020;149:124-7.

56. A Randomized Multicenter Trial of Accelerated Hypo - vs. Normo-fractionated Radiotherapy for Head and Neck Squamous Cell Carcinoma (IAEA-HYPNO Trial) [Internet]. National Library of Medicine (US). 2014 [cited 06/02/2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT02765503.

57. Prospective Trial of Hypofractionated Pre-Operative Radiation Therapy for Localized, Resectable Soft Tissue Sarcoma of the Extremity or Superficial Trunk (HYPORT-STS) [Internet]. National Library of Medicine (US). 2018 [cited 06/02/2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT03819985.

58. NCRI's CTRad to lead COVID RT: a UK-wide initiative to study the impact of COVID-19 on radiotherapy services and patient outcomes 2020 [updated 04/28/2020. Available from: https://www.ncri.org.uk/news/covid19-radiotherapy-initiative/.

59. New COVID-19 Cancer Registry Aims to Understand Impact on Patients During Pandemic, Inform Future Care. 2020 [updated 04/10/2020. Available from: https://www.asco.org/about-asco/press-center/news-releases/new-covid-19-cancer-registry-aims-understand-impact-patients.

Figure Legends

Figure 1a. Curative-intent recommendations: number of COVID-era recommendations coded by quality of evidence, plotted against the quality of evidence of the corresponding routinely used highest-quality schedule (p-value = 0.022). Site-specific palliative, general palliative and cutaneous recommendations are excluded.

Figure 1b. Site-specific palliative recommendations: number of COVID-era recommendations coded by quality of evidence, plotted against the quality of evidence of the corresponding routinely used highest-quality schedule (p-value < 0.001).

Figure 2a. Curative-intent and cutaneous consensus scores: multiple regression lines, each representing a disease group, of the shifts in the quality of evidence from routinely used highest-quality curative-intent schedules to COVID-era schedules. Dotted black line (slope of 1) represents no change in the quality of evidence. Paired t-test comparing the regression lines' slopes to the diagonal slope of 1 was significant (p-value < 0.01). Lines are truncated to avoid extrapolation outside of known data points. CNS = central nervous system; GU = genitourinary; GI = gastrointestinal.

Figure 2b. Site-specific palliative consensus scores: multiple regression lines, each representing a disease group, of the shifts in the quality of evidence from routinely used highest-quality site-specific palliative schedules to COVID-era schedules. Dotted black line (slope of 1) represents no change in the quality of evidence. Paired t-test comparing the regression lines' slopes to the diagonal slope of 1 showed mixed results (e.g., cutaneous had a slope of 1 while CNS had a slope of 0). Lines are truncated to avoid extrapolation outside of known data points. CNS = central nervous system; GU = genitourinary; GI = gastrointestinal.

Figure 3. Curative-intent consensus scores: shifts in the quality of evidence from the highest-quality curative-intent schedules to the highest-rated and most frequently recommended COVID-era schedules within each disease site. The size of the bubble is proportional to the weight of the shift, with the weight determined from a 6-point scale incorporating the highest-ranked schedule's quality of evidence and the number of levels of shift separating it from the in-COVID recommendation. Variance among the weights was not significant (p = 0.074) although difference above and below the median of 3 was (p < 0.0001). NSCLC = non-small cell lung cancer; CNS = central nervous system; SCLC = small cell lung cancer; HN = head and neck; Gyn = gynecologic.

Table 1. Percentages of consensus scores ranking the quality of evidence of the highest-rated routinely used fractionation schedules as compared with the recommended COVID-era schedules for curative and palliative treatments.

	Curative		**Curative, cutaneous**		**Palliative, disease site-specific**		**Palliative, general**	
ASTRO quality of evidence	Highest quality	COVID era N = 146	Highest quality	COVID era N = 14	Highest quality	COVID era N = 65	Highest quality	COVID era N=9
High	51.4%	4.8%	0%	0%	16.1%	1.5%	55.6%	33.3%
Moderate	33.3%	17.1%	0%	0%	5.4%	13.9%	11.1%	33.3%
Low	9.7%	28.8%	83.3%	83.3%	39.3%	21.5%	33.3%	22.2%
Opinion	5.6%	49.3%	16.7%	16.7%	39.3%	63.1%	0%	11.1%

ASTRO = American Society of Radiation Oncology

N = number of recommended dose-fractionation schedules