Altered radiotherapy fractionation: what did we learn during the Global COVID-19 Pandemic and what do we take forward to optimize radiotherapy fractionation for the future

This white paper is written to inform on the complex issue of altered radiotherapy treatment in response to the pandemic and presents our philosophy on this, discusses the issues involved and suggests a way forward to support decision making.

Background

The global COVID-19 pandemic resulted in disruption to cancer services worldwide. Initial data from Wuhan, China, suggested a poorer outcome for patients treated for cancer during the pandemic and there were fears of hospital services being overrun, a workforce crisis, and lockdowns preventing patients attending hospital. International advice quickly emerged as to which cancer patients and treatment modalities should be prioritized.[1] Radiotherapy (RT) quickly emerged as a major cancer treatment which could and should continue during a pandemic and indications for RT increased both in curative (switches from surgery to RT) and palliative (switches from chemotherapy to RT) settings. National and international organizations published recommendations to use, where possible, hypofractionated radiotherapy schedules (where more dose is delivered per day over a fewer total number of fractions), to limit the number of daily patient attendances thus reducing the interactions of patients and staff and risk of nosocomial transmission, and address potential resource limitations from depletion in work force due to staff sickness and self-isolation. Other recommended strategies included the avoidance and/or deferral of RT. These approaches were considered to various degrees by different countries and different RT departments and implemented at different times as the pandemic swept across the world. Various rapid national audits of RT disruptions and changes in patient volumes were undertaken and published; these provided rapid communication amongst RT centres[2-7] with planned future audits of resultant patient treatment outcomes.

The Global Coalition for RT was formed at the height of the pandemic and in a series of 3-weekly digital meetings between April and July 2020, RT professionals from around the world from Wuhan, Singapore, Italy, New York, Japan, Australia and the UK shared their frontline experience as the pandemic reached its peak. A website was developed to document that experience and was updated daily with publications which were accessed by over 1,000 individual professionals over the first six critical months.

The Global Coalition for Radiotherapy next wanted to consider the global RT status in late 2020, 9 months after the WHO declared the pandemic. Questions that remain are: What should we learn from the various suggestions for RT alterations? What is needed until the pandemic ends? How can we as a global RT community "*Build back better*"? This white paper addresses the specific issue of

altered fractionation guidelines, integration of disaster risk-reduction measures into the restoration of physical infrastructure after the peak of the pandemic, and the strengthening of RT for the future.

The basis of radiotherapy concerns

Ensuring the continued access of patients to high-quality RT during a pandemic is challenging, particularly where there are severe resource constraints or patients are unable to attend for daily treatments due to sickness. RT delivery is a multistep multidisciplinary technical outpatient cancer treatment needed in around 50% of cancer patients and involved in around 40% of cures. To address an emergency pandemic situation, RT services may need to be rationed or rationalized. This can be achieved by prioritization (in extreme circumstances), changing working practices (team working, digital and technology solutions) and/or reducing number of times patients are required to attend by using hypofractionation. Hypofractionation can either be:

(i) using the same RT technique and treatment volume but increasing the RT dose per fraction

(ii) in some limited cases, reducing the treatment volume by changing the technique - usually stereotactic ablative radiotherapy (SBRT)

The former is considered in this white paper.

Hypofractionation delivered to standard treatment fields can be moderate, increasing from 1.8=2Gy per fraction to 2-2.6Gy per fraction reducing attendance often by 20%, or extreme, increasing to $\geq$ 5Gy per fraction potentially reducing attendance by 80%. However, there are biological questions around the equivalence of such altered fractionation schemes; do they produce the same local tumour control benefits and levels of early and late side effects i.e., is the therapeutic ratio maintained? Which patient groups are likely to benefit? How does concomitant chemotherapy and/or immunotherapy affect this?

Meeting of the Global Coalition for Radiotherapy 13th October 2020

A key paper published in October 2020 by an international collaboration "*Radiation Fractionation Schedules Recommended During the COVID-19 Pandemic: A Systematic Review of the Quality of Evidence and Considerations for Future Development*"[8] (See Presentation) which reviewed the range of suggested altered fractionations and the evidence base for them was presented by one of the lead authors.

Key Discussion Points

The discussions held with attendees at the meeting are summarised below – see list of contributors and discussants below and Appendix 1 for a list of attendees.

Evidence arising from the publication

The presented publication[8] assessed the quality of evidence for 233 recommended COVID-19-adapted dose fractionation schedules published in 54 articles between February and June 1st 2020, and compared them to the highest quality schedules in routine use. This was achieved by naming and grading the highest quality schedules in routine use and then independently rating each of the COVID-19 recommended fractionation schedules. The shifts in quality score from 'pre-COVID' to 'in-COVID' were compared within and between disease sites. The main conclusion was that COVID-19 hypofractionation recommendations were supported by a lower quality of evidence than the highest-quality routinely used dose fractionation schedules, with a shift from high quality evidence to often low quality evidence or opinion. However, there were variations in the shift in quality of evidence depending on disease site; for example, the use of shorter fractionated schedules in breast radiation was underpinned by high- to moderate- quality evidence, whereas for head and neck cancer there was a shift from high quality evidence for routinely used conventional fractionation to low-quality evidence for the most commonly recommended hypofractionation schedules.

Understanding the Evidence Base

The COVID-19 crisis provides an opportunity to understand the evidence base for dose fractionation schedules, to what degree altered treatment was implemented, and whether on reflection some changes were not warranted or desirable. A range of practices across the world depended on the severity of the outbreak, the degree of regulation within countries, and how much freedom was given to departments. For example, some RT departments had more resilience than envisaged due to previous experience in infectious control; China, Japan and Singapore had prior knowledge from the 2003 SARS outbreak and did not implement changes from conventional protocols. In New York, the standard of care did not change to hypofractionation; however, this may partly be because fewer patients were treated as the number of patients presenting for treatment was lower than expected. In some regions of the world there were unique scenarios related to geographically bounded access, financial considerations, too much or too little regulation, and in these areas a change to hypofractionation may not have been desirable or possible or would have involved significantly more challenging obstacles.

Reimbursement

RT has advanced substantially during the past couple of decades allowing for shorter, more patient friendly fractionation schemes but an analysis of how health services pay for RT across Europe shows that reimbursement schemes have lagged behind this clinical and technical evolution[9]. This may have resulted in there being more evidence to support hypofractionation than previously appreciated but it may have been ignored due to revenue risk. The key driver to implement these changes has been the COVID-19 pandemic where the advantage of fewer hospital visits became attractive and resulted in improved RT value. Going forward, reimbursement based simply on the numbers of fractions, needs to be addressed to ensure that access to quality RT for patients is not compromised.

Backlog of Cancer Patients

There is a COVID-19 induced cancer backlog globally due to disruption in screening services and patients accessing health care. While current RT services are generally coping (current overall declines in referral for RT are around 10-20% 9 months into the pandemic) consideration is needed for the shape of future RT services in both dealing with the backlog and future ways of working.

Treatment disruptions and changes in RT delivery

Disruption to cancer patient RT treatment varied across the world and has now reduced since the height of the pandemic. There was much geographical variation dependent on the local effects of the pandemic, quality of infectious disease measures, service delivery models, initial base line capacity, and priority given to RT services. There had been a shift to a need for additional palliative RT services. In some areas such as Italy, RT departments adapted and worked as hubs to treat cancer patients referred from general hospitals that became COVID-19 centres.[4,10]

Prostate, breast (*frequent tumours, high level of evidence for hypofractionation*), lung (*frequent tumour, but rather low level of evidence for hypofractionation*), cervix and head and neck (*rare tumours and low evidence for hypofractionation*) may be suitable for moderate hypofractionation and these cancer sites represent over a half of the radiotherapy indications in high income countries. Implementing moderate hypofractionation for these allowed a reduction from 12 to 8 working hours at the radiotherapy department (33% reduction) but was associated with an increase of 25% in medical physicists and a decrease of 30% in RT technologists. The cost per RT course increased 5%.[11]

Summary

The COVID-19 pandemic brought new challenges to most of the world's RT departments. Temporarily moving to hypofractionation schedules in cases where the risk to the cancer patient of contracting COVID-19 sometimes outweighed the risk of potential suboptimal therapeutic ratio was a commonly proposed strategy at the start of the pandemic. There was a need however to use the best technology available to optimise hypofractionation such as image guidance radiotherapy IGRT, or intensity modulated radiotherapy IMRT, quality assessment protocols etc.)

Hypofractionation may also help to treat more patients so the wider access to RT will be possible in the areas of low middle income countries.

However, as a community there is a need to return to evidence based fractionation schedules to ensure we do not sleepwalk into RT treatment compromises which have long lasting effects in terms of reduced tumour control or increased late normal tissue effects.

The ability of all RT departments to maintain or return to evidence-based treatment fractionation practice depends on many of the factors discussed above, the challenges RT already faced, the backlog of cancer that has developed, and the investment in RT provided to recover during and after the pandemic.

Evidence based RT fractionation personalized for individual patients which is correctly reimbursed will be needed to achieve sustainable RT services, reduce the cost of overall cancer care, and save patient lives.

Key recommendations were derived considering the global status of technical radiotherapy, adaptions that had been considered and developed during the pandemic and which had been discussed by the various international groups during the pandemic at the Global Coalition for Radiotherapy digital meetings. The group developed key recommendations for the post pandemic sustainability and development of radiotherapy globally following the pandemic particularly with respect to hypofractionation.

Key Recommendations

1. RT is used to treat 50% of patients with cancer and offers curative treatment in 40% of cases.[12] Improving access to high quality RT is estimated to save an additional 1 million lives per year.[13] Evidence based RT should be consolidated and practiced to deliver this goal.
2. RT should continue during the COVID-19 pandemic and beyond without compromising patient care. It should be prioritized within the overall cancer pathway with acknowledgement that it provides effective curative and palliative outpatient treatment and is a high technology therapy.
3. The use of hypofractionation should be considered carefully while understanding the risk and potential for compromises to the therapeutic ratio; the quality of evidence varies with different clinical situations.
4. Local RT departments should be supported in solving their individual challenges such as patient access and workforce shortages.
5. Reimbursement should be addressed to allow the highest quality of care for patients and to move away from conventional models where reimbursement is based on number of fractions and treatment schedules.
6. The cancer backlog will put a further strain on services. Digital and technical solutions for delivering equitable quality RT to all patients is needed, which requires investment and training.
7. COVID-19 has been a wake-up call to Governments. Healthcare needs to be given a bigger priority given the major negative economic consequences of the poor health of nations. RT is one of the solution to improved cancer care during the pandemic and beyond and should be invested in further. It is a relatively inexpensive and highly cost-effective treatment which saves lives and can reduce overall health care costs.
8. Global collaboration and discussion are needed to solve problems unique to RT.
9. Altering RT treatments in response to severe resource constraints or pandemic situations should be:
   (i) Seen in the context of the overall workload of a department and not in silos of individual tumour sites, with a blended and flexible approach within a department;
   (ii) Ideally reserved for where there is a robust evidence base and always with full patent consent;
   (iii) Approached with caution when used with concurrent chemotherapy;
   (iv) Considered after other approaches to provide resilience in the workforce have been introduced, including optimal infection control, regular testing, and networking with other centres with a focus on staff wellbeing;
   (v) With consistency across classes and stages of cancer treated in the department, to enable auditing of RT treatment outcomes in the future.
10. The future of "building back better" should entail more focus on evidence based, patient focused treatment and strategies to build further resilience in the workforce and the technology.
11. Competing forces will need to be addressed:

State of the art treatment	Reimbursement
Economics/social impact	Workforce

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