



Original Article

The Impact of COVID-19 on Radiotherapy Services in Scotland, UK: A Population-based Study



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Abstract

Aims: The effect of the COVID-19 pandemic on cancer radiotherapy services is largely unknown. The aim of the present study was to investigate the impact of the resultant contingency plans on radiotherapy cancer services in Scotland.

Materials and methods: Detailed data of radiotherapy activity at our centre were collected from 1 April 2019 to 31 March 2021. Differences in mean weekly radiotherapy courses, dose and fractionation patterns and treatment intent were compared with corresponding pre-pandemic months for all treatment sites. Qualitative data were collected for a subgroup of radical radiotherapy patients.

Results: Total radiotherapy courses decreased from 6968 to 6240 (–10%) compared with the previous year, prior to the pandemic. Average weekly radiotherapy courses delivered were 134 (standard deviation ±13), decreasing by 10% to 120 (standard deviation 15) (Welch’s *t*-test, *P* < 0.001). The greatest decrease in new start treatment courses was observed from May to August 2020 (–7.7%, –24.0%, –16.7% and –18.7%) compared with the corresponding months in 2019. A significant reduction was seen for female patients <70 years (–16%) compared with females >70 years (–8%) or their male counterparts (–7% and –6%, respectively). By diagnosis, the largest reductions between pre- and post-pandemic levels were for anal (–26%), breast (–18%) and prostate (–14%) cancer. Contrarily, a significant increase was found for bladder (28%) and oesophageal (11%) cancers.

Conclusions: Over the first 12 months of the COVID-19 pandemic, radiotherapy activity significantly decreased compared with the 12 months prior. Due to issued guidance, the use of hypofractionated regimens increased, contributing to the reduction in treatments for some tumour sites. An increase in other tumour sites can probably be attributed to the reduction or cancellation of surgical interventions. These results will inform our understanding of the indirect consequences of the pandemic on radiotherapy services.

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Key words: COVID-19; pandemic; radiotherapy; SARS-CoV-2; Scotland; UK

Introduction

In March 2020, the World Health Organization declared a global pandemic of the coronavirus disease (COVID-19) [1]. As a result, the UK’s National Health Service was redeployed and restructured to cope with the increased demand on healthcare services [2]. Cancer screenings were initially

suspended, routine diagnostic investigations were deferred and elective surgeries were postponed. The impact of the efforts used to control the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on cancer services is of particular interest.

From the outset of the pandemic, there was significant concern that cancer patients were at increased risk of serious COVID-19-related complications due to immunosuppression and co-morbidities [3]. Service providers, commissioners and professional bodies within the UK, and internationally, issued revised guidance for cancer care

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[2,4,5]. For this cohort of patients, a risk–benefit management strategy was used, balancing the need to reduce patients' risk from the SARS-CoV-2 infection with the need for continued access to diagnostic intervention and the delivery of optimal treatment [6].

Radiotherapy is a crucial treatment modality in cancer management, estimated to be responsible for 40% of all cures, with 60% of all patients receiving radiation at some stage in their disease [7]. To allow radiotherapy services to continue, site-specific guidance was issued [8]. With the aim of reducing the number of hospital attendances and exposure of high-risk patients to COVID-19, recommendations such as the omission or delay in radiotherapy treatments, the use of radiotherapy to replace surgery and changes to radiotherapy treatment doses and schedules (hypofractionation) were provided [9].

Understanding the impact that these adapted radiotherapy practices have had at a population level is challenging. A limited number of population-based studies have been carried out assessing the impact of COVID-19 on cancer services within the UK [10] during the first wave of the pandemic. No studies have been carried out to assess the effects of the pandemic on radiotherapy services beyond this short interval. The aim of the present study was to determine the changes in radiotherapy cancer care in Scotland and to quantify the impact on patients' treatments, by comparing data from 12 months before and after the pandemic. Our centre is one of the largest cancer centres in the UK and the largest in Scotland, serving around 60% of the Scottish population. Each year, our centre sees more than 8000 new patients, delivers over 25 000 courses of chemotherapy and over 6500 courses of radiotherapy [11].

Materials and Methods

Study Design

A detailed cross-sectional dataset of radiotherapy activity within our centre was collected and analysed. Following institutional approval, we extracted anonymised data from the electronic radiotherapy health record on International Classification of Diseases (ICD-10) code, age, gender, radiotherapy dose/fractionation and treatment start dates for the period 1 April 2019 to 31 March 2021.

In May 2020, a national UK-wide initiative was launched by the National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRad) that aimed to study the impact of COVID-19 and the contingency plans on the radiotherapy cancer services within the UK. CTRad produced guidance and a minimum dataset (Table 1) for data collection to ensure that prospective data quality was consistent across all centres. All adult cancer patients for whom radiotherapy was considered or given in the curative definitive or adjuvant treatment setting from 1 March 2020 were eligible for inclusion. The data fields were attached to all external beam radiotherapy courses across all tumour sites registered from 1 April 2020 to 1 October 2020 within the ARIA CarePath

Table 1

Clinical and Translational Radiotherapy Research Working Group minimum dataset utilised for data collection

Question	Response options
Category of radiotherapy treatment	Primary, neoadjuvant, radiotherapy as a replacement for surgery, adjuvant, radiotherapy as a bridge to surgery or other.
Has treatment timing changed due to COVID-19?	Radiotherapy proceeding as normal, radiotherapy omitted due to clinical decision or patient refusal, radiotherapy deferred/delayed due to clinical decision or patient refusal or other.
Has radiotherapy intent changed?	Radical to palliative, palliative to radical, unchanged, or other.
Is the patient having concurrent chemotherapy?	No, full chemotherapy, reduced chemotherapy, chemotherapy omitted, chemotherapy modified or other.
Is this patient receiving standard of care pre-COVID-19?	Patient receiving pre-COVID-19 standard of care, hypofractionated treatment, stereotactic (including stereotactic ablative body radiotherapy) treatment.

workspace (Varian Medical Systems, Palo Alto, CA, USA). Data collection continued for a reduced number of sites (bladder, brain, head and neck, oesophagus, pancreas and colorectal cancers) until 28 February 2021. The referring clinician or delegate completed a questionnaire for each individual patient. These qualitative data were used to explore the reasons for deviations to the accepted standard of care across all tumour sites.

Data Analysis

Radiotherapy activity was summarised as the mean number of weekly radiotherapy courses per month, allocated to the week in which they began. Weeks were derived from course start date and defined as beginning on a Monday. Week 1 of the year was defined as the week that included both 4 January and the first Thursday of the year (using the SAS WEEK function and the 'V Descriptor'), equivalent to the International Organization for Standardisation calendar. Weeks were then allocated to the months in which they began to account for weekly variability and seasonality.

The radiotherapy activity for the period 1 April 2019–31 March 2020 (year 1) was compared with 1 April 2020–31 March 2021 (year 2) by intent of radiotherapy (palliative or radical), age (<70 years versus ≥70 years), sex and diagnosis (anal, bladder, brain, breast, cervix, head and neck, lung, lymphoma, oesophageal, prostate, rectal, skin cancer and other diagnoses). Change in treatment fractionation was determined for specified diagnoses (radical treatments)

and palliative radiotherapy overall. For radical radiotherapy, the dose per fraction for each course was calculated and assigned a category (<2 Gy, 2–2.49 Gy, 2.5–4.99 Gy, \geq 5 Gy). The mean number of weekly courses per month and the standard deviations were calculated for each diagnosis, stratified by fractionation category. Palliative courses were categorised separately based on the number of prescribed fractions only (single, 2–5, 6–10, \geq 10 fraction(s)). The proportion of radiotherapy activity per fractionation category was calculated by diagnosis, and separately for palliative treatments. Means and standard deviations of the weekly radiotherapy courses were calculated with changes reported as percentages. Group comparisons used Welch's *t*-test at a 5% significance level. All statistical analyses were carried out using SAS version 9.4. All plots and figures were created in R version 3.6.1.

Results

The total number of radiotherapy courses analysed was 13208 over 24 months. Of these, 1491 had completed questionnaires available for qualitative analysis. Radiotherapy courses decreased from 6968 in year 1 to 6240 in year 2, a decrease of 10%. The average weekly radiotherapy courses delivered was 134 (standard deviation \pm 13), decreasing by 10% to 120 (standard deviation 15) (Welch's *t*-test, $P < 0.001$) in year 2. The first wave of the COVID-19 pandemic from March 2020 to June 2020 showed the greatest impact on average weekly radiotherapy courses: May (–7.7%), June (–24.0%), July (–16.7%) and August (–18.7%) compared with the corresponding months in 2019 (see [Supplementary Table S1](#)). In fact, the mean radiotherapy delivery remained depressed throughout year 2, only noting a slight increase by March 2021, compared with year 1. These trends are summarised in [Figure 1](#).

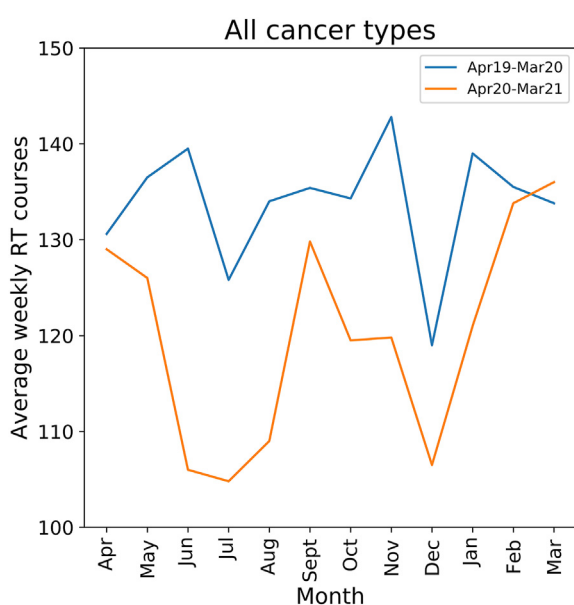


Fig 1. Total average weekly radiotherapy courses between April 2019 and March 2020 (blue) and April 2020 and March 2021 (orange).

The distribution of radiotherapy delivery between radical and palliative treatment courses showed a greater reduction in radical treatments (4472 versus 3900 courses) than palliative treatments (2496 versus 2340 courses) (see [Supplementary Table S1](#)). The average weekly radiotherapy courses of radical treatment significantly decreased from 86 (standard deviation 10) in year 1 to 75 (standard deviation 11) in year 2, a decrease of 13% (Welch's *t*-test, $P < 0.001$). The single largest monthly change in radical radiotherapy delivery was June 2020 (–33.3%). Overall, the mean monthly delivery of radical radiotherapy remained depressed in year 2 relative to year 1, as of March 2021. The average weekly radiotherapy courses of palliative radiotherapy courses showed more variation, with the annualised rates, at 48 (standard deviation 6) in year 1 and 45 (standard deviation 8) in year 2, a non-statistically significant 5% drop (Welch's *t*-test, $P = 0.16$). The single biggest decrease was in November 2020 (–23.6%) and the single biggest increase was in March 2021 (16.4%).

The average weekly radiotherapy courses were also analysed by gender and age, with a threshold of <70 or \geq 70 years given the early data that SARS-CoV-2 was particularly lethal in this age group [12] (see [Supplementary Table S1](#)). A significant reduction in the average weekly radiotherapy courses was seen in women compared with men over the 2-year period (means 136, 117, Welch's *t*-test $P < 0.001$). The reduction was greatest in women <70 years, with an average decrease of –16% compared with pre-pandemic (Welch's *t*-test, $P < 0.005$). By contrast, the male <70 years, female \geq 70 years and male \geq 70 years cohorts all saw decreases, but none were statistically significant (see [Supplementary Table S1](#)).

Changes in mean weekly curative treatment courses and attendances by diagnoses are provided in [Supplementary Table S2](#). The largest relative reduction in courses from April 2020 to March 2021 was observed in anal cancer, with an overall decrease of –26% from the previous year, shown in [Figure 2a](#). Decreases in mean weekly curative treatment doses were also seen in breast (–18%), brain (–10%), head and neck (–13%), lung (–9%), prostate (–14%) and colorectal (–7%) cancers ([Figure 2b](#)) when compared with pre-pandemic levels. Only breast ($P < 0.001$) and prostate ($P = 0.03$) were statistically significant. Bladder (+28%), oesophageal (+11%) and skin (+38%) had increases in average weekly radiotherapy courses; none were statistically significant.

Mean weekly courses for breast cancer decreased 18%, as shown in [Figure 3](#). Prior to the pandemic, the historical standard dose and fractionation regimen of 40.05 Gy in 15 fractions accounted for 96.9% of breast treatments; average weekly radiotherapy courses 33.53. This decreased to 9.62 and accounted for 37.0% of all radical breast treatments between April 2020 and March 2021. The adoption of hypofractionated radiotherapy of 26 Gy in five fractions significantly increased from average weekly radiotherapy courses of 1.02 (2.65%) to average weekly radiotherapy courses of 11.98 (46.1%). Per the qualitative data for breast patients ($n = 481$), the timing, intent and indication for breast radiotherapy remained unchanged during the

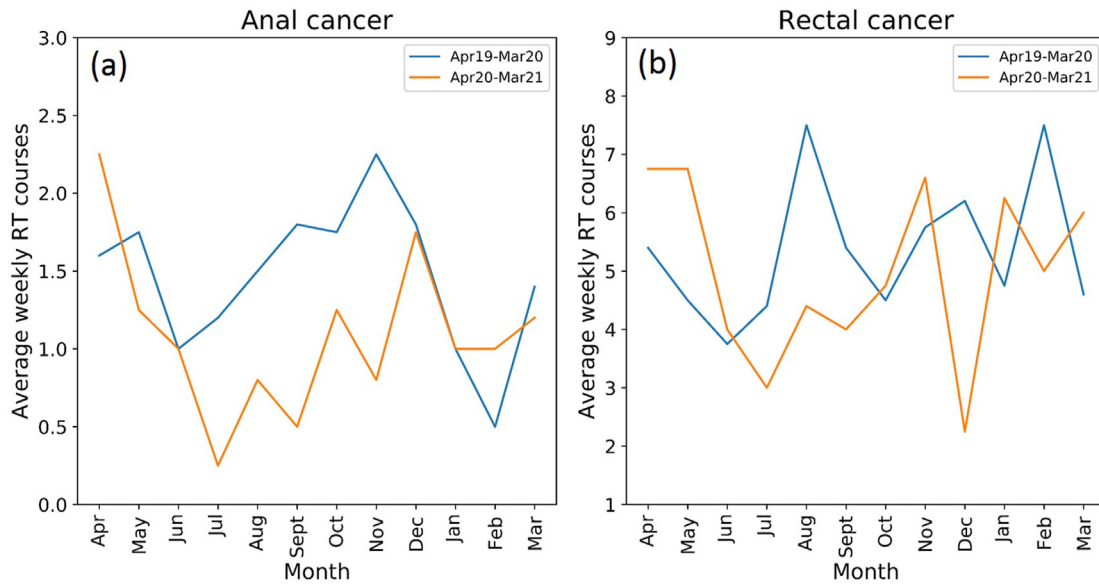


Fig 2. Total average weekly radiotherapy courses between April 2019 and March 2020 (blue) and April 2020 and March 2021 (orange) for (a) anal and (b) colorectal cancer.

pandemic, with only 3.5% receiving a deferred or modified treatment schedule. The main reasons for altered treatment timing were the delay of chemotherapy or surgery prior to radiotherapy treatment. However, in all breast cases where 26 Gy/5 fractions was prescribed, the reason attributed was ‘hypofractionated for COVID’.

The use of hypofractionated radiotherapy varied significantly in other tumour sites. 25 Gy/5 fractions in the neoadjuvant treatment for rectal cancer significantly increased (400%) from 0.35 mean weekly courses (10.47% of all colorectal treatments) to 1.75 (51.12% of all colorectal treatments). However, the rationale for selecting 25 Gy in 5 fractions was given as ‘hypofractionated for COVID’ in only

18% of cases, with one case receiving radiation as replacement for surgery. The timing and intent for rectal radiotherapy was unchanged.

Prostate cancer saw a drop in average weekly radiotherapy courses, with April (−27.5%), May (−58.0%), June (−42.8%), July (−12.6%) and December (−20.5%) noting the largest decreases compared with similar months in 2019. Trends are summarised in Figure 4. Of all prostate patients, for which radiotherapy was decided as their primary treatment, 14.5% of treatments were deferred. These deferrals mostly coincided with decisions made in May, June, July and September 2020, with most patients receiving their deferred treatments in July, August, September and October

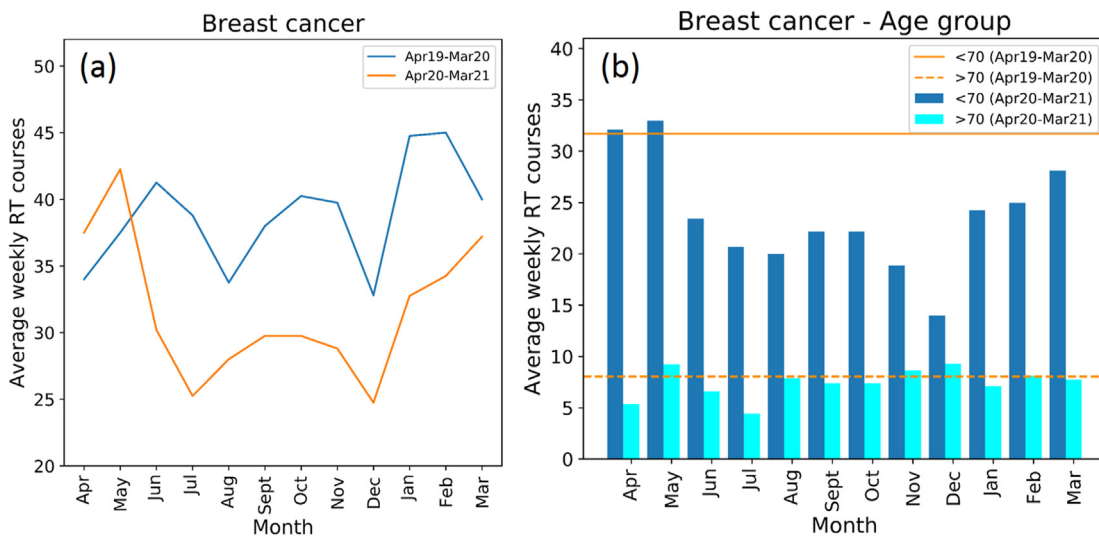


Fig 3. (a) Total average weekly radiotherapy courses between April 2019 and March 2020 (blue) and April 2020 and March 2021 (orange) and (b) average weekly radiotherapy courses between age groups for breast cancer between April 2019 and March 2021 (orange threshold lines showing mean values for April 2019 to March 2020).

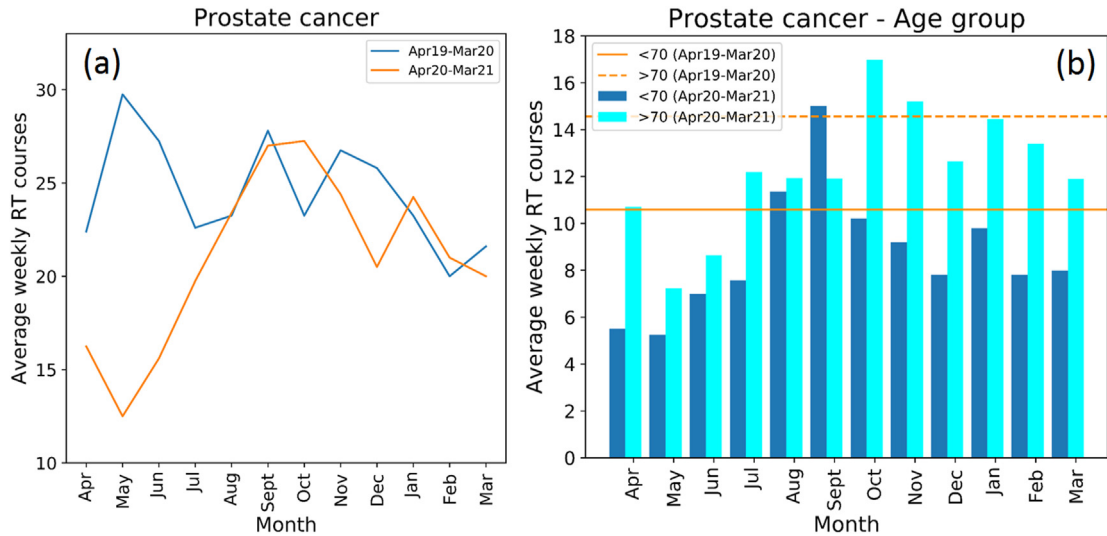


Fig 4. (a) Total average weekly radiotherapy courses between April 2019 and March 2020 (blue) and April 2020 and March 2021 (orange) and (b) average weekly radiotherapy courses between age groups for prostate cancer between April 2019 and March 2021 (orange threshold lines showing mean values for April 2019 to March 2020).

2020. Of the 337 prostate patients for whom qualitative data were collected, only six of those underwent radiotherapy as a replacement for surgical intervention. Twelve patients (3.5%) had their treatment hypofractionated from 74 Gy in 37 fractions to 60 Gy in 20 fractions to reduce the number of hospital attendances.

All bladder patients were treated with the standard 55 Gy in 20 fractions regimen. Average weekly radiotherapy courses increased 28% post-COVID compared with the previous year. Significant increases were found in April (172.7%), May (214.3%) and June (48.6%) 2020 when compared with equivalent months in 2019 (Welch’s *t*-test *P* = 0.006), as summarised in Figure 5a. Interestingly, of those

completed questionnaires, there was no increase in responses suggesting that radiotherapy indication had changed, with all indicating that radiotherapy was the primary treatment. Ten per cent (3/28) of patients received some modification of concurrent chemotherapy.

Oesophageal patients were treated with the standard 50 Gy/25 fraction dose and fractionation schedule. The average weekly radiotherapy courses for oesophageal cancers significantly increased in April (125.0%), May (50%), July (150.0%) and August (40.0%) in 2020 compared with the equivalent months in 2019, as summarised in Figure 5b. The incidences of radiotherapy treatment courses for oesophageal cancers decreased in the months September 2020 to

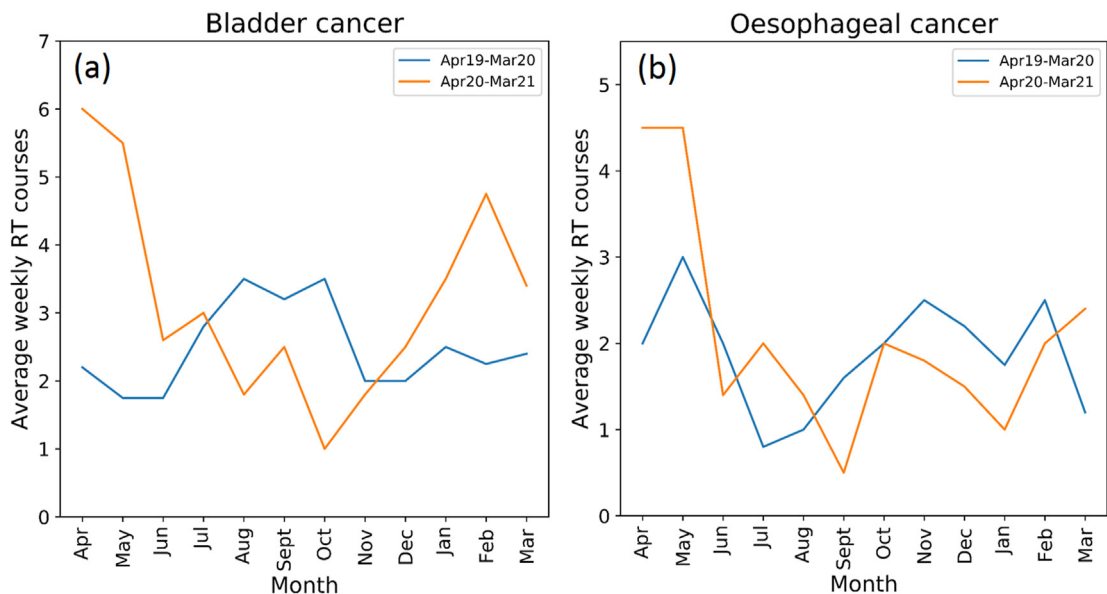


Fig 5. Total average weekly radiotherapy courses between April 2019 and March 2020 (blue) and April 2020 and March 2021 (orange) for (a) bladder and (b) oesophageal cancer.

February 2021, increasing again in March 2021 by 100.0%. Within the completed questionnaires, 97% (35/36) were receiving radiotherapy as either primary treatment or replacement of surgery.

There was no notable reason for the marked decreases for brain, head and neck and lung treatments. For each of these disease sites the radiotherapy intent remained unchanged, with a low deferral rate (between 0.8 and 2.4%) as per the patient request.

Radiotherapy treatment waiting times for all treatments were evaluated as part of this study. Current standards for cancer waiting times are that 95% of all eligible patients should wait no longer than 62 days from referral from primary care clinician with suspected cancer to first cancer treatment, or 31 days from decision to treat to first cancer treatment [13]. The extent to which the COVID-19 pandemic impacted these results was analysed using these waiting time criteria. In year 1, it was found that 265 patients (3.8% of total patients) exceeded the 31 day waiting time and 216 patients (3.1% of total patients) exceeded the 62 day waiting time. In year 2, it was found that 196 patients (3.1% of total patients) exceeded the 31 day waiting time and 46 patients (0.7% of total patients) exceeded the 62 day waiting time.

The proportion of patients whose treatment notes reflected that their radiotherapy treatments were interrupted due to a COVID-19 infection for year 2 were also assessed. The number of cancelled appointments was analysed and found that only 58 patients had alterations to their treatment due to COVID-19. Of those patients, 13 patients requested their treatment be deferred due to concerns about COVID-19 or waiting for vaccination. Twenty-two patients had their treatment start date delayed or had a change in their treatment schedule due to having COVID-19 or being a close contact (two palliative). Within our centre, the service-efficiency machine was used as the designated treatment machine for patients with COVID-19 or suspected COVID-19. Following hygiene and distancing measures, this allowed 23 patients to be treated with adjusted breaks in their treatment schedule.

Discussion

As far as we are aware, these are the first data to assess the effect of the COVID-19 pandemic on radiotherapy delivery in the UK over a full 12-month period. By examining the first 12 months since 1 April 2020 we can assess the effect of both the first and second waves, when most of the population were unvaccinated and health systems had to rely on social mitigations. A full year comparison with the 12 months leading up to the pandemic provides a more rigorous assessment (without short-term changes) and, thus, can better assess genuine shifts. A comprehensive study carried out by Spencer *et al.* [10] assessed the indirect consequences of the COVID-19 pandemic on radiotherapy services in England between February and June 2020 compared with corresponding months in 2019. Thus, although it covered a larger population, it captured only a

brief snapshot of the pandemic's effects on radiotherapy activity. However, up-to-date follow-up data of radiotherapy activity changes due to COVID-19 are publicly accessible from the National Radiotherapy Dataset (RTDS) of providers of radiotherapy services in England [14].

We have shown that the number of patients receiving radiotherapy in the West of Scotland cancer network fell significantly (572 fewer radical treatments) between April 2020 and March 2021, compared with the previous year. It is not possible from the observational nature of these data to ascertain the exact cause. However, the curtailment of diagnostic services almost certainly resulted in a decrease in referrals for treatment. This fall is also masked, to an extent, by significant increases in the use of radiotherapy in bladder and oesophageal cancers. This trend is clearly seen between April and June 2020, but over the 12 months most tumours showed non-significant reductions. The nature and extent of the recovery is also important as this has not previously been shown. We show that although service recovery occurred, it remained depressed relative to 2019. Therefore, it is likely that smaller numbers of patients across all tumour types were diagnosed, referred and deemed suitable for radical treatment. From a population perspective, one could hypothesise that this may result in a future uptick in cancer-related mortality.

The one significant outlier in the data is breast radiotherapy, partly due to a change in practice, accelerated by the pandemic, in the administration of hypofractionated radiotherapy [9]. Prior to the pandemic, hypofractionated radiotherapy accounted for about 1% of breast radiotherapy and almost half during. Although the pivotal phase III clinical trial FAST-Forward [15] was published at the outset of the pandemic, it is interesting that all clinicians still attributed the use of 26 Gy/five fractions to COVID-19. It could reflect the rapid adoption of a change that would normally take longer to incorporate. The change was most significant in women under the age of 70 years. Although early reports revealed that more men died as a result of COVID-19 [16], studies have shown that women were more indirectly affected by the COVID-19 pandemic [17]. This was partly a consequence of women bearing the brunt of the social and economic effects [18]. This burden, alongside reallocation of health screening resources for 50–70 year olds [19], may further explain the significant decrease in overall radiotherapy treatments in women <70 years.

The use of hypofractionation also significantly increased in rectal cancer. In contrast to breast cancer, only 18% of the subset in the qualitative study were due to COVID-19, reflecting the longstanding use of 25 Gy/5 fractions in rectal radiotherapy [20] and guidance that proposed greater adoption during the pandemic [21]. Most diagnostic and treatment pathways in the detection and management of lower gastrointestinal cancer were severely affected [22]. The initial phases of the COVID-19 service reorganisation led to the National Health Service Bowel Cancer Screening Programme being paused in March 2020, resuming in October 2020, and the main diagnostic tests of colonoscopy and computed tomography colonography being limited to emergency settings. This would have resulted in many

patients with suspected lower gastrointestinal cancer experiencing delay in both diagnosis and treatment.

Prostate cancer is the most common cancer in men over the age of 50 years [23]. In Scotland, more than 3000 men are diagnosed with prostate cancer every year. Guidance on external beam radiotherapy prostate cancer treatment at the onset of the COVID-19 pandemic was to defer any patients who had not yet started radiotherapy until the disruption had eased [5]. Randomised evidence has shown that the delivery of external beam radiotherapy can be delayed up to 6 months between diagnosis and treatment if patients receive neoadjuvant hormonal therapy or undergo active surveillance. The decrease in radiotherapy treatments for men (−8%) and prostate treatments (−14%) might be a consequence of decisions to employ watchful waiting and active surveillance strategies for low-risk prostate cancer, and deferring treatments for those in the high-risk categories.

Although guidance for most treatment sites adopted the Remote, Avoid, Defer, Shorten (RADS) principle [4] for radiotherapy treatments at the onset of the pandemic, bladder and oesophageal cancers were treated with radiotherapy as an alternative to surgery [5]. This change of practice was adopted due to the widespread cancellation of cystectomies and oesophagectomies for bladder and oesophageal cancers, respectively, together with the omission or reduction of chemotherapy. The marked increase (28%) of new-start courses of bladder radiotherapy treatments observed may be attributed to the introduction of radical radiotherapy with a radiosensitiser (gemcitabine) adopted within our centre. Similarly, an increase of 11% was found for oesophageal cancers, with 97% of cases receiving radiotherapy as their primary treatment or as a replacement for surgery. As the use of surgical interventions is the standard approach to the primary care treatment of bladder and oesophageal cancers, the effects on excess deaths due to limitations to surgical services and the replacement of such with radiotherapy are not yet known.

Despite routine diagnostic services and screening programmes being reinitiated towards the end of 2020, average weekly radiotherapy courses remained lower than the year prior to the pandemic. In Scotland, the COVID-19 pandemic has impacted patient waiting times, with some Boards highlighting staffing and capacity issues as the main contributing factors [13]. However, the waiting time statistics showed that COVID-19 had no impact on our centres' waiting times and treatments remained well within the 5% tolerance level for both 31 and 62 days. This suggests that the reduction in treatments reflects a lower throughput of patients further up the treatment pathway, for example in diagnostic and screening services, many of which were suspended.

Finally, the effect of routine referrals from general practitioners has not been considered as part of this study. However, with patients being urged to only present if they had major or urgent health concerns will have had unknown consequences on cancer services. Additionally, the introduction of remote appointments and consultations meant fewer patient examinations, which could have led to

a higher proportion of missed diagnoses, leading to fewer radiotherapy treatments.

Conclusion

From the onset of the COVID-19 pandemic, and the first national lockdown, many healthcare services were suspended or operated at a substantially reduced capacity, leading to a reduced number of people seeking health care. The significant fall in new-start radiotherapy treatments can probably be attributed to the initial suspension of cancer diagnostic services and interventional surgeries, together with the rapid increase in the use of hypofractionated treatment regimens across several treatment sites.

Due to frequent changes in local and national lockdown measures, and healthcare guidance over the course of the pandemic, it will be challenging to interpret further associations between COVID-19 and radiotherapy treatments. The qualitative data collected as part of this study provided a succinct and robust method for data collection, ensuring consistency among clinicians; it did not allow for interpretation on why specific changes were made. Therefore, assumptions were made as to the reasoning behind the results found in the population.

As there is no centralised data collection in Scotland with this extended dataset, the impact of COVID-19 has to be assessed by each radiotherapy centre independently, making the process of data collection time-consuming. Data collection for a follow-up study looking at the subsequent effect 2 years post-COVID-19 is currently underway, with the additional aims of assessing the effect of stage migration due to COVID in treatment patterns, as well as cancer-specific outcomes.

A recent publication [24] estimated the excess deaths worldwide due to the COVID-19 pandemic and reported that the full impact has been much greater than indicated by reported deaths due to COVID-19 alone. As no longer-term cancer-outcome data are currently available, the effects on patient outcomes from changes in radiotherapy activity are not yet known and require urgent review. Outcomes and post-treatment survival rates in the medium (1 year) and long (5 year) term will be of significant interest in the future.

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Author Contributions

All authors wrote, read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clon.2022.11.018>.

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