Journal of Radiotherapy in Practice

cambridge.org/jrp

Impact of COVID-19 pandemic on the oncologic care continuum: urgent need to restore patients care to pre-COVID-19 era

Ernest Osei[1,2,3,4], Ruth Francis[5], Ayan Mohamed[6], Lyba Sheraz[7] and Fariba Soltani-Mayvan[8]

[1]Department of Medical Physics, Grand River Regional Cancer Centre, Kitchener, ON, Canada; [2]Department of Physics and Astronomy, University of Waterloo, Waterloo, ON, Canada; [3]Department of Systems Design Engineering, University of Waterloo, Waterloo, ON, Canada; [4]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada; [5]Department of Biology, University of Waterloo, Waterloo, ON, Canada; [6]Faculty of Applied Health Sciences, University of Waterloo, Waterloo, ON, Canada; [7]Faculty of Science, School of Interdisciplinary Science, McMaster University, Hamilton, ON, Canada and [8]Reza Radiation Oncology Center, Mashhad, Razavi Khorasan Province, Iran

Literature Review

Cite this article: Osei E, Francis R, Mohamed A, Sheraz L, and Soltani-Mayvan F. (2021) Impact of COVID-19 pandemic on the oncologic care continuum: urgent need to restore patients care to pre-COVID-19 era. *Journal of Radiotherapy in Practice* page 1 of 11.
doi: 10.1017/S1460396921000303

Received: 12 February 2021
Accepted: 11 March 2021

Key words:
clinical trial; COVID-19; follow-up; radiotherapy; surgical treatment; systemic treatment

Author for correspondence:
Ernest Osei, Department of Medical Physics, Grand River Regional Cancer Centre, Kitchener, ON, Canada. Tel: (519) 749 4300.
E-mail: ernest.osei@grhosp.onca

Abstract

Background: Globally, cancer is the second leading cause of death, and it is estimated that over 18·1 million new cases are diagnosed annually. The COVID-19 pandemic has significantly impacted almost every aspect of the provision and management of cancer care worldwide. The time-critical nature of COVID-19 diagnosis and the large number of patients requiring hospitalisation necessitated the rerouting of already limited resources available for cancer services and programmes to the care of COVID-19 patients. Furthermore, the stringent social distancing, restricted in-hospital visits and lockdown measures instituted by various governments resulted in the disruption of the oncologic continuum including screening, diagnostic and prevention programmes, treatments and follow-up services as well as research and clinical trial programmes.

Materials and Methods: We searched several databases from October 2020 to January 2021 for relevant studies published in English between 2020 and 2021 and reporting on the impact of COVID-19 on the cancer care continuum. This narrative review paper describes the impact of the COVID-19 pandemic on the cancer patient care continuum from screening and prevention to treatments and ongoing management of patients.

Conclusions: The COVID-19 pandemic has profoundly impacted cancer care and the management of cancer services and patients. Nevertheless, the oncology healthcare communities worldwide have done phenomenal work with joint and collaborative efforts, utilising best available evidence-based guidelines to continue to give safe and effective treatments for cancer patients while maintaining the safety of patients, healthcare professionals and the general population. Nevertheless, several healthcare centres are now faced with significant challenges with the management of the backlog of screening, diagnosis and treatment cases. It is imperative that governments, leaders of healthcare centres and healthcare professionals take all necessary actions and policies focused on minimising further system-level delays to cancer screening, diagnosis, treatment initiation and clearing of all backlogs cases from the COVID-19 pandemic in order to mitigate the negative impact on cancer outcomes.

Introduction

Cancer is the second leading cause of death globally, and it is responsible for an estimated 9·6 million deaths in 2018.[1,2] It is estimated that over 18·1 million new cases are diagnosed every year which approximate about 50,000 newly diagnosed patients every day who will require treatment.[1,2] There has been very substantial progress in cancer treatment over the last 40 years, and the decline in mortality has been associated with timely prevention programmes, early disease diagnosis and treatment, the improvement of the quality of available treatment modalities and increased accessibility to these services.[3–6] However, the current COVID-19 pandemic has significantly impacted almost every aspect of the provision and management of cancer care as evidenced by published guidelines and recommendations by oncological societies and national and international authorities.[6–12] Several studies have reported that the COVID-19 pandemic has disrupted prevention, screening, early diagnosis and treatment delivery services; the management of cancer patients; the continuity of cancer research and clinical trials and has also introduced new risks for cancer patients.[3,13–29] According to some studies, the time-critical nature of COVID-19 diagnosis and the large number of patients requiring hospitalisation necessitated the rerouting of the already limited resources

CAMBRIDGE UNIVERSITY PRESS

available for current cancer services and programmes to the care of COVID-19 patients in several hospitals and clinics.[13,14,18,30] In response to the increase in COVID-19 prevalence in several countries, healthcare professionals in several hospitals and clinics worldwide took immediate initiatives and implemented multiple changes in the provision of cancer care including modification of treatment schedules, movement of some care delivery to telehealth, reorganised some cancer services and updated guidelines for medical staff and guidance for patients with the purpose to help diminish cancer patients and staff exposure to COVID-19 and also to mitigate its repercussions on the provision of cancer care.[3,15,21,30–32] However, the stringent social distancing, restricted in-hospital visits and lockdown measures instituted by various governments resulted in the disruption of cancer screening and prevention programmes, primary cancer diagnosis services, delayed surgical treatment, radiotherapy services and systemic therapy services. Rivera et al.[32] and Patt et al.[21] reported that these treatment interruptions are of utmost concern in tumours such as head and neck and cervical cancers for which even the modest delay in treatment could significantly impact outcomes. According to Patt et al.,[21] the consequence of disruption in cancer screening programmes and delays in early diagnosis is the presentation of the cancer at an advanced stage which most often will require more complex care, will have lower likelihood of responding to therapy and curable. Thus, the goal of this narrative review paper is to describe the impact of COVID-19 on the cancer patient care continuum from screening and prevention to treatment and ongoing care.

Materials and Methods

The following databases PubMed, PMC, NCBI, PNAS, Springer Link, Wiley Online Library, Lacent, Science Direct, Medline were searched from October 2020 to January 2021 for relevant studies published in English in 2020 and 2021 and reporting on the impact of COVID-19 pandemic on the cancer care continuum. The literature search used the following keywords: 'covid-19 and oncology care', 'covid-19 and cancer screening', 'covid-19 and cancer prevention', 'covid-19 and radiotherapy', 'covid-19 and systemic therapy', 'covid-19 and chemotherapy', 'covid-19 and follow-up of cancer patients', 'covid-19 and surgical treatment of cancer', 'covid-19 and research', 'covid-19 and clinical trials'. The searches were not limited by study design and included conference abstracts, full research articles and reviews. Several publications on the management of cancer patients were identified and we excluded articles reporting on the impact and management of cancer care but are not related to the COVID-19 pandemic. For the current report, we reviewed articles reporting on the impact of COVID-19 on oncologic services and patients.

Impact of COVID-19 Pandemic on Cancer Screening and Prevention

Cancer screening is integral to cancer control and prevention and plays a significant role in early cancer detection, and it is capable of detecting precancerous changes before cancer develops or the early detection of cancer before the onset of symptoms.[33–42] Myers et al.[34] reported that screening of women who are at average risk for breast cancer is associated with approximately 20% reduction in breast cancer mortality and according to Ladabaum et al.[35] increasing the screening rates of colorectal cancer from 62 to 80% in individuals aged 50–75 years would prevent about threefold more deaths at one-third the incremental cost. Several studies have reported that cancer screening is an effective preventative measure that significantly reduces cancer incidence and mortality[33,36–39,43–45]; however, the COVID-19 pandemic has disrupted almost all aspects of cancer prevention and screening services. Most prevention and screening services were either cancelled, suspended or severely restricted in several institutions and many patients fearful of exposure to COVID-19 or who do not want to overburden the healthcare services elected to reschedule or completely decline screening during the pandemic which has resulted in fewer cancer screenings and diagnosis.[21,30,33,46] Cancino et al.[33] reported that the weekly volumes of screenings for breast, colon and cervix cancers in the United States decreased by 86–94% between 20 January and 21 April 2020. Several studies have reported that most healthcare centres will be faced with significant challenges for the management of all the screening backlog cases.[21,36–38,43,47–49] According to Issaka et al.,[47] delaying colorectal cancer screening for the 23 million adults in the United States who are past due will lead to delayed diagnosis and increased cancer mortality, will widen persistent ethnic and socio-economic mortality disparities and will also overwhelm healthcare systems burdened by long screening backlogs when elective procedures resume. Furthermore, it is also reported that an estimated 1 million people in the United Kingdom have not been invited for colorectal cancer screening, and approximately 8,500 people who received a positive faecal immunochemical test before the national lockdown are still awaiting an appointment for a follow-up colonoscopy which would potentially lead to an overall increase in the number of preventable deaths from this cancer.[50] The COVID-19 pandemic disruption to cancer screening and prevention services may have a significant impact on patients, healthcare practitioners and health systems as the interruption in cancer screening and prevention may result in delayed diagnosis, an increased proportion of patients presenting with advanced disease, delayed treatments and potentially detrimental effects on survival.

Patt et al.[21] investigated the impact of COVID-19 on screening of new patients, gaps in access to care and disruption of treatment journeys in the United States cancer population. They observed a substantial decrease in cancer screenings from March to July 2020 compared to the same period in 2019. They reported 85, 75, 74 and 56% decline in screenings for breast, colon, prostate and lung cancers, respectively, at the peak of the pandemic in April 2020. They concluded that the disruption of cancer care services due to COVID-19 pandemic in the United States has led to significant decreases and delays in identifying new cancers, and if these problems are not mitigated will increase cancer morbidity and mortality in coming years. London et al.[48] analysed data from 20 healthcare institutions with over 28 million patients in the United States to quantify the effects that efforts to control the COVID-19 pandemic have had on cancer diagnosis encounters. They reported a decline in breast cancer screening of 5·0, 9·1, 43·8 and 89·2% in January to April 2020, respectively, and a similar decline in colorectal cancer of 0·7, 5·6, 38·4 and 84·5% in January to April 2020, respectively, compared to the same period in 2019. They concluded that the COVID-19 pandemic has resulted in a substantial decline in cancer-related patient encounters, and if it is not resolved, it will have serious implications for future cancer care. Peng et al.[38] conducted a population-based study to investigate the level of influence of the COVID-19 pandemic on breast cancer screening in Taiwan. They reported that the number of mammography screening examinations in hospitals declined from 41 to 57% from March

to May 2020 compared to the previous 3 years. Furthermore, the number of screening mammography examinations in mobile mammography vans also declined by 23–27% in March, 62–64% in April and 53–57% in May 2020. Yong et al.[36] used a mathematical simulation model to estimate the potential impact of suspending colorectal and breast cancer primary screening for up to 12 months and followed by 6–24 month transition periods of reduced screening volumes on cancer outcomes in Canada. They projected a surge of cancer cases when screening resumes after the lockdowns and estimated that an additional 310 cases would be diagnosed at advanced stages and an extra 110 deaths in 2020–2029 for a 3-month disruption of breast cancer screening. They also projected that a 6-month disruption of breast cancer screening could lead to an additional 670 advanced cancers and 250 cancer deaths and approximately 40,000 life-years lost. Furthermore, a 6-month suspension of primary screening for colorectal cancers would increase the cancer incidence by 2200 cases and additional 960 cancer deaths over the lifetime. They concluded that interruptions in cancer screening could have a significant adverse impact on long-term cancer outcomes and recommended the immediate restoration of cancer screening and prevention services when it is safe with adequate prioritisation strategies to mitigate any harm. Vanni et al.[37] conducted a study to estimate the effect of the suspension of breast Cancer screening during the COVID-19 lockdown. They reported that an estimated 10,000 patients could have a missed diagnosis during the three months and for a six-month period the number of patients who will not receive a diagnosis will increase to 16,000. They concluded that breast cancer screening should be resumed as soon as possible to avoid missing to diagnose any breast cancers and reduce the potential impact of delayed diagnosis.

Impact of COVID-19 Pandemic on Cancer Diagnosis

The early diagnosis of cancer has several proven benefits such as potential cure, improved treatment outcomes, reduced morbidity and increased survival.[30,51–58] On the other hand, it has also been reported that delayed diagnosis is associated with a more advanced stage disease at diagnosis, poorer survival, greater disease-related and treatment-related morbidity, higher mortality for some cancers and psychological distress for patients.[51,55,57] Several recent studies have reported that the COVID-19 pandemic has significantly impacted timely access to various routine and urgent diagnostic procedures and tests for cancer diagnosis as well as altered referrals in symptomatic cancer diagnosis and health-seeking behaviours especially during lockdowns in various countries.[21,30,43,46,54,59–61] The need to redirect healthcare staff and resources by various authorities to address the pandemic led to reduction and cancellation of several cancer diagnostic services in several hospitals.[16,30] According to Richards et al.,[30] the Welsh and Scottish governments suspended screening programmes for breast, cervical and bowel cancer in March 2020 which led to a reduction in referrals and an estimated 2000 fewer cancers diagnosed each week. They also reported over 90% reduction in the number of endoscopies in the United Kingdom in April 2020 compared to the first three months of 2020. Jones et al.[16] also reported that the UK national cancer screening programmes which account for approximately 5% of all cancer diagnoses each year in the country was suspended due to the COVID-19 pandemic. Sud et al.[54] reported that during the COVID-19 lockdown, referrals via the 2-week-wait urgent pathway for suspected cancer in England, UK, declined by about 84%. Richards et al.[30] also reported that urgent referrals of patients with cancer by primary-care physicians in Scotland reduced by over 70% by mid-April 2020. The suspension of screening services due to the pandemic has most likely resulted in a large backlog of patients, and it is predicted to place significant pressure on diagnostic services, impact other areas of the cancer pathway, potentially delay the early diagnosis from screening and could make only symptom-based diagnosis more important.[16] Therefore, there is an urgent need for interventions strategies to manage these backlog within the diagnostic services to mitigate the anticipated impact of the COVID-19 pandemic on patients care.

Maringe et al.[46] conducted a nationwide population-based modelling study to assess the impact of diagnosis delays due to the COVID-19 pandemic on patient survival, the number of additional deaths expected due to cancers and the additional years of life lost. They analysed data on 32,583 breast, 24,975 colorectal, 6744 oesophageal and 29,305 lung cancer patients aged 15–84 years. They estimated about 281–344 (7·9–9·6%), 1445–1563 (15·3–16·6%), 1235–1372 (4·8–5·3%) and 330–342 (5·8–6·0%) additional deaths due to breast, lung, colorectal and oesophageal cancers, respectively, within 5 years after diagnosis compared with pre-pandemic data. Furthermore, they projected about 59,204–63,229 total additional years of life lost for the four cancers. They concluded that a substantial increase in the number of avoidable cancer deaths in England is to be expected as a result of diagnostic delays due to the COVID-19 pandemic. Thus, urgent policy interventions are needed to manage the screening backlog within routine diagnostic services to mitigate the expected impact of the COVID-19 pandemic on cancer patients. Sud et al.[54] used a modelling approach to examine the impact of different scenarios of lockdown-accumulated backlog in cancer referral on cancer survival and the impact on survival per referred patient due to delayed referral during the COVID-19 pandemic for 20 common cancer types in the United Kingdom. They assessed three scenarios of a 3-month period of lockdown during which 25, 50 and 75% of the normal monthly volumes of symptomatic patients delayed their presentation until after lockdown. Assuming an average presentational delay of 2 months per patient, they estimated the national toll of presentational delay accrued over a 3-month lockdown period of 181 extra deaths and 3316 life-years lost, 361 added deaths and 6632 life-years lost and 542 additional deaths and 9948 life-years lost for a backlog rate of 25, 50 and 75%, respectively. They also estimated that delay in additional diagnostic capacity with provision spread across months 3–8 after lockdown would result in 401 extra lives and 7332 life-years lost due to diagnostic delays under the 25% backlog scenario, 811 extra lives and 14,873 life-years lost under the 50% backlog scenario and 1231 additional lives and 22,635 life-years lost under the 75% backlog scenario. They concluded that there is a clinically significant impact in lives and life-years lost if delays to the UK 2 week-wait pathway are extensive and prolonged. Andrew et al.[59] performed a study to assess changes in skin cancer diagnosis in the United Kingdom during the COVID-19 pandemic. They analysed data from the Northern Cancer Network from 23 March 2020 to 23 June 2020 and compared with the same period in 2019. They reported a decrease of 68·61% in skin cancer diagnoses in the first 3 months of the pandemic compared to the same period in 2019.

Impact of COVID-19 Pandemic on Cancer Treatment

Surgical treatment, radiation therapy and chemotherapy either alone or in combination are the definitive treatment modalities

for most malignancies; however, the timely delivery of these cancer treatments during the COVID-19 pandemic has faced significant challenges in several cancer centres worldwide potentially leading to some treatment delays.[13,30,62,63] Several studies have reported that delays in the initiation of radical treatments are generally associated with decreased local control rates and overall survival, thus extending or delaying the treatment time of definitive treatments can have detrimental effects on the expected treatment response and quality of life of oncology patients.[30,63–66] According to Kumar and Dey[63] and Herschbach et al.,[67] fear of disease progression or recurrence is quite common amongst cancer patients awaiting treatment, and elevated levels of such fear can affect patients' well-being, quality of life, social functioning and can lead to psychological stress. Therefore, in order to maintain timely patient care during the COVID-19 pandemic, several cancer centres developed guidance based on expert opinion to provide a framework for clinical practices and management of cancer patients.

Surgical treatment

Surgical procedures continue to be used for the diagnosis, staging and treatment of several cancers and for the relief of symptoms to improve patients' quality of life. Moreover, preventive or prophylactic surgery has also been used to prevent or lower the risk of developing certain types of cancer.[68–71] However, the COVID-19 pandemic has had an unprecedented impact on surgical services and on cancer patients awaiting surgery in several hospitals, as a result of the high demand for ventilators, hospital space and staff to provide additional critical care capacity for patients with COVID-19.[54,72–79] The surgical capacity in several hospitals has significantly been reduced and has led to the deprioritisation of non-emergency clinical services, postponement of some oncology surgeries and cancellation of elective and non-urgent procedures in order to preserve resources and to limit patients exposure to COVID-19.[54,72–74,79] According to Chan and Kudo,[18] about 20% of COVID-19 patients require intensive care and/or assisted ventilation support, thus resulting in a shortage of anaesthetists for surgeries related to cancers. Several studies have reported that delay in some surgical treatment is associated with increased overall mortality.[54,80–84] According to Sud et al.,[54] any delay in surgical treatment has the risk of patients' tumours progressing from potential curable (with near-normal life expectancy) to likely incurable, (with much reduced life expectancy). Hanna et al.[82] reported that every four weeks delay in surgical treatment for bladder, breast, colon, rectum, lung, cervix and head and neck cancers is associated with a 6–8% increase in the risk of death. Therefore, in order to mitigate the negative effects of the COVID-19 pandemic on patient's surgical treatments, international and national surgical societies and local institutions developed and provided guidelines for patients' surgical care.[30,78,85]

Dotzauer et al.[77] conducted an online survey to quantitatively assess the global effects of the COVID-19 pandemic in surgical and oncological clinical practice in urology and received responses from 235 urologists from 44 countries. They reported cancellation rates of 27% for transurethral resection of bladder tumour, 21–24% for radical cystectomy, 21% for nephroureterectomy, 18% for radical nephrectomy and 8% for radical orchiectomy. They concluded that the COVID-19 pandemic has significantly affected the clinical practice of 93% of urologists worldwide, and the impact of implementing surgical prioritisation protocols with moderate cancellation rates for oncological surgeries and delay or reduction in surgical treatment will need to be evaluated in post-pandemic. Yin et al.[72] investigated the effect of COVID-19 on breast cancer surgery in the United States from 2 February to 11 April 2020. They observed a significant decline after the COVID-19 outbreak in March 2020 and reported a 20·5% weekly decline in breast surgeries. They concluded that the COVID-19 has had a significant impact on the number of patients undergoing surgical treatment for breast cancer. The COVIDSurg Collaborative[85] conducted a study in 193 United Nations member countries to assess projections for the proportion of elective surgeries that would be cancelled or postponed during the 12 weeks of peak disruption due to COVID-19 pandemic. They estimated that 28,404,603 surgeries would be cancelled or postponed globally during the peak 12 weeks of disruption due to COVID-19 pandemic and 90·2% will be surgeries for benign disease and 8·2% for cancer surgeries. They concluded that a very significant number of surgeries will be cancelled or postponed due to disruption caused by the pandemic and if countries are to increase their normal surgical volume by 20% post-pandemic, it would take a median 45 weeks to clear the backlog of surgeries. Consequently, governments and surgical processionals should mitigate against this major burden on patients by developing recovery plans and implementing strategies to safely restore normal surgical activity.

Sud et al.[54] investigated the impact of different durations of delay of cancer surgeries on cancer outcomes in order to help inform healthcare prioritisation and resource allocation as well as compared resource-weighted outcomes with hospital management of COVID-19 patients. They reported that a surgical delay of 3 months will lead to 17% reduction in survival and 6 months delay will result in over 30% reduction in survival for patients with stage 2 or 3 cancers of the bladder, lung, oesophagus, ovary, liver, pancreas and stomach. Furthermore, they reported that a surgical delay of 3 months across all incident solid tumours over 1 year would cause 4755 excess deaths, which will rise to 10,760 excess deaths for a 6-month delay. They concluded that modest delays in surgical treatments for aggressive cancers will incur significant impact on survival and to avoid consequential public health crisis of preventable cancer deaths, the cancer surgical pathways must be maintained at normal throughput, with prompt attention to any backlog already accrued due treatment disruptions. Hanna et al.[82] conducted a systematic review to quantify the association of cancer treatment delay and mortality for each four-week increase in delay for bladder, breast, colon, rectum, lung, cervix and head and neck cancers. They reported a mortality risk of 1·06–1·08 for each four weeks delay of surgery of these cancers. Søreide et al.[74] conducted a review relating to COVID-19 and surgery using electronic databases, society websites, webinars and preprint repositories. They concluded that cancer patients have been deprived of access to surgical treatment with an indeterminate risk of adverse prognosis as a result of the pandemic. Consequently, surgical services in hospitals will need a contingency plan for maintaining surgical services in an ongoing or post-pandemic era.

Radiation therapy

Radiation therapy is an effective and a significant mode of definitive cancer treatment with well-established accomplishment of local tumour control, especially in the treatment of localised tumours.[3,86–91] The percentage of cancer patients receiving radiotherapy as part of their treatment during their illness has been increasing steadily with a global goal of about 50% in most developed countries.[88,92] Several studies have reported that radiotherapy of cancers can significantly prolong patient survival, improve local

tumour control rates, can be used in palliative settings or could be used as an alternative to surgery thus yielding better cosmetics for patients.[3,86,89–91] According to Veness et al.,[90] radiation therapy can result in greater than 90–95% local tumour control rate. However, significant delays and/or interruptions (i.e. treatment gaps) in radiotherapy delivery can significantly compromise treatment success, local tumour control and overall survival.[91,93–96] According to Nagar and Formenti,[91] delaying the start of adjuvant radiotherapy over 8 weeks after surgery will double the risk of local recurrence in breast cancer patients and every week of radiotherapy delay beyond 2 weeks after surgery for high-grade gliomas patients increases the risk of death by 8·9%. Several studies have reported a significant impact of the COVID-19 pandemic on radiotherapy delivery in several cancer centres.[32,86,87,91,97–104] Consequently, international and national oncology societies and local institutions developed and provided guidance based on expert opinion to provide a framework for clinical practice and management of cancer patients requiring radiation therapy to reduce clinic visits for patients while maintaining timely treatment schedules.[27,31,32,87,90,91,99,102–111] Zaorsky et al.[112] reported on the development of the RADS (remote visits, and avoidance, deferment, and shortening of radiation therapy) framework which consists of recommendations to safely manage prostate cancer patients during the COVID-19 pandemic and suggested that the framework is also applicable to other disease sites to help with decision making in a global pandemic.

Slotman et al.[31] reported on a survey conducted by the European Society for Radiotherapy and Oncology of 500 European radiation oncology departmental heads from 6 May to 20 May 2020 to evaluate the impact of COVID-19 on patients' management and received 139 responses from 29 countries. They observed that 60% of the respondents reported a decline in patient volume and 58% reported deferring some of new patients' treatments. Furthermore, the respondents reported treatment delays in 62% of low-risk, 40% of intermediate-risk and 20% of high-risk prostate cancer patients; 31% of early-stage breast cancer patients; 25% of palliative non-emergent indications; 16% of non-melanoma skin tumours; 38% of non-malignant indications; 16% of low-grade gliomas and 10% of oligometastatic diseases. Martinez et al.[108] also conducted a survey in Latin America cancer centres from 6 May to 30 May 2020 to determine the impact of COVID-19 on radiation oncology practices and received responses from 115 out of 229 practices from 15 countries. They observed that 97% of the respondents reported that they continued to provide radiotherapy services during the pandemic, and 80·9% reported a reduction in patient volumes. Furthermore, 42·6, 24·3, 67, 41·7 and 13·9% of the respondents reported delays in radiotherapy for early-stage breast cancers, low-grade gliomas, low-risk prostate cancers, intermediate-risk prostate cancers and high-risk prostate cancers, respectively. Achard et al.[104] conducted a national survey of 30 radiation oncology centres in Switzerland from 7 April to 24 April 2020 to assess the early impact of the COVID-19 pandemic on radiation oncology practices and received responses from 22 cancer centres. They noted that 90·9% of the respondents reported delaying prostate cancer radiotherapy if not considered detrimental for low-risk and intermediate-risk diseases, and 91% respondents used hypo-fractionated schedules for prostate cancer patients. Furthermore, they reported that 50% respondents dropped radiotherapy boost for breast cancer patients unless the patient presented with significant risk factors of relapse, 50% respondents adopted endocrine therapy to delay the start of radiotherapy for new breast cancer patients and an increased 18% respondents used moderate hypo-fractionation for breast radiotherapy. Chauhan et al.[87] retrospectively evaluated the impact of the COVID-19 pandemic on 1412 patients receiving radiotherapy from 1 January to 31 May 2020 and whether the impact correlated with patient's age, gender, disease site and intent of radiotherapy and also assessed the compliance to radiotherapy and treatment modifications. They stratified patients into those who received radiotherapy before a nationwide lockdown and patients who received radiotherapy during the lockdown in India. They reported a 10·5% decline in female patients receiving treatment and a 12% increase in patients receiving palliative intent radiotherapy during the lockdown. They observed no significant difference in compliance to radiotherapy between the two groups and reported significant increase in the use of single fraction radiotherapy for palliative patients. Desideri et al.[106] prospectively assessed cancer patients' satisfaction on doctor–patient interaction in a high-volume cancer centre in Italy during the COVID-19 pandemic and reported a high level of outpatient satisfaction despite the strict COVID-19 control measures implemented at the centre. Alterio et al.[101] assessed the dedicated procedures for head and neck cancers, radiotherapy scheduling and protection used by healthcare professionals from 1 March to 30 April 2020 at a radiotherapy department in Italy. They concluded that adequate, well-timed and efficient organisation strategies are required to ensure effective radiotherapy for head and neck cancer patients and staff safety. Reuter-Oppermann et al.[98] conducted an online survey of medical physicists in three different countries from 23 March to 26 March 2020 to evaluate how radiotherapy centres assess the COVID-19 situation and received 154 responses. They noted that 72% (81/112) of the respondents reported a significant impact on their processes and observed that 54% (65/120), 43% (51/120) and 37% (44/120) of the respondents reported longer processing times, patients not showing up for appointment and staff reduction, respectively. They concluded that most radiotherapy centres were cognizant of the challenges faced in the pandemic and implemented preventive measures to maintain patient care.

Systemic therapy

Systemic therapy is a treatment type that uses medications through patients' bloodstream to treat cancer cells throughout the body and may include chemotherapy, immunotherapy, hormone therapy or targeted therapy.[113–117] Several investigators have reported that the COVID-19 pandemic has significant consequences for people with an immunocompromised immune response such as cancer patients and has also substantially challenged systemic therapy for cancer patients.[17,23,27,62,118–122] Furthermore, various studies have reported that cancer patients undergoing systemic treatment such as chemotherapy could be at a higher risk of COVID-19 infection due to their immune-compromised status and if infected may be at a higher risk of developing severe and critical complications and increased risk of mortality from COVID-19.[17,30,120,121] Consequently, in order to reduce potential patient's exposure to COVID-19 in hospitals, cancer treatments in several cancer centres were scaled down in response to published guidelines and the site for systemic treatment for many patients were also relocated.[62,118,123] Sigorski et al.[62] reported that some changes such as delayed treatment, modified chemotherapy regimens, prolonged intervals between treatment cycles or even terminated therapy were implemented in systemic treatment during the pandemic in several hospitals. Furthermore, they reported that many patients were also unwilling to start new systemic treatment

or return to the clinics, since they perceived that they can be infected with COVID-19 during frequent contact with the health service and that the infection is a more life-threatening condition than the cancer itself, potentially adding to the number of treatment delays. According to Ueda et al.,[118] there could be a significant problem when dealing with treatment delays for continuing or new chemotherapy patients, particularly for haematology cancer patients who are vulnerable and more susceptible to being negatively affected by treatment delays. Saklani et al.[123] reported that, although the effect of treatments reductions on the prognosis of cancer patients is not yet known, the impact on patient concerns about their treatment has been substantial during the pandemic.

Lee et al.[121] conducted a prospective observational study to investigate the clinical and demographic characteristics and COVID-19 outcomes in 800 cancer patients as well as evaluated the impact of chemotherapy and other anticancer treatments on COVID-19 disease phenotype. All patients presented as symptomatic COVID-19 disease and were enroled into the UK Coronavirus Cancer Monitoring Project (UKCCMP) from 18 March to 26 April 2020. They observed 28% (226) mortality among the patients, and the risk of death was significantly associated with advanced patient age, being male and the presence of other comorbidities such as hypertension and cardiovascular disease. They reported that 281 (35%) patients had received chemotherapy within 4 weeks before testing positive for COVID-19, and after adjusting for age, gender and comorbidities, they observed that the chemotherapy had no significant effect on COVID-19 mortality when compared with patients with cancer who had not received chemotherapy. Furthermore, they observed no significant effect on COVID-19 mortality for patients on immunotherapy, hormonal therapy and targeted therapy. They concluded that COVID-19 mortality in cancer patients is mainly due to advanced age and other non-cancer comorbidities and reported that chemotherapy or anticancer treatments do not increase the risk of mortality from COVID-19, and thus delivery of effective anticancer regimens should continue during the pandemic. Lin et al.[28] examined the prevalence and characteristics of treatment modifications in 282 patients (93 males and 189 females) with a median age of 61 years to investigate the factors leading to treatment modifications decision as well as evaluated the effect of disease status, treatment purpose, nature of treatment regimen and preferences of physicians or patients in electing for treatment modification. They indicated that 246 patients were on chemotherapy (i.e. 87 patients were on adjuvant or neoadjuvant chemotherapy and 159 patients were on palliative treatment of metastatic disease), 25 patients were on only endocrine therapy or bone-modulating therapy and 11 patients were receiving treatment of non-malignant disease. They reported treatment modifications in 56% (159/282) of patients which comprises of 41·4% (36/87) patients undergoing adjuvant and neoadjuvant treatment, 63% (100/159) patients on palliative treatment, 76% (19/25) patients on injectable endocrine or bone-modulating treatments and 36% (4/11) patients on non-malignant treatment. They observed that treatment modifications in 70% (112/159) patients were recommended by physicians and the 30% (47/159) were initiated by the patients and the most common modification strategy was to skip or postpone a scheduled treatment. Among the treatments with no modifications, they reported that treatment regimens were maintained in 37% patients who tolerated the treatment well, 22% of treatments with curative intent and in 14% of symptomatic patients who required treatment. They concluded that the primary goal of the treatment modifications was to decrease potential patient's exposure to COVID-19. Moreover, they recognised the negative impact of the pandemic on healthcare providers who struggle to make right recommendations on individualised patient basis, incorporating multiple factors, such as tolerance, potential toxicity, nature of the treatment, severity of disease and route of treatment.

Ramaswamy et al.[120] conducted an observational study between 12 April and 10 June 2020 to evaluate all-cause mortality within 30 days of COVID-19 diagnosis, COVID-19 attributable mortality and factors predicting mortality in 230 confirmed COVID-19 cancer patients with a median age of 42 years (range: 1–75 years) who were on active systemic therapy. They observed that COVID-19 infection severity level was mild, moderate and severe in 195, 11 and 24 patients, respectively. They observed no mortalities in the 31 paediatric patients; however, they reported that 23 patients died within 30 days of COVID-19 diagnosis and was primarily attributable to COVID-19 in 15 patients, while the remaining eight patients' death was likely due to uncontrolled cancers status or treatment-related complications with COVID-19 infection being a concurrent illness. Furthermore, they reported mortalities of 71% (17/24) patients with severe COVID-19 compared with 9% (1/11) with moderate and 2·6% (5/195) with mild COVID-19 disease. They concluded that COVID-19 infection with cancer is not unusual, and mortality rates in this cohort appear marginally elevated, but active disease control via appropriate treatment is of paramount importance to prevent cancer and concurrent COVID-19-related mortality. Sigorski et al.[62] conducted a multicentre, prospective, non-interventional study to investigate the relationship between the level of cancer-related anxiety and SARS-CoV-2-related anxiety as well as the clinical factors associated with a higher level of anxiety in 306 cancer patients (age $\geq$ 18 years) who were actively on systemic therapy between 11 May and 15 May 2020. They reported significantly elevated fear and anxiety associated with SARS-CoV-2 in women compared to men and was also tumour type-dependent, with the highest anxiety observed in patients with breast cancer. Furthermore, they reported that the fear and anxiety associated with cancer was higher in women than men, in patients treated with curative than palliative intention and in patients aged $\leq$65 years than >65 years. They concluded that cancer remains the main life-threatening disease during the COVID-19 pandemic in patients on active treatment, and there is a need for more psychological care for patients, especially breast cancer patients, or patients under 65 years of age and those being treated with curative intent, as these factors are associated with a higher level of anxiety.

Impact of COVID-19 Pandemic on Patients' Follow-up

Follow-up during and after cancer treatment is an integral part of the management of oncology patients since it is essential for the monitoring of ongoing treatment, assessment of clinical response to treatment, management of any early side-effects, identification of treatment late effects, early detection of residual or recurrences and second malignancies, as well as symptomatic and supportive treatment if required.[4,18,63,124] Follow-up is also imperative for the provision of ongoing supportive care to patients and their families, provision of information and reassurance or identification of any psychosocial problems.[4,124,125] According to Greenfield et al.,[124] some important benefits of follow-up include the enablement of oncology experts to focus on acute care, ease of referring patients back to specialist centres as needed, establishment of stronger relationships with patients and reduction in patient anxiety. Lewis et al.[126] reported that the fear of disease recurrence is a major

source of anxiety for cancer patients; however, they derive reassurance from follow-up appointments with their clinicians. Cancer patients frequently require close follow-up appointments for antineoplastic treatment and monitoring of treatment toxicities; however, the COVID-19 pandemic has significantly disrupted these services.[18,63,125] According to Kumar and Dey,[63] the most significantly impacted patient group in the follow-up stage during the pandemic has been patients who developed symptoms of recurrences or second malignancies and may require further diagnosis and treatment interventions. Several studies reported a significant decline in patients' face-to-face appointments with primary-care providers and the switch to teleconsultations for routine services in many oncology centres unless an in-person consultation was deemed essential.[11,18,19,30,127] In order to ensure the continuity of care for oncology patients during the COVID-19 pandemic, the European Society for Medical Oncology (ESMO) for the management and treatment of cancer recommended the prioritisation of follow-ups for cancer patients as either low, medium or high depending on risk of relapse.[30,127] Moreover, the American Society of Clinical Oncology (ASCO)[11] also recommended the postponement of any clinic visits that can safely be done without risk to the patient, including the routine surveillance of patients who have completed treatment or patients on active surveillance who are considered to be at relatively low risk of recurrence or disease progression. However, Richards et al.[30] caution that the reprioritisation may have long-term implications for the detection of disease progression and complications that may impact cancer outcomes. Although these recommendations are important to maintain a level of continuity of care while at the same time avoiding potential spread of COVID-19, they may likely reduce opportunities for early detection of symptoms of disease recurrence. Additionally, they may potentially reduce the likely detection of patient's psychological distress which may be exacerbated in the pandemic, reduce the provision of psychological support through the healthcare systems and many patients may also have difficulties accessing their usual support networks. According to Richards et al.,[30] although survivorship and psychological support services are adapting to provide remote services when possible, there is still a risk of digital exclusion of patients who may not have routine internet access and for the elderly and patients with lower digital literacy. Thus, follow-up services during the pandemic should ensure equity among patients and that any approach used for patients follow-up should consider reaching the majority if not all patients.

Ratnasekera et al.[125] conducted a situational analysis to provide supportive care for 25 randomly selected oral cancer patients who had surgical treatment but had difficulties accessing post-surgical treatment services and medication due to COVID-19 lockdown in Sri Lanka. They reported that 60% of the patients were facing acute post-surgery complications such as pain and swallowing difficulties; however, the supportive care provided via the phone by healthcare professionals and tailored to the patients' needs was considered a simple but helpful follow-up intervention. They concluded that follow-up intervention tailored to patients' needs could offer better supportive care for cancer patients in COVID-19 pandemic era. Gultekin et al.[20] conducted a patient survey in 16 European countries to capture the gynaecological cancer patients' perceptions of the COVID-19 implications and the worldwide imposed treatment modifications and received 1388 responses but rejected 137 incomplete responses. They indicated that 54·7, 19·6, 17·3 and 8·4% of the respondents were ovarian, uterine or endometrial, cervical and other rarer cancer patients, respectively. They reported that 864 patients expressed concern about cancer progression if their follow-up was cancelled or postponed, 644 patients expressed fear of contracting COVID-19 from the hospital or clinic while receiving their oncologic treatment or follow-up and 160 patients reported that their follow-up was postponed or delayed. De Joode et al.[128] conducted a nationwide survey in the Netherlands between 29 March and 18 April 2020 to assess the impact of the pandemic on cancer patients' perception on oncological care and received 5302 responses of which 2661 (50%) patients had completed cancer treatment and were in the follow-up stage. They reported that 30% of the patients on follow-up experienced some level of disruption of their follow-up and was mostly initiated by the hospital.

Impact of COVID-19 Pandemic on Research and Clinical Trials

Clinical trials have for the longest time been the principal methodology for the evaluation and validation of new drugs, and treatments and the approval of several new drugs and treatments into clinical practise have been established based on successful trials into the safety and efficacy of the new drug or therapy.[25,30,129–131] Tolaney et al.[130] reported that clinical trials are essential for the advancement of cancer treatment and the provision of access to novel and potentially effective treatments for patients. According to Richards et al.,[30] there are currently over 12,000 active clinical trials in the area of cancer treatment and diagnosis and suspending many of them will have long-lasting health and financial consequences. Despite that, the COVID-19 pandemic has presented unique challenges and disrupted several clinical trials and other cancer-related research worldwide.[30,130–137] According to Harris,[135] several charity organisations or governmental institutions that fund and support cancer research have been severely impacted due to loss of income from public donors, grants and industries. Consequently, universities and other research centres have been a source of innovation and development, and the main sites for fundamental cancer research have been under severe threat of loss of funding. Numerous studies reported that several clinical trial research organisations suspended the initiation of new trials, had difficulties recruiting new patients, experienced significant reduction in follow-up for ongoing trials or encountered challenges to continue trials under lockdown restrictions.[25,30,129,131,132,135] Thus, to properly manage clinical trials during the COVID-19 pandemic and to ensure the safety of trial participants, professional institutions such as the National Cancer Institute, USA Food and Drug Administration, the European Medicines Agency, ASCO, American Association of Cancer Institutes and the American College of Surgeons published guidelines and recommendations for the safe delivery of study medications, treatments and structural information on changes and protocol deviations.[14,25,30,134]

According to the Medidata Solutions Inc[138] who has continuously monitored the global impact of COVID-19 on clinical trials, there was a worldwide decline in the average number of new patients entering clinical trials of about 65, 79 and 74% in March, April and May 2002, respectively, compared to the same time in 2019. They reported a decline in new patient recruitment of 33–95% in Asia, 33–98% in Europe and 66–83% in North America. Marcum et al.[134] reported an average patient enrolment rate for non-interventional and interventional procedures of 31 and 40 per month, respectively, between July 2019 and February

2020 at their academic medical centre; however, in March 2020, the enrolment for non-interventional and interventional dropped to 15 and 29 per month, respectively, when COVID-19 restrictions were introduced at the centre. Upadhaya et al.[133] investigated the impact of COVID-19 pandemic on the management of ongoing oncology clinical trials using a combination of surveys, interviews of oncology clinical investigators and analysing IQVIA and ClinicalTrials.gov oncology clinical trials data between 23 March and 3 April 2020. They recounted that patients' enrolment in active oncology clinical trials was negatively affected by the COVID-19. They observed that about 60, 86 and 20% respondents from the United States, Europe and Asia, respectively, reported continuing new patients' enrolment but at a significantly lower rate, whereas 20% respondents from the United States and Asia reported suspending new patients' enrolments. Furthermore, they specified that the respondents reported patient care, type of cancer treatment and route of administration as the considerations for new patient enrolment. They reported the suspension of over 200 interventional oncology studies in March and April due to the COVID-19 pandemic based on ClinicalTrials.gov. Tolaney et al.[130] prospectively monitored the number of open-label clinical trials, new patient enrolments, in-person and virtual patient visits, dispensed or shipped oral trial medications, research biopsies and blood samples from oncology clinical trials at Dana-Farber Cancer Institute from 1 January 2018 to 30 June 2020. They reported retaining almost all patients already on interventional treatment trials; however, new patient enrolments were reduced to under 50% of the pre-pandemic rate. Furthermore, they reported an average increase from 0 to 74 per week of the number of trial prescriptions sent to patients and an average increase from 0 to 107 per week of the number of telemedicine appointments from March to June 2020. In addition, there was a significant decrease in research biopsies and blood samples after the Center implemented COVID-19-related policies in March 2020.[130] Although the COVID-19 pandemic has negatively impacted several clinical trials, several studies have reported that the extraordinary speed employed in the design and implementation of clinical trials for COVID-19 vaccines has demonstrated that certain aspects to trials approval, unnecessary administrative barriers and several trials practices could significantly be improved, streamlined or made efficient in ways that would benefit patients, practitioners and researchers, and it is imperative to incorporate these lessons learned into the conduct of future trials to ensure the highest quality possible.[129,134,136]

Conclusion

Oncologic care and the management of cancer services and patients have been profoundly impacted by the COVID-19 pandemic. However, the oncology healthcare communities around the world have done phenomenal work with joint efforts to continue to give safe and effective treatments for cancer patients throughout the pandemic while at the same time protecting patients, healthcare professionals and the general population from the spread of COVID-19. The response of the healthcare communities has been very collaborative, utilising best available evidence-based guidelines to maintain services while keeping patient and staff safety as a priority. Nevertheless, the stringent social distancing, restricted in-hospital visits and lockdown measures introduced in the pandemic have caused several healthcare centres to be confronted with significant challenges with the management of huge backlog of oncologic cases. Consequently, it is imperative that urgent policy interventions are necessary, particularly the need to minimise system-level delays to cancer screening, diagnosis, treatment initiation and clearing of all backlogs cases from the COVID-19 pandemic in order to mitigate the anticipated negative impact of the pandemic on cancer outcomes. Prompt provisions of additional capacity to address the backlog cases while maintaining routine oncologic services will minimise the potential mortalities due to additional delays that could add up to those already predicted as a consequence of presentational delays in the pandemic. Prioritisation of patients for whom delays would result in most life-years lost warrants consideration as an option for mitigating the aggregate burden of mortality in patients. In addition, several studies have provided valuable data from various centres worldwide on the impact of COVID-19 pandemic on cancer care services and on outcomes for cancer patients, as well as important insights on lessons learned from the pandemic to inform oncology managements and professionals on how cancer services can be utilised most effectively during any future pandemic.

Acknowledgement. None.

Conflict of Interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin 2018; 68 (6): 394–424.
2. WHO. Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed on 02 February 2021.
3. Raymond E, Thieblemont C, Alran S, Faivre S. Impact of the COVID-19 outbreak on the management of patients with cancer. Target Oncol; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7243433/. Accessed on 02 February 2021.
4. Rose PW, Watson E. What is the value of routine follow-up after diagnosis and treatment of cancer? Br J Gen Pract 2009; 59 (564): 482–483.
5. Brenner DR, Weir HK, Demers AA, et al. for the Canadian cancer statistics advisory committee. Projected estimates of cancer in Canada in 2020. CMAJ 2020; 192 (9): E199–E205. doi: 10.1503/cmaj.191292.
6. Tsamakis K, Gavriatopoulou M, Schizas D, et al. Oncology during the COVID-19 pandemic: challenges, dilemmas and the psychosocial impact on cancer patients (Review). Oncol Lett 2020; 20 (1): 441–447.
7. Al-Quteimat OM and Amer AM. The impact of the COVID-19 pandemic on cancer patients. Am J Clin Oncol 2020; 43 (6): 452–455.
8. National Comprehensive Cancer Network (NCCN). Coronavirus disease 2019 (COVID-19) Resources for the cancer care community. https://www.nccn.org/covid-19/ Accessed on 02 February 2021.
9. The Royal College of Radiologists. Coronavirus (COVID-19): clinical information. https://www.rcr.ac.uk/college/coronavirus-covid-19-what-rcr-doing/coronavirus-covid-19-clinical-information. Accessed on 02 February 2021.
10. European Association of Neuro-Oncology (EANO). COVID-19 and neuro-oncology: considerations for daily care of brain tumor patients. Vienna: EANO, 2020. https://www.eano.eu/. Accessed on 02 February 2021.
11. American Society of Clinical Oncology (ASCO). Coronavirus resources. https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19. Accessed on 02 February 2021.
12. American College of Surgeons. COVID-19: guidance for triage of non-emergent surgical procedures. https://www.facs.org/covid-19/clinical-guidance/triage. Accessed on 02 February 2021.
13. Li J, Wang H, Geng C, et al. Suboptimal declines and delays in early breast cancer treatment after COVID-19 quarantine restrictions in China: a

national survey of 8397 patients in the first quarter of 2020. EClinical Medicine 2020; 26: 100503.
14. Chen-See S. Disruption of cancer care in Canada during COVID-19. Lancet Oncol 2020; 21 (8): e374.
15. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19. Ann Intern Med 2020; 172 (11): 756–758.
16. Jones D, Neal RD, Duffy SRG, Scott SE, Whitaker KL, Brain K. Impact of the COVID-19 pandemic on the symptomatic diagnosis of cancer: the view from primary care. Lancet Oncol 2020; 21 (6): 748–750.
17. Vivarelli S, Falzone L, Grillo CM, Scandurra G, Torino F, Libra M. Cancer management during COVID-19 pandemic: is immune checkpoint inhibitors-based immunotherapy harmful or beneficial? Cancers 2020; 12 (8): 2237.
18. Chan SL, Kudo M. Impacts of COVID-19 on liver cancers: during and after the pandemic. Liver Cancer 2020; 9 (5): 491–502.
19. Moraliyage H, De Silva D, Ranasinghe W, et al. Cancer in lockdown: impact of the COVID-19 pandemic on patients with cancer. Oncologist 2021; 26: e342–e344. doi:10.1002/onco.13604.
20. Gultekin M, Ak S, Ayhan A, et al. Perspectives, fears and expectations of patients with gynaecological cancers during the COVID-19 pandemic: a Pan-European study of the European Network of Gynaecological Cancer Advocacy Groups (ENGAGe). Cancer Med 2021; 10 (1): 208–219.
21. Patt D, Gordan L, Diaz M, et al. Impact of COVID-19 on Cancer Care: how the pandemic is Delaying Cancer Diagnosis and Treatment for American Seniors. JCO Clin Cancer Inf 2020; 4: 1059–1071.
22. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21 (3): 335–337.
23. Weinkove R, McQuilten ZK, Adler J, et al. Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance. Med J Aust 2020; 212 (10): 481–489.
24. Lancia A, Bonzano E, Bottero M, Camici M, Catellani F, Ingrosso G. Radiotherapy in the era of COVID-19. Expert Rev Anticancer Ther 2020; 20 (8): 625–627.
25. Passaro, A., Addeo, A., Von Garnier, C., et al. ESMO Management and treatment adapted recommendations in the COVID-19 era: lung cancer. ESMO Open 2020; 5 (Suppl 3): e000820.
26. Vecchione L, Stintzing S, Pentheroudakis G, Douillard J, Lordick F. ESMO management and treatment adapted recommendations in the COVID-19 era: colorectal cancer. ESMO Open 2020; 5 (Suppl 3): e000826.
27. Saini KS, de las Heras B, de Castro J, et al. Effect of the COVID-19 pandemic on cancer treatment and research. Lancet Haematol 2020; 7 (6): e432–e435.
28. Lin DD, Meghal T, Murthy P, et al. Chemotherapy treatment modifications during the COVID-19 Outbreak at a Community Cancer Center in New York City. JCO Glob Oncol 2020; 6 (6): 1298–1305.
29. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group. Oncologist 2020; 25 (6): e936–e945.
30. Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. Nat Cancer 2020; 1 (6): 565–567.
31. Slotman BJ, Lievens Y, Poortmans P, et al. Effect of COVID-19 pandemic on practice in European radiation oncology centers. Radiother Oncol 2020; 150: 40–42.
32. Rivera A, Ohri N, Thomas E, Miller R, Knoll MA. The Impact of COVID-19 on radiation oncology clinics and patients with cancer in the United States. Adv Radiat Oncol 2020; 5 (4): 538–543.
33. Cancino RS, Su Z, Mesa R, Tomlinson GE, Wang J. The impact of COVID-19 on cancer screening: challenges and opportunities. JMIR Cancer 2020; 6 (2): e21697.
34. Myers ER, Moorman P, Gierisch JM, et al. Benefits and harms of breast cancer screening: a systematic review. J Am Med Assoc 2015; 314 (15): 1615–1634. doi: 10.1001/jama.2015.13183.
35. Ladabaum U, Mannalithara A, Meester RGS, Gupta S, Schoen RE. Cost-effectiveness and national effects of initiating colorectal cancer screening for average-risk persons at age 45 years instead of 50 years. Gastroenterol 2019; 157 (1): 137–148. doi: 10.1053/j.gastro.2019.03.023.
36. Yong JH, Mainprize JG, Yaffe MJ, et al. The impact of episodic screening interruption: COVID-19 and population-based cancer screening in Canada. J Med Screening 2020. doi: 10.1177/0969141320974711.
37. Vanni G, Pellicciaro M, Materazzo M, et al. Lockdown of breast cancer screening for COVID-19: possible scenario. Vivo (Athens) 2020; 34 (5): 3047–3053.
38. Peng S, Yang K, Chan WP, et al. Impact of the COVID-19 pandemic on a population-based breast cancer screening program. Cancer 2020; 126 (24): 5202–5205.
39. Mazzone PJ, Gould MK, Arenberg DA, et al. Management of lung nodules and lung cancer screening during the COVID-19 pandemic: CHEST expert panel report. Chest 2020; 158 (1): 406–415.
40. Villani A, Fabbrocini G, Costa C, Scalvenzi M. Melanoma screening days during the coronavirus disease 2019 (COVID-19) pandemic: strategies to adopt. Dermatol Ther (Heidelb) 2020; 10 (4): 525–527.
41. DuBois RN. COVID-19, cancer care and prevention. Cancer Prev Res (Phila) 2020; 13 (11): 889–892.
42. National Cancer Institute. Causes and prevention. https://www.cancer.gov/about-cancer/causes-prevention. Accessed on 02 February 2021.
43. Dinmohamed AG, Cellamare M, Visser O, et al. The impact of the temporary suspension of national cancer screening programmes due to the COVID-19 epidemic on the diagnosis of breast and colorectal cancer in the Netherlands. J Hematol Oncol 2020; 13 (1): 147.
44. D'Ovidio V, Lucidi C, Bruno G, Lisi D, Miglioresi L, Bazuro ME. Impact of COVID-19 pandemic on colorectal cancer screening program. Clin Colorectal Cancer; March 2021; 21 (1): e5–e11.
45. Tsai H, Chang Y, Shen C, Chung W, Tsai H, Chen F. Effects of the COVID-19 pandemic on breast cancer screening in Taiwan. Breast (Edinburgh) 2020; 54: 52–55.
46. Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol 2020; 21 (8): 1023–1034.
47. Issaka RB, Somsouk M. Colorectal cancer screening and prevention in the COVID-19 era. JAMA Health Forum 2020; 1 (5): e200588.
48. London JW, Fazio-Eynullayeva E, Palchuk MB, Sankey P, McNair C. Effects of the COVID-19 pandemic on cancer-related patient encounters. JCO Clin Cancer Inf 2020; 4 (4): 657–665.
49. Gralnek IM, Hassan C, Dinis-Ribeiro M. COVID-19 and endoscopy: implications for healthcare and digestive cancer screening. Nat Rev Gastroenterol Hepatol 2020; 17 (8): 444–446.
50. The Lancet Gastroenterology & Hepatology. Resuming bowel cancer screening post-COVID-19. Lancet Gastroenterol Hepatol 2020; published online June 25. https://doi.org/10.1016/S2468-1253(20)30200-4. Accessed on 02 February 2021.
51. Hamilton W, Walter FM, Rubin G, Neal RD. Improving early diagnosis of symptomatic cancer. Nat Rev Clin Oncol 2016; 13 (12): 740–749.
52. Gulati R, Cheng HH, Lange PH, Nelson PS, Etzioni R. Screening men at increased risk for prostate cancer diagnosis: model estimates of benefits and harms. Cancer Epidemiol Biomark Prev 2017; 26 (2): 222–227.
53. Grimaldi AM, Incoronato M. Clinical translatability of "identified" circulating miRNAs for diagnosing breast cancer: overview and update. Cancers (Basel) 2019; 11 (7): 901.
54. Sud A, Torr B, Jones ME, Broggio J, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. Lancet Oncol 2020; 21 (8): 1035–1044.
55. Redaniel MT, Martin RM, Ridd MJ, Wade J, Jeffreys M. Diagnostic intervals and its association with breast, prostate, lung and colorectal cancer survival in England: historical cohort study using the clinical practice research datalink. PLoS One 2015; 10 (5): e0126608.
56. Tørring ML, Frydenberg M, Hansen RP, Olesen F, Hamilton W, Vedsted P. Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care. Br J Cancer 2011; 104 (6): 934–940.
57. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer 2015; 112 (S1): S92–S107.
58. Hamilton W, Stapley S, Campbell C, Lyratzopoulos G, Rubin G, Neal RD. For which cancers might patients benefit most from expedited symptomatic

diagnosis? Construction of a ranking order by a modified Delphi technique. BMC Cancer 2015; 15 (819): 820.
59. Andrew TW, Alrawi M, Lovat P. Reduction in skin cancer diagnoses in the UK during the COVID-19 pandemic. Clin Exp Dermatol 2021; 46 (1): 145–146.
60. Ding Y, Ramakrishna S, Long AH, et al. Delayed cancer diagnoses and high mortality in children during the COVID-19 pandemic. Pediatr Blood Cancer 2020; 67 (9): e28427–n/a.
61. National Cancer Institute. How cancer is diagnosed. 2019; https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis. Accessed on 02 February 2021.
62. Sigorski D, Sobczuk P, Osmola M, et al. Impact of COVID-19 on anxiety levels among patients with cancer actively treated with systemic therapy. ESMO Open 2020; 5 (5): 1–8.
63. Kumar D, Dey T. Treatment delays in oncology patients during COVID-19 pandemic: a perspective. J Glob Health 2020; 10 (1): 010367.
64. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. Radiother Oncol 2007; 87 (1): 3–16.
65. Xu F, Rimm AA, Fu P, Krishnamurthi SS, Cooper GS. The impact of delayed chemotherapy on its completion and survival outcomes in stage II colon cancer patients. PLoS One 2014; 9 (9): e107993.
66. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. Ann Surg 2007; 246 (2): 173–180.
67. Herschbach, P, Dinkel, A. Fear of progression. Psychooncology 2014; 197: 11–29.
68. Pusic A, Liu JC, Chen CM, et al. A systematic review of patient-reported outcome measures in head and neck cancer surgery. Otolaryngol–Head Neck Surg 2007; 136 (4): 525–535. doi: 10.1016/j.otohns.2006.12.006.
69. Canadian Cancer Society. Surgery in cancer treatment. https://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/surgery/?region=on. Accessed on 02 February 2021.
70. National Cancer Institute. Surgery to treat cancer. https://www.cancer.gov/about-cancer/treatment/types/surgery. Accessed on 02 February 2021.
71. American Cancer Society. How surgery is used for cancer. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/surgery/how-surgery-is-used-for-cancer.html. Accessed on 02 February 2021.
72. Yin K, Singh P, Drohan B, Hughes KS. Breast imaging, breast surgery, and cancer genetics in the age of COVID-19. Cancer 2020; 126 (20): 4466–4472.
73. Topf MC, Shenson JA, Holsinger FC, et al. Framework for prioritizing head and neck surgery during the COVID-19 pandemic. Head Neck 2020; 42 (6): 1159–1167.
74. Søreide K, Hallet J, Matthews JB, et al. Immediate and long-term impact of the COVID-19 pandemic on delivery of surgical services. Br J Surg 2020; 107 (10): 1250–1261.
75. Magno S, Linardos M, Carnevale S, et al. The impact of the COVID-19 pandemic on breast cancer patients awaiting surgery: observational survey in an Italian University hospital. Breast J 2020; 26 (8): 1597–1602.
76. Kiong KL, Guo T, Yao, CMKL, et al. Changing practice patterns in head and neck oncologic surgery in the early COVID-19 era. Head Neck 2020; 42 (6): 1179–1186.
77. Dotzauer R, Böhm K, Brandt MP, et al. Global change of surgical and oncological clinical practice in urology during early COVID-19 pandemic. World J Urol 2020; 4: 1–7.
78. Acea-Nebril B, García-Novoa A, García-Jiménez L, et al. Impact of the COVID-19 pandemic on a breast cancer surgery program. Observational case-control study in a COVID-free hospital. Breast J 2020; 26 (12): 2428–2430.
79. Chang EI, Liu JJ. Flattening the curve in oncologic surgery: impact of Covid-19 on surgery at tertiary care cancer center. J Surg Oncol 2020; 122 (4): 602–607.
80. Bleicher R. Timing and delays in breast cancer evaluation and treatment. Ann Surg Oncol 2018; 25 (10): 2829–2838.
81. Lee Y, Kung P, Wang Y, Kuo W, Kao S, Tsai W. Effect of length of time from diagnosis to treatment on colorectal cancer survival: a population-based study. PLoS One 2019; 14 (1): e0210465.
82. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ 2020; 371: m4087.
83. Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A. Longer wait times increase overall mortality in patients with bladder cancer. J Urol 2009; 182 (4): 1318–1324.
84. Eaglehouse Y, Georg M, Shriver C, Zhu K. Time-to-surgery and overall survival after breast cancer diagnosis in a universal health system. Breast Cancer Res Treat 2019; 178 (2): 441–450.
85. COVIDSurg Collaborative. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. Br J Surg 2020; 107 (11): 1440–1449. doi: 10.1002/bjs.11746. Epub 2020 Jun 13. PMID: 32395848; PMCID: PMC7272903.
86. Mohindra P, Buckey CR, Chen S, Sio TT, Rong Y. Radiation therapy considerations during the COVID-19 pandemic: literature review and expert opinions. J Appl Clin Med Phys 2020; 21 (5): 6–12.
87. Chauhan R, Trivedi V, Rani R, et al. The impact of COVID-19 pandemic on the practice of radiotherapy: a retrospective single-institution study. Cancer Res Stat Treat 2020; 3 (3): 467–474.
88. Xu L, Osei B, Osei E. A review of radiation genomics: integrating patient radiation response with genomics for personalised and targeted radiation therapy. J Radiother Pract 2019; 18 (2): 198–209.
89. Orth M, Orth M, Lauber K, et al. Current concepts in clinical radiation oncology. Radiat Environ Biophys 2014; 53 (1): 1–29.
90. Veness MJ. Hypofractionated radiotherapy in patients with non-melanoma skin cancer in the post COVID-19 era: time to reconsider its role for most patients. J. Med Radiat Oncol 2020; 64 (4): 591–594.
91. Nagar H, Formenti SC. Cancer and COVID-19 – potentially deleterious effects of delaying radiotherapy. Nat Rev Clin Oncol 2020; 17 (6): 332–334.
92. Yap ML, Zubizarreta E, Bray F, Ferlay J, Barton M. Global access to radiotherapy services: have we made progress during the past decade? 2016; 2 (4): 207–215.
93. Yusoff AL, Mohamad M, Abdullah R, Bhavaraju VMK, Idris NRN. RTtxGap: an android radiobiological tool for compensation of radiotherapy treatment interruption. J Phys Conf Ser 2016; 694 (1): 12012.
94. González Ferreira JA, Jaén Olasolo J, Azinovic I, Jeremic B. Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: review of the literature. Rep Pract Oncol Radiother 2015; 20 (5): 328–339.
95. Hunter AJ, Hendrikse AS. Estimation of the effects of radiotherapy treatment delays on tumour responses: a review. SA J Oncol 2020; 4: e1–e9.
96. Tarnawski R, Skladowski K, Swienrniak A, Wygoda A, Mucha A. Repopulation of tumour cells during radiotherapy is doubled during treatment gaps. J Theor Med 2000; 2 (4): 297–305.
97. Vordermark D. Shift in indications for radiotherapy during the COVID-19 pandemic? A review of organ-specific cancer management recommendations from multidisciplinary and surgical expert groups. Radiat Oncol 2020; 15 (1): 140.
98. Reuter-Oppermann M, Müller-Polyzou R, Wirtz H, Georgiadis A. Influence of the pandemic dissemination of COVID-19 on radiotherapy practice: a flash survey in Germany, Austria and Switzerland. PLoS One 2020; 15 (5): e0233330.
99. Lewis PJ, Morris EJA, Chan CSK, Darley K, Sebag-Montefiore D, Evans M. COVID RT – assessing the impact of COVID-19 on radiotherapy in the UK. A National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group Initiative in Partnership with the Royal College of Radiologists, the Society of Radiographers and the Institute of Physics and Engineering in Medicine. Clin Oncol 2021; 33 (1): e69–e72.
100. Kang JJ, Wong RJ, Sherman EJ, et al. The 3 Bs of cancer care amid the COVID-19 pandemic crisis: "Be safe, be smart, be kind"—a multidisciplinary approach increasing the use of radiation and embracing telemedicine for head and neck cancer. Cancer 2020; 126 (18): 4092–4104.
101. Alterio D, Volpe S, Marvaso G, Turturici I, Ferrari A, Leonardi MC, et al. Head and neck cancer radiotherapy amid COVID-19 pandemic: report from Milan, Italy. Head Neck 2020; 42 (7): 1482–1490.
102. Bajaj A. The impact of COVID-19 on radiation oncology department workflow in the United States. Appl Radiat Oncol 2020; 9 (2): 6–7.

103. Beddok A, Calugaru V, Minsat M, et al. Post-lockdown management of oncological priorities and postponed radiation therapy following the COVID-19 pandemic: experience of the Institut Curie. Radiother Oncol 2020; 150: 12–14.
104. Achard V, Aebersold DM, Allal AS, et al. A national survey on radiation oncology patterns of practice in Switzerland during the COVID-19 pandemic: present changes and future perspectives. Radiother Oncol 2020; 150: 1–3.
105. Curigliano G, Cardoso MJ, Poortmans P, et al. Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemic. Breast (Edinburgh) 2020; 52: 8–16.
106. Desideri I, Francolini G, Ciccone LP, et al. Impact of COVID-19 on patient-doctor interaction in a complex radiation therapy facility. Supportive Care Cancer 2020; 1–7.
107. Gasparri ML, Gentilini OD, Lueftner D, Kuehn T, Kaidar-Person O, Poortmans P. Changes in breast cancer management during the Corona Virus Disease 19 pandemic: an international survey of the European Breast Cancer Research Association of Surgical Trialists (EUBREAST). Breast (Edinburgh) 2020; 52: 110–115.
108. Martinez D, Sarria GJ, Wakefield D, et al. COVID's impact on radiation oncology: a Latin American Survey Study. Int J Radiat Oncol Biol Phys 2020; 108 (2): 374–378.
109. Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. The COVID-19 pandemic breast cancer consortium. Breast Cancer Res Treat 2020; 181: 487–497. doi:10.1007/s10549-020-05644-z. Accessed on 02 February 2021.
110. Yu D, Hu W, Chen L, Fu Z, Song Q, Li X. Effect of radiotherapy interruption due to COVID-19 outbreak. Radiother Oncol 2021; 155: 1–2.
111. Guckenberger M, Belka C, Bezjak A, et al. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: an ESTRO-ASTRO consensus statement. Radiother Oncol 2020; 146: 223–229.
112. Zaorsky NG, Yu JB, McBrid SM, et al. Prostate Cancer Radiation Therapy recommendations in response to COVID-19. Adv Radiat Oncol 2020; 5 (4). doi: 10.1016/j.adro.2020.03.010.
113. Kelly H and Goldberg RM. Systemic Therapy for Metastatic Colorectal Cancer: current options, current evidence. J Clin Oncol 2005; 23 (20): 4553–4560.
114. Meyerhardt JA, Mayer RJ. Systemic Therapy for colorectal cancer. N Engl J Med 2005; 352 (5): 476–487.
115. Canadian Cancer Society. Chemotherapy and other drug therapies. https://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/?region=on. Accessed on 02 February 2020.
116. National Cancer Institute. Follow-up medical care, https://www.cancer.gov/about-cancer/coping/survivorship/follow-up-care. Accessed on 02 February 2021.
117. American Cancer Society. Types of cancer treatment. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types.html. Accessed on 02 February 2020.
118. Ueda M, Martins R, Hendrie PC, et al. Managing cancer care during the COVID-19 pandemic: agility and collaboration toward a common goal. J Natl Compr Cancer Network 2020; 18 (4): 1–369.
119. Saavedra C, Esteban J, Sanz L, Soria A. Impact of Covid-19 in cancer patients treated with immunotherapy: a review. Clin Toxicol 2020; 10 (5): 1–4.
120. Ramaswamy A, Nayak L, Roy Moulik N, et al. COVID-19 in cancer patients on active systemic therapy – Outcomes from LMIC scenario with an emphasis on need for active treatment. Cancer Med 2020; 9 (23): 8747–8753.
121. Lee LY, Cazier J, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020; 395 (10241): 1919–1926.
122. Power R, O'Donohoe C, Enright C, et al. Analysis of systemic therapy delivery for gastrointestinal cancer patients during the COVID-19 pandemic. J Clin Oncol 2020; 38 (29_suppl): 301.
123. Saklani A, Pandey D, Patel S. RAPIDO protocol: a promising approach for high-risk locally advanced rectal cancers. Lancet Oncol 2021; 22 (1): 2–3.
124. Greenfield DM, Absolom K, Eiser C, et al. Follow-up care for cancer survivors: the views of clinicians. Br J Cancer 2009; 101 (4): 568–574.
125. Ratnasekera N, Perera I, Kandapolaarachchige P, Surendra G, Dantanarayana A. Supportive care for oral cancer survivors in COVID-19 lockdown. Psychooncology 2020; 29 (9): 1409–1411.
126. Lewis RA, Neal RD, Hendry M, et al. Patients' and health care professionals' views of cancer follow-up: systematic review. Br J Gen Pract 2009; 59: 533–540.
127. ESMO. European Society for Medical Oncology. Cancer patient management during the COVID-19 pandemic. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic. Accessed on 02 February 2021.
128. de Joode K, Dumoulin DW, Engelen V, et al. Impact of the coronavirus disease 2019 pandemic on cancer treatment: the patients' perspective. Eur J Cancer 2020; 136: 132–139.
129. van Dorn A. COVID-19 and readjusting clinical trials. Lancet 2020; 396 (10250): 523–524.
130. Tolaney SM, Lydon CA, Li T, et al. The impact of COVID-19 on clinical trial execution at the Dana-Farber Cancer Institute. J Natl Cancer Inst 2020; 113 (11): djaa144.
131. Moujaess E, Kourie HR, Ghosn M. Cancer patients and research during COVID-19 pandemic: a systematic review of current evidence. Crit Rev Oncol/Hematol 2020; 150: 102972.
132. Sathian B, Asim M, Banerjee I, et al. Impact of COVID-19 on clinical trials and clinical research: a systematic review. Nepal J Epidemiol 2020; 10 (3): 878–887.
133. Upadhaya S, Yu JX, Oliva C, Hooton M, Hodge J, Hubbard-Lucey VM. Impact of COVID-19 on oncology clinical trials. Nat Rev Drug Discovery 2020; 19 (6): 376–377.
134. Marcum M, Kurtzweil N, Vollmer C, et al. COVID-19 pandemic and impact on cancer clinical trials: an academic medical center perspective. Cancer Med 2020; 9 (17): 6141–6146.
135. Harris AL. COVID-19 and cancer research. Br J Cancer 2020; 123 (5): 689–690.
136. Bailey C, Black JRM, Swanton C. Cancer research: the Lessons to Learn from COVID-19. Cancer Discovery 2020; 10 (9): 1263–1266.
137. Auletta JJ, Adamson PC, Agin JE, et al. Pediatric cancer research: surviving COVID-19. Pediatr Blood Cancer 2020; 67 (9): e28435.
138. Medidata. COVID-19 and clinical trials: the Medidata perspective. Release 6.0. https://www.medidata.com/wp-content/uploads/2020/06/COVID19-Response6.0_Clinical-Trials_2020615_v4.pdf. doi: 10.1158/2159-8290.CD-20-0823. Accessed on 30 January 2021.