Cancer in the context of COVID-19: Summary of emerging evidence (7)

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The CRI presents a selection of emerging research articles and clinical practice guidelines related to cancer and COVID-19, with a summary of their key findings/recommendations (links to the articles are embedded as hyperlinks in the titles). This is the seventh of our weekly compilation, which we plan to update and disseminate as the pandemic evolves globally and nationally.

This week, we highlight latest research related to management of breast cancer patients and older cancer patients during COVID-19,the impact of COVID-19 on cancer diagnoses and regulatory agency recommendations for ongoing cancer trials, some of which has been shared in the past week via the **CRI Twitter page (@UctCri)**. We hope that insights from these pieces of evidence will help guide how we rethink cancer prevention, treatment and care in the context of the ongoing pandemic, in view of its unprecedented implications for patients, healthcare providers and the community in general. We are keen to include research and guidelines from African settings and will profile these as they become available. Previous weeks' editions can be found on the **CRI website**.

Dietz et al (on behalf of the COVID-19 pandemic breast cancer consortium) Recommendations for prioritisation, treatment, and triage of breast cancer patients during the COVID-19 pandemic. Breast Cancer Research and Treatment, 2020 Apr 16. https://doi.org/10.1007/s10549-020-05644-z.

Country context: Global

The paper draws from the experiences of experts from multiple cancer care organisations to categorise breast cancer patients into priority levels (A, B, C) for urgency of care across all specialties. In addition, it provides treatment recommendations for each of these patient scenarios:

Priority A category: Priority A patients have a condition that is immediately life threatening, clinically unstable, or completely intolerable and for whom even a short delay would significantly alter the patient's prognosis. Assuming efficacious treatment, these patients are given top priority even if resources become scarce, requiring urgent treatment for preservation of life or control of progressing disease or symptomatic relief.

Priority B category: Patients in the Priority B category are patients who do not have immediately life-threatening conditions but for whom treatment or services should not be indefinitely delayed until the end of the pandemic. Most BC patients will fall under Priority B. If conditions in a geographic location only allow for Priority A patients to receive treatment, then treatment for Priority B patients can be delayed for a defined period of time during the

pandemic. A short delay (e.g. 6–12 weeks) would not impact overall outcome for these patients. Longer delays could impact outcomes in some Priority B patients and triage may become necessary to justify which patients should undergo treatment versus further delay. Patients within the Priority B category will be sub-stratified as B1 (higher priority), B2 (mid-level priority), and B3 (lower priority) as defined by each BC subspecialty.

Priority C category: Patients in Priority C category are patients for whom certain treatment or services can be indefinitely deferred until the pandemic is over without adversely impacting outcomes.

Treatment recommendations for each of the priority categories are summarised in the table below:

Priority	Patient description	COVID-19 treatment considerations
Priority A		
A	Patients with oncologic emergencies (e.g. febrile neutropenia, hypercalcemia, intolerable pain, symptomatic pleural effusions or brain metastases, etc.)	Initiate necessary management
Priority B		
B1	Patients with inflammatory BC	Neoadjuvant chemotherapy
B1	Patients with TNBC or HER2 + BC	Neo/adjuvant chemotherapy (Neoadjuvant for ≥ T2 or N1)
B1	Patients with mBC for whom therapy is likely to improve outcomes	Initiate chemotherapy, endocrine, or targeted therapy
B1	Patients who already started neo/adjuvant chemotherapy	Continue therapy until complete (if neoadjuvant and responding, can extend treatment if necessary to defer surgery further)
B1	Patients progressing on neoadjuvant therapy	Refer to surgery or change systemic therapy
B1	Patients on oral adjuvant endocrine therapy	Continue therapy
B1	Premenopausal patients with ER + BC receiving LHRH agonists (adjuvant or metastatic)	- If on aromatase inhibitor, continue LHRH agonist and consider long acting 3 month dosing or home administration - If on tamoxifen, consider deferring LHRH agonist
B1	Patients with clinical anatomic Stage 1 or 2 ER + /HER2- BCs	Neoadjuvant endocrine therapy for 6 to 12 months to defer surgery (may consider gene expression assay on core biopsy)
B2	Patients receiving treatment for Stage 1 HER2 + breast	Ado-trastuzumab emtansine may be substituted for paclitaxel/ trastuzumab
B3	Patients with ER + DCIS	Consider neoadjuvant endocrine therapy to defer surgery

Priority	Patient description	COVID-19 treatment considerations
B3	Patients with mBC for whom therapy is unlikely to improve outcomes	Consider deferring chemotherapy, endocrine, or targeted therapy
B3	Patients with HER2 + mBC beyond 2 years of maintenance antibody therapy (trastuzumab, pertuzumab) with minimal disease burden	Consider stopping antibody therapy with monitoring for progression every 3–6 months
B3	Patients with HER2 + BC receiving adjuvant antibody treatment	Consider curtailing antibody treatment after 7 months instead of 12 months
Priority C		
C	Patients receiving zoledronic acid, denosumab	Discontinue bone antiresorptive therapy unless for hypercalcemia
C	Patients with stable mBC	Interval for routine follow-up restaging studies can be delayed
C	Patients with lower risk imaging findings needing follow-up (e.g., small pulmonary nodules)	Interval follow-up can be delayed
C	Patients who are candidates for prevention measures (e.g. family history, LCIS or ADH, BRCA1/2 +)	Consider endocrine therapy (as appropriate), delay surgery and screening imaging
C	Patients in long-term follow-up for early BC	Defer routine in-person visit
C	Patients on aromatase inhibitors	Defer bone density testing (baseline and follow-up)

BC breast cancer, TNBC triple negative breast cancer, mBC metastatic BC, LHRH luteinising hormone releasing hormone, ER estrogen receptor, HER2 human epidermal growth factor receptor 2, DCIS ductal carcinoma in situ, LCIS lobular carcinoma in situ, ADH atypical ductal hyperplasia

Mourey et al. Taking care of older patients with cancer in the context of COVID-19 pandemic.Lancet Oncology.https://doi.org/10.1016/S1470-2045(20)30229-1

Country context: France

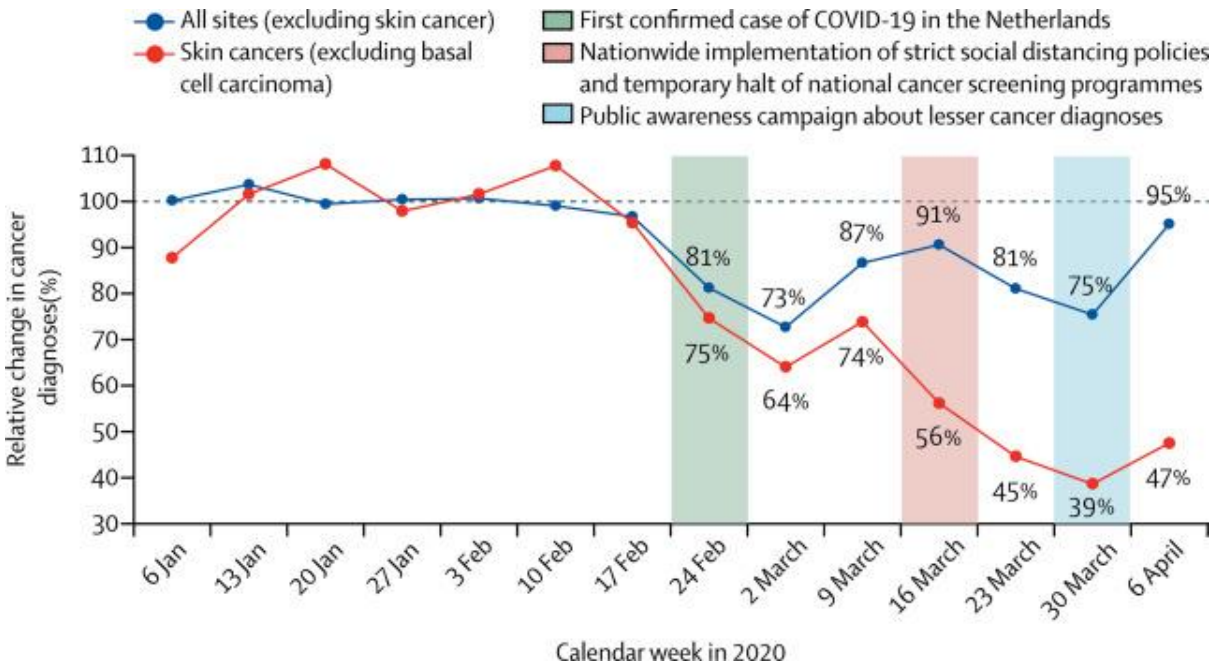
This correspondence outlines some approaches to caring for older patients with cancer during the COVID-19 pandemic. It recommends the following:

- In light of the potential for patients with cancer to be infected with SARS-CoV-2 during this pandemic, treatment decision making should take into account cancer type, disease extent, prognosis, and treatment opportunities irrespective of a patient's age, but acknowledge the excess risks associated with viral infection in older patients.
- Evaluation of life expectancy should be part of treatment decision making.
- As much as possible, alternatives to standard therapy that have few side-effects on the immune system (eg, endocrine therapy *vs* chemotherapy) should be favoured, and are preferred to no treatment, which might lead ultimately, long after the epidemic, to excess cancer-related deaths.
- Barrier measures and confinement, supportive care, and adjustment of treatment schedules (eg, increased intervals between treatments, dose reductions, and alternative radiotherapy fractionation) should be widely used, as in younger patients when appropriate.

Dinmohamed et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands Lancet Oncology. https://doi.org/10.1016/S1470-2045(20)30265-5

Country context: The Netherlands

This paper uses data from the nationwide Netherlands Cancer Registry in the period between February and April 2020 (which are based on initial case ascertainment through pathological cancer notifications from the Nationwide Network of Histopathology and Cytopathology) to show that there has been a substantial decrease in cancer diagnoses when compared with the period before the COVID-19 outbreak. The main results are presented in the chart below:



Jones et al. Impact of the COVID-19 pandemic on the symptomatic diagnosis of cancer: the view from primary care. https://doi.org/10.1016/S1470-2045(20)30242-4

Country context: UK

In this commentary, the authors describe how the entire landscape of cancer management in primary care, from case identification to the management of people living with and beyond cancer, is evolving rapidly in the face of the COVID-19 pandemic. For instance, they narrate how the UK national cancer screening programme, which accounts for approximately 5% of all cancer diagnoses each year, has been suspended. The paper shares some approaches to dealing with such challenges, including behavioural interventions to encourage the timely symptomatic diagnosis of cancer.

Talha Khan Burki. Cancer guidelines during the COVID-19 pandemic. Lancet Oncology. https://doi.org/10.1016/S1470-2045(20)30217-5

Country context: Global

This news article briefly outlines how oncology societies and national authorities have been quick to issue guidelines on cancer care during the pandemic. It highlights some key recommendations of the featured guidelines, including those of the European Society for Medical Oncology (ESMO), National Health Service (NHS) and American Society of Clinical Oncology (ASCO).

de Paula et al. Recommendations from national regulatory agencies for ongoing cancer trials during the COVID-19 pandemic. Lancet Oncology. https://doi.org/10.1016/S1470-2045(20)30226-6.

Country Context: Global

This article presents a summary of guidance for cancer clinical trial sponsors and study sites to ensure the safety of trial participants while maintaining compliance with Good Clinical Practice and minimising risks to study integrity. The guidelines are highlighted below:

Food and Drug Administration (FDA), USA. April 2, 2020

- Sponsors should make a list of contingency measures and record participants who are affected by the study's interruption because of COVID-19 in a specific study document or section of the study
- Establish procedures to describe approaches to protect study participants and manage study conduct during a possible disruption to the study as a result of COVID-19 control measures at study sites
- Consider optimising use of central and remote monitoring programmes to maintain supervision of clinical sites if needed
- The future of ongoing studies should be decided by consultation with sponsors, investigators, and institutional review boards (IRBs) or independent ethics committees (IECs)
- Alternative safety assessments should be implemented if needed (eg, telephone medical review or virtual visit)
- Consultation with the appropriate review division is recommended regarding protocol modifications for the collection of efficacy endpoints, including, for example, virtual assessments and assessment delays
- Additional safety monitoring (including potential withdrawal of treatment) might be needed when a patient's access to the investigational medicinal product (IMP) or study site is lost
- Changes implemented in new or existing processes will vary according to the protocol and the local situation
- Changes to a protocol are generally not implemented before review and approval by the IRB or IEC and, in some cases, by the FDA
- Prioritise patients' safety
- Inform patients about changes to the study that might affect them

Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Colombia. March 17, 2020

- When doing risk assessments, prioritise the most important aspects of the protocol and ascertain how these will be done
- Periodically assess patients' ongoing participation in the study by weighing up risks and benefits
- Consider remote follow-up visits (and monitoring) or visit delays, when visits to the study centre are not absolutely necessary

- Sponsors or clinical research organisations should provide safe transport and protection to minimise the risk of infection for study participants when attendance at the study centre is required
- Recruitment to continue according to the specific measures and restrictions of local government

Norwegian Medicines Agency (NoMA), Norway. March 19, 2020

- Changes and new safety measures can be taken as soon as possible, even before NoMA approval
- Source data verification, when necessary, can be done remotely but should resume on sites once the situation returns to normal
- Take precautions about infection control
- Telemedicine use is necessary, when medically justifiable
- Study drugs can be delivered to patients but must be received directly by the patient themselves (i.e., not sent by post), and drugs must not be sent directly by the sponsor
- When necessary, study-related assessments can be done by non-study personnel and at different sites, if considered acceptable by the PI, patient, and trial team

Medicines and Healthcare Products Regulatory Agency (MHRA), UK. March 24, 2020)

- Teleconferences and videoconferences are encouraged to maintain trial oversight; remote monitoring is acceptable, assuming patient confidentiality can be ensured
- Avoid extra burden on clinical staff because of increased pressure
- Inform MHRA if there is a direct participant safety issue or drug supply issue in halted trials
- Amendment must be sought if changes are made to protect participants' safety when restarting a halted trial
- Reduction in participant visits because of COVID-19 will not need a substantial protocol amendment, but appropriate documentation of rationale and risk assessment must be done
- Telephone calls are acceptable to replace visits in person, when possible
- Delivery of IMP to a patient's home is acceptable without needing an amendment notification; confirmation by telephone call can be used instead of a delivery signature

Bulgarian Drug Agency (BDA), Bulgaria. March 18, 2020

- Sponsors and principal investigators (PIs) should collaborate to decide which study visits can be done remotely (eg, by telephone) and which can be delayed or cancelled, applying a risk-based approach (including a study amendment) when necessary
- Patients can be transferred to another study centre should this be necessary to provide continuous treatment
- New trials shall not begin
- The sponsor should consider closing a study centre, and how to do so safely, if it is not possible for the centre to continue their involvement, and the BDA should be informed about how this is done

- A risk assessment should be undertaken to ascertain if patients' recruitment should be suspended

State Institute for Drug Control, Czech Republic. March 20, 2020

- Always ascertain the infection and quarantine status of the participant and their household by telephone
- Exchange patient's physical follow-up visits with telephone calls when possible, and provide patients with appropriate personal protective equipment when study visits are required
- Study drugs can be couriered to patients from the trial site, or to a pre-agreed family member, and delivery should be confirmed by telephone and recorded
- Laboratory tests can be done at the patient's home, or booked in advance if on-site.

European Medicines Agency, Europe. March 27, 2020

- Specific national legislation and guidance must be taken into account
- Sponsors should consider a risk assessment to modify ongoing trials and consider measures such as converting physical visits to remote visits, postponing or cancelling visits, halting or suspending recruitment to trials, and closing trial sites
- Consider transfer of participants to alternative study sites, and doing study assessments (eg, laboratory tests and imaging) at other centres, when necessary, to ensure participant safety
- Submit a substantial amendment application if changes are likely to affect the safety or wellbeing of the participants or the scientific value of the trial
- Risk assessments by the sponsor should be ongoing and documented
- Implement measures that prioritise patient's safety and data validity
- When consent needs to be reobtained from patients for studies, visits to centres solely for documentation of consent should be avoided; consent can be obtained using other means (eg, verbally over the telephone or by video-call with email confirmation)

Sites:

American Cancer Society. COVID-19 and cancer resources.

Country context: US

This page provides a compilation of of COVID-19 related resources for oncology care providers and patients, including research articles, news articles and other resources.

Children's Oncology Group: COVID-19 information for survivors of childhood, adolescent, and young adult cancers.

Country context: Global

This page provides free COVID-19 related information for survivors of childhood, adolescent, and young adult cancers.