Practical considerations for the management of cancer patients during the COVID19 pandemic

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Endorsed by the Medical Oncology Group of Australia (MOGA)

on19.3.2020 and the Clinical Oncology Society of Australia (COSA)

on 7.4.20

Updated 20 April 2020 with additions highlighted

Introduction

The pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hereafter referred to as COVID19, will have far-reaching impacts across society and cause a substantial disruption to health and health care systems globally for a prolonged period. Despite planning, the rapidly evolving and uncertain environment leaves patients and health care workers in

uncharted waters. Public health measures and information for the general community is constantly updated across all media. However, detailed information for patients with specific conditions and for their treating clinicians is not readily available. Across Australia and New Zealand, clinical craft groups have responded variably, with those directly impacted, such as intensive care, rapidly producing expert-led consensus guidelines[1]. These 'living' documents provide broad principles and outline key issues, forming a framework to facilitate harmonization of the response to COVID19 across jurisdictions and allowing rapid updating and dissemination of craft specific information. The paper "Managing haemato-oncology patients during the COVID19 pandemic: Interim guidance"[2], authored by a group of expert hematologists predominantly from New Zealand, outlines a high level yet practical framework for decision-making for this cohort of patients and their clinicians. Focusing on hematological malignancies, it describes a three-step approach to guide service management according to pandemic stage. Cancer Care Ontario has also published guidelines for Ontario Health services, Canada during the current pandemic[3], whilst The American Society for Clinical Oncology (ASCO) has an active webpage for COVID19 Clinical Oncology Frequently Asked Questions (FAQs).[4] Publications are rapidly appearing reinforcing these general principles.[5]

The impact of COVID19 on cancer patients has broad ramifications for both individuals and services, affecting diagnostic tests, monitoring, treatment and follow-up. Multidisciplinary care, lying at the heart of the cancer patient's journey, will inevitably be affected at multiple points due to the reduced available of fundamental services such as diagnostic tests, cancer surgery (with predicted hospital overloaded with COVID19 patients) and shortage of expert staff. Preliminary data from China reports that the case fatality rate (CFR) for cancer patients diagnosed with COVID19 is approximately double that for all patients (5.6% vs 2.3%).[6,7]

To produce a detailed document of practical, specific and granular advice for guide cancer clinicians in this COVID19 crisis, we urgently convened a diverse group of medical oncology experts, covering public and private settings, medical, nursing and allied health, across all States and Territories of Australia. It was recognized that there is, obviously, little evidenced based literature in this field, but the process of broad engagement and expert peer review has been a rapid yet robust substitute,

born of necessity. The group first endorsed the recommendations by Weinkove et al[2] and did not seek to revisit issues covered in that paper. Rather, this set of guidelines focuses on the

many areas in medical oncology affected by COVID19 that have not yet been the subject of expert advice; such aspects as communication and the psychosocial impact of COVID19 on cancer patients, as well as tumour specific considerations that will now rapidly be thrust onto those delivering or administrating cancer clinical practice. The broad guiding principles of this consensus group are summarized in Table 1.

Table 1: Broad principles for cancer patients and COVID19

Risk

- Define the efficacy of treatment in each particular patient and weigh against risk of COVID19 as well as usual risks; make appropriate adjustments not only for new patients but patients currently on therapy.
- Use of a nomogram to assess the risk of chemotherapy toxicity is encouraged e.g. https://www.evidencio.com/models/show/520
- Discuss and document likely prognosis, in order that patients are assessed appropriately for care if they contract COVID19. Be aware that their usual clinician may be off sick or allocated to other work so clear documentation in notes and letters (beyond a single institution's record) are important
- Employ validated tools particularly in the elderly to assess risk of toxicity and benefit (unrelated to COVID19) to inform conversation that then includes COVID19 risks

<u>Prioritising resources and choosing therapy</u>

- Focus resources on patients having treatment with curative intent
- Consider treatment breaks for patients with low volume and/or stable metastatic disease
- Consider mono-agent therapy and upfront dose reduction in the frail and the elderly (or a treatment break)
- Use alternate SACT regimens with less visits.
- Reduce the use of combination immunotherapy agents that although can have survival advantages have a much higher risk of toxicity requiring hospital admission, including pneumonitis
- Use oral anticancer agents where possible but weigh any different toxicities with convenience and efficacy.
- Use oral pre-medications including anti-emetics, steroids, antihistamines that patient can take prior to entering the CDU in order to shorten in-centre time.
- Minimise face to face visits including monitoring, treatment administration and staging, with shift to telehealth and community-based care where available.
- Defer non-essential investigations and routine follow-up

<u>Patient Support during treatment</u>

- Add growth factor support with G-CSF/pegG-CSF to reduce risk of neutropenia
- If available, use a home-based service for port flushes, chemotherapy disconnections and other suitable procedures
- Use community practices for blood collection, imaging and support services rather than in-hospital services; only order essential tests
- Provide clear recommendations for each patient on how to act when having symptoms such as

fever or dyspnea

- Deploy proven telehealth initiatives and new models of care to manage oncology patients with fever
- Advise patients for timely influenza vaccination
- Utilise telehealth to support patients via local support staff and national cancer and non-cancer helplines
- Extra vigilance should be used to screen for the presence of anxiety and/or depression symptoms especially in those with a history of mental health concerns.

Supporting staff

- Maintain the health of oncology health professionals and have clear pathways for administering cancer care if significant numbers of expert staff are ill e.g. chemotherapy trained nurses in a cancer day unit
- Prioritize redeployment of staff from non-time essential cancer services such as familial cancer clinics and survivorship clinics
- Staff should be monitored for signs of fatigue, distress and depression and workload should be carefully monitored

Government and regulatory bodies

- Free up access to SACT where benefit is proven but reimbursement or registration not is currently available, recognizing that traditional treatment pathways may put patients at increased risk
- Coordinate patient and family support services, ensuring equity of access and engagement of all stakeholders
- Remove restrictions on in-person requirements such as signing prescriptions; limitations on medication supply and delivery

SACT: Systemic anticancer therapy; G-CSF: granulocyte colony stimulating factor; pegG-CSF: pegylated-granulocyte colony stimulating factor; CDU: Cancer Day Unit

During this pandemic, we need to consider how best to focus our delivery of cancer to individual patients as well as systems. It is incumbent on us to ensure that we do not, through ignorance or slow pace of adjustment, expose our patients to a greater risk of severe COVID19 infection and death, by failing to adapt our usual treatment paradigms to account for the impact of this new and lethal disease. As a risk for competing cause of rapid death, COVID19 has jolted us to shift away from our familiar risk-benefit paradigms into unknown territory. This is especially pertinent to patients perceiving palliative systemic anti-cancer therapies (SACT), as well as those who may already be cured but undertake adjuvant therapy for potential benefits that are real but sometimes small and not yet able to be predicted at an individual level. Beyond the pandemic, there will be a need to manage patients who may have missed out on some aspects of cancer

treatment and/or have a multitude of other consequences that will impact on them as a person living with cancer. Like other guidelines, the information in this paper can form the start of a living document, focusing on specific issues relating to COVID19 and patients with cancer (outlined in Table 2), as new information and learnings come to hand.

Table 2: Specific issues to consider in patients with solid tumour malignancies

- Most chemotherapy agents and many other SACT for solid tumours can cause neutropenia. Concerns have traditionally related to bacterial infection, however lymphopenia is also common, particularly with certain agents such as temozolamide.
- Corticosteroids, a risk factor for COVID19, are widely used, often in high doses and repeated courses, for indications ranging from anti-emesis to treatment of immunotherapy side effects to treatment of disease related symptoms such as pain, cord compression or brain metastases.
- Many treatments cause mucositis, with breach of mucous membranes likely a risk factor for COVID19 infection and exposure to spreading of virus by aerosol[8].
- Pneumonitis is a recognised and not uncommon toxicity associated with some SACT, particularly IO. Distinguishing this from infective pneumonic processes may be clinically difficult.
- Treatment of inflammatory pneumonitis with high dose steroids and immunosuppression appears to be contraindicated for COVID19 – associated ARDS, as it might exacerbate associated lung injury[9], so care with diagnosis is critical.
- Many cancer patients are current or ex-smokers with underlying lung pathology.
- Cancers have varying underlying prognoses, many that have changed with recent therapeutic advances that may not be familiar to non-oncology clinicians.

SACT: systemic anti-cancer therapies; immuno-oncology agents (IO); ARDS: Acute Respiratory Distress Syndrome

Epidemiology of cancer and COVID -19

In 2018, there were an estimated 18 million cancer cases around the world (population approximately 7.6 billion), comprising 9.5 million men and 8.5 million women. Lung and breast cancers were the most common on a global scale, each contributing around 12% of the total number of new cases. Globally, colorectal cancer was the third most common.[10] Based on 2015 data, there are an estimated 1.1 million people currently living with cancer in Australia, representing at least 4.6% of the total population[11]. Whilst the increase in cancer rates over the past decade is small, population expansion and ageing, as well as significant improvements in treatment, has resulted in a significant increase both in newly diagnosed patients and those living with cancer.

Cancer remains the leading cause of death in Australia, despite significant improvements in 5-year survival. In 2018 there were over 140 000 new cases of cancer and just under 50 000 deaths from cancer in Australia.[11] Approximately 50% of patients with cancer in Australia are over 65 years of age. This is against a backdrop of 4 million Australians in this age bracket, a factor that imparts a higher risk of severe and deadly COVID19[12].

In addition to their risk in the community as an immunocompromised cohort, cancer patients have an increased risk of nosocomial transmission while in hospital settings[13], although no data specific to COVID19 is available yet. Such outbreaks may lead to worse outcomes and prolonged infectiousness in immunosuppressed patients.[14]

Figure 1 shows the rise of cases globally after China gained control of their epidemic.

For every diagnosed case of COVID19, it is estimated there may be many undiagnosed cases. It was estimated that only 9.2% of cases were reported in China.[15]

Testing for COVID19 is currently restricted in many countries due to shortage of test kits, so disease is likely underestimated and undetected transmission may occur in hospital settings frequented by oncology patients, such as the emergency department, ICU, oncology ward or day chemotherapy units. Infection may be transmitted by staff or patients to vulnerable or immunosuppressed oncology patients. Cancer is a risk factor for more severe outcomes of COVID19 and COVID19 has caused nosocomial infections in admitted patients.[16] Bacterial or viral co-infection is also a risk for immunosuppressed patients, especially as the influenza season approaches.[17]

COVID19 is an enveloped virus, which can be spread by droplet, contact and airborne routes. Studies have shown extensive contamination in a room of a patient with COVID19, including on Personal Protective Equipment (PPE) worn by a health worker.[18] It can persist on surfaces for 4-6 days, but is inactivated by chlorine or alcohol based disinfectants[19], so cleaning of surfaces in hospital wards and chemotherapy units must be meticulous and frequent. Practical tips for infection control in cancer (chemotherapy) day units (CDU) and wards include fever screening for staff or visitors entering the area, spatial separation of patients, frequent disinfection of high-touch areas and surfaces, mask wearing by febrile patients, and clinical triage

protocols for febrile oncology patients to enable isolation, testing and management. Testing with a multiplex viral and bacterial PCR may help if another cause of infection is identified. Co-infection with COVID19 and other pathogens can occur but is rare.[17]

Febrile cancer patients

As community transmission of SARS COV-2 increases, it is realistic to expect that patients receiving SACTs will be disproportionately part of the cohort who present with fever due to COVID19, needing to be distinguished from febrile neutropenia and other 'usual' infections. Patients with cancer may have fever for many other reasons, including large tumour burden or as a reaction to therapy, e.g. the night after gemcitabine administration. These may be overlooked with the current emphasis on fever and COVID19, particularly if experienced staff are in short supply.

For febrile patients receiving SACT, it is imperative that standard timely management is undertaken in addition to consideration of COVID19 infection. It is important to avoid sending potentially immunocompromised patients to overloaded emergency departments and COVID19 fever clinics. Newer models of care should be encouraged, particularly nurse-led Symptoms Urgent Review Clinics (SURC), initially piloted at Western Hospital in Victoria and then more widely implemented in Victoria's metropolitan public hospitals and some public and private regional clinics. The SURC model was developed to address identified gaps within CDU to support patients experiencing treatment related toxicities. There are a variety of different models of patient assessment using clinic visits and telehealth, based on the 24-Hour Triage Tool from the United Kingdom Oncology Nursing Society, adapted for use in Australia.[20] Further tools for establishing SURC clinics are detailed for both a paediatric and adult service.[21,22]

The SURC model could be readily and rapidly be adapted to triage cancer patients with fever. We propose additional questions to the telephone triage toolkit in the context of COVID19, covering cough, coryzal symptoms, dyspnoea, underlying lung disease, recent treatment, travel and contact history. Cancer patients deemed to be at high risk of COVID19 could be triaged to either to a

general COVID19 clinic or, appropriate in a larger centre, a specialised 'high risk' COVID19 fever clinic for immunocompromised and frail patients, which could include other high-risk cohorts such as transplant patients. This would allow for enhanced PPE for staff e.g. consider respirators rather than masks.[23] It is important not to delay antibiotics for neutropenic patients whilst they are being assessed for COVID19, particular giving the time lag to COVID19 testing results.

Patients screened as having a low risk of COVID19 could be triaged as per usual pathway for oncology patients, except where this involves attending the Emergency Department for assessment. In this case a separate pathway allowing assessment by oncology trained staff in a dedicated area able to be fully disinfected could be rapidly established.

Clinical Trials and Research

Evidence based care underpins optimal medical oncology practice. It should be recognised that there has been a major shift over the past 5-10 years, with clinical trials in oncology now part of standard of care, often very early in the treatment pathway and offering access to treatments that can significantly improve outcomes. The impact of COVID19 on cancer trials is potentially extensive, including impacting resources, posing governance, and ethics dilemmas and affecting the logistics of trial conduct and timelines.[24] Anecdotally some centres have ceased all recruitment to all clinical trials including simple registrational trials. If possible, clinical trials should continue to be supported, unless there is a specific issue relating to COVID19 with a particular protocol, with pragmatic adjustments to minimise risk to patients whilst maintaining good clinical practice (GCP), as outlined in Table 3. Many centres have adopted such approaches and are pragmatically using telehealth consultations where safe and appropriate to do so. Guidelines from government, industry and academic sponsors are rapidly being produced and these are likely to be modified depending on the impact of the pandemic.[25]

Table 3: Recommendations for cancer trials during the pandemic

Activity	Expert group suggestions

Study selection and prioritisation	• For strained resources, rationalise new studies and place existing poorly recruiting or 'less impactful' studies on hold • Preferentially select/continue studies where: - positive outcomes are anticipated e.g. 'breakthrough' targeted drugs -schedule has less visits, allows local rather than central bloods and imaging; amenable to telehealth consultations -immunosuppression is less, including mandated use of high doses of steroids - protocols should allow growth factor support -limited to ECOG 0 or 1 • Take into account the particular risks of COVID19 in the trial population e.g. lung cancer
Site Selection and Site initiation	• Conduct remotely as far as possible; minimising travel and human-to-human contact. Liaise with CRA and study sponsor. • Postpone new trial startups where possible
Governance and Ethics	• Continue procedures as per local policy; consideration needs to be given to detailing additional risks of COVID19 in patient information sheets. This would require rapid approval through Ethics/Governance committees.
Patient screening and selection	• Take into account the potential benefit of study participation, the incremental risk of the study intervention and the risk of COVID19.
Patient management on trial	• Closer monitoring of patients at high risk of COVID19 – preferably by remote contact. These can occur more frequently than the study visit schedule. • Document all contacts and contact attempts. • Safety of patients and staff is of utmost priority
Monitoring visits	• All onsite monitoring visits should be replaced by remote visits in accordance with the study visit schema.
Protocol violations	• The safety of the patient takes precedence. • If patients run out of Investigational product (IP) due to missed on-site visits they should be captured as a temporary withhold of IP • Keep in contact with patients for continued engagement and safety reporting. • If protocol violations are made for safety reasons for example (reduced imaging frequency or no central blood samples taken), record this in the patient file. • All significant safety issues, urgent measures and serious breaches impacting patient safety and rights should be reported. • Non-serious breaches should be recorded but it is likely that allowance will be made for a post-COVID19 deviation report for many trials.

CRA: Clinical Research Associate

Older patients

The median age of patients in Australia at time of initial cancer diagnosis cancer is 67.8 years; 44% of patients are over 70 at diagnosis; 30% are over 75; 19% are over 80 and 9.6% are older than 85.[26] The higher CFR for cancer patients reported from the Chinese COVID19 outbreak may be confounded by the fact that cancer is commoner in older adults, nevertheless, this highlights the need for special care for elderly patients.

The management of older adults with cancer during the COVID19 pandemic remains guided by the general principles of geriatric oncology, however more rigorous and systematic application of screening and assessment tools is strongly recommended. Both American Society of Clinical Oncology (ASCO) and the National Cancer Centre Network (NCCN) guidelines recommend that all older adults being considered for cancer treatment should undergo some form of geriatric assessment[27-29], which helps to estimate life expectancy, discover vulnerabilities that may not be noted with routine questioning and guide supportive care strategies. Evidence supports that at a minimum, function; comorbidity; falls; depression; cognition and nutrition should be assessed.[30]

As a full geriatric assessment takes considerable time, screening tools such as the G8 https://www.siog.org/files/public/g8_english_0.pdf. or VES13[31] can be used to triage the need for a more comprehensive assessment with guided interventions.[32] Adequate assessment informs decision making in many ways, such as by considering competing cause of death due to age and comorbidities for decisions about adjuvant therapy or determining "what matters most" to patients treated with palliative intent[33]. Toxicity of chemotherapy can be predicted using calculators such as the Hurria prediction tool[34] that include geriatric variables.[35] If you work in a group, it would be sensible to choose the same tools to become familiar and share experience.

Indigenous and regional / remote communities

Aboriginal and Torres Strait Islander people represent 3.3% of total Australian population and represent issues common to indigenous populations around the world. Around 19% of indigenous Australians live in remote or very remote areas, compared to 1.5% of non-indigenous people. Almost half of the population living in very remote areas are indigenous.[36] Safety and effectiveness of cancer care delivery in regional Australia during the current COVID19 crisis warrants special mention due to the health and social circumstances of Indigenous Australians and the well described disparities in their cancer outcomes.[37 38]

In breast cancer, indigenous cancer patients have been shown to present with a more advanced cancer stage and have more comorbidities.[39,40] Diabetes (30%), cardiovascular (23%) and respiratory diseases (14%) are the most prevalent comorbidities.[41] Older patients hav higher levels of comorbidities ($p< 0.001$), and those with the greatest comorbidity burden are more likely to be diagnosed with advanced stage cancer than those with less or no comorbidities. Any-cause survival as well as cancer-specific survival is lower in those with comorbidities.[39] Moreover, daily smoking rates in adults aged 18 and above is 3 fold higher in indigenous Australians.[42]

As well as the adverse impact of age, reports from China highlight that the CFR was elevated among those with pre-existing comorbid conditions—10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer.[43] The male sex predisposition of severe COVID19 pneumonia might be associated with the much higher smoking rate in men compared to in women in China; it was concluded that smoking itself did not appear a risk factor.[44]

Due to these factors, it could reasonably be speculated that indigenous people with cancer and / or taking immunosuppressive therapy would be at a greater risk of complications, including death, from COVID19. This should now form part of the discussion with patient and family regarding the potential benefits and risks of any new or ongoing cancer treatment, ensuring the usual context of cultural appropriateness and meaning, with the support of an interpreter and indigenous liaison officer (ILO) or health practitioner involvement.

Logistics and services are particularly important considerations. The majority of Australians living in very remote areas need to travel to remote or outer regional facilities for delivery of SACT.

Due to anticipated restrictions on movement of people between the communities, some people living in very remote areas may not be able to access their cancer treatment unless they decide to stay away from their family and country for an extended period of time. Impacting on this decision may be a higher risk of COVID19 exposure in the more populated area they move to.

Quarantine measures imposed on very remote communities could result in difficulties in accessing medication in a timely manner, due to lack of local compounding / manufacturing units and reliance on long distance freight. Similarly, access to local and interstate multidisciplinary meetings could be limited. Given the small pool of cancer clinicians and support staff such as ILOs, staff illness may have a major impact. A shortage of resources including technology and technological support for telehealth, especially for very remote communities, means that implementation of telehealth is more challenging than in larger and more metropolitan services.

Although many factors relating to COVID19 are not specific to indigenous people, the pandemic is likely to exaggerate the existing gaps in cancer care, with a high chance of a poorer outcome and significant psychosocial distress. Each unit / centre needs to develop a structured and tailored business continuity plan for optimal care delivery while minimising the predisposition for severe COVID19 complications.

Oncology Telehealth

Robust literature supports the use of telehealth in the provision of consultations, supervision of oral and intravenous therapies, supervision of administration of intravenous therapies and educational activities[45]. Recent evidence has also emerged for performing various aspects of clinical trials.[46,47]

Telehealth provides an ideal opportunity to contribute to social distancing measures by keeping patients away from busy clinical settings in the setting of epidemics and pandemics. The Australian Government rapidly recognized this potential and incorporated telehealth into their COVID19 control measures by revising criteria for reimbursement for telehealth consultation. The requirement for residence in a remote area was removed and eligibility was expanded to include

patients over the age of 70 or with chronic illness or immunosuppression. Initial reimbursement was less for telephone contact without video but this was quickly equalized, so as not to discriminate against those in the lower socioeconomic income bracket or with other disadvantages. Doctors can also consult from home if they are in self-isolation from confirmed COVID19 infection or exposure.

Communicating in meetings by videoconference is familiar to most oncologists but experience with patient consultations less so. A rapid uptake of the technology is required, including training and support for both users and patients. General guidelines for maintaining safety and quality for tele-oncology systems are outlined in the COSA Clinical Practice Guidelines for Teleoncology[46], including ensuring privacy and maintaining adequate documentation. Coordination between patients and practices is an important component for success in this model of care. Multi-way conversations to include interpreters and family members (particularly in lockdown circumstances) add complexity.

An example is given to illustrate this model of care: Mr Citizen is on capecitabine for metastatic colorectal cancer and is usually seen every 3 weeks in the clinic with blood results. In this situation, the administrative officer sets up the link, ensuring all results are available. By video, clinical staff confirm patient identity (particularly for phone consults) review side effects, visually examine for hand foot syndrome and rashes (photos can be sent if no video), check results and make ongoing recommendations. It is important to continue good documentation practices. This model can be applied in encounters involving many therapies. If home intravenous chemotherapy services are available, a joint consultation during the visit of the chemotherapy nurses can also enhance this model of care.

Adjustment of routine follow-up attendances

Reducing the risk of staff, patients and relatives of contracting COVID19 rests on the principle of social distancing, which includes limiting contact with healthcare facilities. It is also fundamental to protect individuals at high risk, such as cancer patients needing treatment, who

cannot avoid contact with a healthcare facility/provider due to the necessity or urgency of their condition.

Follow-up visits fulfil multiple needs for patient and clinicians: detection of recurrence; reassurance; management of ongoing toxicities; detection of second malignancies (where relevant) and survivorship care. The significant increase in the number of patients cured of or living with cancer extended periods has placed a large service demand on cancer clinics.

Co-ordination should occur with other cancer clinicians who may also be following up the patient e.g. surgeon, radiation oncologist. As the pandemic worsens, protection of patients and staff and rationalisation of services will alter the usual recommendations for follow-up. Clear communication of changes and their rationale is important. Here we provide advice on a number of common scenarios:

Patients attending for surveillance of recurrence after curative intent therapy; not on therapy or well-maintained on therapy with no symptoms and no evidence of disease at last review.

For example, patients with early colorectal cancer on a standard follow-up schedules or patient with breast cancer who is tolerating long term adjuvant hormone therapy.

Many follow-up protocols have little evidence base that early detection influences survival outcome (e.g. breast cancer); for others, standard follow-up is of proven benefit, such as for colorectal cancer. The risk of recurrence for almost all tumours decreases significantly with time. Recurrence after 3 years for many tumours is relatively uncommon (caveat: varies with tumour type) and decreases continuously with time. It is important to consider the predicted recurrence rate for each individual patient, taking into account the multiple known clinico-pathological features for their tumour. In advising the patient of appointment deferral, advice should be given regarding making contact if new symptoms concerning for recurrence occur. For patients with a high risk of recurrence but no symptoms, routine scans should not be performed unless there is proven evidence of benefit. Coordination should occur with other cancer clinicians who may also be following up the patient eg surgeon, radiation oncologist.

Recommendation:

a) without resource constraints: replace with video/telehealth consultations; delegate to nurse practitioners, experienced cancer nurses or less senior medical staff with appropriate oversight. GPs are unlikely to have capacity during much of the COVID19 emergency but could be considered in remote areas.
b) with resource constraints: for patient > 3 years since diagnosis, defer and increase intervals between appointments.

Patients with low volume, incurable metastatic disease who are stable on oral or home-based therapy and who have few symptoms

For example, a patient on imatinib for metastatic GIST, a patient receiving endocrine / hormone therapy for metastatic breast or prostate cancer or an EGFR TKI for lung cancer.

Recommendation:

a) without resource constraints: in person visits should be replaced with video/telehealth consultations. Ensure adequate medication supply.
b) with resource constraints: extend time between routine review appointments but emphasize need to contact (and provide details) if new symptoms or toxicity.

Patients with low volume metastatic disease who are having a break from therapy and whose disease is unlikely to rapidly progress off treatment

For example, a patient with low volume metastatic colon cancer on a break from chemotherapy or an asymptomatic patient with ovarian cancer with a slowly rising CA-125.

The necessity of appointments should be determined on a case by case basis and should be replaced with video/telehealth consultations where possible.

Recommendation:

a) without resource constraints: in person visits should be replaced with video/telehealth consultations and internal between subsequent visits can be extended with appropriate patient education.

b) with resource constraints: defer appointments by a 2-month interval initially (this may vary according to service and site and may change quickly). Coordinate so restaging tests are done in proximity to schedule visits so results are not missed. Emphasize need to contact (and provide details) if new symptoms or toxicity.

Patients with metastatic disease on long term therapy with stable toxicity, where disease is unlikely to rapidly progress off treatment.

For example, a patient with stage IV melanoma, non-small cell lung cancer or renal cell carcinoma receiving a single agent PD-1 inhibitor who has had a complete response or substantial partial response to treatment.

Recommendation:

a) without resource constraints: in person visits should be replaced with video/telehealth consultations and time between subsequent visits can be extended. Consideration should be given to a treatment break.
b) with resource constraints: reduce frequency of visits; institute treatment breaks.

Patients with metastatic disease where no further therapy is planned

For example, a patient with metastatic cancer has had all lines of appropriate systemic therapy and is moving to a best supportive care situation.

Recommendation:

In person visits should be replaced with video/telehealth consultations or transfer of care to a community palliative care service or GP, noting their reduced capacity also during the pandemic. Patients not yet referred to palliative care should be referred, with provision of information so this is easily accessible in the community. Care plans should be discussed. Documentation on latest status should be easily accessible to all potential care providers.

<u>Communication and psychosocial care</u>

Many patients with cancer are rightly concerned and distressed since the worldwide spread of COVID19 as evident from the increased demand on cancer hotlines and treatment centres (CL personal communication). Layered on top of a cancer diagnosis, this requires health care providers to be extra vigilant in screening for and managing psychosocial distress (Table 4). The majority of patients will benefit from an acknowledgement of the normality of increased concerns during this period of global uncertainty and in the setting of a cancer history. Specifically, the extent and speed of the COVID19 pandemic is likely to cause additional concerns for cancer patients (Table 5).

Table 4: Psychosocial considerations for care of cancer patients relating to COVID19

Concern	Current practice	Expert panel recommendations and considerations
Anxiety and depression including exacerbation of existing mental health issues	It is recommended that all patients with cancer be evaluated for symptoms of depression and anxiety at periodic and key times across the trajectory of care	Extra vigilance should be used to screen for the presence of anxiety and/or depression symptoms especially in those with a history of mental health concerns.
Screening & Assessment	Formalised routine screening and assessment for anxiety and depression in patients with cancer should be performed using validated, published measures and procedures	Multiple validated screening for distress tools are used in clinical settings. These include the Distress Thermometer[32] and the Edmonton Symptom Assessment System.[48] Consider remote administration.
Symptoms and severity	Treatment pathways are recommended based on levels of symptoms and supplementary information	People with cancer and pre-existing mental health conditions should continue with their treatment and be aware of new or worsening symptoms as the uncertainty of COVID19 may exacerbate anxiety. Consider early referral to psycho-oncology services as these resources may have limited availability.

Stepped care	As per Butow et al[49]	Psychological first aid is a proven beneficial response to trauma[50]: o Calm people & reduce distress o Make people feel safe & secure o Identify & assist with current needs o Establish human connection o Help people understand the disaster & its context o Help people identify their own strengths & abilities to cope o Assist with early screening for people needing further or specialised help o Get people through the first period of high intensity and uncertainty
Impact of Quarantine		The impact of specific stressors relating to quarantine should also be assessed including: o separation from loved ones o loss of freedom o uncertainty over disease status There is some evidence that rates of suicide, substantial anger and frustration can rise during quarantine.[51] A balance between social distancing/quarantine and connection with others is important – even if this is through telephone and internet-based contact.[52]

Table 5: Patient Concerns Specific to Cancer and COVID19

Concern	Recommendations
Patients are concerned that they may not have access to their cancer treatments due to increased demand on the health service and depleted workforce.	• Clinicians and administrators should openly communicate the constraints on the health service and expected impacts on treatment including alternatives to treatment regimes, location of treatment and follow up care.
Access to critical care services (e.g. intubation, ICU) could be limited or simply not offered due to their cancer diagnosis.	• Ensure Advanced Care Plans and Goals of Care/Treatment have been discussed and documented. • Clinicians should be aware of the need to strongly advocate for access to appropriate critical care services, especially in patients having curative or potentially curative treatment. Ensuring decision makers understand the

	individual's prognosis is important, but a truthful estimate will help prioritise in worst case scenario.
As the impacts and recommendations regarding COVID19 are rapidly evolving, patients are uncertain and anxious about how they should now be managing their life with cancer.	• Ready availability of information is key, coupled with effective and rapid communication. The provision of links to reputable online information and telephone hotlines is important (see resources table) as well as the most up to date information from State and Federal Departments of Health.
A history of cancer, regardless of stage, may make patients / survivors more vulnerable to the virus. Isolation from family / friends may be more pronounced in this group and they may self-impose even stricter measures than those mandated by heath authorities recommend in order to maintain current health. Patients may feel overwhelmed and/or exhausted by what could be perceived as yet another invisible threat to self. Elderly patients may avoid (with or without advice) children including grandchildren and other relatives	• Ensure that patients with a history of cancer follow guidelines to reduce their exposure to COVID19. Additionally, those who are finding the experience of isolation extremely trying (e.g., missing significant life events like weddings or births) might experience anger, frustration which should be normalised.
Patients may have a family or relative die from COVID19. Due to the nature of the virus, they would be unable to visit or say goodbye to their loved one. This may lead to difficulties around grief and loss.	• The use of technology to close the gap in connection with others should be explored where possible.

<u>Prioritization</u>

A number of scenarios that range from possible to probable will provoke the need to make decisions about cancer services for individuals as well as service-wide level. Planning must foreshadow that capacity of oncology units is likely to be significantly reduced due to staff infection and quarantine after exposure or for social reasons. The number of health care workers infected in Australia and New Zealand may reflect the up to 20% reported in Italy.[53] Additionally, closure of schools without alternative childcare arrangements and in the face of restricted contact with

elderly (eg grandparents or other carers) could result in healthcare workers having to remain at home. In a worst-case scenario, hospital resources including equipment for SACT administration, availability of pathology and imaging services, transport etc. is likely to be insufficient to meet demand for provision of cancer therapy.

In these severe but increasingly likely circumstances, prioritization decisions should be pro-active and should not be left to individual clinicians. Those in the front line of deciding care for severely unwell patients, including Emergency and Intensive care clinicians, have addressed this for their craft group, as we attempt to do here for cancer care providers.

First, all reasonable steps should be taken to ensure that patients on or requiring therapy continue to receive optimal care. This may require outsourcing of treatment to facilities with capacity that are outside of usual referral pathways, including private facilities. Administrators and funders should ensure that these plans are made early and are easy to activate. There should be no cost or individual discrimination for access. Other novel service delivery models should be employed particularly telehealth and SURC clinics.

Second, government funders and regulators should remove reimbursement restrictions for SACT, in particular, medicines stipulating sequencing (such as the requirement for docetaxel chemotherapy prior to use of novel anti-androgens, that persists despite good evidence for earlier use), medicines not reimbursed for rare cancers and oral medication. This could be done quickly with a list produced in consultation with oncology professionals, including specialised oncology pharmacists.

In the worst-case scenario, prioritization of treatments may become unavoidable. The ethical principles of beneficence and justice need to be carefully considered. Harmonisation with guidelines from other groups is essential to avoid conflicting opinions for individual patients at a time of critical illness, which can be very rapid with COVID19 infection.

Table 6: Factors for prioritization of cancer treatment

- The balance of risk and benefit will change depending on patient factors, therapy factors, resources and the period and extent of community transmission at the time.
- Patients on later lines of chemotherapy e.g. 3rd or 4th line (caveat: will vary by tumour type) should have current treatment reviewed[54].
- Patients with ECOG 3 or 4 derive limited benefit from chemotherapy in either the adjuvant or palliative context and therapy should be discontinued in most cases.
- Patients with ECOG 2 also derive lower benefits and use of SACT should be only be considered where there is a strong rationale in these patients.
- Patients with metastatic disease with prolonged stable disease or complete response should be considered for treatment holidays. For some tumours e.g. CRC there is evidence of no detriment with this approach.
- Patients with low likelihood of benefit from adjuvant therapy, or where adjuvant therapy has an unproven survival gain should receive lower priority for access than those with higher potential benefit.
- It should be explicitly acknowledged that there is a mortality rate for most adjuvant chemotherapies (usually quoted 0.5-4%);[55,56] there is almost certainly additional risk from COVID19 with immune suppression.

CRC: colorectal cancer

Table 7: Priorities for continued therapy under significant resource constraints

- Patients on palliative treatment can miss at least 1 cycle of their therapy without significant consequences in most circumstances.
- Patients on combination intravenous and oral therapy can have their regimen rationalized to just the oral therapy in many circumstances e.g. capecitabine plus bevacizumab for metastatic CRC; here, the bevacizumab can be omitted with only minimal impact particularly in the short term.
- Prior to drug preparation, verification that the patient is not affected by COVID19 will save resources and allow substitution of another patient for treatment.
- Use of validated tools e.g. ESMO magnitude of clinical benefit scale[57], with curative therapies given highest priority, followed by palliative therapies with scores 5 then 4 then 3. Therapies of score 1 and 2 should be ceased.

CRC: colorectal cancer; ESMO: European Society of Medical Oncology

Immunotherapy

Immune checkpoint inhibitors (CPI) have an established role in the management of melanoma, non-small cell lung cancer, urothelial and renal cancers, Hodgkin lymphoma, microsatellite-high cancers irrespective of site of origin, squamous cell carcinomas of the head and neck, and other sites to a lesser extent.

The evidence relating to CPI and viral infections has been conflicting. Whilst they reverse the inactivation of T-cells and could potentially enhance the host response to viral infections[58],it is unclear whether this potentially positive action has been outweighed by an increase of immune related adverse events curtailing treatment, and indirectly compromising outcome. Early studies raised concerns that the use of CPI with the seasonal influenza vaccine could potentially exacerbate immune-related adverse events (irAE), including Guillain-Barré syndrome.[59]

Additionally, patients who develop immune related adverse events also frequently receive immunosuppressive agents including prednisone, mycophenolate, infliximab, and anti-thymocyte globulin. The use of these agents in patients with viral infections could cause significantly worse health outcomes for affected patients. However, despite initial concerns, data has shown that influenza vaccination does not increase irAE in patients treated with checkpoint inhibition.[59-62]

Management of patients on CPI therapy in the context of COVID19 remains challenging. Anti-PD1 therapy is associated with a small but clinically important incidence of pneumonitis, which exceeds 5% in patients with combination CPI.[63] The hallmarks of pneumonitis share many similar features with COVID19 infection, including fever, dry cough, shortness of breath, and bilateral ground-glass opacities on CT scan of the chest. Whereas treatment of choice for irAE due to checkpoint inhibition is immunosuppression, usually with high dose prednisone in the first line setting, it is likely that this unhelpful and may even be harmful in the setting of COVID19. In this challenging clinical situation, current recommendations must be to recommend immediate immunosuppression with facilitation of rapid testing for COVID19. Of note is that the sensitivity of detection depends on the method of testing, and patients with severe respiratory symptoms may need bronchoscopy.[64]

Due to the duration of therapy on CPIs and the increasing number of patients treated with these therapies, CPI treatment now represents a significant burden of CDU activity. PK modelling suggests that higher dose with reduced frequency results in similar AUC to standard dosing.[65 66]

Clinical trial data demonstrating equal efficacy however are lacking resulting in initial rejection from the FDA for this approach.[67] Whereby infusion services are under extreme pressure due to infected and absent staff, switching to longer-interval higher-dose schedules based on PK data may be a highly rational strategy to reduce service burden.

Combined checkpoint inhibition with CTLA-4 and PD-1 inhibitors has shown extended survival in renal cell carcinoma and sub-populations of patients with metastatic melanoma. However, the incidence of grade 3 and 4 toxicity exceeds 50%.[68,69] Given the high rate of severe complications requiring immunosuppression, we recommend that combination therapy be reserved for highly selected patients. Even in the absence of data defining safety or enhanced toxicity in relation to COVID19, the implications of immune suppression and the consumption of health resources in the context of a pandemic makes the selection of combined therapy undesirable for most clinical situations.

Cancer patients and access to Intensive/Critical Care

It is increasingly acknowledged that COVID19 infections are anticipated to overwhelm available health care resources. The concept of tertiary triage refers to the allocation of critical resources for patients already in the hospital environment.[70] Following an outbreak of avian influenza (H5N1), protocols for tertiary triage were developed for the setting of a pandemic.[71] While such triage is necessary, it may cause distress for patients, families and healthcare workers alike.

Cancer patients may be excluded as a group from access to critical care depending on the level of severity of resources. Guidelines from Emergency and Intensive Care seek to define groups with lower chance of survival from COVID19. Oncologists may be called on to participate in discussions around individual patients and should give as much input as possible for policy decisions.

The key issues of particular relevance to oncology are:

-true assessment of prognosis by clinician and corresponding understanding by patient and family, with clear goals of care documented in widely disseminated clinical notes (not just within the main hospital record)

- appropriate understanding of the complexity and variation in prognosis by critical care workers, particularly the impact of recent treatment advances such as immunotherapy.

It is important to have early discussion around prognosis, life expectancy and goals of care with all patient commencing SACT, this is even more true during the current COVID19 crisis. Even for patients who have already commenced treatment, goals of care in the face of COVID19 should be clarified. An Australian study reported that 71% of patients with a terminal illness want to be informed of their prognosis, while only 18% actually are[72]. Conversely, oncologist self-report frequently disclosing a terminal diagnosis without discussing expected survival[73].

Patients with metastatic solid organ malignancies have poor survival outcomes after ICU admission[74-77], although it is noted that prognostication can be difficult[77]. A large study from Brazil and France reported the predictors for poor outcome in patients accepted into ICU with solid tumours included lung cancer, the extent of systemic disease, the need for invasive mechanical ventilation or renal replacement therapy or vasopressor support[75].

The COVID19 pandemic is unprecedented in our lifetime and we may have to make difficult and distressing decisions about care. It is incumbent on us as an oncology community, to both advocate for our patients, but also provide realistic guidance for this cohort with mixed outcomes from their underlying malignant disease. We endorse the approach of The Australia and New Zealand Intensive Care Society guidelines[1]. Table 8 attempts to categorise groups to assist the thinking of other clinicians who may have various experience and expertise but may from necessity (speed of illness, lack of oncology expert resources) have to make decisions involving cancer patients.

Table 8: Broad guide for life expectancies for various cancer scenarios

Treatment intent	Life expectancy estimates
Cure	• Long term, although acute clinical situations may have life threatening prognosis e.g. febrile neutropenia
Prolonged survival in presence of metastatic disease (for example hormone receptor positive, HER2 negative breast cancer; low volume metastatic prostate cancer; melanoma with good control on immunotherapy)	• Years, often 3-5 years; not >10 years in most cases
Treatable metastatic disease with a short median prognosis (for example small cell carcinoma of the lung; metastatic pancreatic carcinoma)	• Months; < 50% of patients live > 1-2 years (remember real life versus clinical trial populations)
Malignancy in frail patients- ECOG 2-4 or heavily pre-treated metastatic disease and limited options for further active treatment	• Usually months; almost all < 1 year

Workforce and supply issues

Early reassigning of staff within cancer clinics where timelines are not critical e.g. familial cancer clinics, survivorship clinics and clinical, translational and laboratory project or research staff, will increase the workforce to maintain critical cancer service delivery. Home based services are critical but relatively time inefficient; coordination of logistics is essential. Liaison with community allied health providers, particularly pharmacists to identify and upskill designated workers should occur early. Health administrators will likely repurpose most staff away from cancer in the event of overwhelming demand from COVID19; cancer clinicians are likely to be asked to take on care of patients outside their expertise. The rapid publishing of COVID19-related literature and almost daily updating of procedural guidelines across multiple areas of general and patient-specific logistics can be overwhelming. Choosing reliable sources of information (Table 9), maintaining good

communication with colleagues and seeking assistance for personal impact is vital to minimise distress on an individual and health service level with this worst-case scenario.

Table 9: Cancer specific COVID19 resources

ASCO: https://www.asco.org/asco-coronavirus-information NCCN: https://www.nccn.org/COVID19/default.aspx Patient resources: https://www.cancer.org.au/cancer-and-COVID19.html

Treatment of COVID-19 positive cancer patients.

There are no accepted guidlelines for when it is safe to reinstitute anti-cancer therapy. Reinfection rates are unknown, so the risks of further immunosupressive therapy needs to be weighed against the need to treat the patients malignancies. Because of false negative rate of exisiting nasopharyngeal swab tests, a least 2 negative tests in the absence of symptoms is recommended. Decisions should be made in individual cases in consultation with Infectious disease physicians. Although serological assays to identify SARS-CoV-2 antibodies are being developed, these are not yet widely available[149,150]. Once available, such assays may be useful to identify patients with previous exposure and who have developed immunity.

Each State government has guidelines for the release of COVID -19 patients from isolation. In Victoria release from isolation will be actively considered when all of the following criteria are met:

- the person has been afebrile for the previous 72 hours, and
- at least **ten days** have elapsed after the onset of the acute illness, and
- there has been a noted improvement in symptoms, and a risk assessment has been conducted by the department and deemed no further criteria are needed[151]

Tumour specific guidelines

The principle of evaluating each treatment for each patient provides a framework but there is a need for more granular information which may assist less experienced oncologists or those who are asked to care for patients outside their subspecialty. In addition, treatment may be affected by

changes in surgical or radiation treatment including change of operation (eg mastectomy to obviate need for radiation for early breast cancer) and shortening or other change to radiation treatment dose and delivery schedules. Table 10 provides a guide of treatment decisions for consideration by medical oncologists in various scenarios across common tumours. It is aimed a provoking thought and discussion, with key references for treatment options, but in no way intends to dictate care for all patients.

Table 10: Specific treatment suggestions by disease type considering risk of COVID19

Specific Considerations for COVID19	
EARLY BREAST CANCER	
Neoadjuvant Therapy	• ER-positive/HER2-negative carcinomas, especially of the lobular histology and luminal A-like subtype, are generally less responsive to primary chemotherapy and may benefit more from primary endocrine therapy.[78] • Try to identify patients where more immunosuppressive treatments can be avoided and use endocrine therapies.

Adjuvant Therapy	• Small absolute benefits in lower risk ER positive patients may be outweighed by the risk of receiving chemotherapy if the patient is considered more vulnerable based on comorbidity or age. Clinical decisions must be individualized. (This is a practice point expert opinion and cited from COVID19 Clinical Oncology Frequently Asked Questions) • Multigene panels, such as MammaPrint, Oncotype DX, EndoPredict etc. used in conjunction with clinico-pathological factors to guide challenging treatment decisions such as luminal B-like/HER2-negative and node-negative/nodes 1–3-positive breast cancer can help identify patients that do not require immunosuppressive chemotherapy.[79]
3rd Generation Adjuvant Regimens	• Avoid concomitant anthracyclines and taxanes as sequential use is superior and much less toxic.[80] • Avoid the concomitant use of 5-FU and anthracycline i.e. FEC regimens as they increase toxicity without improving efficacy.[81] • Strongly consider the use of primary prophylactic G-CSF or peg-GCF in all 3rd generation adjuvant chemotherapy regimens, to reduce duration and severity of neutropenia in an otherwise at-risk population.[82,83]
2nd Generation Adjuvant REgimens	• Non-anthracycline, taxane-based regimens, such as 4 cycles of TC, may be used as an alternative to 4 anthracycline-based chemotherapy. These are more efficacious but have higher rates of neutropenia, with Grade 3-4 neutropenia rates 61% for TC and 55% for AC.[84] • Strongly consider the use of primary or secondary prophylactic G-CSF. • Febrile neutropenia is much higher in observational cohorts than t in randomized trials.[85]
Her2 positive (HER2+)	• In small, node-negative, mostly ER-positive, HER2-positivetumours with no other risk factors, the combination of single agent paclitaxel and trastuzumab provided excellent outcomes in a single-arm phase II study. Identify patients suitable for less intensive chemotherapy regimens.[86] • Switch patients to subcutaneous adjuvant trastuzumab after completion of parenteral chemotherapy to reduce hospital visits. • 30 minute wait time between pertuzumab and trastuzumab can be omitted from cycle two. •
Bisphosphonates	• Prophylactic use in postmenopausal women improves breast cancer-specific survival. There is no data indicating superiority of a specific bisphosphonate • Consider switching intravenous zoledronic acid to oral options such as risedronate, alendronate, or clodronate weekly to avoid hospital visits.[87]

Follow-up/ surveillance	• Convert in person follow-up to telehealth consultation. • Reassure patients that short delays in screening or follow-up breast imaging is possible and appropriate to avoid unnecessary visits • Use Nurse Practitioner led follow-up clinics if available. • Provide education regarding patient's specific level of immune suppression on various long-term adjuvant therapies and after chemotherapy.[88]

ADVANCED BREAST CANCER	
Hormone receptor positive (HR+)	• Avoid immunosuppressive chemotherapy as the first line treatment for hormone receptor (HR) positive advanced breast cancer[78] and use endocrine therapy and CDK4/6i. Although neutropenia rates were high, febrile neutropenia is uncommon with these regimens.[89]
CK4/6 inhibitors	• Monitoring for neutropenia is required, especially during the first 2 cycles. • Delay cycles until neutrophils have recovered to at least 1000/lL; consider dose reduction. • Abemaciclib causes less neutropenia but more diarrhoea.[90]
Everolimus and Exemestane	• Non-infectious pneumonitis is a known complication of mTOR inhibition; up to 50% any grade.[91] • In the setting of community COVID19 transmission, consider alternate endocrine options such as Fulvestrant (+/-AI, CDK4/6i) particularly in older patients where increased toxic deaths have been observed.
HER2+	• Consider carefully the taxane partner for pertuzumab and trastuzumab. Docetaxel is associated with grade 3-4 neutropenia rates of 50% thus primary or secondary prophylactic G-CSF should be strongly considered. Docetaxel also requires more dexamethasone.[92] • Paclitaxel administered weekly causes less neutropenia and reduced dexamethasone premedication however requires more frequent hospital visits. Consider reducing frequency of blood tests for patients with repeatedly normal blood counts.
HR+ HER2+	• Consider combination of endocrine therapy plus anti-HER2 therapy as maintenance therapy for ER+ /HER2+ ABC after initial chemotherapy or as an early switch to reduce immunosuppression and hospital visits in suitable patients with lower volume disease and or comorbidities placing them in higher risk categories. [93]
Triple Negative Breast cancer with germline BRCA mutation	• Consider PARP inhibitor monotherapy as an oral option for after previous chemotherapy but note that although not a chemotherapy, anemia, neutropenia and sepsis are toxicities. [94]
Chemotherapy	• Single agent chemotherapy is preferable. [95] • Choose oral agents to reduce visits to CDU: capecitabine, vinorelbine. • Consider chemotherapy schedules with less frequent administration. schedule: pegylated liposomal doxorubicin given q28 days using 40 mg/ m^2 to reduce toxicity (consensus of the reference committee).[96] • For patients with low burden of disease or significant co-morbidities, consider deferring or delaying chemotherapy
COLORECTAL CANCER	
Neoadjuvant Therapy	• Consider short course radiotherapy as neoadjuvant treatment rather than long course CRT because of lower toxicity, less hospital visits, less blood tests. [97]
Adjuvant Therapy	• Low risk Stage II colon cancer: consider no chemotherapy as curative benefit is minimal.[98,99]

	• High risk Stage II colon cancer e.g. T4: preference for maximum 3 months chemotherapy.[100] • Stage III, low risk (T3N1): strongly consider stopping after 3 months, based on results of IDEA trial.[101,102] • Stage III, high risk (T4N+/T3N2): consider using a 3-week schedule such as CAPOX[101]. Keep in mind that capecitabine causes more diarrhoea (therefore hospital presentations and admissions); choose mFOLFOX where diarrhea pre-exists or is a concern. • Omit oxaliplatin in high risk patients such as elderly (>70y) where there is no evidence for benefit.[103,104] • Rectal cancer: evidence for adjuvant therapy following neoadjuvant chemoradiation is weak for survival advantage, especially when pathological CR.[105] • For dMMR tumours: no adjuvant therapy for Stage II; consider risk-benefit carefully for low risk Stage 3.[106]
Metastatic Therapy	• Strong preference for doublet regimen (+/-biologic), unless triplet required for: maximal tumor shrinkage in borderline operable disease; BRAF mutant tumours; rapid disease control.[107] • In case of triplet (mFOLFOXIRI), add G-CSF or p-GCSF routinely. • Preference for 3 weekly schedules such as oxaliplatin plus capecitabine (CAPOX) or irinotecan q3w (350 mg/m²) monotherapy. If at risk for diarrhea, then preference for mFOLFOX. • Cetuximab should be given biweekly as equally beneficial as weekly.[108] • In case of low tumor burden or stable disease consider treatment holiday or maintenance capecitabine. • In case of operable disease, postpone elective surgery and continue with lowest toxic schedule of chemotherapy +/- biological agent. • Use short course radiation schedules for symptom control.
GASTRO-ESOPHAGEAL CANCER	
Neoadjuvant Therapy	• For gastric cancers most commonly a FLOT-like schedule is used; all patients should have G-CSF given high rate (29%) of grade 3-4 neutropenia[109]; caution regarding mucositis. • In high risk patients (elderly, comorbidities) consider switching to FOLFOX or CAPOX[110] with a preference for a lower dose of capecitabine of 1000 mg/m² bd to avoid diarrhea. Consider the alternative of a definitive schedule of CRT particularly for squamous cell cancers if surgery is likely to be postponed due to hospital (particularly ICU) resources.
Adjuvant Therapy	Ensure patient is fully recovered and in good physical and nutritional status. Especially for older patients, more robust assessment of capacity is required (see section on elderly assessment).

Metastatic Therapy	• First line preference for either FOLFOX q2w or CAPOX q3w with capecitabine at a dose of 1000 mg/m² bd given the higher chance of diarrhea.[111] • Preference for oxaliplatin over cisplatin as shorter duration. • Second line preference for 3 weekly schedules with either taxanes or irinotecan. In case of third line setting clearly balance risk/benefit ratio as survival benefit is small (<2 months median gain).[112]
PANCREATIC AND BILIARY CANCER	
Adjuvant Therapy	• In patients treated with adjuvant mFOLFIRINOX, add G-CSF or pegG-CSF • Gemcitabine monotherapy or no adjuvant treatment is alternative for less robust patients.
Metastatic Therapy	• The survival gain of chemotherapy is small thus consider less toxic schedules such as gemcitabine monotherapy or FOLFOX / CAPOX with palliative emphasis.[113,114]
EPITHELIAL OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CANCER	
First line therapy for advanced disease – Stage 3/4	• Systemic chemotherapy prior to debulking surgery can potentially reduce postoperative complications without compromising efficacy or overall survival[84]. Consider availability of surgery which may be affected by COVID19.
Second line chemotherapy (Platinum sensitive disease)	• Treatment with systemic chemotherapy for patients with asymptomatic relapse (e.g. rising Ca125 only) is not indicated. Observation alone is a valid management strategy[115]. • Carboplatin and pegylated liposomal doxorubicin (q4w) is associated with improved progression free survival and reduced toxicity in comparison to carboplatin and paclitaxel q3w.[116] It is given less frequently and may result in less carboplatin hypersensitivity reactions. • If IV chemotherapy is to be avoided consider oral cyclophosphamide at a dose of 150mg daily D1-14 q4weekly [152]or the continuous, metronomic dosing regimen of 50mg daily[153] • Oral chlorambucil has also been used in the treatment of patients with platinum sensitive disease[154].
Platinum resistant/refractory	• Patients who primarily progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit may not benefit from additional therapy.[117] • If chemotherapy is warranted and intravenous treatment is not possible consider oral cyclophosphamide (in doses as above)
Low grade serous carcinoma	• Although no prospective, randomised trial evidence, the use of hormone therapy (e.g. letrozole, anastrozole, tamoxifen) could be considered due to less toxicity than combination chemotherapy. [118]
ENDOMETRIAL CANCER	

Metastatic therapy	• Consider hormone therapy for lower-grade endometrioid histologies, particularly if small tumour volume or an indolent growth pace.[119]
SMALL CELL LUNG CANCER	

Limited stage	• Patients should continue to receive platinum/etoposide with radiotherapy. Substitution of oral etoposide is not recommended as comparative efficacy has not been studied.
Extensive stage	• Given high rates of comorbidities and treatment induced neutropenia, routine prophylaxis with G-CSF or peg-GCSF should be Considered. • Oral etoposide may be substituted for intravenous etoposide at the correct conversion dose as noted in chemo administration guidelines (https://www.eviq.org.au). Noting the evidence to support this is lacking but that the clinical circumstances during the COVID19 crisis may justify this approach in selected patients and clinics. • In platinum refractory disease (no response to first line therapy) or platinum resistant disease (disease free interval <3 months post first line platinum/etoposide) response to further lines of cytotoxic therapy are rare, and best supportive care only is recommended. • If second line therapy is considered (noting small benefit), single agent regimens are preferred to cyclophosphamide/doxorubicin/vincristine due to more favourable side effect profiles.[120]
NON SMALL CELL LUNG CANCER (NSCLC)	
Adjuvant Therapy	• Adjuvant therapy confers a benefit in the order of 5% at 5 years) appropriate in patients with stage II and III disease, and in some patients with high risk stage 1 disease (primary tumour > 4cm). • For cisplatin+ vinorelbine regimen, consider substituting oral vinorelbine to avoid the Day 8 clinic visit.[121] [122] This is associated with more nausea and vomiting though so need increased be prepared to increase anti-emetics. • In patients with non-squamous NSCLC, consider using cisplatin/pemetrexed to reduce clinic visits and risk of neutropenia.[123][124] • Selected patients with activating EGFR mutations may be considered for EGFR TKIs as an alternative to chemotherapy.[125,126] • For squamous cell NSCLC, cisplatin/docetaxel has fewer clinic visits and lower rates of febrile neutropenia but more mucositis and hair loss; cisplatin/gemcitabine has the lowest febrile neutropenic rate with the same number of clinic visits.
Chemoradiation	• For patients with non-squamous NSCLC consider platinum/pemetrexed regimens to limit the number of clinic visits[127] • For patients with squamous cell NSCLC use of the weekly carboplatin/paclitaxel regimen will reduce the number of day unit visits compared to cisplatin/etoposide[128] • Following chemoradiotherapy patients can receive durvalumab as per the PACIFIC trial. This study used fortnightly dosing at 10mg/kg.[129] Consideration can be given to administering durvalumab at 20mg/kg Q4w to reduce clinic visits.

Metastatic therapy	• Patients on small molecule inhibitors for oncogene driven tumours can remain on therapy. Clinicians need to be aware of the potential for pulmonary infiltrates and pneumonitis from some agents (e.g. EGFR TKIs and ALK inhibitors).[125,130,131] • Patients receiving Dabrafenib/Trametinib for BRAF mutant NSCLC can present with drug related fevers, similar to melanoma patients.[132] • Use three weekly regimens to minimize patient visits for 1st line therapy. • For 2nd line nivolumab, four weekly dosing is preferred, but consider monitoring with 2 weekly bloods and telehealth visits if patient is in first 12 months of treatment. • For 2nd or later line, consider oral vinorelbine or switch to a checkpoint inhibitor.

OTHER THORACIC CANCERS	
Mesothelioma	• Consider limiting first line therapy to four cycles of platinum doublet (instead of extending to six cycles). • Maintenance pemetrexed should not be used due to lack of evidence of benefit.[133] • In patients with early or rapid progression after first line, there is minimal benefit for subsequent therapy.
Thymoma/thymic carcinoma	• Patients with thymoma may have underlying hypogammaglobulinaemia. Measurement of immunoglobulin levels is important. • Use G-CSF or peg-GCSF prophylaxis with multi-drug regiments.
GENITOURINARY CANCER	
Hormone Sensitive Metastatic Prostate Cancer	• Novel anti-androgens (eg enzalutamide, abiraterone) may be considered in preference to docetaxel chemotherapy. • Docetaxel remains an established standard of care in combination with ADT. Clinicians will have to weigh the benefits of chemotherapy using patient factors (age, comorbidities etc.) and tumour factors (Gleason grade, volume of metastatic disease). • Be very cautious of docetaxel in older patients, especially with its steroid requirements. • Strongly consider addition of G-CSF or peg-GCSF. • Consider using ADT schedules that reduce the number of visits required for implant/injection (4-6 monthly depots) or use home or GP
Castration Resistant Prostate Cancer	• 1st Line: consider novel anti-androgens (abiraterone or enzalutamide) in preference to chemotherapy given the lower risk of toxicity and reduced need for hospital visits. • Continue novel anti-androgen therapy where safe e.g. slowly progressive disease on imaging or slowly rising PSA. • Consider risk/benefit of chemotherapy in older men. • Use G-CSF or pegG-CSF with chemotherapy to reduce neutropenia rates. • Consider using ADT schedules that reduce the number of visits or use community settings for implant/injections. • Do not use mitoxantrone as no survival benefit over BSC. [134]
Metastatic Renal Cell Carcinoma	• Consider observation with delayed commencement of 1st line therapy for patients treated low volume disease and minimal symptoms.[135] • For first line patients who have responded to nivolumab/ipilimumab induction therapy consider use of four weekly maintenance nivolumab. • High dose interleukin-2 should not be used as a treatment strategy at the current time given the significant resources required to deliver this therapy.
Urothelial Carcinoma	• If MVAC regimen is to be used, the dose dense regimen with growth factor support involves fewer visits, shorter treatment duration and better tolerance.[136] • For metastatic disease, consider single agent immunotherapy in preference to chemotherapy given lower risk toxicity.
Testicular and Germ Cell Tumours	• High cure rate even with metastatic disease needs to be emphasized for patients who become sick with COVID19. • Low risk stage 1 testicular cancer patients should be offered active surveillance.

	• Patients receiving BEP or EP should receive G-CSF or pegGCSF. • Patients with metastatic disease should be managed by or in cooperation with specialist centres as interruptions to their cytotoxic regimen can compromise survival outcomes. • Patients should be monitored for bleomycin pulmonary toxicity as per standard care. Bleomycin pulmonary toxicity can present with fever, dry cough and exertional dyspnoea with a differential including COVID19 infection.
MELANOMA	
Adjuvant Therapy	• Stage 2 – recommend surveillance only • Stage 3A – observation may be preferred due to modest benefit and potential for immunosuppression in otherwise healthy patients; toxicity of therapies can overlap with presentation of COVID19 • Stage 3B – D: for patients with BRAFmut consideration could be given to BRAFi due to lower contact with CDU and simpler to monitor remotely, although the fevers with MEKi agents can present diagnostic dilemmas where there is community spread of COVID19. • Oral therapy is preferred where there it is an option of similar therapeutic benefit.
Metastatic therapy	• Combination IO should be limited , given high toxicity and high requirement for immunosuppression for irAE. • Minimise patients treated with this approach; document potential complications of immunosuppression for toxicity and its impact • For patients on IO, switch to prolonged interval higher dose schedules. • For patients with prolonged stable disease, encourage treatment holiday • For patients with activating BRAF mutations, consider initial therapy with combination BRAF-MEK inhibition as there is faster reversibility of toxicity, less need for immune suppression for complications and less CDU use.
CANCERS OF THE HEAD AND NECK	
Newly diagnosed	• Primary treatment or post-operative treatment with radiotherapy ± drug therapy improves survival. Commonly used drugs like high dose cisplatin and cetuximab are not usually myelosuppressive or associated with a high risk of infection. • Weekly regimens should be avoided because of the need for multiple hospital visit, increased risk of mucositis and skin breakdown (cetuximab) or limited data for efficacy (weekly platinum). • Weekly platinum regimens should also be avoided due to the lack of strong evidence for survival benefit; increased visits and high steroid use • Adequate barrier precautions for breaches of mucosa will be important. • Avoiding multi-drug neoadjuvant treatment should also be considered, as often these having very limited evidence of survival benefit compared to standard chemo-radiation; timely surgery may not be available. • Patients >70 years old do not benefit from addition of chemotherapy to radiotherapy.

Recurrent disease	• Consider less myelosuppressive drugs with less steroid requirements such as a platinum or IO. • Preference monotherapy over combination therapy to reduce toxicity given no evidence of survival benefit with combination therapy
BRAIN CANCER	
Newly diagnosed GBM (Grade 4)	• Although not curative, post-operative concurrent radiotherapy with temozolomide is the only treatment to offer a survival benefit and should be offered with careful patient selection and monitoring.[137] • To mitigate the risk, strategies in order of importance: minimise steroid use/dose; close monitoring of neutrophils and lymphocytes used to appropriately dose-adjust. • make treatment choices based on relative (but not absolute) lack of benefit with temozolomide for MGMT unmethylated tumours.[138] • Although rates of lymphopenia in the elderly are higher (27% with concurrent temozolomide) there is no increase in infections, and elderly patients still benefit from addition of chemotherapy.[139] Consider short course radiotherapy in the elderly to reduce hospital visits.
GBM Recurrent disease	• Chemotherapy has not been conclusively shown to increase survival, therefore this should be discussed on a case-by-case basis, in consultation with the patient and family, particularly for elderly patients. • Bevacizumab may be a better alternative option as it does not cause myelosuppression and can reduce steroid requirements.
Grade 2/3 disease	• Post-operative radiotherapy and chemotherapy increase survival quite significantly in subsets of lower grade tumours[140-142] • Chemotherapy regimens such as PCV are associated with low rates of lymphopenia (4% in one study); clinically significant infections are less frequent. • Delaying treatment a few months for selected patients with grade 2/3 gliomas is reasonable as the timing of when to treat is less clear.
Recurrent disease	As for GBM
SUPPORTIVE CARE	
Steroid use	• As anti-emetics: use less steroids than traditionally prescribed; multiple alternative agents are now available e.g olanzepine, NK1 inihibitors • As anti-allergy prophylaxis: old schedules eg for docetaxel administration or weekly taxanes can still recommend very high doses of steroids which particularly if no previous reaction to the chemotherapy, can be reduced
Bone targeting therapies	• Switch intravenous bone therapy to subcutaneous (denosumab) or oral options (ibandronate). Patients could be taught to self-administer denosumab if necessary. • Depending on the indication, treatment could be safely delayed or suspended for many patients.
Granulocyte colony stimulating factors (G-CSF)	• Although guidelines recommend against the use of primary prophylactic G-CSF if the estimated febrile neutropenia rate is <20%, in the COVID19 crisis, primary prophylaxis is likely to be appropriate in many settings. Risk models can be used.[143] • Daily G-CSF is available, but pG-CSF is preferred to minimise injections. • Consider more liberal use to reduce the risk of neutropenic fever. • Alternatively, dose reductions and delays are appropriate in non-curative treatment settings.

	• Avoidance of G-CSFs in patients receiving concomitant chemoradiotherapy for either head and neck cancer or lung cancer is recommended because of adverse effects and poorer treatment outcomes[144]
Vaccinations	• All Oncology patients should receive the inactivated influenza vaccine annually[145]. The COVID19 pandemic in the Southern Hemisphere will co-incide with the onset of the influenza season, a factor not present in many of the Northern Hemisphere countries reporting COVID19 outcomes. • The inactivated influenza vaccine is safe to administer to immunosuppressed patients; side-effects are similar to those in healthy individuals. • Although vaccination before start of chemotherapy is preferred to ensure optimal protection in adults with solid tumours, also vaccination during chemotherapy can reduce influenza-related complications considering the overall trends in serological response. • Conflicting evidence regarding the safety of the flu vaccine in patients being treated with IO has caused uncertainty among clinicians. Recent data suggests no increase in incidence or severity of irAEs with vaccination within approximately 2 months of IO.[146]
Central venous access devices	• Peripherally inserted central catheters (PICC) require more intensive maintenance (e.g. weekly flushes if not used) and have higher risk for catheter-related deep venous thrombosis and other adverse events compared with PORTs.[147] • PORT flushes can be reduced to 8-10 weekly in situations of resource limitation. • PORTs take more specialised resources in Imaging/Interventional Radiology than PICC insertion.
Scalp cooling devices	• Due to significant increase in time in treatment centre for patient and heavy use of nurse time as well as risk of scalp burns, this is not recommended during COVID9 crisis.
Exercise and nutrition	• Emphasize importance of this particularly for patients in quarantine and with social distancing
Psychosocial care	• See separate section
Complementary therapies to “boost immunity”	• Beware of claims of ‘immune boosting’ properties that cancer patients may be particularly vulnerable to during the COVID19 crisis. • Many complimentary therapies have known adverse impacts; interaction with COVID19 is unknown • Intravenous complimentary therapies e.g. Vitamin C should be discouraged due to lack of efficacy and unnecessary exposure
Uninterrupted medication supplies	• Anticipating prolonged quarantine or production/resource shortage, patients should have extra supplies of their anticancer therapies and supportive medication. • Increased quantities should be supplied. • Governments should move to make extended supplies as easy as possible to obtain

	• Medication should be able to be delivered to those in quarantine. • Scripts should be able to be filled by fax or email or messaging within guidelines to ease requirements for in person visits.
Palliative care	• Demands for palliation for COVID19 illness and death in the wider community is likely to exceed current supply of services.[148] • Early referral and transfer of patient with appropriate documentation to community services will lessen load on hospital-based services. • Ensure patients have completed Advance Care Directives and discussed and documented discussions regarding ceiling of care using appropriate forms. Ensure patients have copies of these documents endorsed for out of hospital use.

ER: estrogen receptor; SURC: SACT: systemic anti-cancer therapies 5FU: 5-Fluouracil; FEC: 5-Fluorouracil Epirubicin and 5-Fluouracil and oxaliplatin Cyclophosphamide; TC: docetaxel and cyclophosphamide; AC: adriamycin and cyclophosphamide; G-CSF: granulocyte colony stimulating factor; pegGCSF: pegylated granulocyte colony stimulating factor; ABC: advanced breast cancer; PARPi: PARP inhibitor; capOX: capecitabine oxaliplatin; dMMR: deficient mismatch repair genes; mFOLFOX: modified regimen of 5-Fluouracil and oxaliplatin; mFOLFOXIRI: modified regimen of 5-Fluouracil and oxaliplatin and irinotecan; FLOT: 5-Fluouracil and oxaliplatin and docetaxel; NSCLC: non-small cell lung cancer; FNP: febrile neutropenia; EGFR: Epidermal Growth Factor receptor; TKI: tyrosine kinase inhibitors; ADT: androgen deprivation therapy; BSC: best supportive care; MVAC: methotrexate and vinblastine and adriamycin cisplatin; BEP: bleomycin and etoposide and cisplatin; EP: etoposide and cisplatin; CRT: chemoradiation; MGMT: 0-6methylguanine- DNAmethyltransferase; PCV: procarbazine and lomustine and vincristine; NK1: neurokinin 1; irAE: immune-related adverse events; IO: immuno-oncology agents; BRAFmut: BRAF mutant; BRAFi: BRAF inhibitors; CDK4/6i: CDK4/6 inhibitors; bd: twice per day; q2w: every 2 weeks; CR: complete response;

Conclusion

COVID19 has appeared rapidly, causing an unprecedented impact on health services and the broad community and way of life of every country in the world. The capacity of health systems to cope with illness in patients and staff is a challenge not faced by the modern world. Cancer clinicians and patients are profoundly affected and need reassurance from colleagues and professional bodies about reasonable changes to practice. This document is the most detailed yet to guide not only subspecialists with great knowledge and experience, but also more junior doctors and other clinicians who may be called on to care for cancer patients during this pandemic.

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Confirmed new cases (n)
1 incubation
period from lockdown
2nd incubation
period from lockdown
14000
12000
10000
8000
6000
4000
2000
0
Lockdown of Wuhan and
Other cities Jan 23 2020
Change in WHO
Reporting
Daily case count
Exceeds highest count
In China
First case outside China
(Thailand)
Seafood market
closed
Jan 1 2020
Dec 31 2019
Jan 2 2020
Jan 4 2020
Jan 6 2020
Jan 8 2020
Jan 10 2020
Jan 12 2020
Jan 14 2020
Jan 16 2020
Jan 18 2020
Jan 20 2020
Jan 22 202
Jan 24 2020
Jan 26 2020
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Feb 25 2020
Feb 27 2020
Feb 29 2020
March 2 2020
March 4 2020
March 6 2020
March 8 2020
March 10 2020
March 12 2020
March 14 2020
March 16 2020
China
Other
Date from December 31 2019 to 2020
Data sources: PROMEDmail, WHO, media reports