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LEVINE CANCER INSTITUTE APPROACH TO PANDEMIC CARE OF CANCER PATIENTS

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INTRODUCTION AND BASIC PRINCIPLES OF MANAGEMENT:

The recent onset of the Covid-19 pandemic has created an unprecedented set of medical management problems, largely because of the rapid global speed of onset, the severity of management problems for around 5-10% of patients, prevalence of asymptomatic carriers, and general lack of experience internationally in this type of pandemic care (1). The bat-human transmission of a novel coronavirus originated in Wuhan, China in December 2019, and had spread to most continents and 150 countries by March 11, 2020 when it was declared to be a pandemic. What has made this situation unique is the potential for spread by contact and aerosolized droplets with a potential dwell time of some hours in the air and longer on surfaces, with symptoms that can arise 2-14 days or longer after exposure (2), with predominantly asymptomatic spread. Although the symptoms are quite characteristic, with fever, cough, fatigue, sputum production, dyspnea and myalgia predominating, there is substantial overlap with the common cold, influenza and seasonal allergies, making early diagnosis more challenging (1). Sudden onset of loss of taste sensation has been described, although this is less helpful for the patient already on chemotherapy.

Limited data exist for Covid-19 infection outcomes in cancer patients. Early reports from China suggest that cancer patients are twice as likely to become infected and are at high risk for severe clinical events defined as a need for ventilation, admission to an intensive care unit, or death (3,4). An additional study of 138 hospitalized patients in Zhongnan Hospital of Wuhan University suggested that hospital-acquired transmission accounted for 41.3% of admitted patients (5). Together, these findings highlight a critical need to redefine treatment goals and safety of our current cancer care delivery paradigm.
General principles of management were established during the evolution of the SARS and Zika virus epidemics, and many have been applied de facto to the current situation (Table 1). However, the rapidity of global spread and the features above have mandated the development of creative strategies of management when scant definitive information is available in the literature.

Levine Cancer Institute (LCI) is a 25-site academic-hybrid, multi-site cancer institute in North Carolina and South Carolina, serving urban and rural populations. LCI employs more than 2000 staff, including more than 150 clinicians and scientists, and cares for more than 17,000 new cases per year, with 200,000 visits per year. Around 2000 patients are entered into cancer trials annually, with 65,000 patients seen in outreach education and cancer prevention activities, and more than 600 bone marrow transplants and 50 CAR-T treatments since LCI was established within the Atrium Health System. Atrium Health is comprised of more than 40 hospitals in three states, providing care at 12 million encounters annually. Thus draconian new approaches have been urgently required both for our health system and cancer institute to deal with the pandemic. As the cancer institute involves a major teaching hospital, several rural and urban smaller hospitals and office-based practices, we have designed an approach that caters to each setting. This paper codifies these approaches to guide others in view of the paucity of published information.

GAINING INFORMATION FROM OTHER SITES:

The standard LCI approach of tumor-specific management by multi-disciplinary teams, blending evidence-based data and clinical expertise and in-house data, has provided a platform for modified approaches to pandemic care, based on an amalgam of risk- and outcome-based considerations.
We have initiated teleconferences with international physician leaders who have set treatment policies for patients affected by Covid-19, including an international webinar presented by the American Association for Gynecological Laparoscopy. We have learned from the scant peer-reviewed literature.

One of our authors (LM) has had extensive experience in epidemic management of human immunodeficiency and Zika viruses at the National Institute of Allergy and Infectious Disease and with Doctors Without Borders. There has also been extensive and ongoing communication with other cancer centers.

TABLE 1: PARAMETERS OF PANDEMIC MANAGEMENT FOR CANCER PATIENTS

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>PRE-ARRIVAL</th>
<th>AT CLINIC/HOSPITAL</th>
<th>AFTER DEPARTURE</th>
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<tbody>
<tr>
<td><strong>SOCIAL INTERVENTION</strong></td>
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<tr>
<td>Education re. implications of virus</td>
<td>Internet</td>
<td>Clinic staff and physicians Brochures Signage</td>
<td>e-mail messaging nurse navigator contact</td>
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<tr>
<td></td>
<td>Scheduling phone contact</td>
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<td></td>
<td>Outreach to media</td>
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<tr>
<td></td>
<td>Brochures &amp; signage</td>
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<tr>
<td>Social Distancing</td>
<td>Triage</td>
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<tr>
<td></td>
<td>• maximize virtual visits</td>
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<td></td>
<td>• reschedule as clinically appropriate</td>
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<td></td>
<td>Alert re. no visitors – encourage to Skype/phone into consult</td>
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<tr>
<td></td>
<td>Use of home nursing services</td>
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<tr>
<td>Protection of Individual (patients and staff)</td>
<td>Telephone pre-screening for risk</td>
<td>Initial screening outside facility for risk factors and temperature check</td>
<td>Printed educational materials and web access for home use</td>
</tr>
<tr>
<td></td>
<td>Temperature and vital sign assessments at home when possible**</td>
<td>Secondary/tertiary screens</td>
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<tr>
<td></td>
<td></td>
<td>Masking for staff</td>
<td></td>
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<td></td>
<td></td>
<td>Masking for pts - controversial</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Prioritize when shortage of PPE</td>
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<tr>
<td>Staffing</td>
<td>Reduce staffing need by delay of non-essential*** visits by 2-3 months</td>
<td>Alternate staff schedules – 14 days on/off – see text</td>
<td>Telephone and virtual follow-up</td>
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<tr>
<td></td>
<td>Decrease infusion times</td>
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<td></td>
<td>Reduce non-essential lab draws</td>
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<tr>
<td></td>
<td>Maximize virtual visits to reduce patient-facing visits</td>
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<tr>
<td><strong>MEDICAL ISSUES</strong></td>
<td></td>
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<tr>
<td>Primum non nocere</td>
<td>Define aims of treatment</td>
<td>Clearly defined and rational aims in context of Covid-19</td>
<td>Monitor for complications of Rx and virus together</td>
</tr>
<tr>
<td></td>
<td>Timing of treatment critical # Anticipate complications</td>
<td>Choosing Wisely principles</td>
<td>Dose adjustment vs. risks in subsequent Rx</td>
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<td></td>
</tr>
<tr>
<td>Balance between medical need and number of visits</td>
<td>Adjust protocols for chemotherapy:</td>
<td></td>
<td>Ensure extra phone follow up schedule for patients with</td>
</tr>
</tbody>
</table>
In-person check vs. virtual check depends on patient & regimen

| Treatment planning for covid-positive patients (alters with severity of pandemic conditions) | Consider prognosis and likely outcome; impact of virus? Isolate – role for Rx center for Covid-positive patients | Protection for staff/other pts Spacing in clinic Delay chemo till resolved Delay radiotherapy if safe Only urgent/semi-urgent surgery | Repeat testing Close monitoring for myelosuppression Respiratory function – bleomycin – close monitoring |

*except specific indications – end of life, ICU, physical assistance needed, children; visitors must be screened for symptoms/exposures/travel

** realizing that most carriers are asymptomatic and screening questions have false negative rate

*** non-essential at that time and Covid-19 context – e.g. routine long-term follow-up, well-check ups.

# e.g. use adjuvant rather than neo-adjuvant chemotherapy if no significant difference in cancer outcome

PRACTICAL ASPECTS:

The essence of management for oncology patients during a pandemic is protection, focused on patients, their caregivers and families and clinical staff (Table 1). To achieve this, interventions should include consideration of the demography of the patients and available physical facilities, staffing, and information technology (I-T). Other external factors, such as the response from government, level of social chaos, policies developed by health insurance payers and local government are crucial, but beyond the scope of this paper. The risk/benefit ratio is important in the choice of approach – the patient who is likely to be in a curative setting requires different considerations than one facing management of treatable but incurable disease or one with end-of-life management. Equally, the likely toxicities of treatment (especially myelosuppression and cardio-pulmonary toxicity) need to be considered carefully for patients at risk of Covid-19 infection.

Patient Management:

The size of the clinical practice will dictate the scope and range of interventions that can be offered to individual patients – a huge multi-site multi-disciplinary cancer practice will perforce have a great range and volume of extant resources at baseline, but the principles remain unchanged, and can
be adapted considering the available staffing, clinical and fiscal resources. For example, although our practice has been able to draw on virtual clinical and social support of patients by more than 30 nurse navigators, a reasonable alternative for small clinical practices would be to use an amalgam of nurse and/or office managers, augmented perhaps by a social worker or community social support resources to achieve similar goals.

Irrespective of the size of the facility, social distancing is one of the foremost aspects of care, supported extensively by experience in China and Europe. Of importance, Taiwanese health officials have been meticulous in documenting travel histories and symptoms in the local population (after absolute border closure), and have used cell phone contact and tracking, augmented by fiscal penalties, to ensure that at-risk and affected patients practice social isolation meticulously. In the oncology clinic, social distancing can be achieved by the following:

(i) selection of patients for delay of appointments or virtual visits by telephone or video conferencing to reduce absolute numbers and crowding; this is influenced by acuity and severity of the clinical problem, whether the patient is on active treatment or in post-treatment “well” surveillance; at the same time, pre-screening for symptoms of Covid-19 and exposures take place;

(ii) physical distancing and separation in the clinic, with improved efficiencies to reduce waiting times (e.g. lengthened appointment times to 20 minutes), spacing of chairs in waiting areas;

(iii) adjustment of treatment regimens to reduce the need for patients to be in the hospital or clinic, provided that safety and outcome are not substantially affected (e.g. alteration of intravenous to oral etoposide for small cell carcinoma, altered radiotherapy fractionation for bone pain, use
of intravenous bone stabilizing agents in metastatic prostate cancer on androgen deprivation therapy); (iv) use of day hospital or urgent cancer care unit to reduce visits to the Emergency Department, augmented by expanded home nursing services by staff trained to manage oncology issues.

These considerations are implemented prior to the arrival of patients, during clinic or hospital visits and after departure, as summarized in Table 1. Criteria for “Patient Under Investigation” (PUI) testing have been defined by our health system and include Influenza-Like-Illness (ILI) (fever $\geq$100.4F, subjective fever, plus cough or dyspnea), plus one risk factor (immunocompromised, lung disease [including asthma or COPD], person from long-term care, homeless or prison). Availability of testing kits obviously influences implementation.

**Staffing Issues:**

Similarly, safety of staff is also of paramount importance. LCI has initiated an alternative staffing roster, such that teams are “on deck” and “away”, mostly for 14 day shifts in view of the incubation time for Covid-19 (2) and this ensures a constant supply of Covid-negative staff. For high acuity, intense services, such as bone marrow transplant, the “on deck” team spends a week on the BMT Unit and a week in outpatient clinics, and the teams then swap. The “away” team returns to service at 14 days, removing the first team from patient contact. When staff numbers do not permit this, options include amalgamation or simply closing units that are no longer able to provide staff because of the numbers of Covid-positive staff who are ill or in surveillance. Teams are constructed using physicians and maximizing the use of Advanced Practice Professionals (APPs), emphasizing their operations at the upper end of their licenses. Universal masking for all patient-facing staff is emphasized, contingent on supplies, and staff are required to wear scrubs or other washable clothing for patient facing. In view of
PPF shortages, we have developed a 3D printing mechanism to create our own clear plastic masks. If Covid-19 becomes ubiquitous, the rotation may be maintained to avoid staff exhaustion.

Special considerations have been created for pregnant staff members – specifically rostered away from proven Covid-positive patients, and wherever possible, away from patient-facing roles.

At LCI, we have developed a specific clinic for Covid-positive “well” patients (without clinical syndrome of viral infection), staffed by volunteers. Increased personal protective equipment and more rigorous standard operating procedures have been evolved for this site, beyond the scope of this manuscript.

Communication:

It is obvious that clear and defined communication for patients and families is essential in any cancer treatment algorithm, but this is even more important in the setting of a pandemic where fear and uncertainty abound. Verbal and written communication for patients and families is important to define the key issues surrounding cancer management as well as the modifications created to deal with the pandemic, and clear explanation for the reasons underlying those changes. Equally important is clear and repeated communication to staff, both written and by virtual meetings, most particularly about the changing demography and epidemiology of the pandemic, the supply of personal protective equipment, and repeated definition of the emphasis of safety for patients and staff. Presence of leadership in the clinical environment is also important in supporting morale, creating a calm environment and reducing fear.

All multi-site tumor conferences, lectures and teaching activities are carried out using virtual technology, with the majority of peer review conducted in most cases by the team rotated to non-patient-facing duties in the 14 day rotations.
ELECTRONICALLY ACCESSIBLE PATHWAYS:

LCI created an electronic clinical pathways tool, Electronically Accessible Pathways (EAPathways), to provide standardized, evidence-based, continually updated clinical pathways for all LCI network providers and staff. The goal was to standardize care, provide access to patient services and clinical trials, promote specialized care by local providers, and deliver care in a standardized manner across a wide geographical region, giving access to standardized treatment approaches, diagnostic and molecular testing, clinical trials, and patient resources. The clinical pathways can be updated in “near-real-time” based on the urgency of information. Users have easy access to updated clinical trials information, clinical notifications, patient and provider teaching documents, program information (e.g. tobacco cessation), and other clinical resources centralized to a single site.

During the COVID-19 pandemic, we have created a new section covering the COVID-19 updates reflecting the rapidly changing hospital operations and policies within hours, a litmus test on our pathway technology platform. For example, as infusion time slots and staffing presented new challenges, we have made system-wide changes to utilize particular regimens which save infusion visits and time without compromising patient safety or efficacy. These edits occurred on the treatment pages so providers were informed and directed on how to proceed. While this is a somewhat sophisticated approach that has leveraged an extant system, similar outcomes can be achieved using editable white boards or computerized share-point sites in a small office.

RADIATION ONCOLOGY:

The Radiation Oncology Department at the LCI is a nine-site network that has ensured continued state of the art treatment while using social distancing (Table 1). All follow-ups and consults are now conducted as virtual visits. The only patients who come to the clinic are those deemed after physician
review to need treatment, and simulations and radiation are scheduled contemporaneously. Existing patients continue treatment to completion, but with no visitors. Weekly on-treatment medical visits occur via virtual technology, to maintain the family engagement in the care of the patients. Social distancing is enforced via widely spaced on-deck chairs. Secretarial and dosimetry staff work from home and the physics staff have limited in-clinic hours. An alternate week staffing model for all patient-facing aspects is in place. Each “unit” of therapists per machine is self-contained with no rotational coverage from other staff. Each unit also is socially distanced from the other units. The at home physicians and advanced practice providers continue to engage in full support of the clinic and are the primary providers of remote follow-ups and consultations as well as peer review. The team has worked closely with the referring clinicians to establish triage strategies that ensure that a delay in treatment should have minimal adverse effect on patient outcome. The most common delayed treatments include low risk breast cancer and DCIS patients as well low risk prostate cancer patients. When each case is peer reviewed, the reviewing physician also assesses for consideration of delay or alternate fractionation with consideration of hypofractionation, although we routinely adhered to the ASTRO Choose Wisely guidelines for short palliative courses prior to the epidemic. Two low-volume centers were closed allowing transfer of staff to the remaining centers to facilitate alternating teams. The treatment processes and documentation are standardized and electronic, facilitating staff transfers seamlessly.

BONE MARROW TRANSPLANTATION AND CAR-T:

Based largely on experience with other respiratory viruses, recipients of hematopoietic stem cell transplants (HCT), CAR-T cells, or other immunosuppressive therapies are known to be at high risk of developing severe clinical infection. Thus, most HCT and CAR-T cell procedures have been canceled or delayed, based on parameters like chance of sustained disease-free survival, disease aggressiveness, and
comorbidities. Patients are reviewed by disease-specific teams and then prioritized by the cellular therapy team. Recipients and donors are instructed to follow protective behavior prior to procedures. Recipients are screened and tested for COVID-19 within 72 hours of conditioning or lymphodepleting therapy.

Specific guidelines for management of COVID-19 positive patients, patients in whom COVID-19 infection is suspected, and COVID-19 negative patients have been developed for protection of patients and staff. COVID-19 negative inpatients with hematologic malignancies are housed on a protected environment floor with physicians, APPs, and nurses using appropriate PPE. COVID-19 positive patients are placed on a COVID-19 positive floor. Workflow for neutropenic febrile patients incorporates standard COVID-19 risk stratification with clinical judgment. Direct patient exposure is minimized. Visitors are prohibited with very few exceptions, and, where possible, telemedicine is utilized for patient interactions. One physical exam is performed each day by an APP or a physician. Rounding by the inpatient team is virtual. We work collaboratively with palliative care for goals of care discussions.

Similar principles are followed for outpatients as outlined for other specialties above. Oral therapies are substituted for parenteral therapies wherever safe and effective. Non-essential labs and infusion visits are minimized. Transfusion guidelines have been revised and more strictly enforced with lower red cell (Hemoglobin 7 gm%) and platelet (10,000/ul) thresholds, commensurate with the clinical context. Oral electrolyte replacement therapy is utilized wherever possible. For transplant recipients and others receiving inhaled or IV pentamidine for PCP prophylaxis, Bactrim or atovaquone has been substituted. Similar considerations apply to patients with sickle cell disease and other non-cancer hematologic disorders, in all cases emphasizing patient safety.
GYNECOLOGIC ONCOLOGY:

The challenges in Gynecologic Oncology are somewhat different in that faculty take primary responsibility for the delivery of chemotherapy in addition to extended time spent in the Operating Room. Clinic operations are symmetrical with other departments within LCI (see above). In order to decrease exposure risk, new patients are limited to those with known or suspected cancer, pelvic mass, or high grade pre-invasive disease. New patient referrals with low grade pre-invasive disease, ovarian cysts unlikely to represent malignancy, or hereditary mutations are delayed for 2-3 months. For established patients, LCI guidelines (see above) are followed, including policies to reduce non-essential visits, etc. Infusion duration has been shortened when possible in conjunction with pharmacy. A rotational staffing model is employed. Surgical considerations are summarized below.

SURGICAL CONSIDERATIONS:

The Departments of Gynecologic Oncology, Surgical Oncology, Hepatobiliary Surgery and other subspecialty groups have adhered to a common approach to cancer surgery, again predicated on urgency of need versus patient and staff safety. All cases are categorized as essential or non-essential surgery; non-essential surgery is delayed in order to conserve resources and prevent exposures. In Gynecologic Oncology, essential surgeries are categorized according to a prioritization based on known cancer that requires urgent resection to obtain the best outcomes, known cancer that could be treated with an alternative strategy to achieve equivalent outcomes, preinvasive high grade disease or pelvic mass with normal markers, and elective surgery; these follow the SGO guidelines. Similar guidelines have been established by other specialty surgical societies.

Route of surgery and COVID-19 status are important considerations and are summarized in the Joint Statement by AAGL, SAGES and related organizations. Controversy surrounds the respective merits
of laparoscopic versus open surgery in this context, with consideration of evacuating any smoke plume during open surgery or pneumoperitoneum into a closed system being crucial, with the number of participating personnel being minimized. Clinic operations are the same as other LCI departments.

**SUPPORTIVE ONCOLOGY:**

LCI has made a major commitment to patient and caregiver support. The Department of Supportive Oncology incorporates sections of Palliative Medicine, Cancer Integrative Medicine, Psychological Oncology, Cancer Rehab, Cardio-Oncology, Cancer Nutrition, Cancer Navigation, and Cancer Survivorship. Many centers have simply discontinued many of these services, whereas our approach has been to leverage Virtual or Tele Medicine wherever possible. Non-urgent appointments have been rescheduled, with urgent meetings altered to virtual consults, and new patients carefully triaged depending on acuity. For new patients, referring clinicians are routinely contacted to determine urgency and need for in-person versus virtual consultation. Virtual platforms are used routinely except when in-person visits are required, meticulous personal protection and room sterilization protocols are followed. LCI is built on an extensive Nurse Navigator program, with more than 30 subspecialist navigators distributed throughout our network – their entire program has been shifted to telephone and virtual platforms, with carefully scripted Voice Mails for outgoing messages and telephone ID blocking to facilitate incoming calls on personal cell phones. Navigators are available by telephone or video to participate in in-person medical consultation if needed. All the clinical Sections conduct weekly interdisciplinary team meetings to ensure frail and/or complex patients have an effective, coordinated and well communicated Plan of Care. The department has also developed electronic support materials aimed at cancer patients, caregivers and clinicians in this challenging time.
CLINICAL TRIALS

Clinical trials have been affected by the COVID-19 pandemic. The safety of patients and clinical trials staff remain paramount. We thus have shifted to a dual team model, similar to that described for the clinical treatment teams, in which half the research staff work in-person and half remotely in 2-week periods. Staff who do not need to be patient-facing work exclusively remotely. Each disease section reviewed their respective clinical trial portfolios, keeping in mind that clinical trials which afforded opportunities for treatments otherwise not available would be prioritized. Registry, specimen collection, and other non-urgent patient treatment studies have been temporarily suspended to avoid added patient and staff exposure. Every attempt is made to adhere to clinical trial protocols, but when patient safety dictates variation from protocol, the deviation is reported accordingly.

SUMMARY:

The onset of the Covid-19 pandemic has created a complex set of management problems for patients with cancer, in which patients, care-givers and staff are potentially placed at increased risk. Protection for all participants is the hallmark of successful approaches to the situation, accompanied by social distancing, careful review of the aims and urgency of treatment, extensive use of virtual consultation, and modification of therapeutic approaches to reduce patient-facing contact whenever appropriate and safe. To make this more acceptable for patients and staff, meticulous strategies of communication are essential. We have summarized the approach taken in a large, multi-site multi-disciplinary cancer center to prioritize quality and safety of care.
REFERENCES:


