



The Impact of the COVID-19 Pandemic on Urooncological Care and the Future

Introduction

COVID-19 caused by severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) has become a pandemic and posed a great threat to humanity. With over 200 countries affected by the pandemic, more than Globally, as of 2:34pm CET, 2 January 2021, there have been 82,356,727 confirmed cases of COVID-19, including 1,815,433 deaths, reported to WHO.¹

It is also known that COVID-19 disproportionately harms elderly persons and those with comorbid conditions. A current or past cancer diagnosis appears to place infected patients at substantially increased risk. In early reports from China, patients with cancer who acquired COVID-19 had a higher risk for significant morbidity, including requirements for ventilatory support or death.²

There are increased chances of disease recurrence due to delay in anti-cancer treatment. Worldwide the oncologists face the following situations in clinical practice -a) Patient with cancer and symptomatic SARS-CoV-2 infection; b) Cancer patients tested positive for SARS-CoV-2 in contact screening, but asymptomatic and c) Asymptomatic cancer patient with undetermined SARS-CoV-2 status. Patients in oncology outpatient clinics can be from the following categories - a) those who are under evaluation for suspected cancer or recently diagnosed with cancer, b) those who are already on active anticancer treatment, c) those who are on follow-up after completion of active anticancer treatment. Further, the underlying cancer can be either localized or locally advanced where intention of treatment is cure or metastatic disease where intention of treatment is palliative.

The Localized disease can be deferred without compromising the oncological outcomes in most urooncological disease except a few like testicular cancer some cases of kidney cancer and high-grade urothelial cancer. In metastatic disease the patient should be sorted out: Who should be treated without

delay and whose treatment can be deferred? How much treatment is safe and optimal? Any alternative safe approach e.g. less toxic but effective if possible should be determined We need to optimize follow up program to minimize their hospital visits.

The task is extremely difficult. Risks must be balanced carefully, public health strategies implemented thoroughly, and resources utilized wisely. Furthermore, the policies and procedures developed today will serve as the basis for addressing the next outbreak or similar crisis. We need a guideline for management of GUC patients during the current COVID-19 pandemic with the primary aim of providing optimum cancer treatment which is safe for the patients during the current Covid Era without compromising oncological outcomes and minimizing risk of SARS-CoV-2 infection to our patients and health care staff.³

Urothelial tract cancers

Approximately 75% of BC is non-muscle invasive (NMIBC) and include disease confined to the mucosa, pTa, carcinoma in situ (Cis) or to the submucosa, pT1. Muscle invasive BC (MIBC) accounts for 25% of BC diagnosed. The WHO grading system categorize BC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade (LG) and high-grade (HG) papillary urothelial carcinoma. Urothelial cell carcinoma (UCC) is the most common histological type.

Non Muscle invasive bladder cancer:

Most of the patients (75 %) with bladder cancer present as superficial bladder tumors. High-grade non-muscle invasive cancer can be treated with trans-urethral resection of bladder tumor [TURBT] +/- intravesical BCG and cystoscopy surveillance. Patients with low-grade superficial bladder tumors can be treated with a single dose of immediate intravesical gemcitabine after TURBT [4]. The risk of getting SARS-CoV-2 infection is much higher than the benefit of intravesical BCG if a patient has to attend a health care facility frequently.

Muscle invasive bladder cancer/upper urothelial tract cancers:

Cisplatin based neoadjuvant chemotherapy (NACT) followed by radical cystectomy is the standard treatment for muscle invasive bladder cancer in cisplatin eligible patients. Gemcitabine- cisplatin [GC] should be considered as the regimen of choice due to lesser toxicity and similar efficacy⁵, despite absence of a phase 3 randomized control trial [RCT] over MVAC (Methotrexate, vinblastine, doxorubicin, cisplatin) and dose dense MVAC (ddMVAC).

Prior studies (before the NACT era) have shown that delaying bladder cancer surgeries by a few weeks is detrimental and may lead to worse outcomes.⁶ But during this pandemic, it may be worthwhile to defer surgery for 4-6 weeks for relatively asymptomatic patients and those with incidental diagnosis. A phase III RCT suggested that delaying chemotherapy till relapse did not result in worse survival as compared to immediate chemotherapy post-cystectomy.⁷ For patients who underwent upfront surgery and have pT3 /pT4, N0 or N1 disease, adjuvant chemotherapy can be deferred for at least 90 days without compromising the outcome.

Advanced / metastatic disease:

A newly diagnosed patient with suspected metastatic disease will require blood tests to check organ functions and computed tomography (CT) of chest and whole abdomen as baseline staging evaluation. A biopsy or fine needle aspiration is necessary for confirmation of diagnosis before starting treatment. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1 and who are cisplatin eligible we use 3-weekly gemcitabine (1000 mg/m² Day 1 and Day 8) and cisplatin (70 mg/m² Day 1 only) regimen with growth factor support, to the patients who can maintain adherence to treatment owing to restriction of movements during this pandemic. This will reduce the hospital visits as compared to recommended gemcitabine-cisplatin 4 weekly cycles wherein gemcitabine is given on D1, D8, D15 and cisplatin is administered on D2. Dose dense MVAC should be avoided in view of higher toxicity and comparable efficacy with the gemcitabine - cisplatin regimen. If possible, day 8 chemotherapy can be given at a community health center to avoid frequent visits. Cisplatin ineligible patients will be offered gemcitabine - carboplatin.⁸

Patients with Eastern Cooperative Oncology Group performance status (ECOG PS 2, 3 and 4) should be offered palliative care. Gemcitabine induced lung injury, though rare, can mimic symptoms of COVID -19 and should be kept in mind.^{8,9}

Immune check-point inhibitors [ICIs] are approved as first-line treatment in platinum ineligible patients and can be used in patients with high PD-L1 score. It should be clearly discussed that only a few percentage of patients get a prolonged response with anti PD-L1 therapy. Patients who are already on anti PD L1 therapy and have achieved a good response can consider a treatment break and restart therapy upon disease progression or after the pandemic is controlled. Pembrolizumab can be given 400 mg every 6 weeks as per the latest USFDA approval and nivolumab can be given 480 mg every 4 weekly as opposed to routine cycles and thus hospital visits can be reduced by 50%.

Five ICIs are approved in 2nd line treatment of urothelial tract cancer, out of which nivolumab, atezolizumab, durvalumab and pembrolizumab are available in India. However, the benefit is limited to few patients only. ICIs can cause pneumonitis, which might be difficult to differentiate from SARS-CoV-2 infection and treatment of both is drastically different. Patients should be warned of this side effect and upon developing any such symptoms the patient should contact the nearest health care facility immediately. ICIs remain the drug of choice after platinum failure and are relatively well tolerated with few grade 3 or 4 ICIs induced pneumonitis. The third and subsequent line of treatment should be avoided as the standard of care is not available in India and risk-benefit ratio is high for any experimental therapy during this pandemic. If a patient is responding clinically, imaging may be deferred for 3 to 4 cycles.⁹

Prostate Cancer:

Prostate cancer is a disease of older adults, who often have other comorbid conditions. They are at high risk of acquiring SARS-CoV-2 infection and optimum care should be given to them during this pandemic. Prostate cancer patients' management demands prioritization, adjustments, and a tailored approach during the unprecedented SARS-CoV-2 pandemic. Benefit of care from treatment must be carefully weighed against the potential of infection and morbidity from COVID-19.

Furthermore, urologists need to be cognizant of their obligation for wise consumption of restricted healthcare

resources and protection of the safety of their coworkers. Noncurrent in-person clinic visits should be postponed or conducted remotely via phone or teleconference. Prostate cancer screening, imaging, and biopsies may be suspended in general. Treatment may be safely deferred in low and intermediate risk patients. Surgery may be delayed in most high-risk patients and neoadjuvant ADT is generally not advocated prior to surgery.

Initiation of long-term ADT coupled with EBRT subsequent to the pandemic may be favored as a feasible alternative in high-risk and very high-risk disease. In patients with cN1 disease, treatment within 6 weeks is advocated. Pre surgery assessment should include testing for COVID-19 and preferably a chest imaging. In the presence of SARS-CoV-2 infection, surgery should be postponed whenever possible. All protective measurements suggested by national/international authorities must to be diligently followed during perioperative period. Strict precautions specific to laparoscopic/robotic surgery are required, considering the unproven but potential risk of aerosolization of SARS-CoV-2 virus and spillage with pneumoperitoneum. Regarding radiotherapy, shortest safe EBRT regimen should be favored and prophylactic whole pelvic RT and brachytherapy avoided. Chemotherapy should be avoided whenever possible.

It should not be perceived as rigid guidelines established from high level of evidence, but rather as reasonable perspectives on risk/benefit ratio in specific clinical scenarios. A particular advice may not apply to all countries, regions, or institutions, as a number of variables, including the stage of the pandemic, local healthcare capacity, risk of infection to a certain individual, stage and grade of cancer, presence of symptoms, comorbidities, age, and details of the treatment, must be weighed in the equation

Screening

National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU), and the Canadian Framework advise against routine PC screening, including prostate specific antigen (PSA) testing and digital rectal examination (DRE), for all asymptomatic individuals until the pandemic subsides.²¹ This is based on the fact that the risks of a delay in diagnosis of up to 6–12 months would be marginal for most PC.

Localized prostate cancer

Prostate cancer is generally a slowly progressing disease, with low and intermediate risk disease amenable for radical prostatectomy, radical radiotherapy as well as active surveillance, on a case to case basis. The question is - how long can we delay the surgery? Korets et al [10] in their study on 1561 men with localized prostate cancer opting for surgery, concluded that a delay of > 60 days was not associated with any adverse pathological outcomes. Additionally, it did not correlate with worse biochemical recurrence free survival. Therefore, patients can be re-assured that delaying treatment in the current scenario, would not adversely affect their outcomes.

Another clinical dilemma is regarding the surgical approach- whether it should be an open or a minimally invasive surgery? The potential benefits of minimally invasive (robotic/laparoscopic) surgery include lesser blood loss, well-visualized operative field, lesser post-operative discomfort and lesser in-hospital stay. However, there have been realistic concerns regarding the risk of dissemination of SARS-CoV-2 during minimally invasive surgery, which is considered an aerosol generating procedure.¹¹ Particles in surgical smoke have been demonstrated to contain a variety of toxic and virulent materials potentially capable of infecting through inhalation. In a nutshell, a surgical delay for patients with localized prostate cancer may not be very harmful, and if needed- surgery should preferably be performed via an open approach. Adjuvant radiotherapy if indicated can be delayed till recurrence. If radical radiotherapy is planned, then hypo fractionation [once weekly x 5-6 weeks] should preferably be used.

Locally advanced prostate cancer

Radical Prostatectomy may be performed if the patient is having a high-risk prostate cancer may be compounded with ADT and Radiation therapy if the margins are positive. Locally advanced prostate cancer may also be treated with IMRT Plus (RT+ ADT + Chemotherapy) may be chosen but chemotherapy may be deferred during the Covid Era. Neoadjuvant ADT may be safely given for 4-6 months and may offer some preventive to Covid infection.²² Consider use of 3 or 6 monthly formulations over monthly injection. Hypo fractionated external beam radiotherapy may be delayed up to 6 months.¹⁴

Metastatic hormone sensitive prostate cancer [mHSPC] The treatment of mHSPC has witnessed a paradigm shift in the last few years. Androgen deprivation therapy

(ADT) alone is the treatment of choice for a minority of mHSPC. ADT with chemotherapy (docetaxel) or androgen receptor (AR) targeted therapy (abiraterone acetate, enzalutamide, apalutamide) is the new standard of care in majority of mHSPC patients.¹²⁻¹³

Coronavirus disease 2019 (COVID-19) affects men significantly more than women^{22,23} Male patients with COVID-19 are reported to die at twice the rate of females when they contract the virus[24]. Lower levels of testosterone result in the upregulation of ACE2 and TMPRSS2 receptors, facilitating SARS-CoV-1 entry into the alveolar cells, and deregulating a lung-protective pathway.²⁵

Decreased testosterone levels in critically ill males negatively affect endothelial cell functioning, promote defective immune response, impair the ability to clear the virus, and promote systemic inflammation. Obesity among males also generates more pro-inflammatory cytokines important in cell signaling, emanating in increased vulnerability, severe disease, and worst outcome.

Lower serum testosterone level is a poor prognostic indicator for patients with COVID-19 by deregulating pulmonary protective pathways.²⁶ Thereby conceptually it may be hypothesize that low testosterone levels in males have a direct correlation with the severity of disease and a worse outcome in COVID-19.

Aim of therapy in the present time is to minimize hospital visits without compromising oncological outcomes. For symptomatic patients, use of GnRH antagonist is preferred, which is rapid acting and also minimizes the risk of testosterone flare. Once initiated, patients should be encouraged to take further injections at peripheral centers and follow up 3-4 monthly. For asymptomatic patients, GnRH analogues may be considered, which can be used at 3 or 6 monthly intervals. Surgical castration is better avoided. Interim follow-up can be done by telemedicine.²⁷

It is prudent to avoid chemotherapy during this pandemic, as there are higher chances of myelosuppression, febrile neutropenia and resultant morbidity. Amongst all available trial results of ADT with other agents in patients with mHSPC, enzalutamide remains the safest and should be first choice during this pandemic followed by abiraterone acetate-prednisolone. Chemotherapy should be considered as the least preferable option and if required,

can be delayed up to 4 months.¹⁴ Follow-up intervals should be increased to 2-3 months and patients can be monitored telephonically with local lab tests. Radiological tests should be postponed unless there is some urgent clinical indication like, cord compression or fracture.

Castrate resistant prostate cancer

Various factors including patient's age, comorbidities, ECOG PS, duration of response to prior treatment and disease burden determine the choice of therapy. The available options include chemotherapy (docetaxel, cabazitaxel), AR targeted therapy (abiraterone acetate, Enzalutamide), poly ADP ribose polymerase (PARP) inhibitors (olaparib) for those with germline BRCA/ATM mutations, and ICIs for those with tumor positive for microsatellite instability.

Chemotherapy, olaparib and immunotherapy may be avoided due to associated myelosuppression and immunosuppression. AR targeted therapy should be preferred because they are less toxic, require less frequent monitoring and fewer hospital visits. Patients who have progressed on multiple lines of therapy and are symptomatic should be offered hospice care at a local health facility or oral cyclophosphamide [15]. Bone modifying agents, like - zoledronic acid can be given at 3 monthly intervals.

Renal Cell Cancer (RCC)

Early stage disease

Radical nephrectomy remains the treatment of choice from stage 1 to stage 3 renal cell cancers and should be practiced. Patient can be kept on close observation in small size tumor (<2 cm) or surgery can be delayed for few weeks in relatively asymptomatic patients. Open surgery can be preferred over laparoscopic surgery to avoid aerosol generation. Alternative approach like - radiofrequency ablation or transarterial embolization can be attempted in place of radical surgery in small tumors or those with borderline fitness. Adjuvant use of tyrosine kinase inhibitors [TKI] should be discouraged in view of minimal survival advantage with very high treatment related toxicities.

Metastatic disease- upfront therapy

Last decade has seen a significant change in the management of metastatic clear cell renal cell cancer (RCC). Vascular endothelial growth factor (VEGF) targeted therapies and very recent ICIs +/- vascular endothelial growth factor (VEGF) targeted therapies

have become the new standard first-line therapy for mRCC [16-18]. In addition to systemic imaging, all patients should be assigned a risk category (favorable, intermediate and poor) based on International Metastatic RCC Database Consortium criteria which includes Karnofsky PS, haemoglobin, platelet count, absolute neutrophil count, corrected calcium, and time from diagnosis to systemic therapy.

A recent phase III randomized controlled trial demonstrated that sunitinib alone was not inferior to sunitinib followed by cytoreductive nephrectomy in mRCC. However, there is a role of cytoreductive nephrectomy in a small subset of patients (in those with Oligo-metastatic disease, very low burden disease or with indolent course). During the ongoing pandemic, it is prudent to delay cytoreductive nephrectomy.

Either VEGF targeted therapy or ICIs should be considered as the first line therapy in clear cell mRCC. Recent studies have shown pembrolizumab + axitinib, avelumab + axitinib, ipilimumab + nivolumab and bevacizumab + atezolizumab to have superior efficacy to sunitinib. Complete response rates are higher with these agents compared to VEGF targeted agents alone. Specific susceptibility to bacterial or viral infections in patients receiving ICI have not been studied. There is a possibility that patients undergoing ICI based therapy could be more immunocompetent than cancer patients undergoing chemotherapy. Also there is a possibility of cytokine release syndrome with use of ICI which can account for higher COVID-19 related complications.¹⁹ Pembrolizumab can be used 400 mg every 6 weeks and nivolumab can be used 480 mg every 4 weeks as per the latest USFDA recommendation.²⁰ There can be overlapping features of cytokine storms due to ICI and SARS-Cov-2 infection. Thus, the decision to use ICI over VEGF TKI should be carefully discussed with patients. Use of therapy will require more hospital visits, but has a higher chance of complete response with long-term control. At minimum, for elderly, frail and patients with multiple comorbidities – it may be judicious to use VEGF targeted therapy, while for others, immunotherapy combination / VEGF targeted therapy are the options.

2nd line and subsequent line of therapy

Patients who have progressed on the first line anti VEGF TKI may be treated with nivolumab, lenvatinib + everolimus or axitinib. Another active agent, cabozantinib is not available in India. Among these, axitinib or nivolumab [4 weekly schedule] might be better options because lenvatinib + everolimus is associated with higher toxicity, and dose reduction is needed in approximately 45% of patients. Further, everolimus is

immunosuppressive and can cause interstitial lung disease, mimicking the symptoms of COVID-19.^{19,20}

Testicular Germ cell Tumors

Testicular germ cell tumors (TGCT) are the most common solid organ cancers in males between the age of 15-40 years. These are highly curable malignancies. Since the intention of treatment is cure in all stages, it is imperative to adhere to the standard treatment. Some of the changes / precautions which can be considered in treatment for GCT patients during this period

For stage 1 seminoma, instead of active surveillance, a single cycle of carboplatin with Area Under Curve x 7 can be preferred. This will require less frequent hospital visits and will not compromise the efficacy. In advanced stages, avoid etoposide, ifosfamide and cisplatin [VIP] based chemotherapy as it is more myelosuppressive than EP or BEP. Bleomycin toxicity can mimic symptoms of Covid -19. For standard risk and intermediate risk disease, etoposide & cisplatin [EP] should be the treatment of choice. For high risk disease, there is a trade-off between bleomycin, etoposide & cisplatin [BEP] and VIP

In conclusions, the following principles of treatment should be used during treatment of patients with GUC during this COVID -19 pandemic.²⁷ Delay any treatment whenever feasible if oncological outcome is not compromised. To avoid exposure, minimize hospital visits. Use telecommunication in the form of telephonic consultation or telemedicine. Germ cell tumors should not be denied chemotherapy due to high cure rates.

Alternative to chemotherapy and immunosuppressive therapy may be sorted out, whenever feasible and shortest duration external beam radiotherapy regimen may preferably be used.²⁸ For patients receiving oral targeted therapies, lab tests can be done at local labs and can be consulted on telephone or telemedicine. Targeted therapy is safer and should be preferred over chemotherapy during COVID-19 pandemic. Surgery may be delayed whenever possible. Open approach instead of minimally invasive surgery should be preferred.

Prophylactic growth factors should be used liberally with chemotherapy. All patients & health care staff should follow the universal precautions laid down by local & national health authorities to prevent contracting SARS-CoV-2 infection.²⁹

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