



## IMPACT OF COVID-19 ON CANCER CARE

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**ABSTRACT**

The Corona Virus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has significantly changed health care delivery to cancer patients. We have reviewed the available literature on COVID-19 to provide comprehensive information about the impact on the delivery of health care in Cancer Care Facility and adaptations in oncological services. We carried out a literature search in English language using online databases PubMed, Up To Date and Embase with keywords: 'COVID-19', 'coronavirus' and 'SARS-CoV-2', 'cancer' from January 2020 to 30th June 2020 focusing on cancer care and different strategies to continue surgical services to cancer patients. Here, we have summarized all currently available information regarding the global impact on the delivery of surgical oncological care and adaptations in Cancer Treatment Protocols due to COVID-19 disease.

**KEYWORDS :** COVID-19 Pandemic, Cancer Hospital, Cancer Care Facility, Cancer Treatment Protocols

**INTRODUCTION**

The Corona Virus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has significantly changed health care delivery to cancer patients. To mitigate the spread of disease to patients and healthcare workers, measures like postponement of elective non-urgent operations and reduced patient visits to the health care facility undertaken. Preservation and judicious use of health resources are of paramount importance during the pandemic. Though cancer surgery is not absolutely elective, it requires prioritization due to limitations of staffing, Personal protective equipment, and beds. Telemedicine use has expanded and used more frequently for patient consultations. These measures, possibly reduced potential of contact and possibly spread of the disease, yet can delay diagnosis of malignancy and even presentation with an advanced illness, which eventually could lead to stress on health services for palliative care. Before treating cancer, the

benefits of treatment and the risk of SARS-CoV-2 exposure must be balanced for risk-benefit until the pandemic wanes or a vaccine develops. Studies have shown that patients with cancer and COVID -19 have a high case fatality rate<sup>(1)(2)</sup> Enrolment in clinical trials has reduced, and only trials that are most likely to benefit patients have been continued. New ethical concerns arose when health resources are to be prioritized and made available to patients in which treatment is more likely to be successful rather than patients with late-stage disease and comorbidities. Early colon cancer surgery was put on hold; the advanced disease was considered for neoadjuvant therapy balanced against risks of immunosuppression and advanced rectal cancer with long course chemoradiotherapy or total neoadjuvant therapy.<sup>(3)</sup> Several national groups have formulated guidelines for triage and treatment of cancer patients during the COVID-19 pandemic to preserve hospital resources for virus-infected individuals by deferring cancer treatments but also

attempting to avoid significantly compromising cancer care. These guidelines will continue to get revised as the pandemic evolves, and new considerations arise.<sup>(4)</sup>

### IMPACT ON BREAST CANCER.

As a result of pandemic screening services, diagnostic imaging and procedures are either restricted or postponed. Many breast surgeries and reconstructive procedures have been deferred. Neoadjuvant systemic therapy had been increasingly used for the treatment of breast cancer patients. This led to increased use of genomic tumor profiling to guide the treatment. National groups like NCCN, ESMO, COVID-19 Pandemic Breast cancer Consortium have formulated guidelines for triage and treatment of breast cancer according to the stage, tumor biology, comorbidities, and available hospital resources.<sup>(5)</sup> The impact of COVID -19 on breast and colorectal cancer is estimated to cause a 1 % increase in mortality in the United States.<sup>(6)</sup> The patients have been triaged into categories A, B, C for surgical care, imaging, hormonal, or chemotherapy during the pandemic in decreasing order of urgency.<sup>(7)</sup> Category A includes patients who require immediate medical care like associated breast abscess in septic patients, expanding hematoma in unstable patients, oncologic emergencies like febrile neutropenia, hypercalcemia, intolerable pain, bleeding, painful inoperable locoregional disease, progressive disease during Neoadjuvant chemotherapy. Category B patients include patients whose treatment can be delayed for a short period but not indefinitely. Most of the breast cancer patients fall under this category. Patients who have completed neoadjuvant chemotherapy for inflammatory carcinoma, progressive on treatment, TNBC, and HER2+ patients are to be operated. Patients with stage clinical anatomic stage I or 2 ER+ /HER2 – Breast cancer neoadjuvant endocrine therapy to defer surgery for 6-12 months. Clinical stage T2 or N1 ER+ /HER2 –ve tumors are considered for hormonal therapy, and surgery is delayed. Category C patients include patients whose treatment can defer until the pandemic is over like ER – DCIS, positive margins for invasive cancer. Prophylactic surgeries, reconstruction surgeries, and biopsies likely to be benign are postponed.<sup>(7)</sup> There has been a paradigm shift from operative management of breast cancers to endocrine therapies and chemotherapies. Another hurdle for the treatment of breast cancer services is the growing shortage of inpatient beds and services due to COVID -19 cases.<sup>(8)</sup>

### IMPACT ON THORACIC CANCER

Treatment and care of thoracic cancer patients during the COVID-19 pandemic poses several challenges. Lung cancer patients on antitumor treatment are immunocompromised and have a high risk of getting infected with SARS-CoV-2. Lung cancer patients have symptoms of fever, cough, respiratory distress, which are also seen in SARS-CoV-2 infection. It is difficult to identify new onset pneumonia in these patients. Viral pneumonia, radiation pneumonia, and cancer progression are the other possible diagnosis.<sup>(9)</sup> Thoracic cancers are aggressive cancers in which delay in treatment affects patient outcomes. Prompt surgery improves the likelihood of survival in these patients. During the epidemic surgery is deferred when there is a high likelihood of ICU stay or prolonged hospitalization after surgery.<sup>(10)</sup> Intraoperative procedures like bronchoscopy, cross-field, and jet ventilation, tracheostomy, sputum suctioning needs to be avoided as possible as these are high-risk procedures. The minimally invasive approach concerns the spread of infection via CO<sub>2</sub> aerosolization, but this is not the case with VATS as CO<sub>2</sub> is not always used in procedures.<sup>(11)</sup> Priority A includes patients who require treatment within two weeks. This includes patients with SVC syndrome, bleeding, airway obstruction, spinal cord compression who require surgery. Patients who are on the neoadjuvant whose outcome of the residual tumor

will get adversely affected by delaying surgery are considered to undergo surgery. Priority B (treatment within 2-6 weeks) includes patients with solid lung tumors who did not undergo induction chemotherapy. These patients are favored for surgery. Patients on maintenance immunotherapy and maintenance chemotherapy for more than six months and in whom surgery or radiation is indicated are included in this category. Priority C (treatment can be postponed to more than six weeks) includes patients who are on maintenance immunotherapy > 2 years and are in post-op surveillance.<sup>(4)</sup>

### IMPACT ON COLORECTAL CANCER

Screening, diagnostic imaging, and treatment have been delayed due to the pandemic. Colonoscopic investigations are avoided due to the potential risk of enteric virus shedding.<sup>(12)</sup> NHS UK guidance recommended delaying colorectal cancer surgeries for 2-3 months.<sup>(13)</sup> Difficult triage situations and new ethical challenges arose due to the pandemic. The risks of delaying treatment versus the risk of getting infected with SARS-CoV -2 have been weighed against each other.<sup>(14)</sup> Cases were prioritized into A, B, C depending on the urgency of treatment. Priority A (urgent) includes patients with obstructing colon and rectal cancer, intestinal perforation secondary to cancer, acute hemorrhage from malignancy with transfusion dependence. Priority B (non-urgent but priority) patients include colon and rectal cancer cases who have completed neoadjuvant therapy. Priority C (elective) patients include newly diagnosed rectal cancer for whom neoadjuvant therapy is encouraged, staging right hemicolectomy for appendiceal carcinoma. For these patients surgery can be postponed for a few months.<sup>(4)</sup> Alternative treatments are given priority over surgeries to reduce the risk of Covid infection. Locally advanced resectable cancers are considered for neoadjuvant chemotherapy, Total neoadjuvant therapy (TNT), short course radiation. In downstaged tumors post neoadjuvant therapy, surgery is delayed for 12-16 weeks. Embolization and radiation therapy for bleeding from cancer and stenting for near obstructing cancers are considered to delay surgery.<sup>(15)</sup> These measures are done to conserve institutional resources /ICU/ventilators for COVID-19 patients, but surgery cannot be delayed indefinitely for these patients, and patients might present with advanced disease with complications due to delay in diagnosis.

### IMPACT ON HEPATOBILIARY CANCER

Hepatobiliary cancers are treated mainly by surgery in the early and middle stages. Treatment of patients with hepatobiliary system tumors who are already immunocompromised increases the likelihood of infection with COVID-19 and risk of serious illness.<sup>(16)</sup> In the context of hepatobiliary and pancreatic cancer, CT scans, and tumor markers like CA19-9, CEA, and AFP are prioritized as it determines the course of treatment. Patients are classified into High priority (Priority A: treatment required within two weeks), Moderate priority (Priority B: within 2-6 weeks), Low priority (Priority C: treatment can be postponed for six weeks or longer). Patients included under high priority are considered for surgery if the patient has life-threatening complications like bleeding, fistulas, cholangitis, pancreatitis, perforations. A patient who is already on neoadjuvant protocols and delay in surgery could adversely affect the outcome are considered for surgical management. Patients are to be prioritized depending on tumor characteristics. Drainage procedures, PVE (Portal venous embolization), TACE (Transarterial chemoembolization), and TARE (Transarterial radioembolization) , are considered a high priority. Modality, which includes the least frequent hospital visits, are favored. Priority B includes patients stable on neoadjuvant, and patients who can receive additional chemotherapy cycles, and whose surgery can delay for 2-6 weeks without adversely affecting

the outcome. Patients in priority B upgraded to Priority A after 2-6 weeks. Priority C includes patients with premalignant conditions like IPMN (Intraductal papillary mucinous neoplasm).<sup>(4)</sup> Unlike other malignancies, treatment can only be postponed for a few weeks. The clinical outcomes of surgery for hepatobiliary pancreatic malignancy during the COVID-19 pandemic are yet to be elucidated. Apart from delays in diagnosis and treatment, surgery for liver cancer poses new problems. Hepatic resection increases the susceptibility to SARS-CoV-2 due to increased expression of ACE-2 demonstrated in mouse models.<sup>(17)</sup> After hepatectomy, life-threatening complications like post hepatectomy liver failure can affect the metabolism of drugs used in the treatment of COVID-19, and in turn, COVID-19 infections could be responsible for Post Hepatectomy Liver Failure. Lung injury due to COVID-19 is also an independent risk factor for morbidity and mortality after COVID-19.<sup>(18)</sup> Biliary malignancies, which are less common when compared to colon and breast, tend to present in an advanced stage, thereby becoming unresectable diagnostic procedures and surgery is delayed, which will lead to increased mortality and stress on palliative care.

### IMPACT ON HEAD AND NECK CANCER

Surgery had been considered first-line therapy in head and neck cancers. Conduction of safe surgery has many new barriers during the pandemic, preoperative screening, diagnostic procedures of the upper aerodigestive tract like laryngoscopy, bronchoscopy, endoscopy have a higher risk of transmission of the virus. Patients tend to present at an advanced stage of the disease. Non-surgical alternatives to treatment had been emphasized during the pandemic to limit the spread of disease. Chemoradiotherapy is considered the first line of management during the pandemic for head and neck cancers. Most of the patients of Head and Neck Cancer tend to be elderly who are at increased risk of contracting the infection. Chemotherapy might lead to immunosuppression and thereby increase the chance of infection. Risk stratification and evaluating the options by multidisciplinary tumor board and shared decision making with patients will help in choosing the best option. There will also be a surge in cases due to delayed presentation and increased presentation to hospital for complications due to malignancy. The increase in visits to a health care facility after the relaxation of lockdown measures also lead to a surge in cases.<sup>(19-21)</sup> Omitting systemic therapy for patients > 70 years or younger with comorbidities such as diabetes and cardiovascular diseases is one of the strategies to reduce the chance of infection as survival benefit is not there with chemotherapy.<sup>(21)</sup> Surgery for head and neck surgery carries a high risk of transmission due to lengthy and potential aerosol-generating procedures like laryngectomy, tracheotomy.<sup>(21)</sup> Patients are divided into priority A, B, C. Priority A includes patients with upper aerodigestive tract cancers, metastatic tumors, medullary/poorly differentiated/anaplastic cancers, aggressive tumors for whom treatment is to be started immediately. Priority B patients include well-differentiated thyroid cancer, stable metastatic disease in which surgery and adjuvant therapy are delayed for 6-8 weeks. Priority C includes patients with the parathyroid disease and benign tumors for whom treatment is postponed.<sup>(4)</sup> Care of head and neck cancer patients is weighed against the risk of transmitting infection. The procedures include manipulation of the aerodigestive tract, exposing patients and health care providers at higher risk of infection. It raises ethical challenges as we care for individuals and also has to fulfill responsibilities to society.<sup>(22)</sup>

### IMPACT ON GYNAECOLOGIC CANCER

Delay in treatment for pelvic gynaecological malignancy is an

independent factor that contributes to mortality per se. Due to diversity in infra-structure of health care system it is not wise to advocate "one size fits all" protocol for patients with cancer limiting risks associated with the virus. These patients have a four to eight fold increased risk of developing severe respiratory complications, at times fatal, with COVID-19 compared to the general population. Risk increases if they have undergone surgery or chemotherapy in preceding week. Therefore, if a patient with pelvic gynaecological malignancy presents with COVID-19 it is best to postpone surgery by two weeks. Patients with early stage endometrial cancer of low or intermediate risk ideal management is primary surgery, hysterectomy with bilateral salpingo-oophorectomy and sentinel node sampling. Surgery can be postponed by 4-8 weeks in women with FIGO (International federation of Gynecology and Obstetrics) stage IA on MRI and grade 1-2 endometrioid cancer on endometrial biopsy. Women with advanced endometrial cancer (Stage III & IV) should be offered first line medical treatment. Women diagnosed with cervical cancer should be offered radiotherapy and concomitant radiochemotherapy as first-line treatment instead of surgery. Lymph node staging can be reviewed on a case-by-case basis depending on site, imaging and stage of disease. Advanced cases of ovarian malignancy neo-adjuvant chemotherapy should be preferred over primary debulking surgery. Women requiring interval surgery should receive six cycles of chemotherapy followed by surgery. It is not advisable to perform hyperthermic intra-peritoneal chemotherapy (HIPEC) during the ongoing pandemic. For those with vulvar cancer surgery remains standard of care. In elderly women where tumor size has not progressed treatment may be postponed by few weeks. Women with vaginal cancer usually present in advanced stage. They require radiotherapy/chemotherapy/brachytherapy. Lymph node staging can be reviewed on a case-by-case basis depending on site, imaging and stage of disease. Trophoblastic tumors are curable but have high metastatic potential. Patients with low risk (FIGO  $\leq$  6) should receive methotrexate at home. High risk trophoblastic tumors should be administered multi-drug regimen without delaying treatment. Molar pregnancy require suction curettage under ultrasound guidance. Follow up with telemedicine is an option. For women with endometrial and cervical cancer follow up requires clinical examination which is not possible on telemedicine. It is time to reconsider our policy for managing these patients and limit risk of infection to them.<sup>(23)</sup> There is a significant impact of COVID-19 on gynecological malignancy, leading to delayed diagnosis and evaluation. Postponement of surgeries leads to adverse outcomes in these patients. High priority patients include radiologically confirmed bowel perforation, peritonitis, complications after radiotherapy, uterine/pelvic hemorrhage. Hysterectomy with bilateral salpingo-oophorectomy in newly diagnosed endometrial cancer is considered a medium priority. Stage I A tumors can be postponed up to 2 months. Low priority patients include carcinoma in situ lesions. Total pelvic exenteration, risk-reducing surgeries, resection of slowly growing central recurrence is postponed until after the epidemic.<sup>(24)(25)</sup> Decisions on individual cases are to be taken by multidisciplinary boards and depending on hospital resources and weighing the risk of infection, surgical outcomes, and benefit of treatment.

### IMPACT ON GENITOURINARY CANCERS

#### Kidney

Radical treatment is preferred in renal masses of >cT2b or symptomatic renal mass or renal mass with IVC or renal vein thrombus on priority. Tyrosine kinase inhibitors are preferred in Metastatic RCC irrespective of IMDC risk category. Partial or radical nephrectomy for other small asymptomatic renal masses can be deferred for 6 months. <sup>(26)(27)</sup>

**Upper tract urothelial carcinoma (UTUC)**

Radical nephroureterectomy (RNU) with bladder cuff excision is preferred in high risk (Size >2 cm, variant histology, presence of hydronephrosis, multifocality), nonmetastatic UTUC or for palliative care like in persistent hematuria and excruciating pain. Low risk UTUC unifocal disease, Size <2 cm or non-invasive UTUC on CT urography are deferred at least for 3 months. (28) **Bladder**

Transurethral resection of bladder tumor (TURBT) is done on priority in cases of bladder tumor with hematuria, large bladder mass, residual tumor after initial resection, restage TURBT in cases of T1 high grade histopathology on initial resection. Radical cystectomy with urinary diversion is advised in cT2-4N0M0 or BCG refractory bladder cancer. Chemoradiation was offered to improve local control in cases of inoperable locally advanced tumours and adjuvant chemotherapy was offered in pT3-T4, pN1-N2-N3 disease. (29)(30)(31)

**Prostate**

Screening for prostate cancer was deferred and upfront mpMRI was considered for high risk and symptomatic patients followed by prostate biopsy. Treatment for low risk localized cancer was deferred and radiotherapy was considered in intermediate risk either as hypofractionation (20x3 Gy) or Ultra hypofractionation (5x7 Gy) starting with neoadjuvant ADT. For high risk localized ca prostate, radical prostatectomy was preferred. For locally advanced prostate cancer (including cN1) long term ADT + EBRT was considered. For metastatic hormone sensitive prostate cancer, systemic treatment with ADT and for metastatic castration-resistant prostate cancer abiraterone acetate plus 5 mg daily prednisone or enzalutamide was offered. Chemotherapy (Docetaxel) was avoided due to risk of neutropenia requiring frequent hospital visits. (32)(33)(34)(35) **Testis**

High inguinal orchiectomy was done on priority in patients with testicular mass suspicious of malignancy. Active surveillance (AS) was advised in CS I of seminoma and NSGCT, if patient not willing for AS in high risk CS I consider one cycle of carboplatin in seminoma and one cycle of BEP in NSGCT. 3 cycles of BEP were offered in CSIIA, II B and IGCCCG (International Germ Cell Cancer Collaborative Group) good risk metastasis of both seminoma and NSGCT. Radiotherapy can be considered in stage IIA seminoma. Four cycles of BEP were offered in Metastatic disease (Stage II C and III) IGCCCG Intermediate and High Risk group NSGCT and intermediate risk seminoma. (35) **Penis**

Total or partial penectomy was done on priority in cases of penile growth to relieve urinary obstruction and excruciating pain. Radical inguinal lymphadenectomy were offered in cN1-2 and Ipsilateral pelvic dissection if pN2/pN3 in ipsilateral groin. Neo-adjuvant chemotherapy advised in T4/cN3 and surgery was considered in responder patients. Adjuvant chemotherapy was delayed in pN2/3 inguinal nodes. (36)(37)

**CONCLUSIONS**

COVID-19 Pandemic is going to stay for long, cancer patients being vulnerable population needs special attention and strategies to continue delivery of services. Modalities of treatment that are less immunosuppressive and can be done on an outpatient basis should be prioritized. Although many articles and literature are being available for the management of cancer during the COVID-19 pandemic, there is no high-level evidence regarding the same. The management strategies will continue to change as time progresses with accumulating evidence depending on age, sex, and organ of origin.

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