PHILIPPINE SOCIETY OF MEDICAL ONCOLOGY (PSMO) CONSENSUS RECOMMENDATIONS IN THE MANAGEMENT OF BLADDER CANCER DURING COVID-19 PANDEMIC IN THE CORONAVIRUS DISEASE 2019 (COVID-19) ERA

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I. INTRODUCTION

Bladder cancer (BC) is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012 [1]. In the United States, approximately 80,000 new cases and 18,000 deaths occur each year due to bladder cancer [2]. In Europe, there were an estimated 118,000 cases and 52,000 deaths in 201 [3]. Bladder cancer is typically diagnosed in older individuals, with a median age at diagnosis of 69 years in men and 71 in women. The incidence increases with age from 142 to 296 per 100,000 in men aged 65 to 69 years and 85 and over, respectively, and from 33 to 74 per 100,000 in women in the same age groups. Among bladder cancer cases, about 47% are estimated to be Ta/Tis at initial presentation, 21% stage I, 11% stage II, 4% stage III, and 6% stage IV disease in the US [4]. With regard to mortality risk from COVID-19, 63% of patients with BC have one comorbidity (such as hypertension, cardiovascular, or pulmonary), 32% have two or more comorbidities, and the risks of dying from BC or from a competing disease are similar at 5-year after diagnosis.

II. GENERAL RECOMMENDATIONS

A. Prioritization

The tiered approach of European Society of Medical Oncology (ESMO) for cancer patients in general during the COVID-19 pandemic [5] is designed across three levels of priorities, namely: Tier 1 (HIGH PRIORITY), Tier 2 (MEDIUM PRIORITY), Tier 3 (LOW PRIORITY) as follows:

- **HIGH PRIORITY**: Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (i.e. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL])
- **MEDIUM PRIORITY**: Patient's situation is non-critical but delay beyond six (6) weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for immediate priority
- **LOW PRIORITY**: Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of the benefit (i.e. no survival gain with no change nor reduced QoL)

B. Screening for COVID-19

All patients and their companions should be screened for symptoms relating to SARS-COV-2 [6-7]. Due to the different contexts of various countries and areas within the countries, it is recommended that testing be accorded to local guidelines and present directives. Should tests be available and allowed, SARS-COV-2 testing should be done before surgery or any invasive procedure, and before initiating immunosuppressive therapies, especially high dose chemotherapy, regardless of symptoms [8-9].

Recommendations regarding screening will depend on the availability of tests

to the health facility as well as local and institutional guidelines. At present, only real-time reverse transcription polymerase chain reaction (rRT-PCR) assays can be used to confirm COVID-19 infection using nasopharyngeal, oropharyngeal swabs, or other bodily fluids [10]. Should another test (e.g. rapid antigen tests) be used as initial screening, this should be confirmed with an rRT-PCR.

C. Outpatient Visits and Telemedicine

Below are the recommendations for outpatient visits based on levels of priorities as adopted from ESMO guidelines:

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Patients with muscle-invasive disease should be evaluated for potentially curative therapy • Patients with new presentation of advanced disease • Patients rapidly progressing on first-line immune therapy • Patients with suspected cancer-related emergency such as brain metastasis or spinal cord compression	• Ongoing assessment for patients on treatment and assessment of response/progression to therapy • Follow-up visits while on surveillance post-chemotherapy • Further investigations (re-TURB) and initiation of treatment with BCG or discussion of cystectomy where feasible in high-/intermediate-grade or recurrent/BCG-refractory non-muscle-invasive disease	• Follow-up visits in clinically asymptomatic patients without evidence of metastatic disease (prefer teleconsulting if necessary) • Low-risk non-muscle-invasive disease

The following patients can be attended to via telemedicine: on-treatment patients with new symptoms or side effects (depending on severity of symptoms or side effects and burden of progression), established patients with no new issues, survivorship follow-up, and psychological support visits. Safety monitoring of patients on oral chemotherapy or endocrine therapy plus biological agents may be intensified [11].

D. Supportive and Palliative Care

a. There is no known role for prophylactic antiviral therapy for COVID-19 in any patient, including immune suppressed patients [12].
b. Flushing of ports can occur at intervals as long as every 12 weeks, and patients who are capable of flushing their own devices should be encouraged to do so [12].
c. Transfusions should be given according to usual practice guidelines, if possible, with consideration of erythropoietin-stimulating agents if severe or life-threatening anemia is anticipated or if blood products become scarce due to lack of donations. If anemia is due to bleeding, tumor embolization, volume expanders, and antifibrinolytic agents (e.g tranexamic acid) can be offered as a temporizing measure; iron infusions are another option for those in less immediate need [12].
d. For patients in need of other blood products such as fresh frozen plasma (FFP) or platelets, care should be individualized based on the indications, severity, and alternatives. Donor-directed transfusions should be encouraged from patient family members in order to help sustain blood product supply during the pandemic [12].
e. For patients who are febrile and likely to be neutropenic based on the timing of their cancer treatments, it may be reasonable to prescribe empiric antibiotics if the patient seems stable by clinical assessment (in person or via telemedicine evaluation). It is preferable that further evaluation be pursued, if necessary, outside of the emergency department [12].
f. Although myeloid growth factor support is typically administered for those at high risk for febrile neutropenia (>20 percent), it may be reasonable for patients with a lower level of expected risk for febrile neutropenia with treatment (eg, >10 percent) to be prescribed prophylaxis with growth factor support [12].

III. RECOMMENDATIONS ON MANAGEMENT FOR SPECIFIC CANCER TYPES: BLADDER

A. Diagnosis and Imaging

QUESTION	**Among patients presenting with gross hematuria, what are the diagnostic tests recommended at the least?**
ANSWER	Ultrasound (US) and Computed Tomography – Intravenous Urography (CT-IVU) can be done in patients with visible (macroscopic) hematuria. Cystoscopy can be done in patients with visible (macroscopic) hematuria without clots (It should be abandoned in cases with unequivocal lesion on US or CT-IVU). In such a situation we should proceed immediately to Transurethral Resection of the Bladder - TURB).

QUESTION	**Who are the patients we need to prioritize to undergo imaging?**

ANSWER	Urgent situations that necessitate immediate imaging are those patients whose disease need stage classification (locally advanced or metastatic) to provide an exact treatment plan, patients who need to be restaged during/after neoadjuvant chemotherapy, patients with clinically urgent situations (bleeding, fractures, high-grade toxicities of checkpoint inhibitors that need to be clarified), and those patients whose imaging results show suspicious for relapse or metastatic disease. (HIGH PRIORITY) Patients who need the imaging to assess response to ongoing therapy (MEDIUM PRIORITY), asymptomatic patients who need follow-up imaging and patients with non-muscle invasive disease (LOW PRIORITY) can have their imaging postponed at the latest recommended timepoint.

Below are the recommendations for imaging based on levels of priorities as adopted from ESMO guidelines [5]:

HIGH PRIORITY	**MEDIUM PRIORITY**	**LOW PRIORITY**
• All imaging that is necessary to clarify disease stage (locally advanced or metastatic) to provide an exact treatment plan (surgery or systemic treatment) • Restaging during/after neoadjuvant chemotherapy • All imaging that needs to be done in clinically urgent situations (bleeding, fractures, high-grade toxicities of checkpoint inhibitors that need to be clarified) • Imaging in patients clinically suspicious for relapse or metastatic disease	• On-treatment assessment of response to therapy	• Follow-up imaging in asymptomatic patients (postpone imaging at latest recommended timepoint) • Imaging for non-muscle-invasive disease

B. Treatment: Non-Muscle Invasive Bladder Cancer (NMIBC)

According to the European Association of Urology (EAU) recommendations, any surgical intervention can be classified as per the following tier [11]:

- **EMERGENCY**: Cannot be postponed for more 24 hours. Life threatening situation.
- **HIGH PRIORITY**: The last to cancel, prevent delay of > 6 weeks. Clinical harm (progression, metastasis, loss of organ function and deaths very likely if postponed > 6 weeks.
- **INTERMEDIATE PRIORITY**: Cancel but reconsider in case of increase in capacity (not recommended postponing more than 3 moths: Clinical harm (progression, metastasis, loss of organ function) possible if postponed 3-4 months but unlikely)
- **LOW PRIORITY**: Clinical harm (progression, metastasis, loss of function) very unlikely if postponed 6 months.

QUESTION	**Among patients with non-muscle invasive bladder cancer classified as EMERGENCY (i.e. life-threatening situation or opioid-dependent pain), how early should a diagnosis be made?**
ANSWER	Conditions as such should be diagnosed within < 24 hours.

QUESTION	**Among patients with non-muscle invasive bladder cancer, what conditions can be classified as EMERGENCY, what is the most we can offer?**
ANSWER	TURB in patients with visible (macroscopic) hematuria and clot retention requiring bladder catheterization.

QUESTION	**For patients diagnosed with non-muscle invasive bladder cancer, should surgery be done without postponement?**
ANSWER	Cystectomy should not be delayed unless neoadjuvant chemotherapy is given and be performed in preferably non-COVID-19 hospitals. Non-urgent cystectomies, such as for NMIBC or non-cancer reasons, may be delayed until a more chronic phase of the pandemic has occurred. There may be scenarios where giving or extending neoadjuvant therapy may optimize the timing on cystectomy. Clearly every decision has to be made on a case-by-case discussion and tailored to locally available resources and the current pandemic status.

QUESTION	**When should a Transurethral Resection of the Bladder (TURB) and 2nd TURB be done?**
ANSWER	TURB in patients with bladder lesion and intermittent macroscopic hematuria or history of high-risk NMIBC (HIGH PRIORITY) should be

	performed within less than 6 weeks. Second TURB in patients with visibly residual tumor after initial resection and large or multiple T1HG at initial resection without muscle in the specimen is also included in this tier of patients, hence must be addressed within less than 6 weeks. TURB in patients with any primary tumor or recurrent papillary tumor > 1cm and without hematuria or without history of high-risk (HG) NMIBC (MEDIUM PRIORITY) can be done before end of 3 months. TURB in patients with small papillary recurrence/s (< 1 cm) and history of Ta/1 low grade tumor (LOW PRIORITY) can be deferred but not indefinitely, up to 6 months. Further, second TURB in patients with visibly complete initial TURB of T1 lesion with muscle in the specimen can be deferred up to 6 months.

QUESTION	**What are the other treatment options for patients with non-muscle invasive bladder cancer?**
ANSWER	Intravesical instillations and radical cystectomy are other options for treatment.

QUESTION	**When should an intravesical instillation be done?**
ANSWER	Among the HIGH PRIORITY group of patients, intravesical BCG immunotherapy with one year maintenance in patients with high-risk NMIBC should be administered within < 6 weeks. Early post-operative instillation of chemotherapy in presumably low or intermediate-risk tumors can be delayed up to 6 months, as well as intravesical BCG or chemotherapy instillations in patients with intermediate-risk NMIBC.

QUESTION	**When is radical cystectomy an option?**
ANSWER	Immediate radical cystectomy in patients with highest-risk NMIBC, and early radical cystectomy in patients with BCG unresponsive tumor or BCG failure.

QUESTION	**Is radiotherapy an option for treatment of patients with non-muscle invasive bladder cancer?**
ANSWER	Radiotherapy should not be seen as an attractive alternative to surgery as it is associated with its own challenges.

QUESTION	**When should a repeat cystoscopy be performed?**
ANSWER	Follow-up cystoscopy in patients with NMIBC and intermittent hematuria (HIGH PRIORITY) should be done within <6 weeks. Follow-up cystoscopy in patients with the history of high-risk NMIBC without hematuria (INTERMEDIATE PRIORITY) can be prolonged up to 3 months. Follow-up cystoscopy in patients with the history of low- or intermediate-risk NMIBC without hematuria can be deferred up to 6

	months.

QUESTION	**Alternatively, what other surveillance methods can be done among the LOW PRIORITY patients with non-muscle invasive bladder cancer?**
ANSWER	Upper tract imaging in patients with the history of high-risk NMIBC.

C. Treatment: Muscle Invasive Bladder Cancer (MIBC)

QUESTION	**Can we delay radical cystectomy from diagnosis/transurethral resection of bladder tumor (TURBT) of MIBC?**
ANSWER	**Delay in radical cystectomy should NOT be greater than 12 weeks from diagnosis/TURBT*.*** Significant delay of radical cystectomy increases risk of death. Russell, et al [13], conducted a systematic review and meta-analysis of studies assessing delay in radical cystectomy. In patients with median delay of 30-93 days between diagnosis and radical cystectomy, hazard ratio is 1.34 for overall survival. A delay from TURBT to radical cystectomy had a hazard ratio of 1.18. The shortest cutoff for delay among the studies included in the systematic review and meta-analysis is less than 12 weeks from diagnosis or TURBT. NCCN guidelines recommends cystectomy to be done within 3 months of diagnosis if no neoadjuvant therapy is given [14].

QUESTION	**Can we delay radical cystectomy after neoadjuvant chemotherapy?**
ANSWER	**Consider NOT delaying cystectomy of more than 10 weeks after neoadjuvant chemotherapy.** The studies included in the systematic review of Russel, et al. [13] found mixed results between a delay in radical cystectomy and overall survival in patients who received neoadjuvant chemotherapy, with the meta-analysis finding no significant association. In a prospective study by Boeri et al. [15], they found that time to cystectomy of greater than 10 weeks was associated with a significantly worse overall survival (HR 1.87, p=0.002) and cancer-specific mortality (HR 2.25, p<0.001).

QUESTION	**Can we delay neoadjuvant chemotherapy after diagnosis of MIBC/TURBT in those eligible for Cisplatin-based therapy?**
ANSWER	**Consider NOT delaying neoadjuvant chemotherapy greater than 8 weeks after diagnosis of MIBC.** A delay of greater than or equal to 8 weeks to start neoadjuvant chemotherapy was significantly associated with a higher risk of upstaging and lymph node positivity (HR 1.27, p 0.031) [16].

QUESTION	**In MIBC with variant histology, can radical cystectomy be delayed?**
ANSWER	**Consider NOT delaying cystectomy of more than 8 weeks after diagnosis of MIBC with variant histology.** In a study by Lin-Brande et al. [17], an 8-week delay in in cystectomy in those with variant histology had a statistically worse survival (P = 0.03). Median overall survival for patients who underwent surgery ≤8 and >8 weeks from diagnosis was 84 and 23 months, respectively for pathologic variants (diagnosed after cystectomy). For clinical variant (diagnosed after TURBT), the median overall survival was 84 and 5 months for surgery ≤12 and >12 weeks, respectively. Among patients with pathologic variant, the 5-year OS estimate was 64% for cystectomy ≤8 weeks and 35% for >8 weeks from diagnosis (p=0.02). For clinical variant, the 5-year OS estimate was 61% and 36% (p=0 .04) for cystectomy ≤12 weeks and >12 weeks from diagnosis, respectively.

QUESTION	**Can we omit adjuvant chemotherapy after radical cystectomy in those who did not receive neoadjuvant chemotherapy?**
ANSWER	**Consider giving adjuvant chemotherapy, especially in pathologic node positive MIBC.** The earlier Advanced Bladder Cancer (ABC) Meta-analysis Collaboration in 2005 concluded insufficient evidence in the need of adjuvant chemotherapy because of the impact of trials that stopped early, of patients not receiving allocated treatments or not receiving salvage chemotherapy [18].However, an update on this meta-analysis included 9 randomized trials with 945 patients and showed that there is a benefit for overall survival (HR 0.77, p = 0.049) and disease-free survival (HR 0.66, p=0.014) in MIBC patients who underwent adjuvant chemotherapy after radical cystectomy compared with those who underwent surgery alone. Additionally, lymph node–positive patients benefit more than lymph node–negative patients in terms of disease-free survival (p = 0.010) [19].

QUESTION	Can we omit adjuvant radiotherapy after cystectomy?
ANSWER	**Given that there are no conclusive data in demonstrating improvements in OS, we can omit adjuvant radiotherapy where risks will outweigh the benefits.** No updated randomized trials have assessed the benefit of adjuvant radiotherapy in MIBC. One randomized study was done in 1992 where pT3a and pT4a bladder cancer demonstrated improved disease-free survival and local control compared to surgery alone [20]. A more recent phase II randomized trial 120 patients with >=pT3b, grade 3, or node positive disease. The population was composed with high proportion of squamous cell carcinoma (46.7%). They found significant improvement in local control and marginal improvements in OS and DFS in favor of the sequential chemotherapy and radiation arm as opposed to chemotherapy alone [21].

QUESTION	Can concurrent chemoradiotherapy for bladder preservation be done instead of cystectomy?
ANSWER	**Concurrent chemoradiotherapy and bladder preservation can be an option in select patients.** Optimal candidates for bladder preservation are those patients with solitary tumors, tumor size <6 cm, negative nodes, no extensive or multifocal Tis, no tumor-related hydronephrosis, and good pre-treatment bladder function. Tumors should allow a visually complete or maximal debulking TURBT [14]. In some localities where elective surgeries cannot be accommodated, this remains a reasonable alternative.

QUESTION	What are the options of adjuvant/neoadjuvant therapy recommended in the setting of a pandemic?
ANSWER	**Gemcitabine and Cisplatin given in a 21-day cycle is preferred more than dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin).** Gemcitabine and Cisplatin, and ddMVAC reigmens are both preferred perioperative options in NCCN [14]. In a pandemic setting, a regimen with minimal immunosuppression is preferred to decrease acquisition of infection from COVID-19. A systematic review and meta-analysis by Yu, et al. [22] investigated 13 studies with 2,174 patients with MIBC given with either Gemcitabine and Cisplatin (GC) regimen or MVAC regimen. GC regimen was associated with significantly improved pathological complete response compared to MVAC regimen (OR 1.37; 95% CI 1.01–

	1.87; P = 0.04). GC regimen was associated with a significant decrease risk in Grade 3-4 neutropenia, mucositis, and febrile neutropenia, but a significant increase risk in Grade 3-4 thrombocytopenia. There was no significant difference in OS, DSS, and DFS when compared the two regimens.

D. Treatment: Metastatic

The use and choice of systemic therapies in patients with new BC metastases should be individualized according to symptoms, risk of infection with SARS-CoV-2, and unfavorable course of COVID-19, and likely prognosis.

QUESTION	**Can chemotherapy be delayed in the treatment of metastatic bladder cancer?**
ANSWER	First-line treatment should commence when possible for metastatic urothelial carcinoma and should not be stopped without justification.

QUESTION	**What treatment regimen to choose for metastatic bladder cancer: chemotherapy vs immunotherapy?**
ANSWER	During the COVID-19 pandemic, risks and benefits of systemic therapy should be considered on an individual level, taking into account disease characteristics (ie, PD-L1 positivity), tumor load and dynamics, patient performance status, geographical COVID-19 burden, and hospital resources.

QUESTION	**What is the recommended chemotherapy as treatment for metastatic bladder cancer during COVID-19 pandemic?**
ANSWER	Cytotoxic chemotherapy remains the treatment of choice for the majority of patients with advanced or metastatic BC. A regimen comprising cisplatin and gemcitabine with granulocyte colony-stimulating factor, rather than methotrexate, vinblastine, doxorubicin/adriamycin, and cisplatin (MVAC), should be considered, given the higher likelihood of neutropenia in patients receiving MVAC [23], which may be dangerous during the COVID-19 pandemic.

QUESTION	**What is the recommended Immunotherapy as treatment for metastatic bladder cancer during COVID-19 pandemic?**
ANSWER	Immunotherapy rather than chemotherapy may be given preferentially to patients with PD-L1– positive tumors. In patients with previously untreated programmed death ligand1 (PD-L1)-positive locally advanced and metastatic urothelial carcinoma, immune-checkpoint inhibitors may be more attractive than cytotoxic chemotherapy due to a reduced likelihood of immunosuppression [24].

	However, immune-checkpoint blockade is associated with potentially serious side effects, including those requiring ICU-level resources and need for high-dose glucocorticoids [25], which may be in short supply in the current environment.

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