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ESMO Management and treatment adapted recommendations in the COVID-19 era: Pancreatic Cancer

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ABSTRACT

The COVID-19 pandemic is challenging the capacities of health systems in many countries. National healthcare services have to manage unexpected shortages of healthcare resources that have to be re-allocated according to the principles of fair and ethical prioritisation, in order to maintain the highest levels of care to all patients, ensure the safety of patients and healthcare workers, and save as many lives as possible. Also, cancer care services have to pursue restructuring, following the same evidence-based dispositions. In this article, we propose a guidance to the management of pancreatic cancer during the pandemic, prioritised according to a three-tiered framework, and based on expert clinical judgement and magnitude of benefit expected from specific interventions. Since the availability of resources for diagnostic procedures, surgery and postoperative care, systemic therapy and radiotherapy may differ, the authors have separated the prioritisation analyses. The impact of postponing or abrogating cancer interventions on outcomes according to a high, medium or low priority scale is outlined and discussed. The implementation of healthcare services using telemedicine is explored; it reveals itself as functional and effective for limiting patients' need to travel to centres and thereby has the potential to reduce diffusion of SARS-CoV-2. Pancreatic cancer demands a considerable amount of medical resources. Therefore, the redefinition of its diagnostic and therapeutic algorithms with a rigorous method is crucial in order to ensure the highest quality of continuum of care in the broader context of the pandemic and the challenged healthcare systems.

INTRODUCTION

As of 19 April 2020, 2 245 872 cases and 152 707 confirmed deaths have been reported across more than 213 countries due to the COVID-19 pandemic.[1] National governments are engaged in limiting the spread of the SARS-CoV-2 infection, while healthcare systems' capacities are challenged or even overwhelmed worldwide: intensive care units (ICUs) are often unable to admit patients with severe respiratory conditions and many countries have suspended elective surgery.[2] It is a rapidly evolving challenge that requires a redefinition of every healthcare department structure and an allocation of the scarce medical resources (healthcare professionals, diagnostic, therapeutic and preventive interventions) by following strict prioritisation criteria. The objective is protecting patients and healthcare professionals' safety, maximising benefits, and allocating resources in a way they are most likely to save lives.

The ethical concept of prioritisation is applied commonly in medicine—for example, to patients awaiting an organ transplant. During the COVID-19 outbreak, entire nations are experiencing it, and not only a defined group of persons.[3 4] However, avoiding the *distraction effect* of the COVID-19 epidemic is mandatory: mortality from other diseases, like cancer, remains consistent.[5] Literature about the impact of the SARS-CoV-2 infection in an oncological population is limited. Eighteen cancer patients reported from China had an increased risk of death and/or ICU admission (OR 5.4, 95% CI 1.8 to 16.2) as compared with a large series of 1578 patients without known cancer, for whom comorbidities and older age represented the most significant risk factors.[6] In another retrospective series of 28 cancer SARS-CoV-2 positive patients, severe deterioration of clinical conditions and poor outcome were assessed. The risk of adverse events was higher if chemotherapy treatment was administered within the last 14 days.[7] In the context of overcharged healthcare systems, oncological care systems have to reorganise themselves and adapt their diagnostic and therapeutic algorithms, in order to minimise patient exposure to healthcare facilities and reduce anticancer treatment-induced complications of COVID-19.[8] These modifications should equally follow the prioritisation concept, influenced by the magnitude of potential treatment benefit, the therapeutic intent, and the availability of resources.[9]

The present work aims to provide a supportive guidance for the management

of pancreatic cancer patients during the COVID-19 pandemic, according to the above mentioned principles.

Methodology for the selection of priority interventions

The present article reports international expert consensus-based recommendations to guide healthcare professionals involved in pancreatic cancer care during the COVID-19 pandemic. These recommendations are not a substitute for current guidelines. They represent rather an adaptative and not a definitive guidance for pancreatic cancer treatment during the COVID-19 pandemic. Experts' discussions, producing all the adaptations and prioritisations, took place via teleconference and email.

In order to create a framework for the medical community response to COVID-19, the European Society for Medical Oncology (ESMO) has followed a tiered approach, defining three levels of priorities for medical interventions: tier 1 (high priority), tier 2 (intermediate priority), and tier 3 (low priority)—informed by the Ontario Health Cancer Care Ontario framework of resource prioritisation and by the ESMO Magnitude of Clinical Benefit Scale (MCBS), a public health tool for the evaluation of benefit derived from oncological interventions.[10 11]

The tiered framework developed incorporated both the information on the value-based prioritisation and clinical cogency of the interventions:

- Tier 1 (high priority): patient's condition is immediately life-threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (eg, significant overall survival gain and/or substantial improvement in the quality of life (QoL));
- Tier 2 (medium priority): patient's situation is non-critical but delay beyond 6–8 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority;
- Tier 3 (low priority): patient's condition is stable enough to allow services to be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (eg, no survival gain with no change or reduced QoL).

The clinical guidance defined by ESMO follows the Global Norms of the WHO, that recommend ensuring the essential services to all, prioritising per value.[12] Moreover, the ESMO position must be dynamically and globally contextualised in every national and regional health systems provisions against the COVID-19 pandemic: desirable adequate and safe work conditions for healthcare professionals, and policy testing for symptomatic and asymptomatic healthcare workers, patients and the overall population.

Outpatients visit priorities

Assuring the continuity in cancer care during a pandemic is challenging: clinical activities must be reorganised in order to ensure as much as possible that cancer patients are not exposed to SARS-CoV-2 infection. As a consequence, telemedicine (web-video consulting or telephone calls) should be considered, whenever feasible, the first-choice instrument, minimising travelling and hospital visits, but maintaining a sufficient contact between healthcare professionals and cancer patients, with their physical and psychological needs. Hospitals and oncology care units should be provided at the entrance with triage areas, assessing the presence of symptoms of potential COVID-19 infection and measuring body temperature of outpatients and healthcare professionals. In case of suspicion, COVID-19 testing should be carried out according to national health system guidelines. Admission to the hospital should be restricted to patients; with very few exceptions, visitors should not be given access.[8]

Stable patients with newly diagnosed resectable pancreatic cancer are high priority patients. A face-to-face consultation may be replaced by a video consultation in order to assess performance status and general medical conditions. What is urgent is a remote multidisciplinary team consultation in order to plan oncological surgery as soon as possible, provided hospital ICU and surgical resources are available.

In the outpatient setting, patients with symptoms consistent with anastomotic leak, bleeding, acute pancreatitis, fistulae and pneumonitis (usually more common during the post-surgery recovery period), or acute abdominal pain, require a prompt clinical evaluation and eventually hospitalisation. No management changes can be applied in these clinical scenarios, even during the COVID-19 pandemic.

Symptomatic patients with newly diagnosed pancreatic cancer in advanced stage necessitate a rapid physical examination in order to avoid known complications and define the optimal treatment strategy.

Telemedicine represents the preferred contact with medium level priority-established patients: it allows a rapid triage of newly complained symptoms (particularly important in the case of a tumour biology with a high risk of relapse) and consultations about laboratory or imaging results. It constitutes the first phase of a two-step approach that permits healthcare professionals to promptly organise patient's admittance to the ambulatory consultation, second level diagnostic interventions or medical treatments in case of suspicion of progressive disease.

Survival follow-up of established patients out of clinical trials belongs to a low level of prioritisation. Consider postponing scheduled visits, if feasible, and/or convert to telemedicine according to the patient's desire.

These recommendations are described in table 1. Tables were designed according to the indications for the management of pancreatic cancer during the COVID-19 pandemic approved by ESMO, and are available at: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gastrointestinal-cancers-pancreatic-cancer-in-the-covid-19-era.

Cancer patients are used to some level of uncertainty, and therefore usually understand and accept

Table 1 Outpatients visit priorities for the management of pancreatic cancer

High priority	Medium priority	Low priority
Patients with newly diagnosed resectable cancer—convert as many visits as possible to telemedicine appointments and schedule a multidisciplinary assessment in order to plan surgery	Established patients with new minor to moderate problems or symptoms—convert as many visits as possible to telemedicine appointments	Postoperative patients with no complications
Potentially unstable patients (complications in the post-surgery recovery period: anastomotic leak, bleeding, acute pancreatitis, fistulae, pneumonitis; jaundice; acute abdominal pain consistent with upper or lower intestinal occlusion; symptomatic ascites)	Follow-up visits considering patients at high risk of relapse	Established patients with no new issues
Patients newly diagnosed with non-resectable (locally advanced) or metastatic cancer and symptoms such as jaundice, pain, weight loss		Survival follow-up visits out of clinical trials

the modifications on clinical assessments caused by the severity of the COVID-19 outbreak. Nevertheless, they are concerned about their illness and the potential harm of the pandemic on the success of the therapeutic strategy. Therefore, every variation affecting the oncological path and its rationale should be transparently discussed with them (face-to-face vs telemedicine vs delayed consultations).

Radiological imaging and diagnostic procedures priorities

Consider, as a general recommendation, outsourcing of imaging procedures to sites as close as possible to the patient's residence.

The aggressive biology of pancreatic cancer and its common life-threatening clinical presentations, especially if located in the head of the pancreas (jaundice, intestinal occlusion), do not allow for any delay in the diagnostic assessment. A total body CT with contrast should be performed in order to confirm the clinical suspicion and assess the disease stage (table 2). This assessment is mandatory in order to discuss the clinical case in a multidisciplinary board and quickly refer the patient to the adequate oncologic path: surgery, in the case of resectable lesions; histo- or cytologic diagnosis of the primary tumour in the case of borderline or locally advanced lesions, requiring neoadjuvant treatment, or of metastatic sites in the case of advanced disease (table 3).

Table 2 Imaging priorities for the management of pancreatic cancer

High priority	Medium priority	Low priority
Symptomatic patients (intestinal occlusion, jaundice)	Restaging after surgical treatment.	Routine follow-up assessments outside the context of clinical trials
Diagnostic imaging for clinical suspicion of pancreatic cancer (CT scan, followed by EUS in the case of non-metastatic disease)		
Established patients with new problems or symptoms from treatment		

CT, computed tomography; EUS, endoscopic ultrasound.

Symptomatic patients constitute a high priority subgroup that should be rapidly assessed and properly treated in order to stabilise their QoL and prevent rapid life-threatening deterioration of their health status.

Tumour restaging after definitive surgical treatment should be considered as a medium priority level depending on histopathology and the interval between the last CT scan and surgery, taking into account that adjuvant curative treatment should be started until up to 12 weeks after resection.[13 14] Furthermore, a CT scan performed ≥3 months before the start of treatment might not be adequate.[15]

Routine radiologic follow-up assessments and radiologic response evaluations, in the neoadjuvant and first line setting, can be postponed if patients are clinically stable, not complaining of new symptoms, and laboratory values are not getting out of range. In case of clinical variations consistent with progressive disease, or urgent need of response evaluation in order to plan for curative surgery, these conditions must be referred again to high priority (table 2).

Surgical oncology

Surgical resection and subsequent adjuvant chemotherapy represent the only chance for long-term survival in resectable pancreatic cancer.[16] When pancreatic ductal adenocarcinoma becomes clinically detectable, its progression from low to high stage runs quickly.[17] Pancreaticoduodenectomy is one of the major surgical interventions with the highest rate of overall and severe postoperative complications, 75% and 30%, respectively, and an 8% mortality. The less complicated distal pancreatectomy (including the resection of the spleen) is associated with severe complications in 25% of cases and a mortality rate of 3%.[18] During the COVID-19 public health emergency, all invasive interventions with high morbidity and mortality which could overload the already over-burdened healthcare resources should be deferred. However, the benefit/risk ratio should be carefully evaluated, and re-evaluated, along with the evolution of the pandemic. A critical factor is the delay from diagnosis to surgery that can be tolerated in pancreatic cancer surgery.

Table 3 Priorities for pancreatic cancer: surgical oncology and image-guided surgical procedures

High priority	Medium priority	Low priority
Resectable cancers (primary or after neoadjuvant treatment) including resectable cystic lesions with suspicion of malignancy	Hepatojejunostomy (or hepatogastrojejunostomy in case of gastric obstruction) in case of biliary obstruction and recurrent cholangitis in patients with non-resectable localised or metastatic disease, good PS and life expectancy >3 months	
Borderline cancers in patients not fit for neoadjuvant treatment	Duodenal stent and/or PEG tubes in case of gastroduodenobiliary obstruction in symptomatic patients in BSC	
Endoscopic placement of biliary stent in case of biliary obstruction in non-resectable or metastatic cancers		
Endoscopic placement of biliary stent in case of biliary obstruction: in resectable cancers with active cholangitis and bilirubin >250 µmol, or non-resectable localised cancers assigned to neoadjuvant or palliative treatment		
Post-surgery complications (anastomotic leak, bleeding, acute pancreatitis, fistulae)		
Histologic assessment: CT scan or EUS guided in case of urgent therapeutic consequences such as curative resection or symptom relief		

BSC, best supportive care; EUS, endoscopic ultrasound; PEG, percutaneous endoscopic gastrostomy; PS, performance status.

Data are lacking, but a registry analysis on 16 673 patients affected by pancreatic cancer in stage I-II showed that a medium time to surgery of 15–42 days does not correlate with worse survival. A delay up to 3 months could select patients with a less aggressive cancer biology and allow a preoperative medical optimisation of patient comorbidities before elective surgery.[19] Nevertheless, the immune-depressive but potentially curative pancreatic cancer resection still retains a high priority to be evaluated in a multidisciplinary team consultation, discussing available resources in the pandemic, life expectations, and complications associated with an eventual SARS-CoV-2 infection.

Every tailored medical and surgical decision during the COVID-19 pandemic, in respect to current national and international guidelines, should be derived from a multidisciplinary experts' consultation, balancing the pros and cons of every evidence-based therapeutic option.[2 9]

After completion of neoadjuvant chemotherapy patients should receive curative surgery without deferrals, especially if operating rooms and ICU capacity are not over-utilised at that moment. In the case of acute over-utilisation of resources of the healthcare system, and when surgery postponement is unavoidable, the addition of an extra chemotherapy cycle might be considered in order to maintain the achieved results (table 3).

In the case of intervention deferral, psychological support to patients should always be proposed.

Gastric obstruction and jaundice management should be performed promptly with the aim to relieve symptoms and create a better condition to allow for subsequent curative or palliative treatments, depending on the extent of disease. Gastric tube decompression, endoscopic guided biliary drainage and/or stent placement are the preferred treatment options.

Emergency major surgery for jaundice palliation should be avoided; if necessary, in the case of recurrent cholangitis in an advanced setting, a hepatojejunostomy should be performed with a medium level of prioritisation, after a multidisciplinary team consultation.

Priorities in localised and locally advanced disease

Once a priority scale of medical oncological interventions has been established (table 4), the major challenge is offering patients the highest quality treatment option achievable, guaranteeing the safest condition of administration and a careful monitoring of its side effects in the context of the anti-pandemic restriction measures.

The ESMO-MCBS is a standardised and reproducible tool for evaluation of the magnitude of benefit of cancer treatments; it was created before the COVID-19 pandemic to assist the prioritisation of medicines in cancer care—aspects that should be addressed in every environmental context. The curative setting grading ranges from A to C in a descending scale.[11] The newly established approaches for adjuvant treatment in pancreatic cancer are considered to be of major benefit; therefore, initiation of adjuvant treatment with combined chemotherapy regimens should be pursued with a high level of priority.[20] In the case of COVID-19 pandemic hindering access to care, a delay within 12 weeks from surgery can be considered without any negative impact in terms of survival.[13–15] Ongoing adjuvant treatments should be completed, maintaining the right dose density and intensity.

Table 4 Priorities for pancreatic cancer: medical oncology in localised and locally advanced disease

High priority	Medium priority	Low priority
Initiation of neoadjuvant or adjuvant treatment not yet initiated	Adjuvant treatment to be initiated, if patient condition after surgery has not recovered (to be postponed only within 12 weeks from surgery)	Follow-up imaging and restaging studies in asymptomatic patients, taking into account pathological stage
Completion of neoadjuvant or adjuvant treatment that has already been initiated	In case of elderly patients with cardiovascular or other comorbidities not fit for a triple regimen, evaluate risk/benefit ratio of a mono-chemotherapy	
Continuation of treatment in the context of clinical trial		

Table 5 Priorities for pancreatic cancer: medical oncology in advanced/metastatic disease

High priority	Medium priority	Low priority
First line chemotherapy in patients fit for a combined regimen likely to improve survival and quality of life outcomes in metastatic disease	In case of asymptomatic or pauci-symptomatic elderly patients consider with caution the risk/benefit ratio derived from monotherapy treatment	Follow-up imaging and restaging studies in asymptomatic patients
Continuation of treatment in the context of a clinical trial	Consider with caution starting or prosecution of second line treatment according to the patient's condition	Antiresorptive therapy (zoledronic acid, denosumab) that is not needed urgently for hypercalcaemia

Borderline resectable or locally advanced diseases are high priority conditions; the most active neoadjuvant treatment should be offered, given that in case of subsequent response and eligibility for surgery, operative and ICU capacities exist. In case of shortages, the addition of more chemotherapy cycles, as previously discussed, might be considered.

Priorities in advanced and metastatic disease

The favourable impact of combined first line chemotherapy on QoL and survival is known.

The non-curative setting grading of ESMO-MCBS ranges from 5 to 1 in a descending scale.[11] In metastatic disease, ESMO-MCBS recognises that a triple regimen achieves a substantial benefit with a rate of 5, while a double combination would have a moderate to low impact; however, both combinations are recommended as first line standard, and in some countries regulatory agencies allow the administration of a double chemotherapy only in the first line setting. Consequently, in the ESMO prioritisation scale we recommend as a high priority intervention the initiation and continuation of a first line treatment, especially if the treatment is of a high magnitude of benefit (table 5).

All other regimens with a modest activity, either in first line in the case of reduced performance status or beyond first line, should be considered with caution due to their minor benefit.[21 22] A drug-free period in asymptomatic patients might be the most appropriate option.

The best supportive care approach should be encouraged, even more so during this pandemic. The small benefits usually achieved in pretreated patients are not comparable with the not well defined but present risks associated with a possible infection of SARS-CoV-2 in chemotherapy-treated cancer patients.

Antiresorptive infusional therapies (zoledronic acid, denosumab) should be rescheduled with a longer interval (every 3 months), except in the case of hypercalcaemia.

Up to 19 April 2020, the existing literature about the treatment of COVID-19 patients does not provide conclusive evidence for or against the use of corticosteroids, usually administered as anti-emetic premedication and pain relievers. Corticosteroids appear effective in reducing the early immunopathological damage in various human studies, but concerns about the subsequent imbalance of pro-inflammatory and anti-inflammatory cytokines promoting a viral rebound and association with adverse events (including acute respiratory distress syndrome) are present.[23 24] Consequently, the prescription of corticosteroids should be considered with caution.

Another topic of debate is the primary prophylactic use of cytokine G-CSF (granulocyte colony-stimulating factor) to minimise neutropenia-associated risks. Differing opinions have been expressed about the potential boost of the immune system and the possible decrease of lymphocytic response, essential in the case of viral infection. Other studies reported higher levels of G-CSF in COVID-19 patients treated in the ICU.[8] The lack of data does not allow for definitive statements, but we should keep in mind that the severe neutropenia percentage[25] of combined regimens commonly used in pancreatic cancer care are around 38% with gemcitabine-based chemotherapies in curative and palliative lines,[26 27] and around 30% and 45% with mFOLFIRINOX in the adjuvant and metastatic settings, respectively. The rate of febrile neutropenia associated with combined chemotherapy is around 5%.[13 28]

Appropriate venous thromboembolic prophylaxis should be provided, since these events are very frequent in pancreatic cancer patients and recent evidence associates the high risk of thromboembolism with a poorer outcome and rapid deterioration in the case of SARS-CoV-2 infection.[29 30]

Cancer research during the COVID-19 pandemic

The US Food and Drug Administration and the European Medical Agency have produced special guidance for the conduction of clinical trials during the COVID-19 pandemic. Paramount is the overall well-being and best interests of the trial participants. Sponsors and investigators should cooperate in order to define the most appropriate measures to be followed in relation to the local risk situation and the national and regional provisions in terms of mobility and social distancing. Physical visits should be converted to phone or video visits whenever possible, and laboratory, imaging or diagnostic tests should be allowed to be done at a local certified laboratory. Starting a new clinical trial or accrual of new trial participants in an ongoing trial should be critically evaluated, with consideration of a postponement of trial activation, or a temporary halt or a slowing down of recruitment. In case of issues at the centre, patients should be referred to the nearest, and not over-burdened, active centre. Protocol deviations are expected and should be discussed in order to reduce their impact in terms of results reliability. Study centre staff should be offered, if possible, smart working solutions.[31 32]

Every obstacle, even a huge disaster for the healthcare systems like COVID-19, may bear positive aspects: as medical oncologists we could collect real-world outcome data of non-inferiority or de-escalated and delayed cancer treatment strategies.[8]

CONCLUSIONS

The proposed remodelling of pancreatic cancer management during the COVID-19 pandemic must be established in a global cancer care reorganisation required to preserve the continuity of oncological treatments along with the multidimensional challenges of the SARS-CoV-2 infection.

In view of a shortage of medical and instrumental resources and the absence of solid scientific data to orient adjustments to standard oncological treatments, priority and benefit-based guidelines are needed. Of note, pancreatic cancer requires demanding surgical interventions, with high morbidity and considerable mortality, and chemotherapy regimens with a consistent percentage of adverse events. In the context of the COVID-19 pandemic, some concerns might be expressed in terms of the consumption of resources for a disease with such a poor prognosis. Our recommendations aim to help and orient oncologists in this pandemic scenario, to maintain the highest possible quality of care during this worldwide medical emergency.

Useful information can be found at https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gastrointestinal-cancers-pancreatic-cancer-in-the-covid-19-era

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