



COVID-19 epidemic Proposed alternatives in the management of digestive cancers A French intergroup clinical point of view (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR)

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Title: COVID-19 epidemic: proposed alternatives in the management of digestive cancers: A
French Intergroup clinical point of view (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR)

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ABSTRACT

Introduction: Patients treated for malignancy are considered at risk of severe COVID-19. This exceptional pandemic has affected countries on every level, particularly health systems which are experiencing saturation. Like many countries, France is currently greatly exposed, and a complete reorganization of hospitals is ongoing. We propose here adaptations of diagnostic procedures, therapies and care strategies for patients treated for digestive cancer during the COVID-19 epidemic.

Methods: French societies of gastroenterology and gastrointestinal (GI) oncology carried out this study to answer two main questions that have arisen (i) how can we limit high-risk situations for GI-cancer patients and (ii) how can we limit contact between patients and care centers to decrease patients' risk of contamination while continuing to treat their cancer. All recommendations are graded as experts' agreement according to the level of evidence found in the literature until March 2020.

Results: A proposal to adapt treatment strategies was made for the main GI oncology situations. Considering the level of evidence and the heterogeneous progression of the COVID-19 epidemic, all proposals need to be considered by a multidisciplinary team and implemented with patient consent.

Conclusion. COVID-19 epidemic may significantly affect patients treated for digestive malignancies. Healthcare teams need to consider adapting treatment sequences when feasible and according to the epidemic situation.

Running Title: Management of digestive cancers during the COVID-19 epidemic period

Keywords: COVID-19 infection, Digestive cancer, Chemotherapy, Surgery,—French Clinical Practice Guidelines

INTRODUCTION

The current coronavirus (SARS-CoV-2) (COVID-19) epidemic is an exceptional situation. It requires us to rethink our practices in digestive oncology and raises many questions:

- Should common practices be changed for the next few weeks?
- What practical recommendations can be made based on the literature and the experience of Chinese teams?
- Is COVID-19 infection different from other viral infections with pulmonary tropism?

The scientific answer to these questions is not yet fully known. However, a study published in 2019, before the appearance of COVID-19, retrospectively evaluated 1,503 cases of viral pneumonia admitted to the emergency medicine department of a Korean hospital between 2010 and 2015. Altogether, 9.4% of cases were due to a Coronavirus. Patients with cancer were not more likely than other patients to have a Coronavirus infection. The distribution of the different types of viruses was not influenced by the presence of cancer. In contrast, among patients infected with a Coronavirus, the 30-day mortality rate was significantly higher in those with cancer (24.4% versus 3.0%, $p < 0.001$) (1). In this study, the risk factors for death at 30 days at multivariate analysis were: age over 65 years (OR 1.661; 95% CI: 1.062-2.598, $p = 0.026$), viral and bacterial co-infection (OR 1.609; 95% CI: 1.045-2.478, $p = 0.031$), the presence of cancer (OR 2.257; 95% CI: 1.499-3.400, $p = 0.001$) and initial shock (OR 2.121; 95% CI: 1.028-4.373, $p = 0.042$).

Coronavirus pulmonary infection was thus a serious event in cancer patients, with a 25% risk of death at 30 days in those with severe forms of the infection. In two large published series of 99 and 201 cases of pneumonitis with biological evidence of COVID-19, there were only two cancer patients (2, 3).

In the Chinese prospective database of patients with proven COVID-19 ($n=2007$) from 31 provinces, 417 were excluded due to insufficient clinical history data. Among the 1590 analyzed cases, 1% (18 patients) had a personal history of cancer. This figure was higher than the number expected in the Chinese population (0.29%) suggesting that the infection could be more common

in subjects with a personal history of cancer. Results also highlighted that a severe infection was more frequent in patients with a history of cancer than in those without cancer (7/18 or 39% versus 124/1572 or 8%, $p = 0.0003$). Moreover, in cases with surgery or chemotherapy in the preceding month, the infection was severe in 3 out of 4 cases (75%), representing a relative risk of 5.34 (95% CI 1.80-16.18, $p = 0.0026$) as compared to others (4). However, this study had several limitations, including the size and characteristics of the study population corresponding to 18 patients classified in the cancer group but with 9 of them with a history of cancer dating back more than 4 years.

However, due to the absence of other reports to date, we have to consider that severe COVID 19 leading to patients' death will be more frequent in subjects suffering from cancer. Finally, due to frequent limitations in health care resources during rapidly growing epidemics, cancer patients, especially those with metastatic diseases treated by palliative systemic treatments, may not have access to intensive care units in case of severe COVID 19 infections (5). In this context, the aim is to discuss the adaptations of therapies and/or strategies for patients treated for a gastrointestinal cancer (GI). Moreover, considering the mechanisms of COVID-19 transmission, the main modifications of pathology and endoscopy procedures have been also discussed.

METHODS

Formulation of the questions

The method was based on recent Chinese articles suggesting a modification of practices with the following two main objectives (6-8).

- **Limit very high-risk situations: surgery and intensive chemotherapy**
- **Limit patients' exposure to the SARS-Cov-2 and particularly in care centers**

The multidisciplinary proposals are presented in the form of a table (see Table 1) reporting therapeutic adaptations listed organ by organ. The proposals are guided by the two objectives above, and take into account the possibility of limited access to technical platforms. Of note, the adaptations of surgical procedures in digestive oncology have also been reviewed, discussed,

detailed and published by a group of French surgeons. However, their proposals will not be detailed in the present paper (9).

Lastly, we also suggest an adaptation of surveillance in two distinct situations: during treatment and post-therapy.

Data on COVID-19 are still too fragmentary to allow robust conclusions. The recommendations are therefore pragmatic with a low level of evidence and based solely on agreement or expert advice.

Methodology

The current coronavirus (COVID-19) epidemic is an exceptional health situation that has prompted the French-speaking Federation of Digestive Cancerology (FFCD) to react quickly. The text is based on data from the literature and experience in China.

The text was first reviewed by the members of the FFCD board during an audio conference on March 16, 2020 and was validated by members of the Steering Committee (COPIL) and the heads of the various sections of our national guidelines group (TNCD) on March 23, 2020. All scientific societies involved in digestive oncology, namely SNFGE, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR, ACHBT and also GTE-RENATEN and NETSARC for neuroendocrine tumors (NETs) and gastrointestinal stromal tumors (GISTs), contributed to the discussion. Modifications concerning hepatocellular carcinoma (HCC) and cholangio-carcinomas were discussed with experts from the AFEF (French Association for the Study of the Liver). The recommendations of expert pathologists (SFP) and experts in endoscopic procedures (SFED) were also discussed in order to select appropriate measures to implement during the epidemic. A complete version, including the indications for pathology and endoscopy procedures (SFP), has been published on our TNCD website (see online: "<http://www.snfge.org/download/file/fid/3784>"). Lastly, a cohort project coordinated by Professor Astrid Lièvre will be started with the network of Cooperative Groups in Oncology in France (GCO).

The grading of recommendations includes 4 levels of evidence (A, B, C, agreement or expert opinion) (Table 1).

RESULTS

1-Proposals of the French Pathology Society (SFP)

The amount of SARS-Cov-2 virus excreted in the stool may be high. The recommendations of the French Microbiology Society (SFM) concerning the management of samples specify that samples containing stools carry a high risk of contamination. Given the incubation time and the percentage of asymptomatic patients, all samples should be considered potentially infected.

A recent publication has shown that fixation in formalin can inactivate the SARS-Cov-2 virus (10). The risk of toxicity linked to formalin exposure appears to be less serious than that linked to the handling of fresh, non-fixed tissue potentially carrying SARS-Cov-2.

The French Society of Pathology (SFP) published on 18/03/2020 advice for the management of sputum and bronchoalveolar lavage based on the recommendations of the SFM but without specific advice on the management of fresh digestive surgery samples and fixation in formalin.

RECOMMENDATIONS

- None

OPTIONS

- It seems difficult to issue specific advice for the management of fresh colectomy or small intestine resection samples, except to work with gloves, glasses and mask (**expert agreement**)
- There are not enough data to decide on the management of samples for immunofluorescence (**expert agreement**)
- Some centers recommend **fixing endoscopic or operative digestive samples immediately in formalin**, with the exception of extemporaneous examinations and suspected lymphoma, sarcoma, tuberculosis (micro-biology), pediatric tumors or special protocols (contact with the reference pathology laboratory). (**Expert opinion**)

- **For digestive samples from a suspect or known COVID-19 patient**, it is important to inform the pathology laboratory before sending the specimens (specific circuit) (**expert agreement**)
- Management sheets for biological samples from COVID-19 suspected patients have been drawn up by the SFM. https://www.sfm-microbiologie.org/wp-content/uploads/2020/03/Fiche-COVID19_V3_SFM.pdf (**expert agreement**)

2-Proposed therapeutic alternatives organ by organ

RECOMMENDATIONS

- None

OPTIONS (see details in Table 2) (**expert agreement**)

- Proposals must be interpreted according to the intensity of the epidemic and its impact on the organization of healthcare structures
- Therapeutic adjustments must be recorded or discussed during a multidisciplinary concertation meeting (MCM), which should include a small number of participants or use videoconference systems, if feasible
- Whenever possible, the patient should be informed of the increased risk of severe COVID-19 under chemotherapy
- The benefit/risk ratio must be taken into account when prescribing chemotherapy, and especially poly-chemotherapies
- Oral treatments are to be preferred so as to limit patients' exposure in care centers, and tele-consultations should be preferred to physical consultations
- Whenever possible (lesions < 3 cm), particularly for HCC and liver metastases, percutaneous thermoablation is to be preferred (outpatient or 48-hour hospitalization without morbidity)
- The postponement of the majority of complex surgeries (esophago, pancreatic or hepatic) with high morbidity must be proposed depending on the phase of the epidemic

CLINICAL TRIAL

- COVID-19 Cohort Project (FFCD-GCO) (Coordinator Pr. A Lièvre (Rennes))

3-Proposed adaptation of endoscopy activity (SFED recommendations)

The French Society of Digestive Endoscopy (SFED) has proposed an adaptation of digestive endoscopy procedures due to the COVID-19 epidemic (**expert agreement**)

The adaptation of endoscopic procedures in healthcare establishments has **two objectives**:

- 1) strengthen and amplify all the resources of healthcare institutions in terms of anesthesia-resuscitation and medical care
- 2) facilitate the management of emergency cases of digestive disease (not linked to COVID-19) in order to minimize the loss of opportunity that a possible delay in diagnosis or treatment would engender

A /Emergency situations:

In the digestive tract:

- Upper gastrointestinal bleeding
- Severe lower gastrointestinal bleeding
- Caustic ingestion (in accordance with recommendations)
- Sigmoid volvulus
- Gastrointestinal tract obstruction requiring endoscopic stent or percutaneous endoscopic gastrostomy

Bilio-pancreatic tract:

- Cholangitis
- Acute pancreatitis
- Bile duct Obstruction
- Necrosectomy
- Abscess drainage

B / Indications for which the procedures will not be delayed:

- diagnosis and regional involvement (endoscopy, echo-endoscopy +/- fine-needle aspiration)
- Positive fecal-immunochemical test (FIT test)
- Iron deficiency anemia

This list is not exhaustive but any endoscopy which can be postponed for a few weeks must be discussed in the interests of the patient.

4-Proposed adaptations for follow-up

For patients undergoing systemic treatment, the monitoring of marker kinetics has shown its clinical interest in patients with increased tumor markers at baseline, particularly for colon and metastatic pancreatic cancers (28,29). In this exceptional situation of COVID-19, marker kinetics combined with remote clinical monitoring make it possible to postpone imaging examinations during the epidemic period.

RECOMMENDATIONS

- None

OPTIONS (**expert opinion**)

- Postponement of imaging scheduled during the epidemic period
- Evaluation by clinical examination and tumor marker kinetics
- The particular case of patients treated for metastatic colorectal cancer with potentially resectable metastases justifies the maintenance of timely imaging examinations.

For patients in a post-therapeutic setting, an adaptation of the follow-up is required.

RECOMMENDATIONS

- No reference

OPTIONS (**expert agreement**)

- Postponement of consultations and imaging examinations until after the epidemic period.

DISCUSSION

Coronavirus 2019 (COVID-19) is causing an emerging viral infectious disease that is currently spreading worldwide. Although limited clinical cancer-specific data are available, patients with cancer are regarded as having a high risk of COVID-19-related death and the question of adapting diagnostic procedures, therapies and care strategies during the epidemic period has thus arisen. Moreover, in this particular context, in which hospitals are being submerged by incoming patients requiring intensive care, it is essential to preserve a functioning healthcare system. This situation is a major issue for all patients, whether infected with COVID-19 or not.

One of main questions is thus, how can we limit the risk of infection for cancer patients for a period of 2 to 3 months without excessively compromising the control of their cancer? In the current exceptional context, it is accepted in France that usual medical practices may be profoundly modified by the impact of the COVID-19 epidemic on our healthcare system. The epidemic phenomenon is known to be composed of five stages. Stage 1 is the "calm before the storm" where non-emergency care is delayed, fewer patients turn up at emergency departments, and specific departments are ready to receive patients with COVID-19. Stage 2 is the peak, varying in intensity within the same country as was the case in China and Italy. The peak can be relatively well controlled in countries that have previously experienced similar situations, such as Korea or Japan, which anticipated and attenuated the peak by adopting preventive measures such as generalized mask wearing, barrier measures in social networks, massive testing and regular disinfection of public places. In contrast, Western countries appear to be less well prepared and when the capacity of the health system is exceeded, the epidemic peak has a major impact on care for other diseases. Next comes phase 3, known as the "plateau", characterized by the continuous influx of infected patients, thereby neutralizing the healthcare system's ability to take care of other illnesses in accordance with current guidelines. The duration of phase 3 is logically linked to peak

intensity as well as the availability of resources (5). Phase 4 is the "the recession", the duration of which depends on the previous stages and their consequences on healthcare teams. Phase 5 is "the return back to normal situation", and includes the management of newly diagnosed patients as well as patients whose care has been postponed during the previous phases. Each phase will affect therapeutic choices at every level from the standard of care to possible adaptation of strategies or even forced postponement. During phase 1, which is ongoing in France today, some proposals may appear inappropriate, even though they are already necessary in several regions or countries in phase 2 and 3. The goal of the present manuscript is to suggest adaptations of diagnostic procedures, therapies and care strategies, based on expert opinion, that can be proposed in patients treated in France for GI cancer during the epidemic period. The impact of COVID-19 on the adaptations of cancer strategies proposed here is not yet known and further modifications may become necessary in the light of future publications with higher levels of evidence.

CONCLUSION

COVID-19 is an exceptional epidemic phenomenon that affects all countries at every level: social, political, economic and healthcare. Considering that the COVID-19 epidemic is expected to peak in France in a few weeks' time, strategies in cancer care, and in particular for patients treated for a GI tumor, will be need to be adapted in the vast majority of cases. Taking into account that the adaptations proposed in this paper were based on a multidisciplinary overview and experts' agreement, further studies are needed to clearly evaluate the impact of these adaptations during the COVID-19 epidemic period.

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Table 1: Grading system used for these recommendations

Grade	Corresponding level of evidence
A	Strong recommendation based for example on a high-powered randomized comparative trial (s), a meta-analysis of randomized comparative trials, or an analysis of decision based on well-conducted studies.
B	Recommendation based on a scientific presumption from low-power randomized controlled trials, well-conducted non-randomized comparative studies or cohort studies.
C	Recommendation based on a low level of evidence from case-control studies, comparative studies with significant biases, retrospective studies, case series, descriptive epidemiological studies (transverse, longitudinal).
Expert Agreement or Opinion	Recommendation based on an expert agreement or an expert opinion in the absence of sufficient data from the literature

Table 2: Proposed therapeutic adjustments by organ (* expert agreement / ** expert opinion)

Organ	Oncologic situation	Proposals
Rectum locally advanced	Chemo-radiotherapy completed or in progress	<ul style="list-style-type: none"> Postpone surgery (delay of 11 or 7 weeks no difference (GRECCAR 6, (11)) but more morbidity and more difficult excision) ** Beyond 12 weeks, reconsider according to hospital possibilities (availability of operating room and resuscitation unit) *
	Preoperative chemo radiotherapy planned	<ul style="list-style-type: none"> Discuss preoperative short course radiotherapy (5x5 Gy) without CT and delayed surgery at 12 weeks depending on the epidemic and hospital possibilities (12) *
	Special cases <ul style="list-style-type: none"> T4 Major response to CT-RT (GECCAR 2 criteria) 	<ul style="list-style-type: none"> Give priority to CAP50 RT regimen and surgery at 12 weeks depending on the epidemic and hospital possibilities * Consider organ preservation with local excision or Watch and Wait strategy (13, 14) *
Colon localized	<T4 (symptomatic and non-symptomatic)	<ul style="list-style-type: none"> Surgery within the usual delay if possible, without neoadjuvant CT ** However, some experts recommend postponing surgery (9) **
	Specific cases <ul style="list-style-type: none"> T4 Obstruction Frail patients 	<ul style="list-style-type: none"> Primary chemotherapy, favoring the oral route with oxaliplatin when feasible (CapOx regimen) and surgery after the epidemic period (15, 16) * colostomy and surgery for 4 to 6 weeks * Postpone surgery for 4 to 6 weeks according to the risk/ benefit ratio *
	Indication for adjuvant chemotherapy: stage III and stage II (T4b)	<ul style="list-style-type: none"> Prefer CapOx over FOLFOX (3 or 6 months) * Depending on the local situation, for low risk, consider replacing oxaliplatin with capecitabine monotherapy alone (17) * For frailly patients, consider omitting CT *
Colorectal metastatic (1st and 2nd line)	Resectable	<ul style="list-style-type: none"> Postpone surgery until the end of the epidemic period (+/- neoadjuvant CT depending on tumor characteristics (favor the regimens with capecitabine or CapOx) ** Low morbidity surgery or thermal ablation can be considered within the usual time limits (local situations) **
	Potentially resectable	<ul style="list-style-type: none"> CT with mono (favor capecitabine) * or doublet regimen (CapOx * or CapIri **) +/- targeted therapies, and avoid triplet regimen * The association CapOx plus anti-EGFr need

		to be consider with cautious (18)
	Non resectable	<ul style="list-style-type: none"> CT: mono (favor capecitabine) or doublet regimen ((CapOx * or CapIri **) +/- targeted therapies, avoid triplet regimen * The association CapOx plus anti-EGFr need to be consider with cautious (18). If maintenance strategy, consider capecitabine alone +/- bevacizumab *
Colorectal metastatic under treatment	Non resectable	<ul style="list-style-type: none"> Consider oral treatments in stable or slowly progressive disease (capecitabine) in order to limit hospital stays (19), and with telemedicine or telephone follow-up * Consider CT break of 2 months In patients with stable disease *
Colorectal Metastatic under treatment beyond 2nd line	Non resectable	<ul style="list-style-type: none"> Regorafenib using the ReDOS schedule starting at 80 mg daily (20) * Consider a CT break in case of stability * Careful use of Trifluridine-Tipiracil due to the risk of leuko-neutropenia * (21)
Pancreatic adenocarcinoma	Localized with proven histology	<ul style="list-style-type: none"> Postpone surgery until after the epidemic period ** (lack of ICU beds, increased morbidity and mortality) depending on local possibilities and the evolution. Consider neoadjuvant CT: prefer FOLFOX * over FOLFIRINOX ** with regard to the risk of severe complications due to chemo-induced immunosuppression (reconsider after the epidemic). In cases of FOLFIRINOX, used the modified regimen (without 5FU bolus and irinotecan 150 mg/m2) and systematic GCSF *
	Postoperative	<ul style="list-style-type: none"> Modified FOLFIRINOX due to the magnitude of the survival benefit, and with systematic GCSF in the context of epidemic period * (22)
	Locally advanced	<ul style="list-style-type: none"> Chemotherapy to be discussed (gemcitabine or doublet CT based on 5FU or capecitabine) *
	Metastatic	<ul style="list-style-type: none"> CT according to the general condition (monotherapy with gemcitabine, doublet CT or triplet CT depending on the clinical situation) *. If FOLFIRINOX, no bolus and systematic GCSF Consider a CT break or maintenance in case of stability by favoring capecitabine *
Intrahepatic Biliary tract	Resectable	<ul style="list-style-type: none"> Surgery on time if possible, without neoadjuvant CT * Peri-hilar cholangiocarcinoma: in case of icteric cholestasis, bile ducts drain and portal embolization in preparation for hepatectomy which can be postponed *
	Post-operative	<ul style="list-style-type: none"> Capecitabine *
		<ul style="list-style-type: none"> CT depending on the clinical situation

	Non resectable or metastatic	(gemcitabine-platinum or GemOx *) • Discuss alternative CApOx regimen (23)
Eso-gastric	Localized (junction and stomach): Perioperative chemotherapy	CT adapted to the clinical situation: • FLOT if possible due to the magnitude of the survival benefit, by adding systematic GCSF * (24) • Failing this, doublet platinum-based CT (CapOx) * • If surgery, favor intervention without thoracic approach *
	Localized (esophagus): Preoperative chemo radiotherapy	• Consider paclitaxel-carboplatin plus radiotherapy regimen * • In cases with complete clinical response: discuss careful surveillance or delayed surgery * (25)
	Metastatic	• CapOx first-line chemotherapy +/- trastuzumab (if HER2 positive) *
Hepatocellular Carcinoma	Resectable	• No postponement of curative treatments except in the case of a single small nodule without threatening and / or poorly evolving vascular relationship * • If waiting for a liver transplant: postpone the transplant until after the epidemic by implementing any appropriate interim treatments that may be necessary *
	Non operable or metastatic	• Oral treatment (sorafenib / regorafenib / cabozantinib) * • Reconsider loco-regional treatments on a case-by-case basis after the epidemic *
Squamous cell Anal carcinoma	Localized with indication of chemoradiotherapy	• Favor the Capecitabine-Mitomycin C plus radiotherapy * regimen (26)
	Recurrence or metastatic	• CapOx bi-chemotherapy or carboplatin-capecitabine (less toxic and easier to manage than 5FU-cisplatin or DCF) **
Neuroendocrine Carcinoma	Resectable	• Do not postpone surgery or consider neoadjuvant CT or chemoradiotherapy for the rare curable forms *
	Non Resectable	• Do not postpone CT for the start of treatment (1st line, up to a total of 6 cycles of platinum-etoposide regimen) * • Do not use oral etoposide * • 2nd and 3rd line are to be discussed on a case-by-case basis, as well as therapeutic breaks if possible *
Well Differentiated NET	Resectable	• Postpone all surgeries if the patient is asymptomatic *
		• Loco-regional procedures (hepatic embolization, thermo-ablation, surgical cytoreduction) are maintained on a case-by-case basis if it is necessary to control a refractory secretory syndrome. Favor teleconsultations for patients who do not need IV treatment (somatostatin analog, everolimus, sunitinib, temozolomide +/- capecitabine) * • Favor oral chemotherapy (TemCap) over IV

	Non Resectable	<ul style="list-style-type: none"> if possible * Consider a break from IV chemotherapy as soon as possible (often possible after 3 months of effective chemotherapy) * Peptide Receptor radionuclide therapy (PPRT) is maintained on a case-by-case basis depending on the facilities available, the state of the disease / patient, as long as the treatment is provided* Evaluate the dose-intensity of each treatment, in particular in patients with neutropenia-lymphopenia (especially on everolimus) *
	Surveillance	<ul style="list-style-type: none"> Patients being treated <ul style="list-style-type: none"> o asymptomatic: postpone follow-up exams and continue the therapeutic line * o symptomatic: maintenance of imaging examinations. Marker kinetics have not demonstrated any clinical interest * (27) Post-therapeutic monitoring: postpone follow-up exams until after the epidemic period *
GIST	Resectable	<ul style="list-style-type: none"> Surgery within the usual time limits if possible * <ul style="list-style-type: none"> o except "frailly " patients * o except complex surgery (duodenopancreatectomy, proctectomy) or lesions that are difficult to resect = initiate or continue an interim treatment with imatinib *
	Post-operative Imatinib adjuvant treatment	<ul style="list-style-type: none"> Continuation of imatinib * Temporary discontinuation of TKI if suspected infection * Prioritize support for tele-consultation * Postpone follow-up imaging until after the epidemic *
	Locally advanced or Metastatic	<ul style="list-style-type: none"> Continuation of the TKI * Temporary discontinuation of TKI if suspected infection * Give priority to teleconsultation support * Postpone assessment imaging until after the epidemic* Postponement of surgery or heat-ablation until after the epidemic with interim treatment with TKI *

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