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## **JVS - Review**

# **Treatment of primary and metastatic peritoneal tumors in the Covid-19 pandemic**

## **Proposals for prioritization from the RENAPE and BIG-RENAPE groups**

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## **Abstract**

The Covid-19 pandemic is profoundly changing the organization of healthcare access. This is particularly so for peritoneal neoplastic diseases, for which curative treatment mobilizes substantial personnel, operating room and intensive care resources. The BIG-RENAPE and RENAPE groups have made tentative proposals for prioritizing care provision.

A tightening of the usual selection criteria is needed for curative care: young patients with few or no comorbidities and limited peritoneal extension. It is desirable to prioritize disease conditions for which cytoreduction surgery with or without associated hyperthermic intraoperative peritoneal chemotherapy (HIPEC) is the gold-standard treatment, and for which systemic chemotherapy cannot be a temporary or long-term alternative: pseudomyxoma peritonei, resectable malignant peritoneal mesotheliomas, peritoneal metastases of colorectal origin if they are resectable and unresponsive to systemic chemotherapy after up to 12 courses, first-line ovarian carcinomatosis if resectable or in interval surgery after at most six courses of systemic chemotherapy. Addition of HIPEC must be discussed case by case in an expert center. The prioritization of indications must consider local conditions and the phase of the epidemic to allow optimal peri-operative care.

## **Key words**

Coronavirus, Covid-19 ; Primary peritoneal tumor ; Peritoneal metastases

## **Introduction**

For several weeks now, France has been facing an unprecedented epidemic that is forcing its care systems to make rapid, far-reaching adjustments. The channeling of resources toward care for persons infected by SARS-CoV-2 has had to be balanced with ensuring continued provision necessary for other patients. This health emergency setting impacts the treatment of peritoneal cancer diseases, which is not clearly defined.

In most cases, gold-standard curative treatment combines complete cytoreduction surgery (sometimes major and extensive) with hyperthermic intraperitoneal chemotherapy (HIPEC). The scant and still insufficient epidemiological data that we have reports an excess mortality risk in patients infected by SARS-CoV-2. For palliative care, pressurized intraperitoneal aerosol chemotherapy (PIPAC), alone or combined with systemic chemotherapy, is a therapeutic approach proposed by expert centers that also requires time in the operating room. PIPAC is still being evaluated and has not yet proved its efficacy in Phase III.

For these cancer conditions, local and national governing bodies have mostly opted to de-schedule major surgery and prioritize systemic chemotherapy as a delaying strategy, without yet planning later care. The impact of these changes in therapeutic strategy on the prognosis of patients eligible for curative care, patients potentially eligible after neoadjuvant treatment or those receiving palliative treatment, can be marked and so deserves analysis. This is the aim of the CAIRN-carcinomatosis prospective observational study conducted by the BIG-RENAPE group, in which the first patient inclusions were made. A second French cohort, GCO-02 CACOV-19, promoted by the French-speaking Cancer Federation (FFCD), collects data on patients with both cancer and Covid-19 to gain more knowledge on this disease association.

While these data are being collected, the existing evidence must be considered. Some peritoneal cancers, such as pseudomyxoma peritonei, do not respond to systemic chemotherapy or only weakly. In other cancers, prolonged preoperative chemotherapy has a negative impact on prognosis (e.g. peritoneal mesothelioma) or is still controversial (e.g. resectable ovarian

carcinomas). For still other cancer sites, the response to systemic chemotherapy is very uncertain (e.g. gastric and colorectal).

To make progress in the difficult task of coping with the demands of this epidemic in terms of mobilizing resources and ensuring the continuity of the care we owe all our patients, the BIG-RENAPE group offers some proposals, as ways forward rather than guidelines, that can help practitioners and local and national governing entities make informed choices.

### **General considerations**

- In the last decade major advances have helped optimize the selection of patients and set perioperative care, thereby markedly reducing morbidity (1, 2). Efficient network organization, twice certified by the French National Cancer Institute (INCa) (RENAPE), has allowed these practices to be generalized nationwide.
- One fundamental feature of this improved patient selection is the generalization of exploratory laparoscopy, an examination that offers a higher sensitivity for evaluating small intestine involvement, which is necessary to determine a patient's resectability. In the setting of the Covid-19 epidemic, suspending these interventions and preferring peritoneal MRI is an option that can be considered.
- All the patients involved and infected by Covid-19 must have all anti-neoplasia treatment suspended, be closely monitored (not necessarily with hospitalization) and have their treatment reassessed every two weeks based on the proposals presented here, according to the evolution of their infection and their cancer.
- The advent of this unprecedented situation has produced a highly uneven pattern of adaptation among different health centers across France. Our purpose here is not criticism, but rather to raise awareness of the need to ensure care provision for patients with peritoneal cancer to ensure continuity and equity of care. A process of narrowing therapeutic indications is now engaged, and it is right that healthcare authorities respond by setting in place an organization that clearly separates non-Covid-19 care facilities.

## **Influence of the epidemic phase**

The French National Digestive Cancer Thesaurus (TNCD) describes five phases in the Covid-19 epidemic that will influence our strategic choices according to their impact on our healthcare capacities (3).

In Phase 1, the de-scheduling of many surgical operations for peritoneal cancer seems excessive except for patients at risk of severe forms of SARS-CoV-2 infection. The buildup of patients awaiting care will cause an increase in time-to-surgery pre- and post-epidemic, with a resulting loss of life chances for all these patients.

In Phases 2 and 3, shortage of material and human resources will cause many deferrals of major surgery. These phases are probably those that most obviously justify suspending major surgery. However, forward-planned solutions for externalizing care to ringfenced non-Covid-19 centers can probably be implemented.

In Phases 4 and 5, the constitution of specific Covid-19-positive and Covid-19-negative circuits, and more clarity on available and projected means, will enable delayed or de-scheduled cancer care to be prioritized over non-urgent care. This prioritization must be imposed by authorities and governing bodies to minimize loss of life chances caused by the modification of care strategy in Phases 2 and 3. At this stage, given the likely shortage of human resources, and the very gradual freeing up of beds in intensive care, means must be allocated as a priority to absorb the backlog of delayed or de-scheduled surgery.

## **Proposal**

- **In Phases 4 and 5: give priority to resources for curative cancer surgery**

### **Restricted selection criteria for curative surgery**

Whichever the epidemic phase, a restriction of the usual selection criteria is necessary. For this purpose, a new pre-operative assessment report with screening for a SARS-CoV-2 infection, a thoraco-abdominopelvic CT scan and peritoneal MRI with reading by a designated expert radiologist (4-6) will help this stricter selection with the assessment of a new benefit/risk/means balance: de-scheduling of surgical exploration if the probability of non-resectability is deemed high, deferral if the risk of post-operative complications linked to the number of digestive resections seems too great, and screening for Covid-19-related pneumonia.

Priority must be given to young patients and those with the fewest comorbidities, given the impact on post-operative mortality and morbidity rates these have (7, 8).

Priority must also be given to the two main prognostic factors, irrespective of cancer type, namely (i) the possibility of complete cytoreduction surgery, and (ii) the extension of the cancer evaluated using the *Peritoneal Cancer Index* (PCI). Cases with a more moderate PCI calling for lighter surgery, with less risk of post-operative complications and a better prognosis are to take priority.

### **Proposals:**

- **Make a new pre-operative assessment report with a thoraco-abdominopelvic CT scan and peritoneal MRI read by a designated expert radiologist (structured report).**
- **Give priority to young patients, those with the fewest comorbidities, and with limited peritoneal disease.**

### **Systemic chemotherapy, surgery or no therapy**



Peri-operative infection by SARS-CoV-2 is reported to increase mortality risk. Accordingly, a group of French surgeons have recently published proposals for adjustment strategies in surgical practice (9). For most major digestive surgery (pancreatic, esophageal) that is similar to peritoneal surgery in the resources it requires and the risks it incurs, they advocate deferral of surgery.

However, no data is yet available to objectively assess, in a cancer case, (i) the relative risk of a severe form of Covid-19 a context of systemic chemotherapy or major surgery, or (ii) the respective prognostic impact of no therapy, prolonged chemotherapy, and major surgery. The preliminary data that we have, which are from studies with low levels of proof, suggests that Covid-19 is more serious in subjects with cancer, with a risk of a severe form five times higher than in the population without cancer, and a risk of fatal outcome multiplied by eight (10-12). The risk of contracting the infection is reportedly three times higher in cancer patients. No risk comparison has yet been made between surgery and chemotherapy that would suggest that chemotherapy carries a lower risk of fatal outcome than surgery.

As regards the no therapy option and deferred surgery, the end of the epidemic is not in sight, and so surgery will not only be delayed indeterminately, but will be carried out in a future context in which medical and paramedical personnel will be less able, sick or exhausted.

**Proposals:**

- **Make no recommendations for prioritizing chemotherapy over surgery or over no therapy based on Covid-19 risk and the implied excess mortality.**
- **Discuss care pathways in multidisciplinary concertation meetings (RCPs) to define the most appropriate therapeutic strategy for the patient and the local situation.**

**Prioritization according to prognosis and the impact of different therapeutic strategies on that prognosis**

*Pseudomyxoma peritonei*

The recent international recommendations of the PSOGI and EURACAN for the treatment of pseudomyxoma peritonei (PMP), which integrate an exhaustive analysis of the literature and a Delphi process based on three rounds of voting by 80 international experts, give the cytoreduction-HIPEC combination as the gold standard treatment for this pathology (13). This strategy gave overall survival rates of more than 60% at 10 years in the two main literature series, and a median disease-free survival time of 98 months in expert centers (14, 15). Neoadjuvant chemotherapy must not be proposed for low-grade PMP. No study has reported any benefit from it and three studies report an adverse effect on overall disease-free survival. For high-grade PMP with signet-ring cells, two small-cohort studies report a benefit of neoadjuvant chemotherapy for overall disease-free survival. FOLFOX is the recommended chemotherapy.

Surgical indications and their urgency will depend on histological grade, extent of peritoneal disease and symptomatic picture. Grade is difficult to estimate pre-operatively. In cases of low-grade disease, evolution is generally fairly slow, but complete cytoreduction must be ensured, being the main prognostic factor. The risk incurred by a delaying strategy lies in the major surgery then required, with a higher risk of complications, and in the less radical solution with a risk of earlier recurrence. In cases of high-grade disease, treatment must be started promptly. The theoretical indication of cytoreduction-HIPEC can then be weighed against neoadjuvant chemotherapy. Patients with non-resectable symptomatic PMP have no alternative other than palliative debulking surgery.

**Proposals:**

- **Propose cytoreduction surgery with HIPEC, the gold-standard treatment for resectable pseudomyxoma peritonei, as first-line treatment.**
- **If local scheduling is impossible:**
  - **For low-grade asymptomatic PMP, propose deferral.**
  - **For high-grade PMP with signet-ring cells, propose systemic chemotherapy (FOLFOX or CapOx in this epidemic setting to reduce contacts).**

### *Peritoneal mesotheliomas*

The international recommendations of PSOGI and EURACAN, drawn up using the same procedure as for pseudomyxoma, specify three pictures: (i) immediately resectable and operable patients, (ii) non-resectable and/or non-operable patients, and (iii) borderline-resectable patients (16). The association of cytoreduction surgery and HIPEC is the gold-standard curative treatment when the condition is resectable. Systemic chemotherapy alone yields median survival times of one year, against more than 50 months after complete cytoreduction with HIPEC in expert centers. Rate of response to standard neoadjuvant chemotherapy is about 40%. Italian and French experiments report a negative effect of neoadjuvant chemotherapy on overall survival of resectable patients (17, 18). Borderline resectability forms, usually identified by exploratory laparoscopy, are given bidirectional neoadjuvant treatment with systemic and intraperitoneal chemotherapy, which results in secondary resectability in half of cases (19). In the current epidemic setting, in non-resectable or borderline-resectable cases and/or with poor prognosis factors (sarcomatoid or biphasic histological forms, Ki-67 > 9%) first-line systemic chemotherapy with cisplatin + Alimta is recommended. In immediately resectable cases, cytoreduction surgery-HIPEC must be the priority.

#### **Proposals**

- **As first line treatment for resectable malignant peritoneal mesothelioma, propose gold-standard cytoreduction surgery with HIPEC without systemic neoadjuvant chemotherapy.**
- **If local scheduling is impossible, or if there is doubt about the possibility of carrying out complete resection, or if poor prognosis factors are present, propose systemic chemotherapy with cisplatin (or carboplatin) and pemetrexed.**
- **For asymptomatic borderline histological forms of mesothelioma (multicystic, well-differentiated papillary), appropriate surgery can be deferred until the epidemic has waned.**

### *Peritoneal metastases of colorectal origin*

Since the French PRODIGE 7 randomized trial, complete cytoreduction surgery associated with perioperative systemic chemotherapy has been the gold-standard curative treatment for colorectal peritoneal metastases, giving a median survival time of more than 40 months (20). HIPEC has not yet demonstrated any benefit for overall disease-free survival when associated with complete cytoreduction surgery. However, some monocentric studies have reported survival times longer than 60 months in cases of surgery plus HIPEC (21).

Systemic chemotherapy, even if it is less effective on peritoneal metastatic disease (especially when mucinous) than on liver or lung metastases (22), can still control the disease to an extent. Median survival time with modern systemic chemotherapy protocols is 24 months (23). Histological analysis of resected peritoneal metastases showed that this chemotherapy achieved a significant tumor response in more than 30% of patients, of which 10% were complete responses on all the samples from the same patient (24). It is difficult to predict poor response to chemotherapy. Factors such as *RAS* and *BRAF* mutations, location to the right of the primary tumor or a mucinous component accounting for >30% could help grade patients for this risk. Patients whose tumor presents microsatellite instability are potentially more sensitive to immunotherapy, which could be offered to them on condition of marketing authorization, and suspension of inclusion in clinical trials for the duration of the Covid-19 epidemic.

**Proposals:**

- **Complete cytoreduction surgery associated with perioperative systemic chemotherapy is the gold-standard treatment for resectable colorectal peritoneal metastases.**
- **Systemic neoadjuvant chemotherapy, if effective and well-tolerated, can allow cytoreduction surgery to be delayed, and can be repeated up to 12 times, with appraisal, albeit difficult, of the risk of an evolution toward non-resectability during that time.**
- **Give priority to cytoreduction surgery for resectable colorectal metastases that are unresponsive to systemic chemotherapy.**
- **Discuss addition of HIPEC case by case in an expert center. It must not increase the risk of post-operative complications.**

*Peritoneal metastases of gastric origin*

This condition is the one for which discussion of curative treatment strategies is most difficult in the current epidemic setting. There are three main reasons for this: (i) its poor prognosis with median survival times of 18 months in the latest study associating cytoreduction surgery and HIPEC (25), (ii) the high risk of post-operative complications with this therapeutic association, and (iii) the difficulty pursuing the current recommended neoadjuvant chemotherapy, FLOT, for toxicity reasons.

In cases of peritoneal metastases, systemic chemotherapy alone does not give median survival times of more than one year. A recent French multicentric study (25) reports a significant survival benefit for the cytoreduction-HIPEC association over surgery alone, irrespective of the subgroups studied in a population of strictly selected patients in whom there was a possibility of obtaining remissions in cases of limited disease (26). Median survival was not attained at 5 years follow-up with this therapeutic association in the subgroup of patients with favorable histology (no independent signet-ring cells).

There is therefore a marked difference in prognosis between a major surgery strategy (with HIPEC) requiring intensive post-operative care and with high risk of severe post-operative complications and a strategy of systemic chemotherapy that soon meets problems of tolerance and efficacy. The patients involved are often young (mean age in the HIPEC group of the CYTO-CHIP trial was 51 years).

**Proposal:**

- **Propose complete cytoreduction surgery associated with HIPEC for patients with resectable limited metastatic disease of gastric origin, but with strengthened selection, given the epidemic setting, for age, general health status, tolerance, response to systemic chemotherapy and number of therapy courses already undergone.**
  - **Pursue systemic chemotherapy by FLOT or FOLFOX (or alternatively CapOx), if it is effective and well-tolerated, for the time the local conditions do not allow curative care.**
- Give these patients priority for re-scheduling.**

*Peritoneal metastases of ovarian origin*

If an immediately resectable ovarian metastasis of limited extension is diagnosed (with few or no digestive resections expected) in a patient with an uneventful medical history, primary surgical cytoreduction is the gold-standard treatment. It presents a prognostic advantage in terms of survival over neoadjuvant chemotherapy according to the recent recommendations of the French National Cancer Institute (INCa) (27). In the epidemic setting it must therefore take priority according to local possibilities. The same picture in a patient with a major risk of post-operative complications (advanced age, obesity, severe cardiovascular pathology, ASA III or IV) would justify neoadjuvant chemotherapy.

In cases of diffuse cancer requiring major cytoreduction surgery with potentially prolonged post-operative intensive care, the start of neoadjuvant chemotherapy can be discussed, as there was no difference survival rate between the two strategies in the main randomized trial that evaluated it (28). This strategy must be discussed, in particular for patients with marked comorbidities.

For interval surgery in patients who have already started their neoadjuvant chemotherapy, addition of HIPEC with cisplatin to complete resection has recently shown its potential for survival benefit in a randomized study (29), with no increase in postoperative complications being reported. However, the place of HIPEC remains largely controversial in the current context of intense development of targeted therapies. Delayed interval surgery (after at most six chemotherapy courses) must be discussed case by case in a multidisciplinary meeting, considering local conditions and chemotherapy response. Interval HIPEC must also be discussed case by case in expert centers.

In cases of recurrence, a recent study has challenged the impact of surgery (30) relative to systemic chemotherapy alone with an anti-angiogenic. We await definitive results from the DESKTOP study evaluating the impact of complete surgery on platinum-sensitive recurrences with AGO selection criteria (31). Although the results come out significantly in favor of surgery for disease-free survival, impact of overall survival is not yet known.

HIPEC in platinum-sensitive recurrence is still being evaluated in randomized trials (CHIPOR in France – NCT01376752 et HORSE in Italy – NCT01539785) and so cannot be recommended outside those trials.

In cases of platinum-resistant recurrence, the best reported results were obtained with the association of surgery and complete cytoreduction with HIPEC (32).

**Proposals:**

- **Prioritize primary complete cytoreduction surgery for immediately resectable ovarian metastases and of limited extension according to local possibilities.**
- **Prefer neoadjuvant chemotherapy for immediately resectable peritoneal cancer if local scheduling of cytoreduction surgery is impossible or the cancer is more extensive.**
- **Discuss delayed interval surgery (after six courses at most) in multidisciplinary meetings in the light of local conditions and response to chemotherapy.**
- **HIPEC**
  - **Is not recommended for first line primary surgery, or in cases of platinum-sensitive recurrence,**
  - **Must be discussed case by case in expert centers in interval surgery and in cases of platinum-resistant recurrence.**

*Peritoneal metastases of unusual origin*

The results of the cytoreduction surgery-HIPEC association for certain rare indications in patients strictly selected in expert centers have been collected by the international PSOGI group. That work has revealed notably long survival times for some of these unusual indications (urachus, mucinous ovarian tumor, cholangiocarcinoma, liver cell carcinoma and others) (33). The same prognostic factors were found in this population as in peritoneal metastasis of more frequent origin (complete cytoreduction surgery and PCI).

The level of scientific proof given by these limited retrospective cohorts is admittedly not high, but the possibility must be considered of offering access to treatment for some of these patients with clearly resectable disease and favorable tumor biology, reflected in good, prolonged response to chemotherapy, that could result in long survival or even complete remission.



**Proposals:**

- **Discuss in expert centers the indication and possibility of performing complete cytoreductive surgery with HIPEC for peritoneal metastases of varied histological type despite the epidemic setting.**
- **Consider local conditions when prioritizing indications to ensure optimal perioperative care.**
- **Prioritize systemic chemotherapy whenever it can control the disease with an acceptable tolerance until the epidemic has abated.**

**Conflicts of interest**

None

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