BIG RENAPE

BASECLINICO-BIOLOGICBASECLINICO-BIOLOGICOFMENTASTASES PERITONEALESO'ORIGINEDIGESTIVE

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SYNOPSIS

Title

BIG-RENAPE: Clinical-biological basis of peritoneal metastases of digestive origin

Rational

Peritoneal metastases are a classic and common evolution of many digestive cancers: 10 to 20% of colorectal cancers, 20 to 50% of gastric and pancreatic cancers. Long considered as the terminal stage of these pathologies and treated palliatively with no hope of cure, the medians of survival of the rare prospective studies did not exceed 3 to 6 months, regardless of its origin. Over the past 20 years, new curative therapeutic approaches have developed: cytoreduction surgery and peritonectomy, immediate post-operative intraperitoneal chemotherapy, intraperitoneal chemotherapy, perioperative systemic chemotherapy using targeted therapies. These different approaches have been particularly developed in France for secondary peritoneal metastases of digestive origin and for rare peritoneal tumours. Today, they make it possible to envisage prolonged survival and even healing for selected patients. Patients are selected mainly on the primary origin of peritoneal metastasis, its extension (Peritoneal Cancer Index), its resectability, its response to systemic treatments. These services are complex, cumbersome, specialized and require optimal coordination between the various health actors. Despite these advances, many patients will experience (i) advanced stage at diagnosis, (ii) non-response or incomplete response to treatment, (iii) early or extraperitoneal recurrence, (iv) altered quality of life. The therapeutic approaches currently proposed are not very standardized. It seems important to intensify research on these developments by setting up a broad and ambitious tool to answer the scientific questions of today and tomorrow. This research must use a personalized approach to identify the clinical and patho-biological determinants of resistance to antitumor treatments, while seeking to explain epidemiological, social and behavioural characteristics. The creation of a national prospective database dedicated to patients with peritoneal metastases, including epidemiological, clinical, surgical, patho-biological, monitoring, human and social science data and based on quality biological resources from tumour libraries and serotheques is therefore a major and essential challenge in France. The BIG-RENAPE project brings together the majority of the clinical teams of the University Hospitals and cancer centres in France that manage the majority of these peritoneal metastases. It also relies on the existing RENAPE network, supported by INCa since 2009, dedicated to rare peritoneal tumours and on a database recognized and valued internationally by numerous collaborative projects. In particular, it made it possible to validate an international TNM classification in peritoneal mesotheliomas and to participate in an international registry of 2298 patients with peritoneal pseudomyxoma. The participation of all the national teams involved in the management of peritoneal metastases underlines the major scientific interest of the project as well as the already existing structure of clinical research in France for this pathology. The visibility of the project, whose construction has begun, and the support teams allow us, even before the first inclusions, to make this BIG-RENAPE database an essential pillar for future European and international collaborations.

Assumptions

The personalized approach to digestive peritoneal metastases is emerging and requires rapid and multidisciplinary development. As the management of peritoneal metastases is heavy, complex, heterogeneous and resistance to locoregional and systemic treatments is frequent, new epidemiological and clinical studies, based on biological collections, must be carried out on a large scale. The creation of a prospective clinical-biological database dedicated to digestive peritoneal metastases is essential for the development of such projects.

Objectives of the project

Main objective

Identify factors related to resistance to anti-tumor treatments in patients treated for peritoneal metastases of digestive origin, through the development of a clinical-biological and multicentric database.

Secondary objectives

- Describe diagnostic and therapeutic management;
- Evaluate the impact of therapeutic strategies on, recurrence, survival (overall and without recurrence);
- Compare the individual, social and behavioural characteristics of patients according to the modalities of their therapeutic management;
- Evaluate the impact of therapeutic strategies on quality of life;

- Evaluate the impact of therapeutic strategies on the intensity of pain perceived by the patient;
- Identify the epidemiological and socio-demographic determinants of delay in access to care and initiation of treatment;
- Identify and validate new prognostic and predictive biomarkers of treatment response.

Experimental design

Inclusion (D0)

After checking the inclusion and non-inclusion criteria, the investigator informs the patient and then collects his written and signed consent. During the inclusion visit, 24 ml of blood is to be collected (2 dry tubes of 4 mL + 3 EDTA tubes of 4 Ml + 1 heparin tube of 4 ml) for patients included in the centres participating in the blood collections.

The MOS-SSS and HADS questionnaires are to be completed as well as an EVA. Finally, the self-assessment questionnaire for quality of life, QLQ-C30, and its corresponding complementary module (QLQ-CR29/STO22), are to be completed by the patient.

Clinical follow-up of patients

Follow-up visits are follow-up visits for these patients as part of their regular management. No additional visits beyond the usual practices of the centres are required.

However,

- ***Quality of life self-assessment questionnaires*** to be completed by all patients according to the time of their care
- 1/ Before surgery: 1 month postoperatively and then every 3 months up to 1 year
- 2/ Post surgery: every 3 months until 1 year old then every year until recurrence
- 3/ In follow-up: every year until recurrence
- 4/ On a palliative basis: every 3 months until 1 year then every year
- 5/ In recidivism, repeat diagram 1 or 4

The completed questionnaires should be returned to the coordination team for computerization. The questionnaires are made confidential by a code containing the 1st letter of the surname, the 1st letter of the first name, the centre number and the patient number.

Biological collection (blood serum)

For patients included in the centres participating in the blood collections, 24 ml of blood is collected (2 dry tubes of 4 mL + 3 EDTA tubes of 4 Ml + 1 heparin tube of 4 ml) at each treatment line or in case of recurrence or relapse.

Biological collection (tumor material)

For all patients included in the study, paraffin blocks consisting of pre-, post-therapeutic or surgical biopsies will be collected (with *systematic* biopsy in the case of exploratory laparotomies and non-resectable peritoneal metastases).

Ancillary study (only for patients included in the CHLS)

Study based on non-directive and semi-directive interviews. For each patient, the interviews will take place in 5 successive stages and will follow the rhythm of the consultations that structure the usual management and follow-up of patients after their discharge from hospital.

- **Time #1 :**
  Interview conducted a few days before discharge from hospital following surgery;
- **Time #2 :**
  Interview conducted during the so-called "post-operative" consultation at 1 month (4 to 6 weeks) after discharge from hospital;
- **Time #3 :**
  Interview conducted 3 months (+/- 4 weeks) after discharge from hospital (only for colostomized patients);
- **Time #4 :**
  Interview conducted 12 months (+/- 4 weeks) after discharge from hospital;
- **Time #5 :**
  Interview conducted no later than 24 months (+/- 4 weeks) after discharge from hospital.

Study population

Inclusion criteria

- Male / female over 18 years of age;
- Management or follow-up for peritoneal metastases of digestive origin confirmed histologically and/or radiologically;
- Patient affiliated to a social security system or similar;
- Patient who has given free, informed and signed consent.

Criteria for non-inclusion

- Minor patient;
- Adult person unable to express consent;
- Patient under legal protection measure;
- Refusal of the patient to participate in the study.

Number of subjects required

The annual incidence of peritoneal metastases of digestive origin is estimated at 10,000 new cases per year. This study is intended to be exhaustive, but for feasibility reasons, recruitment will be limited to the 36 specialized centres (University Hospital or CLCC) that most frequently handle metastases of digestive origin. Assuming that 10% of patients will refuse to participate in the study, we estimate that by combining a prospective and retrospective collection of cases, we will include 15,000 patients from all centres combined.
Depending on the etiology, the 5-year survival rate varies from 25% (gastric), 33% (adenocarcinoma of the small intestine) to 41% (colorectal) with, if necessary, changes in therapeutic strategies within 5 years of initial management. These events reflect phenomena of potential resistance to anti-tumor treatments with mechanisms that are still poorly understood. Also, this sample size and expected event rates should be sufficient to identify predictive factors (clinical, biological andtumour).

Risk/benefit balance

No major risks are associated with this research because it does not involve any major and additional invasive procedures compared to the management of these patients. Theoretical risks may be associated with blood sampling at each therapeutic time: bleeding and vagal discomfort. In addition to the collection of tumour samples from pre-, post-therapeutic and surgical biopsies and surgical specimens as part of the usual therapeutic management for these patients, additional biopsies are systematically requested in the case of exploratory laparotomies and non-resectable peritoneal metastases.
This research will increase scientific knowledge about prostate cancer in order to improve the long-term management of people with the disease and to describe their biological, tumour and evolutionary characteristics in order to better understand resistance to treatment in some cases.
Quality of life questionnaires will provide essential information about the quality of care for these patients and their social environment. This research will then provide an opportunity for health care teams to adapt their approach to the patient and the way they communicate with them. This will include, for example, strengthening the support, guidance and listening of patients and thus proposing strategies to improve their emotional state and promote their overall adaptation. More generally, this research will provide information about how patients cope with the disease and how to help themcope.

Associated centres

See **Annex 1**

ABBREVIATIONS

ANSM : National Agency for the Safety of Medicines and Health Products

ARC: Clinical Research Assistant

ARS : Regional Health Agency

GCP: Good Clinical Practices

CCRM: Metastatic Colorectal Cancer

CCTIRS: Advisory Committee on the Processing of Health Research Information

CHIP: Chemotherapy Intraperitoneal Hyperthermia

CNIL: Commission Nationale de l'Informatique et des Libertés

CPP: Committee for the Protection of Persons

CSP: Public Health Code

eCRF: electronic Case Report Form

EORTC : European Organisation for Research and Treatment of Cancer

EVA: Visual Analogue Scale

HADS : Hospital Anxiety and Depression Scale

ICH : International Conference on Harmonisation

INCa : Institut National du Cancer

MESR: Ministry of Higher Education and Research

MOSS: Medical Outcome Study-Social Support Survey

NCI-CTCAE : NCI Common Terminology Criteria for Adverse Events

QLQ : Quality of Life Questionnaire

RBM: Biomedical Research

RCP: Multidisciplinary Consultation Meeting

TABLE OF CONTENTS

Peritoneal metastases are defined as an attack of the peritoneum by a malignant tumor, regardless of its origin[1]. Peritoneal metastases can be either primary, related to the tumor development of peritoneal cells, or secondary by local-regional or metastatic extension of tumors from the abdominal cavity.

Peritoneal metastases have long been considered a terminal metastatic stage of digestive cancers, but its development, natural history and response to systemic treatments are different from those of hepatic and/or pulmonary metastatic disease. The spontaneous prognosis was very unfavourable (median survival at 12 months)[2, 3].

Over the past 20 years, new therapeutic strategies have been developed for the management of peritoneal metastases of digestive origin: targeted therapies and perioperative chemotherapies, *early postoperative intraperitoneal chemotherapy* (*EPIC*), maximum cytoreduction surgery and associated perioperative CHIP. The results of these treatments have radically transformed the prognosis of peritoneal metastases, whether primary or secondary, and suggest curative prospects and prolonged survival in selected patients.

1. PERITONEAL METASTASES OF COLORECTAL ORIGIN

Peritoneal metastases are present at diagnosis in about 15% of colorectal cancers [3, 4]. His spontaneous and very pejorative prognosis has long led them to consider it as a therapeutic dead end where only palliative treatments had their place. The drugs currently validated for CHIP in Phase II in these indications are mainly oxaliplatin and mitomycin C. The overall morbidity is between 30% and 50% of grade III, IV with a specifically surgical morbidity of around 30%. Surgical mortality is low, less than 4% [5].

The survival of colorectal peritoneal metastases has been evaluated in several Phase II studies. Overall survival at 5 years was 48.5% with a median survival of 60 months in the Elias study, which used oxaliplatin as a chemotherapy agent, for CHIP [5]. In the multicenter retrospective study conducted by Glehen and including 506 patients, the median overall survival was 19.2 months despite the bias of including heterogeneous therapeutic procedures in a retrospective study [6].

Finally, the randomized Dutch Phase III monocentric study comparing CHIP with standard surgery combined with chemotherapy such as 5FU/folinic acid showed a significant gain in survival: a median survival rate of 42.9 months and 43% survival at 5 years for patients with complete excision [7, 8].

Currently, despite advances in systemic chemotherapy and targeted therapies, the median survival rate for metastatic colorectal cancers not accessible for resection surgery is at best below 20 months [2, 9].

One study compared the fate of two groups of patients who were fully comparable in terms of peritoneal metastases. The first group was able to benefit from CHIP because patients had access to a centre providing this treatment, the other not, as patients were referred to a health care facility that did not have this therapeutic method at the time. The medians of survival are very significantly different ($p<0.0001$): 60 months for patients treated with CHIP, 24 months for those who did not benefit from it. More recently, the study of 563 patients in the CFL series reported by Elias found an overall median survival of 33 months with 41% survival at 5 years [10]. Finally, in the bicentric series of 146 patients treated with oxaliplatin and irinotecan, the median survival was 41 months [11].

The interest of CHIP in the treatment of colorectal peritoneal metastases is currently being evaluated in a multicentre Phase III study (PRODIGE 7/ACCORD 15; ClinicalTrials.gov Identifier: NCT00769405) in which patients benefit from perioperative chemotherapy and complete cytoreduction surgery randomized to CHIP. Inclusions ended in December 2013 and a total of 264 patients were randomized between the two arms.

2 PERITONEAL METASTASES OF GASTRIC ORIGIN

The results obtained by combining complete cytoreduction surgery with CHIP in gastric peritoneal metastases are much less encouraging than in rare peritoneal tumours or colorectal peritoneal metastases. In the series published by the AFC, the median survival was 15 months with 25% survival at 5 years for patients undergoing complete resection [12]. Only a few small Phase II studies, mainly in Asia, have shown significant results in adjuvant situations. No significant results are published

in a situation of recidivism or catch-up [13-15].
On the other hand, a very extensive literature seems to show a clear benefit in a prophylactic situation. A multi-center therapeutic trial including prophylactic CHIP (GASTRICHIP) for locally advanced gastric tumors T3 and T4 is currently underway [16] (ClinicalTrials.gov Identifier: NCT01882933).

3 ADENOCARCINOMAS OF THE HAIL IN PERITONEAL METASTASES

Their management may also combine cytoreduction surgery and CHIP with results comparable to those obtained for colorectal peritoneal metastases. The series published by the AFC has a 33% survival rate at 5 years [12]. Translational research work equivalent to that carried out for colorectal peritoneal metastases can be considered (biopsies, serum) to identify new prognostic and predictive markers.

4 HISTOLOGY AND MOLECULAR CHARACTERISTICS

Colorectal tumours are heterogeneous at the histological and molecular levels. Histologically, they are dominated by classical lieberkuhnian adenocarcinomas, but other recently individualized subtypes are included in the latest classification [17]. At the molecular level, 3 major molecular groups are traditionally individualized, with different prognostic impacts WHO [17].

Chromosome instability (CIN, *chromosomal instability*), which is objective in 80% of colorectal cancers, is characterized by the loss of chromosome material, leading to the inactivation of tumor suppressor genes such as *TP53* or the activation of oncogenes such as *KRAS*.

Epigenetic instability (CIMP*, CpG Island Methylator Phenotype*) is present in about 20% of colorectal tumor cases. It is characterized by the inactivation of certain genes by hypermethylation of the promoter.

Microsatellite instability (MSI*, microsatellite instability* or dMMR for *MisMatch Repair deficient*), which is objective in 15% of colorectal cancers, corresponds to a deficiency in the base mismatch system occurring during replication. It results in the appearance of frequent mutations in repeated nucleotide sequences, called microsatellites.

Prognostically, the MSI group is associated with a much more favourable clinical course than the other groups, probably due to an immune response induced by tumor neo-antigens.

Recently, a molecular signature of colorectal cancers has been proposed. It has 6 different prognostic impact groups: stem cell phenotype, "normal" CIN phenotype, festooned CIN phenotype, mutated *KRAS*, MSI phenotype and under-regulated immunotype (or according to Anglo-Saxon terminology: "stem cell phenotype-like, CIN normal-like, CIN serrated phenotype-like, *KRAS* mutated, MSI and immune down")[18]. Stem cell phenotype and under-regulated immune phenotype groups are characterized by the most pejorative prognosis.

Little is known about the molecular and phenotypic aspects of colorectal peritoneal metastases. A preliminary study based on a retrospective series [19] showed that peritoneal metastases were characterized by a pure or mixed mucinous histological form in more than half of the cases, whereas this subtype is observed in primary tumours in only 10% of the cases. In addition, these mucinous types had better survival without recurrence compared to classical peritoneal metastases of the Lieberkünian type (p=0.04). At the molecular level, peritoneal metastases whose tumours are not mutated for the *KRAS* and *BRAF* genes had higher overall survival compared to mutated forms, including *BRAF*.

These data call for some comments. The high proportion of mucinous form observed in this series suggests a particular affinity for peritoneum for this histological subtype. Nozoe et al. also showed significant differences in the natural evolution of mucinous and non-mucinous colorectal tumours. The rate of peritoneal metastases was thus higher in patients with mucinous colorectal carcinoma (22%) compared to patients with a non-mucinous type (6%) [20]. In addition, the incidence rate of liver metastases was lower in the mucinous colorectal tumour subgroup. These results were recently confirmed by a Dutch team [21]. Numata et al. also reported peritoneal metastases and higher rates of progression for mucinous tumours[22]. Paul Sugarbaker's team pointed out that, in this type of tumor, mortality was more related to a phenomenon of tumor extension than to the presence of distant metastases [23].
All these findings underline the need to dismember metastases at the histological and molecular level

based on large prospective clinical-biological cohorts. The aim of this approach is to better understand the evolution of peritoneal metastases by identifying clinical-biological entities and identifying the most appropriate therapeuticperspectives.

5 TUMOROUS ENVIRONMENT

While genetic alterations of the tumor play a major role in tumor progression and response to cancer treatments, the tumor environment has a recognized place in the natural history of tumor disease. The immune response has recently been identified as a major prognostic factor for many solid tumours, particularly colorectal ones [24].

The immune system could prevent or slow tumor development through immunosurveillance mechanisms. Thus, the presence of a dense infiltration of CD3+, CD8+ (cytotoxic), CD45+ (memory) T cells at the intra- and peritumoral level is associated with a better prognosis than tumors that do not have these characteristics [24].

The majority of studies conducted to objectify the immune response in solid cancers have been based on retrospective series of patients in early stages of the disease. These studies were based on a limited number of markers evaluated in immunohistochemistry. However, it seems that the immune response also has a strong impact in metastatic situations. In colorectal liver metastases, Halama et al. reported a statistically significant association between a significant contingent of cytotoxic T cells located at the tumor tissue-healthy tissue interface and treatment response [25]. To date, there are no major studies that have analyzed the involvement of lymphocyte infiltration and tumor microenvironment in peritoneal metastases of digestive origin, particularly colorectal. Moreover, no study has focused on the role of tumor microenvironment in resistance mechanisms in this localization [26].

All these arguments underlie the need to develop translational research studies on the tumor microenvironment in peritoneal metastases of digestive origin based on prospective and functional clinical-biological bases.

6 RETURN TO THE HOME OF THE POINT OF VIEW OF THE PATIENTS, TAKEN IN RESPECT OF DISEASE AND CORPORATE EXPERIENCES (ancillary study)

The international medical literature has shown that people with cancer face many harmful effects that can be observed in the more or less long term, in connection with surgical and chemotherapy treatments. Overall, as the authors involved in the VICAN 2 survey (Cancer Plan 2009-2013), which focused on the daily lives of people treated for cancer, point out, people with cancer must manage functional limitations over varying periods of time that prevent some of them from resuming their activities and that, in all cases, change their life course [27].

The difficulties observed are on several levels: the physical difficulties induced by the treatments can become chronic, even irreversible (pain, fatigue, gastric dysfunction, food, digestive pocket management, sexual difficulties, etc.).

The medium- to long-term psychological effects are now identified and recognized: episodes of depression, anxiety and distress, and damage to self-image [28].

Finally, there are three types of social consequences: return to the family environment, professional reintegration and life in the group (s) to which they belong [29].

In the CORCAN study (ClinicalTrials.gov Identifier: NCT01560533) conducted in patients treated for peritoneal metastases (with or without CHIP), return home emerged as one of the major concerns addressed by patients [30-33].

Two problematic axes, by soliciting the points of view of patients concerned by the test of peritoneal digestive metastases (colorectal or gastric), are distinguished:

- How patients live, name and endure the ordeal of the disease and its treatments, and what are the repercussions of the disease on the quality of daily life, on the intimate and social life of patients: We open this first questioning to patients in order to understand the explanations they

give to the disease experience, and to identify the least identified and expressed vulnerabilities, because they are considered to be logically reactive to the times of the disease and the forms of treatment to which the patient must submit in a care objective.

- What are the strategies used by patients to cope with the different levels of difficulties of the disease and its treatments as perceived by the patients themselves.
  What are the strategies used by patients and the essential supports that patients say they can rely on to cope with the difficulties described? We will thus identify personal resources and approaches (cognitive, psychological, even artistic and/or spiritual), and relational and environmental supports where destabilizing feelings of momentary ruptures in physiological, psychological and social security can be expressed. In this perspective, we will identify, with reference to a number of research studies, attempts to self-monitor, anticipate breakdowns, preserve coherence and physical safety, as well as the challenges of empowerment and self-restoration developed by patients.

In the post-hospitalization period, the patient no longer delegates all disease management initiatives to the physician, but is more or less actively involved in the care management process [34]. Active participation in disease management promotes the acquisition of therapeutic knowledge and practices.
It seems important to us to address in parallel and in articulation with the practices of recourse to medical institutions, the different therapeutic recourses to alternative medicines as well as all individual practices of prevention (self-preservation) and self-care.

We will question patients undergoing peritoneal metastases of colorectal or gastric origin about these different axes of hypotheses relating to cognitive, physical, relational, material and psychological dimensions by referring on the one hand to the notion of social representations[35], subjective theories of health and disease[36] and profane theories of the body, essentially the sick body[37, 38]. On the other hand, we will refer to the notion of
"patient's work" of A. Strauss, which covers all the acts, gestures and tasks developed by the patient to control the course of the disease and regain greater safety and comfort [39]. The issue of emotion management is also essential to consider [40]. It is effective in the different expressions of experience and different situations of management of the disease and its treatments.

The "social support" dimension as well as the role of the local and peer environment are major areas to be explored. Most patients seek and receive significant help from family members, whether emotional or materia l[41]. Most studies that have examined the impact of social support on emotions (emotional regulation) have found that family-based social support is associated with a good adjustment to the disease [42, 43]. Overall, its protective role in addressing emotional distress and quality of life has been demonstrated. In this perspective, the role of patient organisations is not sufficiently addressed.
The various patient associations have largely favoured the active patient model [44]. In this model, the patient no longer delegates all disease management initiatives to the physician, but intervenes in the decision-making process [34]. Active participation in disease management promotes the appropriation of knowledge and therapeutic recourse practices.

7 EXPECTED FALLS BACK

The establishment of a national clinical-biological database on peritoneal metastases of digestive origin as proposed in the project will make it possible to:

- Establish national biological collections (tumour material, serum) according to standardised sampling and conservation criteria and in accordance with current standards and recommendations;
- Homogenize and standardize a prospective collection of epidemiological, socio-demographic, clinical, biological and histological data;
- Identify clinical and biological factors with prognostic and predictive characteristics;
- Facilitate the initiation and implementation of multi-centre research projects.

Ancillary study:

- Provide new knowledge about the experiences of the patients concerned, their personal, relational and environmental resources to cope with them;

- Innovate support systems and new care schemes that are personalised and adapted to patients' level of autonomy by enabling them to put into practice their skills in assessment, analysis and participation in their care journey.

8 OBJECTIVES

8.1 Main objective

Identify factors related to resistance to anti-tumor treatments in patients treated for peritoneal metastases of digestive origin, through the development of a clinical-biological and multicentric database.

8.2 Secondary objectives

- Describe diagnostic and therapeutic management;
- Evaluate the impact of therapeutic strategies on recurrence, survival (overall and without recurrence);
- Compare the individual, social and behavioural characteristics of patients according to the modalities of their therapeutic management;
- Evaluate the impact of therapeutic strategies on quality of life;
- Evaluate the impact of therapeutic strategies on the intensity of pain perceived by the patient;
- Identify the epidemiological and socio-demographic determinants of delay in access to care and initiation of treatment;
- Identify and validate new prognostic and predictive biomarkers of treatment response.

Ancillary study:

This study will only concern patients under surgical management at the Centre Hospitalier Lyon Sud.

- Describe the meaning that patients give to daily experiences of returning home: the modalities and strategies by which they reinvest the space of daily life (domestic, family, social, professional) and mobilize material, cognitive, psychological and social resources and skills to cope with this return and the post-hospitalization period;
- Identify the most critical situations and moments in the disease trajectory as perceived by patients;
- Describe the activities and approaches used by patients to manage and cope with the effects of the disease;
- In collaboration with the healthcare team, build and model a post-hospitalization response and support system adapted to the experiences, difficulties and resources of patients treated for digestive cancer. This system is to be designed on the updating and enhancement of the patient's skills.

9 EVALUATION CRITERIA

9.1 Main evaluation criteria

Clinical, biological and tumour factors related to resistance will be evaluated based on clinical and biologic data. Resistance to treatment is defined as a change in the therapeutic strategy used in CPR, recurrence or death of the patient.

9.2 Secondary evaluation criteria

- Diagnostic and therapeutic management methods and compliance with standards and recommendations;
- Survived, overall and without recurrence, at 3 years, measured from the time between inclusion and the occurrence of the event;
- Sociodemographic data: age, sex, professional activity
- Behavioural data: MOS-SSS and HADS questionnaire scores obtained at inclusion (D0),
- 1/ Before surgery: at 1 month postoperatively and then every 3 months up to 1 year
- 2/ Post surgery: every 3 months I up to 1 year then every year until recurrence
- 3/ In follow-up: every year until recurrence

- 4/ On a palliative basis: every 3 months until 1 year then every year
- 5/ In recidivism, repeat diagram 1 or 4
-

  MOS-SSS [45] evaluates the social support perceived by patients with chronic diseases. The short version of 4 items, validated in French by a Canadian team [46], will be used in this study. For the 4 items, the evaluation is based on a 5-point Likert scale (**Appendix 2**).

  The **HADS of** Zigmond et al [47], validated in cancerology, in French, by Razavi et al [48] allows to detect anxiety or depressive disorders in patients suffering from a somatic disorder. It consists of two subscales, each with seven items to which patients respond by surrounding the response that best defines their current condition. Four answers are systematically proposed and each corresponds to a score between 0 and 3 (**Appendix 3**).
- Quality of life will be measured using the following inclusion tools (J0),
- 1/ Before surgery: at 1 month postoperatively and then every 3 months up to 1 year
- 2/ Post surgery: every 3 months I up to 1 year then every year until recurrence
- 3/ In follow-up: every year until recurrence
- 4/ On a palliative basis: every 3 months until 1 year then every year
- 5/ In recidivism, repeat diagram 1 or 4
  - The **QLQ-C30 of the** EORTC (European Organization for Research and Treatment of Cancer) measures the quality of life of cancer patients. It is composed of 30 items measuring overall quality of life, physical condition, activity limitation, cognitive, emotional and social functioning, and the appearance of frequent symptoms associated with cancer or treatment. Participants are asked to answer on an ordinal scale of four (not at all, a little, enough, enough, a lot) or seven points (from 1 - very bad - to 7 - excellent)
    49] (**Appendix 4**).
    In addition to the QLQ-C30 self-questionnaire, two additional modules will be offered:

    The QLQ-CR29[50] module is a specific assessment of the quality of life of patients with colorectal cancer. It is composed of 29 items/scales assessing the symptoms of the disease and/or adverse effects of treatment, as well as the impact of the disease on the patient's quality of life (**Appendix 5**).

    The QLQ-STO22[51] module is a specific assessment of the quality of life of patients with gastric cancers. It is composed of 29 items/scales assessing the symptoms of the disease and/or adverse effects of treatment, as well as the impact of the disease on the patient's quality of life (**Appendix 6**).
  - The intensity of pain will be measured using **EVAs** from the left position for no pain (0) to the right position for unbearable pain (10). An EVA will be offered to the patient at inclusion (D0), 1/ Before surgery: at 1 month postoperatively then every 3 months up to 1 year
  - 2/ Post surgery: every 3 months I up to 1 year then every year until recurrence
  - 3/ In follow-up: every year until recurrence
  - 4/ On a palliative basis: every 3 months until 1 year then every year
  - 5/ In recidivism, repeat diagram 1 or 4

- The individual or collective determinants of delay in diagnosis will be assessed by conventional epidemiological (socio-demographic, socio-economic and geographical), psychological adjustment (MOS- SSS, HADS) and quality of life (QLQ-C30 and QLQ-CR29 / STO22) indicators based on the data collected by the self-administered questionnaires.
- Prognostic and predictive factors for treatment response will be evaluated based on the clinical-biological data collected.

10 EXPERIMENTAL PLAN - METHODOLOGY

10.1 Type of study

Open, multicentric, non-randomized, non-randomized cohort follow-up intervention study, with longitudinal follow-up of patients after the intervention, and constitution:

- A **prospective clinical-biological database:** clinical, biological, epidemiological data as well as the characteristics of patients' treatments will be collected in a dedicated electronic observation booklet (eCRF);

  At the same time, the **integration of retrospective data** from the various associated centres is also planned to reconstruct historical cohorts
- From a **collection of serums and blood plasmas: for a** given patient, blood samples will be taken at his inclusion and then at the end of each treatment administered as part of his therapeutic management (= therapeutic time) or during a recurrence or relapse. These examinations will be carried out locally by each centre involved in recruitment;
- A **collection of tumour material** (paraffin block) constituted from pre-, post-therapeutic or surgical biopsies.

A descriptive, exploratory, longitudinal and monocentric ancillary study (Hospices Civils de Lyon) will be conducted only on a population of patients who have received surgical management.

10.2 Conduct of the study

10.2.1 Inclusion (D0)

After verification of the inclusion and non-inclusion criteria, the investigator informs the patient and then collects the patient's written and signed consent (**Appendix 7**).
In order to benefit from a reflection period, patients can return their signed consent at the next consultation or hospitalization.
To make the final inclusion, only after signing the consent, the investigator must complete the inclusion form on the eCRF dedicated to the study and thus obtain the patient identification code in the study. This is automatically generated by the eCRF platform and the confirmation of inclusion is sent instantly by email to all investigators in the centre and to the coordination centre. A unique identifier is assigned to each patient: 1st letter of the surname, 1st letter of the first name, centre number and patient number.
During the inclusion visit, 24 ml of blood should be collected (2 dry tubes of 4 mL + 3 EDTA tubes of 4 Ml + 1 heparin tube of 4 ml) from patients included in the centres participating in the blood collections.
The MOS-SSS and HADS questionnaires are to be completed as well as an EVA of pain. Finally, the self-assessment questionnaire for quality of life, QLQ-C30, and its corresponding complementary module (QLQ-CR29/STO22) are to be completed by the patient.

10.2.2 Clinical follow-up of patients

Follow-up visits are follow-up visits for these patients as part of their regular management. No additional visits beyond the usual practices of the centres are required.

- However, in addition, there are self-assessment questionnaires on quality of life to be completed according to the different times of care
- 1/ Before surgery: 1 month after surgery then every 3 months up to 1 year
- 2/ Post surgery: every 3 months until 1 year old then every year until recurrence
- 3/ In follow-up: every year until recurrence
- 4/ On a palliative basis: every 3 months until 1 year then every year
- 5/ In recidivism, repeat diagram 1 or 4

The completed questionnaires should be returned to the coordination team for computerization. The questionnaires are made confidential by a code containing the 1st letter of the surname, the 1st letter of the first name, the centre number and the patient number.

10.2.3 Biological collections (tumor material, blood serum)

The biological samples collected may be used in subsequent research projects to study the impact of different parameters on disease progression and response to treatment and may also be used by public or private partners, from the national or international territory
No identifying genetic analysis will be performed on these samples.

10.2.3.1 Sampling methods

For patients included in the centres participating in the blood collections, 24 ml of blood is collected (2 dry tubes of mL + 3 EDTA tubes of 4 Ml + 1 heparin tube of 4ml) at each treatment line or in case of recurrence or relapse.

10.2.3.2 Preparation of samples

The structure of the identification number and the method of identifying the samples constituting the bio- and tumour library will be listed as such: 1st letter of the surname, 1st letter of the first name, Centre No. and Patient No.
The serum tubes will be technical (centrifugation, fractionation of serum, plasma), aliquoted (5 samples of 500 µl serum and 5 samples of 500 µl plasma or 10 samples/patient/visit) then stored in a "serum" box at -75°C. A specific "BIG-RENAPE" label will be provided for the conservation of the tubes within each centre until they are collected (depending on the collection frequency) by a specialized carrier.

In addition, from pre-, post-therapeutic or surgical biopsies, a block of paraffin-embedded tumor tissue is specifically dedicated to BIG-RENAPE and then stored locally in accordance with current quality charters, before delivery (with *systematic* biopsy in the event of exploratory laparotomies and non-resectable peritoneal carcinoses).

10.2.3.3 Centralization and storage of samples

The paraffin tubes and blocks are centralized in SeroBioTec (Pr A. Traverse-Glehen / Dr N. Fabien - Centre Hospitalier Lyon Sud, 69495 Pierre-Bénite) for their conservation. A routing circuit via a specialized carrier has been defined to guarantee appropriate transport conditions and traceability of shipments.

10.2.4 Ancillary study

Study based on non-directive and semi-directive interviews conducted by researchers in the humanities and social sciences trained in qualitative practice and having experience in researching and conducting interviews in the field of cancer and hospital care (GRePS EA 4163, Université Lyon 2). These interviews are carried out in the General and Digestive Surgery Department (Centre Hospitalier Lyon Sud, Pierre-Bénite).

A member of the team will attend (as a simple observer) all consultations carried out as part of the follow-up in order to observe the discourse, expectations and requests addressed by patients to their doctors (and the place occupied by the family member(s) in this therapeutic dialogue) and to identify, in this context, the types of interactions between the patient and the doctor and the caregivers.

For each patient, the interviews will take place in 5 successive stages and will follow the rhythm of the consultations that structure the usual management and follow-up of patients after their discharge from hospital.

- **Time #1 :**
  Interview conducted a few days before discharge from hospital following surgery;
- **Time #2 :**
  Interview conducted during the so-called "post-operative" consultation at 1 month (4 to 6 weeks) after discharge from hospital;
- **Time #3 :**
  Interview conducted 3 months (+/- 4 weeks) after discharge from hospital (only for colostomized patients);
- **Time #4 :**
  Interview conducted 12 months (+/- 4 weeks) after discharge from hospital;
- **Time #5 :**
  Interview conducted no later than 24 months (+/- 4 weeks) after discharge from hospital.

The proposed ancillary study will be carried out in 2 stages.

Step 1: Exploratory phase

A first series of interviews is exploratory (about 5 to 6 interviews). The interviews conducted in this first phase are not very well conducted in the exchange. They will be based on a simple and identical instruction for each of the interviews. These exploratory interviews will make it possible to take into account the reconstruction of patients' priorities as they are experienced and explained by themselves. It is important to encourage and respect the emergence of underestimated or unknown thematic approaches (including taking into account the way in which interviewees introduce them into their discourse and the importance they attach to them) and to explore in the form of follow-up the axes of hypotheses proposed by the interviewees themselves. Thus, it seems very important to understand the priority concerns that patients express and argue.

Step 2: Conduct interviews on the basis of a thematic grid

The interviews are followed by a structured and systematically organised thematic grid based on the emerging themes collected during the first exploratory period (Step 1).

We include in our questioning grid the thematic content (collected in CORCAN post-care research from patients who have had surgery and intraperitoneal chemotherapy at 1 month and 3 months after the procedure).

- Re-enrollment in daily life: re-enrollment in daily life, identifying its usefulness, regaining a place in domestic life, redistributing daily tasks differently, restoring the body's activity / getting out of passivity, fighting fatigue, pain;
- Management of the relationship to food: integration of new sensations, body expression, pocket management, resumption of transit, reorganization of the relationship to food in line with dietary requirements, food attractions and digestive pocket management;
- Reorganization of the body image: integration of ruptures, scarring, new openings, reformulation of new body boundaries. If the body mourns its most elementary functions, it is also perceived in a transformation towards an acceptable state, a transformation in the consideration of its reactions and possibilities;
- Change of outlook and definition of another existential positioning, adjustment to new life standards;
- Role assigned and place occupied by carers: professionals, relatives, friends, neighbours, associations;
- Relation to the lethal dimension of illness, death, emotional regulation;
- Use of the most common care, perception of symptoms and recognition of "alerts", use of alternative medicine professionals.

11 POPULATION STUDIED

11.1 Inclusion criteria

- Male / female over 18 years of age;
- Management or follow-up for peritoneal metastases of digestive origin confirmed histologically and/or radiologically;
- Patient affiliated to a social security system or similar;
- Patient who has given free, informed and signed consent.

11.2 Criteria for non-inclusion

- Minor patient;
- Adult person unable to express consent;
- Patient under legal protection measure
- Refusal of the patient to participate in the study.

11.3 Number of subjects required

The annual incidence of peritoneal metastases of digestive origin is estimated at 10,000 new cases per year. This study is intended to be exhaustive, but for feasibility reasons, recruitment will be limited to the 37 specialized centres (University Hospital or CLCC) that most frequently manage peritoneal metastases of digestive origin. Assuming that 10% of patients will refuse to participate in the study, we estimate that by combining a prospective and retrospective collection of cases, we will include approximately 15,000 patients out of 37 centres.
Depending on the etiology, the 5-year survival rate varies from 25% (gastric), 33% (adenocarcinoma of the small intestine) to 41% (colorectal) with, if necessary, changes in therapeutic strategies within 5 years after initial management [10, 12]. These events reflect phenomena of potential resistance to anti-tumor treatments with mechanisms that are still poorly understood.
Also, this sample size and expected event rates should be sufficient to identify predictive factors (clinical, biological and tumour).

12 DATA ANALYSIS

The statistical analyses will be carried out under the supervision of a statistical and data management manager. Once the data management steps have been completed, a data export (multi-format) can be carried out with a view to their exploitation

statistics in the context of multicentric research projects that have received prior approval from the Scientific Committee. The data will be treated in a strictly anonymous and confidential manner, on a secure system.
This paragraph presents the main analyses that will be carried out and will serve as a basis for drafting the detailed statistical analysis plan. This plan may be revised during the course of the study to adapt to any amendments. The statistical analysis will be carried out independently of the investigators to ensure the objectivity of the results. All analyses will be carried out at the 5% significance level.

12.1 Initial characteristics

All initial patient characteristics will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum and maximum for quantitative and actual variables with percentages for qualitative variables).

12.2 Main judgment criteria

The influence of clinical, biological and tumour factors, defined in collaboration with the scientific committee, will be tested on resistance to treatment using univariate and multivariate logistic regression.

12.3 Secondary Judgement Criteria

- The modalities of diagnostic and therapeutic management as well as compliance with the guidelines and recommendations will be described;
- Overall survival as well as 3-year non-recurrence survival will be described using Kaplan-Meier survival curves and median survival times will be estimated (if applicable);
- The patients' socio-demographic and behavioural data will be compared according to the therapeutic management modalities. Qualitative variables will be compared using a Chi-square test or the exact Fisher test if the application conditions are not met. The quantitative variables will be compared using an ANOVA, after checking the normality of the distributions. In case of non-normal, the Kruskal Wallis non-parametric test will be used;
- The impact of therapeutic strategies will be tested on the evolution of quality of life using a regression model based on repeated measurements;
- The impact of therapeutic strategies will be tested on the evolution of the pain perceived by the patient using a repeated measurement regression model;
- The influence of socio-demographic, epidemiological, psychological and quality of life factors will be tested in terms of time to access care and start treatment using a linear regression model;
- The influence of clinical biology data will be tested on treatment response using univariate and multivariate logistic regression.

Ancillary study:
Patient interviews will be analyzed according to the thematic content that will confirm, invalidate or complete the hypotheses derived from the literature [52, 53]. Meaning units will thus be identified, categorized and linked in order to identify axes of transversal and temporal meanings throughout the corpus.

13 ADVERSE EVENTS

13.1 Definitions of the terms

13.1.1 Adverse event (AE)

Any harmful event occurring in a person who is the subject of research, whether or not it is related to the research.

The intensity of ARs will be estimated according to the NCI-CTCAE classification version 4.0 (grades 1 to 5). Only major postoperative complications of grade ≥ 3 occurring within 90 days after surgery will be reported in the E-CRF.

The intensity of ARs not listed in this classification will be assessed according to the following qualifiers:

Lightweight	**Grade 1**	Does not affect the patient's usual daily activity
Moderate	**Grade 2**	Disrupts the patient's usual daily activity
Severe	**Grade 3**	Prevents the patient's usual daily activity
Very Severe	**Grade 4**	Imposes resuscitation measures/ threatens vital prognosis
	Grade 5	Death

13.1.2 Serious Adverse Event (SAE)

Any event is considered a Serious Adverse Event (SAE):

- Leading to death;
- Involving a life-threatening prognosis;
- Leading to hospitalization or prolongation of hospitalization;
- Causing permanent disability or severe temporary disability;
- Causing a congenital anomaly, fetal malformation or abortion;
- Medically significant.

The terms disability and incapacity refer to any temporary or permanent physical or psychological disability that is clinically significant and has an impact on the patient's physical activity and/or quality of life. Any clinical event or laboratory result considered serious by the investigator and not meeting the severity criteria defined above is considered medically significant. They may put the patient at risk and require medical intervention to prevent an outcome that meets one of the severity criteria mentioned above (examples: overdosage, second cancers, pregnancies and new facts may be considered medically significant).

In this study, only deaths (regardless of cause and nature), considered serious adverse events, will be reported immediately by the investigator. Other serious adverse events will be reported in the CRF.

13.2 Declaration of Serious Adverse Events

13.2.1 Investigator's responsibilities

The investigator shall report all deaths to the Sponsor using the most accurately documented, dated and signed "Serious Adverse Event Report" form within **24 business hours of** their discovery to:

Vigilance unit " BIG-RENAPE "
Hospices Civils de Lyon
Fax: 04 72 11 11 51 90

This initial notification shall be the subject of a written report and shall be followed, if necessary, by additional detailed written report(s).

The investigator should best document the event and establish a causal relationship between the serious adverse event and the research.

13.2.2 Proponent's Responsibilities

The promoter will declare in accordance with the Law of August 9, 2004:

- All unexpected serious serious adverse reactions to ANSM, CPP and Eudravigilance,
  - without delay and at most within 7 calendar days after receipt, in the event of life-threatening prognosis or death of the subject and within 8 days for follow-up declarations,
  - without delay and at most within 15 calendar days of receipt, for all other unexpected serious adverse reactions and within 8 days for follow-up reports,
- Security developments at ANSM and CPP as soon as possible and no later than 15 calendar days after becoming aware of them and within 8 days for follow-up declarations.

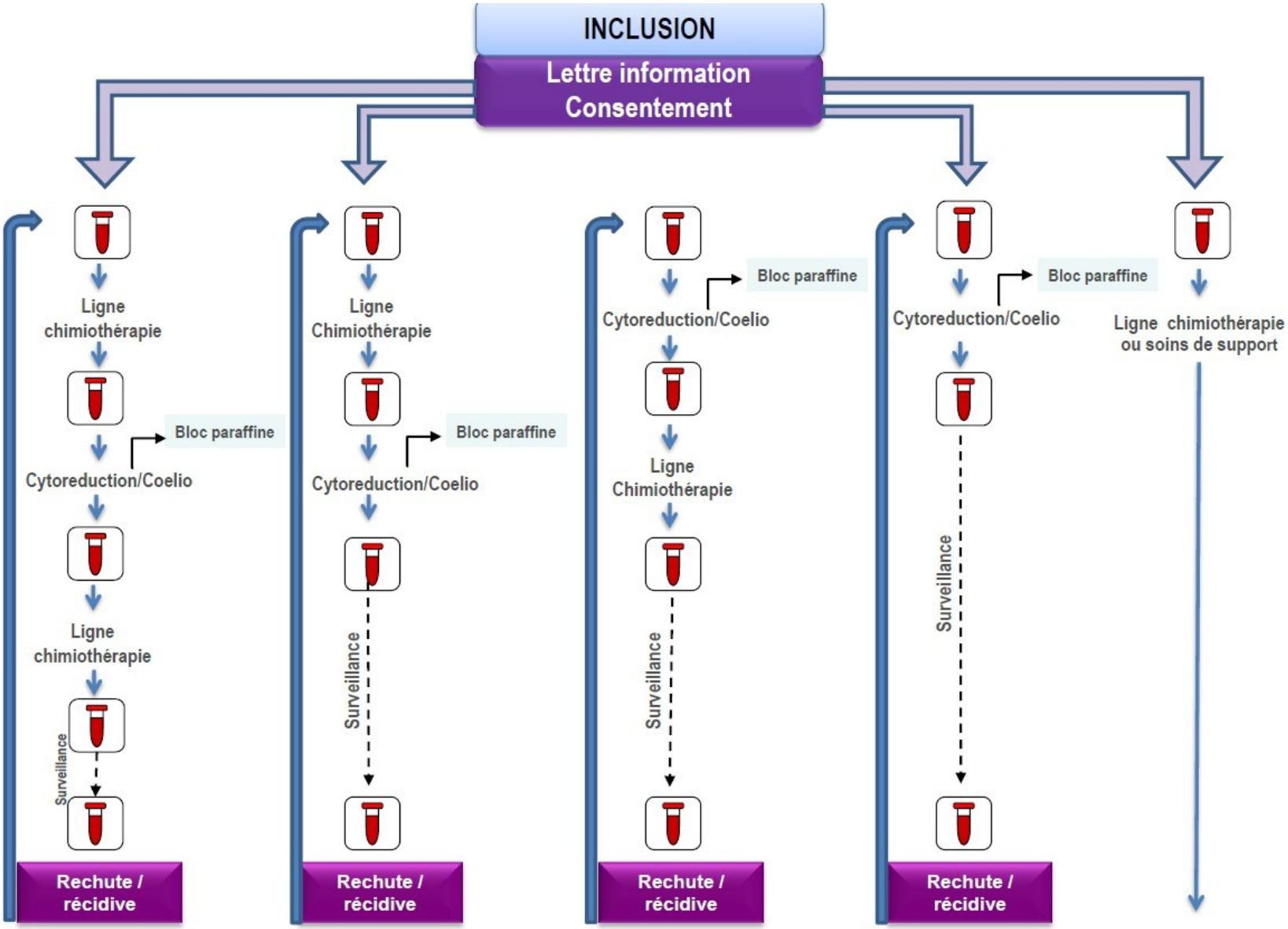
It will also prepare an annual safety report that will be sent to the ANSM and CPP within 60 days of the anniversary date of the study.

13.3 Monitoring of ISGs

The investigator is responsible for the appropriate medical follow-up of patients until the resolution or stabilization of the effect or until the patient's death. This may sometimes mean that this follow-up extends beyond the patient's discharge from the study.

It shall keep records of the suspected adverse reaction in order to allow, if necessary, to complete the information previously transmitted.

It responds to the promoter's requests for additional information to document the death.


INCLUSION
Lettre information
Consentement
Ligne
chimiothérapie
Bloc paraffine
Cytoreduction/Coelio
Ligne
chimiothérapie
Surveillance
Rechute /
récidive
Ligne
Chimiothérapie
Bloc paraffine
Cytoreduction/Coelio
Surveillance
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Rechute /
récidive
Bloc paraffine
Cytoreduction/Coelio
Surveillance
Rechute /
récidive
Ligne chimiothérapie
ou soins de support

Figure 1a

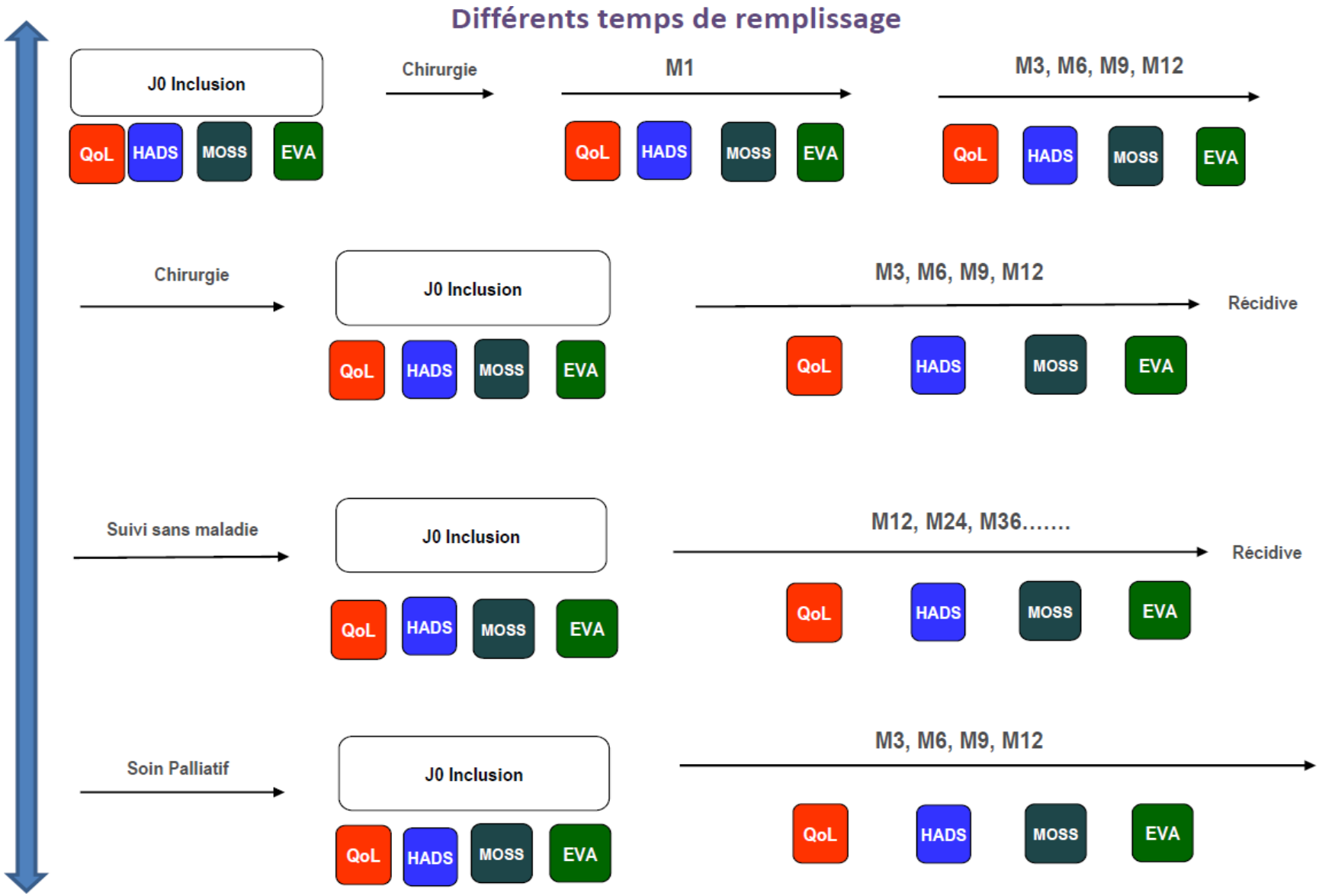

Figure 1a-1b : *Conduct of the study*

13.4 Independent Oversight Committee

As the project aims to collect clinical, biological and tumour data and to use descriptive questionnaires, the establishment of an independent monitoring committee is not considered useful.

13.5 Description of the rules for permanent or temporary cessation

13.5.1 Rules for the permanent or temporary termination of a person's participation in research

A patient's participation will be definitively terminated and the patient considered to have left the study early in the following cases:

- Withdrawal of consent;
- Secondary appearance of a non-inclusion criterion;
- Patient's death;
- Breach of protocol: A breach of protocol is defined as any event that violates the right, safety or well-being of the patient, or affects the integrity of the research. This will include, for example, non-compliance with the inclusion and non-inclusion criteria;
- By decision of the investigator, who may remove a patient from the study for safety reasons: in the event of an adverse event considered severe and likely to endanger the patient's health.
- Patient lost sight of.

13.5.2 Rules for permanent or temporary cessation of research

The search can be stopped temporarily or permanently:

- By decision of the coordinating investigator in agreement with the Scientific Committee, the Sponsor or the Competent Authority;
- In the event of repeated major violations of the protocol;
- In the event of knowledge of data compromising the conduct of the study for patient safety reasons;
- In the event of the publication of new scientific data that calls into question the research;
- In the event of an adverse event considered to be severe and likely to affect the health of patients not clearly established as being unrelated to the research.

The Promoter shall inform the CPP and the Competent Authority of the early termination of the study, in accordance with the regulations in force.

13.5.3 Involvement of an individual in the research

A patient's participation in the study is stopped if he or she withdraws. The patient may withdraw his or her consent at any time during the study. His withdrawal does not alter his relationship with the investigating doctor, who will offer him medical follow-up adapted to his clinical situation.
In the event of withdrawal from the study, the clinical-biological data collected up to the date of withdrawal will be analysed, unless the patient expressly requests it.

13.5.4 Prohibition of simultaneous participation in other research and exclusion period

No prohibition on participating in any other observational or intervention research.
At the end of the study, there is no exclusion period before possible participation in another study.

14 QUALITY CONTROL & ASSURANCE

14.1 Investigators' responsibilities

Investigators undertake to accept quality assurance audits carried out by persons mandated by the sponsor as well as inspections carried out by the Competent Authorities. All data, documents and reports are subject to regulatory audits and inspections without the possibility of medical confidentiality.

14.2 Proponent's Responsibilities

A clinical research associate mandated by the Sponsor will visit the investigator centre(s) on a regular basis during the research and according to the rate of inclusions. During these visits (monitoring), the following elements may be verified:

- Informed consent;
- Compliance with the protocol and defined procedures;
- Quality of the data collected in the eCRF and consistency with the source documents.

All visits will be the subject of a monitoring report by written report.
On these occasions, the principal investigator and associate investigators will agree to make themselves available to the clinical investigator.

14.3 Source documents

Source documents are the original documents, data and records from which patient data are reported in the electronic observation booklet. These include, but are not limited to, test results reports, patient monitoring at the hospital and/or medical notes, questionnaires and scales, dispensation notes and medical correspondence.

14.4 Electronic Case Report Form (eCRF)

The data required for the study are collected using an eCRF from information extracted from the source documents (patient medical records and their appendices). Two separate databases will be created: one with patient identification data and the other with data collected for the analysis (Figure 2).

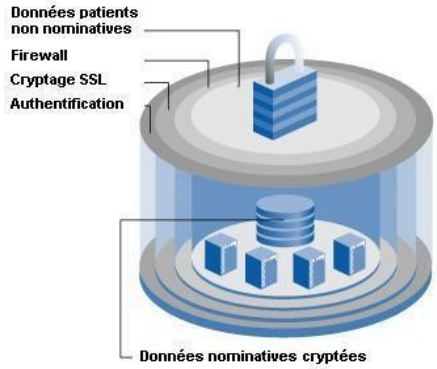

Figure 2 :

The eCRF will allow investigator centres to directly enter data on the visits concerned, for each patient included, as and when they visit.
Access to the data is secure and restrictive according to the rights given to each of the user profiles. Access to the eCRF is by means of a username and password known only to the user.
The investigator has a right of access, entry and rectification only on the data of his own patients. Members of the coordination team have the right to read patient data from all centres and have the right to export the data. In no way will the promoter or the coordination centre have the right to write on the data and may make requests for clarification. Any correction or modification of the data is logged via the computerized platform (audit trail).

14.5 Archiving

The following documents related to this research are archived by the principal investigator in appropriate and locked premises in accordance with Good Clinical Practices throughout the period of the study and data analysis:

- Protocol with annexes, possible amendments;
- The original copy of the participants' signed informed consents (kept in each investigating centre);
- Study follow-up document;
- All administrative documents and correspondence related to the study;
- Study reports.

At the end of the study, all documents to be archived will be transferred to the archiving site and archived by the study managers for a period of 15 years after the end of the research in accordance with GCP. No destruction

cannot be carried out without the agreement of the promoter. Study documents will be archived according to the procedures specific to each centre.

15 DATA COLLECTED

List of data collected in **Annex 8**.

16 ETHICAL & REGULATORY CONSIDERATIONS

The study is conducted in accordance with:

- To the study protocol (and its appendices);
- To the guidelines of the French and European Good Clinical Practices;
- To the Helsinki Declaration in its latest version (Seoul 2008);
- To the recommendations of the ICH (International Conference on Harmonisation), Guideline for Good Clinical Practice;
- The Law on RBMs of the Public Health Code (Law 2004-806 of 9 August 2004 and its implementing decrees);
- The Bioethics Law (Law 2004-800 of 6 August 2004).

16.1 Research qualification

In addition to the examinations and procedures carried out as part of the usual care for these patients, there are also examinations and procedures,
for all patients who will be included:

- Blood serum samples, repeated at each therapeutic time, for the constitution of a serum library in patients included in the centres participating in the blood collection;
- A collection of tumour samples based on pre-, post-therapeutic and surgical biopsies from the usual therapeutic management for these patients (with *systematic* biopsy in the case of exploratory laparotomies and non-resectable peritoneal carcinoses);
- A longitudinal collection of behavioural data (MOS-SSS and HADS questionnaires);
- A longitudinal collection of quality of life (QLQ-C30 and QLQ-CR29 or STO22 questionnaires) and pain assessment (EVA) data

Consequently, this study therefore meets the definition of a Non-Health Product RBM within the meaning of Law n°2004-806 of 9 August 2004.

16.2 Profit / Risk balance

There is no direct benefit for patients participating in this research.
No major risks are associated with this research because it does not involve any major and additional invasive procedures compared to the management of these patients. For patients included, theoretical risks may be associated with blood sampling at inclusion and at each therapeutic time: appearance of hemorrhage and vagal discomfort. In addition to the collection of tumour samples from pre-, post-therapeutic and surgical biopsies and surgical specimens as part of the usual therapeutic management for these patients, additional biopsies are systematically requested in the case of exploratory laparotomies and non-resectable peritoneal metastases.
This research will increase scientific knowledge of peritoneal metastases in order to improve, in the long term, the management of patients and to describe their biological, tumoral and evolutionary characteristics in order to better understand resistance to treatment in some cases.
Quality of life questionnaires will provide essential information about the quality of care for these patients and their social environment. This research will then provide an opportunity for health care teams to adapt their approach to the patient and the way they communicate with them. This will include, for example, strengthening the support, guidance and listening of patients and thus proposing strategies to improve their emotional state and promote their overall adaptation. More generally, this research will provide information about how patients cope with the disease and how to help them cope.
The benefit/risk balance for a patient to participate in the study is therefore quite acceptable.

16.3 Committee for the Protection of Persons and Competent Authority

Before any implementation of the research, the sponsor will request the opinion (valid authorization) of the CPP South-East IV (28 Rue Laennec 69008 LYON) as well as the authorization of the competent authority the ANSM in accordance with article L 1121-1 of the Public Health Code as they result from laws n°2004-806 of 9 August 2004 and n°2006-450 of 18 April 2006

relating to public health policy.

The constitution of biological collections has been declared to the CPP, the MESR and the ARS, in accordance with Decree No. 2007-1220 of 10 August 2007 by the responsible body, the Hospices Civils de Lyon.

Any modification of the elements contained in the declaration file which will be likely to lead to a substantial change in the research purpose or a substantial change in the conditions under which the declared activities are carried out shall be notified without delay to the CPP, the MESR and the ARS by the responsible body.

16.4 Substantial changes

After the start of the study, any substantial modification to the study protocol must be notified to CPP South East IV (28 Rue Laennec 69008 LYON) in order to verify that the proposed modifications do not at any time alter the guarantees given to persons who lend themselves to research. At the initiative of the coordinating investigator and in agreement with the Scientific Committee (cf. §18), any substantial modification must obtain, prior to its implementation, a favourable opinion from the CPP and an authorisation from the Competent Authority (ANSM), if necessary.

16.5 Patient information and written informed consent form

In accordance with Good Clinical Practices and the legal provisions in force (Law 2004-800 of 6 August 2004 and Law 2004-806 of 9 August 2004 of the CSP relating to biomedical research), any pre-selected patient is informed in advance by the investigator of the objectives of the study, its methodology, its duration of participation, its constraints and the foreseeable risks. He is reminded that he is entirely free to refuse to participate in the study or to withdraw his consent at any time without incurring any liability. A written document summarizing the information provided by the investigator is provided (**Appendix 7**).

After ensuring that the information provided is clearly understood, the investigator seeks the patient's written consent to participate in the study (consent to research and the establishment of a biological collection).

The patient accepts that biological samples and medical information available during his or her care may be collected, stored and used by a care facility participating in BIG-RENAPE or transferred for use by other scientific teams within the framework of BIG-RENAPE, until they are exhausted (total use).

The patient can leave the study if he/she wishes, at any time during his/her follow-up.

Two copies of the information and consent forms are then signed by the patient and the investigator. One copy is then given to the patient and the other is kept by the investigator for a period of 15 years.

Any amendment that changes patient management or the benefits, risks and constraints of research is the subject of a new information document. The information of the data subjects follows the same procedure as above.

16.6 Commission Nationale Informatique et Liberté

The data are computerized, and processed anonymously and confidentially, on a secure system in accordance with the law on data processing, files and freedoms (law 78-17 of 6 January 1978 amended by law 2004-801 of 6 August 2004) and complies with the general regulation on data protection.

Data hosting is provided by an authorized host that meets the highest security standards and can meet the regulatory requirements for medical data hosting (21 CFR Part 11, ITIL v3).

As this is research involving the processing of personal data and during which directly nominative data are collected (propsectively and retrospectively), a procedure to obtain the CCTIRS' favourable opinion on the one hand, and then the CNIL's authorisation, was carried out by the promoter before any data processing.

The use of directly nominative data is justified by the need to be able to

- Reconcile the various collection documents (quality of life questionnaires) completed throughout the patient follow-up process;
- Identify individually and completely all patients included in order to evaluate the modalities of their long-term follow-up and limit the rate of loss of sight.

CCTIRS issued a favourable opinion on 13/05/2015 (No. 15-559) and the CNIL gave its authorisation to implement the data processing on 25/01/2016 (Decision DR 2016-002).

The data controller is the promoter. The legal basis for this data processing is Article 6 of the General Data Protection Regulations (GDR), namely the performance of a task in the public interest entrusted to the controller and the legitimate interests pursued by him. In addition, under section 9 of the DGMP on

controller may exceptionally process special categories of data, including health data, in particular for scientific research purposes.

16.7 Confidentiality

In accordance with the provisions of Article R. 5120 of the CSP, the person in charge of the collection and any person called upon to collaborate in the tests are bound by professional secrecy, in particular with regard to the persons who lend themselves to it and the results obtained, subject to the provisions of Article L. 1123-9 of the Public Health Code.

They may, without the agreement of the responsible body (Hospices Civils de Lyon), provide information on the study only to the Competent Authorities, including inspectors as mentioned in Article L.209-13 of the Public Health Code.

16.8 Storage - duration of use

Biological resources can be conserved as long as their stability allows for their analysis.

16.9 Insurance

In accordance with the provisions of Law No. 2004-806 of 9 August 2004 of the Public Health Code, the promoter has taken out insurance for the entire duration of the study to cover its own civil liability and that of any doctor involved in carrying out the study. It will also ensure full compensation for the harmful consequences of the research for the person who lends himself to it and his successors in title, unless he can prove that the damage is not attributable to his fault or that of any intervener, without the possibility of an action by a third party or the voluntary withdrawal of the person who initially consented to the research being opposed. This insurance has been taken out with SHAM (Société Hospitalière d'Assurance Mutuelle), 18 Rue Edouard Rochet, 69372 LYON Cedex 08, contract n°144 244.

16.10 Funding and institutional support

The BIG-RENAPE research is supported and funded by INCa within the framework of the 2013 national call for projects **"Constitution of national multicentric multicentric clinical-biological databases in cancerology"**.

16.11 Audit and inspection

The health authorities and/or an independent auditor appointed by the sponsor may audit any investigator site or sponsor during or after the end of the study, in order to monitor the conduct of the study and the quality of the data.
Investigators agree to comply with the sponsor's requirements, and allow direct access to source documents for monitoring, audits and inspections by authorized persons. The audit will be applicable at all stages of the study, from the development of the protocol to the publication of results, and the classification of the data used or produced as part of the study. All data, documents and reports may be subject to regulatory audits and inspections without the possibility of medical confidentiality.

17 EXECUTIVE COMMITTEE

An executive committee of the study was formed to:

- Ensure the coordination of the associated centres;

- Manage logistical, technical and financial administrative aspects;

- Enable the development of the database and ensure its proper functioning: quality control, analysis of the evolution of inputs and monitoring, query and export of data,... .. .;

- Write interim reports for the Scientific Committee.

It includes the following persons:

- **Prof. Olivier GLEHEN** (National Coordinator)
  General and Digestive Surgery Department - Centre Hospitalier Lyon Sud (Lyon)
- **Dr Frédéric BIBEAU** (national co-coordinator) Department
  of Pathology - Cancer Institute (Montpellier)
- **Evelyne DECULLIER**
  Data Management Team / Data Analysis BIG-RENAPE - IMER cluster, HCL (Lyon)
- **Christine DURIF-BRUCKERT**
  University of Lyon 2 - Institute of Psychology (Lyon)

- **Peggy JOURDAN-ENFER**
  General and Digestive Surgery Department - Centre Hospitalier Lyon Sud (Lyon)
- **Christelle MAURICE**
  Data Management Team / Data Analysis BIG-RENAPE - Public Health Unit, HCL (Lyon)
- **Adeline ROUX**
  Data Management Team / Data Analysis BIG-RENAPE - Public Health Unit, HCL (Lyon)
- **Laurent VILLENEUVE**
  Coordinator of the National Network for the Care of Rare Tumours of the Peritoneum, RENAPE (Lyon)

18 SCIENTIFIC COMMITTEE

A scientific committee has been set up to:

- Define the scope of the database and its substantial changes;
- Validate a charter for the use and exploitation of data;
- To decide on proposals for scientific collaborations;
- Decide on requests for data and/or biological samples to be made available (if necessary, in the case of similar projects proposed by different teams, the Scientific Committee may propose collaborations between the teams);
- Instruct the integration of new centres and the exclusion of participating centres;
- Monitor the progress of the work undertaken.

The Scientific Committee is composed of the following members:

- **Prof. Olivier GLEHEN (National Coordinator)**
  General and Digestive Surgery Department - Centre Hospitalier Lyon Sud (Lyon)
- **Dr. Frédéric BIBEAU (national co-coordinator)**
  Department of Pathology - Cancer Institute (Montpellier)
- **Pr Cécile BRIGAND**
  General and Digestive Surgery Department - CHRU Hautepierre (Strasbourg)
  - Cécile CARON
  Department of cell differentiation and transformation - Institut Albert Bonniot (Grenoble)
  - Dr. Peggy DARTIGUES
  Department of Pathological Anatomy and Cytology - Gustave Roussy Institute (Villejuif)
  - **Christine DURIF-BRUCKERT**
  University of Lyon 2 - Institute of Psychology (Lyon)
- **Pr Dominique ELIAS**
  Department of Digestive and Hepatobiliary Surgery - Gustave Roussy Institute (Villejuif)
- **Dr Olivier FACY**
  Digestive and Cancer Surgery Department - CHU Bocage (Dijon)
- **Pr Marilène FILBET**
  Palliative care unit - Centre Hospitalier Lyon Sud (Lyon)
- **Dr. Diane GOERE**
  Department of Digestive and Hepatobiliary Surgery - Gustave Roussy Institute (Villejuif)
- **Dr Laurent GHOUTI**
  General and Digestive Surgery Department - CHU Purpan (Toulouse)
- **Dr. Sylvie ISAAC**

Department of Pathological Anatomy and Cytology - Centre Hospitalier Lyon Sud (Lyon)

- **Dr. Julien Perron**
  Medical Oncology Department - Centre Hospitalier Lyon Sud (Lyon)
- **Prof. Frédéric MARCHAL**
  Service de Chirurgie Cancérologique - Institut de Cancérologie de Lorraine A. Vautrin (Vandœuvre-Lès-Nancy)
- **Pr Marc POCARD**
  Digestive Surgery Department - Lariboisière University Hospital (Paris)
- **Dr François QUENET**
  Oncological Surgery Department - Cancer Institute (Montpellier)
- **Laurent VILLENEUVE**
  Coordinator of the Network for the Management of Rare Tumours of the Peritoneum (RENAPE)
- **Dr. Benoît YOU**
  Medical Oncology Department - Centre Hospitalier Lyon Sud (Lyon)

19 CALENDAR

- Regulatory approaches and implementation: November 2014 - February 2016
- Expected start of inclusions: February 2016
- Duration of inclusions: 42 months of inclusions
- Duration of follow-up: 3 years

20 PUBLICATION RULES

A- No publication or presentation of the results of this study may be made without the agreement of the Sponsor and the Scientific Committee.

B- Only the works whose synopsis will be validated by the BIG-RENAPE Scientific Committee, can claim to be a study of the Network. This synopsis must include a proposal for publication rules. The members of the Scientific Committee are requested by email and the absence of a reply is equivalent to consent beyond 15 days.**C- At the** time the study is launched, the referent "investigator" is clearly identified in each structure (it is therefore appropriate that there be a discussion locally, and if necessary, in each centre, that removes any ambiguity on this point).

D- When submitting a work in abstract form and then as a publication, it is recommended, as far as is reasonable and consistent with the application of the other rules, to involve as many people as possible.

E- The coordinators and co-coordinators of the Network renounce to be systematically cited as the last authors.

F- The fact of having recruited patients at a given time or even having completed a data sheet is not sufficient to be considered as an author. A substantial contribution to scientific work is expected. In this sense, when you are an "author", it is absolutely essential to proofread the manuscript within a reasonable time (15 days) before sending it. Otherwise, the "potential" author will lose his "place".

G- For authors appearing mainly because of their contribution to recruitment, the following alternation rule should be applied:

The centre with the lowest recruitment is present among the authors of the first publication (only one name). The centre for higher recruitment (in ascending order) is cited among the authors of the second publication and so on according to the increasing numbers posted by the participating centres.

For centres with high recruitment, according to the same principle, the centre with the highest recruitment signs in useful place the first publication (2^{nd} or 3^{rd} behind the one who writes). Then, the second centre with the highest recruitment (in descending order) is cited on the second publication and so on according to the decreasing numbers posted by the participating centres.

H- When a work is based on referring pathologists from the network, at least one anatomopathologist must be associated with the publication.

I- When a work is based on an existing base, the funder(s) of the base should be thanked. Study managers and non-medical staff involved in filling and managing the database will be mentioned at the end of the article. Exceptionally, one of them may be in the authors if the Scientific Committee considers it justified.

J- The BIG-RENAPE network will be mentioned after the authors.

K- All participants not included in the authors will be mentioned at the end of the article.

L- The promoter of BIG-RENAPE (Hospices Civils de Lyon) will also be mentioned at the end of the article.

M- *The data* source will be cited as,"... data from the BIG-RENAPE Network's national database" (*The study was conducted on data from BIG-RENAPE (Clinical and biological French Database on Digestive Peritoneal Carcinomatosis) working group)*.

N- Before submitting the article, the opinion of the Scientific Committee is formally requested. The list of suggested authors is well argued (patients included, nature of the substantial contribution). The members of the Scientific Committee are requested by email and the absence of a reply is equivalent to consent beyond 15 days. In order not to delay the submission of abstracts, this validation process by the Scientific Committee will not be applied.

O- When the work is entrusted to an intern, the latter will be the first author. But this work is carried out under the responsibility of a senior (last author) and must be carried out within the time limit set.

LIST OF APPENDICES

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