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Changes of health-related quality of life 6 months after high-risk oncological upper gastrointestinal and hepatobiliary surgery: a single-centre prospective observational study (*ChangeQol Study*)

Julien Maillard ,[1] Nadia Elia ,[1,2] Frédéric Ris ,[2,3] Delphine S Courvoisier ,[2,4] Dina Zekry ,[2,5] Intidhar Labidi Galy,[2,6] Christian Toso ,[2,3] Stefan Mönig ,[2,3] Isabelle Zaccaria ,[1] Bernhard Walder [1,2]

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For numbered affiliations see end of article.

Correspondence to
Julien Maillard;
Julien.Maillard@hcuge.ch

ABSTRACT

Introduction Postoperative health-related quality of life (HRQoL) is an essential outcome in oncological surgery, particularly for elderly patients undergoing high-risk surgery. Previous studies have suggested that, on average, HRQoL returns to premorbid normal levels in the months following major surgery. However, the averaging of effect over a studied cohort may hide the variation of individual HRQoL changes. The proportions of patients who have a varied HRQoL response (stable, improvement, or a deterioration) after major oncological surgery is poorly understood. The study aims to describe the patterns of these HRQoL changes at 6 months after surgery, and to assess the patients and next-of-kin regret regarding the decision to undergo surgery.

Methods and analysis This prospective observational cohort study is carried out at the University Hospitals of Geneva, Switzerland. We include patients over 18 years old undergoing gastrectomy, esophagectomy, pancreas resection or hepatectomy. The primary outcome is the proportion of patients in each group with changes in HRQoL (improvement, stability or deterioration) 6 months after surgery, using a validated minimal clinically important difference of 10 points in HRQoL. The secondary outcome is to assess whether patients and their next-of-kin may regret their decision to undergo surgery at 6 months. We measure the HRQoL using the EORTC QLQ-C30 questionnaire before and 6 months after surgery. We assess regret with the Decision Regret Scale (DRS) at 6 months after surgery. Key other perioperative data include preoperative and postoperative place of residence, preoperative anxiety and depression (HADS scale), preoperative disability (WHODAS V.2.0), preoperative frailty (Clinical Frailty Scale), preoperative cognitive function (Mini-Mental State Examination) and preoperative comorbidities. A follow-up at 12 months is planned.

Ethics and dissemination The study was first approved by the Geneva Ethical Committee for Research (ID 2020-00536) on 28 April 2020. The results of this study will be presented at national and international scientific meetings, and publications will be submitted to an open-access peer-reviewed journal.

Trial registration number NCT04444544.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addresses an important evidence gap, since there is no current knowledge on the proportion of patients with deteriorated health-related quality of life 6 months after major abdominal surgery for cancer.
⇒ Health-related quality of life, regret, as well as exposure variables such as frailty and disability are measured with validated questionnaires and scores.
⇒ The limitations of the study are as follows: single-centre study; the risk of selection bias due to patients' study acceptance, differential attrition due to treatment success (refusal of follow-up), the lack of a control group (patients not undergoing surgery).

INTRODUCTION

Background and rationale

Several gastrointestinal cancers have a low 1 year survival rate, particularly tumours involving the oesophagus, stomach, pancreas and liver.[1] Conservative treatments for non-resectable tumours have heterogeneous prognosis with an overall median survival varying between 6 months and several years, depending on the location and the stage of the tumour.[2–5] Surgical treatments of these abdominal cancers seem to increase survival rate,[4 6] but are associated with high risk of severe postoperative complications, severe disability and significant health and social costs.[7 8] The postoperative morbidity and mortality are high in elderly and/or frail patients[7 9] and the likelihood of successfully

rescuing patients from postoperative morbidity is lower than for a younger and/or fit population.[10]

While young patients seem to be willing to accept aggressive treatments in order to increase their survival time, regardless of the risks of adverse events, data suggest that this may not be the case for elderly patients who rather prioritise health-related quality of life (HRQoL) over length of life.[11 12] The National Health Service in the United Kingdom issued guidelines on shared decision making, emphasising the importance of placing the patient at the centre of the decision process, with their concerns playing a significant part in decisions.[13] The preoperative decision-making should include the added value and harm of the surgical cancer treatment, but also expected patient-reported outcomes (PRO).[14–17] Compared with classical outcomes such as mortality or hospital length of stay, data on PRO, including HRQoL, are still sparse in the setting of surgical oncology.

HRQoL is a subjective integration of the health-related impact of symptoms on a patient's autonomy, happiness and satisfaction in life.[18] It is an accepted and relevant outcome in general cancer care[19] and guidelines from the American Society of Clinical Oncology state that medical or surgical treatment can be recommended even if an improvement in survival is not expected, as long as it improves HRQoL.[20] This statement underlines the high relevance of HRQoL as a PRO in the context of cancer management, particularly in older patients.[12 21]

Oncological surgery may impact short-term and long-term HRQoL. In the best-case scenario, surgery improves HRQoL; in the worst-case, surgery deteriorates HRQoL.[22–25] There is some evidence that mean HRQoL does not change significantly 6–12 months after cancer surgery compared with preoperative mean HRQoL.[26–29] This apparent perioperative stability of HRQoL may be real, reflecting a low variability during the perioperative period. However, there may also be considerable variability, with some patients experiencing improved, stable or deteriorated HRQoL after cancer surgery. The description of these different patterns of HRQoL changes is lacking in oncological surgery. In the setting of aggressive abdominal cancer surgery for rapidly evolving tumours, the risk of deteriorated HRQoL may be increased and, therefore, the description of HRQoL changes is relevant. Identification of preoperative variables potentially associated with change of postoperative HRQoL is crucial to better identify patients at risk. Age and pre-existing frailty may be of particular importance in predicting the risk of postoperative HRQoL decline.

Postoperative decisional regret, a measure of 'distress or remorse after a healthcare decision',[30] has rarely been studied after aggressive abdominal surgery, but appears to be quite common following major surgery.[31] Furthermore, knowledge about the potential association between postoperative HRQoL and postoperative regret in patients and next of kin is very limited.

Hypotheses and objectives

We hypothesise that there are different patterns of HRQoL changes 6 months after aggressive abdominal cancer surgery. We expect that the patients with deteriorated HRQoL (compared with baseline) may more often regret their decision to undergo surgery than those whose HRQoL remains stable or improves and that the regret of the patients will not be associated with the regret of the next of kin.

Our primary objective is to describe three relevant subgroups: patients with improvement, stability or deterioration of HRQoL. Our secondary objectives are to describe the potential regret of patients and their next of kin.

Outcomes

Primary outcomes

- Proportion of patients within three different HRQoL changes (improvement, stability or deterioration) at 6 months after surgery.

Secondary outcomes

- Proportion of patients who regret their decision to undergo surgery at 6 months.
- Proportion of next of kin who regret the patient's decision to undergo surgery at 6 months.

Other outcomes

- Proportion of patients within three different HRQoL changes (improvement, stability or deterioration) at 12 months after surgery.
- Proportion of patients who regret their decision to undergo surgery at 12 months.
- Proportion of next of kin who regret the patient's decision to undergo surgery at 12 months.
- Proportion of patients living at home 12 months after surgery.
- To assess risk factors associated with HRQoL at 6 months after surgery.

METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES

Study design

The ChangeQol study is a prospective, observational, single-centre cohort study.

Study settings

The study is currently running at the University Hospitals of Geneva, Switzerland. The University Hospitals of Geneva is a tertiary hospital with more than 2000 beds. Study inclusions started on 7 September 2020. Due to the COVID-19 pandemic, several major surgeries were postponed for months or performed in another centre which delayed optimal inclusion regimen. To date (date: 18 November 2022), 136 patients were included.

Participants

Inclusion criteria

Patients eligible for the study must comply with all the following at inclusion:

- Adult patients (≥18 years)
- Scheduled for an elective abdominal cancer surgery (by laparoscopy or laparotomy): gastrectomy; esophagectomy; pancreas resection or hepatectomy

Exclusion criteria

- Hepatic metastasectomy
- Mental impairment (severe enough to make the patient unable to understand and answer the study questionnaires)
- Psychotic diagnoses (i.e., schizophrenia)
- Dementia (mini-mental score (MMSE) <18)
- Inability to understand the information sheet
- Visual impairment (unable to perform the visual part of the MMSE)

Variables

Outcomes

Primary outcome measures: preoperative and postoperative health-related quality of life (HRQoL)

We assess the preoperative and postoperative HRQoL using the QLQ-C30 Summary Score, based on the EORTC QLQ-C30 questionnaire (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire),[32] an English validated, and French translated and validated cancer health-related quality-of-life questionnaire. As explained in more detail below, a decrease in HRQoL is defined as a decrease of ≥10 points compared with baseline of the HRQoL score, and an improvement as an increase of ≥10 point compared with baseline of the HRQoL score. Any change in between is considered as stable.

With the wide range of scales included in the QLQ-C30, this instrument provides a comprehensive overview of a patient's HRQoL. The multitude of scales presents statistical challenges due to multiple testing and the resulting risk of type I errors.[33] In most cancer studies, to avoid the problem of multiple testing, the two-item global health (GH) status/quality of life scale is used as a primary endpoint.[28 34–36] However, the GH scale of the QLQ-C30 may not be sensitive enough to capture the relevant health-specific aspects for a given cancer population. To overcome this issue, the QLQ-C30 Summary Score has been developed as an additional scoring algorithm, and the EORTC Quality of Life Group now recommends this QLQ-C30 Summary Score to supplement the 15-outcome profile generated by the QLQ-C30.[37] The QLQ-C30 Summary Score was shown to be as discriminative as the best-performing single scales of the QLQ-C30 regarding tumour stage, performance status and change over time.[37] It has also been demonstrated as more discriminative than any single scale in the QLQ-C30, including the GH scale.[38] In consequence, we use the QLQ-C30 Summary Score as our primaryutcome.

The mean HRQoL Summary Score assessed with EORTC QLQ-C30 for an abdominal cancer patient is reported to be 68.2 points (SD±19.9).[38] Several studies have suggested that a change of 10 points (=0.5 of SD) on an EORTC QLQ-C30 scale score is clinically relevant and associated with changes in the supportive care need.[39–41] Furthermore, the concept of minimal clinically important difference (MCID), to discriminate the smallest meaningful change that a patient can detect with confidence,[42] has been repeatedly assessed for EORTC QLQ-C30; MCID was also estimated to be a decrease of 0.5 of SD (corresponding to 10 points) of an EORTC QLQ-C30 scale score.[43 44] Therefore, as mentioned above, a decrease in HRQoL is defined as a decrease of ≥10 points compared with baseline of the HRQoL score, and an improvement as an increase of ≥10 point compared with baseline of the HRQoL score. Any change in between is considered as stable.

The EORTC QLQ-C30 questionnaire takes about 5–8 min to be answered.

Secondary outcome measures: postoperative regret

The postoperative regret is assessed with the Decision Regret Scale (DRS).[30] The DRS assesses whether a patient/next-of-kin feels regret regarding the decisions made to undergo surgery. This scale is validated for patients and is composed of five items converted to a score ranging from 0 to 100. A higher score indicates greater regret.[45] Although not formally validated in French, a translated version is available (https://decisionaid.ohri.ca/eval_regret.html) and has already been used in cancer surgery setting.[46] We have chosen to use the DRS rather than the Treatment Associated Regret Scale described by Clark[47] since the latter only focuses on treatment-related regret itself, is not translated in French and has mainly been used in prostate cancer, whereas the DRS is commonly used in a more heterogeneous oncological population.[48] We administer the DRS to all included patients at 6 and 12 months. We also administer this questionnaire to the patient's next of kin (or caregiver) at 6 and 12 months because regret could differ between the patient and their next of kin.[49] To date, the DRS is not validated for next-of-kin; no other measurement tools have been developed/validated for this population. The DRS takes about 2 min to be answered.

Other outcome measures: preoperative and postoperative place of residence

Preoperative and postoperative place of residence is evaluated at 12 months after surgery. At the time of the preoperative and 12 months assessments, we ask patients to tell us where they live (i.e., where they have spent most of the previous month) according to the following four categories: home without nurse help; home with nurse help or adapted residency with 24 hours assistance available or living with family for daily care assistance; skilled nursing facilities; rehabilitation centre or hospital. The lack of a single database shared between hospitals and rehabilitation centres in Switzerland makes the use of other outcomes such as 'days at home' or 'days at home after surgery' at 12 months after surgery difficult and imprecise, with a consequent risk of recall bias.

Additional variables and study procedure

All patients benefit from an anaesthesia consultation at least 3 weeks before the date of their scheduled surgery. Eligible patients are identified by a study nurse from the weekly preadmission clinic list. A member of the research team calls all eligible patients at home in the days preceding the consultation in order to inform them of the existence of the study and offer them the possibility to participate. On the day of the anaesthetic consultation, a study nurse meets each patient to confirm their intention to participate and have them sign the informed consent form. Once the informed consent form has been signed, the study nurse asks the patients to fill in four baseline questionnaires: EORTC-QLQ-C30 (HRQoL), Hospital Anxiety and Depression Scale (HADS), WHODAS 2.0 (Functionality and Disability) and Mini-mental state examination (MMSE). The MMSE is always completed in person. The patient may choose one of two options for completing the other preoperative questionnaires. The first option consists of answering the questionnaires immediately, with one of the investigators or a trained research assistant. The second option is for the patient to take the questionnaires at home and then to return them by post or email. In this case, a phone assistance is offered that is available every weekday. Additionally, patient may contact the research team via email. Preoperative questionnaires, such as the EORTC QLQ-C30, should be completed no earlier than 30 days prior to surgery and at least 1 day before surgery. Therefore, if the surgery takes place more than 30 days after the initial assessment, a member of the research team calls the patient to repeat the EORTC QLQ-C30 assessment. All questionnaires are completed in paper format and then entered by trained members of the research team into a e-CRF specifically designed for this study (RedCAP) (figure 1, online supplemental appendix)

Research collaborators additionally fill out two classification tools: Charlson Comorbidity Index (CCI) and the Clinical Frailty Scale (CFS). The CFS is directly assessed by a trained research collaborator during the interview with the patient. Trained researchers record other information regarding baseline patient and tumour characteristics as defined below. During the perioperative period, researchers systematically record predefined perioperative variables that may impact on postoperative HRQoL as defined below and in the online supplemental appendix. All these variables are extracted from the patient's medical records by trained research nurses and checked by the principal investigator (JM). The source documents are the anaesthesia consultation, the surgical consultation and any medical discharge letters from the last 6 months. Patients are contacted 6 months and 12 months after surgery by a member of the research team, to answer to EORTC-QLQ-C30 (HRQoL) together with the DRS (figure 1). This is performed either by phone or during a face-to-face interview. The next of kin selected by the patient at the inclusion is asked to fill out their regret scale simultaneously.

We chose to evaluate frailty with CFS as it is the most robust to predict postoperative mortality to date.[50] CFS is validated in French.[51] We chose to measure anxiety and depression symptoms (with HADS) because of strong evidence that anxiety and depression contribute independently to various dimensions of HRQoL, particularly in cancer patients.[52] We classify postoperative complications using the Clavien-Dindo classification system[53] (grading postoperative complications from 1 to 5 according to the necessary therapy to correct the complication) occurring at any moment during acute hospital stay (i.e., before discharge to rehabilitation or home). Complications are extracted by a member of the research team as reported in the postoperative intermediate care

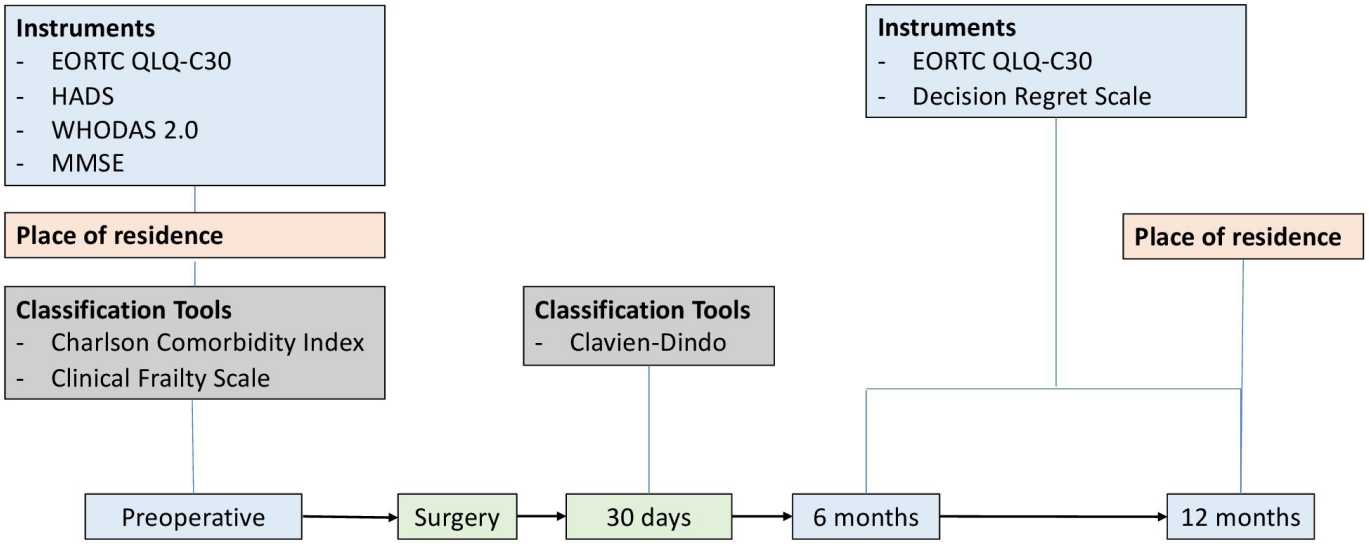

Figure 1 Study procedure. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HADS, Hospital and Anxiety Scale; MMSE, Mini-Mental State Examination; WHODAS 2.0, WHO Disability Assessment Schedule V.2.0.

unit and the surgical ward discharge letters and from all computerised follow-up notes recorded during the acute hospital stay.

Additional preoperative and perioperative data are fully described in the online supplemental appendix.

Bias

We tried to identify and address potential biases resulting from the design and population of the study.

The main risk of bias for this study is selection bias. As usual, patients who refuse to participate may represent a special population that is different from those who agree which may impact generalisability of our findings. To optimise the acceptance rate, we call patients several days before the anaesthesia consultation to present the study and answer their question. To minimise dropouts, we call patients who do not answer up to three times for the 6 months and 12 months follow-up.

To minimise the risk of measurement bias, standardised questionnaires are used, research nurses are trained and supervised by the principal investigator and all members of the research team are provided with a standard operating procedure, listing of source documents, and clear definitions of all variables.

Sample size

Based on a previously published study in non-surgical oncology, we expect to find the following distribution of patients according to the three patterns of HRQoL changes at 6 months after surgery: 10% of patients with improved HRQoL, 70% with unchanged HRQoL (stability) and 20% with deteriorated HRQoL compared with preoperative HRQoL.[54] We computed the required sample size on this 20% of patient with HRQoL deteriorated, with a 95% CI and a 5% margin of error, so 246 patients are needed. As we expect a loss of follow-up of about 20% (death, study withdrawal or loss to follow-up), we will recruit 295 patients. We plan to include 3 patients/week; hence we need about 2 years to recruit all the patients.

Quality check

Internal validation check are planned at regular intervals to verify the completeness and adequacy of the collected data. These verifications are performed by two experienced research nurses who are not involved in the study.

Methods: data analysis

Statistical analysis

Statistical methods outcomes

Characteristics of the patients, tumour, perioperative surgical and non-surgical factors, CFS, CCI, MMSE, HADS and WHODAS 2.0 will be described for the entire cohort and by group (each of the three patterns of HRQoL changes). For continuous variables, we will use mean and SD for normally distributed variables or medians and IQR+range otherwise. For categorical variables, we will use frequencies and percentages.

Primary outcome

The distribution of patients across different HRQoL changes (deterioration (≥10 points decrease from baseline), improvement (≥10 points increase from baseline) and stability (change anywhere between 10 point decrease up to 10 point increase) will be described using the EORTC QLQ-C30 Summary Score at baseline and 6 months.

Secondary outcomes

The distribution of patients across different HRQoL changes will be performed at 12 months. Overall EORTC QLQ-C30 Summary Score difference and difference in the subgroups will be presented with means differences and their 95% CI.

Regret DRS score of the patient (respectively of the next-of-kin) at 6 months and 12 months will be reported using means and 95% CI or medians and IQR. Similar summary statistics will be reported according to each of the three patterns of HRQoL changes. The association between the DRS score at 6 months and the Summary Score difference will be tested using a nonparametric Wilcoxon Rank Sum Test.

The measure of reliability between the DRS at 6 months and 12 months filled by patients and the same questionnaire filled by next-of-kin will be assessed using the Intraclass Correlation Coefficient. Landis and Koch's subjective classification will be used to determine whether the agreement is average, good, or excellent.[55]

In addition, we will graphically represent the concordance between these two questionnaires, by items, using the Bland and Altman graphical method.[56] The limits of maximum acceptable differences are defined by ± 1 point.

The 6 and 12 months DRS scores will be dichotomised (0=no regret 1–100=regret)[57] and summarised in a 2×2 table to highlight the discrepancies (regret at 6 months and no regret at 12 months and vice versa). In addition, a McNemar test will be performed.

Other outcomes

Description of place of residence

We will describe the place of residence at 12 months with categorical frequencies. We will describe the proportion of patients previously living at home that have not returned home at 12 months.

Additional analyses

We will look for risk factors associated with a decreased HRQoL at 6 months after surgery. The potential association between predefined variables of interest and the phenotype deterioration (compared with the other phenotypes together) will be tested individually in a univariable logistic regression model. Depending on the number of events, a multivariable logistic regression model will be performed, using elastic net regularisation for model selection.

Statistical analyses will be performed using SAS V.9.3 (SAS Institute). A p-value <0.05 will be considered statistically significant.

Handling of missing data

All efforts will be made to collect information about the outcome event. We will report the number and percentage of missing data for each variable. No imputation will be made.

The adjustment for expected dropouts is explained in the paragraph *sample size*.

Patient and public involvement (PPI)

There was no direct involvement of patients or the public in the design of the study. The public, especially elderly in the community, were consulted to ensure that informed consent was fully understandable. Comments and feedback from participants during the course of the study will be taken into account when planning future research. We will inform participants and the public about the progress and results of the study through the public research website of the University Hospitals of Geneva (https://recherche.hug.ch/etudes/ChangeQoL).

ETHICS AND DISSEMINATION

Ethics approval

This protocol, the case report form (CRF) and the informed consent forms have been reviewed and approved by the local ethical committee (ID 2020-00536) on 28 April 2020. To date, three amendments have been submitted

- 3 September 2020: Amendment 01: Modification exclusion criteria: 'hepatectomy for metastasis' for 'hepatic metastasis', to only exclude metastasectomy performed without hepatectomy.
- 20 May 2021: Amendment 02: Addition of secondary objectives at 12 months (follow-up of HRQoL and regret). Addition of the possibility to use a version of MMSE designed to be used by phone call, in exceptional cases.
- 15 June 2022: Amendment 03: Increase in sample size and extension of the expected end date of the study.

Perspective

The perspective of the present study is to identify the proportion of patients who fall in each of three HRQoL changes group (improvement, stability or deterioration) 6 months after major abdominal surgery for cancer. These data will potentially confirm that behind the apparent average stability of HRQoL 6–12 months after high-risk oncological surgery, some patients suffer from a significant and persistent decrease in HRQoL. This information should therefore prompt clinicians and researchers to consider this group of patients more carefully and develop validated predictive tools to better inform them of the possibility of such an outcome and to implement potential preventive or supportive measures. Furthermore, these data could allow us to perform exploratory analysis on potential variables associated with the deteriorated postoperative HRQoL. These variables could then be formally tested in future prediction models. Finally, we will explore the incidence of postoperative regret expressed by the patients and their next-of-kin and its relationship with changes of HRQoL. This information is essential for patients and their next of kin and could potentially be included during the shared decision-making process.

All these results should open new perspectives on shared decision-making and potential perioperative preventive and supportive measures, particularly for elderly and or frail patients.

Dissemination

Study results will be widely disseminated through open-access, peer-reviewed, international journals and conference presentations.

Author affiliations
[1]Anaesthesiology, Pharmacology, Intensive Care and Emergency Medicine, University Hospitals of Geneva, Geneva, Switzerland
[2]Faculty of Medicine, University of Geneva, Geneva, Switzerland
[3]Division of Digestive Surgery, Department of Surgery, University Hospitals of Geneva, Geneva, Switzerland
[4]Division of Quality of Care, University Hospitals of Geneva, Geneva, Switzerland
[5]Department of Internal Medicine for the Elderly, University Hospitals of Geneva, Geneva, Switzerland
[6]Department of Oncology, University Hospitals of Geneva, Geneva, Switzerland

Contributors JM and BW conceived the study. JM, BW, NE, FR, CT, ILG, DSC and DC initiated the study design, CT and SM helped with implementation. IZ provided statistical expertise in the study design, helped implement and check the case report form, performed the statistical plan and will be responsible for the conduct of regular consistency checks and the final statistical analysis. JM and BW are grant holders. All authors contributed to the refinement of the study protocol and approved the present protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Julien Maillard http://orcid.org/0000-0002-7496-1280
Nadia Elia http://orcid.org/0000-0003-1787-9288
Frédéric Ris http://orcid.org/0000-0001-7421-6101
Delphine S Courvoisier http://orcid.org/0000-0002-1956-2607
Dina Zekry http://orcid.org/0000-0002-6263-7803
Christian Toso http://orcid.org/0000-0003-1652-4522
Stefan Mönig http://orcid.org/0000-0002-1256-7755
Isabelle Zaccaria http://orcid.org/0000-0002-6323-6067
Bernhard Walder http://orcid.org/0000-0003-4293-6563

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