Outcomes of elective cancer surgery during the COVID-19 pandemic crisis: an international, multicentre, observational cohort study (CovidSurg-Cancer)

CovidSurg-Cancer Final Study Protocol V6.0

With additional longer term outcomes assessment following cancer surgery for H&N malignancy – a bolt-on follow-up elements (page 9 onwards)

CovidSurg-Cancer H&N Follow-Up Study Protocol V1.0 19-Apr-2021

Primary aim

- To evaluate the 30-day postoperative pulmonary complication rate following elective cancer[1] surgery during the COVID-19 pandemic.

Secondary aims

- To evaluate the 30-day SARS-CoV-2 infection rate following elective cancer[1] surgery.
- To compare the 30-day postoperative mortality rate in cancer surgery patients that develop COVID-19 infection versus those who do not.
- To explore the scale of resource constraints related to the COVID-19 pandemic, and their impact on outcomes of elective cancer surgery of curative intent[2,3].
- To explore variation in the selection of patients for continuing elective cancer surgery during the COVID-19 pandemic.
- To evaluate the impact of the COVID-19 pandemic on treatment pathways for cancers with a decision for surgical resection with curative intent up to 6-months after their initial treatment decision.

Inclusion criteria

Any centres performing elective cancer surgery[1] are eligible for participation. Centres will be stratified according to their national burden of COVID-19 infections using data from the World Health Organisation, and their COVID-19 status (designated COVID-19 free 'cold', COVID-19 affected 'hot' surgical units, or undesignated units with or without an emergency department co-located).

CovidSurg-Cancer study will capture:

- Patients with a multidisciplinary team (tumour board) decision for curative cancer surgery[2,3] that have surgery completed during the COVID-19 pandemic.
- Patients that **would have been planned** for curative cancer surgery by the MDT (tumour board) in the **pre-COVID-19 era** that have surgery delayed, cancelled, or receive an alternative treatment strategy (e.g. radiotherapy) during the pandemic.

[1]Any intracranial tumour (benign or malignant) may be included for neurosurgical patients. This applies throughout the protocol when reference is made to 'cancer'.
[2]Curative intent is not required for the inclusion of patients with intracranial tumours. This applies throughout the remainder of the protocol when reference is made to 'curative intent'.
[3]In gynaecological oncology, a plan for surgery with curative intent or life-prolonging intent are both eligible.

Patient inclusion criteria:

- Adults (age ≥18 years) with a confirmed diagnosis of an included cancer type[1].
- Multidisciplinary team (tumour board) decision for (or **would have been made** for) surgical management with a curative intent during the pre-COVID-19 era[2,3].

Patient exclusion criteria:

- Surgery planned with non-curative intent.
- Planned chemo- or radiotherapy without a firm date for surgery, or awaiting restaging.

Patient enrolment

Centres can elect to include **one or more** cancer types in the study, in any combination, depending on local expertise and capacity. Investigators can enrol patients with confirmed diagnoses of Colorectal, Oesophagogastric, Head & Neck, Lung, Hepatopancreatobilary, Urological, Gynaecological, Breast cancers, soft-tissue or bone Sarcoma, and Intracranial tumours (both benign and malignant). As a rapid response study to the COVID-19 pandemic, included cancer types have evolved following a short pilot period.

Study period

Investigators should identify a start date, which represents the start of the emergence of COVID-19 in their hospital (or city/area if designated COVID-free hospital). At that stage, they should capture all patients who have had a decision for surgery at this time point, and then all patients with a new diagnosis and with a decision to surgery for the next 3 months (representing the peak period of the COVID-19 pandemic). We envisage most sites completing registration before August 2020 and completing follow-up by December 2020. However, changes to dates may be necessary as the disease changes, and we may develop a third phase for longer follow-up in selected sites with the capacity to do so.

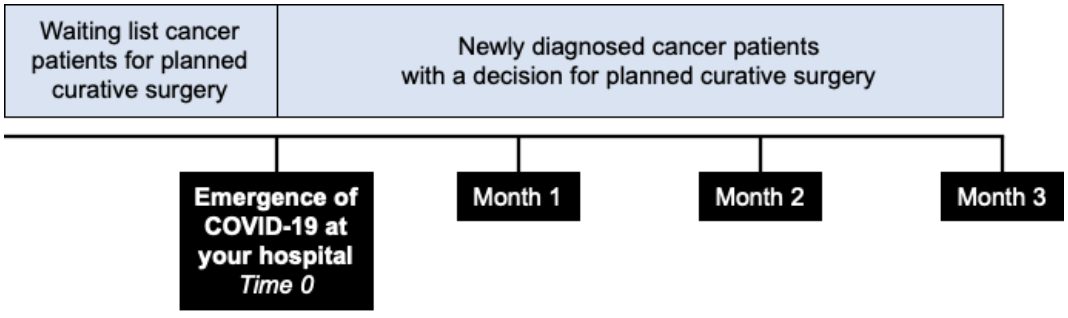

Figure 1. Timeline for patient identification within CovidSurg-Cancer

Primary outcome measure

- 30-day postoperative pulmonary complication rate.

Secondary outcome measures

- 30-day postoperative SARS-CoV-2 infection rate.
- 30-day postoperative mortality rate.
- Postoperative critical care utilisation rate in high-risk cancer surgery patients.
- Proportion of patients with delay of greater than 4 weeks from decision for surgery to date of surgery.
- Proportion of non-operated patients with progression to incurable disease by up to 6-months after decision for surgery.

Follow-up period

- Outcomes for **operated patients** will be collected up to **30-days** postoperatively (with Day 0 as the day of surgery).
- Outcomes for **non-operated patients** should be collected up to **a maximum of 6-months** from their study entry (**closing 31st August 2020**).

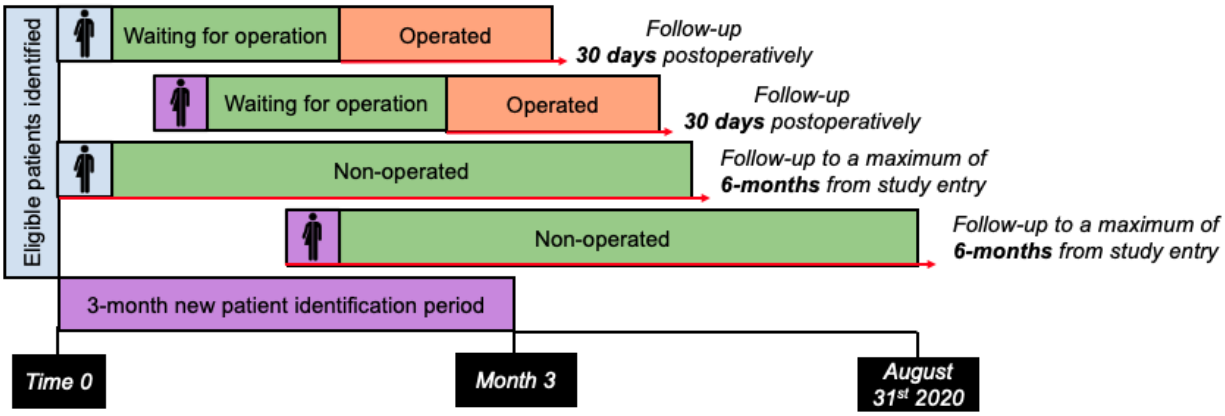

Figure 2. Timing of outcome assessment in CovidSurg-Cancer

Data collection

Data will be collected and stored online through a secure server running the Research Electronic Data Capture (REDCap) web application. REDCap allows collaborators to enter and store data in a secure, encrypted system. A designated collaborator at each participating site will be provided with REDCap project server login details, allowing them to securely submit data on to the REDCap system. REDCap has previously been successfully used for a range of other international cohort studies led by the central unit, including the GlobalSurg (www.globalsurg.org) and European Society of Coloproctology Audits and Cohort studies (https://www.escp.eu.com/research/cohort-studies). The REDCap server is managed by the University of Birmingham, UK. Only anonymised data will be uploaded to the database. No patient identifiable data, and no specific dates will be collected.

Data collected will include baseline demographic data, cancer-specific data, timelines for dates of diagnosis, decision for surgery and operation or completion of follow-up (summarised at a week

level), operative and nonoperative cancer-related treatment, treatment related to COVID-19 (where applicable), pathology and clinical outcome data. Restricted additional cancer group-specific data will be collected to support individual cancer-level analyses. Data can be collected prospectively, or retrospectively where required, depending on the COVID-19 status of your hospital. A centre-level survey will collect data on departmental decision making processes, and the impact of COVID-19 on elective surgical services in each included hospital.

Roles within the data collection team

The principal investigator at each site should identify a team to:

- Identify patients waiting for curative surgery at the estimated start date.
- Proactively identify patients with a new decision for (or would have had a decision made for curative surgery in the pre-COVID-19 era) during the study window.
- Monitor this patient cohort at regular intervals (e.g. weekly) to check their status up to completion of follow-up.
- Acquire outcome data at 30 days postoperatively for operated patients, and at 3- and 6-months from study entry for non-operated patients.

No limits to the size of this team are imposed, and can be flexible to local capacity and service demands.

Local approvals

The principal investigator at each participating site is responsible for obtaining necessary local approvals (e.g. service evaluation, audit approval, research ethics committee or institutional review board approval). Local approvals should cover inclusion of all cancer types within this study. Collaborators will be required to confirm that relevant local approval is in place at the time of uploading each patient record to the study database. The study will be carried out in accordance with national and international guidelines, as well as the basic principles of the protection of the rights and dignity of Human Beings, as set out in the Helsinki Declaration (64th Assembly Fortaleza, Brazil, in October 2013), and according to current legislation.

Where an audit approval is needed, this can be either registered as service evaluation, or to benchmark against an auditable standard. For example, NHS Delivering Cancer Waiting Times - Good Clinical Practice Guide (2014):

- *A maximum of one month wait from the date between a decision to treat (DTT) to the first definitive treatment for all cancers (including surgery).*

Available at: www.england.nhs.uk/wp-content/uploads/2015/03/delivering-cancer-wait-times.pdf

Prior to formal local study approval, collaborators may prospectively collect data on hard copy case report forms (available at https://globalsurg.org/cancercovidsurg/), but this should not be uploaded to the REDCap database until approval is confirmed.

Analysis

A detailed statistical analysis plan will be published online at globalsurg.org/cancercovidsurg. Analyses will be overseen by the independent data monitoring committee (DMC). Reports will

include description of the primary and secondary outcomes in the cohort. Interim analyses will be performed as guided by the independent DMC, and rapidly disseminated to the global healthcare community using social media, blog sites and health education platforms. The first analysis will be performed once 100 patients have been entered onto the database, and the frequency of subsequent analyses will be agreed with the DMC. The decision to submit data for publication will be agreed by the CovidSurg-Cancer steering committee upon consultation with the DMC. Hospital-level data will not be released or published.

Authorship

All collaborators from sites who contribute at least one patient will be recognised on any resulting publications as PubMed-citable co-authors. Flexible to service demands, no authorship limits will be imposed at a centre level; as many collaborating investigators are required, and work to support the project will be recognised on all future outputs.

A corporate authorship model will be used under CovidSurg Collaborative group, for example: https://pubmed.ncbi.nlm.nih.gov/29452941.

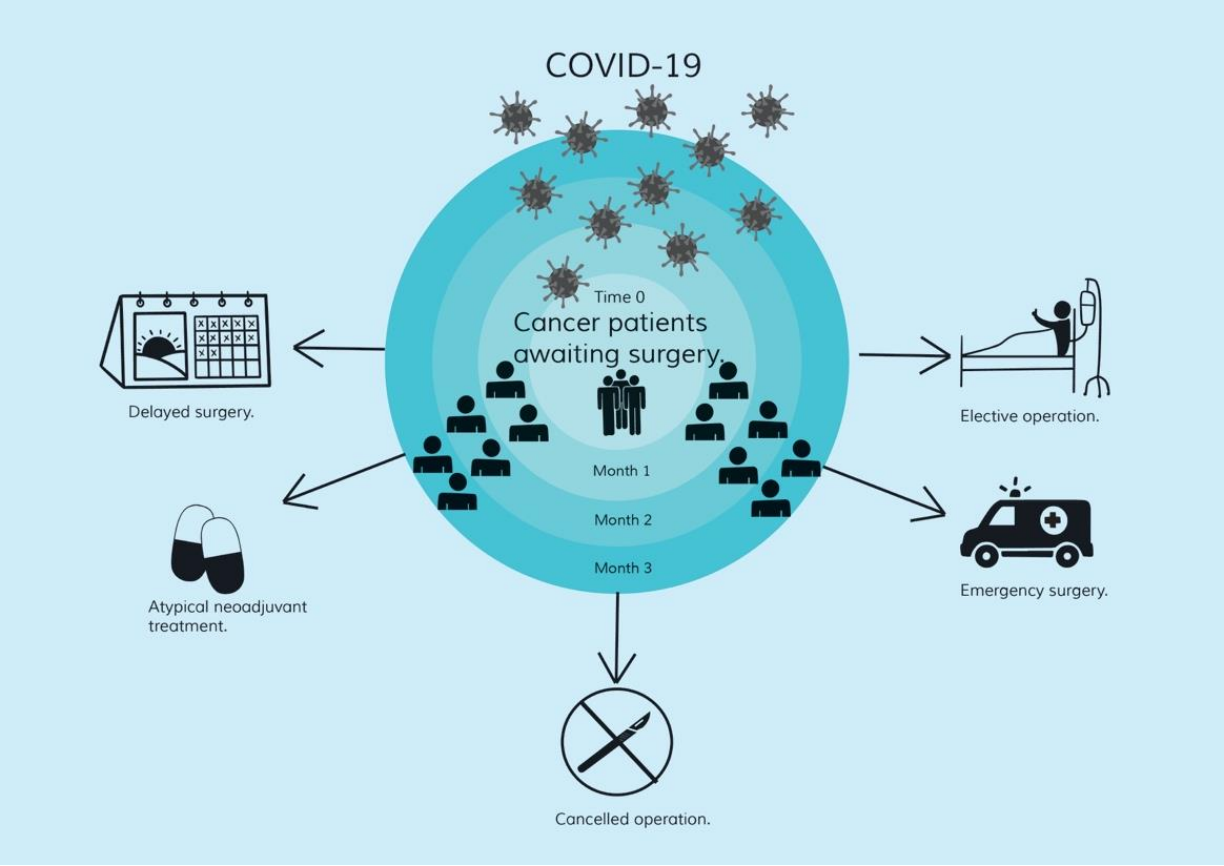

Figure 3. Overview of patient and pathways captured within CovidSurg-Cancer protocol.

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BOLT-ON HEAD & NECK FOLLOW-UP STUDY PROTOCOL

Long term outcomes of elective cancer surgery for malignancies of the Head & Neck during the COVID-19 pandemic crisis: an international, multicentre, observational cohort study (*CovidSurg-Cancer HEAD & NECK Follow-Up Study*)

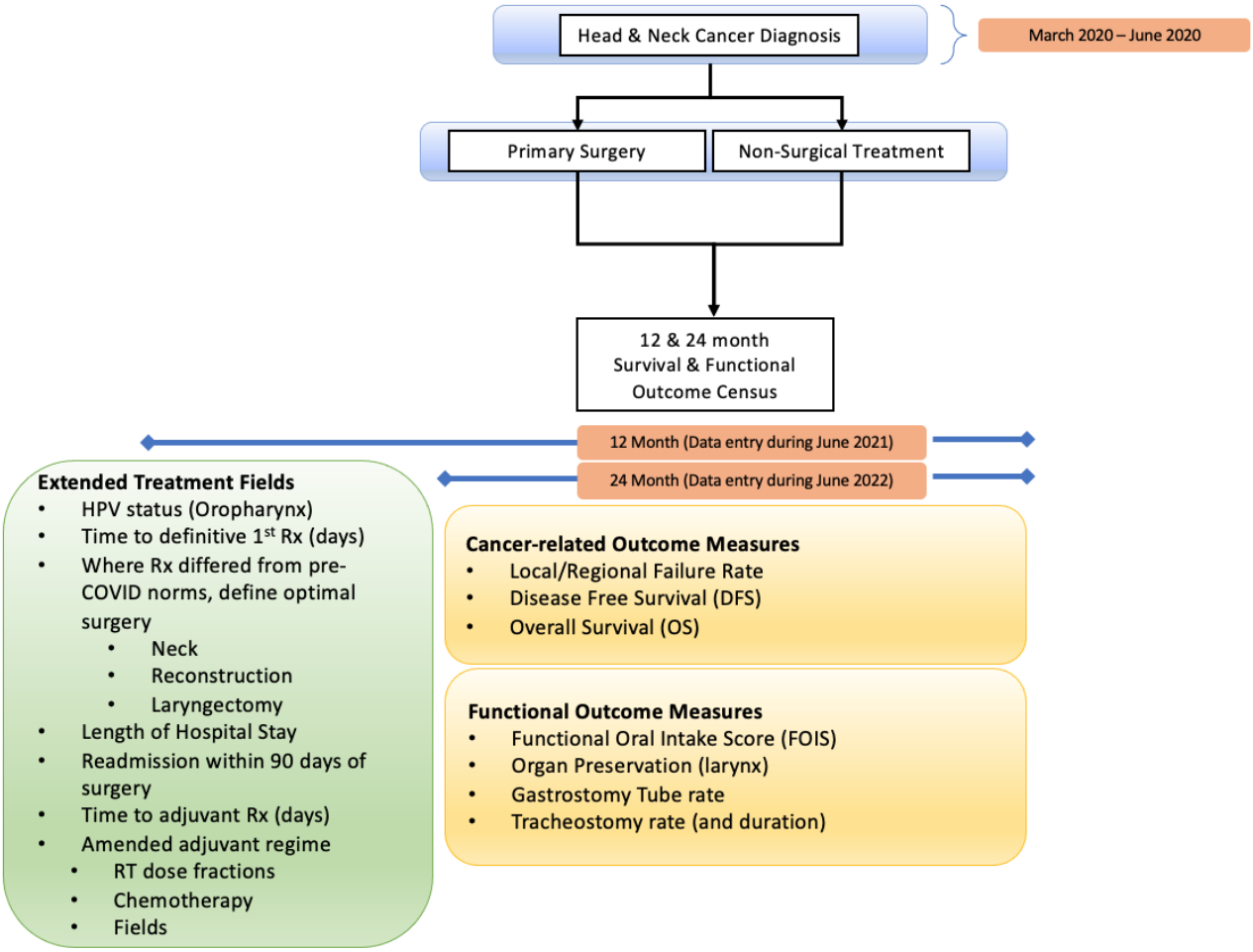
The primary intention of the COVIDSurg-Cancer study was to evaluate the 30-day SARS-CoV-2 infection rates in elective cancer surgery. The end points for that project were restricted to evaluation at a timepoint only four months following the first enrolled case (June 2020) however significant clinically relevant questions that cannot be addressed within the intended study window remain, particularly functional and survival outcomes for Head & Neck Cancer patients. Of paramount importance for this patient group, is assessment of whether the changes in care, deemed necessary at the time, have had a long-term impact on patient outcomes.

To that end, we will extend follow up analysis for Head & Neck cancer patients through inclusion of mature (12 & 24 month) outcome data and of additional data fields of specific H&N importance, including aspects such as the influence of modified surgical practices on functional outcomes and disease-free intervals. These data points and assessment timepoints were beyond the remit of the original CovidSurg-Cancer study.
This follow-up study seeks to address the hypothesis that the COVID-19 pandemic, and unintended consequences of alteration in clinical management, have negatively impacted upon outcomes (survival or otherwise).

Study Period
Patients enrolled during the 3-month study period of the COVIDSurg-Cancer Study (early 2020) will be followed up for an additional 24 months.
There are two data entry periods for the COVIDSurg follow-up study. These timepoints correspond to approximately 12 and 24 months post patient entry into COVIDSurg. They are:

- 1st – 30th June 2021
- 1st – 30th June 2022

A timeline for the study is shown in the flow diagram below, including refined treatment-related fields and outcome assessments planned for the two census dates (month of June 2021 & month of June 2022).



COVIDSurg-Cancer HEAD & NECK Follow-up timeline schema

All patients who were included in COVIDSurg-Cancer with diagnosis of Head & Neck malignancy are eligible for long-term follow-up at 12 and 24 months post study entry date

Data Collection

Data will once more be collected via the REDCap web application hosted by the University of Birmingham, UK. Only anonymised, routinely recorded data will be collated and uploaded by the local site team. Individual collaborators will be provided with (or confirmed to continue with) REDCap project server login details, allowing them to securely submit data on to the REDCap system.

The study database is managed by the Birmingham Centre for Prospective and Observational Studies (BiCOPS) at the University of Birmingham, UK.

Data collection will utilise (and extend) the original COVIDSurg REDCap dataset for each patient.
Data fields will include, cancer-specific, diagnostic and therapeutic timelines, MDT decisions, dates of recurrence, upstaging and other oncological events. Changed or amended original MDT recommendations, management of disease or completion of follow-up, operative and nonoperative cancer-related treatment, pathology and clinical outcome data (complications and functional) will also be collected.

Local Approval
Local approval (ethical, audit or institutional review board) as required for the initial COVIDSurg Cancer Study must be reviewed and resubmitted as necessary for the CovidSurg-Cancer HEAD & NECK Follow-Up Study. Review and resubmission is the responsibility of the participating centre and it is necessary to ensure that approval remains in place for extended follow-up.

Authorship
For all collaborators from sites, the corporate authorship model will be followed, as was the case in the parent COVIDSurg and COVIDSurg Cancer Studies [https://pubmed.ncbi.nlm.nih.gov/32479829/]. Those collaborators who contribute follow-up data on at least one patient will be recognised on any resulting publications as PubMed-citable co-authors. Flexible to service demands and given the longer-term nature of data capture, no authorship limits will be imposed at a centre level; as many collaborating investigators are required, and work to support the project will be recognised on all future outputs.

Head & Neck cancer - study aims and data points
Aim
To evaluate the impact of treatment delay and/or case management alteration of patients treated during the COVID-19 pandemic (March-June 2020) in terms of survival and function.

Inclusion Criteria
Patients enrolled in the COVIDSurg-Cancer Cohort Study with Head & Neck cancer – including patients who would have been planned for curative cancer surgery by the MDT (tumour board) in the pre-COVID-19 era that have surgery delayed, cancelled, or receive an alternative treatment strategy (e.g. radiotherapy) during the pandemic

Primary data points of interest at 12 and 24 months

- Disease Free Survival (DFS)
- Overall Survival (OS)
- Oncologic data
    - Date and site of recurrence (local/regional/distant)
        - Neck failure rate in oral cavity cancer
        - Organ preservation rate in larynx cancer
- Functional data

- Swallow function (Functional Oral Intake Score (FOIS))
- Tube dependency rate (Nasogastric/PEG/RIG)
- Tracheostomy retention rate (days to decanulation)

Supplemented/extended Treatment-related fields

- Surgical Intervention
  - Actual date of surgery (for delayed primary surgery; e.g. Thryoid)
  - HPV status (p16 ± ISH/PCR) for oropharyngeal SCC
  - Readmission within 90 days of primary surgery
  - Reoperation within 90 days of primary surgery
- Non-surgical Intervention
  - Time to commencement of primary non-surgical treatment (days after MDT decision)
  - Time to commencement of adjuvant treatment (days post surgery)
  - Delivered adjuvant regime
    - RT (dose/fractions)
    - Chemotherapy (drug/dose/frequency)
    - Fields

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