Research protocol for a diagnostic study of non-invasive exhaled breath analysis for the prediction of oesophago-gastric cancer

Sheraz R Markar,1 Jesper Lagergren,2 George B Hanna1

ABSTRACT

Introduction: Despite improvements in a range of chemo, radio and surgical therapies, the overall survival at 5 years from oesophago-gastric cancer remains poor and ranges from 10% to 30%. Early diagnosis is a key strategy to improve survival but early disease stage has non-specific symptoms that are very common while the warning clinical picture often indicates advanced disease. The aim of this research is to validate a breath test to predict oesophago-gastric cancer therefore allowing earlier diagnosis and introduction of treatment.

Methods and analysis: The study will include 325 patients and be conducted across four major oesophago-gastric cancer centres in London, UK. This research will utilise selected ion flow-tube mass spectrometry (SIFT-MS) exhaled breath analysis, for comparison of predicted cancer risk based on the previously developed volatile organic compound exhaled breath model, with endoscopic findings and histology biopsies. This will determine the overall diagnostic accuracy for non-invasive breath testing for the diagnosis of oesophago-gastric cancer.

Ethics and Dissemination: Approval was gained from NRES Committee London, on 16 July 2014 (REC reference 14/L0/1136) for the completion of this study. Different methods of dissemination will be employed including international clinical and patient group presentations, and publication of research outputs in a high-impact clinical journal. This is to ensure that the findings from this research will reach patients, primary care practitioners, scientists, hospital specialists in gastroenterology, oncology and surgery, health policymakers and commissioners as well as NHS regulatory bodies.

Trials registration number: UKCRN18063; Pre-results.

INTRODUCTION

In the UK, upper gastrointestinal (GI) symptoms account for at least 3% of consultations in primary care,1 and the national oesophago-gastric (OG) cancer audit (2013) suggested the number of patients per annum diagnosed with OG cancer was approximately 11 500 with only 35% treated with a curative intent.2 Current UK referral guidelines for OG cancer focus on alarm symptoms such as dysphagia and odynophagia, despite these symptoms having poor sensitivity and specificity for cancer, and often only occurring in advanced disease, translating into poor outcome and overall survival. There is a wide range in the rates of OG-duodenoscopy (OGD) performed among general practice populations in England, and it appears on average that patients with OG cancer belonging to practices with the lowest rates of OGD performed are at greater risk of poorer overall outcome.3

OGD remains the gold-standard investigation for the assessment of patients with upper GI symptoms and considered at risk of OG cancer. OGD is an expensive investigation, uncomfortable for the patient, and not without important risks including visceral perforation and bleeding. Furthermore, due to a lack of clear guidance regarding the utilisation of OGD, the identification of OG cancer currently only occurs in 2% of all OGDs in the UK,2 and often at a late and incurable stage.

Our group undertook a systematic review to evaluate the clinical evidence for the utilisation of volatile organic compound (VOC) analysis from breath in the assessment of GI disease.4 Eleven studies comprising 934 patients were included. Significant differences in the VOC profiles from exhaled breath of patients with gastro-oesophageal cancer were observed, suggesting this may have a future role as a non-invasive diagnostic test. No studies reported any adverse events associated with VOC breath analysis. Breath analysis has been shown to be acceptable and of diagnostic value in routine clinical practice for the detection of Helicobacter Pylori and intestinal bacterial overgrowth,5 and in the diagnosis and assessment of asthma.6 7
Previous research undertaken by our group, using selected-ion flow-tube mass spectrometry (SIFT-MS), demonstrated the presence of specific VOCs from the headspace of urine and gastric content that were associated with OG cancer. Following this, our group focused research on the analysis of VOCs from exhaled breath. In an initial pilot study, we found four VOCs that significantly differed between patients with cancer and positive-control patients. We extended this initial research to a larger cohort of 220 patients in whom we developed a model based on the analysis of 12 VOCs for the prediction of OG adenocarcinoma. Further work undertaken over the past year in a follow-up cohort of 60 patients further refined this diagnostic VOC breath model to nine VOCs (propanoic acid, butyric acid, pentanoic acid, hexanoic acid, pentanal, heptanal, octanal, nonanal and decanal) from two chemical groups (fatty acid and aldehyde) (sensitivity 95% and specificity 69%) with improved mechanistic understanding of their derangement in OG adenocarcinoma. Previous research has identified specific VOC breath signatures associated with lung, biliary tract and head and neck cancers that do not overlap with the VOC breath signatures associated with lung, biliary tract and head and neck cancers.11 

In preparation for this multicentre study, we investigated factors that influence the loss of target VOCs from bags to eliminate time for transport between centres as a confounding factor. Samples can be stored for up to 48 h at room temperature within GastroCHECK steel breath bags with no evidence of loss of VOCs. We further studied the variation seen in the concentration of trace VOCs within ambient air, and demonstrated that this may represent a confounding factor and must be sampled regularly when undertaking multicentre breath analysis. The next stage of this research and the subject of this current proposal is to externally validate the model for OG cancer in this study.13-16

Inclusion criteria: Patients aged more than 18 years with upper GI symptoms attending for endoscopy or surgery. In the cancer cohort, only patients with non-metastatic OG adenocarcinoma (stage I-III) will be included.

Exclusion criteria: Patients with a documented active infection or known liver failure, and those unable to provide informed consent or unable to provide a 500 mL breath sample.

Intervention(s) or method

Breath sampling methodology: All patients will be asked to sign a consent form to be included in this study (see online supplementary appendix A), and will be given an information leaflet (see online supplementary appendices B and C). Patients will fast for a minimum of 6 h prior to their breath sample collection. Patients will rest in the same area for at least 20 min prior to breath sampling and all breath samples will be retrieved prior to endoscopy. Patients will be asked to perform a single deep nasal inhalation followed by complete exhalation via their mouth into a secure GastroCHECK steel breath bag (500 mL) via a 1 mL Luer-Lok syringe (Terumo Europe, Leuven, Belgium). For each VOC measurement, the syringe plunger will be removed from the 1 mL Luer-Lok syringe and the GastroCHECK bag will be directly connected via the syringe barrel to the sample inlet arm of the SIFT-MS instrument. Patients with OG adenocarcinoma will be sampled prior to the induction of neoadjuvant therapy (neoadjuvant naïve).

VOC analysis using SIFT-MS: The principle of SIFT-MS is as follows: selected precursor ions are formed in a microwave discharge source and are selected according to their mass-to-charge ratio, m/z, by a mass filter and injected into a helium carrier gas where they are convected as a thermalised swarm along a flow tube. H5O+, NO+, O2+ precursor ions are used to ionise the trace gases in an air sample that is introduced into the helium at a known flow rate; these ions selectively ionise VOCs present within the sample, resulting in characteristic product ions. By measuring the count rate of both, precursor ions and the characteristic product ions at the downstream detection system, a real-time quantification is achieved, realising the absolute concentration of trace and volatile compounds at the parts-per-billion by volume or parts-per-million by volume. Samples will be analysed using the multi-ion monitoring mode, selective VOCs from breath will be analysed for a total of 60 s and measured concentrations will be averaged over this time for each VOC.

End point: The diagnostic accuracy of the exhaled breath test for the prediction of OG cancer.

Quality assurance

Calibration to water: The concentration of water in human breath is approximately 6%. All samples will...
be tested using SIFT-MS to ensure that the percentage of water from the exhaled breath sample within the bag is between 5% and 6.5%. If this is not the case the sample will be discarded as it is likely to be unreliable.

- **Ambient room air:** Weekly samples will be taken from the ambient room air at the different hospitals where patients are being breath sampled and also from the laboratory air where samples are analysed. This is to ensure that there is no contamination from the ambient room air to cause anomalous results; contamination represents an important confounding factor that must be measured.

- **Standardisation of breath sampling methodology:** Human factor analysis previously undertaken by our group has shown several potential sources of error in breath sampling that can affect the results of analysis. All clinicians and researchers participating in this clinical trial will go through a credentialing process involving observation of consent, performing breath sampling and storage of samples, prior to inclusion in the study.

- **Cross-platform validation:** In a subset of 50 patients, an additional breath sample will be taken and analysed using Thermal Desorption Gas Chromatography Mass Spectrometry (TD-GC-MS). This analytical technique allows accurate compound identification, with SIFT-MS permitting accurate compound quantification.

- **Data monitoring committee:** Professor David Smith FRS (University of Keele, UK) and Professor Patrik Spanel (J Heyrovsky Institute of Physical Chemistry, Prague, Czech Republic) will provide independent data monitoring of the quality of breath analysis results obtained. Both are experts in the field of breath analysis and selected-ion flow-tube mass spectrometry (SIFT-MS). Professor Jasper Lagergren (Karolinska Institutet, Stockholm, Sweden) will monitor clinical data.

### Statistical analysis and plan, including:

- **Sample size and power calculations:** Based on 50% of patients in the study population having cancer (one benign patient will be recruited to one patient with cancer) and maintaining a sensitivity and specificity of 80% for the diagnostic model derived from our previous research, the sample size estimated for the multicentre external validation study is 325 patients; 162 patients with oesophageal or gastric cancer and 163 patients with benign conditions or a normal upper GI tract. From previous research undertaken, it is anticipated that 5% of patients recruited are likely to be withdrawn due to inconsistencies in breath sampling technique and transport. Therefore, the target recruitment for this study is 342 patients; 171 with oesophageal or gastric cancer and 171 with benign conditions or a normal upper GI tract. This sample size calculation was performed by Asif Johar, Statistician, Karolinska Institutet, Stockholm, Sweden.

- **Statistical tests:** Comparison of predicted cancer risk and actual OGD findings or histology from endoscopic biopsies (gold standard) will then be made, and the overall diagnostic accuracy (sensitivity, specificity, positive and negative predictive value, receiver operator curve analysis) for this non-invasive diagnostic investigation will be determined. Potential confounding factors across the study groups will be evaluated by employing the Kruskal-Wallis test for continuous variables and $\chi^2$ test for discrete variables. Linear regression models will be used to assess any influence of patient demographic factors, or medications (this data will be collected using the Case Report Form online supplementary appendix d) on VOC concentrations measured.

- **Blind analysis:** OGD findings with or without histology from endoscopic biopsies will provide the gold standard against which the results of the breath analysis model will be tested. Data will be sent to Fredrik Mattsson, senior biostatistician in Jesper Lagergren’s group at Karolinska Institutet, Stockholm, Sweden, who will be blinded to the results of the OGD and histology, and he will generate the predicted cancer risk using the model previously developed and based solely on breath analysis results gained. Comparison of predicted cancer risk and actual OGD findings or histology from endoscopic biopsies will then be made.

### Ethics

- **Ethics committee approval:** NHS Health Research Authority (NRES Committee London—Camden and Islington) approval gained on 16 July 2014 (REC reference 14/LO/1136).

- **Interim analyses and stopping rules:** No interim analysis will be performed, and the data will be analysed when the target recruitment of 325 patients has been reached.

### DISSEMINATION

Different methods of dissemination will be employed so that the findings from this research will reach patients, primary care practitioners, scientists, hospital specialists in gastroenterology, oncology and surgery, health policymakers and commissioners as well as NHS regulatory bodies. We plan to present the findings of this research at international gastroenterology, oncology and surgical research meetings. We will also present the findings of this research to relevant patient groups including NIHR-INVOLVE and the Oesophageal Patient Association. Following generation and validation of this robust model for the prediction of OG cancer, we plan to publish the results of this research in a high impact factor clinical journal to allow widespread dissemination of this research.

### Contributors

SRM was involved in the study design, acquisition of funding and drafting of full protocol. JL was involved in the study design and
statistical analysis plan. GBH was involved in the study conception, design and drafting of full protocol.

Funding National Institute for Health Research—Doctoral Research Fellowship (DRF-2014-07-088) with NIHR clinical trial adoption. SRM was supported by the National Institute for Health Research (NIHR), UK (Grant Number DRF-2014-07-088). This research was supported by the National Institute for Health Research (NIHR) Diagnostic Evidence Co-operative London at Imperial College Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests None declared.

Ethics approval NRES Committee London (REC reference 14/LO/1136).

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES
PARTICIPANT CONSENT FORM

Non-invasive diagnostic testing for Gastro-intestinal disease

Principal Investigator:
Professor George Hanna PhD FRCS
Professor of Surgical Sciences / Consultant Surgeon
Imperial College, St Mary’s Hospital, London

Please initial box

1. I confirm that I have read and understood the information leaflet (dated 14/07/2014 version 7.0) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I may withdraw consent to my samples being included in the study at any time without justifying my decision and without affecting my medical care or legal rights.

3. I agree to donate my samples and allow their use in the medical research as described in the Patient Information Leaflet.
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records that are relevant to this research.

5. I understand that my samples will not be used to undertake any genetic tests.

6. I understand that the samples are a gift and that I will not benefit from any intellectual property privilege that result from the use of the samples in research studies.

7. I would like to be contacted if the result of any research carried out on my samples can help me during my treatment course.

8. The samples which I hereby consent to donate are:
   
   a. Breath
   b. Urine

_______________________  __________________  __________________
Name of Patient     Signature     Date

___________________  __________________  __________________
Researcher     Signature     Date

Copy to be given to the participant. Copy in medical notes and original to Mr Sheraz R Markar or Mr Stefan Antonowicz or Mr Tom Wiggins, Clinical Research Fellow, Imperial College Healthcare.
Non-invasive diagnostic testing for Gastro-intestinal disease

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Professor of Surgical Sciences / Consultant Surgeon
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Co-investigators:

Mr Sheraz Markar MRCS
Clinical Research Fellow
Imperial College London

Mr Tom Wiggins MRCS
Clinical Research Fellow
Imperial College London

Mr. Sacheen Kumar MRCS
Clinical Research Fellow
Imperial College London

Dr. Juzheng Huang PhD MRSC
Research Scientist
Imperial College London

Date: 14/07/2014

Dear Sir/Madam

You are being invited to take part in the above titled research study. This information sheet explains the nature of the research being undertaken and what the process involves. Please take your time to read the following information and discuss with others if you wish. Should you require any further information or
have any questions, please ask us. Take time to decide whether or not you wish to participate. Thank you for reading this information sheet.

**What is the purpose of the study?**
We are trying to develop a new way to diagnose cancer of the oesophagus, stomach, colon and rectum in a way that doesn’t involve having an endoscopy. To do this we are collecting breath and urine samples. These samples contain metabolites, chemicals produced by cancer cells that can be analysed and may show whether cancer is present. If this analysis is successful we hope to develop a test that can detect cancer without the need for an endoscopy at an early stage when treatment is likely to be more successful.

**Why have I been chosen?**
You have been chosen for this research study as you have been diagnosed with cancer of the gullet, stomach or bowel cancer. We believe that by comparing breath and urine from patients with cancer and healthy individuals, we shall be able develop a test to detect cancer without the need for an endoscopy at an early stage. If you have had surgery for gastrointestinal cancer, breath and urine tests are being conducted to provide further information on chemicals found in breath and urine, and this will not affect the your current standard treatment.

**Do I have to take part?**
Participation in this research study is entirely voluntary. It remains your decision at all times whether or not to take part. If you chose to take part, you will be provided with a copy of this information sheet to keep and requested to sign a consent form. Should you decide at any point that you do not wish to continue with your participation in this research study, you are free to withdraw at anytime. A reason for withdrawal need not be given. A decision not to take part or to withdraw at any time shall not affect the standard of care you receive throughout your treatment.

**What do I have to do?**
You are not required to do anything specific. In accordance with endoscopy and theatre protocol, we request for you not to eat or drink anything for at least 6 hours prior to attending the hospital. You shall undergo your investigations and treatment as planned. The collection of breath and urine will not interfere with your planned treatment nor shall it result in any change to your planned treatment. No additional invasive procedures will be undertaken for the purposes of the research study. We also request your permission to access your hospital records for the purpose of the research study only, including blood tests, radiology and pathology results. All your hospital records shall be handled with strict confidentiality in accordance with the Data Protection Act 1998.

**How much of my breath and urine will be taken?**
Before your procedure, you will be asked to blow twice in a special device which stores this breath in a plastic bag for analysis later. You will also be asked to pass a small quantity of urine (20mL) into a container for analysis later. No extra needle pricks or vein punctures are required. The sample shall undergo analysis via our mass spectrometry instrument. If you are undergoing surgical treatment
for your condition we will ask you to provide one set of samples before your surgery and one further set of samples 6 – 8 weeks after surgery.

**What will happen to the samples?**
All breath and urine samples shall be discarded after completion of analysis.

**Will I be contacted again in the future?**
You shall need to indicate on the consent form whether or not you would like to be contacted again. We shall only contact you to obtain an update on your condition and to inform you of the results of any research carried out on your samples. Whether or not you chose to be contacted shall not impact in any way on the standard of care that you receive; this information may be discussed with you by your Hospital Consultant.

**What if something goes wrong?**
We do not believe that you would be harmed by donating breath or urine samples during this study. Your treatment pathway shall remain the same irrespective if you choose to participate in this research study. If you wish to complain, or have any concerns about the way you have been approached or treated during the course of this study, the standard National Health Service complaints procedure is available to you.

**Will I receive payment for the samples that I donate to the study?**
There shall be no payment or remuneration for any sample provided. We shall treat your samples as a gift to the St. Mary’s Hospital Upper GI Research Group, London and you would therefore relinquish any interest in the samples provided.

**Who is organising and funding body of the tissue bank and the study?**
Division of Surgery, Department of Surgery & Cancer, Imperial College London, St. Mary’s Hospital, Praed Street, London, W2 1NY.

**Who has reviewed the ethical considerations of the study?**
This study has been reviewed and given favourable ethical opinion for conduct in the NHS by Camden & Islington REC.

*Thank you again for taking the time to read this information leaflet. Your participation in this research is most appreciated.*
I have some more questions, with whom may I get in contact?

**Professor George B Hanna PhD FRCS**  
Professor of Surgical Sciences / Consultant Upper GI Surgeon  
Department of Surgery & Cancer  
10th Floor, QEQM Building  
St Mary’s Hospital, London  
Praed street,  
London  W2 1NY  
Tel:  0207 886 2124  
Fax:  0207 886 1810  
E-mail: g.hanna@imperial.ac.uk

**Mr Sheraz Markar**  
Clinical Research Fellow  
Department of Surgery & Cancer  
Room 1089  
10th Floor, QEQM Building  
St Mary’s Hospital, London  
Praed street,  
London  W2 1NY  
E-mail: s.markar@imperial.ac.uk

Alternatively, you can seek impartial advice from the Patient Advice and Liaison Service (PALS), at PALS, Ground Floor QEQM, St Mary’s Hospital, 41 Praed Street, London W2 1NY, Tel: +44(0)2078867777, Fax: +44(0)2078861753

Lastly, the trust R&D provide a third point of contact: Ms Christine Buicke AHSC Joint Research Compliance Office, 510B, 5th Floor Lab Block, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF Tel: +44 (0) 203 311 0212 Fax: +44 (0) 203 311 0203  c.buicke@imperial.ac.uk
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**Why have I been chosen?**
You have been chosen for this research project because you are having an endoscopy to diagnose the cause of your gastrointestinal symptoms. We want to see if new non-invasive tests on your breath and urine an also help to diagnose the cause of your symptoms and possibly replace the need for some endoscopies in the future.

**Do I have to take part?**
Participation in this research study is entirely voluntary. It remains your decision at all times whether or not to take part. If you chose to take part, you will be provided with a copy of this information sheet to keep and requested to sign a consent form. Should you decide at any point that you do not wish to continue with your participation in this research study, you are free to withdraw at anytime. A reason for withdrawal need not be given. A decision not to take part or to withdraw at any time shall not affect the standard of care you receive throughout your treatment.

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**MMOG/NID CRF Baseline**

To be completed after completion of consent form

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**B1. Gender**

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 0</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

VOCB/TWLC Patient Identifier: ...

**B2. Ethnic Origin (tick more than one for mixed)**

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>□ 0</td>
<td>□ 1</td>
</tr>
<tr>
<td>Black / African / Caribbean / Black British</td>
<td>□ 0</td>
<td>□ 1</td>
</tr>
<tr>
<td>Asian / Asian British</td>
<td>□ 0</td>
<td>□ 1</td>
</tr>
<tr>
<td>Arab</td>
<td>□ 0</td>
<td>□ 1</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>□ 0</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

**B3. Height | Weight | Recent BMs/HBA1c | Last ate**

<table>
<thead>
<tr>
<th>m</th>
<th>kg</th>
</tr>
</thead>
</table>

**B4. Presenting Complaint**

**A. Current symptom (mark 1,2,3 in order of importance to patient)**

<table>
<thead>
<tr>
<th>Heartburn</th>
<th>Chest pain</th>
<th>Cough</th>
<th>Hoarseness</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abdo pain before eating</th>
<th>Abdo pain after eating</th>
<th>Dysphagia</th>
<th>Odynophagia</th>
<th>Gi Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight loss (kg/mo)</th>
<th>Vomiting</th>
<th>Reduced PO intake</th>
<th>NG</th>
<th>NJ</th>
<th>TPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 0</td>
<td>□ 0</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

**B. Describe in free text including prior history of A**

**C. Recent illness**

| □ 1 | Recent Antibiotics/Laxatives | □ 1 | Recent diarrhoea | □ 1 |

**D. Medication use including length and duration of PPI & NSAIDs**

**E. Reason for initial referral**

**F. Nutrition & FHx history**

**B5. Smoking History**

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Never</th>
<th>Ex-</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 2</td>
<td></td>
</tr>
</tbody>
</table>

Specify pack/ years

Specify units/type

**B6. ASA Grade**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
B7. Past Medical History (detail all below)

- Known Barrett’s
  - □ 0
  - □ 1

- Previous cancer anywhere
  - □ 0
  - □ 1

- Diabetes
  - □ 0
  - □ 1

- Renal impairment
  - □ 0
  - □ 1

- Any inflammatory condition
  - □ 0
  - □ 1

- Pulmonary Impairment
  - □ 0
  - □ 1

Describe above and any others as fully as possible.

B8. Endoscopy findings (Attach report. If participant is consented at endoscopy, then go to B14)

Specify using size and grade of any inflammation or dysplasia

B9. Clinical staging (attach notes)

Specify using TNM, grade and cm

B10. Prior oncological treatment for this cancer

Specify with dates

EOX □ ECX □ RT □ Other (specify) □ ......................... No. of cycles ..................

Dates ..................

B11. Dates

Date of operation dd/mm/yyyy

B12. Operation Performed


B13. Operative findings/pStage/R status

Specify using TNM

B14. Samples taken

- Blood □ 1
- Urine □ 2
- GC □ 3
- Tissue □ 4
- Breath □ 5