Study Title: An observational study to correlate the results of ploidy and stroma analysis with prognosis in early rectal cancer

Internal Reference Number / Short title: Ploidy and stroma in early rectal cancer

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£5000 award from Occtopus charity to cover sample retrieval costs

Chief Investigator Signature:

The investigators declare no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY STUDY CONTACTS

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2. SYNOPSIS

Study Title	An observational study to correlate the results of ploidy and stroma analysis with prognosis in early rectal cancer	
Internal ref. no. (or short title)	Ploidy and stroma in early rectal cancer	
Study Design	Observational study	
Study Participants	Rectal cancer patients	
Planned Sample Size	150 patients	
Follow up duration	Minimum 18 months	
Planned Study Period	2 years	
	Objectives	Outcome Measures
Primary	To compare results of [A] ploidy and [B] stroma analysis with outcome after surgery to remove early rectal cancer	Correlation between [A] ploidy status and [B] tumour: stroma ratio with local recurrence of cancer
Secondary	To compare results of [A] ploidy and [B] stroma analysis with survival after surgery to remove early rectal cancer To assess predictive value of [A] ploidy and [B] stroma analysis for outcome after surgery to remove early rectal cancer To compare results of [A] ploidy and [B] stroma analysis with outcomes by use of adjuvant treatment	Correlation between [A] ploidy and [B] stroma analysis with overall survival after TEM surgery to remove rectal cancer Contribution of [A] ploidy and [B] stroma analysis to a regression model for local recurrence after TEM surgery to remove rectal cancer Subgroup analysis comparing [A] ploidy and [B] stroma results with local recurrence and survival for patients who did and did not receive adjuvant chemo- or radiotherapy

3. ABBREVIATIONS

CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Independent Review Board

MRN	Medical Records Number
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Patient Information Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SDV	Source Data Verification
SOP	Standard Operating Procedure
TEM	Transanal endoscopic microsurgery
TMF	Trial Master File

4. BACKGROUND AND RATIONALE

Early rectal cancer can be removed by minimally-invasive surgery, and the standard pathological assessment of the removed tumour gives valuable information about how advanced the tumour is. This information is very important in indicating whether the cancer is likely to recur, and therefore in advising the patient after surgery whether further treatment is advisable, and if not, what is the most appropriate follow-up regime. However there is still a lot of uncertainty in these predictions about recurrence of the cancer, and better tests are being sought. This study aims to look at two further pathology tests, ploidy and stroma ratio in the tumour, and compare these test results with outcome in patients who have had an early rectal cancer removed. This will allow us to assess whether these two tests can give greater accuracy in predicting outcome. If so, we would be better able to advise patients with early rectal cancer about their prognosis and further management.

Routine histopathology analysis of a rectal cancer specimen removed at surgery includes assessment of tumour size, depth of invasion, vascular, lymphatic and perineural invasion, tumour involvement of resection margins and nodal involvement. This information is valuable in predicting outcome. For example, predicted rates of local recurrence at 36 months following local excision of rectal cancer by transanal endoscopic microsurgery (TEM) based on tumour size, depth of invasion and lymphatic invasion have been tabulated [1]. However such models are not perfect, and leave room for improvement. Ploidy and stroma ratio are two further tests which have shown some promise in predicting outcome.

Ploidy refers to the number of sets of chromosomes in a cell nucleus. Most human cells are normally diploid, with two sets of 23 chromosomes. Abnormal tumour cells may have a different number of sets of chromosomes, or be aneuploid, having some replicated or deleted chromosomes. In general, aneuploidy in cancer cells is associated with a worse prognosis. An early study of DNA ploidy in rectal cancer using flow cytometry showed an independent but small predictive effective of aneuploidy on survival [2]. Technological advances now allow more accurate and detailed assessment of ploidy. The DNA ploidy status of tumour cells in early ovarian cancer has been found to predict which patients will

benefit from adjuvant chemotherapy after surgery to remove the ovarian tumour and is used routinely in some centres to aid in decision-making [3].

Stroma ratio refers to the tumour: stroma ratio. A lower proportion of tumour cells or, conversely, a higher percentage of stroma, in a cancer tends to be associated with a poorer prognosis. This ratio has been found to be strongly associated with tumour growth and invasion in colorectal cancers, and to independently predict survival in patients undergoing surgery to removal colorectal tumours [4]. However previous studies have looked mainly at more advanced colon cancers, rather than early rectal cancers, and have used only cancer-related death as the endpoint, rather than looking at local recurrence and response to adjuvant treatments.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To compare results of [A] ploidy and [B] stroma analysis with outcome after surgery to remove early rectal cancer	Correlation between [A] ploidy status and [B] tumour: stroma ratio with local recurrence of cancer	Time between surgery for rectal cancer and local recurrence
Secondary Objectives To compare results of ploidy and stroma analysis with survival after surgery to remove early rectal cancer To assess predictive value of [A] ploidy and [B] stroma analysis for outcome after surgery to remove early rectal cancer To compare results of [A] ploidy and [B] stroma analysis with outcomes by use of adjuvant treatment	Correlation between [A] ploidy and [B] stroma analysis with overall survival after TEM surgery to remove rectal cancer Contribution of [A] ploidy and [B] stroma analysis to a regression model for local recurrence after TEM surgery to remove rectal cancer Subgroup analysis comparing [A] ploidy and [B] stroma results with local recurrence and survival for patients who did and did not receive adjuvant chemo- or radiotherapy	Time between surgery for rectal cancer and death

6. STUDY DESIGN

This is an observational study comparing results of two specialised pathology tests with outcome after surgical removal of early rectal cancer. No extra interventions will be carried out on patients.

Over 170 patients have already had an early rectal cancer removed by minimally-invasive surgery (transanal endoscopic microsurgery or TEM) since 2007 in Oxford, and more operations take place each month. Data about the tumour and follow-up on these patients is routinely collected in the Oxford TEM database to ensure that patients receive the appropriate investigations and management after surgery, and that any recurrence of the tumour is promptly detected and treated.

For patients who agree to take part in this study, or who consented to donation of tissue for research at the time of surgery, we will perform the extra pathology tests on the tissue which is stored in the Oxford pathology department as standard practice, and compare the test results with the outcome information contained in the TEM database.

The extra pathology tests will be undertaken in a specialist department in Oslo, Norway. The study will involve sending a small section of the preserved tissue from each consenting patient to Norway for analysis. After analysis, any residual parts of the samples will be returned to the Oxford pathology department.

7. PARTICIPANT IDENTIFICATION

7.1. Study Participants

Participants diagnosed with rectal cancer that is operable and patients who have already had rectal cancer removed by TEM surgery in Oxford since 2007.

7.2. Inclusion Criteria

- Participant is willing and able to give informed consent (in English) for participation in the study, or gave informed consent for donation of tissue for research at the time of surgery.
- Male or Female, aged 18 years or above.
- Diagnosed with operable rectal cancer.
- Due to undergo, or has already undergone, TEM surgery to remove rectal cancer.
- A useable tissue sample has already been, or will be, taken as part of routine surgery.

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Age less than 18
- Adults who are not able to give consent or who are deemed vulnerable.
- Participants who do not have a useable tissue sample will be excluded.

8. STUDY PROCEDURES

8.1. Recruitment

All patients who have undergone TEM surgery to remove a rectal cancer since 2007 are eligible, as well as new patients having surgery over the study period. Data on these patients is recorded as standard practice in the Oxford TEM database. There will be different groups, according to the time of surgery and whether or not potential participants consented for tissue donation, requiring different identification and recruitment strategies.

Already had surgery groups

Screening: A member of the care team will extract a list of patients who have had TEM surgery for rectal cancer since 2007 from the TEM database, identified by MRN (OUH medical records number) only. The care team member will then screen the casenotes for these patients to determine whether or not they consented to donation of tissue for research on the surgical consent form.

- Group A: Those who already consented for tissue donation

The majority of potential participants signed a donation of tissue for research statement at the time of surgery. If this statement has been agreed to, patients will be considered to have consented to participate in the study. The care team member will pass the list of MRNs (and linked anonymized data) for these patients to the researcher.

- Groups B & C: Those who did not consent to tissue donation at the time of surgery

Once these have been identified, the care team member will identify whether these patients are still undergoing follow-up at Oxford hospitals. For those who are undergoing follow-up (Group B) the member of the care team will provide the researcher with the MRN and date of the next follow-up appointment. For those who are no longer under follow-up (Group C), the member of the care team will post an information sheet and consent form to the potential participant.

For Group B the researcher will contact the patient during their follow-up visit and give them an information sheet about the study. They will be invited to sign a consent form if they wish to participate. Group C will receive an information sheet and consent form through the post, and will be provided with a telephone number should they wish to discuss the study further.

New patients who have not yet had surgery (Group D)

New patients, who have not yet had surgery, will be identified at colorectal cancer multi-disciplinary meetings. This will involve reviewing the clinical, histological and radiological investigations with other surgeons, oncologists, radiologists and pathologists as part of the normal clinical review process. Patients who are deemed suitable for TEM surgery will be considered eligible. Identified potential participants will then be approached by an investigator, who is a member of their direct care team, during their routine pre-operative clinic visit. They will be provided with an information sheet and given time to ask questions. Patients agreeing to participate will be recruited on their subsequent visit for surgery.

8.2. Screening and Eligibility Assessment

Not applicable. Participation will be sought from patients undergoing or who have undergone TEM surgery for rectal cancer.

8.3. Informed Consent

Group A: Those who already consented to the anonymous use of donated tissue and anonymised data – these patients will be considered to have consented to surgery and no further consent will be sought.

Group B: Those who did not consent to tissue donation at the time of surgery and are still visiting Oxford hospitals for follow-up – the researcher will contact the patient during their next visit and give them an information sheet. The patient will be given time to read the sheet and ask any questions they wish. They will then be asked to sign a consent form if they wish to participate.

Group C: Those who did not consent to tissue donation at the time of surgery and are not still visiting Oxford for follow-up – these potential participants will receive an information sheet and consent form through the post. They will be requested to sign and return the consent form by post if they wish to participate. The information sheet will contain a telephone number for the patient to call if they wish to discuss the study further

Group D: New patients who have not yet had surgery – potential participants will be approached by an investigator, who is a member of their direct care team, during their routine pre-operative clinic visit. They will be provided with an information sheet and given time to ask questions. Patients agreeing to participate will be asked to sign a consent form at that time, or on their subsequent visit for surgery if they want more time to consider the study.

Groups B, C & D: The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and, if seen in person, verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant and the implications and constraints of the protocol. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

8.4. Study Visit

No specific visit is required. Consent will be taken when the patient attends for surgery, or for patients who have previously had surgery, consent will be taken during a routine follow-up visit or by post.

8.5. Data Handling

For Group A patients, who gave consent at the time of surgery, a member of the care team will extract the relevant data, including tumour characteristics, any (neo-)adjuvant treatment details and outcome information, identified only by MRN, from the TEM database. The care team member will then securely transfer this anonymised data, identifiable by MRN only, to the research team. The research team will then allocate each participant a study ID according to the recruitment log, and replace the MRN with the unique study ID. The transfer will be done using a password protected spreadsheet sent via encrypted email. For all other patients, who sign a specific study consent form, the researcher will prepare the data extract from the TEM database, identified only by MRN, and then replace the MRN with a study ID. The researcher will securely provide a list of MRNs, with date of surgery, to the pathology department. The MRNs will be linked to a unique study ID in a separate recruitment log.

8.6. Sample Handling

A list of MRN (medical record numbers) and date of the relevant surgery for consenting patients will be provided to the histopathology department so that the relevant tissue samples can be identified. The study tissue samples will be extracted from the removed surgical specimens by a pathologist after the routine pathological assessment. These sections will be anonymised and transported to the Institute for Cancer Genetics and Informatics in Oslo for further specialist histological assessment to obtain DNA ploidy of the tumour cells and the tumour: stroma ratio. These samples will be identifiable by their study ID only. Any residual parts of the sections will be returned to Oxford to be held in the cellular pathology department, in line with standard practice for diagnostic surgical specimens.

The DNA Ploidy test is done on monolayers prepared from 50µm sections after microdissecting the tumour area (a video of the laboratory procedure is available at www.youtube.com/watch?v=ERq17Bi3nGI). The stroma measurement is done on standard HE sections (3µm).

8.7. Discontinuation/Withdrawal of Participants from the Study

Each participant has the right to withdraw from the study at any time.

No additional procedures or observations will continue to be required after withdrawal.

Withdrawal from the study will result in the exclusion of the data for that participant from analysis if the patient withdraws their consent to inclusion of their data.

Withdrawn participants will be replaced by further recruitment to the study.

The reason for withdrawal will be recorded in the CRF.

8.8. Definition of End of Study

Receipt of the final analysis from Oslo of the last sample.

9. STATISTICS

9.1. Description of Statistical Methods

All data will be stored in an Excel worksheet and analysed using Excel and R (a statistical programme).

The DNA ploidy results and tumour: stroma ratio will be correlated with local recurrence and survival. A subgroup analysis will additionally correlate ploidy and stroma with local recurrence and survival with and without adjuvant treatment.

A regression model will be developed incorporating ploidy and tumour: stroma ratio, along with a number of other known prognostic factors that are routinely collected, to assess whether ploidy and stroma have independent prognostic value in determining length of survival free of local recurrence, and length of disease-free survival.

9.2. The Number of Participants

The study will recruit 150 participants, including both those who have already had surgery since 2007 and new patients having surgery after the study commences. Similar studies using these techniques of ploidy and stroma analysis compared to outcome after colorectal, breast and ovarian cancer that have produced significant results have generally used between around 150 and 300 patients [ref 3-6]. We expect to be able to recruit 150 patients, from amongst both those who have already had surgery and new patients, within a reasonable time-frame of 18 months.

9.3. Analysis of Outcome Measures

Data from all participants, excluding any that withdraw consent, will be used in the analysis. The primary outcome measure is the correlation between [A] ploidy status and [B] tumour: stroma ratio with local recurrence of cancer. Secondary outcome measures are i) correlation between [A] ploidy and [B] stroma analysis with overall survival after TEM surgery to remove rectal cancer, ii) the contribution of [A] ploidy and [B] stroma analysis to a regression model for local recurrence after TEM surgery to remove rectal cancer, and iii) Subgroup analysis comparing [A] ploidy and [B] stroma results with local recurrence and survival for patients who did and did not receive adjuvant chemo- or radiotherapy

9.4. The Level of Statistical Significance

A 0.05 level of significance will be used.

9.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

All available data will be used. Missing data will not be imputed. Spurious data will be re-checked, and if valid will be included in the analysis.

9.6. Inclusion in Analysis

All patients who consent to the study will be included in the analysis.

9.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Not applicable. The analysis involves only simple statistical measures of readily available data.

10. DATA MANAGEMENT

10.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory records, diaries, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number, not by name.

10.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution to permit study-related monitoring, audits and inspections.

10.3. Data Recording and Record Keeping

For Group A patients who consented at the time of surgery, a member of the care team will prepare a data extract for all participants from the TEM database, in the form of an Excel spreadsheet, and securely transfer this anonymised data, identifiable by MRN only, to the research team. The research team will then allocate each participant a study ID according to the recruitment log, and replace the MRN with the unique study ID. For all other patients, who sign a specific study consent form, the researcher will prepare the data extract from the TEM database, identified only by MRN, and then replace the MRN with a study ID. All subsequent study data will be entered into the Excel spreadsheet. Data from this study will be generated at the Oxford University Hospitals and Institute for Cancer Genetics and Informatics, Oslo. Data will be analysed at the Oxford University Hospitals by the research investigators. Personal data will be stored and accessed by the investigators for less than 3 months. Research data will be stored for 10 years after the completion of the study.

The participants will be identified by a unique study specific number in the study database. For those who previously consented for tissue donation the MRN will be linked to the unique study number in the recruitment log. All other participants who consent will also be assigned a unique study identifier linked to their personal information. The name and any other identifying detail will NOT be included in any study data electronic file.

All electronic data will be password-protected and anonymised. All hard copy files and data will be kept in a locked cabinet within a locked office with restricted access. Access to the data will be restricted to study team members. The NHS Code of Confidentiality will be followed. This study will follow the sponsor organisation's policy regarding data storage and the NHS Code of Confidentiality. Information derived from the study will be stored on a single, secure (password encryption) NHS computer. This will be positioned within a secure location in the hospital.

Participants will be informed using patient information sheets of how data will be stored (only participants who did not sign a tissue donation form at the time of surgery will receive patient information sheets). The principal investigators will constantly review the security of research data files.

11. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

The study may be monitored or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3. Approvals

The protocol, informed consent form and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), the Confidentiality Advisory Group (CAG) and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4. Reporting

The CI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the REC, host organisation and Sponsor.

12.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study

will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. No participant will be identified in any publication of the results in any way.

12.6. Expenses and Benefits

No visits additional to normal care are anticipated, so there is no expectation of patients incurring any expenses.

12.7. Other Ethical Considerations

The majority of potential patients will have consented to tissue donation and anonymous use, and use of anonymous data for research at the time of surgery. In order to link the tissue and data, the tissue must be made identifiable. It is not feasible to contact this participant group for consent to link the data and tissue; as the surgical procedures date back to 2007, many potential participants may have moved from the Oxford area and some may be deceased. The data and sample will be linked using the hospital MRN number. This is a trust-specific reference number outside the OUHFT participants are not identifiable by this number. Once linked the data and samples will also be re-anonymised (or linked anonymised). There will be no onward disclosure of patient data outside the care team, as the researcher is also part of the participants' care team.

Tissue samples will be transferred outside the UK. A material transfer agreement will be in place to cover the terms of the transfer of the samples to the Institute of Cancer Genetics and Informatics in Oslo. The samples will be identifiable by study ID only, when they are transferred to Norway. Participants consent to the transfer of their linked anonymised samples to Norway.

13. FINANCE AND INSURANCE

13.1. Funding

Internal funding from Nuffield Division of Clinical and Laboratory Sciences, Oxford will cover the costs of retrieving the pathology specimens, and from the Institute for Cancer Genetics and Informatics, Oslo will cover the processing and analysis of the specimens.

13.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge the source of funding for the study. Authorship will be determined in accordance with the ICMJE guidelines and all other contributors will be acknowledged.

15. REFERENCES

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16. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.