GCA-GLOBE Short Study Summary

International Treatment and Outcome Study of Appendiceal Goblet Cell Adenocarcinoma

SHORT STUDY SUMMARY VERSION 1.0 · JUNE 2026

Short study summary and protocol synopsis Version: v1.0-short **Date:** 12 June 2026 **Status:** COLLEAGUE REVIEW DRAFT. The study has not yet opened for data collection. Study initiation remains subject to colleague and steering-group review, feasibility assessment and ethics approval.

Title

GCA-GLOBE: International Treatment and Outcome Study of Appendiceal Goblet Cell Adenocarcinoma

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Study Design

International multicentre retrospective observational cohort study with planned prospective follow-up extension. Initial active recruitment will primarily use European surgical, pathology and oncology networks, while eligible centres outside Europe may also participate.

A consent-based patient-reported experience and survivorship subanalysis and separate CT interpretation/texture-analysis, colonoscopy-yield and healthcare-utilisation subanalyses may be developed where the required data, approvals and operational arrangements are feasible.

Case Capture Period

The proposed retrospective case capture period is **1 January 2010 to 31 December 2025**.

This period may be refined after centre feasibility assessment, but any change will be documented before final database lock.

Background

Appendiceal goblet cell adenocarcinoma is a rare malignancy that has historically been reported under heterogeneous terminology, including goblet cell carcinoid and adenocarcinoid. Modern WHO terminology recognises goblet cell adenocarcinoma as an adenocarcinoma-like entity rather than a classical neuroendocrine tumour.

Due to rarity, changing nomenclature and heterogeneous reporting, uncertainty remains regarding diagnosis, staging, treatment pathways, completion surgery, systemic therapy, surveillance and long-term outcomes.

Primary Aim

To describe international real-world treatment pathways and outcomes in patients with appendiceal goblet cell adenocarcinoma.

Secondary Aims

- To describe diagnostic and treatment variation across participating countries and centres.
- To evaluate the pathway from index appendectomy or initial diagnosis to staging, multidisciplinary decision-making and definitive treatment.
- To evaluate the role of initial pathology reporting in subsequent management.
- To describe treatment strategies, including appendectomy, completion right hemicolectomy, systemic therapy and treatment of peritoneal disease.
- To describe ovarian assessment and management in female patients, including recommendations for and pathological yield of bilateral salpingo-oophorectomy.
- To explore whether inclusion of the mesoappendix and regional lymph node tissue during index caecal cuff/pole resection is associated with a different subsequent multidisciplinary recommendation.
- To explore whether age, frailty/comorbidity, WHO grade and the pre-WHO versus post-WHO 2019 terminology era influence the MDT/MOC recommendation for surveillance versus completion right hemicolectomy.
- To quantify the oncological yield of completion right hemicolectomy, particularly how often at least one previously unrecognised positive regional lymph node is identified in clinically non-metastatic patients.
- To describe concordance between relevant guideline or local-policy recommendations, MDT/MOC recommendations and treatment actually received.
- To quantify the yield and management impact of postdiagnosis colonoscopy.
- To describe healthcare utilisation and consequences of additional treatment in localised low-grade GCA.
- To explore whether pragmatic radiologist review or quantitative acute-phase CT texture analysis can distinguish GCA from non-neoplastic appendicitis.
- To explore associations between CT features, WHO pathological grade and other adverse pathological characteristics.
- To describe whether incidental histopathological detection of GCA led to clinically relevant additional staging, surveillance or treatment.
- To assess recurrence patterns and long-term oncological outcomes.
- To evaluate five- and ten-year outcomes where sufficient follow-up is available.
- To support future international collaboration and consensus development for this rare disease.

Study Population

Adult patients with histologically confirmed primary appendiceal goblet cell adenocarcinoma, or historical diagnosis compatible with appendiceal goblet cell adenocarcinoma, treated, discussed or followed at participating centres.

Historical terminology eligible for screening may include goblet cell adenocarcinoma, goblet cell carcinoma, goblet cell carcinoid, adenocarcinoid, adenocarcinoma ex-goblet cell carcinoid, mixed carcinoid-adenocarcinoma and related historical diagnostic labels.

Ambiguous cases will be reviewed through a diagnostic eligibility process involving local pathology input and, where needed, central pathology advice.

Inclusion Criteria

- Age 18 years or older at diagnosis.
- Primary appendiceal goblet cell adenocarcinoma, or historical appendiceal diagnosis compatible with goblet cell adenocarcinoma.
- Diagnosis within the predefined case capture period.
- Patient treated, discussed or followed at a participating centre.
- Availability of basic clinical, pathology, treatment and follow-up information.

Exclusion Criteria

- Non-appendiceal primary tumour.
- Classical well-differentiated appendiceal neuroendocrine tumour without goblet cell adenocarcinoma component.
- Conventional appendiceal adenocarcinoma without goblet cell adenocarcinoma component.
- Appendiceal mucinous neoplasm without invasive goblet cell adenocarcinoma.
- Paediatric patients.
- Cases in which diagnostic compatibility with appendiceal goblet cell adenocarcinoma cannot be confirmed after local or central eligibility review.
- Duplicate records from the same patient; in such cases, records will be merged and counted once.

Patients with a previous or synchronous colorectal adenocarcinoma or other malignancy will not be automatically excluded, but this will be recorded and considered in interpretation.

Participating Centres

Each participating centre should appoint at least a local surgical investigator and a local pathology investigator.

Radiology input is encouraged and may be required for centres participating in imaging-related analyses. Additional collaborators, including medical oncologists, peritoneal malignancy specialists, geneticists, specialist nurses, psychologists, data managers or research coordinators, may be included where locally relevant.

Initial active recruitment will focus on European centres to maintain feasibility and coherent governance during study start-up. Centres outside Europe may participate as part of an international extension cohort, subject to appropriate ethics approval, data-transfer arrangements and adherence to the common dataset. Geographic region and healthcare setting will be recorded and considered in interpretation and subgroup analyses.

Data Collection

Data will be collected retrospectively from medical records, pathology reports, imaging reports, multidisciplinary team records, oncology records and follow-up documentation.

Variables will be divided into:

- **Core variables**, prioritised for all centres.

- **Extended variables**, collected where available and used for predefined subanalyses.

Core domains will include:

- Patient demographics and presentation.
- Diagnostic pathway.
- Initial operation and definitive treatment.
- Pathology diagnosis, staging and key risk features.
- Multidisciplinary decision-making.
- Systemic therapy where applicable.
- Follow-up, recurrence and survival.

Extended domains may include:

- Detailed imaging review.
- Detailed pathology review.
- Tumour marker trajectories.
- Molecular or immunohistochemical data.
- Systemic therapy response.
- Patient-reported experience of the care pathway.

Patient-Reported Experience and Survivorship Subanalysis

A separate consent-based subanalysis may evaluate how patients experience the transition from presumed appendicitis or unexpected appendectomy pathology to a rare cancer diagnosis, additional staging, treatment and long-term survivorship.

This subanalysis will aim to identify informational, emotional and organisational needs, long-term symptoms, recurrence anxiety, decision regret, quality of life and coordination between specialist and primary care.

Additional Feasibility-Dependent Subanalyses

- **Colonoscopy yield:** frequency, completeness, detected polyps, advanced adenomas, synchronous colorectal carcinoma and management-changing findings.
- **Guideline concordance:** comparison of guideline or local-policy recommendations, MDT/MOC advice and treatment received, including reasons for differences.
- **Healthcare utilisation:** additional investigations, consultations, operations, admissions, complications, readmissions and surveillance in localised low-grade GCA.

Pragmatic CT Interpretation Subanalysis

A separate feasibility-driven imaging subanalysis may cross-match eligible preoperative contrast-enhanced CT examinations with radiologists from other participating centres who routinely report acute abdominal CT. Using a short standardised review form and blinded to pathology and outcome, readers will indicate whether they would suspect an underlying appendiceal or caecal neoplasm and whether the findings would have altered the proposed initial management pathway.

The initial analysis will be descriptive and will not assume that radiological suspicion should automatically result in immediate right hemicolectomy. Where feasible, a limited matched control sample of non-neoplastic appendicitis CT examinations will be included to estimate false-positive suspicion.

Outcomes

Main outcomes will include:

- Treatment patterns.
- Completion surgery rates.
- Recurrence patterns.
- Overall survival.
- Disease-free survival.
- Five- and ten-year outcomes where available.

Overall survival will be measured from the date of pathological diagnosis to death from any cause. Disease-free survival will be measured from completion of definitive curative-intent treatment to recurrence or death among patients rendered free of macroscopic disease. MDT/MOC recommendation and treatment actually received will be analysed as separate outcomes.

Additional exploratory outcomes may include associations between pathology features, imaging findings, systemic therapy, tumour markers and oncological outcomes.

An additional exploratory pathway outcome will compare MDT/MOC recommendations after index caecal cuff/pole resection with versus without mesoappendix or regional lymph node tissue in the pathology specimen. Where available, the number of lymph nodes retrieved and whether completion right hemicolectomy, surveillance or no further surgery was recommended will be recorded. This analysis is hypothesis-generating and does not treat mesoappendix excision as equivalent to a formal oncological lymphadenectomy.

The oncological yield of completion right hemicolectomy will be reported using a prespecified denominator of patients who were clinically non-metastatic and had no confirmed regional node-positive disease before completion surgery. Outcomes will include detection of at least one positive regional lymph node, residual tumour, management-changing findings and postoperative morbidity.

Further exploratory pathway analyses will evaluate age, frailty/comorbidity, WHO grade and WHO terminology era as determinants of surveillance versus completion right hemicolectomy. MDT/MOC recommendation and treatment actually received will be analysed separately. The study will also describe the proportion of incidental GCA diagnoses that resulted in a clinically relevant change in staging, surveillance or treatment.

The GCA-GLOBE cohort cannot by itself establish whether routine histopathological examination of all appendectomy specimens is safe or cost-effective, because only diagnosed GCA cases are included. A separate denominator-based companion study of all appendectomies, conceptually modelled on the FANCY selective gallbladder histopathology study, may evaluate unexpected clinically consequential diagnoses, missed lesions under a selective strategy, pathology workload and costs.

Five-year outcomes will be evaluated in patients with at least five years of follow-up, or in patients diagnosed early enough to allow potential five-year follow-up within the available records. Ten-year outcomes will be evaluated analogously where at least ten years of follow-up is available.

Prespecified Subgroups

Prespecified subgroup analyses may include:

- European versus non-European centres and geographic region, where numbers permit.
- Pre-2019 versus post-2019 WHO terminology era.
- Younger versus older patients and patients with versus without documented frailty/comorbidity, using clinically appropriate categories defined before analysis.
- Incidental diagnosis after appendectomy versus suspected tumour before or during surgery.
- Appendectomy alone versus completion right hemicolectomy.

- Appendectomy alone versus appendectomy with caecal cuff/pole resection or limited ileocaecal resection.
- Appendectomy with caecal cuff/pole resection with versus without mesoappendix or regional lymph node tissue in the index specimen.
- Node-negative versus node-positive disease.
- Localised disease versus peritoneal metastatic disease.
- Perforated versus non-perforated cases, where perforation status is reported.
- Lower-grade versus higher-grade disease, where grading is available.
- Patients receiving systemic therapy versus no systemic therapy.
- Patients with sufficient five-year follow-up versus recently diagnosed patients included for prospective follow-up extension.

Subgroup analyses will be considered exploratory and hypothesis-generating. They are not intended for confirmatory inference and may be limited or omitted if case numbers or event numbers are insufficient.

Feasibility and Sample Size

The study is feasibility-driven because appendiceal goblet cell adenocarcinoma is rare. A centre feasibility survey will be performed before full data collection to estimate eligible case numbers, available follow-up and data availability.

A cohort of at least 150 patients is considered the minimum analyzable feasibility threshold. The principal international recruitment target is approximately 300 patients, with a stretch target of 500 or more patients if broad participation across European and non-European networks is achieved. Final targets will be refined after the international centre feasibility assessment.

Statistical Analysis

Descriptive statistics will summarise patient characteristics, pathology features, treatment pathways and outcomes.

Categorical variables will be reported as counts and percentages. Continuous variables will be reported as means with standard deviations or medians with interquartile ranges, depending on distribution.

Group comparisons may use chi-square or Fisher's exact tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables, as appropriate.

Survival outcomes will be analysed using Kaplan-Meier methods and compared using log-rank tests where appropriate.

Where p-values are reported, two-sided tests will be used and a p-value below 0.05 will be considered statistically significant. Given the descriptive and exploratory nature of the study, p-values will be interpreted cautiously and in the context of effect sizes, confidence intervals, missingness and multiple comparisons.

Regression analyses may be performed where event numbers permit. Candidate covariates for outcome modelling may include age, sex, year of diagnosis, incidental versus suspected diagnosis, pT stage, pN stage, grade, perforation status, margin status, lymphatic invasion, venous invasion, perineural invasion, peritoneal disease, surgical strategy and systemic therapy use.

Comparisons involving completion surgery or adjuvant treatment will be interpreted cautiously because of confounding by indication and immortal-time bias. Where feasible, landmark or time-dependent sensitivity analyses and methods accounting for centre-level clustering will be used.

Multivariable modelling will follow an events-per-variable principle. As a default, at least 10 outcome events per candidate variable will be required for standard Cox regression. If event numbers are insufficient, analyses will remain descriptive, univariable or limited to parsimonious models.

Missing data will be reported per variable. No variable with substantial missingness will be used for primary multivariable modelling unless missingness is judged acceptable and clinically interpretable. Complete-case analyses will be the default for

regression models. Multiple imputation may be considered for selected variables in sensitivity analyses if missingness patterns and sample size permit.

The final statistical analysis plan will be completed before database lock and before outcome analyses are performed. Any deviations from this preregistered plan will be documented and reported transparently as protocol amendments or post-hoc analyses.

Governance

The study concept, preregistration and core protocol were initiated by the coordinating investigators.

National delegates and site investigators will be invited to contribute to centre recruitment, local approvals, data collection, interpretation and manuscript development.

Authorship, writing group roles and collaborator recognition will be determined transparently according to contribution, data delivery and participation in analysis and manuscript preparation.

Governance structures may be expanded to include regional or international representatives as participation grows.

The steering group will approve protocol amendments, analysis proposals, writing groups and external data-access requests. Participating centres remain responsible for local approvals and data accuracy. Authorship and collaborator recognition will follow transparent contribution-based principles and applicable journal guidance.

Ethics and Data Protection

This is a non-interventional retrospective observational study. Ethics approval will be sought through the lead coordinating centre, with local approval or confirmation of coverage according to national and institutional requirements.

Data will be collected in coded or pseudonymised form. Each participating centre will retain the local re-identification key. No directly identifiable patient data should be transferred to the coordinating centre.

International data transfers will require appropriate agreements and safeguards according to the laws and institutional requirements applicable to the participating centres.

The patient-reported experience subanalysis will require separate ethics approval and informed consent.

Funding and Conflicts of Interest

No dedicated external funding has yet been secured at protocol synopsis stage. Funding sources and relevant conflicts of interest will be declared in the full protocol and resulting publications.

Registration Note

This short study summary is intended to provide a clear description of protocol version 1.0 for steering group approval, collaborator recruitment and feasibility assessment before data collection.