



Prognostic impact of positive peritoneal cytology (POPEC) in gastric cancer: Multi-centre European retrospective cohort study



Richard Owen^{a,b}, Swathikan Chidambaram^c, Khalid Shamiyah^a, Jessie A Elliott^d, Jakob Hedberg^h, Sivesh Kamarajah^m, Frederik Klevebroⁿ, Marcel Andre Schneider^p, Lana Fourie^q, Christian Gutschow^p, Magnus Nilsson^m, Ewen Griffiths^l, Riccardo Rosati^j, Javed Sultan^{g,r}, Manuel Pera^j, Peter Grimminger^k, Guillaume Piessen^f, Clarisse Eveno^f, Jelle Ruurda^o, Richard van Hillegersberg^o, John V. Reynolds^d, Mark van Berge Henegouwen^{i,s}, Suzanne Gisbertz^{i,s}, Jimmy B.Y. So^e, Nick Maynard^a, Sheraz Markar^{a,*}, on behalf of POPEC study group (Vanessa Peronace^t, Ellen A. Boyle^t, Aileen Pang^u, Candy Yap^u, Daryl Chia^u, Guowei Kim^u, Asim Shabbir^u, Amina Youcef^v, Khalid Bhatti^w, Kammy Keywani^x, Riccardo Calef^y, Eren Uzun^z, Mariagiulia Dal Cero^{aa}, James Halle-Smith^{ab}, Tim Bagnell^{ac}, Lianne Triemstra^{ad}, Matthias Josef^{ae}, Kerstin Neuschütz^{af}, Andrea Cossu^y, John Saunders^w)

^a Department of Surgery, Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, UK

^b The Ludwig Institute for Cancer Research, University of Oxford, Oxford, UK

^c Academic Surgical Unit, Department of Surgery and Cancer, Imperial College London, St Mary's Hospital, London, UK

^d Department of Surgery, Trinity St. James's Cancer Institute, Dublin, Ireland

^e Department of Surgery, National University of Singapore, Singapore

^f Department of Digestive and Oncological Surgery, Claude Huriez University Hospital, Lille, France

^g Greater Manchester oesophago-gastric unit, Northern Care Alliance, Salford Royal NHS Hospital, Salford, UK

^h Department of Surgical Sciences, Disciplinary Domain of Medicine and Pharmacy, Uppsala University, Uppsala, Sweden

ⁱ Department of Surgery, Amsterdam UMC location University of Amsterdam, Amsterdam, the Netherlands

^j Department of Surgery, San Raffaele Scientific Institute, Milan, Italy

^k Department for General, Visceral and Transplant Surgery, University Medicine of the Johannes Gutenberg University Mainz, Germany

^l Section of Gastrointestinal Surgery, Hospital del Mar, Barcelona, Spain

^m Department of Surgery, Birmingham University Hospitals NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, UK

ⁿ Division of Surgery and Oncology, CLINTEC, Karolinska Institutet and Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden

^o Department of Upper Gastrointestinal Surgery, University Medical Center, Utrecht, the Netherlands

^p Stomach and Oesophageal Tumor Centre, Comprehensive Cancer Center, University Hospital Zurich, Zurich, Switzerland

^q Department of Surgery, Clarunis Universitäres Bauchzentrum, Basel

^r Division of Cancer Sciences, School of Medical Sciences, University of Manchester

^s Cancer Treatment and Quality of Life, Cancer Center Amsterdam, Amsterdam, the Netherlands

^t Department of Surgery, Trinity St. James's Cancer Institute, Dublin, Ireland

^u Department of Surgery, National University of Singapore, Singapore

^v Department of Digestive and Oncological Surgery, Claude Huriez University Hospital, Lille, France

^w Greater Manchester oesophago-gastric unit, Northern Care Alliance, Salford Royal NHS Hospital, Salford, UK

^x Department of Surgery, Amsterdam UMC location University of Amsterdam, Amsterdam, the Netherlands

^y Department of Surgery, San Raffaele Scientific Institute, Milan, Italy

^z Department for General, Visceral and Transplant Surgery, University Medicine of the Johannes Gutenberg University Mainz, Germany

^{aa} Section of Gastrointestinal Surgery, Hospital del Mar, Barcelona, Spain

^{ab} Department of Surgery, Birmingham University Hospitals NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, UK

^{ac} Division of Surgery and Oncology, CLINTEC, Karolinska Institutet and Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden

^{ad} Department of Upper Gastrointestinal Surgery, University Medical Center, Utrecht, the Netherlands

^{ae} Stomach and Oesophageal Tumor Centre, Comprehensive Cancer Center, University Hospital Zurich, Zurich, Switzerland

* Correspondence to: Nuffield Department of Surgery, Churchill Hospital, Old Road, Headington, Oxford OX3 7LE.
E-mail address: sheraz.markar@nds.ox.ac.uk (S. Markar).

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ABSTRACT

Objective: Positive peritoneal cytology is traditionally viewed as representative of metastatic disease and a poor prognostic factor. The objective of this multi-center study was to define the prognostic role of peritoneal cytology in curative gastrectomy, evaluate international variation in cytology sampling, and assess the impact on positive peritoneal cytology yields.

Methods: This was a multi-center international retrospective cohort study of 16 tertiary gastric cancer centers. Adult patients who underwent peritoneal lavage cytology at staging laparoscopy and subsequent gastrectomy between 2009 and 2023 were included. The primary outcome measure was overall survival at five years. Multivariable Cox regression provided hazard ratios (HRs) with 95% CIs, adjusted for relevant confounding factors.

Results: 837 patients with no radiological or macroscopic M1 disease were included, with a mean age of 66 (IQR 58–73) and 71% were male. Non-distal gastric cancer was most common (47%), with 59% and 43% of tumors staged pT3/4 and pN2/3, respectively. 66 patients (7.9%) had positive cytology. Positive cytology was not associated with overall survival in multivariable analysis, controlled for stage and neoadjuvant treatment (HR = 1.0; 95%CI 0.51–2.0). Higher T and N stages were associated with positive cytology ($p < 0.001$). The proportion of patients with positive cytology was variable, depending on how many quadrants were sampled.

Conclusion: Positive peritoneal cytology with otherwise M0 disease was not associated with decreased survival after curative intent gastrectomy in this study, meaning prospective study is needed. The technique of performing peritoneal washings influenced cytology yield and thus must be standardized in a much-needed prospective evaluation of peritoneal cytology.

Synopsis: The POPEC multicenter international retrospective cohort study included 837 patients receiving curative gastrectomy. This study showed the technique of performing peritoneal washings influenced cytology yield, however positive peritoneal cytology was not associated with decreased survival. Therefore, positive peritoneal cytology should not be considered an absolute contradiction to curatively intended gastrectomy.

Introduction

The primary curatively-intended therapeutic approach for locally advanced non-metastatic gastric cancer includes surgical resection combined with perioperative oncological therapies.¹ Historically, survival outcomes for gastric cancer have been poor, so that accurate pre-operative staging is crucial to appropriately counsel patients regarding recurrence risk and long-term prognosis. Positive peritoneal cytology (CY+), defined as the identification of tumor cells in peritoneal wash fluid, has been associated with poor prognosis.^{2,3} In particular, CY+ has been shown as a more accurate predictor of peritoneal recurrence and survival than other postoperative pathological variables including tumor serosal invasion or lymph node involvement.^{4,5} Since peritoneal dissemination represents the predominant pattern of metastasis and recurrence in gastric cancer, the TNM classification defines CY+ as M1 disease.⁶ Although CY+ patients are typically considered for palliative interventions, aggressive multimodal strategies have been recently proposed in both the neoadjuvant and adjuvant settings.^{7–11} Isolated reports suggested D2 gastrectomy in conjunction with perioperative chemotherapy as a viable treatment option in CY+ patients without evidence of macroscopic metastatic disease (CY+M0), and improved survival has been reported for patients who convert from positive to negative cytology during neoadjuvant therapy.^{7,12–14}

In a systematic review and pooled analysis of heterogeneous studies, we have previously shown that CY+ patients without macroscopic peritoneal disease had poorer survival than CY- patients, though there was significant statistical heterogeneity in studies.¹³ However, this review did not include more recent oncological therapies and techniques such as catheter-administered intraperitoneal chemotherapy, pressurized intraperitoneal aerosol chemotherapy (PIPAC) or hyperthermic intraperitoneal chemotherapy (HIPEC), and may therefore underestimate the impact of a multimodal therapeutic strategy in this poor-prognosis group.^{14–19} Nevertheless, the role of peritoneal cytology remains controversial, with no international consensus on its use. Whilst the Japanese Gastric Cancer Association, the Society of American Gastroenterologists and Endoscopic Surgeons, and the European Society for Medical Oncology guidelines recommend staging laparoscopy and peritoneal washings for cytology, studies such as EVOCAPE 2 have questioned the value of peritoneal cytology, showing no independent

association with overall survival in multivariable analysis.^{20–23} Moreover, although the National Comprehensive Cancer Network (NCCN) does not overtly integrate peritoneal cytology into the treatment algorithm, they subsequently recognize positive cytology as a criterion against curative resection.²⁴ Furthermore, there is no consensus regarding the methodology by which cytology is obtained, processed, and interpreted.

The present POPEC study is a multi-center international investigation of tertiary gastric cancer centers. Its aim was to establish the prognosis of CY+ at staging laparoscopy in patients undergoing curative gastrectomy and to identify different protocols for peritoneal washings and their influence upon CY+ yield and outcome.

Methods

Data sources

The POPEC study collected retrospective data from 16 tertiary gastric cancer centers based across Asia and Europe. Data from consecutive patients undergoing curative gastrectomy for gastric cancer between 2009 and 2023 in these centers were retrospectively entered into a dedicated RedCap platform. Supplementary file, Table S1 contains details of reporting periods for each center. Centers uploaded data directly onto the platform, and an independent monitoring team audited data capture to minimize missing data, control concordance and ensure data quality. Missing or inconsistent data were retrieved from the referral center whenever possible. Ethical approval was obtained from local institutional review boards or nationally approved audit, and no over-arching study ethical approval was required as no patient-identifiable data was collected or transferred. The necessary materials transfer agreements to enable data transfer were formalized between Imperial College London and the respective centers. This study followed STROBE statement on reporting the necessary items.

Patients' clinical management

Patients underwent curative-intent gastrectomy for gastric cancer following staging CT, staging laparoscopy, and assessment of peritoneal cytology. Perioperative approach and neoadjuvant treatment decisions

were made by the clinical teams in the involved centers following local policies. Resection margins were determined by pathological assessment of resected specimens alone, irrespective of cytology findings. Indeterminate cytology results were reclassified as CY- for subsequent analysis as per Japanese gastric cancer treatment guidelines.²⁰

Inclusion and exclusion criteria

This cohort study included all adult patients who had staging CT, staging laparoscopy and peritoneal cytology performed, and then underwent curative-intent surgery for gastric cancer (Fig. 1). Data were collected for all patients operated on between the 7th of May 2009 and the 15th of February 2023. Patients who did not have curative-intent surgery, or did not have peritoneal cytology assessed, were excluded.

Data collection

The POPEC database contained specific details about patient demographics, including age, sex, body mass index, and the American Society of Anesthesiologists (ASA) class. Tumor-level characteristics including pathologic TNM staging, histology, and location were also collected. The ‘y’ prefix has been excluded from TNM annotation as not all patients had neoadjuvant treatment. Details of local staging were recorded, including imaging (computed tomography and positron emission tomography) and endoscopy. Operative data such as surgical technique and approach as well as data on oncological therapies (including agents, dose, regime, and duration) were also collected. Details of peritoneal cytology techniques including number and location of quadrants where peritoneal washings were performed were also collated on a per patient basis.

Exposure

The exposure under investigation was positive cytology at initial staging laparoscopy in patients with no other visible metastatic disease (CY + M0) who then received multi-modality treatment including surgical resection.

Covariates

Confounding variables in multivariable statistical models included age (continuous), sex, pathologic T stage (0, 1, 2, 3, or 4), pathologic N stage (0, 1, 2, or 3), and resection margin (R0, R1 or R2).

Outcomes

The primary outcome evaluated included overall survival (OS) at a maximum follow up from staging laparoscopy of five years. Secondary outcomes included disease recurrence at 1, 3, and 5 years from staging laparoscopy, based on radiological or pathological findings. Other outcomes were the regions of the abdomen washed for peritoneal cytology, and the number of quadrants washed.

Statistical analysis

Statistical analysis was performed using R (version 4.3.2).²⁵ Continuous variables were expressed as median and interquartile range (IQR), and categorical variables as number and percentage. Categorical variables were compared using either Fisher’s exact or χ^2 test. Non-parametric continuous data were analyzed using the Wilcoxon rank-sum test. Median survival is given with 95 % confidence intervals (CIs). Five-year overall survival (OS) is visualized with Kaplan-Meier curves and survival compared using the log-rank test. Multivariable survival analysis was performed with Cox proportional hazard models with pathological staging and neoadjuvant therapy as additional measurement variables, deriving hazard ratios (HRs) as effect-size measures with 95 % confidence intervals (CIs). Statistical significance was set at p value < 0.05 for all analyses. Multiple imputation with Random Forest was used in cases of missing data, excepting recurrence data due to large amounts of missing data (proportions of missing data per variable are provided in Supplementary File, Table S2).

Results

Demographics and study population

A total of 919 patients who underwent surgical resection after peritoneal cytology evaluation were included in the study. M1 disease

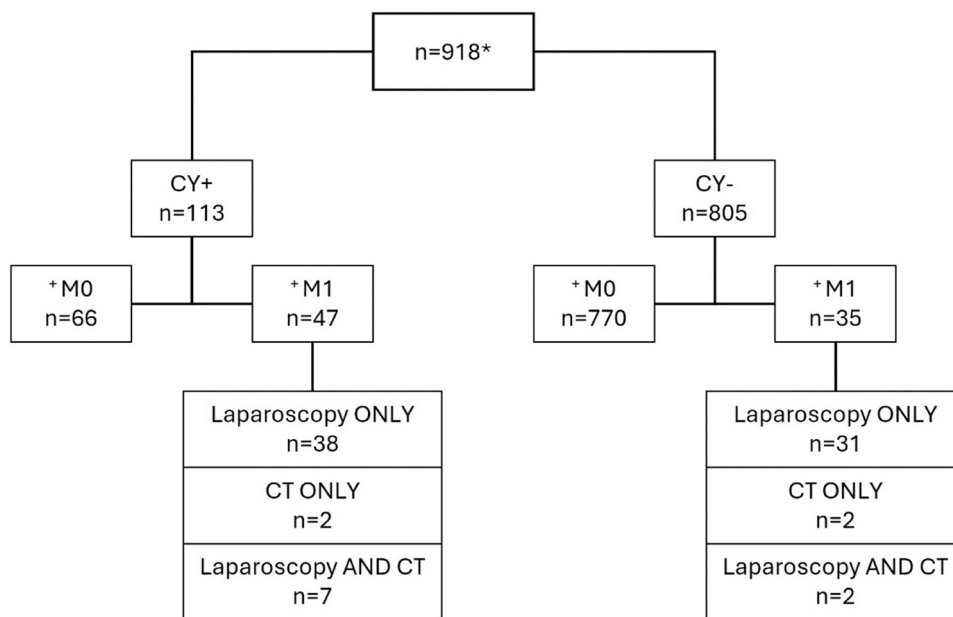


Fig. 1. Flow chart summarizing patient numbers and staging outcomes. *Patients staged with CT, laparoscopy, and peritoneal cytology undergoing curative-intent gastrectomy between 7th May 2009 and 15th Feb 2023. +M stage determined by laparoscopy and CT, irrespective of cytology status.

was identified by laparoscopy or CT in 82 patients who were excluded from subsequent analysis (Fig. 1). In CY+M0 and CY-M0 patients, median follow up was 26.1 months (IQR 13.6–43.8). Main demographic, operative, oncological, and pathological characteristics are provided in Table 1, with additional details provided in Supplementary file, Table S3. The median age of the cohort was 66 (IQR 58–73), 71 % were male, mean BMI was 25.0 (IQR 22.4–28.0), and the majority were ASA 2 and 3 (54 % and 31 %, respectively). Non-distal gastric cancer was most common (47 %), with 59 % and 43 % of tumors stage pT3/4 and pN2/3, respectively. Overall, 6.1 % of patients had an R1 resection. There were 66 CY+ patients (7.9 %), 738 (88 %) cytology negative (CY-) patients, and 33 (3.9 %) cytology results were indeterminate. Most patients underwent neoadjuvant chemotherapy (82 %), while 7 (0.8 %) underwent HIPEC, 1 (0.1 %) had PIPAC, and 8 (1.0 %) received immunotherapy.

Impact of peritoneal cytology

Median survival was 37 months (CI = 25.4 to NA) in CY+ patients and not reached (CI = NA to NA) in CY- patients. Overall, CY+ trended to a worse OS (p = 0.06) (Fig. 2 A). CY+ patients were younger (64 vs 66, p = 0.016) and more likely to be male (91 % vs 70 %, p < 0.001) (Table 1 and Supplementary file, Table S3). Moreover, CY+ was associated with higher pT stage (CY+ pT3/4 = 81.2 % vs. CY- pT3/4 = 57.3 %, p < 0.001), higher pN stage (CY+ pN2/3 = 75.8 % vs. CY- pN2/3 = 40.7 %, p < 0.001), and more had neoadjuvant therapy (CY+ = 98.5 % vs. CY- = 81.3 %, p < 0.001). In multivariable analysis including T stage, N stage, and neoadjuvant therapy, there was no longer a survival difference between CY+ and CY- patients (HR 1.06, CI = 0.61–1.8) (Fig. 2B). Recurrence rates were higher in CY+ patients than in CY- patients at one year (50 % vs 27 %, p < 0.001), but when more advanced diseased patients were compared, this was no longer significant (T3 + N2 + only, 65 % vs 57 %, p = 0.3, Supplementary file, Table S4).

In 66 CY+ patients, (19.5 %) had repeat cytology performed and progressed to resection. Of the patients that had repeat cytology, most converted to CY- (91 %), and those that did not (n = 2) survived for 27 and 9 months, respectively.

Variations in peritoneal cytology techniques

The median number of quadrants washed was 3 (IQR 2–4), however there were significant differences within the cohort, with the majority

having 2 or 4 quadrants washed (Supplementary figure S2A). There was also a wide variation in the locations in which peritoneal lavage was performed, with most patients having subhepatic and subphrenic regions washed (87 % and 87 %, respectively), and fewer patients having bursa or pelvic washings taken (33 % and 41 %) (Supplementary file, Figure S2B).

There was high variability of the incidence of CY+ dependent on the number of quadrants washed, though no clear trend (Fig. 3 A), and an association between number of quadrants washed and OS (p < 0.001, Fig. 3B).

Discussion

The POPEC study evaluated the use of peritoneal cytology in patients with gastric cancer across 16 international gastric cancer centers. CY+ on staging laparoscopy had a trend towards worse OS in patients with otherwise M0 disease, but once adjusted for similar pathological stage and neoadjuvant therapy no association between cytology status and OS was seen. The study also showed substantial variation in cytological sampling techniques, with an influence on CY+ yield and an association between different techniques and overall survival. Finally, pathological variables such as T and N status displayed a strong association with CY+.

The POPEC study highlights a significant variation in the methodology of intraoperative peritoneal cytology and washings. Currently this study highlights that there is a lack of consensus agreement on how cytology should be carried out, with minimal guidance on the procedural technique as well as its post-procedural handling, storage, analysis, interpretation, and reproducibility between observers.²⁶ In the present study, the number of quadrants sampled seemed to influence the frequency of CY+ identification, suggesting that it could represent a modifiable factor amenable to standardization, as has recently been proposed in a national Delphi consensus.²⁷ There is also uncertainty regarding how cytology results are contextualized in a patient’s journey to guide their treatment. For example, CY+M0 patients rarely underwent repeated sampling, hence excluding cytology status as a criterion for surgery in the present series. More broadly, this study was unable to quantify the added benefit of cytological assessment after oncological therapies. Indeed, the participating institutions did not routinely repeat cytology to identify changes after neoadjuvant therapies. Moreover, patients with CY+ at post-treatment reassessment may not have proceeded to gastrectomy, being excluded from the present analyses. Overall, the widespread differences in the modalities of cytological

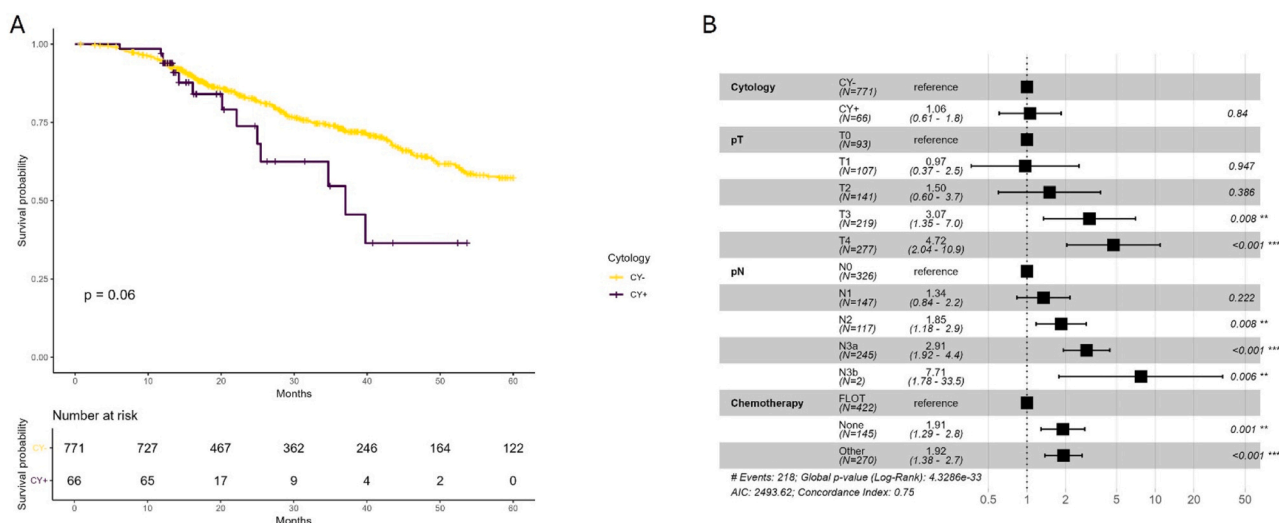


Fig. 2. (A) Kaplan-Meier curves showing overall survival of patients treated in POPEC with positive (CY+) or negative (CY-) cytology. P value provided is from the log-rank test. (B) Forest plot showing effect of cytology on survival, controlled for additional staging and neoadjuvant treatment measurement variables.

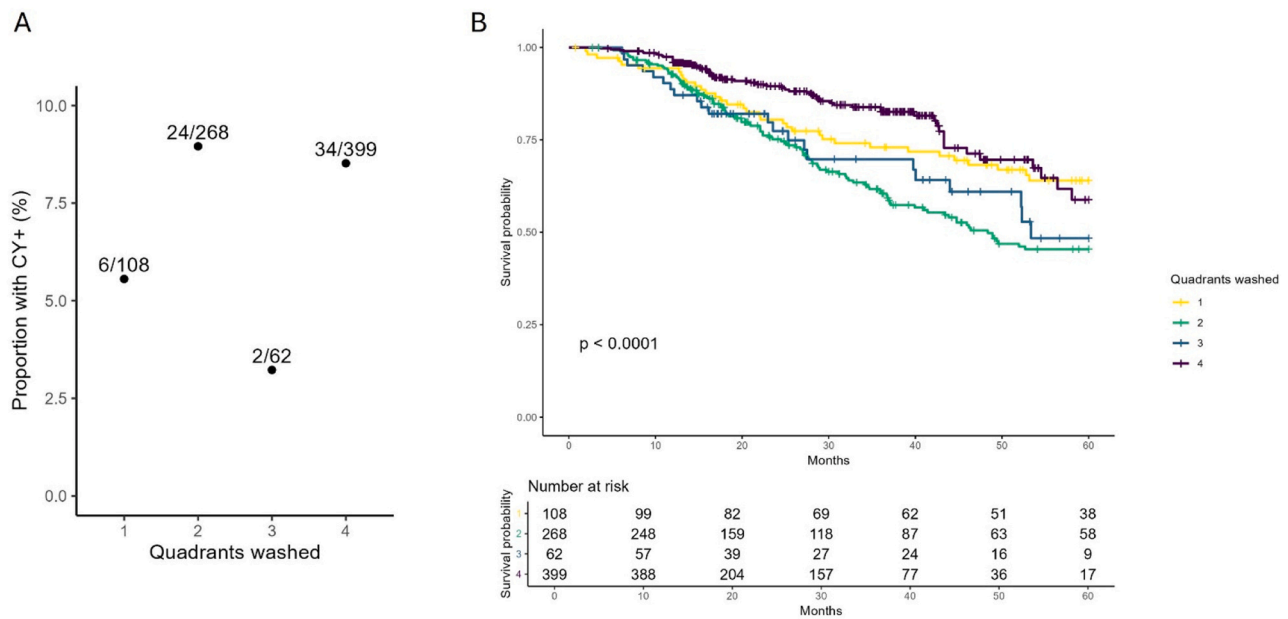


Fig. 3. (A) Plot showing the proportion as a percentage of patients with positive cytology separated by the number of quadrants washed in peritoneal lavage, annotated with absolute proportions. (B) Kaplan-Meier curves showing the overall survival of patients separated by how many quadrants were washed as part of peritoneal cytology assessment. P value provided is from the log-rank test between all strata.

assessment identified in the present study underline the need for standardization of this practice.

The POPEC study has shown that in CY+ otherwise M0 patients treated with neoadjuvant chemotherapy, surgery remains a valid option with a reasonable prognosis, at least in selected cases CY+ is considered a marker of microscopic disease and represents a poor prognostic factor of recurrence and survival.²⁷ In CY+ patients, treatment options can also include HIPEC and neoadjuvant therapy followed by resection if repeat washings are CY-.^{28,29} In POPEC, peritoneal treatments were rarely used, and typically these patients would have peritoneal disease and therefore not qualify for curative-intent resection, thus were excluded from POPEC. Based on our results, we propose that in cases of otherwise M0 disease that is technically amenable to resection, curative surgery may be considered in patients with CY+ , following careful patient counseling and multidisciplinary team discussion. Repeating cytology to assess positive-to-negative conversion may aid in the decision-making process. However, no sufficient evidence on this topic could be derived from the present study, since repeated cytological assessment was carried out in only a minority of the patients. Our results, combined with the recent significant advances in peritoneal treatment modalities, advocate for a more nuanced approach to the diagnosis and management of metastatic disease.

The POPEC study has important limitations. First, this is a retrospective study susceptible to potential selection bias. Second, there was a significant proportion of missing information requiring imputation to resolve. A significant proportion of patients had cytology status as indeterminate, and there was no available information on how this was subsequently investigated or resolved. Third, patients who did not proceed to gastrectomy due to positive cytology at initial staging or disease progression were not captured in the present analyses. Therefore, the performance of peritoneal cytology as a prognostic marker, as compared to other staging modalities, will be affected by a lack of true positives who did not then proceed to gastrectomy. Comparing POPEC results with patients from the same period that did not proceed to gastrectomy would have given additional context and avoided enrichment of a well-performing group of CY+ patients, but survival data was not routinely collected in most centers making this comparison problematic. A further source of bias was the different use of neoadjuvant therapy in the groups. Moreover, it was not possible to

accurately elucidate the impact of PIPAC and HIPEC on cytology status, though several recent and currently recruiting trials may be able to address this more directly.^{9,30} Previous work by Lorenzen et al. highlighted that conversion from positive to negative following chemotherapy conferred a better prognosis, and we would have liked to confirm this in our dataset with more updated chemotherapy regimens.³¹ Finally, most participating centers are from Europe, so that our results may not be generalizable to other continents with a different approach to peritoneal cytology. Looking forward, these limitations could be overcome through a prospective clinical trial with a wider geographical representation and incorporating emerging staging techniques such as circulating tumor DNA measurements.

Conclusion

This retrospective study on patients with gastric cancer from 16 centers worldwide showed that CY+ on staging laparoscopy was not associated with OS in selected patients with otherwise M0 disease, who received multimodality therapy including curative-intent gastrectomy. Moreover, wide variations in the methodology of intraoperative peritoneal cytology were identified, impacting CY+ yield, so that the lack of a standardized methodology potentially carries severe implications for treatment planning.

Funding statement

None

Ethics statement

Ethical approval was obtained from local institutional review boards or nationally approved audit, and no over-arching study ethical approval was required as no patient-identifiable data was collected or transferred. The necessary materials transfer agreements to enable data transfer were formalized between Imperial College London and the respective centers. This study followed STROBE statement on reporting the necessary items.

Declaration of Competing Interest

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.soi.2025.100145](https://doi.org/10.1016/j.soi.2025.100145).

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