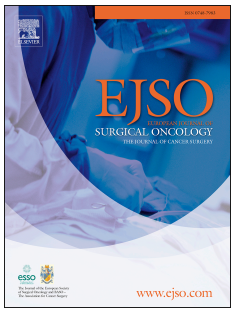

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Contribution	**Author(s)**
Study concepts:	MDM, BI, LM, MD
Study design:	MDM, BI, LM, MD
Data acquisition:	All authors
Quality control of data and algorithms:	All authors
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"All the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *EJSO*".

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Title

Adequate lymphadenectomy and adjuvant capecitabine warrant survival benefit in gallbladder cancer

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Abstract

Background

Significant heterogeneity exists in the management of resectable gallbladder cancer (GBC), regarding the extent of lymphadenectomy and the role of adjuvant chemotherapy (aCTx). This study investigates outcomes of resected GBC according to contemporary surgical oncology principles.

Methods

The international database of the GBC Study Group was queried for patients with resected GBC between 2012–2022. Patients with ≥6 lymph nodes resected and aCTx were compared to those with inadequate lymphadenectomy or inadequate aCTX. Unadjusted and adjusted Cox regression models were employed to assess oncological outcomes.

Results

Out of 656 patients, 300 patients (45.7%) had ≥6 lymph nodes resected, 240 (36.5%) received any aCTx 323 and 118 (17.9%) received capecitabine aCTx. Patients with adequate lymphadenectomy exhibited prolonged disease-free survival (DFS) (HR 0.69, p=0.004 CI 95% 0.55–0.89) and overall survival (OS) (HR 0.68, p=0.002 CI 95% 0.54–0.87) in pN0 but not in pN+ cases. Patients receiving adjuvant capecitabine demonstrated prolonged DFS (HR 1.48, p< 0.001 95%CI 1.20–1.83) and OS followed a similar pattern (HR 1.67, p< 0.001, 95%CI 1.34–2.09). In the multivariable analysis, underlying hepatic disease (HR 2.75, p=0.001, 95%CI 1.49–5.07), adequate lymphadenectomy (HR 0.67, p=0.020, 95%CI 0.48–0.94), T stage (HR 2.14, p< 0.001, 95%CI 1.60–2.86), R status (HR 1.88, p=0.008, 95%CI 1.18–3.00), and capecitabine aCTx (HR 1.27, p=0.039 95%CI 1.01–1.61) were identified as predictors of OS.

Despite presenting with more aggressive disease, patients with adequate lymphadenectomy and aCTx with capecitabine presented prolonged OS (15 vs 7.5 months, HR 0.53, p=0.038, 95%CI 0.29–0.96) compared to those without lymphadenectomy or aCTx.

Conclusions

A significant proportion of patients still did not receive adequate lymphadenectomy and aCTx. Patients treated according to contemporary surgical oncology principles presented a survival benefit. These principles should be further evaluated considering the aggressiveness of GBC.

Manuscript

Introduction

Gallbladder cancer (GBC) is the fifth most common cancer of the digestive system, accounting for 165,000 cancer deaths annually worldwide (1.7% of all global cancer deaths) (1, 2). It is associated with poor oncological outcomes due to its insidious onset, aggressive biology and chemoresistance (2, 3). For GBC T1a, according to the Eighth American Joint Committee on Cancer (AJCC) Staging Manual, cholecystectomy alone is the standard procedure, with recurrences rarely observed (4). For GBC T1b and beyond, cholecystectomy, liver resection, and lymphadenectomy, with or without biliary resection and reconstruction, are recommended (2, 3). Additionally, patients are candidates for adjuvant chemotherapy (aCTx). However, significant heterogeneity exists in the management of GBC, particularly regarding the extent and prognostic value of lymphadenectomy (5-7) and the regimen and outcomes of aCTx (8, 9).

Clinical guidelines define appropriate lymphadenectomy as the resection of at least six lymph nodes at the level of the hepatic hilum or level 12 (2, 3). However, when lymphadenectomy is limited to the hepatic hilum, it can occur in clinical practice that the minimum required number of six lymph nodes is not found in the pathological specimen. Thus, significant heterogeneity exists on the real extent of lymph node resection beyond the hepatic hilum, even among high-volume surgical centres. Additionally, it remains controversial whether lymphadenectomy should be routinely performed for every patient with GBC and what its real prognostic value is.

Similarly, there is a paucity of data on the outcomes of different aCTx regimens for patients with resected GBC (8, 9). High-quality data on the clinical benefit of specific chemotherapy

regimens for these patients is lacking. Most published clinical trials include heterogeneous patient groups, often combining those with GBC and other biliary tract cancers (BTC) (10-13). Currently, the BILCAP trial is the only clinical study assessing the role of aCTx and demonstrating the clinical benefit of a worldwide available drug such as capecitabine for patients with resected BTC (14).The ASCOT trial also demonstrated a survival benefit with adjuvant S-1 in Asian patients with resected biliary tract cancer (15); however, that drug is not yet approved in many western countries for the treatment of GBC. Furthermore, no experimental studies have been published evaluating the benefit of aCTx for resected GBC according to AJCC stage pT/N (16, 17).

Given the lack of high-quality evidence on this issue, this study aims to investigate the outcomes of resected GBC in accordance with contemporary surgical oncology principles, including appropriate lymphadenectomy and the administration of adequate aCTx.

Methods

Study design

This was a retrospective, international, observational study assessing the clinical outcomes of patients with GBC, which included subjects from 37 centres. The study was conducted under the principles of the Declaration of Helsinki and was developed and presented according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (18). The study was registered on ClinicalTrials.gov with the identifier code NCT06061744. An invitation to collaborate was sent via the Clinical Robotic Surgery Association (CRSA) and subsequently extended to other international centres.

Setting and participants

Patients submitted to surgical resection with a diagnosis of GBC between January 2012 and December 2022 were considered for inclusion. Data were collected in an anonymised database.

The dataset included consecutive patients older than 18 years of age with histologically proven GBC in any of the participating centres and submitted to surgical resection with curative intention. Inclusion criteria were: American Society of Anaesthesiologists (ASA)

score below 4, confirmed pathological stage pT1b to pT4. Exclusion criteria were R2 positive resection margins (indicating macroscopic tumour remaining at the end of resection), metastatic disease at the time of surgery and operation with palliative intent. Each centre followed local surgical and post-operative clinical protocols. Similarly, treatment for recurrences (e.g., systemic chemo or palliative care) was prescribed following local clinical protocols.

Institutional and ethical approval was obtained from the research project coordinating (Ethical Committee approval number: 2023/10969) (19). Included centres were mostly tertiary referral HPB centres with centralisation program, however there were no strict inclusion / exclusion criteria for participating centers. An approximate resection volumes and catchment populations is in a Supplementary Table 1.

Variable of interest and outcomes

For each patient, demographic and clinical variables were collected. Demographic data and baseline characteristics included age (in years), gender and the preoperative anaesthetic risk, which was evaluated using the ASA score (20) and data on patients' comorbidity.

The occurrences of post-operative complications were recorded according to the Clavien–Dindo classification. Severe complications were defined as above a grade IIIA (21). Bile leak was defined according to the International Study Group of Liver Surgery (ISGLS) classification (22). Liver wedge resection was defined as taking a margin of the liver at the gallbladder bed. Anatomical and non-anatomical resections were defined according to the Tokyo 2020 terminology of liver anatomy and resections (23). Perioperative mortality was defined as occurring in-hospital, during admission. Resected specimens were evaluated for size, stage, invasiveness and margins by experienced pathologists, following local or national protocols. Staging was based on the eighth edition of the AJCC (2018) for GBC (4). R0 resection margin was defined as when margins showed no microscopic disease. The long-term outcomes, including overall survival (OS) and disease-free survival (DFS), were measured in months. Patients were followed until death, cancer recurrence or for a maximum of 60 months. In cases of loss to follow-up, patients were censored at the last date of contact.

The primary endpoints of the study were short- and long-term oncological outcomes as assessed by OS and DFS. These were analysed in relation to the completion of an appropriate lymphadenectomy, defined as the resection of a minimum of six lymph nodes, and the administration of aCTx, including specific chemotherapy regimens.

Statistical analysis

Baseline characteristics of the study population were expressed as absolute numbers and relative frequency measurements for qualitative variables, whereas mean and standard deviation (SD) or the median and interquartile range (IQR) were used for the quantitative variables. The differences between the qualitative variables of the groups were determined using the X^2 or Fisher's exact test as appropriate. The two groups' quantitative variables were compared using the Student's *t*-test for parametric quantitative variables and the Wilcoxon signed-rank test for non-parametric quantitative variables. Survival data were calculated using the Kaplan–Meier method, and survival differences between groups were assessed using the log-rank test. Multivariable Cox regression models were employed to assess the influence of lymphadenectomy and administration of aCTx on OS and DFS. Adjustments were made in accordance with established clinical predictors associated with deteriorated clinical outcomes. The strength of association between a risk factor identified in multivariable analyses for mortality and complications was determined by calculating the hazard ratio (HR) with 95% confidence intervals (95%CI). A *P* value <0.05 (two-tailed) was considered statistically significant. All the statistical analyses were performed using Stata version 16.0 (StataCorp) (24).

Results

Baseline characteristics

A total of 656 patients underwent liver resection with or without bile duct resection and lymphadenectomy at 37 centres during the study period. The median patient age was 69 years, and there was a slight predominance of female patients (60.1%).

Short- and long-term outcomes

A total of 73 patients (11.1%) presented complications greater than grade II Clavien–Dindo, 67 (10.2%) developed a post-operative bile leak and 14 patients (2.1%) experienced postoperative in-hospital mortality. Histopathological examination revealed that 248 patients (37.8%) were classified as pN0.

The median DFS was 10 months (3–25 months), and the median OS was 13 months (5–28 months), with 1-, 3- and 5-year survival rates being 77%, 53% and 45%, respectively **(Fig. 1**)

Data on harvested lymph nodes and adjuvant chemotherapy received

Adequate lymphadenectomy, defined as the resection of ≥ 6 lymph nodes, was achieved in 300 patients (45.7%). A total of 162 patients (24.9%) had 3–5 lymph nodes harvested, while 194 patients (29.9%) had fewer than 3 lymph nodes harvested. Among them, 87 patients (13.2%) had no lymph nodes harvested.

The utilisation of aCTx varied notably among patients: a majority 333 (58.1%) did not receive any aCTx, 118 patients (20.5%) received capecitabine-based aCTx, 113 (19.7%) received gemcitabine-based aCTx and 9 (1.5%) received other regimens. While the rate of patients not receiving aCTx remained relatively stable over the years, there was a progressive increase in the rate of patients receiving adjuvant capecitabine-based aCTx ($p < 0.001$) (**Fig. 2**). Details on aCTx type used are shown in Supplementary Table 2.

Short- and long-term outcomes according to the extent of lymphadenectomy

Age, gender distribution and baseline characteristics did not show significant differences across lymphadenectomy groups. Patients with adequate lymphadenectomy (≥ 6 nodes) were more frequently treated using minimally invasive approaches and had longer operative times ($p < 0.001$) **(Table 1)**. Importantly, no significant differences in perioperative outcomes were noted, including complications greater than grade II Clavien–Dindo, bile leaks, wound infections, haemorrhage and mortality.

The adequate lymphadenectomy group had more advanced pN tumour stages ($p < 0.001$) and a higher rate of perineural invasion ($p = 0.006$) but showed fewer R1 resections ($p = 0.037$) and more frequent aCTx use ($p < 0.001$).

In the survival analysis, despite patients with adequate lymphadenectomy presenting more distant recurrences (p = 0.036), they showed increased DFS (HR 0.69, p = 0.004, 95%CI 0.55–0.89) and OS (HR 0.68, p = 0.002 CI 95% 0.54–0.87) in pN0 cases, though the benefit was not significant in pN1 cases (**Fig. 3**).

Short- and long-term outcomes according to the adjuvant chemotherapy received

Patients receiving capecitabine were younger than those receiving no aCTx or other regimens (p < 0.001), and they presented a higher rate of preoperative nodal involvement (p = 0.013) and preoperative biliary drainage (p < 0.001). Operative time and estimated blood loss were significantly greater in patients receiving capecitabine compared to those receiving no aCTx (p = 0.029 and p = 0.004, respectively). Consistently, the capecitabine group presented advanced tumour stages (pT3–T4) and more aggressive features, including higher pN1 status (p < 0.001), lymphatic invasion (p < 0.001) and perineural invasion (p < 0.001). Finally, recurrence rates were highest in the capecitabine group (p < 0.001), reflecting a more advanced disease profile in these patients (**Table 2**).

However, in the survival analysis, the capecitabine groups presented increased DFS (HR 1.48, p < 0.001, 95%CI 1.20–1.83) and OS (HR 1.67, p < 0.001, 95%CI 1.34–2.09) in comparison to both no aCTx (HR 1.95, p = 0.007, 95%CI 1.20–3.17) and other CTx regimens (HR 2.99, p < 0.001, 95%CI 1.82–4.90) (**Fig. 4**).

Adjusted analysis of predictors of long-term oncological outcomes

Multivariable analysis identified several significant predictors of reduced OS, including underlying hepatic disease (HR 2.75, p = 0.001, 95%CI 1.49–5.07), advanced T stage (HR 2.14, p < 0.001, 95%CI 1.60–2.86), R1 resection status (HR 1.88, p = 0.008, 95%CI 1.18–3.00), adequate lymphadenectomy (HR 0.67, p = 0.020, 95%CI 0.48–0.94) and the lack of capecitabine aCTx (HR 1.27, p = 0.039, 95%CI 1.01–1.61) (**Table 3**). These findings suggest that both clinical and pathological factors play a critical role in survival outcomes, reinforcing the importance of adequate lymphadenectomy and adjuvant capecitabine in improving the OS of patients with resected GBC.

Short- and long-term outcomes in accordance with contemporary surgical oncology principles

Patients who either received no chemotherapy or had fewer than 6 lymph nodes harvested (n = 212) were compared to those treated with capecitabine and had ≥ 6 lymph nodes harvested (n = 66). The latter underwent minimally invasive surgery more often ($p < 0.001$) and had longer operative times (306 vs 240 minutes, $p < 0.001$) (**Table 4**).

They showed more advanced disease, with higher rates of pN1 stage (48.5% vs 30.8%, p = 0.009), lymphatic invasion (45.5% vs 30.3%, p = 0.023) and perineural invasion (40.9% vs 24.4%, p = 0.009). Additionally, distant recurrence was more common in this group (27.9% vs 15.7%, p = 0.031), reflecting the higher-risk pathology.

Despite these more advanced oncological features, in the survival analysis the capecitabine and ≥ 6 lymph nodes group, presented prolonged and OS (15 vs 7.5 months, HR 0.53, p = 0.038, 95%CI 0.29–0.96) (**Fig. 5**).

Discussion

This study evaluated the impact of contemporary surgical oncology principles, particularly the extent of lymphadenectomy and aCTX, on survival outcomes in patients with resected GBC. The findings highlight that both adequate lymphadenectomy and the use of capecitabine-based aCTX are associated with improved long-term oncological outcomes. These results emphasise the importance of adherence to contemporary surgical oncology principles to enhance patient outcomes.

While controversies still exist regarding the extent, both in terms of number and location, of standard lymphadenectomy in patients with GBC, current guidelines consistently recommend the resection of at least six lymph nodes in patients with GBC(2, 3). The present international multicentre collaborative study showed that 29.9% of patients had fewer than three lymph nodes harvested and 13.2% had no lymph nodes harvested, indicating that 43.1% of patients had inadequate lymph node retrieval. While these findings might be surprising, current literature has already highlighted this significant gap between clinical guidelines and real-life clinical practice (25, 26).

The present series confirmed the potential prognostic value of lymph node resection in staging and disease control, which was particularly pronounced in pN0 cases, while in pN1 patients,

the survival advantage was less evident. Due to the lack of detailed data on the anatomical location of harvested lymph nodes, the study did not attempt to define an alternative minimum node count. Future research should consider whether lymph nodes were retrieved exclusively from the hepatic hilum (station 12), the retropancreatic area (station 13), or other anatomical stations. Nevertheless, the current findings support previous evidence demonstrating a survival benefit from adequate lymphadenectomy as defined by international guidelines(27). Additionally, they align with existing literature, where the prognostic role of lymphadenectomy is evident also in node-negative gallbladder and biliary tract cancers (28-31). What remains unaddressed is the prognostic role of lymph node resection in patients with GBC according to cancer-related prognostic indicators, such as tumour location, stage, and molecular characteristics, in relation to the extent and location of resected lymph nodes (7, 32, 33). Recent studies exploring the role of markers such as indocyanine green in assessing potential lymph node drainage in gastrointestinal tumours have the potential to provide insightful evidence to fill this gap (34, 35). Besides, in the present study, the adjusted Cox regression analysis revealed that some other factors, including hepatic liver disease, bile duct resection, pT and radicality of resection, impacted the OS, albeit adequate lymphadenectomy was confirmed to be protective.

The role of aCTx after GBC resection has been evaluated in several retrospective series (36-38) and RCTs (10-13), but there is limited evidence of its survival benefit. Currently, the BILCAP trial is the only clinical study assessing the role of aCTx and demonstrating the clinical benefit of adjuvant capecitabine for patients with resected BTC (14); recent clinical guidelines have endorsed its findings (2, 3, 39). Interestingly, the present series demonstrated a significant temporal trend in the increased administration of capecitabine in patients with resected GBC following the dissemination of the BILCAP trial findings (14). The study also identified the administration of adjuvant capecitabine as a significant independent predictor of improved long-term oncological outcomes. Notably, capecitabine appeared to confer more benefits in comparison to no aCTx regardless of more aggressive tumour characteristics, including higher rates of pN1 stage, lymphatic invasion and perineural invasion. Patients receiving capecitabine also demonstrated better survival outcomes compared to those who receive other regimens. While retrospectively observed, this finding supports the routine use of capecitabine postoperatively in GBC. On the other hand, no firm conclusions can be drawn

about other chemotherapy regimens due to confounding factors. Patients who received non-capecitabine aCTx typically had more advanced disease, which may have contributed to the limited observed benefit in that subgroup. The ASCOT trial also demonstrated survival benefit with adjuvant S-1 in Asian patients with resected BTC (15). However, that drug is not yet approved in many western countries for the treatment of GBC and none of the patients included in the present dataset was treated with S1. For this reason, a subgroup analysis could not be performed.

Patients receiving both adequate lymphadenectomy and aCTx, especially capecitabine as adjuvant drug demonstrated better outcomes compared to those who received inadequate lymphadenectomy or no aCTx, despite the former presenting with more aggressive disease. While these findings highlight the benefits of current surgical oncology principles, they also emphasise the significant number of patients who did not receive adequate lymphadenectomy or aCTx. These data, corroborated by recent studies addressing this issue (40, 41), demonstrate the need for increased adherence to clinical guidelines and suggest that standardised approaches could help address disparities in GBC outcomes. Adequate lymphadenectomy and aCTx should be recognised as a critical component of curative-intent treatment for resected GBC. Implementing protocols that ensure comprehensive lymph node resection and routine aCTx administration may contribute to more consistent and favourable results across different institutions (7, 42).

Limitations of this study include the lack of data on the specific reasons certain patients did not receive adequate lymphadenectomy or aCTx as well as precise data on the use of chemotherapy (e.g., toxicity, adverse events). Also, its retrospective design may have introduced selection bias and limited control over confounding variables. Although ASA scores were available, the absence of more granular data, such as comorbidity indices or frailty scores, prevented a more refined analysis of long-term outcomes in well-matched patient cohorts. Additionally, the SARS-CoV-2 pandemic may have influenced treatment selection and completion rates during the study period. Also, while the study spanned multiple centres and countries, variations in surgical expertise, pathology practices and patient populations may have introduced variability in the outcomes. Yet, while this study supports the use of

adjuvant systemic therapy, in particular adjuvant capecitabine, no data on the precise duration of aCTx or adverse events or toxicity associated with aCTx were available.

Further prospective, controlled studies are warranted to confirm these findings and determine optimal strategies for lymphadenectomy and aCTx in patients with GBC. Ongoing trials such OPT-INOPT-IN ECOG-ACRIN EA2197 Trial (NCT04559139) will be crucial in addressing these issues (43). Future studies should also explore the role of therapies tailored to the aggressiveness of the disease.

In conclusion, a significant proportion of patients still did not receive adequate lymphadenectomy and capecitabine aCTx. Adherence to contemporary surgical oncology principles was associated with improved survival in resectable GBC. These results advocate for the standardisation of such practices across treatment centres to maximise patient outcomes. Further evaluation of these principles is warranted, particularly in the context of the aggressiveness of GBC.

Declarations of interest: none.

Table 1: Comparison of patients' characteristics and outcomes based on the extent of lymphadenectomy.
Table 2: Comparison of patients' characteristics and outcomes based on the adjuvant chemotherapy received.
Table 3: Adjusted analysis of predictors of long-term oncological outcomes.
Table 4: Comparison of patients' characteristics and outcomes in accordance with contemporary surgical oncology principles.

Figure 1: Temporal trend in the administration of adjuvant chemotherapy regimens.
Figure 2: Overall survival (OS) (Fig. A) and disease-free survival (DFS) (Fig. B) of patients with resected gallbladder cancer according to the extent of lymphadenectomy. Figures C and D present a subgroup analysis of N0 patients with resected gallbladder cancer.

Figure 3: Overall survival (OS) (Fig. A) and disease-free survival (DFS) (Fig. B) of patients with resected gallbladder cancer according to the adjuvant chemotherapy received.

Figure 4: Overall survival (OS) (Fig. A) and disease-free survival (DFS) (Fig. B) of patients with resected gallbladder cancer in accordance with contemporary surgical oncology principles.

Supplementary Figure 1: Overall survival (OS) (Fig. A) and disease-free survival (DFS) (Fig. B) of patients with resected gallbladder cancer included in the present cohort.

Other Supplementary Figures: Survival analysis as detailed in figures

Supplementary Table 1: Reported annual volume of liver resections and the number of patients with resected gallbladder cancer included per participating centre.

Supplementary Table 2: Chemotherapy regimens used, and median number of cycles administered.

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Table 1: Comparison of patients' characteristics and outcomes according to according to the extent of lymphadenectomy.

		Three-group comparison: ≥6 vs 3–5 vs 0–2 LN resected				Two-group comparison: ≥6 vs <6 LN resected	
		≥6 LN resected	3-5 LN resected	0-2 LN resected	p-value*	≥ 6 LN resected	p-value#
		N=300	N=162	N=194		N=356	
Patient age (median, IQR)		69 (62-75)	70 (62-75)	68 (61-77)	0.85	69 (61-76)	0.69
Gender (female) (n, %)		179 (63.3%)	100 (62.5%)	108 (56.8%)	0.34	208 (59.4%)	0.33
ASA score (I and II vs III) (n, %)		114 (39.0%)	57 (37.0%)	73 (38.0%)	0.91	130 (37.6%)	0.7
Clinical history of cardiovascular disease (n, %)		167 (55.9%)	84 (51.9%)	106 (54.6%)	0.71	190 (53.4%)	0.53
Clinical history of chronic pulmonary disease (n, %)		38 (12.7%)	18 (11.1%)	22 (11.3%)	0.84	40 (11.2%)	0.56
Clinical history of chronic kidney disease (n, %)		19 (6.4%)	8 (4.9%)	11 (5.7%)	0.82	19 (5.3%)	0.58
Clinical history of chronic liver disease (n, %)		17 (5.7%)	9 (5.6%)	11 (5.7%)	1	20 (5.6%)	0.97
Clinical history of diabetes (n, %)		64 (21.4%)	33 (20.4%)	44 (22.7%)	0.87	77 (21.6%)	0.94
Gallbladder cancer diagnosed after cholecystectomy (n, %)		137 (54.2%)	84 (54.2%)	85 (48.9%)	0.5	169 (51.4%)	0.51
Preoperative nodal involvement (n, %)		**81 (27.4%)**	**29 (18.4%)**	**30 (15.8%)**	**0.005**	**59 (17.0%)**	**0.001**
Preoperative biliary drainage (n, %)		32 (10.8%)	14 (8.7%)	26 (13.4%)	0.37	40 (11.3%)	0.85
Surgical approach (n, %)	**Open**	**145 (48.3%)**	**97 (59.9%)**	**92 (47.4%)**	**<0.001**	**189 (53.1%)**	**<0.001**
	Laparoscopic	**73 (24.3%)**	**40 (24.7%)**	**78 (40.2%)**		**118 (33.1%)**	
	Robotic	**82 (27.3%)**	**25 (15.4%)**	**24 (12.4%)**		**49 (13.8%)**	
Bile duct resection (n, %)		42 (21.6%)	26 (16.0%)	42 (21.6%)	0.4	68 (19.1%)	0.76
Operative time (minutes) (median, IQR)		**269.5 (203-360)**	**280 (210-360)**	**207.5 (150-285)**	**<0.001**	**240 (180-325)**	**<0.001**
Estimated blood loss (mL) (median, IQR)		**150 (50-300)**	**200 (100-400)**	**150 (50-200)**	**0.029**	**150 (50-300)**	**0.56**
Vascular resection (n, %)		15 (5.3%)	7 (4.4%)	2 (1.1%)	0.055	9 (2.6%)	0.078
Complication > grade II Clavien-Dindo (n, %)		39 (13.0%)	17 (10.5%)	17 (8.8%)	0.33	34 (9.6%)	0.16
Bile leak (n, %)		31 (10.3%)	16 (9.9%)	20 (10.3%)	0.99	36 (10.1%)	0.93
Wound infection (n, %)		10 (3.3%)	4 (2.5%)	5 (2.6%)	0.82	9 (2.5%)	0.54
Postoperative haemorrhage grade BC (n, %)		7 (2.3%)	0 (0.0%)	3 (1.5%)	0.15	3 (0.8%)	0.12
Postoperative mortality (n, %)		4 (1.3%)	2 (1.2%)	8 (4.1%)	0.073	10 (2.8%)	0.19
Reintervention (n, %)		15 (5.0%)	8 (4.9%)	5 (2.6%)	0.38	13 (3.7%)	0.39
ICU admission (n, %)		107 (35.7%)	53 (32.7%)	53 (27.3%)	0.15	106 (29.8%)	0.11
Length of stay (days)		6 (4-10)	6 (5-10)	6 (4-10)	0.81	6 (4-10)	0.69
Readmission (n, %)		37 (12.3%)	17 (10.5%)	22 (11.3%)	0.83	39 (11.0%)	0.58
Adjuvant therapy administered (n, %)		**149 (50.0%)**	**73 (45.1%)**	**65 (33.5%)**	**0.001**	**138 (38.8%)**	**0.004**
pT Stage (n, %)	**pT1b**	**5 (1.7%)**	**8 (5.3%)**	**13 (7.0%)**	**0.066**	**21 (6.2%)**	**0.042**
	pT2	**160 (54.2%)**	**73 (48.0%)**	**104 (55.6%)**		**177 (52.2%)**	
	pT3	**111 (37.6%)**	**60 (39.5%)**	**62 (33.2%)**		**122 (36.0%)**	
	pT4	**19 (6.4%)**	**11 (7.2%)**	**8 (4.3%)**		**19 (5.6%)**	
pN1 stage (n, %)		**139 (46.6%)**	**61 (39.9%)**	**48 (26.2%)**	**<0.001**	**109 (32.4%)**	**<0.001**
Lymphatic invasion (n, %)		126 (42.4%)	56 (35.4%)	70 (36.6%)	0.25	126 (36.1%)	0.10
Perineural invasion (n, %)		**116 (39.2%)**	**54 (34.2%)**	**48 (25.1%)**	**0.006**	**102 (29.2%)**	**0.008**
R1 status (n, %)		**24 (8.1%)**	**23 (14.6%)**	**28 (14.7%)**	**0.037**	**51 (14.3%)**	**0.15**
Recurrence (n, %)		115 (38.9%)	52 (32.5%)	62 (32.0%)	0.21	114 (32.2%)	0.077
Local recurrence (n, %)		58 (19.6%)	31 (19.4%)	42 (21.6%)	0.82	73 (20.6%)	0.75
Distant recurrence (n, %)		**84 (30.0%)**	**33 (21.2%)**	**39 (20.9%)**	**0.036**	**72 (21.0%)**	**0.010**
DFS (months) (median, IQR)		12 (4-24)	12 (4-32)	7 (2-23)	0.79	10 (3-27)	0.47
OS (months) (median, IQR)		14 (6-27)	15 (6-34)	11 (3-25)	0.88	13 (4-29)	0.74

LN: Lymph Nodes; ASA: American Association of Anaesthesiologist; DFS: Disease Free Survival; OS: Overall Survival; SD: Standard Deviation; IQR: Interquartile Range.

* Evaluates statistical differences across three groups based on the number of lymph nodes resected (≥6 vs 3–5 vs 0–2).

Evaluates statistical differences between patients with adequate (≥6) vs inadequate (<6) lymphadenectomy

In bold: p values ≤0.05

Table 2: Comparison of patients' characteristics and outcomes according to the to the adjuvant chemotherapy received.

		Three-group comparison by aCTx: no aCTx vs capecitabine vs other aCTx				Two-group comparison: no-aCTx vs any aCTx	
		No-aCTx	Capecitabine	Other aCTx	p-value*	Any aCTx	p-value#
		N=333	N=118	N=122		N=240	
Patient age (median, IQR)		**70 (62-77)**	**70 (61-75)**	**65 (58-72)**	**<0.001**	**68 (60-73)**	**<0.001**
Gender (female) (n, %)		204 (61.3%)	67 (58.8%)	74 (61.2%)	0.89	141 (60.0%)	0.76
ASA score (I and II vs III) (n, %)		126 (39.0%)	51 (43.2%)	37 (32.2%)	0.21	88 (37.8%)	0.77
Clinical history of cardiovascular disease (n, %)		185 (55.6%)	67 (56.8%)	63 (52.1%)	0.74	130 (54.4%)	0.78
Clinical history of chronic pulmonary disease (n, %)		43 (12.9%)	11 (9.3%)	13 (10.7%)	0.54	24 (10.0%)	0.29
Clinical history of chronic kidney disease (n, %)		23 (6.9%)	4 (3.4%)	4 (3.3%)	0.18	8 (3.3%)	0.064
Clinical history of chronic liver disease (n, %)		22 (6.6%)	5 (4.2%)	4 (3.3%)	0.32	9 (3.8%)	0.14
Clinical history of diabetes (n, %)		70 (21.0%)	33 (28.0%)	28 (23.1%)	0.3	8 (3.3%)	0.21
Gallbladder cancer diagnosed after cholecystectomy (n, %)		167 (54.4%)	57 (50.4%)	57 (49.1%)	0.56	61 (25.5%)	0.29
Preoperative nodal involvement (n, %)		**60 (18.0%)**	**19 (16.7%)**	**35 (29.9%)**	**0.013**	**54 (23.4%)**	**0.12**
Preoperative biliary drainage (n, %)		**32 (9.6%)**	**8 (6.8%)**	**25 (20.8%)**	**<0.001**	**33 (13.9%)**	**0.11**
Surgical approach (n, %)	Open	166 (49.8%)	54 (45.8%)	71 (58.2%)		125 (52.1%)	
	Laparoscopic	100 (30.0%)	36 (30.5%)	34 (27.9%)	0.27	70 (29.2%)	0.86
	Robotic	67 (20.1%)	28 (23.7%)	17 (13.9%)		45 (18.8%)	
Bile duct resection (n, %)		73 (21.9%)	20 (16.9%)	26 (21.3%)	0.51	46 (19.2%)	0.42
Operative time (minutes) (median, IQR)		**240 (180-330)**	**270 (204-385)**	**270 (193-375)**	**0.029**	**270 (198-380)**	**0.009**
Estimated blood loss (mL) (median, IQR)		**150 (50-250)**	**200 (50-300)**	**200 (100-400)**	**0.004**	**200 (100-300)**	**0.001**
Vascular resection (n, %)		12 (3.6%)	4 (3.6%)	6 (5.0%)	0.78	10 (4.3%)	0.65
Complication > grade II Clavien-Dindo (n, %)		39 (11.7%)	8 (6.8%)	10 (8.2%)	0.24	18 (7.5%)	0.097
Bile leak (n, %)		39 (11.7%)	7 (5.9%)	11 (9.0%)	0.18	18 (7.5%)	0.097
Wound infection (n, %)		14 (4.2%)	2 (1.7%)	2 (1.6%)	0.23	4 (1.7%)	0.085
Postoperative haemorrhage grade BC (n, %)		2 (0.6%)	1 (0.8%)	1 (0.8%)	0.95	2 (0.8%)	0.74
Postoperative mortality (n, %)		**13 (3.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0.008**	**0 (0.0%)**	**0.002**
Reintervention (n, %)		**17 (5.1%)**	**1 (0.8%)**	**1 (0.8%)**	**0.019**	**2 (0.8%)**	**0.005**
ICU admission (n, %)		109 (32.7%)	25 (21.2%)	38 (31.1%)	0.06	63 (26.2%)	0.095
Length of stay (days)		**6 (5-10)**	**6 (4-9)**	**7 (5-11)**	**0.038**	**6 (4-10)**	**0.75**
Readmission (n, %)		38 (11.4%)	8 (6.8%)	16 (13.1%)	0.25	24 (10.0%)	0.59
pT Stage (n, %)	**pT1b**	**12 (3.8%)**	**6 (5.2%)**	**3 (2.5%)**	**<0.001**	**9 (3.8%)**	**<0.001**
	pT2	**195 (61.5%)**	**64 (55.7%)**	**34 (28.3%)**		**98 (41.7%)**	
	pT3	**92 (29.0%)**	**42 (36.5%)**	**72 (60.0%)**		**114 (48.5%)**	
	pT4	**18 (5.7%)**	**3 (2.6%)**	**11 (9.2%)**		**14 (6.0%)**	
pN1 stage (n, %)		**102 (32.4%)**	**47 (40.2%)**	**71 (59.2%)**	**<0.001**	**118 (49.8%)**	**<0.001**
Lymphatic invasion (n, %)		**98 (30.0%)**	**51 (44.3%)**	**67 (55.4%)**	**<0.001**	**118 (50.0%)**	**<0.001**
Perineural invasion (n, %)		**73 (22.3%)**	**49 (42.6%)**	**57 (47.9%)**	**<0.001**	**106 (45.3%)**	**<0.001**
R1 status (n, %)		32 (9.8%)	14 (12.3%)	20 (16.7%)	0.13	44 (18.3%)	0.22
Recurrence (n, %)		**80 (24.0%)**	**42 (35.6%)**	**78 (64.5%)**	**<0.001**	**120 (50.2%)**	**<0.001**
Local recurrence (n, %)		**46 (13.8%)**	**26 (22.0%)**	**44 (36.4%)**	**<0.001**	**70 (29.3%)**	**<0.001**
Distant recurrence (n, %)		**51 (15.4%)**	**28 (25.5%)**	**55 (46.6%)**	**<0.001**	**83 (36.4%)**	**<0.001**
DFS (months) (median, IQR)		**6 (2-24)**	**14 (6.5-28)**	**13 (5-21)**	**<0.001**	**13 (6-26)**	**<0.001**
OS (months) (median, IQR)		**9 (2-27)**	**19.5 (10-30)**	**18 (9-30.5)**	**<0.001**	**18.5 (9-30)**	**<0.001**

aCTx: Adjuvant Chemotheraphy; ASA: American Association of Anaesthesiologist; DFS: Disease Free Survival; OS: Overall Survival; SD: Standard Deviation; IQR: Interquartile Range.

* Evaluates statistical differences across three patient groups based on the adjuvant chemotherapy received: none, capecitabine-based, or other regimens.

Evaluates statistical differences between patients who received any adjuvant chemotherapy (aCTx) and those who did not.

In bold: p values ≤0.05

Table 3: Long-term oncological outcomes' predictors, adjusted analysis

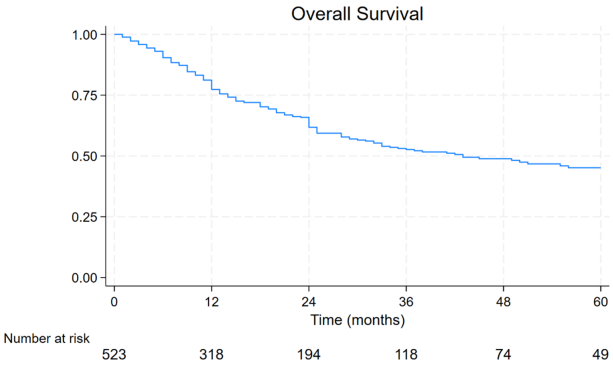
	Data	HR	P value	[95% conf. interval]	
Age (median, IQR)	69 (62-80)	1.011	0.149	0.996	1.027
Gender (female) (n, %)	387 (58.9)	0.988	0.943	0.706	1.382
Hepatic disease (n, %)	**37 (5.6)**	**2.757**	**0.001**	**1.498**	**5.076**
Surgical approach (minimally invasive) (n, %)	322 (49.1)	0.838	0.125	0.669	1.050
Bile duct resection (n, %)	**128 (19.5)**	**1.458**	**0.048**	**1.004**	**2.117**
pT (pT3/4) (n, %)	**271 (41.3)**	**2.142**	**<0.001**	**1.600**	**2.867**
pN (n, %)	248 (37.8)	1.257	0.246	0.854	1.852
Lymphatic invasion (n, %)	252 (38.4)	0.974	0.896	0.660	1.438
Perineural invasion (n, %)	218 (33.2)	1.091	0.646	0.753	1.581
R1 status (n, %)	**75 (11.4)**	**1.882**	**0.008**	**1.180**	**3.004**
Adequate lymphadenectomy (n, %)	**300 (45.7)**	**0.672**	**0.020**	**0.480**	**0.940**
Adjuvant chemotherapy (n, %)	**240 (36.5)**	**1.279**	**0.039**	**1.012**	**1.615**

In bold: p values ≤0.05

Table 4: Comparison of patients' characteristics and outcomes in accordance with contemporary surgical oncology principles

		No-aCTx or <6 LN resected	Capecitabine & ≥ 6 LN resected	p-value
		N=212	N=66	N=122
Patient age (median, IQR)		70 (61.-77)	70.5 (62-76)	0.83
Gender (female) (n, %)		124 (58.5%)	36 (56.3%)	0.75
ASA score (I and II vs III) (n, %)		78 (38.0%)	32 (48.5%)	0.13
Clinical history of cardiovascular disease (n, %)		112 (52.8%)	39 (59.1%)	0.37
Clinical history of chronic pulmonary disease (n, %)		26 (12.3%)	9 (13.6%)	0.77
Clinical history of chronic kidney disease (n, %)		13 (6.1%)	3 (4.5%)	0.63
Clinical history of chronic liver disease (n, %)		15 (7.1%)	4 (6.1%)	0.78
Clinical history of diabetes (n, %)		44 (20.8%)	21 (31.8%)	0.064
Gallbladder cancer diagnosed after cholecystectomy (n, %)		101 (51.8%)	32 (51.6%)	0.98
Preoperative nodal involvement (n, %)		35 (16.5%)	13 (20.0%)	0.52
Preoperative biliary drainage (n, %)		21 (9.9%)	5 (7.7%)	0.59
Surgical approach (n, %)	**Open**	**103 (48.6%)**	**23 (34.8%)**	
	Laparoscopic	**79 (37.3%)**	**19 (28.8%)**	**<0.001**
	Robotic	**30 (14.2%)**	**24 (36.4%)**	
Bile duct resection (n, %)		46 (21.7%)	10 (15.2%)	0.25
Operative time (minutes) (median, IQR)		**240 (163-314.5)**	**306 (220-427)**	**<0.001**
Estimated blood loss (mL) (median, IQR)		150 (50-300)	200 (50-350)	0.091
Vascular resection (n, %)		5 (2.4%)	3 (4.9%)	0.3
Complication > grade II Clavien-Dindo (n, %)		23 (10.8%)	3 (4.5%)	0.12
Bile leak (n, %)		25 (11.8%)	4 (6.1%)	0.18
Wound infection (n, %)		8 (3.8%)	1 (1.5%)	0.37
Postoperative haemorrhage grade BC (n, %)		1 (0.5%)	0 (0.0%)	0.58
Postoperative mortality (n, %)		10 (4.7%)	0 (0.0%)	0.072
Reintervention (n, %)		11 (5.2%)	0 (0.0%)	0.059
ICU admission (n, %)		68 (32.1%)	13 (19.7%)	0.053
Length of stay (days)		6 (4-11.5)	6 (4-9)	0.26
Readmission (n, %)		26 (12.3%)	6 (9.1%)	0.48
Adjuvant therapy administered (n, %)		19 (9.0%)	63 (95.5%)	<0.001
pT Stage (n, %)	pT1b	11 (5.5%)	3 (4.5%)	0.59
	pT2	117 (58.8%)	35 (53.0%)	
	pT3	58 (29.1%)	25 (37.9%)	
	pT4	13 (6.5%)	3 (4.5%)	
pN1 stage (n, %)		**60 (30.8%)**	**32 (48.5%)**	**0.009**
Lymphatic invasion (n, %)		**63 (30.3%)**	**30 (45.5%)**	**0.023**
Perineural invasion (n, %)		**51 (24.4%)**	**27 (40.9%)**	**0.009**
R1 status (n, %)		25 (12.0%)	5 (7.7%)	0.34
Recurrence (n, %)		54 (25.5%)	25 (37.9%)	0.051
Local recurrence (n, %)		33 (15.6%)	14 (21.2%)	0.29
Distant recurrence (n, %)		**33 (15.7%)**	**17 (27.9%)**	**0.031**
DFS (months) (median, IQR)		5 (1-22.5)	11.5 (6-26)	0.43
OS (months) (median, IQR)		**7.5 (2-24)**	**15 (8-27)**	**0.038**

aCTx: Adjuvant Chemotheraphy; ASA: American Association of Anaesthesiologist; DFS: Disease Free Survival; OS: Overall Survival; SD: Standard Deviation; IQR: Interquartile Range.
In bold: p values ≤0.05



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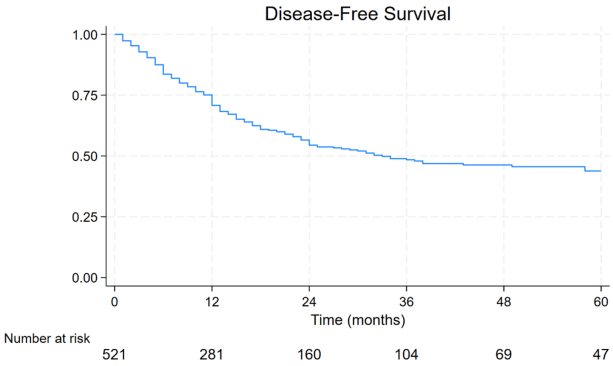

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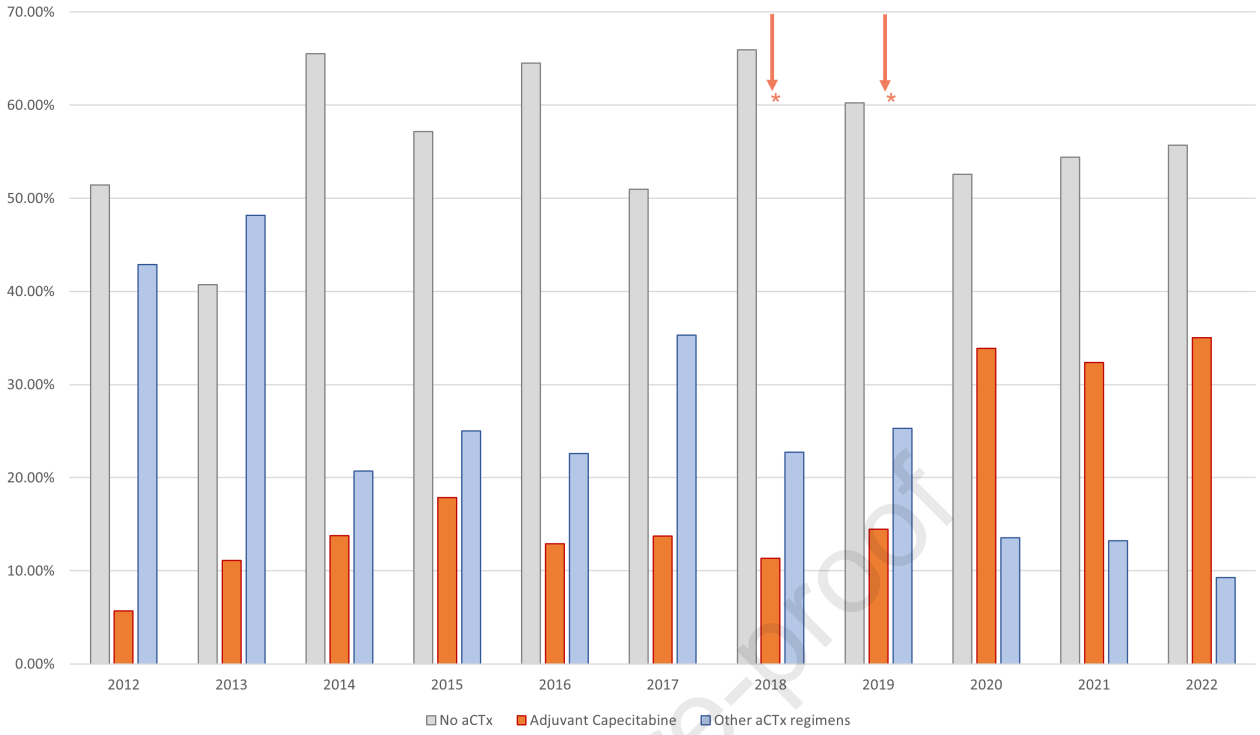

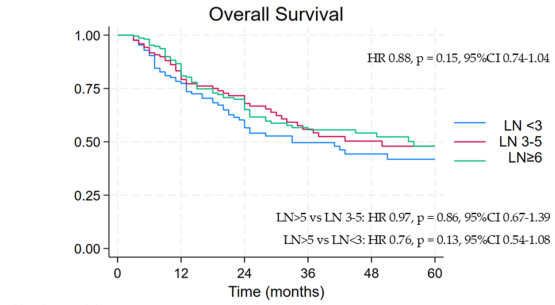

Number at risk

LN <3	131	84	49	32	21	14
LN 3-5	124	83	59	33	21	17
LN≥6	221	151	86	53	32	18

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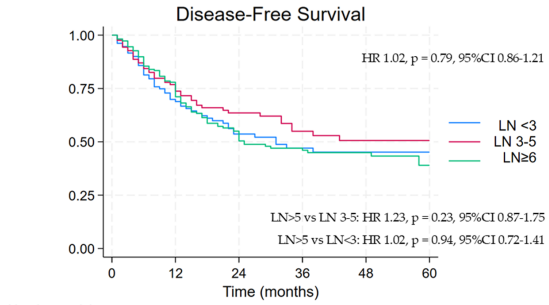

Number at risk

LN <3	131	69	41	27	19	13
LN 3-5	124	75	47	28	20	17
LN≥6	221	137	72	49	30	17

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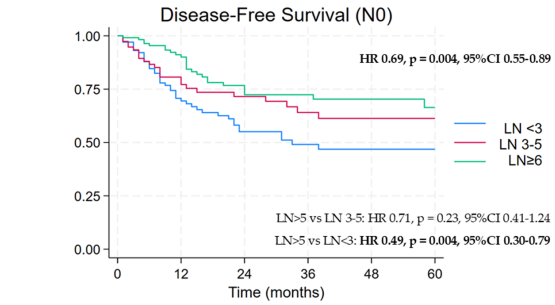

Number at risk

LN <3	102	57	36	24	17	13
LN 3-5	76	46	33	23	18	15
LN≥6	115	82	53	40	25	16

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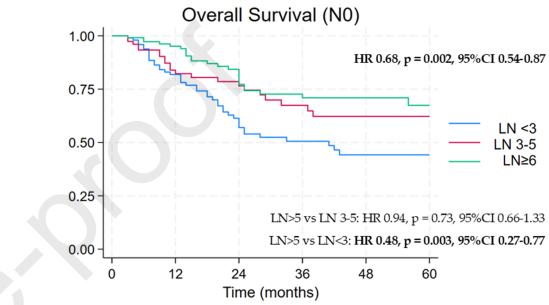

Number at risk

LN <3	102	69	42	27	18	14
LN 3-5	76	50	39	26	18	15
LN≥6	115	87	60	42	26	17

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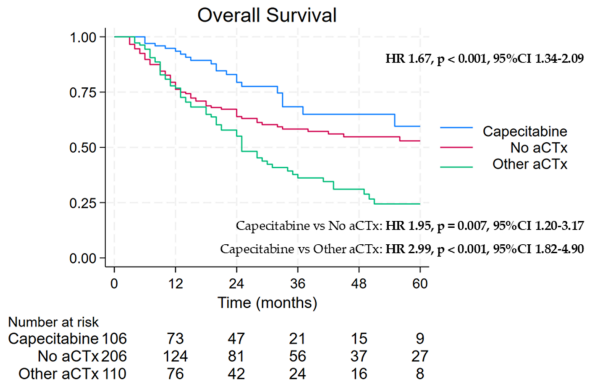

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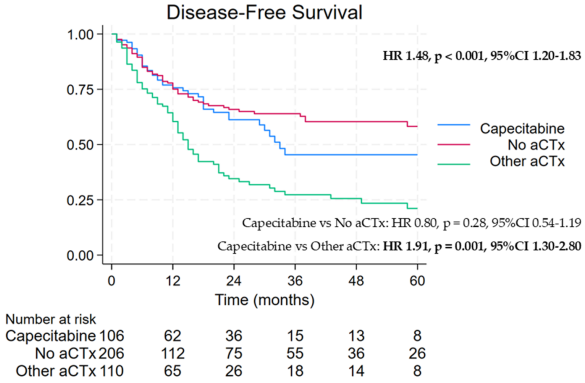

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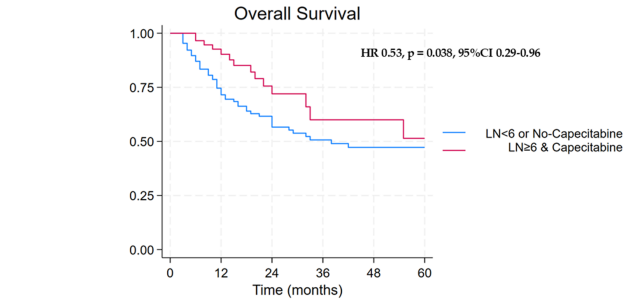

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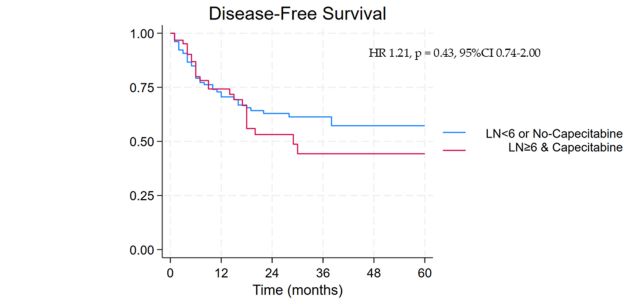

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Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: