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Effect of chemotherapy and tumor clearance in hepatic resections for colorectal liver metastases. A single-centre cohort study.

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ABSTRACT

Background: Colorectal cancer (CRC) is the third most prevalent cancer and accounts for the second leading cause of cancer-related deaths. Up to 50% of CRC patients develop synchronous (10–20%) or metachronous liver deposits (20–30%). Hepatic resection is the gold standard and only curative treatment for colorectal liver metastases (CRLM). While excision significantly improves survival outcomes, more than 50% of patients experience recurrence after primary hepatic resection and usually, within the first 24 months after surgery.

Objective: To determine rates and patterns of recurrence following liver resections for CRLM at The Queen Elizabeth Hospital (Adelaide, Australia), and concurrently, characterise clinical, pathological, and treatment-related factors that could function as predictors of recurrence or survival, particularly neoadjuvant chemotherapy, and tumour clearance.

Methods: Retrospective analysis of a prospectively collected database of 170 patients between 2004 and 2020, who underwent liver resections for CRLM at The Queen Elizabeth Hospital.

Results: The prevalence of recurrence following liver resection for CRLM was 53.5% (84/157), with recurrence most likely to occur during the first 12 months post-surgery (median 209 days). Neoadjuvant chemotherapy was associated with a higher recurrence (X2 = 10.587, p-value = 0.001) rate in the univariate and multivariate analysis while resection margins greater than 1 mm showed to decrease the recurrence rate (X2 3.898, p = 0.047). Recurrence was significantly associated with a decreased overall survival (HR 2.58 [1.73; 3.85], p < 0.001), while neoadjuvant chemotherapy showed a negative non-significant marginal effect.

Conclusion: Despite the development of innovative diagnostic and therapeutic techniques for CRC and CRLM, the recurrence incidence remains high, and survival low. The role and impact of neoadjuvant chemotherapy and resection margins should continue to be reviewed to improve therapeutic outcomes for CRLM.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide. It accounts for the second highest overall cancer-related mortality rates, second only to lung neoplasms [1]. In Australia, the incidence of CRC was only surpassed in prevalence by breast and prostate cancer in 2018. In 2018, 17,000 new cases were diagnosed and 4129 related deaths were reported [2].

Despite recent advances in surgical techniques and multimodal treatments, more than 50% of patients experience recurrence after liver resection, with most recurrences occurring less than 24 months after procedure [3,4]. Colorectal liver metastases (CRLM) can be identified either at diagnosis (synchronous: 10–20%), or later (metachronous: 20–30%) [5]. Currently, liver resection is the gold standard treatment for CRLM with 5-year survival rates of up to 67%. For patients who do not undergo resection, survival rates are as low as 5% [6].

Many factors have been identified as predictors of CRLM recurrence, including TNM stage, chemotherapy, serum levels of Carcinoembryonic Antigen (CEA) and the number of metastases [7]. Proposed additional predictors include embryonic origin, CD 133 overexpression and

Abbreviations: CRC, Colorectal cancer; CRLM, Colorectal liver metastases.

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Table 1
Analysed variables.

Category	Variable	Unit
Demographic:	Age	Years
	Gender	Female/Male
Primary tumour:	Embryonic origin	Midgut, Hindgut, Rectum.
	TNM	
	Treatment (date and procedure)	
Preoperative evaluation:	CT findings	–
	CEA	ng/mL
	Synchronous/ Metachronous	–
	Time to CRLM	months
	Chemotherapy or Radiotherapy	Yes/No
	Performance status	Karnofsky
	ASA	American Society of Anaesthesiologists
Surgery:	Date	–
	Procedure	–
	Portal Embolization	Yes/No
	Intraoperative ultrasound	Yes/No
	Number of metastases	–
	Segments resected	1–8
	Blood loss and transfusions	ml
	Complications	Dindo-Clavien
	Length of stay	Days
Pathology:	Size of metastases	Larger diameter (mm)
	Liver mass resected	gr
	Differentiation	–
	Resection margins	mm
Local recurrence:	Date and time to recurrence	
	Localization	
	Number of metastases	
	Treatment	
	Re-recurrences	

Table 1. Analysed variables and their respective units.

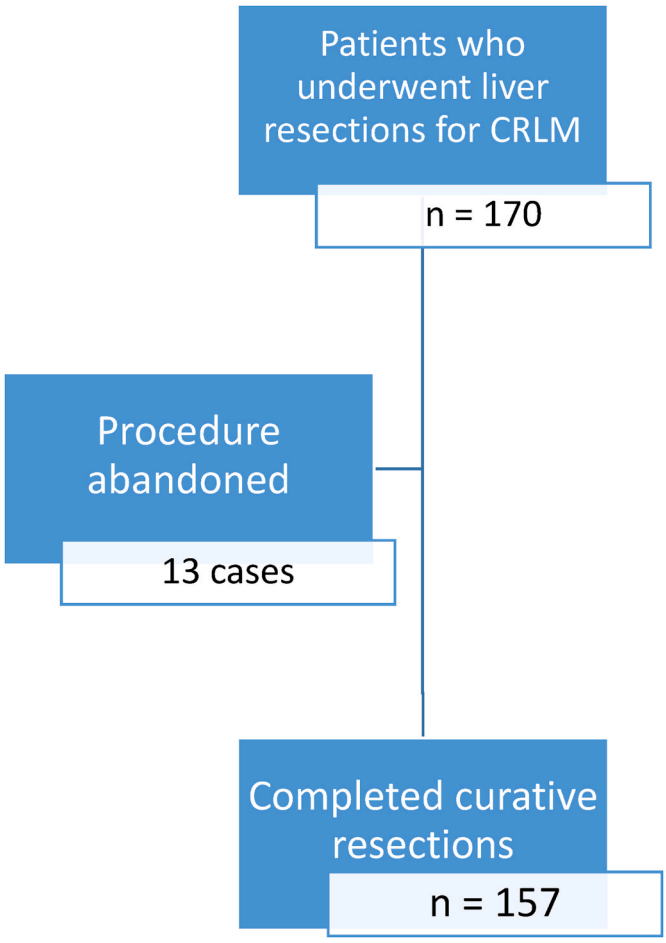


Image 1. Flow chart of participants in the cohort study.

Table 2
Stratifications used.

Variable	Ranges	Analysis
Resection margins:	Abutting = 0	
	≤1 mm = 1	0 vs 1 vs 2 vs 3
	1,1 to 10 = 2	**0–1 vs 2–3***
	>10 mm = 3	0-1-2 vs 3
CEA serum levels:	≤10 = 0	0 vs 1 vs 2
	>10 and ≤ 200 = 1	0 vs 1-2
	>200 = 2	0-1 vs 2
Embryonic origin	Midgut = 1	1 vs 2 vs 3
	Hindgut = 2	1-2 vs 3
	Rectum = 3	1 vs 2-3

Table 2. Selected variables and stratifications defined for analysis.

intraoperative portal pedicle clamping.

2. Objectives

The primary objective of this study is to determine rates and patterns of recurrence following hepatic resections for CRLM in a single-centre cohort. The secondary objectives are to characterise clinical, pathological, and treatment-related factors that may function as predictors of recurrence and survival; particularly, neoadjuvant chemotherapy and tumour clearance.

3. Materials and methods

This is a descriptive, observational study with retrospective analysis of a prospectively collated database. This database included all patients who underwent curative hepatic resections for CRLM at The Queen Elizabeth Hospital (Adelaide, Australia) between December 2004 and September 2020.

4. Data collection

The data for analysis was obtained through the Department of Surgery, The Queen Elizabeth Hospital (TQEH). This database is approved for research use by the TQEH Human Research Ethics Committee, and all data have been managed appropriately under the Australian code for the Responsible Conduct of Research.

This prospectively generated liver database collates epidemiological, clinical, and pathological data regarding the primary CRC and the CRLM. In addition, associated laboratory results, operative protocols, pathology reports and patient follow up/outcomes are also reported (Table 1).

Variables were documented from the date of CRC diagnosis until either a patient's death, loss of follow-up or the end of the study period (September 22, 2020). These factors were recorded for both the primary CRLM and the recurrence. Extrahepatic recurrences were also reported and analysed to calculate disease-free survival.

This work has been reported in line with the STROCSS criteria [22]. It has also been registered at www.clinicaltrials.gov under the UIN NCT05273489.[1]

[1] https://www.clinicaltrials.gov/ct2/show/NCT05273489?term=mauro+perdomo&draw=2&rank=1.

Table 3
Univariate analysis for recurrence.

Variable	Value	p-value	Test
Gender	0.408	0.523	X^2
TNM stage for primary tumor: 1 vs 2 vs 3 vs 4	–	0.739	Fisher's exact test
TNM stage for primary tumor: 1–2 vs 3-4	0.703	0.402	X^2
Synchronicity	0.054	0.816	X^2
Resection Margin Classification 0 vs 1 vs 2 vs 3	5.418	0.144	X^2
Resection Margin Classification 0–1 vs 2–3	**3.898**	**0.048**	X^2
Resection Margin Classification 0-1-2 vs 3	2.049	0.152	X^2
CEA	1504	0.062	Wilcoxon
CEA >10	2.021	0.155	X^2
Coded Pre-Op QT	**10.587**	**0.001**	X^2
Age	0.008	0.994	T Test
Embryonic origin 1 vs 2 vs 3	3.898	0.142	X^2
Time between CRLM diagnosis and resection	**2431.5**	**0.026**	Wilcoxon

Table 3. Univariate analysis for recurrence. For each variable the utilised test, its absolute value and p-value are shown. The statistically associated variables are in **bold letters** (resection margins ≤ 1 mm, neoadjuvant chemotherapy and time between diagnosis and resection).

Table 4
Logistic regression and multivariate analysis for recurrence.

Model	Coeff.	OR (CI 95%)	p-value	AIC
Model 1: Recurrence ~ Neoadjuvant Chemotherapy				209.08
Neoadjuvant Chemotherapy	1.121	3.07 (1.61; 5.95)	**0.001**	
Model 2: Recurrence ~ Time to resection				215.64
Time to resection	0.002	1.00 (1.00; 1.00)	**0.036**	
Model 3: Recurrence ~ Resection margins 1–2 vs 3–4				216.20
Resection margins 1–2 vs 3-4	−0.757	0.47 (0.23; 0.93)	**0.033**	
Model 4: Recurrence ~ Neoadjuvant Chemotherapy + Time to resection + Resection margins 1–2 vs 3–4				209.30
Neoadjuvant Chemotherapy	0.923	2.52 (1.28; 5.03)	**0.008**	
Time to resection	0.001	1.00 (1.00; 1.00)	0.222	
Resection margins 1–2 vs 3-4	−0.499	0.61 (0.29; 1.26)	0.184	

Table 4 – Logistic regression and multivariate analysis for recurrence. The logistic regression was applied for variables that reached significance in the univariate analysis. Models were evaluated according to Akaike Information Criterion (AIC). After applying multivariate model, neoadjuvant chemotherapy continues to be associated to recurrence, but resection margins and time to resection does not.

5. Inclusion criteria

Patients who underwent a liver resection for CRLM at The Queen Elizabeth Hospital between December 2004 to September 2020, were included in this analysis (Image 1).

6. Exclusion criteria

Patients whose procedures were abandoned due to unresectable tumour burden.

7. Statistical analysis

The software "R" version 3.4.1 (The R Foundation) performed the statistical analysis. Chi-square test, Fisher's exact test, Student's test and the Wilcoxon test were utilised to establish association between recurrences and the proposed predictive variables in univariate analysis.

Logistic regression models were then implemented to deduce the recurrence in a multivariate analysis, including those variables that presented significant results in the univariate analyses. With these variables, a Cox regression was adjusted for the survival analysis for both, recurrence, and time to death.

For each quantitative variable, ranges were established according to clinical relevance. They were individually analysed, using a combination of variables when it was considered appropriate. The results were shown in survival curves (Table 2).

A literature search to determine potential predictors of recurrence was conducted and indicated the following variables: gender, TNM, synchronicity, resection margin, CEA, chemotherapy, embryonic origin and time between diagnosis and treatment.

8. Definitions

Recurrence date: date recurrence is verified, regardless of location.

Disease-free time: Time elapsed between the date of resection of the CRLM (R0) and the date of recurrence, in those patients without metastases.

Synchronous metastasis: metastases detected before or during the primary CRC resection. For patients who did not undergo initial resection of the primary tumour, those metastases detected before or at the same time as the CRC were considered synchronous.

Metachronous metastasis: metastases detected after 3 months of the diagnosis of the primary CRC.

Neoadjuvant chemotherapy: Defined as occurring within 100 days of hepatic resection.

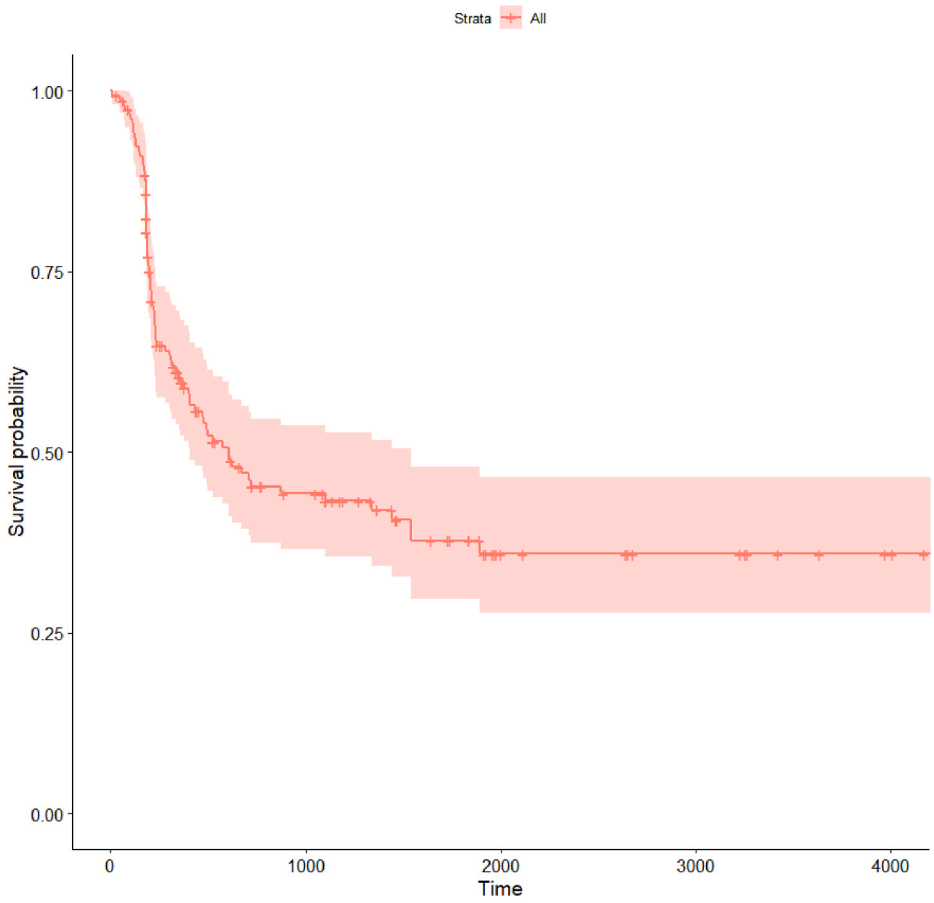
9. Results

From 2004 to 2017, 170 patients were booked for an elective hepatic resection. A total of 13 procedures were abandoned due to extensive disease. 157 patients were included in these analyses. The majority of participants were male (62.4%), with a mean age of 66 ± 11.6 years. Follow up was to September 22, 2020. The mean follow-up time was 1589 days (64–4746).

The median number of CRLM per patient was 2 (range 1–8). Size of metastatic lesions varied between 1 and 136 mm (mean 38.5 ± 23.6 mm). The most common differentiation grade was moderate. Resection margins varied between 0 and 80 mm. The mean resection margin was 6.2 mm (SD 8.4) with the most frequent range being 1–10 mm (n = 69).

The mean time between CRLM diagnosis and resection was 172 ± 188 days (6–1155). Four patients had a hepatic lesion detected and removed during primary bowel resection. The distribution according to the synchronous or the metachronous occurrence of CRLM was similar (78 and 79 cases respectively). The mean time between CRC diagnosis and CRLM for those with metachronous disease was 656 ± 588 days.

A total of 81 patients received neoadjuvant chemotherapy. At TQEH, neoadjuvant chemotherapy is utilised with the goal of shrinking a previously inoperable tumour to a resectable size. This is discussed during multidisciplinary meetings consisting of surgeons, oncologists, radiologists, and pathologists.



Graphic 1. Survival analysis for recurrence
Graphic 1 - Survival curve for recurrence. Mean time to recurrence was **429 days** and the two-year survival rate for recurrence was 46%.

10. Recurrence

A total of 84 patients experienced hepatic recurrence (53.5%). The mean length of time between procedure and detection was 429 days (49–3288 days). Only three patients had hepatic recurrence detected four years post procedure. All three developed distant disease prior to local recurrence. In this study 97 patients experienced distant disease post hepatic resection: 66 patients had both local and distant recurrence, 18 patients experienced local recurrence only, and 31 patients experience distant disease only.

Of the 84 hepatic recurrence patients, 54 (65%) had been prescribed neoadjuvant chemotherapy. The proportion of patients who did not experience hepatic recurrence and were prescribed chemotherapy was 46% (33/72). Neoadjuvant chemotherapy was positively associated with recurrence on univariate analysis (X2 = 10.587, p-value = 0.001) such that patients who were administered neoadjuvant chemotherapy were more likely to experience recurrence. Resection margins equal to 1 mm or less were also positively associated with hepatic recurrence (X2 = 3.898, p = 0.048). Gender, TNM staging, synchronicity, CEA serum levels and embryonic origin were not associated with recurrence (Table 3).

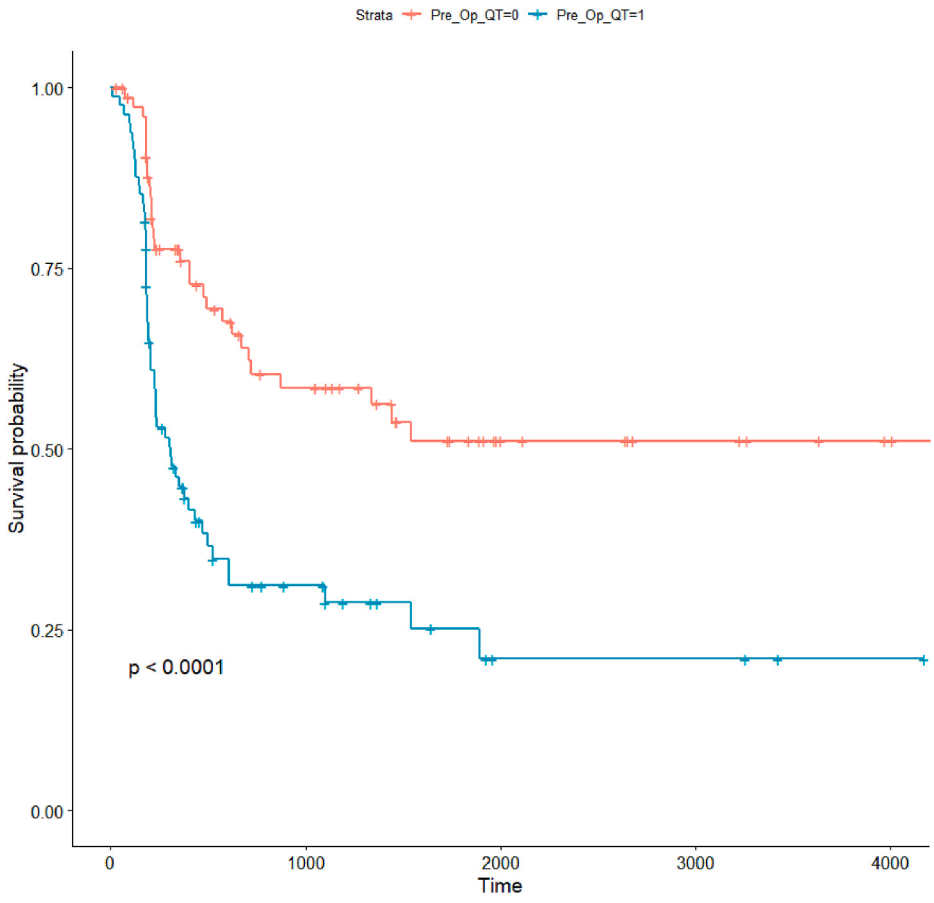
Time between diagnosis and treatment was significant for recurrence (Wilcoxon = 2431.5, p = 0.026). However, the strong association between this variable and neoadjuvant chemotherapy could function as a confounding factor (mean time to resection in patients with and without chemotherapy: 237 vs 72 days respectively). The multivariate analysis (logistic regression) was performed using variables which reached significance in the univariate analysis. Different statistical models were applied and then evaluated according to Akaike Information Criterion (AIC). Model 1 best illustrates our cohort behaviour (AIC = 209.08); these results are presented in Table 4. After applying this multivariate model, neoadjuvant chemotherapy continues to be associated to recurrence, but resection margins and time to resection does not (Table 4).

Survival curves for recurrence are shown in (Graphics 1 to 3). Neoadjuvant chemotherapy was the most strongly associated variable after Cox regression, with a negative impact in the disease-free survival post-liver resection for CRLM (HR 2.49 [1.58; 3.91], p < 0.001 Graphic 4). This effect persist after the multivariate analysis (HR 2.24 [1.39; 3.60]). Resection margins greater than 1 mm were also significant for better disease-free survival outcomes (X2 3.898, p = 0.047). No difference could be determined when comparing other ranges. Time between diagnosis and CRLM resection had also a negative impact in DFS (p = 0.22). Embryonic origin and CEA serum levels showed not association in this aspect (Table 5).

11. Survival

A total of 114 patients died during the study period, with a mean time to death of 1319 ± 918 days. Of them, 99 patients died with local or distant disease. Mean survival time of the series was 1756 days with a median of 1486 days. At the endo of the study 43 patients remain alive, 27 of who are disease free. Mean follow up is 2261 days (and counting). (Graphic 5).

Recurrence was the only variable statistically associated with survival, with a negative effect in the time to death (HR 2.58 [1.73; 3.85], p < 0.001, Graphic 6). Neoadjuvant chemotherapy had a marginal effect that was not significative (HR 1.44 [0.99; 2.10], p = 0,054, Graphic 7). After multivariate analysis, recurrence remains in a significative range (HR 2.49 [1.65; 3.77], p < 0.001 Table 6).



Graphic 2. Neoadjuvant chemotherapy

Graphic 2 – Survival curves for recurrence according to neoadjuvant chemotherapy (red line: no chemotherapy/blue line: chemotherapy) **p < 0.0001.** (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

12. Discussion

Using a prospectively collected database, this study aimed to analyse patterns of recurrence for CRLM patients. The variables selected for analysis following a literature review on this subject included gender, TNM, synchronicity, resection margin, CEA, chemotherapy, embryonic origin and time between diagnosis and treatment. This study excluded review of factors whose correlations have previously been clearly defined, such as number of metastases, resection technique (anatomical vs non-anatomical), largest tumour size, KRAS mutation and instead focused on analysing variables which had not yet been adequately explored [8–10].

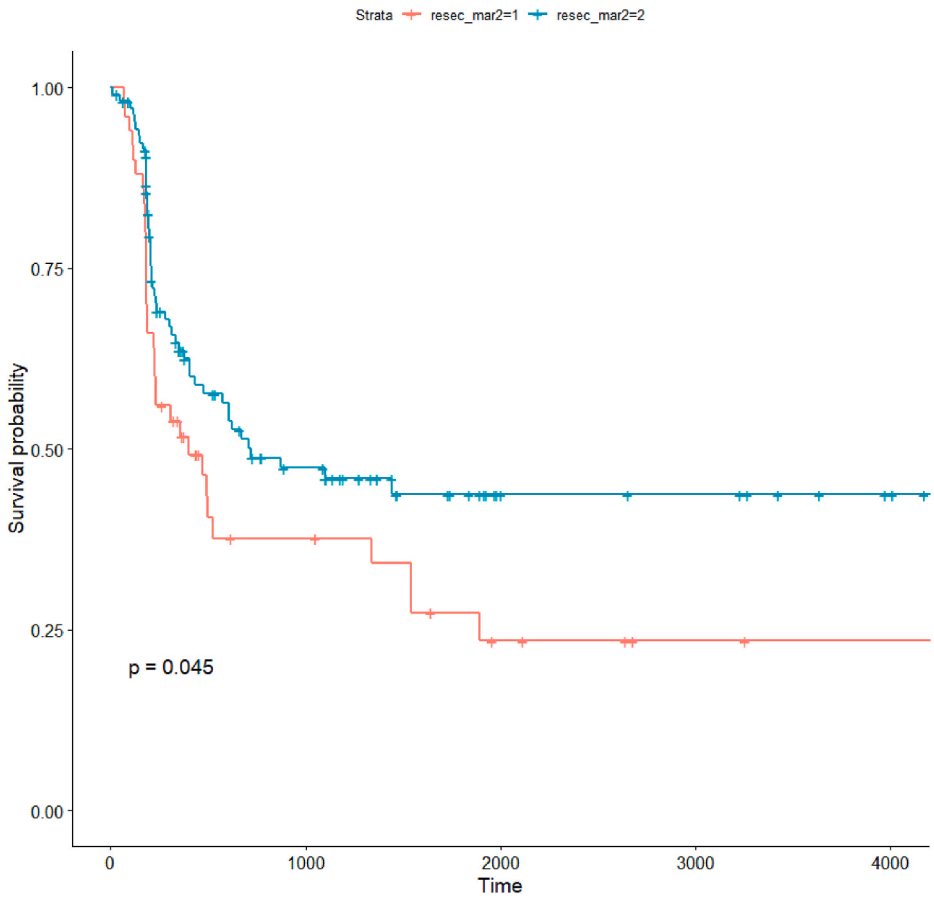
The data analysis revealed that 84 of the 157 patients (53,5%) experienced local recurrence, and most occurred within the first-year post-surgery (median = 209, mean 429 days, SD = 541.8). These figures are consistent with previous Australian studies and global findings [2,7].

In regard to recurrence of CRLM, few statistically significant results were deduced. Some factors whose association with CRLM recurrence had been previously proposed, did not reach statistically significant values in the current study. This may be due to our small sample size. In previous studies, preoperative elevated CEA serum level (>200 ng/ml) has been proposed as predictor for early recurrence and poorer overall survival [11,12]. However, there is no consensus regarding the optimal reference cut-off value, nor the ideal date to measure it. In our cohort CEA serum levels were not associated with CRLM recurrence in the univariate analysis using the continuous value nor when stratification was considered. A considerable bias was the great heterogeneity in the distribution of CEA values and the small sample size.

In the univariate analysis, the factors with statistical association with CRLM recurrence were resection margins, neoadjuvant chemotherapy and time elapsed between diagnosis of CRLM and resection.

The association between the period between the diagnosis of the CRLM and resection, and CRLM recurrence has not been studied until now [13]. In our study it was identified to be a risk factor in the preliminary analysis of the Wilcoxon test. However, after additional multivariate analysis was performed, the association was no longer significant for every model (see Model 4 in Table 4). The logic behind the implementation of these models lies in the fact that neoadjuvant chemotherapy may be associated with a delay in the treatment of CRLM and this could obscure the analysis. However, Model 4 shows that when time to surgery is controlled, the significant association between chemotherapy and recurrence is maintained ($p < 0.001$).

Our findings seems to be similar to those identified in the literature that describe a two-year survival rate close to 50% [14]. The increased recurrence risk associated with neoadjuvant chemotherapy has been reported in previous studies [15,16]. Proposed explanations for this conclusion include that post-chemotherapy, tumour mass margins and additional liver tumour implants are less easily determined, thereby making clean resection more difficult. The role of neoadjuvant chemotherapy in reduced overall survival is also explained by the decreased functional capacity of the remaining hepatic parenchyma after chemotherapy. Chemotherapy-induced liver injury can induce histological changes in the liver parenchyma, i.e. sinusoidal obstruction syndrome (SOS), steatosis and chemotherapy-associated steatohepatitis (CASH) [16]. Moreover, post-neoadjuvant therapy liver tissue may be friable and therefore less favourable for transection and associated with an increased risk of complications.



Graphic 3. Resection margins
Graphic 3 – Survival curves for recurrence according to resection margins (red line: ≤ 1 mm/blue line: > 1 mm) **p = 0.045.** (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The optimal CRLM surgical margin is undetermined [12], and the specific survival benefit of a 10 mm margin compared to a 1 mm disease free boundary is not defined. In the univariate analysis, margins greater than 1 mm showed to be associated with better recurrence rates (p = 0, 045). In Fig. 8 we can observe the pattern of survival curves for recurrence by stratifying resection margins to ≤1 mm (red) vs. >1 mm (light blue).

In consideration of these results, we are able to conclude that within the studied population CRLM resections with margins greater than 1 mm improve the disease-free survival. However, the current findings were unable to verify if margins greater than 10 mm provide any additional advantage. Again, sample size is acknowledged as a limitation and possible source of bias in the current analysis of this variable.

The overall survival analysis showed a mean time to death of 4.81 years (median = 4.07 years) and a strong association with the presence of recurrence (p < 0.0001). This association remains unchanged after the multivariate analysis. Even tough neoadjuvant chemotherapy has a marginal effect in survival this result was not significative (p = 0.054) Fig. XX.

The investigation of other variables including embryonic origin and the CEA value in different stratifications indicated no association with the overall survival of patients undergoing hepatectomies for CRLM. However, these variables may be suitable on an individual level or in a specialised subset of patients for predicting recurrence.

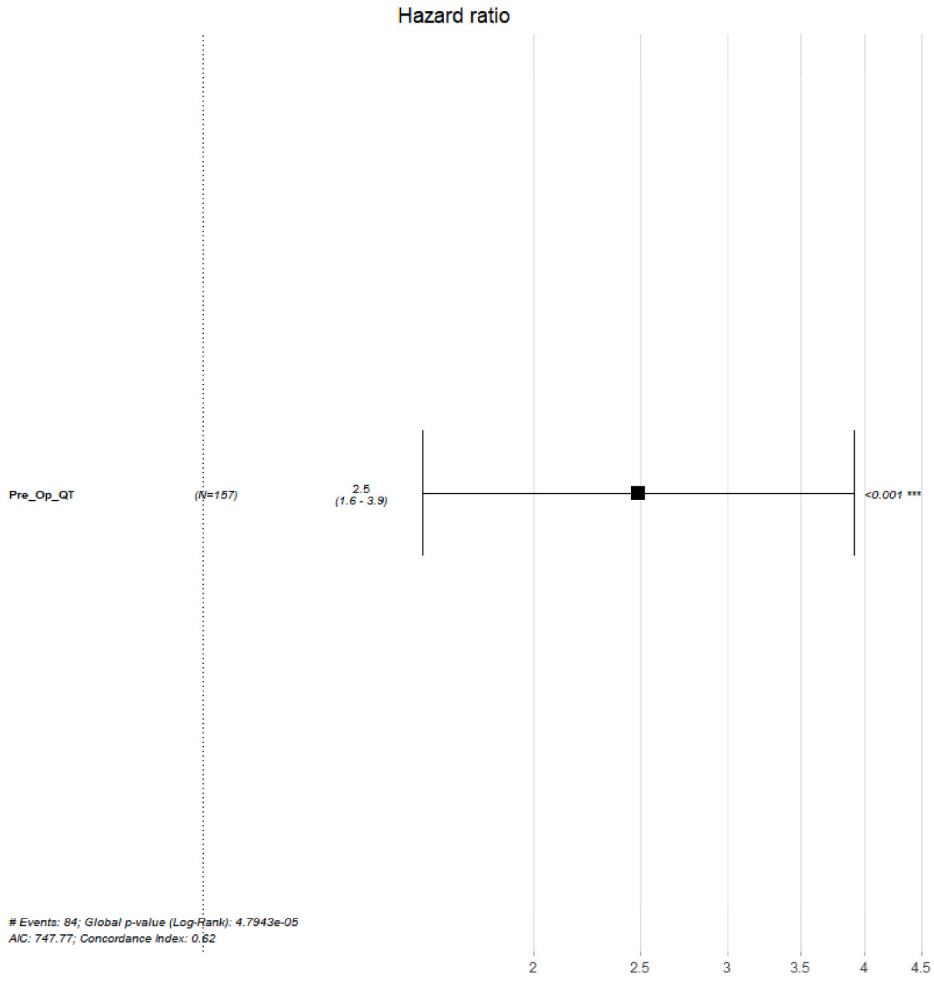
13. Conclusion

CRC and CRLM remain a topic of keen medical interest and focus due to prevalence rates, significant developments in understanding pathological pathways [17] and recent innovation in therapeutic modalities. These advancements have consequently improved global patient survival outcomes. However, despite these developments and the introduction of the multidisciplinary approach, recurrence rates remain high and two-year survival low.

The role of neoadjuvant chemotherapy is currently well utilised by the HPB speciality; however the associated recurrence and survival outcomes warrant ongoing assessment. In the studied cohort, neoadjuvant chemotherapy indicated a negative impact in both the recurrence rates and patient survival time (this last one marginal). Future studies with a higher level of evidence should define or clarify its role in CRLM.

The optimal resection margin has not been well defined [18,19]. The current study findings indicated a significant benefit in survival curves for margins greater than 1 mm. Benefits of greater resection margins could not be established.

Optimal patient selection for this therapeutic pathway is critical due to the complex implications neoadjuvant chemotherapy can have on the hepatic parenchyma. Careful consideration of patient suitability is paramount in the planning or consideration of overall CRLM treatment from both a surgical and functional perspective [14,20,21].



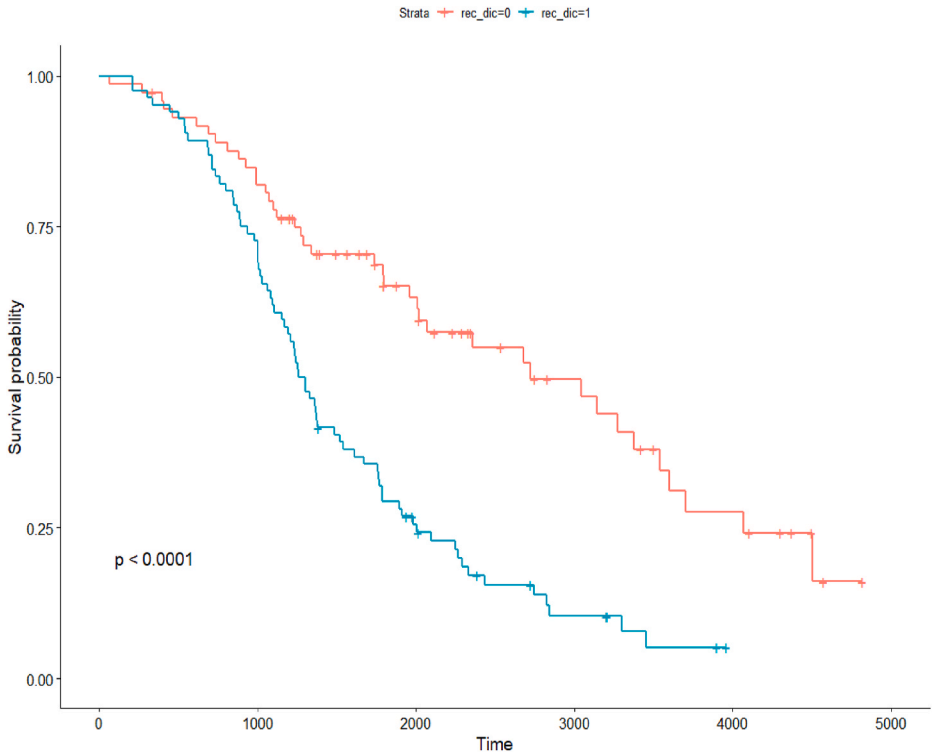
Graphic 4. Hazard Ratio boxplot for recurrence comparing chemotherapy groups. Shows the negative impact of chemotherapy in the disease-free survival post-liver resection for CRLM (**HR 2.49 [1.58; 3.91], p < 0.001.**

Table 5
Cox regression and multivariate survival analysis for recurrence.

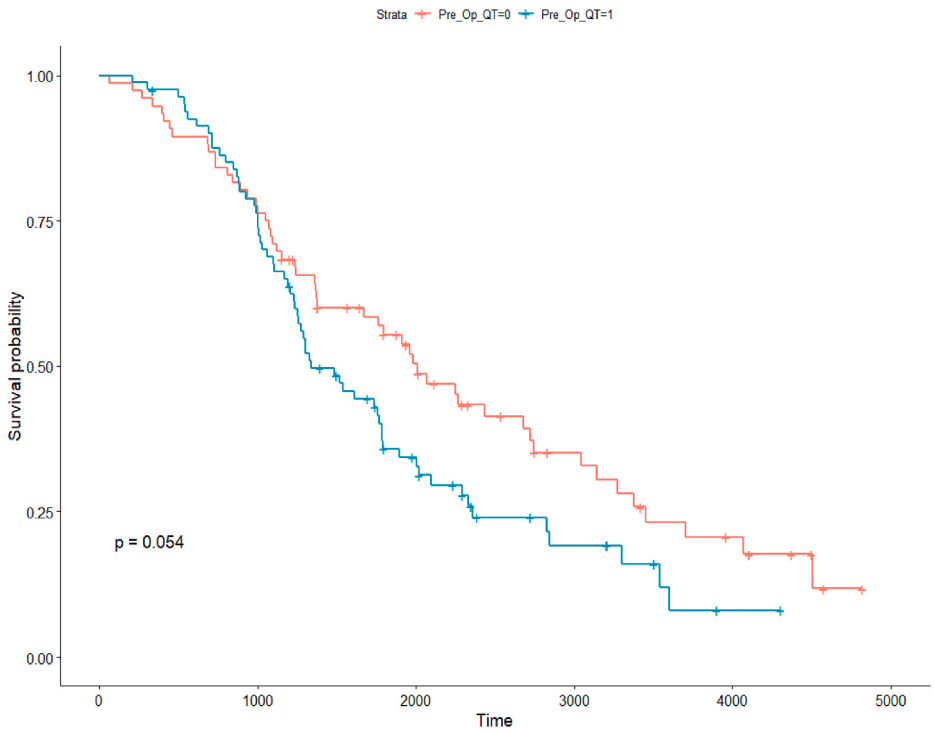
	Coeff.	HR	p-value	AIC
Model 1: Survival ~ Neoadjuvant Chemotherapy				747.77
Neoadjuvant Chemotherapy	0.911	2.49 (1.58; 3.91)	**<0.001**	
Model 2: Survival ~ Time to resection				759.93
Time to resection	0.001	1.00 (1.00; 1.00)	**0.022**	
Model 3: Survival ~ Age				764.26
Age	−0.002	0.99 (0.98; 1.02)	0.831	
Model 4: Survival ~ Resection margins				760.49
Resection margins 1–2 vs 3–4	−0.446	0.64 (0.41; 0.99)	**0.047**	
Model 5: Survival ~ Neoadjuvant Chemotherapy + Time to resection + Resection margins				749.58
Neoadjuvant Chemotherapy	0.806	2.24 (1.39; 3.60)	**0.001**	
Time to resection	0.001	1.00 (1.00; 1.00)	0.330	
Resection margins 1–2 vs 3–4	−0.231	0.79 (0.50; 1.25)	0.322	

Table 5 – Cox regression and multivariate survival analysis for recurrence. The cox regression was applied for variables that reached significance in the univariate analysis. Models were evaluated according to Akaike Information Criterion (AIC. After applying the multivariate model, neoadjuvant chemotherapy continues to be associated to recurrence, but resection margins and time to resection does not.

Graphic 5. Overall survival curve. Mean time to death was 1756 days with a median of 1486 days. 43 patients remain alive.



Graphic 6. Overall survival curves according to recurrence (red curve: no recurrence/blue curve: recurrence). Recurrence showed a significative negative effect in overall survival (p< **0.0001**). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



Graphic 7. Overall survival curves according to neoadjuvant chemotherapy (red curve: no chemotherapy/blue: chemotherapy). Neoadjuvant chemotherapy had a marginal effect that was not significative (HR 1.44 [0.99; 2.10], p = 0,054). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 6
Logistic regression and multivariate analysis for overall survival.

	Coeff.	HR	p-value	AIC
Model 1: Overall survival ~ Recurrence				962.20
Recurrence	0.949	2.58 (1.73; 3.85)	**<0.001**	
Model 2: Overall survival ~ Time to resection				985.30
Time to resection	0.000	1.00 (1.00; 1.00)	0.897	
Model 3: Overall survival ~ Age				985.30
Age	0.001	1.00 (0.99; 1.02)	0.881	
Model 4: Overall survival ~ Neoadjuvant Chemotherapy				981.60
Pre_Op_QT	0.368	1.44 (0.99; 2.10)	0.054	
Model 5: Overall survival ~ Neoadjuvant Chemotherapy + Recurrence				963.80
Pre_Op_QT	0.125	1.13 (0.77; 1.67)	0.530	
rec_dic	0.914	2.49 (1.65; 3.77)	**<0.001**	

Table 6 – Logistic regression and multivariate analysis for overall survival. Recurrence was the only variable statistically associated with survival, with a negative effect in the time to death that remains in a significative range after multivariate analysis (HR 2.49 [1.65; 3.77], **p < 0.001. Model 1** best illustrates our cohort behaviour **(AIC = 962.20)**.

Data statement

This database is approved for limited research use by the TQEH Human Research Ethics Committee and participants were assured raw data would remain confidential and would not be shared.

Data could be provided on reasonable request.

Ethical approval

This is standard of care data routinely collected for self-audit purposes and ethical approval is not required since the database is approved for research use.

All data have been managed appropriately under the Australian code for the Responsible Conduct of Research.

Sources of funding

None.

Author statement

Mauro Perdomo: study design, data analysis; writing.
German Botto: statistical analysis, data analysis.
Jessica Reid: study design, data collection, writing.
Jessie Clarke: data collection, data analysis.
Daniel Gonzalez: data analysis, writing.
Guy Maddern: study design, data analysis.

Research registration Unique Identifying Number (UIN)

ClinicalTrials.gov Identifier: NCT052734489
https://www.clinicaltrials.gov/ct2/show/NCT05273489?term=ch

emotherapy+and+tumor+clearance+in+hepatic+resections&draw=2&rank=1#wrapper.

Guarantor

Mauro Andres Perdomo Perez.

Provenance and peer review

Not commissioned; externally peer reviewed.

Declaration of competing interest

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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijso.2022.100521.

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