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Retrospective Cohort Study

Retrospective cohort study of statin therapy effect on resected colorectal liver metastases

Edward Alabraba, Hussain Ibrahim, Adina Oлару, Iain Cameron, Dhanny Gomez,
Nottingham HPB Surgery Group

ORCID number: Edward Alabraba (0000-0002-6611-687X); Hussain Ibrahim (0000-0002-5595-937X); Adina Oлару (0000-0001-5646-2309); Iain Cameron (0000-0002-7953-5061); Dhanny Gomez (0000-0002-7584-3884).

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Edward Alabraba, Hussain Ibrahim, Adina Oлару, Iain Cameron, Dhanny Gomez, Department of Hepatobiliary Surgery and Pancreatic Surgery, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, United Kingdom

Dhanny Gomez, NIHR Nottingham Digestive Disease Biomedical Research Unit, University of Nottingham, Nottingham NG7 2UH, United Kingdom

Corresponding author: Dhanny Gomez, FRCS, Surgeon, Consultant Surgeon, Department of Hepatobiliary Surgery and Pancreatic Surgery, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, E Floor, West Block, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, United Kingdom. dhanny.gomez@nuh.nhs.uk

Abstract**BACKGROUND**

Above and beyond their role in cardiovascular risk reduction, statins appear to have a chemopreventive role in some gastro-intestinal cancers. In the quest for new chemopreventive agents, some existing established drugs such as statins have shown potential for re-purposing as chemoprevention. Probing existing drugs, whose pharmacodynamics are familiar, for novel beneficial effects offers a more cost-effective and less time-consuming strategy than establishing brand new drugs whose pharmacodynamic profile is unfamiliar. Observational studies show statins decrease the risk of developing colorectal cancer but there are no published studies exploring the potential impact of statins on carcinogenesis in colorectal liver metastases (CRLM).

AIM

To evaluate impact of statins on outcomes of CRLM resection, and secondarily to assess if statins influence CRLM histo-pathology.

METHODS

We conducted a retrospective cohort study of patients operated for CRLM over a 13-year period from 2005 to 2017. Patients were identified from a prospective database maintained in our Tertiary care hospital. All 586 patients included the study had undergone resection of CRLM following discussion at multidisciplinary team meeting, some patients requiring neoadjuvant chemotherapy to downstage CRLM prior to surgery. We analysed patient demographics, operative details, CRLM histopathology, Index of Deprivation, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and chemotherapy

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use in relation to clinical outcome. Statistics were performed using SPSS version 16.0; significance taken at 5%.

RESULTS

Liver resection for CRLM was undertaken in 586 patients at a median age of 68 (range 19 to 88) years. Statin therapy was used by 181 patients. Median follow-up time was 23 (range 12-96) mo and further colorectal cancer metastases developed in 267 patients. A total of 131 patients died. Multi-variate analysis identified 6 independent predictors of poorer disease-free survival: Synchronous presentation, multiple tumours, tumour size ≥ 5 cm, moderate-severe steatosis, peri-neural invasion, and R1-resection margin. Poorer overall survival was significantly associated with neo-adjuvant chemotherapy, major hepatectomy, peri-neural invasion and R1-resection margin. Neither histo-pathological nor radiological traits of CRLM were affected by statins, and, there was no demonstrable effect of statin therapy on patient outcomes.

CONCLUSION

Statin therapy does not affect patient survival following liver resection for CRLM. We postulate the reason for this key finding is that statins do not modulate tumour biology of CRLM.

Key words: : Colorectal liver metastases; Statin; Liver resection; Chemoprevention; Tumour biology; Survival

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Core tip: Colorectal liver metastases (CRLM) develop in 25%-30% of patients with colorectal cancer and disease prevalence has increased with expansion in the at-risk older age group. The need for chemoprevention to inhibit carcinogenesis is an attractive option that has shown promise in patients at high risk of developing CRLM. Observational studies have shown statins are promising chemopreventive agents but no data exist specifically for CRLM. Statins represent a well-established drug group whose pharmacodynamic properties are familiar to clinicians and if they demonstrate effectiveness as chemoprevention for CRLM, repurposing statins for this use will be more cost- and time- effective compared to developing new agents.

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INTRODUCTION

Liver resection gives the 25-30% of patients with colorectal cancer (CRC) who develop colorectal liver metastases (CRLM) a 5-year survival as high as 50%^[1]. More efficacious oxaliplatin- and irinotecan-based chemotherapy regimens and the introduction of biological agents such as bevacizumab and cetuximab have improved survival of patients with CRLM. Availability of these multimodal therapies, including ablation, allows the opportunity to treat CRLM as a chronic disease.

Identifying chemopreventive agents to halt carcinogenesis is a growing interest in many cancers, and one of such agents is Statins. Statins lower blood lipids by inhibiting the enzyme 3-hydroxy-2methylglutaryl coenzyme-A reductase (HMG-CoA), blocking the mevalonate pathway for cholesterol synthesis in the liver. Statins have pleiotropic effects including anti-inflammatory, immune-modulatory and anti-apoptotic or anti-tumour actions. Statins improve survival of patients with sepsis or following surgery and this may be mediated by their modulatory effect on well recognised inflammatory cytokines such as tumour necrosis factor- α and interleukin (IL)-6, acute phase proteins such as C-reactive protein, and inflammatory chemokines such as IL-8^[2]. By indirectly downregulating isoprenoids which are essential for the post-translational modification of GTPases, statins may inhibit local tumour

progression and distant metastasis with an overall beneficial effect on carcinogenesis^[3-5]. Statins inhibit growth and induce apoptosis of CRC cells in vitro studies^[6], and, improve overall survival for CRC patients^[7]. Observational studies show statins decrease the risk of developing colorectal cancer^[8] but no studies have examined their role in modulating CRLM. Our retrospective cohort study is the first study to evaluate the impact of statin therapy on CRLM.

MATERIALS AND METHODS

Aims

Our primary objective was to assess whether survival of patients who have hepatic resection for CRLM is affected by statins. Our secondary objective was to determine whether the histopathology of resected CRLM is affected by statins.

Patients

Using a prospectively maintained database, we identified and included all patients who underwent primary hepatic resection for CRLM with curative intent at our United Kingdom HPB Centre during a 13-year period ending 31, December 2017. Patients who did not actually undergo hepatic resection at the time of surgery were excluded. We eliminated selection bias by selecting cases and controls using these simple clear criteria, thus avoiding convenience sampling. Institutional board approval (project number 18-320c) was obtained and the project adhered to ethical guidelines.

Pre-operative imaging, multidisciplinary team (MDT) work-up, and the use of neo-adjuvant therapy were as described in our previous publication^[9]. Standard pre-operative imaging was computed tomography chest/abdomen/pelvis (CT-CAP) scan, and liver magnetic resonance imaging. Synchronous presentation with CRC primary and CRLM, or the presence of indeterminate lesions led to positron emission tomography scan. Synchronously presenting CRLM are defined as CRLM detected at or before diagnosis of the primary tumour. Conversely, metachronous CRLM are those detected after diagnosis or resection of the primary tumour. All patients were reviewed at MDT meetings made quorate by attendance of at least one of each of the following: hepatobiliary surgeons, hepatologists, oncologists, radiologists, pathologists, and specialist nurses. Liver resection was done without neo-adjuvant chemotherapy whenever it was possible to resect metastases and achieve clear margins whilst preserving sufficient residual liver parenchyma. In cases of synchronous presentation with liver-limited metastases, liver metastases and colorectal primary were simultaneously resected at the same operation if patient fitness and the extent of resections were suitable.

We collected patient demographic, surgical resection, histopathology, clinical outcome, and statin therapy data. Some patients were on statins, prescribed by general practitioners to mitigate cardio-vascular risk. Daily statin dose ranges were 5-20 mg for Rosuvastatin, 10-40 mg for Pravastatin; and 10-80 mg for Simvastatin, Fluvastatin or for Atorvastatin. As our tertiary referral centre covers a wide and varied geographical area, we measured deprivation indices to see if any perceived differences in outcome may be explained by certain areas being more or less disadvantaged. Deprivation was calculated using the English Index of Multiple Deprivation (IMD) 2015, based on postcode of residence in England and combining information from seven domain indices including supplementary indices of income deprivation for children and older people^[10]. We assigned quintiles of relative deprivation to patients based on their postcode at the time of liver resection, the first quintile being the most deprived. We adhered to Strengthening the Reporting of Observational studies in Epidemiology guidelines in presenting our data.

Neo-adjuvant and adjuvant chemotherapy

As described in our previous publication^[9], neo-adjuvant systemic chemotherapy was either Oxaliplatin- or Irinotecan-based and Cetuximab was considered for *KRAS* wild-type patients. Chemotherapy response was assessed by imaging and plans for surgery or further systemic therapy were made at MDT review. Adjuvant chemotherapy was used if R1 resection.

Liver resection surgery

Computed tomography or magnetic resonance imaging findings were confirmed by intra-operative ultrasound and liver resection performed using Cavi-Pulse Ultrasonic Surgical Aspirator. As in our previous study^[9], we dichotomously classed hepatic resections as being less than or at least equal to a hemi-hepatectomy in order to simplify data analysis.

Histopathology

The histopathological parameters recorded were tumour number, maximum tumour diameter, status of resection margin, lymphatic invasion, peri-neural invasion, biliary invasion and vascular invasion^[11].

Post-operative follow-up

All study patients had at least 6-mo follow-up after resection of CRLM. After the initial post-operative review in hepatobiliary clinic at one month, all patients were subsequently seen in the hepatobiliary clinic at 3, 6, 12, 18 and 24 mo later followed by review on an annual basis. As previously described^[9], carcino-embryonic antigen levels were measured and surveillance computed tomography chest/abdomen/pelvis imaging initially performed on a 6-monthly basis during the first two post-operative years followed by extension to yearly interval. Tumour recurrences were treated by re-resection or referred to oncology for palliative treatment after review at MDT meeting.

Statistical analysis

Survival was assessed using the Kaplan-Meier analysis. Clinico-pathological characteristics that influenced disease recurrence and survival were assessed by univariate analysis, and if significant, multivariate analysis was performed by Cox regression (Step-wise forward model). We analysed the relationship between categorical variables using Chi-squared test. SPSS for Windows™ version 16.0 (SPSS Inc, Chicago, Ill, United States) was used to perform statistical analyses, and significance taken at the 5% level. The statistical methods of this study were reviewed by Dr Gomez of the University of Nottingham.

RESULTS

A total of 586 patients had CRLM surgically resected at a median age of 68 (range 19-88) years. There were post-operative deaths and these patients were excluded from subsequent analyses. Disease presentation was synchronous in 225 patients and induction chemotherapy, prior to liver resection, was administered to 135 patients. The regimes used for induction chemotherapy either Oxaliplatin- ($n = 71$), Capecitabine- ($n = 47$), 5-Fluorouracil- ($n = 11$), or Irinotecan-based ($n = 6$). KRAS testing was done in 112 patients and eligible patients ($n = 9$) had Cetuximab added to their downstaging regime. Bowel and liver resections were done synchronously for 6 patients, by liver-first approach for 18 patients, and by bowel-first approach for the remaining patients. One hundred and eighty-one patients were on statin therapy for cardio-vascular co-morbidities. The statins used were Simvastatin ($n = 97$), atorvastatin ($n = 69$), pravastatin ($n = 12$), rosuvastatin ($n = 2$), and Fluvastatin ($n = 1$). The most commonly used daily doses of statins were 5 mg for Rosuvastatin, 10 mg for Pravastatin, 40 mg for Simvastatin, 40 mg for Fluvastatin, and 20 mg for Atorvastatin. During the median follow-up period of 23 (range 12-96) mo, recurrent disease developed in 267 patients and there were a total of 131 patients who died.

Predictors of disease-free and overall survival

Statistical analysis of prognostic factors for disease-free survival (DFS) is shown in **Table 1**: Variables analysed are demographic, clinical and pathological factors. Statistical significance of variables in **Table 1** were as follows: not significant, univariate analysis, multivariate analysis, $P < 0.001$, $P < 0.01$, and $P < 0.05$. Where multivariate analysis Risk ratio is calculated, 95% confidence interval (CI) is also indicated. Multi-variate analysis identified six independent predictors of better DFS: Metachronous rather than synchronous presentation; solitary rather than multiple tumours; tumour size < 5 cm; R0 resection margins; normal liver or mild steatosis rather moderate to severe steatosis status; and the absence of peri-neural invasion. Undergoing major liver resection (hemi-hepatectomy or more), the presence of peri-neural invasion, having involved resection margins, and the use of neo-adjuvant chemotherapy were associated with a poorer OS on multi-variate analysis. **Table 2** shows statistical analysis of prognostic factors for OS: Variables analysed are demographic, clinical and pathological factors. Statistical significance of variables in **Table 2** were as follows: not significant, univariate analysis, multivariate analysis, $P < 0.001$, $P < 0.01$, and $P < 0.05$. Where multivariate analysis Risk ratio is calculated, 95%CI is also indicated. Survival was not affected by the IMD.

Effect of statin therapy on patient and tumour factors

Uni-variate analysis showed taking statin therapy did not significantly alter patient demographic or laboratory blood test data at presentation with CRLM, nor did statin

Table 1 Statistical analysis of prognostic factors for disease-free survival

Demographic, clinical and pathological factors	Disease-free survival [median (range) mo]	Uni-variate analysis (<i>P</i> value)	Multi-variate analysis (<i>P</i> value)	Risk ratio (Confidence interval)
Age		0.637		
< 65 yr (<i>n</i> = 244)	18 (3-165)			
≥ 65 yr (<i>n</i> = 342)	18 (3-160)			
Gender		0.588		
Male (<i>n</i> = 389)	18 (3-165)			
Female (<i>n</i> = 197)	20 (3-153)			
Presentation		< 0.001	0.003	0.684 (0.533-0.877)
Synchronous (<i>n</i> = 225)	15 (3-165)			
Metachronous (<i>n</i> = 361)	20 (3-160)			
Neutrophil-to-lymphocyte ratio		0.272		
< 5 (<i>n</i> = 490)	21 (3-153)			
≥ 5 (<i>n</i> = 96)				
Platelet-to-lymphocyte ratio		0.114		
< 150 (<i>n</i> = 287)	17 (3-165)			
≥ 150 (<i>n</i> = 299)	20 (3-156)			
Neo-adjuvant chemotherapy		< 0.001	0.099	0.789 (0.596-1.046)
Yes (<i>n</i> = 135)	13 (3-165)			
No (<i>n</i> = 451)	20 (3-160)			
Statin therapy		0.340		
Yes (<i>n</i> = 181)	17 (3-160)			
No (<i>n</i> = 405)	19 (3-165)			
Deprivation index		0.083		
1 (<i>n</i> = 101)	13 (3-131)			
2 (<i>n</i> = 120)	18 (3-159)			
3 (<i>n</i> = 115)	18 (3-147)			
4 (<i>n</i> = 142)	20 (3-123)			
5 (<i>n</i> = 108)	21 (3-165)			
Resection < hemi-hepatectomy (<i>n</i> = 368)	20 (3-165)	0.015	0.369	1.124 (0.871-1.449)
≥ hemi-hepatectomy (<i>n</i> = 218)	18 (3-160)			
Largest tumour size		0.007	0.009	1.407 (1.087-1.820)
< 5 cm (<i>n</i> = 406)	20 (3-156)			
≥ 5 cm (<i>n</i> = 180)	16 (3-165)			
Number of metastases		< 0.001	0.001	1.552 (1.204-2.002)
Solitary (<i>n</i> = 294)	22 (3-165)			
Multiple (<i>n</i> = 292)	14 (3-153)			
Steatosis		0.003	0.003	1.285 (1.086-1.520)
None (<i>n</i> = 426)	18 (3-165)			
Mild (<i>n</i> = 97)	20 (3-153)			
Moderate – Severe (<i>n</i> = 63)	12 (3-144)			
Lymphatic invasion		0.002	0.101	0.747 (0.527-1.059)
Positive (<i>n</i> = 67)	15 (3-160)			
Negative (<i>n</i> = 519)	20 (3-165)			
Vascular invasion		0.059		
Positive (<i>n</i> = 264)	16 (3-159)			
Negative (<i>n</i> = 322)	20 (3-165)			
Peri-neural invasion		< 0.001	0.005	0.522 (0.333-0.821)
Positive (<i>n</i> = 38)	12 (3-101)			
Negative (<i>n</i> = 548)	20 (3-165)			
Biliary invasion		0.158		

Positive (<i>n</i> = 181)	18 (3-159)			
Negative (<i>n</i> = 405)	20 (3-165)			
Resection margin (R0)		0.004	0.012	1.399 (1.075-1.821)
R0 (<i>n</i> = 427)	19 (3-165)			
R1 (<i>n</i> = 159)	19 (3-156)			

therapy affect extent of hepatectomy; histo-pathological features of resected CRLM; tumour recurrence or survival outcome of patients. Table 3 shows statistical analysis of statin effect on patient and tumour variables. Variables analysed are demographic, clinical and pathological factors. Statistical significance of variables in Table 3 is denoted using superscripts as follows: n/s (not significant). Chi-squared analysis showed IMD did not have a significant relationship with the use of statins ($P = 0.253$) thus excluding any potential variation in statin usage according to patients' socioeconomic status in the wide geographical area covered by our tertiary referral centre.

DISCUSSION

Despite patients being able to achieve 5-year survival rates as high as 58% after CRLM are resected^[12], long-term series show that as many as 70% of patients in surveillance will develop relapse^[13]. The use of drugs to inhibit carcinogenesis in individuals at high risk of developing disease is called chemoprevention. Discovering novel beneficial effects of existing drugs, termed drug repurposing, is cheaper than establishing new drugs and also benefits from familiarity with the side effects profile of known drugs. Chemoprevention using repurposed drugs is thus an attractive cost-effective option to improve outcomes in gastrointestinal cancers and statins have been investigated as candidate drugs for chemoprevention.

Several observational studies have shown statins decreases cancer risk. Meta-analysis by Meng and associates which included 13 observational studies and over 100000 patients, showed pre- and post-diagnostic use of statins was associated with improved OS in patients with prostate cancer^[14]. Furthermore, Manthravadi and co-workers showed statins improved the overall and DFS in breast cancer patients in their meta-analysis that included 14 prospective or retrospective cohort studies, some of which were registry-based^[15].

Statin therapy has recognised health benefits and a systematic literature review of all statin trials showed statin treatment results in a small average gain in OS^[16]. We thus analysed tumour specific variables so we could distinguish whether any observed survival gains were due to cardiovascular risk reduction or due to CRLM disease modification. The action of statins in CRC is not fully understood, but a suggested mechanism is the inhibition of metastasis-associated in colon cancer-1 (MACC1) gene. MACC1 is widely expressed in primary and metastatic CRC, and independently predicts the formation of metastasis and DFS. High-throughput screening identified statins (mevastatin and lovastatin) as effective inhibitors of MACC1^[17]. MACC1 orchestrates proliferation, invasion and scattering of colon cancer cells by transcriptionally targeting the hepatocyte growth factor receptor^[18]. Lovastatin effectively attenuated liver metastasis in CRC-xenografted mice in a MACC1-dependent manner^[17]. In clinical practice, a recent large CRC cohort study showed statin therapy was associated with improved CRC-specific survival and other causes of mortality^[19]. Similarly, Gray *et al*^[20] showed that the pre-diagnosis use of statins was associated with improved survival in patients with CRC. However, recent studies have failed to observe the beneficial effects of statins in preventing and improving survival of cancer patients. A large meta-analysis by the Cholesterol Treatment Trialists' Collaboration which included 27 randomised trials and 175000 participants showed that statins had no effect on the incidence of cancer and the OS^[21]. In addition, a recent meta-analysis of eight randomized controlled trials failed to show that statins improved survival when added to systemic chemotherapy for seven solid cancers, including CRC^[22]. In the present study, statin therapy was not an independent prognostic factor for both disease-free and OS following liver resection in patients with CRLM. Furthermore, CRLM patients on statin therapy had similar clinical and histo-pathological features, suggesting that statin therapy did not have an effect on tumour biology. Our findings indicate that statin therapy does not affect patients' survival outcomes after they develop CRC metastases. Earlier statin-related studies have concentrated on outcome of CRC rather than alteration to the histology or outcome of CLRM, so cannot be easily compared to our current findings.

Table 2 Statistical analysis of prognostic factors for overall survival

Demographic, clinical and pathological factors	Overall Survival [median (range) mo]	Uni-variate analysis	Multi-variate analysis	Risk ratio (Confidence interval)
Age		0.373		
< 65 yr (n = 244)	39 (3-165)			
≥ 65 yr (n = 342)	35 (3-160)			
Gender		0.236		
Male (n = 389)	35 (3-165)			
Female (n = 197)	38 (3-160)			
Presentation		0.189		
Synchronous (n = 225)	46 (4-165)			
Metachronous (n = 361)	31 (3-160)			
Neutrophil-to-lymphocyte ratio		0.219		
< 5 (n = 490)	41 (4-153)			
≥ 5 (n = 96)				
Platelet-to-lymphocyte ratio		0.902		
< 150 (n = 287)	34 (5-165)			
≥ 150 (n = 299)	41 (3-156)			
Neo-adjuvant chemotherapy		0.002	0.014	0.710 (0.541-0.933)
Yes (n = 135)	37 (3-160)			
No (n = 451)				
Statin therapy		0.459		
Yes (n = 181)	34 (3-160)			
No (n = 405)	38 (3-165)			
Deprivation index		0.324		
1 (n = 101)	31 (4-152)			
2 (n = 120)	38 (3-160)			
3 (n = 115)	31 (5-147)			
4 (n = 142)	41 (4-159)			
5 (n = 108)	36 (4-165)			
Less than hemi-hepatectomy (n = 368)	38 (3-165)	0.002	0.004	1.441 (1.125-1.845)
Hemi-hepatectomy or more (n = 218)	36 (3-160)			
Largest tumour size		0.079		
< 5 cm (n = 406)	38 (3-159)			
≥ 5 cm (n = 180)	33 (3-165)			
Number of metastases		0.015	0.216	1.171 (0.912-1.504)
Solitary (n = 294)	40 (3-165)			
Multiple (n = 292)	34 (4-159)			
Steatosis		0.512		
None (n = 426)	32 (3-165)			
Mild (n = 97)	59 (5-154)			
Moderate - severe (n = 63)	67 (7-159)			
Lymphatic invasion		0.440		
Positive (n = 67)	56 (3-160)			
Negative (n = 519)	35 (3-165)			
Vascular invasion		0.130		
Positive (n = 264)	34 (3-160)			
Negative (n = 322)	40 (4-165)			
Peri-neural invasion		< 0.001	0.002	0.521 (0.342-0.795)
Positive (n = 38)	27 (3-101)			
Negative (n = 548)	38 (3-165)			
Biliary invasion		0.530		

Positive (<i>n</i> = 181)	37 (3-160)			
Negative (<i>n</i> = 405)	37 (4-165)			
Resection margin (R0)		< 0.001	0.004	1.462 (1.130-1.891)
R0 (<i>n</i> = 427)	39 (3-165)			
R1 (<i>n</i> = 159)	34 (4-160)			

The National Cancer Intelligence Network report “Cancer by Deprivation in England” which examined the variation of cancer incidence and mortality by socio-economic deprivation in England^[23] showed that the incidence and mortality for most cancers were higher in the more deprived areas. Cancer-specific survival rate following surgery for CRC is recognised to be lower in patients with lower socio-economic status^[24] but deprivation index does not have the same impact on outcome after resection of CRLM. A single-centre database study of 174 patients who underwent hepatectomy for CRLM showed that socioeconomic deprivation did not influence OS^[25]. A United Kingdom national database study of 13656 patients who presented with synchronous CRC liver-limited metastases^[26] and a single UK study of 303 patients who underwent resection for CRLM^[27] both showed that patients with better socio-economic status were more likely to undergo liver resection. Analyses restricted to patients who underwent liver resection showed the groups did not differ with respect to recurrence and 3-year OS^[26,27]. These observations are in keeping with the findings of the present study as the patient cohort was restricted to those patients who underwent liver resection. The present study used the IMD as it is the preferred index used by the United Kingdom government and is updated every 5-years. A possible explanation for CRLM patients’ outcome not being influenced by IMD may be the effective ‘hub and spoke’ working model between our tertiary HPB unit (hub) and other hospital Trusts in our network (spokes). As such, all liver resection patients receive equitable treatment in our tertiary HPB unit and a standardised follow-up irrespective of the referral centre. As there was no statistically significant relationship between IMD and use of statins or outcome of CRLM, we can conclude that IMD neither affects statin usage nor outcome of CRLM.

The prognostic factors influencing CRLM recurrence have been extensively investigated. Liver disease burden defined by tumour number and size, is recognised to adversely affect outcome after liver resection for CRLM^[28]. A recent meta-analysis to clarify controversy surrounding the role of margin status in determining prognosis of resected CRLM has shown that although an improved prognosis is seen with a margin > 1mm, and further improved survival is noted in patients with a margin > 1 cm^[29]. Previous studies have demonstrated that the effect of resection margin was influenced by tumour burden and tumour aggressiveness^[28]. However, Oshi *et al*^[30] showed that survival outcome did not differ in patients with low or high tumour burden irrespective of margin status, suggesting that response to systemic treatment may be central to achieving satisfactory outcomes. This may be due to the fact that neo-adjuvant systemic chemotherapy is considered for tumours with unfavourable biology.

Our present study also shows that peri-neural invasion (PNI) by CRLM independently predicts poor survival. PNI is a recognized route of neoplastic invasion and has been reported for a variety of tumours but the pathogenesis of PNI remains undefined.

In contrast with our current and previous^[9,11] results where the presence of PNI was associated with poorer OS in patients with treated with liver resection for CRLM, other researchers have not observed this finding irrespective of type of immunohistochemistry staining^[31]. Despite guidance from the National Comprehensive Cancer Network recommending that adjuvant chemotherapy is used in patients with early colon cancer demonstrating PNI^[32], there have been no studies specifically assessing the role of PNI in the management of CRLM.

Our study is the first evaluation of statin’s effect on outcome of curative resection of CRLM in patients who were regular statin users prior to diagnosis of CRLM. We have addressed the important question of whether statins can alter the biology of CRLM. The occurrence of CRLM cannot realistically be predicted for any one patient, so our retrospective study offers the most pragmatic method to study the subject. To ensure validity of results, our analyses incorporated multiple variables known to affect tumour biology. Reflecting real-life clinical practice, our patients were treated with a range of statins.

Statins differ in their pharmacological properties as some may be hydrophilic (such as Rosuvastatin and Pravastatin), others may be lipophilic (such as Atorvastatin, Simvastatin, and Fluvastatin), and there are also differences in their ability to lower

Table 3 Effect of statins on patient and tumour variables

Demographic, clinical and pathological factors	Statin therapy use (n = 181)	No statin therapy use (n = 408)	P value
Age > 65 yr	106	236	0.947
Male gender	119	270	0.827
Synchronous presentation	67	158	0.646
Neutrophil-to-lymphocyte ratio ≥ 5	22	74	0.065
Platelet-to-lymphocyte ratio ≥ 150	88	211	0.436
Neo-adjuvant chemotherapy	38	87	0.894
Hemi-hepatectomy or more	61	157	0.241
Largest tumour size ≥ 5 cm	53	127	0.615
Solitary hepatic metastases	91	203	0.973
Steatosis - None	127	299	0.634
Lymphatic invasion	16	50	0.215
Perineural invasion	13	20	0.276
Vascular invasion	88	176	0.246
Biliary invasion	62	119	0.238
Resection margin R0	133	294	0.823

low density lipoprotein cholesterol. There is no published evidence suggesting that different types of statins differ in the potential beneficial effect on cancer, and so we have not interrogated outcomes for individual statins. It would be interesting to see if a future prospective controlled study to test the role of statins in resected CRLM will detect differences in anti-cancer effect between statin subtypes. The study would have to be sufficiently powered as only 50% of CRC patients develop CRLM of which only 10%-20% are candidates for curative resection^[33].

Our study's limitations are that it is a single tertiary centre retrospective study and may not represent the experience of other centres. We also excluded CRLM patients who did not undergo resection so results apply only to those patients with CRLM treated with liver resection and not to all patients with CRLM. Finally, based on patient preference and tolerance, some switched statin type and doses of individual statins varied over the study period. The heterogeneity in statin type, doses used and length of time particular statins were used at particular doses made it difficult to analyse the effect of specific statins and specific doses as individual numbers were too small. We feel this is an important refinement that can be assessed by well-designed future studies prospectively following up patients who have CRC diagnosis and are taking statins while in surveillance for CRC metastases.

In conclusion, Statins did not affect the tumour traits or survival of patients with CRLM treated by liver resection. It is likely that once metastases are developed, only more aggressive therapy such as cytotoxic chemotherapy may be effective. We did not observe any beneficial effect of statins on OS despite the recognised health benefits of statin therapy. DFS and tumour biology of CRLM were unaffected by statins. Based on our findings, routine use of statin therapy in chemoprevention of CRLM is not currently justified but our findings will need further investigation through large multicentre cohorts.

ARTICLE HIGHLIGHTS

Research background

Liver metastases develop in 25%-30% of patients with colorectal cancer and one-quarter undergo surgical resection, the gold standard treatment, to achieve 5-year survival of 40%-50%. Unresected colorectal liver metastases carry a poor median survival of 3-20 mo. Further recurrences develop in 60% of patients after liver resection and median survival is only 8-10 mo if these are left untreated. Despite available multimodal treatment options, colorectal liver metastases still carry a poor prognosis and effective new treatment strategies are desirable.

Research motivation

There is a growing interest in chemopreventive agents to halt carcinogenesis. Developing new drugs is costly and so it is attractive to repurpose existing drugs for use as chemopreventive agents. Statins have been investigated for anti-tumour effects in other gastrointestinal cancers. Statin therapy has never been previously investigated as chemoprevention for colorectal liver metastases.

Research objectives

The main objective of this study was to assess whether Statins can serve as chemoprevention for colorectal liver metastases by evaluating the effect of Statin therapy on the histopathology of resected colorectal liver metastases and on the outcome of patients after resection of colorectal liver metastases.

Research methods

We included all patients who underwent primary hepatic resection for colorectal liver metastases with curative intent between 2005 and 2017 as identified using our institution's prospectively maintained database. We analysed data on patient demographics, statin therapy usage, liver resection, histopathology of colorectal liver metastases, and patients' clinical outcome.

Research results

Out of 586 patients who underwent resection of colorectal liver metastases at a median age of 68 (19-88) years, 181 patients used Statin therapy. During median follow-up time of 23 (12-96) mo, recurrent colorectal cancer metastases developed in 267 patients and a total of 131 patients died. Six independent predictors of poorer disease-free survival identified by multi-variate analysis were synchronous presentation, multiple tumours, tumour size ≥ 5 cm, moderate-severe steatosis, peri-neural invasion, and R1-resection margin. Four independent predictors of poorer overall survival identified by multi-variate analysis were the use neo-adjuvant chemotherapy, major hepatectomy, peri-neural invasion and R1-resection margin. Statin therapy did not affect histo-pathological or radiological traits of resected colorectal liver metastases, and did not affect patient outcomes.

Research conclusions

The study did not find any association between Statin therapy and the characteristics of resected colorectal liver metastases or patient survival following resection. This suggests that Statin therapy does not modulate tumour biology of resected colorectal liver metastases.

Research perspectives

Our study shows Statins do not affect resected colorectal liver metastases or patient outcomes following resection. The routine use of Statins as chemoprevention cannot be justified in this patient group. However, our study only focused on resected colorectal metastases. Future studies would need to also assess the effect of Statin therapy on non-resected colorectal liver metastases and on the outcome of these patients who do not undergo liver resection. Future studies will also need to assess the effect of specific Statins on colorectal liver metastases.

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