

Prognostic Factors after Liver Resection for Colorectal Liver Metastasis



Factores de Prognóstico após Ressecção de Metástases Hepáticas de Cancro Colo-Rectal

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ABSTRACT

Introduction: Surgery is the only potentially curative treatment for patients with colorectal liver metastases, resulting in 5-year survival rates of 36–58%. Although many studies have been performed to determine prognostic factors for tumor recurrence and survival after resection of colorectal liver metastases, there are few prognostic scoring systems stratifying patients undergoing surgery for colorectal liver metastases into risk group models.

Objectives: To identify, evaluate and compare the existing prognostic scores for survival after surgery for resection of colorectal liver metastases.

Material and Methods: Electronic search in PubMed, Cochrane and Embase from 1990 to 2013 using the terms 'hepatic resection', 'colorectal cancer', 'liver metastasis', 'hepatectomy', 'prognostic', and 'score'. Only studies proposing a prognostic model or risk stratification based on clinical and/or pathological variables were included.

Results: From 1996 to June 2013, 19 scoring systems were identified, including one nomogram. Thirty prognostic factors were identified although none of the factors was common to all prognostic models. The 4 factors most often included were: number of liver metastases, regional lymph node metastization of primary tumor, preoperative CEA level and maximum size of metastases. The median study sample size was 305 patients (81-1 568 patients) and median follow-up was 33 months (16-54 months). All studies were retrospective and used the Cox proportional hazards model for multi-variable analysis.

Conclusion: Several factors have been constantly reported as having prognostic value after liver resection of colorectal liver metastases, although there is no consensus on the ideal scoring system.

Keywords: Colorectal Neoplasms; Hepatectomy; Liver Neoplasms/secondary; Liver Neoplasms/surgery; Prognosis.

RESUMO

Introdução: A ressecção de metástases hepáticas é o único tratamento potencialmente curativo em doentes com metástases hepáticas de cancro colo-rectal, resultando numa sobrevida global de 36-58%. Até à data foram publicados múltiplos trabalhos sobre factores de prognóstico após hepatectomia em doentes com metástases hepáticas de cancro colo-rectal. No entanto, poucos apresentaram modelos de prognóstico que permitam estratificar os doentes em grupos de risco, relacionando-os com sobrevida após metastasectomia hepática.

Objectivos: Identificar, avaliar e comparar os diferentes *scores* de prognóstico após ressecção de metástases hepáticas de cancro colo-rectal.

Material e Métodos: Pesquisa na PubMed, Cochrane e Embase, de artigos publicados entre 1990 e 2013, usando os termos 'ressecção hepática', 'cancro colo-rectal', 'metástases hepáticas', 'hepatectomia', 'prognóstico' e 'modelo'. Apenas os artigos que apresentaram modelos de prognóstico com base em variáveis clínico-patológicas foram incluídos.

Resultados: De 1996 a Junho de 2013, 19 modelos de prognóstico foram identificados, incluindo um nomograma. Foram identificados 30 diferentes factores prognósticos, embora nenhum factor fosse comum a todos os modelos prognósticos. Os factores mais frequentemente incluídos foram: número de metástases hepáticas, envolvimento ganglionar regional do tumor primário, nível sérico de CEA pré-operatório e tamanho máximo das metástases. A amostra mediana foi de 305 doentes (81-1 568 doentes) e o seguimento mediano foi de 33 meses (16-54 meses). Todos os estudos foram retrospectivos e utilizaram o modelo proporcional de Cox para análise multivariada.

Conclusão: Vários factores têm sido constantemente reportados como tendo valor prognóstico após ressecção de metástases hepáticas de cancro colo-rectal, no entanto, não existe consenso sobre o modelo ideal de prognóstico.

Palavras-chave: Hepatectomia; Neoplasias Colo-rectais; Neoplasias Hepáticas/cirurgia; Neoplasias Hepáticas/secundárias; Prognóstico.

BACKGROUND

Colorectal cancer (CRC) is the third most common tumor in men and the second in women, accounting for 10% of all tumor types worldwide.¹ An increasing incidence of CRC has been observed in countries where the overall risk of large bowel cancer was low, while in historically high-risk countries either a decrease (USA, Canada and New

Zealand) or stabilization (Western Europe and Australia) has been reported.^{1,2}

In Europe, colorectal cancer (CRC) is the third most frequent cancer in the 27 countries of the European Union (EU), after breast and prostate, accounting for 13% of all cancer and is the second most frequent cause of death after

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lung cancer.^{3,4}

In 2012, new cancer cases in Europe were estimated to be 342137 (almost 1000 patients per day), comprising 191620 males (56%) and 150514 females (44%). The proportion of rectal cancer cases is variable depending on the cancer registry and classification of recto-sigmoid tumors, ranging from 27% to 58%.^{3,5}

The estimated number of deaths caused by CRC was 149984, comprising 53% males and 47% females.^{3,4}

A considerable variation among different EU countries has been observed. The highest incidence of CRC among males is observed in central European countries compared to very low rates in Greece and Cyprus. Among females, the EU countries with the highest incidence are Denmark and the Netherlands and the lowest incidence in Greece and Finland. Concerning mortality, the variability among countries is lower than variability in incidence, probably related to differences in stage of presentation and management strategies between countries.³

A gradient of increasing incidence and mortality due to CRC between North Western and South Eastern Europe has been observed. The growing incidence of CRC in historically low-risk areas, such as Spain and Eastern Europe reflects modifications in lifestyle behaviors and their consequences such as obesity, high red meat consumption, heavy alcohol consumption, smoking and physical inactivity.¹

In Europe, since the 1980s, survival has markedly improved. From 1980 until 2000–2002, five-year survival for all patients increased from 51% to 60% in northern Europe; from 52% to 62% in western European and from 45% to 58% in southern European registries.³

The relative increase in survival was 2% higher among females than among males across all registries. In general, improvement in survival was lower among patients with 75 years or older.³

Concerning stage at diagnosis, almost no progress in survival was observed among patients diagnosed with metastatic disease, while a markedly improvement in survival was observed among patients diagnosed in local or regional disease.^{3,5}

CRC screening has been shown to be effective in reducing mortality of the population aged 55–74 years and possibly incidence as well. A Cochrane review showed a relative reduction of 16% in the risk of CRC death using fecal occult blood tests (FOBT) every 2 years.^{3,6} Over the last few years, randomized trials have shown convincing evidence of the efficacy of flexible sigmoidoscopy in reducing the incidence and mortality from CRC.^{3,7,8}

Decrease in mortality can be attributed, not only to CRC screening^{9,10} with consequent removal of adenomas, early detection of pre-cancerous and cancerous lesions, as well as the availability of more effective therapies, mainly for early stage disease.¹

Surgical resection is the most effective therapy for metastatic colorectal cancer limited to the liver. Several studies from major centers have demonstrated that resection of as much as 80% of the liver can be performed

with an associated surgical mortality rate uniformly less than 5%.¹¹⁻¹⁷

Surgery is the only potentially curative treatment for patients with colorectal liver metastases (CRLM), with studies suggesting an overall 5-year survival rate of 36–58% in contemporary series.¹⁸⁻²⁵

Many studies have been performed to determine prognostic factors for tumor recurrence and survival after liver resection of CRLM. Nevertheless, only a few studies have presented prognostic scoring systems stratifying patients with CRLM submitted to surgery into risk group models which allow optimal clinical management of each patient.

OBJECTIVES

The aim of this review is to identify, evaluate and compare the existing prognostic scores that evaluate prognostic factors involved in the patient's outcome after liver resection for colorectal liver metastasis.

MATERIAL AND METHODS

An electronic search initially using the PubMed database, and later complemented by Cochrane and Embase databases was performed using the terms ('prognostic' OR 'prognosis') AND ('factors' OR 'factor' OR 'score' OR 'model') AND ('CRC' OR 'colorectal') AND ('metastasis' OR 'metastatic') AND ('liver resection' OR 'hepatic resection' OR 'hepatectomy').

Were found 1 706 articles. Articles published before 1990 (128) were excluded. After analyzing the study abstracts, 194 articles concerning animal studies were excluded. Articles written in other languages than English, French, Spanish and Portuguese were excluded (n = 230). All case reports were also excluded (n = 205). The selection of the articles was performed by the first author of this study.

From the remaining 949 studies, all studies considered irrelevant for the subject or those analyzing prognostic factors (after resection of CRLM) but not presenting a scoring system, or including patients with unresectable disease were also excluded (n = 921). From the selected studies both abstracts and full text were analyzed.

One study²⁶ that compared 2 clinical risks scores and TNM score, but did not present a new model, was also excluded. Studies that presented an external validation of prognostic scores were also excluded (n = 6). One study²⁷ performed an external validation of 5 different prognostic models with the same population.

Two studies presented scoring systems as part of the analyzed prognostic factors, namely Glasgow Prognostic Score (GPS)²⁸ and modified Glasgow Prognostic Score (mGPS).²⁹ These 2 scores took into account the elevation of c-reactive protein (CRP of > 10 mg/L) and hypoalbuminemia (< 35 g/L). However, as these studies evaluated both GPS and mGPS as one of the studied variables, and did not present a newer prognostic score, they were not included in the present study.

Finally, 19 different studies that presented a prognostic

model or risk stratification based on clinical, laboratorial and/or pathological variables were included in this study. (Fig. 1)

The selected articles were analysed (both abstract and full text article). Extracted and analysed data were: year of the study, authors and corresponding centre, number of patients included in each study, number of centres included, period of the study (years), median follow-up of patients (months), endpoint of the study, total number of prognostic factors tested, number and type of independent prognostic factors included in each prognostic score, risk groups evaluated in each prognostic score, 5-years overall survival after resection and type of validation of the score (internal/

external).

Data were analysed using Excel 2010™ and STATA™.

RESULTS

Several studies have correlated demographic, clinical and pathological factors with survival after hepatectomy in patients with CRLM. However, there are few studies that have presented prognostic scoring systems. To our knowledge only 2 review articles about scoring systems have been published analyzing a fewer number of scoring systems.^{30,31}

Between January 1996 and June 2013, we identified 19 scoring systems, including 1 nomogram developed by

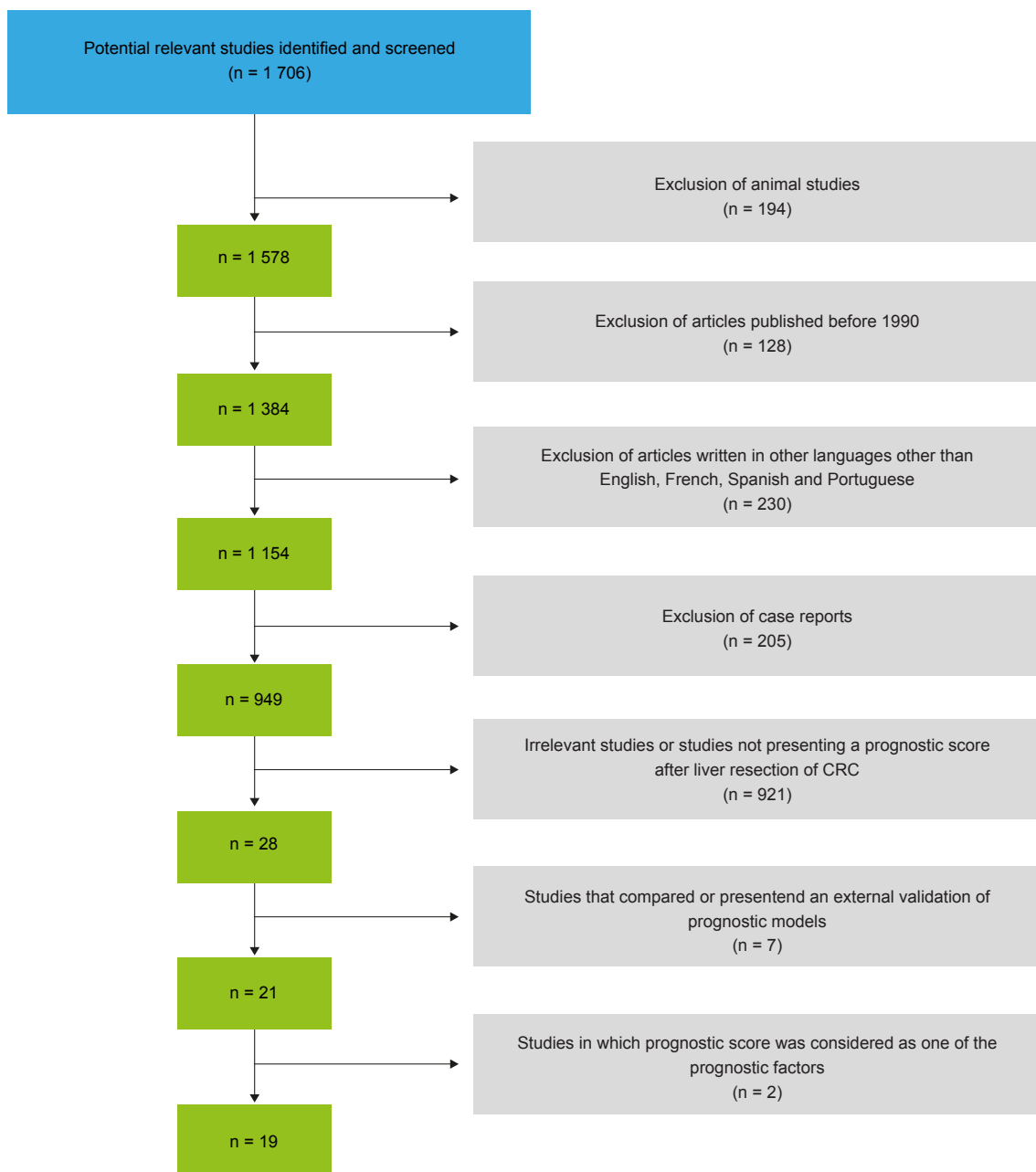


Figure 1 - Diagram representing the systematic selection of articles concerning predictive models for outcomes after liver resection of CRC liver metastasis.

Table 1 - Study characteristics of the evaluated prognostic models for outcome after resection of liver metastasis of patients with colorectal cancer

Authors	Year	N. Patients	N. Centers	Period	Median Follow-up (months)	Center	Endpoint	N.Prognostic Factors (N.tested)	Validation	5-year OS after resection
Nordlinger et al ³³	1996	1 568	85	1968-1990	19.0	85 centers, France	OS	7 (13)	I + E(N)	28.0%
Fong et al ¹¹	1999	1 001	1	1985-1998	32.0	New-York, USA	DFS	7 (13)	E	37.0%
Iwatsuki et al ³⁴	1999	305	1	1981-1996	32.0	Pittsburgh, USA	OS+DFS	6 (16)	E	32.3%
Ueno et al ³⁵	2000	85	1	1985-1996	52.0	Saitama, Japan	OS	5 (18)	N	27.9%
Lise et al ³⁶	2001	132	1	1977-1997	22.0	Padova, Italy	DFS	5 (20)	N	29.0%
Nagashima et al ³⁷	2004	81	1	1981-1997	36.3	Tokyo, Japan	OS	5 (15)	E	X
Tanaka et al ³⁸	2004	149	1	1992-2001	30.0	Yokohama, Japan	OS+DFS	4 (15)	N	49.3%
Schindl et al ³⁹	2005	270	1	1988-2002	16.0	Edinburgh, UK	OS	5 (15)	E	36.0%
Malik et al ⁴⁰	2007	687	1	1993-2006	34.0	Leeds, UK	OS+DFS	2 (11)	N	45.0%
Zakaria et al ⁴¹	2007	662	1	1960-1995	36.0	Rochester, USA	DFS	2 (16)	E(N)	37.0%
Lee et al ⁴²	2008	135	1	1994-2005	47.2	Seoul, South Korea	OS	4 (12)	N	-
Rees et al ²⁰	2008	929	1	1987-2005	26.0	Basingstoke, UK	DSS	7 (20)	I + E(N)	X
Konopke et al ⁴³	2009	201	1	1993-2006	31.0	Dresden, Germany	OS+DFS	3 (13)	I	43.0%
Mitnagawa et al ⁴⁴	2007	369	4	1980-2002	49.0	Tokyo, Japan	OS	4 (22)	E	38.0%
Tan et al ⁴⁵	2008	285	2	1995-2005	54.0	Saint Louis and Nashville, USA	OS	2 (15)	N	48.0%
Yamaguchi et al ⁴⁶	2008	380	18	1992-1996	31.4	Tokyo, Japan	OS	4 (4)	N	30.7%
Adam et al ¹⁷	2011	840	1	1990-2006	38.0	Villejuif, France	OS+DFS	5 (31)	E(N)	28.0%
Hill et al ⁴⁸	2012	280	1	1996-2007	50.1	Louisville, USA	DFS + SAF	2 (11)	N	-
Kattan et al ³²	2008	1 477	1	1986-1999	-	New York, USA	DSS	10	E	-

Internal- E-external; E(N)-non-validated by external validation; DFS- disease free survival; OS- overall survival; DSS- disease specific survival; SAF- survival after recurrence.

Kattan et al,³² concerning factors that influence survival after surgery of CRLM. (Table 1)

Seven scoring systems were proposed from European institutions (UK = 3, France = 2, Italy = 1, Germany = 1), 6 from Asian (Japan = 5, South Korea = 1) and 6 from North American institutions (USA = 6) centers. The median study sample size was 305 patients (range 81–1568 patients) and the median follow-up was 33 months (range 16–54 months). All studies were retrospective in nature and the numbers of groups proposed by the various scoring systems ranged from three to six. All studies used the Cox proportional hazards model for multi-variable analysis.

All prognostic scoring systems were analyzed and prognostic factors, as well as risk group categories included in each model are described in Table 2.

Prognostic factors

From the 18 prognostic scores and one nomogram presented, 30 factors that independently influenced prognosis factors after surgery of CRLM were identified (Table 3).

The most cited factor was the number of liver metastases, identified by 15 different studies^{11,20,32,37,39,40,42-44,46,47} as a negative prognostic factor. Only four studies^{38,41,45,48} did not present it as a negative prognostic factor of survival after resection of CRLM.

Twelve studies referred lymph node positivity for the primary tumor as a negative prognostic factor.^{11,20,32,33,35-37,39,42,44-46}

Nevertheless, six studies^{34,38,40,41,47,48} concluded that regional lymph node metastases of primary tumor was not a significant prognostic factor for survival. This fact was supported by other studies not included in the analysis.⁵⁰⁻⁵⁵ Thus, the prognostic value of lymph node spread of primary tumor remains controversial.

Preoperative elevation of CEA was pointed in nine studies as a negative prognostic factor.^{11,20,32,39,42-44,47,48} However, different studies used different cut-offs ranging from five⁴² to 200 ng/mL.^{11,43,48} Nine studies concluded that preoperative elevation of CEA is not significant as a prognostic factor after resection of CRLM.^{33,35-37,40,41,45}

Maximum size of hepatic metastases was indicated as a prognostic factor in eight studies^{11,20,32,33,34,37,41,46} and was considered without importance in 8 other studies.^{35,36,38-40,42-45,47,48}

Extrahepatic disease (EHD) was considered a poor prognostic factor in seven of the nine prognostic scores that evaluated this parameter.^{11,20,34,37,46-48} In the majority of the analyzed studies patients with EHD were excluded from the analysis as many authors consider EHD a negative prognostic factor being considered as a contraindication for surgery of liver metastases in many institutions. Recently, studies have shown the contrary^{56,57}; that isolated lung metastases when surgically resectable are no longer a contraindication for surgery and long-term survival can be archived with complete resection.^{31,47,57} Adam et al,⁴⁷ developed a prognostic score for patients with resected

CRLM and concomitant extrahepatic disease (EHD) submitted to surgery and concluded that the five negative prognostic factors for survival of this group of patients were: EHD-location other than lung metastases, EHD concomitant to CRLM recurrence, CEA ≥ 10 ng/mL, ≥ 6 liver metastases, and right colon cancer. Therefore, patients with CRLM with metachronous diagnosis of EHD, with < 6 liver metastases at diagnosis, presenting with isolated lung metastases and a CEA level < 10 ng/mL, and in whom the primary tumor is not located in the right colon, had a good long-term survival after complete resection of disease, and were considered optimal candidates for this treatment strategy. Taking into account that surgery of all resectable disease is the best chance of long-term survival, whenever technically possible, surgery should be discussed. However, in an external validation of the referred prognostic model made by Mavros et al,²⁵ none of these factors reached statistical significance, and only EHD other than isolated lung metastases was found to independently predict overall survival.

As for EHD, the presence of positive margins has also been considered, by many authors, as a poor prognostic factor being excluded from analysis in the majority of studies. In only six studies, positive margins were analyzed, being considered as a poor prognostic factor in three^{11,20,34} of the six studies. In 2010, Poultides GA et al⁶⁰ published a revision article about the impact of the surgical margin on the outcome after hepatic resection of colorectal metastases. The authors evaluated multiple studies that have specifically examined the role of a microscopically positive margin on overall survival and reported that, with the exception of one recent report,⁶¹ all previous studies^{11,62-66} have demonstrated consistently that a microscopically positive R1 margin is strongly correlated with worse overall survival. Concerning the optimal size of surgical margin, Poultides GA et al⁶² concluded that, although an R1 resection should clearly be avoided, the actual margin width of an R0 resection does not impact on outcome after resection of CRLM. As such, failure to comply with the 1 cm rule can no longer be considered a contraindication for the surgical resection of CRLM.

There is a wide range in the cut-off interval of time between surgery for primary tumor and diagnosis of hepatic metastases ranging from 12^{11,35} to 30 months.³⁴ Six studies^{11,32,33,34,35,41} considered the interval between the surgery for the primary colorectal tumor and the diagnosis of liver metastases as a prognostic factor, and six other studies^{37,40,43,44,47,48} did not find statistically relevance of this factor.

Bilobar spread was considered a poor prognostic factor in only three studies,^{32,34,38} while in 11 other studies it was considered without importance.^{11,20,33,35,37,39,41,43-45,47}

Poor differentiation of primary tumor was considered a negative prognostic variable in only three studies^{20,38,45} while in four other studies^{34,35,39,44} it was not significantly associated with outcome.

Two studies^{33,37} suggested that serosal invasion of primary tumor was a negative prognostic factor while two others studies did not find any difference.^{35,38}

Table 2 - Prognostic factors, Risk-group, score and 5-years OS evaluated in each scoring system

Authors	Independent prognostic factors	Groups	Score	Outcome (5 years)
Nordlinger et al ³³	Age ≥ 60 years	Low risk (n = 305)	0 - 2	2 year - 79%
	Serosal invasion of primary tumor	Intermediate Risk (n = 738)	3 - 4	60%
	Node-positive primary	High risk (n = 230)	5 - 7	43%
	Liver metastasis < 2 years			
	Liver metastasis ≥ 4			
	Margin ≤ 1 cm Metastasis size ≥ 5 cm			
Fong et al ¹¹	Margin involved	0 (n = 52)	0	60%
	Extra-hepatic disease	1 (n = 262)	1	44%
	Node-positive primary	2 (n = 350)	2	40%
	Liver metastasis < 1 year	3 (n = 243)	3	20%
	Metastasis size ≥ 5 cm	4 (n = 80)	4	25%
	CEA > 200 ng/ml Liver metastasis > 1	5 (n = 14)	5	14%
Iwatsuki et al ³⁴	Liver metastases ≥ 2	Grade 1 (n = 32)	0	48%
	Metastasis size ≥ 8 cm	Grade 2 (n = 112)	1	34%
	Bilobar distribution	Grade 3 (n = 47)	2	18%
	Interval between colorectal and liver resection ≤ 30 months	Grade 4 (n = 47)	3	6%
	Margin involved	Grade 5 (n = 5)	4	1%
	Extrahepatic disease	Grade 6 (n = 62)	R1	0%
			EHD	
Ueno et al ³⁵	Primary site aggressiveness (marked tumour budding /node-positive)	Group A (n = 30)	H-A 0 or either liver metast < 1 year or ≥ 3 liver met	3-year: 80%
	Liver metastasis < 1 year	Group B (n = 46)	H-B Primary site aggres or both liver metast < 1 year and ≥ 3 liver met	55%
	Liver metastases ≥ 3	Group C (n = 9)	H-C- All 3 factors	10%
Lise et al ³⁶	> 30% liver invasion	Group A (n = 38)	0 - 2	3-year: 80%
	Node-positive primary	Group B (n = 36)	3 - 5	55%
	Liver metastasis > 1	Group C (n = 58)	≥ 6	10%
	GPT levels ≥ 55 U/l Non-anatomical resection			
Nagashima et al ³⁷	Serosal invasion of primary tumor	Grade A (n = 28)	0 - 1	85%
	Node-positive primary	Grade B (n = 14)	2 - 3	56%
	Resectable extrahepatic disease	Grade C (n = 13)	> 3	0%
	Liver metastasis >1 Metastasis size 5 cm			

continues...

Table 2 - Prognostic factors, Risk-group, score and 5-years OS evaluated in each scoring system (continued)

Authors	Independent prognostic factors	Groups	Score	Outcome (5 years)
Tanaka et al ³⁸	Poorly-dif. ADC or mucinous carc. (Poor/muc)	Stage I (n = 55)	0 factors	61.1%
	Marked vascular invasion (V)	Stage II (n = 67)	bi-lobular met or short DT	51.3%
	Bi-lobular liver metastasis	Stage III (n = 20)	2 factors marked and/or vascular invasion	0% (mean survival 780d)
	Short doubling time (DT) of the liver tumor	Stage IV (n = 7)	Poor/muc	0% (mean survival 257d)
Schindl et al. ³⁹	Duke's stage C			
	CEA level	Good (n = 33)	0 - 10 points	60 months
	Alkaline phosphatase	Moderate (n = 172)	11 - 25 points	32 months
	Albumin	Poor (n = 65)	> 25 points	22 months
	Liver metastasis > 3			
Malik et al ⁴⁰	Inflammatory response (CRP > 10mg/L or Neut/Linf > 5:1)	0 (n = 382)	0 factors	49%
	Liver metastases ≥8	1 (n = 155)	1 factors	34%
		2 (n = 23)	2 factors	0%
Zakaria et al ⁴¹	Blood transfusion	Group 1	0	55%
	Positive hepatoduodenal nodes (HDN)	Group 2	Blood transfusion	39%
	Liver metastasis ≤ 30 months	Group 3	HDN	20%
	Metastasis size ≥ 8 cm	(Note: n was not stated)		
Lee et al ⁴²	Margin ≤ 5 mm	Low risk (n = 85)	0 - 1	46%
	CEA > 5 ng/ml	Intermediate risk (n = 36)	2	41%
	Node-positive primary ≥ 4	High risk (n = 14)	3 - 4	11%
	Liver metastases > 1			
Rees et al ²⁰	Liver metastases > 3			Preop
	Node-positive primary	0	0	66%
	Poorly differentiated primary	1 - 5	1 - 5	51%
	Extrahepatic disease	6 - 10	6 - 10	35%
	Metastasis size ≥ 5 cm	11 - 15	11 - 15	21%
	CEA > 60 ng/ml	> 15	> 15	2%
	Margin involved	(n was not stated)		

continues...

The prognostic relevance of hepatic lymph node metastases was only evaluated in two studies,^{41,44} and both suggested a negative prognostic value.

Age of 60 years or more was referred by Nordlinger et al³³ as a negative prognostic factor. Age was also included in the nomogram developed by Kattan et al.³²

Some factors have been pointed as negative prognostic factors in only one prognostic score: marked tumour budding (defined as micro-tubular cancer nests or microscopic

clusters of undifferentiated cancer cells) was presented by Ueno et al,³⁵ short doubling time of the liver tumor and marked vascular invasion were identified only in the study by Tanaka et al.³⁸

Synchronous liver metastases was identified as a negative prognostic factor for survival by Konopke et al.⁴³ More than 30% of liver invasion and non-anatomical resection were only referred by Lise et al,³⁶ and surgical margin ≤ 5 mm by Lee et al,⁴² while extensive resection

Table 2 - Prognostic factors, Risk-group, score and 5-years OS evaluated in each scoring system (continued)

Authors	Independent prognostic factors	Groups	Score	Outcome (5 years)
Konopke et al ⁴³	Liver metastasis ≥ 4			Median survival:
	Synchronous liver metastases	Low risk (n = 112)	0	67 months
	CEA ≥ 200 ng/ml	Intermediate risk (n = 74)	1	47 months
		High risk (n = 15)	2	38 months
Minagawa et al ⁴⁴	hepatic lymph node metastasis			Median survival (original cohort)
	≥ 4 colorectal lymph node metastasis	stage 1 (n = 78)	0	7.2 years
	CEA > 50 ng/ml	stage 2 (n = 129)	1	3.5 years
	multiple hepatic metastasis	stage 3 (n = 111)	2 - 3	2.0 years
		stage 4 (n = 4)	hepatic lymph node metastasis	1.3 years
Tan et al ⁴⁵	Tumor Grade (Poorly vs well or moderately-differentiated)	Poor Dif. (n = 44)	Poor Dif.	not referend
	Lymph Node (positive vs negative)	Well/mod. dif. + node negative (n = 86)	Well/mod. dif. + node negative	not referend
		Well/mod. dif. + node positive (n = 122)	Well/mod. dif. + node positive	not referend
Yamaguchi et al ⁴⁶	≥ 5 liver metastasis	Stage A	HT1 + pN0/1 + EM0	53.50%
	Largest liver metastasis ≥ 5 cm	Stage B	(HT2 + PN0-1 or HT2 + pN0-1) + EM0	25.40%
	≥ 4 mesenteric lymph node metastasis	Stage C	HT3 or EM1	5.80%
	Extrahepatic metastasis	(n was not stated)		
Adam et al ⁴⁷	EHD other than isolated lung metastasis	0 (n = 8)	0	64%
	CEA ≥ 10 ng/ml	1 (n = 44)	1	25.6-43.9%
	> 5 liver metastasis	2 (n = 60)	2	4.9-22.2%
	Right colon as the primary CRC location	3 (n = 45)	3	0.2-4.0%
	Diagnosis of EHD concomitant to CRLM recurrence	4 (n = 11)	4	0-0.1%
	5 (n = 2)	5	0%	

continues...

(lobectomy or more) was included on the nomogram by Kattan et al.³²

Other negative prognostic factors included on the evaluated scoring systems were: serum concentration of alkaline phosphatase and albumin, referred by Schindl et al,³⁹ GPT levels ≥ 55 U/l referred by Lise et al,³⁶ inflammatory response (defined by an elevated C-reactive protein (> 10 mg/L) or a neutrophil/lymphocyte ratio of > 5:1), stated by Malik et al,⁴⁰ and necessity of blood transfusion pointed by Zakaria et al.⁴¹

Right colon as the primary colorectal location and diagnosis of extrahepatic disease concomitant to CRLM recurrence were identified by Adam et al⁴⁷ as poor prognostic factors in patients with extrahepatic disease undergoing resection of CRLM. However, as previously stated, in an external validation of the referred prognostic model made by Mavros et al,²⁵ none of these factors reached

statistical significance, and only EHD other than isolated lung metastases was found to independently predict overall survival.

The unique prognostic score that proposed the pattern of recurrence as a poor prognostic factor for survival after recurrence was developed by Hill et al.⁴⁸

Gender and primary cancer site (colon *versus* rectum) were also included in the nomogram developed by Kattan et al.³²

None of the studies included chemotherapy as a prognostic factor because of its failure to achieve statistical significance. Nevertheless, Konopke et al⁴³ pointed that, in the subgroup of high-risk patients, neoadjuvant chemotherapy improved the survival of the patients who underwent both chemotherapy and resection compared with those who underwent resection only. In the future, prognostic scores could be useful in selecting patients who

Table 2 - Prognostic factors, Risk-group, score and 5-years OS evaluated in each scoring system (end)

Authors	Independent prgnostic factors	Groups	Score	Outcome (5 years)
Hill et al ⁴⁸	After recurrence Prognostic Factors:	1		Median OS
	CEA > 200 ng/ml (= 2 points)	2 - 3	1	49.9M
	Pattern of recurrence	4 - 5	2 - 3	29.6M
	.Liver only or lung only (= 1 point)	(n was not stated)	4 - 5	22.0M
	.EHD or liver and lung only (= 2 points)			
	.EHD and liver (= 3 points)			
	After Hepatectomy:			
CEA > 200 ng/ml				
> 1 metastasis				
High Fong score				
Kattan et al ³²	Nomogram	-	-	-
	Nodal status of the primary tumor			
	Disease-free interval			
	Size of the largest metastatic tumor			
	Preoperative CEA			
	Bilateral resection			
	Extensive resection (lobectomy or more)			
	Gender			
	Number of hepatic tumors			
	Primary cancer site (colon vs rectum)			
	Age			

HT1 = (≤ 4 liver metastasis and largest liver metastasis ≤ 5 cm), HT2 = ≥ 5 liver metastasis or largest liver metastasis > 5 cm); HT3 = (≥ 5 liver metastasis and largest liver metastasis > 5 cm), pN0/1 = ≤ 3 mesenteric lymph node metastasis, pN2 = ≥ 4 mesenteric lymph node metastasis, EM1 = presence of extrahepatic metastases, EM0 = absence of extrahepatic metastases, EHD = Extrahepatic disease, DSS = Disease Specific Survival, SAF survival after recurrence; HDN - positive hepatoduodenal nodes

would benefit from neoadjuvant or adjuvant chemotherapy.

Currently, the only nomogram for predicting disease-survival after segmental hepatic resection for CRLM, was developed by Kattan et al³² following analyses of all patients admitted to Memorial Sloan-Kettering Cancer Center (MSKCC) for curative intent for treatment of metastatic disease from CRC between 1986 and 1999. A nomogram was developed as a graphical representation of a Cox proportional hazards regression model, using as prognostic factors: nodal status of the primary tumor, disease-free interval, size of the largest metastatic tumor, preoperative CEA, bilateral resection, extensive resection (lobectomy or more), gender, number of hepatic tumors, primary cancer site (colon vs rectum), and age. The advantage of the nomogram is that, rather than counting risk factors, it takes the specific value for each factor into consideration. For example, instead of considering a preoperative

CEA value above 200 to be a risk factor, the nomogram considers the patient's actual CEA value, and calculates risk accordingly, being more specific to the individual patient and thus predicting more accurately. In order to compare the prediction ability of the nomogram, Kattan et al³² applied the clinical risk score (CRS) developed by Fong et al.¹¹ When refit to those patients used in the original CRS, the nomogram predicted more accurately than did the Fong score when applied to the same validation set.

Later on, in 2013, Reddy et al⁴⁹ presented an external validation of this nomogram using an external cohort of 203 patients who underwent resection of CRLM between 1996 and 2006. After a median follow-up of 30.4 months, Kaplan-Meier estimates for 3, 5 and 8-year post-resection DSS were 56%, 41%, and 32%, respectively; similar to nomogram predicted probabilities for disease specific survival (DSS). The concordance index for the nomogram was higher

Table 3 - Prognostic factors in the analysis of the prognostic scoring systems after resection of liver metastasis of patients with colorectal cancer

Number of studies	16	12	9	8	7	6	3	3	3	2	2
	N liver metast	Node positive primary	Preoperative CEA level	Maximum size of metastases	Extrahepatic spread	Interval between CRC surgery and diagnosis of LM	Positive resection margins	Bilobar spread	Poor different of primary	Serosal invasion of primary	Hepatic lymph node metast.
Nordlinger et al ³³	Y	Y	N	Y	-	Y	-	N	-	Y	-
Fong et al ¹¹	Y	Y	Y	Y	Y	Y	Y	N	-	-	-
Iwatsuki et al ³⁴	Y	N	-	Y	Y	Y	Y	Y	N	-	-
Ueno et al ³⁵	Y	Y	N	N	-	Y	-	N	N	N	-
Lise et al ³⁶	Y	Y	N	N	-	-	-	-	-	-	-
Nagashima et al ³⁷	Y	Y	N	Y	Y	N	-	N	-	Y	-
Tanaka et al ³⁸	N	N	-	N	N	-	-	Y	Y	N	-
Schindl et al ³⁹	Y	Y	Y	N	-	-	-	N	N	-	-
Malik et al ⁴⁰	Y	N	N	N	-	N	N	-	-	-	-
Zakaria et al ⁴¹	N	N	N	Y	-	Y	N	N	-	-	Y
Lee et al ⁴²	Y	Y	Y	N	-	-	-	-	-	-	-
Rees et al ²⁰	Y	Y	Y	Y	Y	-	Y	N	Y	-	-
Konopke et al ⁴³	Y	-	Y	N	-	N	-	N	-	-	-
Minagawa et al ⁴⁴	Y	Y	Y	N	N	N	-	N	N	-	Y
Tan et al ⁴⁵	N	Y	N	N	-	-	-	N	Y	-	-
Yamaguchi et al ⁴⁶	Y	Y	-	Y	Y	-	-	-	-	-	-
Adan et al ⁴⁷	Y	N	Y	N	Y	N	-	N	-	-	-
Hill et al ⁴⁸	N	N	Y	N	Y	N	N	-	-	-	-
Kattan et al ³²	Y	Y	Y	Y	-	Y	-	Y	-	-	-

Y: yes, N: no, -: not evaluated.

(0.602) than for the Fong colorectal risk score (CRS; 0.533). Therefore, the CRLM nomogram was validated by an external cohort and more accurately predicted post-resection survival than the commonly used CRS.

Endpoints

Not all studies had overall survival (OS) as the endpoint. Some studies had disease-free survival (DFS)^{11,36,42} as endpoint and some had both OS and DFS^{34,38,40,43,47}. Hill et al⁴⁸ had as endpoints DFS and survival after recurrence while Kattan et al³² and Rees et al²⁰ had disease specific survival (DSS).

Validation of models

Before prognostic scores can be widely implemented, it is very important their validation. The validation of a model can be internal or external. The majority of the prognostic scores was not validated.

The models developed by Nordlinger et al,³³ Rees et al²⁰ and Konopke et al⁴³ underwent internal validation while models presented by Nagashima et al,³⁷ Schindl et al³⁹ and Minagawa et al.⁴⁴ underwent external validation. The model presented in 2008 by Kattan et al³² was validated in 2009 by Reddy et al⁴⁹ with an unrelated cohort from a different institution. The external validation concluded that the CRLM nomogram more accurately predicted post-resection survival than the commonly used CRS developed by Fong et al.¹¹

The model presented by Adam et al⁴⁷ was externally validated by Mavros et al.²⁵ However the authors concluded that of the 5 proposed risk factors, only EHD other than isolated lung metastases was found to independently predict overall survival. A study presented by Reissfelder et al²⁷ performed an external validation with 281 patients of 5 different prognostic scoring systems for patients undergoing resection of colorectal cancer liver metastases: Nordlinger score,³³ MSKCC score,¹¹ Iwatsuki score,³⁴ Basingstoke index, (Rees et al)²⁰ and Mayo scoring system (Zacaria et al).⁴¹ They concluded that only MSKCC score¹¹ ($p = 0.006$) and the Iwatsuki score³⁴ ($p = 0.01$) provided a statistically significant stratification of patients with regard to survival.

DISCUSSION

Limitations of the prognostic scoring systems

The ideal prognostic score has not yet been defined. All prognostic scores presented have some limitations.

All the studies proposing prognostic scores were retrospective studies. Some studies reported patients submitted to surgery in 1970 and 1980 decades. Since then, much progress has been achieved, not only in surgical techniques, but also, in the anesthesia and pre and post-operative care. Due to this progress, surgical related morbidity and mortality has been decreased in the last decades.

Selection of variables has changed a lot between different prognostic scores. While some variables were pointed as negative factors in many studies (number of liver

metastases, node positive primary, preoperative CEA level, maximum size of metastases), some variables have been reported in only one prognostic score. Thus, the identification of the ideal scoring system remains controversial.

Another important aspect not correctly evaluated by these prognostic scoring systems is the importance of neoadjuvant and adjuvant chemotherapy. In the last 2 or 3 decades many agents have been approved and showed increase survival not only in the adjuvant, but also in the metastatic setting in the colorectal cancer treatment.

The median sample size is 305 patients, ranging from 81 to 1568 patients. Studies with smaller population may have greater risk of bias compared to studies including larger sample sizes.

As referred, the fact that almost all prognostic scoring systems had excluded extrahepatic disease and positive surgical margins of primary tumor, is another important limitation of the analysis because it is not possible to compare strictly different populations.

Another limitation was the fact that different studies had different endpoints, OS, DFS or DSS; and the limited number of studies that were validated. As referred in the results section, only few models were validated.

Thus, an important heterogeneity between studies has been observed, regarding studied population, exclusion criteria, quality of methodology, evaluated prognostic factors, time of follow-up, endpoints, among others.

Clinical application of scoring systems

According to current guidelines, patients with colorectal liver metastases suitable for surgery should be offered surgery in order to resect all macroscopic disease with negative margins, leaving sufficient liver remnant. Surgery of CRLM is the only chance for cure and long-time survival of these patients.^{25,47} Thus, we have to be very cautious with the clinical application of these models, especially when deciding whether to perform surgery of resectable liver metastases of colorectal cancer.

Another important value of these scoring systems is the selection of the patients that can benefit from pre-operative or subsequent chemotherapy associated or not with a biological agent. The scoring system involving prognostic factors may influence the choice of the chemotherapy regimen, especially nowadays, when a lot of different and some recent agents both cytotoxic and target agents are available for the management of metastatic colorectal disease.

CONCLUSION

After an extended research on PubMed, Cochrane and Embase databases, only 19 prognostic models of clinical outcome of patients submitted to liver resection of colorectal liver metastasis were included in this revision.

Several factors have been constantly reported as having prognostic value after liver resection of CRLM. However, none of the evaluated factors were presented in all risk models. Although some models have been externally

validated, there is yet no consensus on the ideal scoring system for the approach of patients with colorectal liver metastases suitable for surgery. Although the absence of consensus of the ideal scoring system, the nomogram developed by Kattan et al³² is undoubtedly a very practical and useful scoring system and should probably be considered when evaluating prognostic factors after liver resection for colorectal liver metastasis.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

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CONFLICTS OF INTEREST

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