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Hepatic Resection for Colorectal Metastases: Can Preoperative Scoring Predict Patient Outcome?

Tom Mala, M.D.,[1] Geir Bøhler, M.D.,[2] Øystein Mathisen, M.D., Ph.D.,[1] Anstein Bergan, M.D., Ph.D.,[1] Odd Søreide, M.D., Ph.D.[1]

[1]Surgical Department, National Hospital, N-0027 Oslo, Norway
[2]Surgical Department, Vest Agder Central Hospital, 4604 Kristiansand, Norway

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Abstract. A retrospective study was performed to define patient selection, safety, and efficacy of hepatic resection for colorectal metastases. The recently proposed preoperative clinical risk score (CRS) for selection of patients for surgery was also assessed. In all, 146 consecutive hepatic resections in 137 patients operated in the period between 1977 and 1999 were studied. Of these patients, 113 were classified into five CRS groups. Perioperative mortality was 1.4% (2 patients; no death in 120 patients operated after 1985) and morbidity was 38%. Five-year actuarial survival (perioperative mortality included) was 29% (median 37 months), and actual 5-year survival was 25% (17/69 patients). Patients operated after 1995 lived longer than those operated before 1995. Multiple regression analyses identified preoperative carcinoembryonic antigen CEA < 100 μg/L, nodal status at resection of primary tumor, and R0 vs. R1/R2 resection as prognostic parameters. CRS grouping had prognostic importance. The relative risk (hazard rate) of tumor recurrence in patients with CRS 3–4 was 2.1, compared to that of patients with CRS 0–2. Five-year actuarial survival in the two groups was 12% and 40%, respectively. Fourteen of 15 long-term survivors (>5 years) classified by the CRS system had CRS of 2 or less. Resection for colorectal liver metastases is safe, and long-term survival rates are acceptable. CRS predicts patient outcome, but the clinical role in patient selection will have to be defined in prospective studies.

Liver resection is the only effective treatment for hepatic metastases to date. A major challenge is preoperative selection of patients who may benefit from resection or from perioperative adjuvant therapy. Several criteria have been identified that can be used for pre- and postoperative staging [1–8].

Fong et al. proposed a scoring system that stratifies patients preoperatively in prognostic groups [1]. Their clinical risk score (CRS) is based on 5 preoperative prognostic parameters; (1) nodal status of primary tumor, (2) disease-free interval from the primary to detection of the liver metastases < 12 months; (3) number of tumors > 1, (4) preoperative carcinoembryonic antigen (CEA) level > 200 μg/L, and (5) size of largest tumor > 5 cm. Each of these parameters is assigned 1 point and the resulting score is used to predict survival.

In this study we present our 22 years of experience with hepatic resection for colorectal malignancies. The purpose is to define patient selection, safety, and efficacy of resection. In addition we assess the predictive value of the CRS [1] for such patients.

Correspondence to: T. Mala, M.D., e-mail: tom.mala@rikshospitalet.no

Patients and Methods

All patients undergoing hepatic resection for colorectal metastases at the National Hospital, Oslo, Norway, between January 1977 and December 1999 were included. The hospital is a tertiary referral center. All case notes reviewed were supplemented by data from The Norwegian Cancer Registry, a register based on compulsory reporting of all patients with cancer in Norway. Follow-up is complete and is facilitated by a unique 11-digit personal identification number allocated at birth.

Preoperative assessment consisted of chest radiograph, clinical biochemistry, and exclusion of any extrahepatic recurrence of the primary tumor. Diagnostic imaging has developed during the study years, and in the first part of the study period angiography and computed tomography (CT) were used regularly. Since 1997 abdominal helical CT has been the standard preoperative investigative tool. CEA was investigated preoperatively in 83% of the patients, and 72% had a CEA concentration of more than 5 μg/L (upper limit of normal). Preoperative fine-needle aspiration cytology (FNAC) or fine-needle biopsy (FNB) was performed in 43 patients (31%).

Hepatic resection was performed on 142 occasions in 137 patients, 72 men and 65 women. Median age was 61 (range 23 to 79) years; 51 (37%) patients were older than 65 years. The median number of hepatic metastases was 1 (range 1 to 10), and median size was 4 cm (range 0.7 to 11). The tumors were synchronous (i.e., occuring within 6 months) in 44 (32%) of the patients. Median follow-up of patients at the time of review (April 2000) was 27 months (range < 1 to 231 months). Patient characteristics are illustrated in Tables 1 and 2.

The operation was performed through an upper transverse laparotomy, with extension in the midline toward the xiphoid process if required. Routine biopsy of lymph nodes of the hepatoduodenal ligament was not performed. Intraoperative ultra-

Table 1. Patient characteristics.

	Number of patients	%
Dukes stage (primary tumor)		
A	3	2
B	48	34
C	62	46
D[a]	20	15
Unknown	4	3
Disease-free interval (months)[b]		
≤ 6	44	32
> 6	85	62
Unknown	8	6
ASA[c] score		
I	18	13
II	56	41
III	49	36
IV	0	0
Not classified	14	14
Number of hepatic metastases		
1	82	59
2–3	40	30
≥ 4	15	11

[a]Hepatic metastases identified at time of primary tumor surgery.
[b]Time from resection of primary tumor to diagnosis of hepatic metastases.
[c]American Society of Anesthesiologists scoring system.

Table 2. Univariate analyses.[a]

	Number of patients	%	Median survival (months)	Log-rank (p)
Sex				
Female	65	47	38	0.966
Male	72	53	37	
Age (years)				
≤ 65	86	63	38	0.342
> 65	51	37	31	
Primary tumor				
Lymphatic spread	82	60	30	0.011
No lymphatic spread	51	37	40	
Unknown	4	3		
Rectum	47	34	35	0.142
Colon	73	53	39	
Not stated	17	12		
Delay from primary tumor (months)				
≤ 12	60	44	33	0.873
> 12	68	50	37	
Unknown	8	6		
Preoperative CEA (μg/L)				
< 100	96	70	40	0.043
≥ 100	17	12	30	
Unknown	24	18		
Number of metastases				
1	82	60	38	0.056
> 1	55	40	33	
Size of largest metastases (cm)				
≤ 5	97	71	37	0.351
> 5	32	23	31	
Not given	8	6		
Distribution of metastases				
Unilobar	112	81	37	0.546
Bilobar	25	19	27	
Blood transfusion				
No transfusion	42	31	36	0.717
Transfusion	95	69	37	
Resection margin				
Free	105	77	39	0.0009
Not free	17	12	17	
Unknown	15	11		
Radicality				
R0	103	75	40	0.0001
R1/R2	19	14	17	
Unknown	15	11		
Type of resection				
Two segments or less	43	31	27	0.027
Larger than two segments	94	69	38	

CEA: carcinoembryonic antigen.
[a]In reresected patients, data from first resection are used in univariate and multivariate analyses.

sound (IOUS) was used routinely beginning in 1988. Type and extent of resection is indicated in Table 3. Resections were classified according to Couinaud [9].

The diagnosis was confirmed in all patients postoperatively by histopathology. A curative (R0) resection was defined as complete removal of all visible tumor and a free resection margin (> 1 mm), R1 removal of all visible tumor but a resection margin involved by tumor at histology. In R2 resections macroscopic tumor tissue was left behind. Resections of two hepatic segments or less were defined as minor resections. All patients were included in long-term analyses of outcome.

Five resections were done laparoscopically, and in two patients the laparoscopic resection was combined with cryotherapy (part of protocol). Reresection was performed in 5 (4%) patients (a left hepatectomy, a left lobectomy, and three local resections). Four of these were R0 resections; one was a R1 resection.

In four patients a minor resection of diaphragm (tumor adherence) was performed. One patient had simultaneous resection of a local recurrence in the perineum (without free margins); one, a resection of an abdominal wall metastases; one, a resection of a tumor in the right ovary; and one, a Bilroth II gastric resection initiated by tumor overgrowth. Two patients had lung resections performed a few months after the hepatic resection.

Perioperative mortality, defined as all deaths within 30 days or before hospital discharge, was included in the long-term analyses of survival.

Patients did not receive adjuvant chemotherapy after resection according to our institutional policy. Patients with recurrent disease after resection, however, were offered palliative chemotherapy at the discretion of the medical oncologists.

In all, 113 patients (82%) were stratified in 5 CRS groups defined by Fong et al. (Table 4). Patients for whom all five criteria were not known were excluded from stratification (n = 24). In the statistical analysis, set-off for the continuous variables (tumor size, delay from primary tumor, number of tumors) was made in accordance with the CRS. However, CEA was categorized as > or < 100 μg/L instead of the original 200 μg/L because there were few patients with a CEA value of more than 200 μg/L (Table 2).

Statistics

Survival was estimated by the Kaplan-Meier method (SPSS version 9.0 and SPLUS version 4.5 for Windows), and the log-rank test was used to compare survival between groups. The relationship between survival rate and the explanatory variables was assessed by multiple Cox regression analyses. The final Cox regression model was found using backward elimination procedures with maximal likelihood. To assure that no further variables

Table 3. Resection data.[a]

Type of resection	Number	%
Right lobectomy (segments IV–VIII)	12	8
Right hepatectomy (segments V–VIII)	60	42
Extended left hepatectomy (segments I–V + VIII)	1	1
Left hepatectomy (segments II–IV)	22	16
Left lobectomy (segments II + III)	8	6
Nonanatomical resection(s)	39	27

[a]In 6 of the patients major resections were combined with a small resection in the remaining lobe.

Table 4. Clinical risk score (CRS).

CRS points	Number of patients (%)	Median postoperative survival (months)
0	17/113 (15%)	40
1	28/113 (25%)	39
2	37/113 (33%)	30
3	24/113 (21%)	20
4	7/113 (6%)	37
5	0	

should be included or excluded in the final model, the test statistics AIC (Akaikes Information Criterion) was used [10]. The proportional hazard assumption was checked by graphing hazard rate on a logarithmic scale and residuals against rank of survival time. The parameters in the Cox analysis were categorized as shown in Table 2.

Results

Free resection margins were achieved in 110 (87%) of the 127 resections with known margin status (110/127). In 17 of the 127 resections (13%) the resection margins were not free. The five patients resected laparoscopically all had free margins. Three patients (2%) had residual macroscopic tumor tissue after resection (R2 resection). One patient had lymphatic node spread to the hepatoduodenal ligament. Extent of resection over the time period studied is demonstrated in Figure 1a.

Median perioperative bleeding was 750 ml (range 50 to 14,000 ml), and perioperative blood transfusion was needed in 70% (99/142) of the resections. Inflow occlusion (Pringle's maneuver) was performed in 43 (30%) of the resections intermittently with a median of 2 (range 1– 4) occlusion periods and median time for each clamping of 20 minutes (range 8–36 minutes).

Complications occurred after 38 (27%) of the resections (Table 5). Perioperative mortality was 1.4% (2 patients). One of the patients died of liver failure; the other, from septic complications. Both had a right hepatectomy performed. There was no perioperative mortality after 1985. Reoperation initiated by complications was performed in 5 patients (3.6%; Table 5).

Five-year actuarial survival was 29%, and median survival was 37 months (range 0-231 months). Seven (20%) of the 35 patients operated before 01.05.1990 have lived > 10 years postoperatively. Seventeen (25%) of the 69 patients operated before May 1, 1995 have lived > 5 years postoperatively. Four of the long-term survivors (> 5 years) have died, two of hepatic recurrence (6 and 12 years postoperatively) and one of a locoregional recurrence (colon) (6 years postoperatively). The fourth patient died of unknown cause 19 years postoperatively. Median survival for the 69 patients operated before May 1, 1995 (32 months) was significantly shorter ($p = 0.007$) than that of the 68 patients operated after May 1, 1995 (41 months) (Fig. 2).

Results of the univariate analyses are shown in Table 2. In the Cox regression analyses preoperative CEA (< 100 μg/L vs. > 100 μg/L), nodal status at resection of the primary tumor, and R0 vs R1/2 resections were identified as predictors of survival. The hazard rate for these factors is indicated in Table 6.

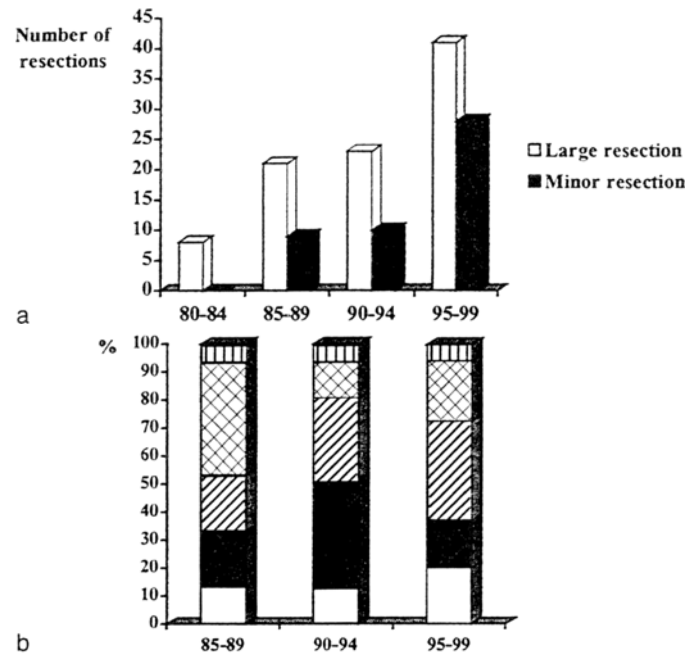

Fig. 1. Number and extent of resection over the time period studied (**a**). The percentage of patients under each clinical risk score (CRS) group for the different 5-year periods is shown in **b** (the 1980–1984 period is not illustrated as only two patients were eligible for CRS stratification). For each bar, the lowest part corresponds to CRS 0, and the second, third, fourth, and top parts, in turn, correspond to CRS 1, 2, 3, and 4.

Table 5. Complications after hepatic resection.

Complications	Number of patients	% of resections
Pneumonia	13	9
Pleural fluid (drainage required)	11	8
Biliary leakage (drainage required)	6	4
Biliary fistula	2	1
Pneumothorax	4	3
Septicemia	3	2
Pulmonary embolism	2	1
Portal vein thrombosis (no inflow occlusion during resection)	1	< 1
Postoperative cardiac arrest (successfully resuscitated)	1	< 1
Reoperation	6	4
Hemorrhage[a]	4	3
Biliary leakage	1	< 1
Wound dehiscence	1	< 1
Mortality[b]	2	1

[a]One patient reoperated twice for hemorrhage.
[b]Both patients died before 1986.

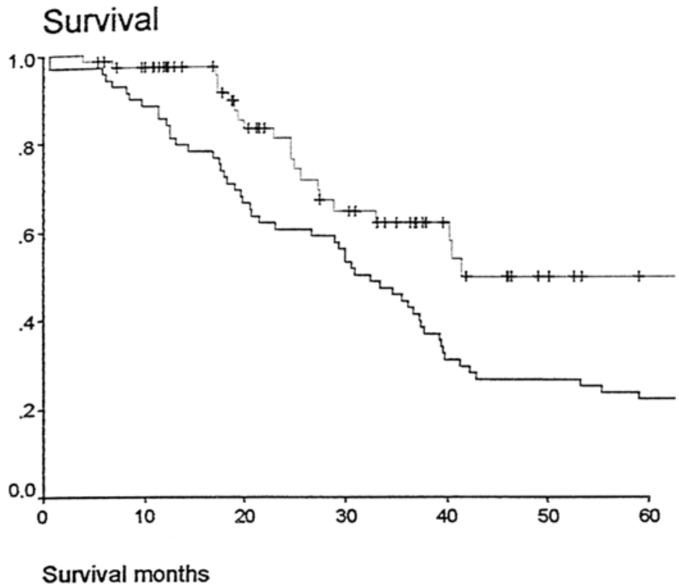

Fig. 2. Postoperative survival (Kaplan-Meier). Patients operated before May 1, 1995 (**lower curve**) and those operated later (**upper curve**).

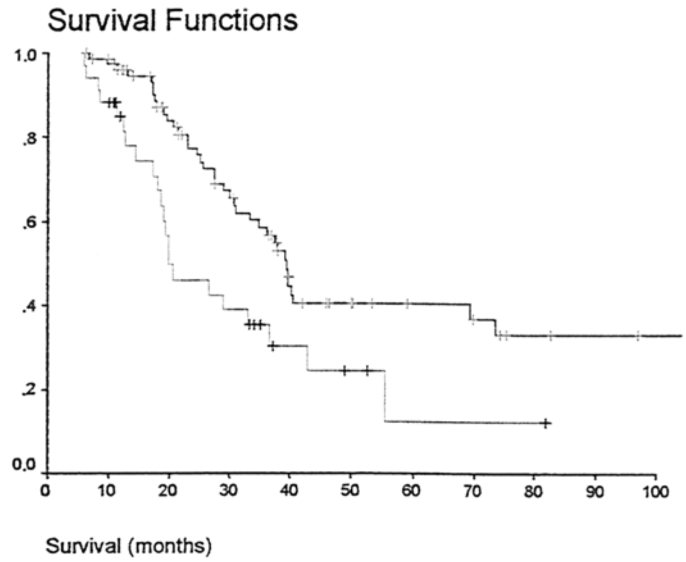

Fig. 3. Postoperative survival related to CRS. CRS group 0–2 (**upper curve**) compared to CRS group 3–4 (**lower curve**).

Table 6. Cox regression analyses.

Variable	HR[a]	95% CI for HR	p-value
CEA < 100 μg/L vs. ≥ 100 μg/L	2.9	1.5–5.7	0.0019
Negative vs. positive nodal status of primary tumor	2.1	1.2–3.9	0.016
R0 vs. R1/R2 resection	8.4	3.7–19.1	< 0.0001

[a]The hazard rate (HR) expresses the risk of death from recurrence of the last group in the variable box compared to the first group.

The stratification of patients to different CRS groups is given in Table 4. The table shows that most patients (73%) had a CRS of 0–2. No patients had a CRS of 5. Figure 1b shows the percentage of patients under each CRS group over time.

Survival was statistically different between the five CRS groups analyzed ($p = 0.03$). There was also a highly significant survival difference between CRS group 0–2 when compared with CRS group 3–4 ($p = 0.006$; Fig. 3). The estimated relative risk (hazard) of tumor recurrence for patients with CRS 3–4 was 2.1 (95% CI 1.2–3.6) of that for patients with CRS 0–2. Fifteen long-term survivors (> 5 years) could be classified according to the CRS system. One of these patients had a CRS of 3; the rest, a score of 2 or less.

Discussion

This study confirms previous reports on liver resection for colorectal malignancies. Mortality and complications are in accord with those reported by others. Today most series describe an operative mortality of less than 5% and a postoperative morbidity in the range of 20% to 50% [2]. The low mortality illustrates the safety of liver resection for colorectal metastases, even though the morbidity is relatively high [2, 4, 6, 11–15]. In our study there was no hospital mortality among the 120 patients operated after 1985 despite the advanced age of many of the patients (38% > 65 years). Pneumonia and pleural effusion were the most frequent complications; serious complications were infrequent (Table 5). The documented morbidity, however, is a significant argument for the need of adequate preoperative patient selection.

The 5-year actuarial survival of 29% is in line with that of other reports, indicating a curative potential of conventional liver resection for colorectal liver metastases [2, 7, 8, 11, 15–17]. The 5-year (actual) survival of 25% (17/69) for patients operated before 1995 supports this assumption. In addition seven (20%) of the 35 patients operated during the first part of the reported period (before 1990) lived more than 10 years postoperatively. This is in accord with previous documentation of long-term outcome after resection of colorectal hepatic metastases [2, 5, 18, 19].

The enhanced survival benefit documented for the patients operated after May 1, 1995 is probably due to improved patient selection, technical advances, and improved perioperative care [3].

The most significant prognostic parameters for patient survival were uninvolved resection margins and removal of all tumor tissue (R0 resection) [1, 3, 4, 20]. Nodal status of primary tumor [1, 4, 5, 15–17, 21, 22] and preoperative CEA were also significant prognostic parameters [1, 3, 5]. There has been a debate over whether the extent of hepatic resection influences survival. Two large nonrandomized series of liver resection for colorectal metastases have reached different conclusions: Fong et al. [1] found improved survival after resections of less than a lobe compared to larger resections (even after correction for perioperative deaths), and Nordlinger et al. could not identify such a difference [4]. In our study no survival difference was documented between patients having large resections versus those with minor resections.

The CRS was found to predict patient outcome; a significant difference in postoperative survival between CRS groups was documented. This is in accord with data from the originators of this model, who concluded that surgical resection is rational therapy for patients with a CRS of 0, 1, and 2 [1]. In our study, 14 of

15 long-term survivors (> 5 years) stratified according to the CRS model, had a CRS of 0–2. However, the clinical role of the CRS in patient selection is yet to be defined in prospective studies.

The five CRS criteria could not all individually predict patient survival; tumor size and number were not significant in the multivariate analysis. Nor did we find the delay from primary tumor resection to detection of hepatic metastases significant in this regard. Even in categorizing number of metastases differently (three or less vs more lesions), the predictive value was not significant. This may be due to the limited number of patients in our study. Other studies that have included < 200 patients have reached a similar conclusion [3, 6, 23]. In two large studies of more than 1000 patients, however, these variables have been found to be significant predictors of survival [1, 4].

To ensure correct stratification, the different criteria contributing to the CRS have to be conclusive. Nodal status of the primary tumor is particularly problematic in this regard [24]. The recommended number of lymph nodes histologically examined to ensure correct staging is 12 or more [25, 26]. In our study the number of nodes examined varied over the years. This introduces some uncertainty to our CRS stratification.

A major advantage offered by the CRS classification is that the five criteria are all easily available from standard preoperative assessment. In this report 24 (18%) patients could not be classified according to the CRS, mainly due to lack of preoperative CEA. Most of these patients were operated during the first part of the study period.

As the CRS criteria predict survival after liver resection for colorectal metastases, the CRS score distribution reflects the survival potential of our patient population (Table 4). This makes the CRS useful in comparative studies of different populations [1]. The survival of subpopulations in our study illustrates the importance of such patient stratification; the 5-year actuarial survival rates of patients with CRS of 0–2 and CRS of 3–4 were 40% and 12%, respectively (Fig. 3).

In conclusion, this report confirms the clinical relevance of the CRS in preoperative evaluation of patients with colorectal liver malignancies. Significant survival differences exist between the CRS groups and liver resection seems particularly beneficial to patients stratified to CRS groups 0, 1 and 2. The safety of hepatic resection for colorectal metastases is documented, with no deaths occurring after 1985. One-third of the patients are expected to live > 5 years.

Résumé. Une étude rétrospective a été réalisée pour définir la sélection des patients, la sûreté et l'efficacité de la résection hépatique pour métastases d'origine colorectale. Le score préopératoire «Clinical Risk Score» (CRS), proposé récemment pour la sélection des patients candidats à la chirurgie, a été évalué chez 146 patients consécutifs ayant eu une résection hépatique entre 1977 et 1999; 113 de ces patients ont été classés en cinq groupes selon le CRS. La mortalité périopératoire a été de 1.4% (2 patients; aucune mortalité parmi 120 patients opérés après 1985) et la morbidité, de 38%. La survie actuarielle à 5 ans (mortalité périopératoire incluse) a été de 29% (médiane de 37 mois) et la survie actuelle à 5 ans a été de 25% (17/69 patients). Les patients opérés après 1995 ont survécu plus longtemps que ceux opérés avant 1995. L'analyse par régression multiple a identifié comme facteurs pronostiques, le taux d'ACE inférieur à 100 ng/l, l'état ganglionnaire au moment de la résection tumorale primitive et une résection R0 vs. une résection R1/R2. Le risque relatif de récidive chez les patients CRS 3–4 a été de 2.1 comparé à celui des patients CRS 0–2. La survie actuarielle à 5 ans a été, respectivement, de 12% et de 40%. Quatorze des 15 survivants à long terme (> 5 ans), classés par le système CRS, avaient un score de 2 ou moins. La résection des métastases colorectales est sure et la survie à long terme, acceptable. Le score CRS prédit l'évolution mais son rôle clinique dans la sélection des patients reste à être défini par des études prospectives.

Resumen. Para seleccionar de manera eficaz y segura a los pacientes subsidiarios de resección hepática por padecer metástasis en hígado de un cáncer colorrectal, se realiza un estudio retrospectivo, en el que se valoró la clasificación reciente de Riesgo Clínico (CRS). Se estudiaron 146 resecciones hepáticas en 137 pacientes intervenidos entre 1977 y 1999. 113 de estos pacientes se clasificaron en alguno de los cinco grupos de la CRS. La mortalidad perioperatoria fue del 1.4% (2 pacientes; no se registró mortalidad alguna en los 120 pacientes intervenidos después del año 1985) y la morbilidad del 38%. La supervivencia actuarial a los 5 años (incluyendo la mortalidad perioperatoria) fue del 29% (media 37 meses) y la supervivencia actual a los 5 años fue del 25% (17/69 pacientes). Los enfermos intervenidos después de 1995 vivieron más tiempo que los operados con anterioridad. Los análisis de regresión múltiple señalaron como parámetros pronósticos: CEA preoperatorio menor de 100 ng/l, grado de afectación ganglionar en la resección del tumor primario y resección R0 vs R1/R2. La clasificación CRS tiene importancia pronóstica. El riesgo relativo de recidiva tumoral en pacientes de los grupos CRS 3–4 fue 2.1 en relación con la de los grupos CRS 0–2. La supervivencia actuarial a los 5 años fue respectivamente del 12% y 40%. 14 de los 15 supervivientes a largo plazo (>5 años) clasificados con el sistema CRS pertenecían a los grupos CRS 2 ó menores. El sistema CRS permite pronosticar los resultados, pero el papel del estudio clínico en la selección de los pacientes ha de definirse mejor en próximos estudios prospectivos.

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