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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

RAS Mutation Decreases Overall Survival After Optimal Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy of Colorectal Peritoneal Metastasis: A Modification Proposal of the Peritoneal Surface Disease Severity Score

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ABSTRACT

Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are currently the most accepted treatment for peritoneal metastases from colorectal cancer. Restrictive selection criteria are essential to obtain the best survival benefits for this complex procedure. The most widespread score for patient selection, the peritoneal surface disease severity score (PSDSS), does not include current biological factors that are known to influence on prognosis. We investigated the impact of including RAS mutational status in the selection criteria for these patients.

Methods. We studied the risk factors for survival by multivariate analysis using a prospective database of consecutive patients with carcinomatosis from colorectal origin treated by CRS and HIPEC in our unit from 2009 to 2017. The risk factors obtained were validated in a multicentre, international cohort, including a total of 520 patients from 15 different reference units.

Results. A total of 77 patients were selected for local análisis. Only RAS mutational status (HR: 2.024; $p = 0.045$) and PSDSS stage (HR: 2.90; $p = 0.009$) were shown to be independent factors for overall survival. Early PSDSS stages I and II associated to RAS mutations impaired their overall survival with no significant

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differences with PSDSS stage III overall survival ($p > 0.05$). These results were supported by the international multicentre validation.

Conclusions. By including RAS mutational status, we propose an updated RAS-PSDSS score that outperforms PSDSS alone providing a quick and feasible preoperative assessment of the expected overall survival for patients with carcinomatosis from colorectal origin undergone to CRS + HIPEC.

TABLE 1 Preoperative variables for univariate analysis

	All patients n = 77 (100%) N (%) or × (± SD)	Overall survival median (95% CI)	Hazard ratio	CI (95%)	p
Sex					
Male	43 (55.8%)	54 (5.23–102.77)	0.793	0.403–1.560	0.502
Female	34 (44.2%)	36 (20.37–51.63)			
Age	58.18 (± 9.89)		1.008	0.967–1.036	0.951
Body mass index	26.62 (± 3.80)		1.056	0.967–1.153	0.226
RAS status					
Wild-type	39 (50.6%)	76 (28.03–123.97)	2.269	1.141–4.512	0.019
Mutated	38 (49.4%)	27 (20.04–33.96)			
MoAb therapy					
No	42 (54.5%)	36 (20.14–51.86)	0.639	0.317–1.288	0.211
Yes	35 (45.5%)	60 (52.98–67.24)			
Neoadyuvant chemotherapy					
No	11 (14.3%)				
FOLFOX	16 (20.8%)				
FOLFIRI	11 (14.3%)	23 (20.50–25.25)	0.968	0.341–2.753	0.952
XELOX	22 (28.6%)	40 (14.96–65.03)			
XELODA	2 (2.6%)				
5/FU	3 (3.9%)				
Others	12 (15.6%)				
No. cycles of neoadjuvant	6 (± 4.11)		0.975	0.901–1.055	0.531
CEA					
Normal (0.5/5 ng/ml)	44 (57.1%)	54 (28.34–79.66)	1.204	0.562–2.579	0.633
Elevated	23 (29.9%)	22 (21.87–24.36)			
Ca 19.9					
Normal (0–37 U/ml)	43(55.8%)	54 (24.52–83.48)	1.319	0.616–2.824	0.476
Elevated	22(28.6%)	28 (13.47–42.53)			
Synchronous LM					
No	65(84.4%)	40 (19.87–60.13)	1.015	0.420–2.455	0.974
Yes	12(15.6%)	55 (7.16–102.84)			
PSS					
No prior surgery or biopsy only	19(24.7%)	76 (5.42–146.6)			
1 region	28(36.2%)	43 (23.65–62.34)	1.111	([a]) 0.436–2.831	0.825
2–5 regions	30(39%)	26 (18.87–33.13)	1.714	([b]) 0.740–4.171	0.235
> 5 regions	0	0			
PSDSS			1.247	([a]) 0.532–2.925	0.009
Stage I	33(42.8%)	55 (33.04–76.96)	3.328	([b]) 1.494–7.415	0.612
Stage II	23(29.9%)	43 (32.61–53.74)			0.003
Stage III	21(27.3%)	20 (16.63–23.37)			
Stage IV	0				

MoAb monoclonal antibody, *PSS* prior surgery score, *PSDSS* peritoneal surface disease severity score, *IQR* interquartile range

Hazard ratio compares: neoadjuvant chemotherapy: yes versus no. PSS: (a) 1 region versus no prior surgery (b) 2–5 regions versus no prior surgery. PSDSS (a) stage II versus stage I (b) stage III versus stage I

Peritoneal metastases (PM) originating from colorectal cancer are currently treated in a curative setting using cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[1] Although a 5-year survival of more than 40% can be reached after optimal CRS and HIPEC, this complex procedure still has high morbidity (16–64%) and mortality rates (0–8%).[2] Furthermore, appropriate patient selection for CRS/HIPEC remains unclear, resulting in certain patients relapsing within 12 months after surgery with consequent minimal survival, hence making CRS + HIPEC an unproductive treatment strategy for these patients.[2–4] Therefore, improving selection criteria is essential for obtaining favourable results with increased survival.

Until now, patient prognosis after CRS + HIPEC has only been assessed using clinical-pathologic factors, such as clinical symptoms, extraperitoneal metastasis, and histology, including differentiation grade and the state of the lymph nodes.[5] These predictors and the preoperative peritoneal cancer index (PCI) have been combined into a clinical score called the peritoneal surface disease severity score (PSDSS) described by Pelz et al. [6] in an attempt to

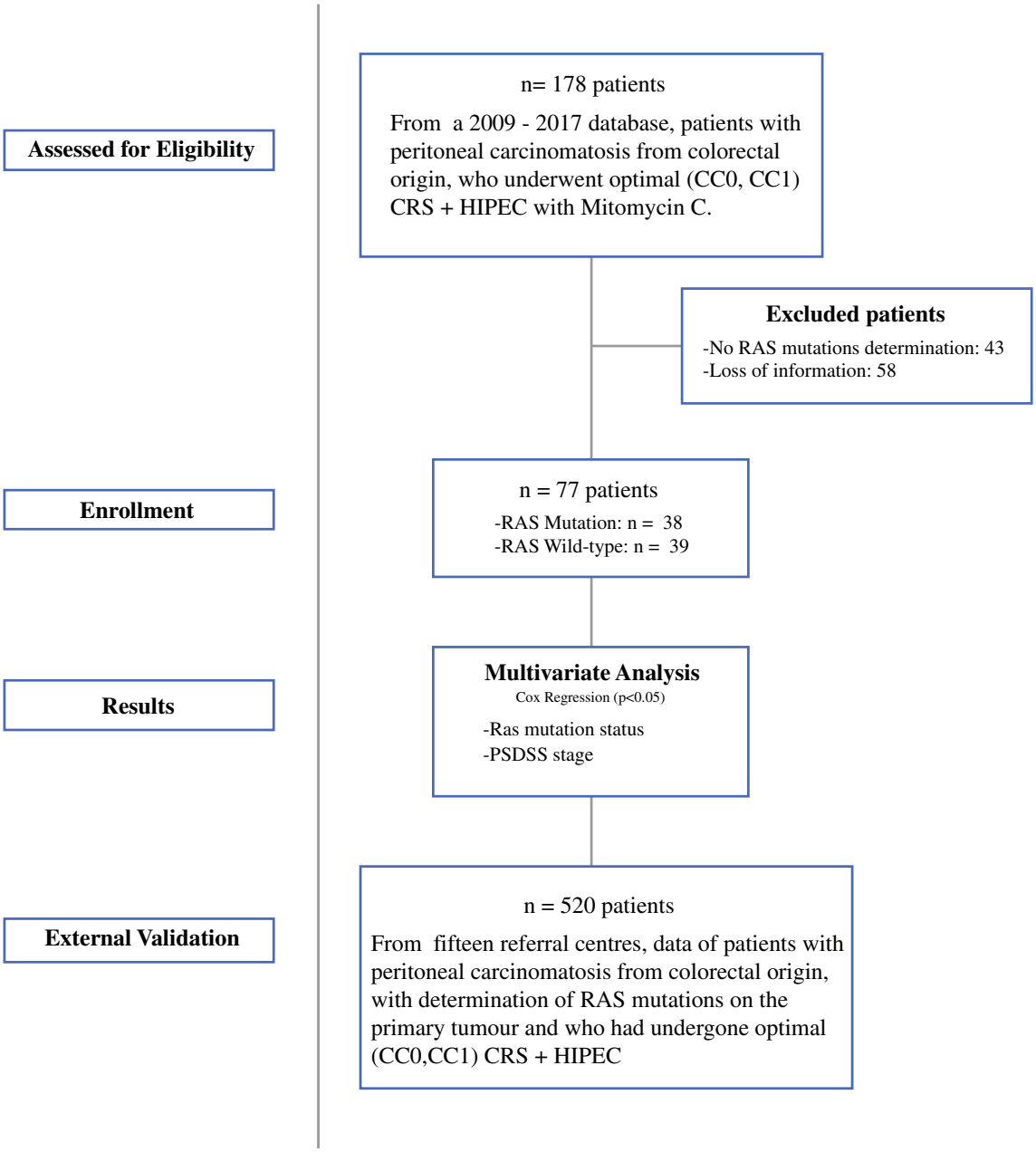

FIG. 1 Flow chart

offer a potential guide to the long-term survival after CRS + HIPEC. Although this score has been validated in other centres, it may not reflect contemporary personalized patient management and outcomes.[7]

Rat sarcoma viral oncogene homolog (*RAS*) mutations have been found in 15–35% of patients with resectable colorectal liver metastasis and have been associated with recurrence and poor overall free survival.[8] *RAS* mutational status is used to select patients for treatment targeting the epidermal growth factor receptor (EGFR) and also has been associated with radiologic and pathologic response in the latest chemotherapy trends.[9,10] We hypothesized that *RAS* mutations, as a direct measure of tumour biology, may be a powerful predictor of outcome in patients undergoing optimal CRS and HIPEC for peritoneal carcinomatosis from a colorectal origin with perioperative modern chemotherapy. We therefore investigated the impact of using RAS mutations in combination with traditional PSDSS to better predict survival after CRS + HIPEC.

PATIENTS AND METHODS

Patients

From July 2009 to April 2017, the data of 178 patients with peritoneal carcinomatosis from colorectal cancer treated by optimal cytoreductive surgery (CC0, CC1) and HIPEC with mitomycin C have been collected in a prospective database maintained in our unit. From this cohort, 77 patients were selected who had all the required variables for the study and had tested for the rat sarcoma viral oncogene homologue (*RAS*) mutational status (Fig. 1). Patients with appendiceal cancer or other origins were excluded from the current study. All patients included in this study were treated via institutional protocol, with written, informed consent and had the approval of our ethics committee.

Variables

The variables collected were demographic characteristics, preoperative clinical symptoms, estimated preoperative peritoneal cancer index (Pre-PCI), histologic diagnosis, including differentiation grade (in the previous biopsy or primary tumour) and affected lymph nodes (imaging tests or primary resected tumour), systemic chemotherapy treatment received, such as neoadjuvant and adjuvant, CEA and CA 19.9 values, and PSS (Prior Surgical Score). The PSDSS was calculated as described by Pelz et al. [6] (Table 1). The primary endpoint was overall survival (OS) defined as the interval between the CRS + HIPEC and the date of death from any cause in months, with a minimum of follow-up of 12 months.

RAS Mutation Profiling

RAS mutations were assessed in DNA in the previous biopsy or primary resected tumour. Routine polymerase chain reaction-based primer extension assay was performed to screen for mutations in KRAS codons 12 and 13 in all patients. Other mutations, such as KRAS codons 61 and 146 and some NRAS, were included as RAS mutations in our analysis.

Surgical Procedure

The volume and extension of tumour deposits were classified using the Peritoneal Cancer Index (PCI). The principles of cytoreductive surgery and HIPEC, as performed at this centre and by this team, have been reported previously.[11] Optimal cytoreduction was considered as completeness of cytoreduction score, CC0 or CC1 (residual tumour < 0.25 cm). HIPEC was performed using the semi-open coliseum technique for 60 min at a temperature of 41–43 °C with mitomycin C (15 mg/m^2) in a 1.5% dextrose solution with a mean flow rate of 1000 ml/min and a global perfusion volume of 4000 cc.

International Multicentre Validation Cohort

An international, multicentre cohort of 520 patients who underwent optimal cytoreductive surgery and HIPEC for peritoneal metastasis from colorectal cancer and RAS mutations status tested was used from 15 different tertiary centre hospitals with extensive expertise in CRS + HIPEC to validate the modified-PSDSS. Patient data (PSDSS, RAS mutations status, overall survival in months) were received and used to validate the updated RAS-PSDSS.

Statistical Analysis

Qualitative data were recorded in a categorical fashion, and quantitative covariates were measured on a continuous or an interval scale. Univariate and multivariate analyses were performed by using the Cox regression model to evaluate the relationship between preoperative variables and overall survival. Only the factors that were found to be significant or approaching significance ($p < 0.15$) in the univariate analysis were included in the multivariate analysis. Living patients were censored at last contact according to the Kaplan–Meier method. A Cox proportional hazard model was constructed for the multivariate

analysis. The Kaplan–Meier survival analysis and the log-rank test were performed to evaluate survival data.

Results are reported as follows: the number of patients (n) and/or the respective percentage (for qualitative covariates), and the mean and standard deviation (SD) (for quantitative covariates). Hazard ratios (HR) and their 95% confidence intervals (CI) were considered for the Cox regression survival analysis. A p value < 0.05 was considered to be significant. There was no imputation of missing data. All statistical analyses were performed with SPSS version 24.0 (SPSS Inc., IBM Corp).

RESULTS

A total of 77 patients (43 men, 34 women, mean age 58 years) from our centre were identified from July 2009 to April 2017 who had known RAS mutation status as well as all the required variables for the study. The data needed to appraise PSDSS was recorded: clinical status (25% none, 70% mild, and 12% severe symptoms), radiological PCI (92% were < 10, and 8% were 10–20). No surgery was performed for estimated PCI > 20) and histology (7.8% well differentiated, 55.8% moderately differentiated, and 36.4% poorly differentiated/signet ring). No patient with a stage IV PSDSS was indicated for surgery in the cohort.

Sixty-six (86%) patients had received neoadjuvant chemotherapy before CRS + HIPEC surgery based on fluoropyrimidine and oxaliplatin. Thirty-five of them (54.5%) had also received monoclonal antibody therapy (cetuximab, panitumumab, or bevacizumab). The mean number of cycles given before surgery was 6 ± 4. Sixty-two (80%) of the patients have some previous surgery before the CRS + HIPEC. More demographic characteristics and outcome data are shown in Tables 1 and 2.

After the univariate analysis, variables shown to be statistically significant on overall survival were *RAS* mutational status and PSS and PSDSS stages. The rest of included preoperative variables did not show any influence on patient survival. After the multivariate analysis, only *RAS* mutational status (hazard ratio [HR]: 2.024; $p = 0.045$) and PSDSS stage (Stage III vs. Stage I: HR: 2.90; $p = 0.009$) were shown to be independent factors associated with overall survival (Table 3). Despite there being significant overall survival differences between the different stages of PSDSS when the *RAS* mutations were introduced (RAS-PSDSS), these differences were not significant between patients with *RAS* mutations and a Stage I (28 months), Stage II (27 months), and Stage III (20 months independently of RAS mutation status) ($p > 0.05$; Fig. 2).

TABLE 2 Intraoperative and postoperative outcomes

	All patients n = 77 (100%) N (%) or × (± SD)
Intraoperative PCI	
≤ 12	51 (66.2%)
13–24	20 (26.0%)
25–36	6 (7.8%)
Surgery time (h)	6.72 (± 2.07)
(CC) score	
CC-0	71 (92.2%)
CC-1	6 (7.8%)
LM resection during CRS	
No	65 (84.4%)
Yes	12 (15.6%)
	p =0.974
Postoperative LOS	13.82 (± 11.6)
Thirty-day postoperative morbidity*	
No	66 (85.7%)
Yes (≥ IIIa)	10 (13.0%)
Thirty-day postoperative mortality	
No	77 (100%)
Yes	0
Lymph nodes involvement (After CRS)	
No	37 (48.1%)
Yes	40 (51.9%)
Disease-free survival	16.31 (± 15.58)
Overall survival	31.12 (± 21.4)

PCI peritoneal carcinomatosis index, *LOS* length of stay, *CRS* cytoreductive surgery, *LM* liver metastases

*Dindo-Clavien classification

TABLE 3 Multivariate analysis using cox-regression

	Hazard ratio	IC (95%)	p
RAS mutation	2.024	1.017–4.025	0.045
PSDSS stage			0.02
PSDSS stage II versus I	1.145	0.486–2.699	0.757
PSDSS stage III versus I	2.901	1.303–6.457	0.009

International Multicentre Validation and Proposal of a PSDSS Modification

In an international multicentre validation cohort of 520 patients from 15 centres, the *RAS* modified-PSDSS was validated as a score that predicts the overall survival of the patients with PM form colorectal cancer operated by optimal CRS and HIPEC. The 5-year overall survival rates with no *RAS* mutations were 61.8%, 39.9%, 24.4%, and 0% for stages I, II, III, and IV respectively ($p < 0.05$). The 5-year overall survival rates with *RAS* mutations were

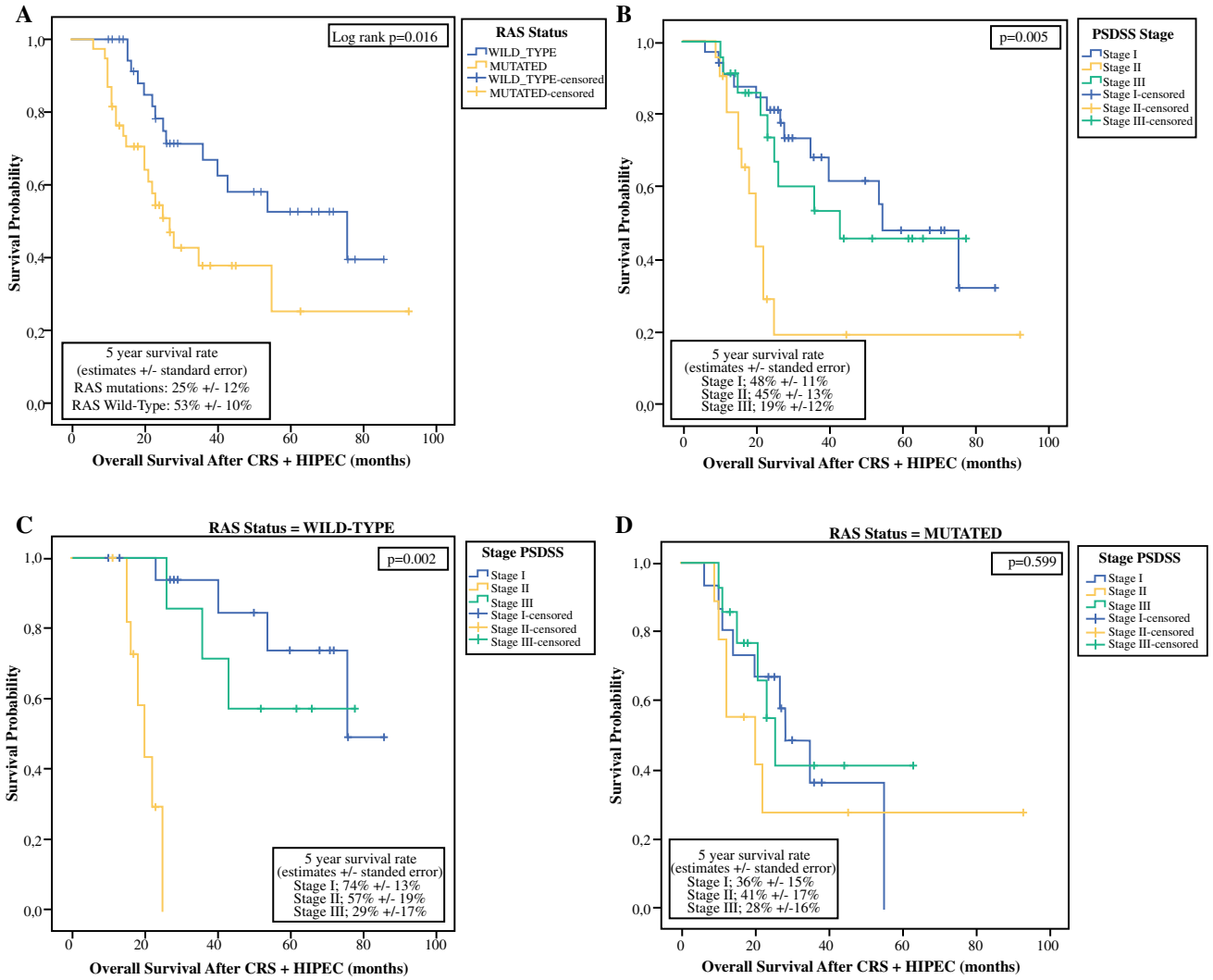

FIG. 2 Kaplan–Meier overall survival curves of our centre data. Log-rank test has been run both including and excluding PSDSS stage IV patients, yielding similar results

28.4%, 26.4%, 27.1%, and 0% for stages I, II, III, and IV respectively ($p > 0.5$; Fig. 3). A score of 2–8 points in PSDSS associated to RAS mutations should be considered as a stage III in the definitive *RAS*-modified PSDSS score (Fig. 4).

DISCUSSION

The PSDSS is the most recognized and widely used clinical score for predicting patient survival suffering from peritoneal metastasis from colorectal cancer after CRS and HIPEC. This score is based on preoperative, clinico-pathological features, but it does not consider any molecular characteristics of the treated tumour, such as the *RAS* mutational status, which is a well-known and significant predictor of survival. In the current study, the PSDSS together with *RAS* mutational status have been identified as significant predictors for impaired overall survival after CRS/HIPEC. In an effort to include this new information about the influence of *RAS* mutations on survival in patient selection for CRS/HIPEC, a modified version of the PSDSS has been developed.

The association of *RAS* mutational status to PSDSS in a new score, RAS-PSDSS, outperforms the former PSDSS by ensuring greater survival predictability in our cohort study as well as in the multicentre, validation cohort. CRS + HIPEC for PM from colorectal cancer is an established treatment option in selected patients achieving increased survival compared with systemic chemotherapy alone.[1,2] The success of this therapeutic approach depends on an optimal selection of patients. Different studies have identified preoperative factors that predict survival after this complex procedure. All of these are based on clinical and pathological features and do not consider the molecular

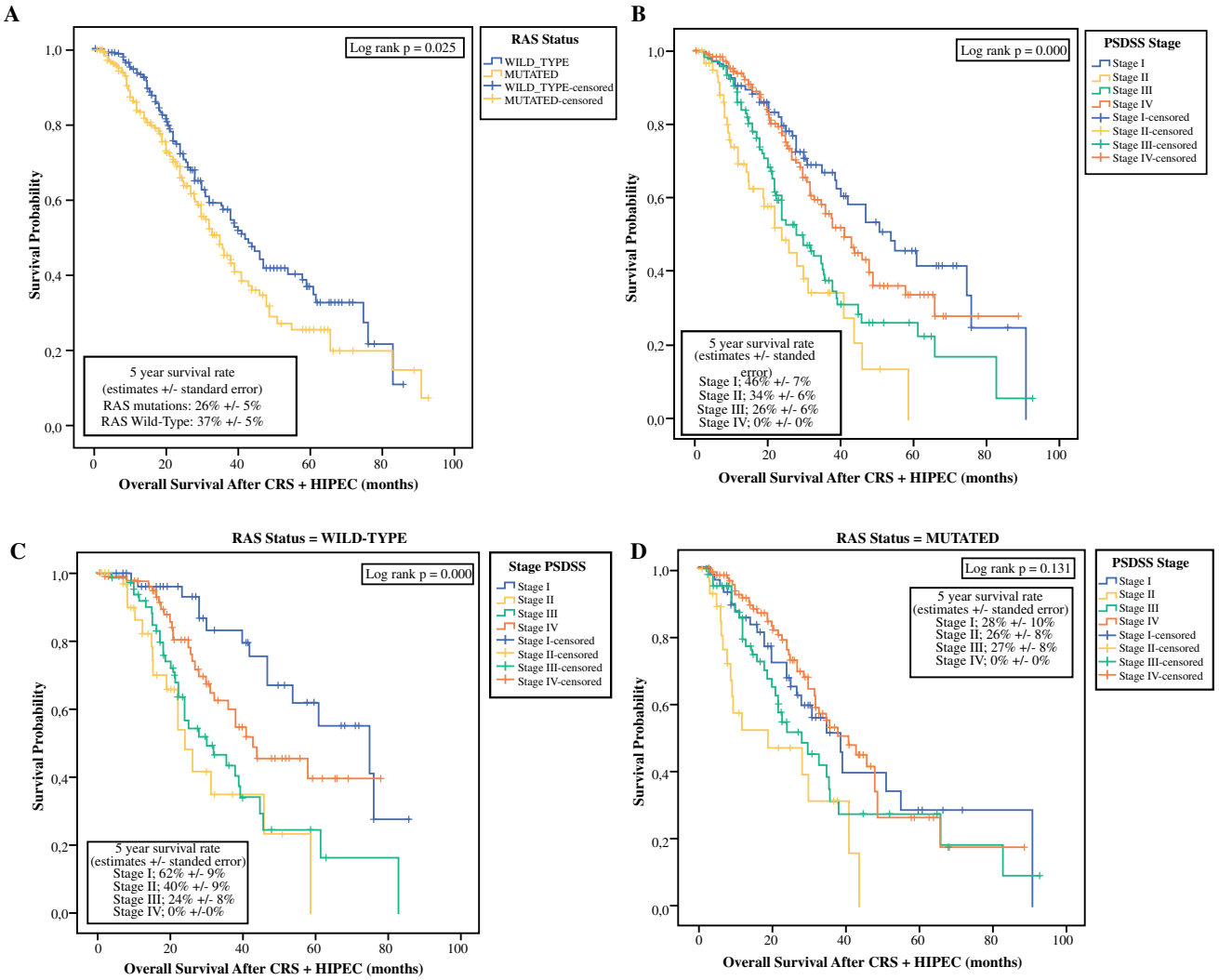

FIG. 3 Kaplan-Meier overall survival curves of multicentre data for external validation. *Log-rank test has been run comparing PSDSS stages I, II, and III with RAS mutations. If we include Stage IV, $p < 0.005$

status of the tumour.[5–7,12] The PSDSS includes preoperative PCI, clinical status and pathological characteristics of the primary tumour as risk factors.[6] After its publication, PSDSS was validated in a multicentre study being established as the selection criteria for these patients.[7]

We considered the PSDSS variable by itself as a risk factor for overall survival in our cohort, and it was demonstrated to be so in the multivariate analysis (Table 3). We have also shown the assessment of this score in our multicentre, international validation. Recently, the COMPASS nomogram was proposed as a substitute for the PSDSS.[12] The preoperative risk factors considered were age, peritoneal carcinomatosis index score, locoregional lymph node status, and signet ring cell histology. They concluded in their primary publication, and so does the external validation, that PSDSS showed a worse discriminative ability than COMPASS.[13] In this mentioned external validation and like our study, age was not identified as risk factor for survival. Considering this, the only modification of the PSDSS would be the incorporation of age to the score, and this variable was eventually found as a non-risk factor in other studies.

The COREP score consists of a feature set that can be assessed preoperatively, including histopathologic parameters, haemoglobin level, white cells count, four serum tumour markers (CEA, Ca 125, Ca 19.9, and Ca 15.3), and their changes over time before surgery.[14] This score has not been widely validated and used yet. For our cohort, as serum tumour markers Ca 125 and Ca 15.3 are not routinely measured for colorectal cancer, we have only included CEA and Ca 19.9 values, and they have not shown to be risk factors for overall survival in the univariate analysis.

Clinical	Pre-PCI	Histology
No symptoms 0	PCI < 10 **1**	G1 G2, N-, L-, V- **1**
Mild symptoms 1	PCI 10-20 **3**	G2 N+ and/or L+ and/or V+ **3**
Severe symptoms 6	PCI>20 7	G3 Signet ring **9**

Clinical Symptoms: Mild symptoms = weight loss < 10% of body weight, mild abdominal pain,some ascites. Severe symptoms = weight loss> 10 % of body weight unremitting pain, bowel obstruction, symptomatic ascites.
Peritoneal Cancer Index (PCI) by imaging (CT,PET, MRI) or Exploration (laparoscopy or evaluation at time of first operation (in synchronous peritoneal carcinomatosis)

Score stages:

I. (2-3 points) + Wild type RAS.

II. (4-7 points) + Wild type RAS.

III. (2-10 points) + Mutated RAS.

(8-10 points) + Wild type RAS.

IV. (>10 points) + any RAS status.

FIG. 4 Modified peritoneal severity disease surgical score (RAS-PSDSS)

To establish an optimal patient selection criteria for CRS and HIPEC, a recent meta-analysis describes three clinical and pathological findings as risk factors for survival.[5] Synchronous liver metastasis treated by resection or ablative techniques showed a negative impact on survival in seven studies, whereas nine studies do not identify any impact on survival. In our study, resection of liver metastasis at the same time of CRS and HIPEC had no impact on survival. A poor performance status, measured by the Eastern Cooperative Oncology Group (ECOG) score (also known as the WHO score), has been considered as a risk factor for survival. Although more data are required to make definitive conclusions about its influence as a marker for patient selection, most of the authors consider that current practice for patient selection should include the ECOG score. In our study, the preoperative clinical condition has been established (as a part of the PSDSS) as a risk factor for survival. The pathologic features that have been significant in this latter study were the lymph node metastasis, tumour differentiation, and signet ring cell histology. These variables are taken into account in the PSDSS with similar prognostics for survival. To calculate the PSDSS, we have included these pathologic features from our cohort and from the other centres' data for external validation of our results. Then, the risk factors showed in this meta-analysis were considered in the PSDSS score, and it reinforced the use of this score for our analysis.

Nowadays, the therapeutic strategy planning for malignant diseases often includes a molecular profile, going towards a personalized treatment for both tumours and patients. In that sense, there is a lack of relevant features for current patient selection criteria for CRS + HIPEC for PM from colorectal cancer, because no score includes molecular tumour characteristic as we described above.

It is known that *RAS* mutations have a negative impact on the survival of patients with metastatic colorectal cancer and have been widely studied and considered for other treatment selection criteria. For example, medical oncologists are using the mutation status of Kirsten rat sarcoma viral oncogene homologue (*KRAS)* gene to select patients with advanced-stage colorectal cancer with wild-type *KRAS* for treatment with monoclonal antibodies that target the epithelial growth factor receptor (EGFR), mainly panitumumab and cetuximab.[9,10,15–18] Recent reports have provided evidence that KRAS mutation status has prognostic value in patients with resectable colorectal liver metastases (CRLM) regardless of treatment with chemotherapy or anti-EGFR therapy.[8,19] Even the most popular score used for selection criteria for CRLM

(Memorial Sloan Kettering Clinical Score), was modified to include the *RAS* mutations, stating the need to renew this traditional clinicopathological score.[20]

Because PSDSS is the most widely used and validated score to select patients for CRS + HIPEC, our intention after our results is not to substitute but improve it by incorporating a patient molecular profile. The RAS-PSDSS is the first score for selecting patients with PM from colorectal cancer to undergo CRS + HIPEC that includes molecular markers. A major strength of this study has been the international multicentric validation, conferring an important ability to predict patient prognosis with the *RAS* modified PSDSS.

This study has several limitations. First, for its retrospective nature, only patients who had *RAS* mutational status studied and optimal CRS and HIPEC with no loss of information were eligible for inclusion. Second, in the external validation, the type of HIPEC and the chemotherapeutic agent used was not described; however, there is not evidence in favour of any particular one, because mitomycin C has similar outcomes than oxaliplatin in different previous studies.[1,2,21,22] Third, lymph node and *RAS* mutational status of the primary tumour may not be available in patients with synchronously peritoneal metastasis at diagnosis. However, the *RAS* mutational status must be analysed in the primary biopsy of the tumour, and the lymph node status could be established by radiologic findings. Finally, the *BRAF* mutational study has not been included in this analysis because of the few patients who had it requested; it is not routinely analysed in our centre, nor could the *NRAS* mutations be analysed at the beginning of the study period. However, both are recognized as adverse prognosticators in metastatic colorectal cancer, so any inadvertent inclusion of *NRAS* and *BRAF* mutations in the wild-type cohort may lead to an underestimation of the impact of *RAS* mutation outcomes.[10,23]

CONCLUSIONS

The new RAS-PSDSS incorporates the *RAS* mutational status, a direct measurement of tumour biology that has previously been associated with a bad prognosis. This updated score outperforms the previous PSDSS and provides a quick preoperative assessment of the expected overall survival benefit in our cohort and in an external, multicentre validation. The RAS-PSDSS should be used in the selection criteria for patients with PM from colorectal cancer who may undergo CRS-HIPEC.

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REFERENCES

1. Mirnezami R, Mehta AM, Chandrakumaran K, et al. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. *Br J Cancer*. 2014;111:1500–8.
2. Arjona-Sánchez A, et al. Peritoneal metastases of colorectal origin treated by cytoreduction and HIPEC: an overview. *World J Gastrointest Oncol*. 2014;6:407.
3. Franko J, Ibrahim Z, Gusani NJ, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. *Cancer*. 2010;116:3756–62.
4. Cavaliere F, De Simone M, Virz S, et al. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol*. 2011; 37: 148–54.
5. Kwakman R, Schrama AM, van Olmen JP, et al. Clinicopathological parameters in patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer metastases: a meta-analysis. *Ann Surg*. 2016;263(6):1102–11.
6. Pelz O, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a peritoneal surface disease severity score in patients with colon cancer and peritoneal dissemination. *J Surg Oncol*. 2009;99:9–15.
7. Esquivel J, Lowy AM, Markman M, et al. The American Society of peritoneal surface malignancies (ASPSM) multi-institution evaluation of the peritoneal surface disease severity score (PSDSS) in 1,013 patients with colorectal cancer with peritoneal carcinomatosis. *Ann Surg Oncol*. 2014;21:4195.
8. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutations status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg*. 2013;258:619–26.
9. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359:1757–65.
10. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy–refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol*. 2010;11:753–62.
11. Arjona-Sanchez A, Cadenas-Febres A, Cabrera-Bermon J, et al. Assessment of RIFLE and AKIN criteria to define acute renal dysfunction for HIPEC procedures for ovarian and nonovarian peritoneal malignances. *Eur J Surg Oncol*. 2016;42:869–76.
12. COMPASS. Simkens GA, van Oudheusden TR, Nieboer D, et al. Development of a prognostic nomogram for patients with peritoneally metastasized colorectal cancer treated with cytoreductive surgery and HIPEC. *Ann Surg Oncol*. 2016;23:4214–21.
13. Demey K, Wolthuis A, de Buck van Overstraeten A, et al. External validation of the prognostic nomogram (COMPASS) for patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2017. https://doi.org/10.1245/s10434-017-6042-9.
14. Cashin PH, Graf W, Nygren P, Mahteme H. Patient selection for cytoreductive surgery in colorectal peritoneal carcinomatosis

using serum tumor markers: an observational cohort study. *Ann Surg*. 2012;256:1078–83.
15. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:1626–34.
16. Douillard J-Y, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023–34.
17. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360:1408–17.
18. Lievre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res*. 2006;66:3992–5.
19. Brudvik KW, Kopetz SE, Li L, et al. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metástasis. *Br J Surg*. 2015;102:1175–83.
20. Brudvik KW, Jones PR, Giuliante F, et al. RAS mutation clinical risk score to predict survival after resection of colorectal liver metastasis. *Ann Surg*. 2017. https://doi.org/10.1097/sla.0000000000002319.
21. Prada-Villaverde A, Esquivel J, Lowy AM, et al. The American Society of peritoneal surface malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol*. 2014. https://doi.org/10.1002/jso.23728.
22. Hompes D, D'Hoore A, Wolthuis A, Fieuws S, Mirck B, Bruin S, et al. The use of Oxaliplatin or Mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. *J Surg Oncol*. 2014;109:527–32.
23. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res*. 2014;20:5322–30.