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ECOG performance status 0 or 1 and symptom classification do not improve the ability to predict renal cell carcinoma-specific survival

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ABSTRACT

Objectives: We tested and compared the improvement in prognostic ability related to the consideration of either ECOG performance status (ECOGPS) and/or symptom classification (S-CLASS) in renal cell carcinoma specific mortality (RCC-SM) predictions.
Methods: Univariate and multivariate Cox regression analyses targeted RCC-SM in 2570 RCC patients treated with either partial or radical nephrectomy. The increment in predictive accuracy related to the addition of either ECOGPS, S-CLASS or both was quantified using Harrell's concordance index.
Results: Follow-up ranged from 0.1 to 23 years (median 3.2) and 610 patients (23.7%) died of RCC. In multivariable analyses, ECOGPS and S-CLASS represented independent predictors of RCC-SM. The addition of ECOGPS to established RCC-SM predictors increased the predictive accuracy by 0.3% ($p = 0.8$) versus 0.6% ($p = 0.5$) for S-CLASS versus 0.6% ($p = 0.5$) for both.
Conclusions: Neither ECOGPS nor S-CLASS improves the ability to predict RCC-SM. Therefore, these variables may be safely omitted when RCC-SM risk is quantified.

1. Introduction

Accurate prediction of survival in renal cell carcinoma (RCC) patients is essential for counselling, for the selection of follow-up and recently for adjuvant treatment selection.[1,2] The latter has become particularly important since the advent of tyrosine kinase inhibitors, which have shown promise despite significant cost.[1] The most accurate assessment of RCC-specific mortality (RCC-SM) can be achieved with several multivariable prognostic models.[3–7] These rely on cancer

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characteristics as well as on performance status and/or symptom classification. Since long, Karnofsky Performance Scale (KPS) has been recognised as a valuable predictor of cancer-specific mortality.[8] The KPS ranges from 0% to 100% and represents the most widely used performance status assessment tool in oncology. Oken et al. introduced the four-tiered Eastern Cooperative Oncology Group performance status (ECOGPS) in 1982, with the intent of simplifying the KPS.[9] Since its inception, ECOGPS has gained wide popularity and represents an integral part in the assessment of cancer patients in many trials, worldwide. Moreover, treatment decisions are often based on ECOGPS. For example, the recommendations for nephrectomy in the context of metastatic disease are restricted to ECOG 0–1 patients.[10,11] Despite wide acceptance of the ECOGPS, European investigators proposed a more intuitive classification, which rests on absence or presence of either local or systemic symptoms in RCC patients. The independent predictor status of this scheme was confirmed in two large studies.[12,13]

Based on these observations, both ECOGPS and symptom classification (S-CLASS) represent independent predictors of RCC-SM. However, these two variables address distinct concepts: symptom type versus performance status. Thus, it might be argued that their combined effect may provide better prognostic ability to predict RCC-SM than when either is used in isolation. We hypothesised that the combined use of both variables could improve the ability to predict RCC-SS in a statistically significant and clinically meaningful fashion. To test this hypothesis, we quantified the gain in predictive accuracy related to the addition of either one or both variables (ECOGPS or S-CLASS) to models that already rely on classic predictors of RCC-SM.

2. Materials and methods

2.1. *Patient population*

Data were retrieved from five combined Institutional Review Board approved databases, which yielded 2570 consecutive patients treated with partial or radical nephrectomy between 1984 and 2001 (Table 1).

2.2. *Clinical and pathologic evaluation*

ECOG performance status and symptom classification were available for all patients in our cohort. Tumours were classified according to the 2002 TNM staging system and according to the Fuhrman grade. Tumour size was based on pathological specimens and was defined as the greatest tumour diameter, in centimetres. Histological subtypes were stratified according to the 2002 AJCC/UICC classifications.[14] Symptoms were prospectively recorded at each of the participating institutions. Three groups were defined according to clinical presentation, as previously described.[12] Asymptomatic status was assigned to patients diagnosed with RCC based on routine imaging. Patients with local symptoms typically complained of lumbar pain, haematuria or palpable mass. Finally, patients with systemic symptoms complained of fatigue, weight loss, fever, night sweats or cough. ECOGPS was also recorded prospectively and was classified in institutional databases on a scale from 0 (no symptoms, fully active, able to work) to 4 (completely bedbound).[9] In this analysis, only patients with ECOGPS 0 or 1 were included, according to previous recommendations for nephrectomy in the context of metastatic disease.[10,11]

Pre-operatively, patients were staged with computed tomography (CT) of the abdomen and pelvis, chest CT or chest X-ray, serum electrolytes, and liver function tests. The pres-

Table 1 – Descriptive statistics for 2570 patients treated with nephrectomy

Variables	Number of patients (%)
Total	2570 (%)
Age	
Mean (median)	60.7 (62.0)
Range	10–91
10–42	216 (8.4%)
>42–91	2354 (91.6%)
Sex	
Male	1716 (66.8)
Female	857 (33.2)
T stage	
T_1	1200 (46.7)
T_2	390 (15.2)
T_3	922 (35.9)
T_4	58 (2.3)
Nodal metastases (N1–2)	241 (9.4)
Distant metastases (M1)	334 (13.0)
Tumour size (cm)	
Mean (median)	6.0 (6.7)
Range	0.5–25.0
Fuhrman grades	
I	677 (26.3)
II	838 (32.6)
III	851 (33.1)
IV	204 (7.9)
Histological type	
Clear cell conventional	2245 (87.4)
Papillary	212 (8.2)
Chromophobe	73 (2.8)
Collecting duct	9 (0.4)
Unclassified	31 (1.2)
Symptom classification	
Asymptomatic	1167 (45.4)
Local	913 (35.5)
Systemic	490 (19.1)
ECOG performance status	
0	1812 (70.5%)
1	758 (29.5%)
Renal cell carcinoma-specific mortality	610 (23.7%)
Other cause mortality	206 (8.1%)
Overall study follow-up time (years)	
Mean (median)	4.7 (3.2)
Range	0.1–23
Time to death (years)	
Mean (median)	2.6 (1.3)
Range	0.1–20
Actuarial time to death (years)	
Mean (median)	15.8 (not reached)

ence of nodal metastases was defined according to lymphadenectomy findings. In all cases, a hilar lymphadenectomy was performed and included all lymph nodes on the ipsilateral side of the great vessels. In select cases, based on surgeon preference, more extensive lymphadenectomies were performed. In all cases, the presence of nodal metastases was confirmed pathologically. The presence of distant metastases was confirmed with radiographic studies.

Follow-up consisted of one post-operative baseline visit and was then performed every 6 months for a minimum of 2 years. Subsequently, minimum follow-up consisted of annual visits. At each visit, CT of the chest or chest radiography accompanied a CT of the abdomen. For those who died during follow-up, the cause of death was either obtained from the medical chart and recorded prospectively or was obtained from the death certificate in a retrospective fashion. RCC-specific mortality included deaths that were directly attributable to kidney cancer.

2.3. *Statistical analyses*

Kaplan–Meier plots were used to graphically illustrate the RCC-specific survival (RCC-SS) for the entire cohort. RCC-SS was also plotted according to ECOGPS or S-CLASS. Life tables were used to determine the proportions of surviving patients at specific time points. Univariable and multivariable Cox regression models addressed the effect of all predictors on RCC-SM. The standard predictors consisted of age, gender, TNM stages, tumour size, Fuhrman grade and histological subtype. The additional predictors consisted of ECOGPS and S-CLASS.

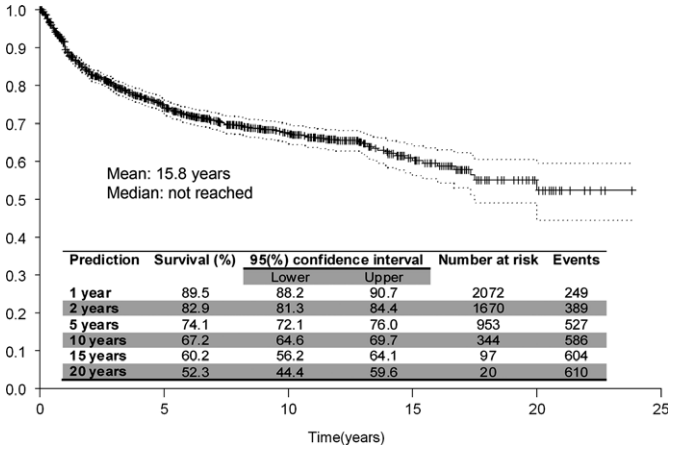
Univariable predictive accuracy was determined for each predictor, including ECOGPS and S-CLASS. Subsequently, the multivariable predictive accuracy was quantified. In order to assess the predictive accuracy gains, four multivariable models were fitted. The initial model (Model 1) relied on standard predictors of RCC-SM, which consisted of TNM stage, tumour size, Fuhrman grade and histological subtype. The subsequent model (Model 2) additionally included ECOGPS. Model 3 consisted of standard predictors and of the variable defining S-CLASS. Finally, the last model (Model 4) included all standard predictors as well as ECOGPS and S-CLASS.

Univariable and multivariable predictive accuracy was quantified with Harrell's concordance index, which represents a modification of the AUC approach, when censored observations are used.[15] Similarly to the AUC methodology, 50% is equivalent to a flip of a coin and 100% represents ideal prediction. To reduce overfit bias and to internally validate the predictive accuracy estimates, all univariable and multivariable models were subjected to 200 bootstrap resamples. All statistical tests were performed using S-PLUS Professional, version 1 (MathSoft Inc., Seattle, Washington). Moreover, all tests were two-sided with a significance level set at 0.05.

3. Results

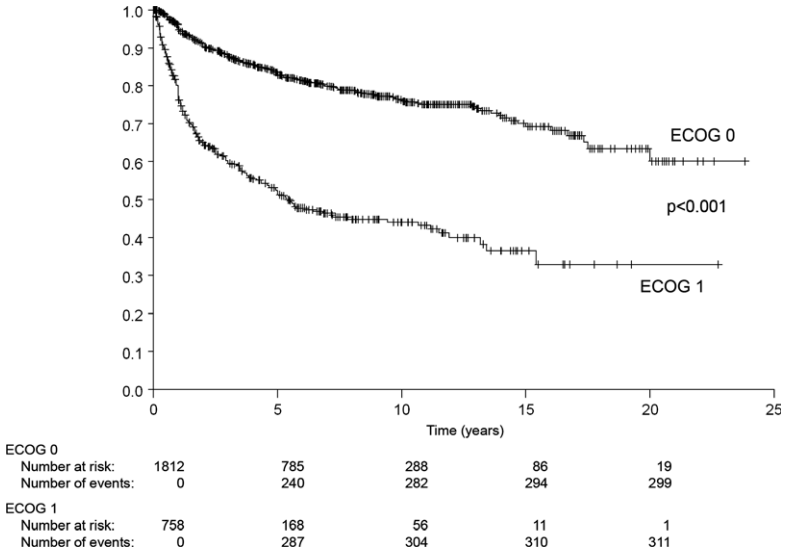
The patient characteristics of the 2570 patients are shown in Table 1. The majority ($n = 1716$, 66.8%) were men and the average age was 60.7 years (median 62, range 10–91 years). Most had pT_1 disease (46.7%). Nonetheless, 35.9% were pT_3. The average tumour size was 6.0 cm (median 6.7, range 0.5–25.0 cm). Clear cell was the predominant histological subtype ($n = 2245$, 87.4%) and was followed by papillary ($n = 212$, 8.2%), chromophobe ($n = 73$, 2.8%), unclassified ($n = 31$, 1.2%) and collecting duct ($n = 9$, 0.4%) variants. Fuhrman II (32.6%) and III (33.1%) represented the most frequent nuclear grades. Nodal metastases were diagnosed in 9.4% ($n = 241$), while 13.0% had systemic metastases ($n = 334$). ECOGPS 1 was present in 758 patients (29.5%). Follow-up ranged from 0.1 to 23 years (mean 4.7, median 3.2). Of all patients, 610 (23.7%) died of RCC. For those who died of RCC, the mean and median time to RCC-specific death were, respectively, 2.6 and 1.3 years (range 0.1–20 years). For all patients at risk, the actuarial mean survival was 15.8 years (median not reached).

Fig. 1a shows RCC-SS of the entire cohort. Figs. 1b and 1c show RCC-SS according to ECOGPS and S-CLASS. ECOGPS can accurately discriminate between those with worse versus better survival (log rank $p < 0.001$). Of note, 5- and 10-year actuarial survival rates were, respectively, 82.9% and 76.0% for patients with ECOGPS 0 versus 51.3 and 44.1% for patients with ECOGPS 1. Similarly, asymptomatic patients fared better than their counterparts with local symptoms (log rank $p < 0.001$) and systemic symptoms (log rank $p < 0.001$). Moreover, patients with local symptoms had better survival than those with systemic symptoms (log rank $p < 0.001$). Five- and 10-year actuarial survival rates were, respectively, 89.7% and 84.0% for asymptomatic patients, 74.5% and 65.1% for



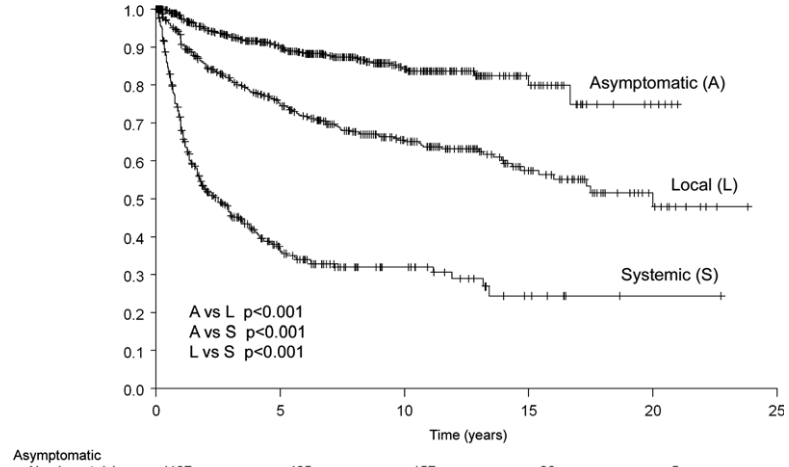
Prediction	Survival (%)	95(%) confidence interval		Number at risk	Events
		Lower	Upper		
1 year	89.5	88.2	90.7	2072	249
2 years	82.9	81.3	84.4	1670	389
5 years	74.1	72.1	76.0	953	527
10 years	67.2	64.6	69.7	344	586
15 years	60.2	56.2	64.1	97	604
20 years	52.3	44.4	59.6	20	610

Fig. 1a – Renal cell carcinoma-specific survival in 2570 patients treated with nephrectomy.



ECOG 0					
Number at risk:	1812	785	288	86	19
Number of events:	0	240	282	294	299
ECOG 1					
Number at risk:	758	168	56	11	1
Number of events:	0	287	304	310	311

Fig. 1b – Renal cell carcinoma-specific survival in 2570 patients treated with nephrectomy stratified according to ECOG performance status.



Asymptomatic					
Number at risk:	1167	485	157	33	5
Number of events:	0	87	104	107	108
Local					
Number at risk:	913	389	159	56	14
Number of events:	0	189	224	235	240
Systemic					
Number at risk:	490	79	28	8	1
Number of events:	0	251	258	262	262

Fig. 1c – Renal cell carcinoma-specific survival in 2570 patients treated with nephrectomy stratified according to symptom classification.

patients with local symptoms and 36.0% and 31.4% for patients with systemic symptoms.

Table 2 shows the univariable analyses addressing RCC-SM. In univariable analyses, both ECOG performance status ($p < 0.001$) and symptom classification ($p < 0.001$) represented statistically significant predictors. All other predictors also reached statistical significance (p-values $\leqslant 0.008$). ECOGPS 1 was associated with a 3.7-fold higher RCC-SM than ECOGPS 0. When compared with their asymptomatic counterparts, patients with local symptoms had a 2.7-fold higher RCC-SM versus patients with systemic symptoms, who had a 9.3-fold higher RCC-SM. In univariable predictive accuracy analyses, symptom classification had higher predictive accuracy than ECOG performance status (73.2% versus 66.2%, $p < 0.001$). Moreover, symptom classification was the third most informative predictor of RCC-SS and was only exceeded by Fuhrman grade.

In multivariate analyses, when ECOGPS and S-CLASS were considered separately (Models 2 and 3), as well as when both variables were included within the same model (Model 4), ECOGPS and S-CLASS both achieved independent predictor status. In multivariable predictive accuracy analyses, Model 1, where neither ECOGPS nor S-CLASS was considered, demonstrated 86.1% accuracy in RCC-SM prediction. Inclusion of ECOGPS (Model 2) resulted in a gain of 0.3% ($p = 0.8$). When S-CLASS (Model 3) was added, predictive accuracy increased

Table 2 – Univariate and multivariate Cox regression models for the prediction of renal cell carcinoma-specific mortality

Predictors	Univariable		Multivariable			
			Model 1	Model 2	Model 3	Model 4
	RR; *p*-value	PA (%	RR; *p*-value	RR; *p*-value	RR; *p*-value	RR; *p*-value
Age (>42-91 versus 10-42)	2.3; <0.001	52.4	2.1; <0.001	2.1; <0.001	2.2; <0.001	2.2; <0.001
T stage	–; <0.001	76.4	–; <0.001	–; <0.001	–; <0.001	–; <0.001
T_2 versus T_1	4.0; <0.001		2.4; <0.001	2.3; <0.001	2.2; <0.001	2.2; <0.001
T_3 versus T_1	9.4; <0.001		3.4; <0.001	3.1; <0.001	2.9; <0.001	2.9; <0.001
T_4 versus T_1	27.3; <0.001		4.0; <0.001	3.9; <0.001	3.8; <0.001	3.8; <0.001
Nodal metastases (positive versus negative)	6.6; <0.001	62.6	2.1; < 0.001	2.1; <0.001	2.0; <0.001	2.0; <0.001
Distant metastases (positive versus negative)	11.0; <0.001	69.3	5.3; < 0.001	4.9; <0.001	4.5; <0.001	4.5; <0.001
Tumour size	1.2; <0.001	73.1	1.1; <0.001	1.1; <0.001	1.1; < 0.001	1.1; <0.001
Fuhrman grade	–; <0.001	74.3	–; <0.001	–; <0.001	–; <0.001	–; <0.001
II versus I	2.3; <0.001		1.0; 1.0	1.0; 0.8	1.0; 0.8	0.9; 0.8
III versus I	7.1; <0.001		1.6; 0.02	1.5; 0.04	1.5; 0.03	1.5; 0.04
IV versus I	16.2; <0.001		2.5; <0.001	2.4; <0.001	2.2; <0.001	2.2; <0.001
Histological type	–; 0.008	51.9	–; 0.1	–; 0.09	–; 0.07	–; 0.06
Papillary versus clear cell	0.8; 0.1		1.3; 0.1	1.3; 0.09	1.4; 0.04	1.4; 0.04
Chromophobe versus clear cell	0.2; 0.004		0.3; 0.07	0.3; 0.07	0.4; 0.1	0.4; 0.09
Collecting duct and unclassified versus clear cell	1.4; 0.3		1.0; 0.9	1.1; 0.8	1.1; 0.8	1.1; 0.7
ECOG (1 versus 0)	3.7; <0.001	66.2		1.7; <0.001		1.2; 0.03
Symptom classification	–; <0.001	73.2			–; <0.001	–; <0.001
Local versus asymptomatic	2.7; <0.001				1.6; <0.001	1.5; 0.001
Systemic versus asymptomatic	9.3; <0.001				2.6; <0.001	2.2; <0.001
Predictive accuracy (PA) (%)			86.1	86.4	86.7	86.7

ECOG, Eastern Cooperative Oncology Group. Model 1 – base model. Model 2 – base model with ECOG. Model 3 – base model with Symptom classification. Model 4 – base model with ECOG and Symptom classification.

by 0.6% ($p = 0.5$). Finally, when both variables were added (Model 4), predictive accuracy increased by 0.6% ($p = 0.5$).

4. Discussion

Although ECOGPS and S-CLASS are both independent predictors of RCC-SM, S-CLASS determines the presence and type of symptoms related to RCC. Conversely, ECOGPS quantifies the degree of functional impairment related to cancer diagnosis. Thus, it might be argued that the combined effect of ECOGPS and S-CLASS may provide better discriminant properties than when either is used in isolation. To address this hypothesis, we quantified the gain in accuracy related to the addition of either ECOGPS or S-CLASS to standard predictors of RCC-SM, namely TNM stage, tumour size, Fuhrman grade and histological subtype. Our objective was to specifically assess whether clinicians should rely on the combined input of these two variables or not. Moreover, we wanted to measure the extent by which each variable can improve the prediction of RCC-SM, when each is added to standard RCC-SM predictors. In several previous analyses, ECOGPS demonstrated independent predictor status in RCC-SM analyses of not only advanced and metastatic RCC,[16] but also localised RCC.[6] Similarly, Patard et al. repeatedly demonstrated that S-CLASS represents an independent predictor of RCC-SM.[12,13]

Our Kaplan–Meier analyses demonstrated that ECOG performance status as well as symptom classification can accurately stratify between those with poor prognosis and those with better prognosis (all log-rank *p*-values <0.001). Moreover, univariable analyses predicting RCC-SM also confirmed that both ECOGPS and S-CLASS represent statistically significant predictors ($p < 0.001$). In multivariable analyses, both ECOGPS and S-CLASS achieved independent predictor status regardless of whether they were included separately (Models 2 and 3) or simultaneously (Model 4) in the multivariable models ($p \leqslant 0.03$). This indicates that both variables are significantly associated with the outcome of interest, namely RCC-SM. However, the presence of a statistically significant association or independent predictor status cannot quantify the gain that is related to the inclusion of these variables to standard predictors of RCC-SS. We have previously demonstrated that independent predictors are not invariably associated with predictive accuracy gains.[17–19] We used the same methodology to quantify the gain related to the addition of ECOGPS and/or S-CLASS.[20] In multivariable predictive accuracy analyses, little accuracy gain was recorded when ECOGPS and S-CLASS were added to the base model (Model 1) that contained all standard predictors of RCC-SM: 0.3% gain from addition of ECOGPS, 0.6% from addition of S-CLASS and 0.6% from addition of both. None of these predictive accuracy gains achieved statistical significance ($p \geqslant 0.5$). Furthermore, none of the gains can be interpreted as clinically meaningful. From a practical perspective, a gain of 0.6% corresponds to correct classification of 6 additional patients out of 1000. In the current study, the knowledge of ECOGPS or S-CLASS would have

resulted in correct classification of 15–16 additional patients out of 2570. Can this relatively marginal gain be interpreted as meaningful? The answers may differ. Those designing large scale clinical trials may opt for inclusion of both variables or at least of one. However, when individual predictions are made, it appears that ECOGPS and S-CLASS may be safely omitted, when standard predictors of RCC-SM are available. Therefore, when prognostic models are developed for use in busy clinical practice and the most parsimonious tools are sought, ECOGPS and S-CLASS are not indispensable.

Moreover, from a clinical perspective, these findings also indicate that patients who present with poor ECOG performance status and/or systemic symptoms do not have worse prognosis than their counterparts who do not exhibit these apparently unfavourable characteristics, as long as the effect of other established markers such as TNM stage, tumour size, Fuhrman grade and histological subtype is considered.

Our findings are important since the use of novel and/or routinely used markers is usually based on their independent predictor status. However, independent predictor status does not always translate into improved ability to predict, as we have previously shown.[17–19] To address the issue of assessment of predictors, Kattan[20] recommends that a variable should not only be judged according to its multivariable independent predictor status. Instead, a variable should also increase the combined predictive accuracy of established standard predictors. This implies that any prognostic marker should be judged by its added value. Our work indicates that neither ECOGPS nor S-CLASS qualifies for the definition of an informative marker, as neither improved the combined predictive accuracy of TNM stage, tumour size, Fuhrman grade and histological subtype.

Despite its strengths, the study has several weaknesses. Since our study represents a surgical series, only patients with ECOGPS 0 or 1 were included. This practice has limited the variability of ECOGPS and has limited its effect. It is possible that the inclusion of patients with ECOGPS 2 or higher might have changed our results. Patients with poor performance status usually present with metastatic disease and are candidates for cytoreductive nephrectomy. The contemporary recommendations to exclude patients with ECOGPS 2 or higher originate from the SWOG and EORTC randomised trials and have been adopted by the urologic community worldwide.[10,11] In consequence, few if any patients with ECOGPS above 2 will be included in surgical series. However, patients who present with de novo metastatic disease and who are not candidates for cytoreductive nephrectomy may have poorer ECOGPS. It needs to be emphasised that our findings are not generalisable to such populations and only apply to patients treated with radical nephrectomy, in whom the TNM stage, tumour size, Fuhrman grade and histological subtype are known and can be considered in the definition of prognosis. We do not have all the information regarding adjuvant and/or salvage treatment regimens of the included patients. Some received adjuvant immunotherapy, while others received immunotherapy at relapse. Finally, some were treated with experimental chemotherapy, while others received only the best supportive care. It is unlikely that adjuvant or salvage therapies have contributed to a significantly longer survival, as the majority of historic regimens are associated with dismal effect on survival.[21] Recent data presented by Negrier et al. actually demonstrated equivalence between medroxyprogesterone, interleukin and interferon and confirm the ineffectiveness of historic systemic regimens.[22] Nonetheless, our survival findings might have been contaminated by the effect of immunotherapy in some individuals. It may be postulated that the effect of ECOGPS and/or S-CLASS can be more pronounced in patients with metastatic RCC. Our study only included 13% of patients with metastatic RCC and these were biased towards those with better prognosis as they qualified for nephrectomy. Moreover, the effect of ECOGPS and/or S-CLASS may be more important if recurrence-free survival represents an endpoint. The study population was treated with nephrectomy between 1984 and 2001. This relatively long time span introduces a certain amount of heterogeneity. For example, the treatment paradigms have changed over that period of time. The use of the classic Robson radical nephrectomy with ipsilateral adrenalectomy has decreased. Conversely, an increasing proportion of patients are treated with partial nephrectomy and more recently with laparoscopy.[23,24] According to the updated European Association of Urology guidelines, laparoscopic nephrectomy represents the standard of care for patients with T1a tumours. Besides the changes in the management paradigms, important stage migration has also occurred in Europe and in the United States during the study period.[25] More contemporary patients tend to present with smaller tumours, lower T stages, fewer symptoms and better performance status. This stage shift is due to larger proportion of incidentally diagnosed renal masses, which are detected when imaging procedures are obtained for a variety of reasons that are unrelated to the renal pathology.[26] Since the stage migration tends to progressively reduce the proportion of patients with symptomatic disease and/or with impaired performance status, it might be postulated that the importance of ECOGPS and/or S-CLASS may actually decrease in the years to come. However, such supposition is speculative and needs to be confirmed with future studies. It might also be postulated that the effects of ECOGPS and S-CLASS might remain more important in populations other than Europeans or North Americans. For example, routine ultrasonography or CT scans are less frequent on continents other than Europe and North America. Therefore, the stage migration and the decrease in the importance of ECOGPS and/or S-CLASS might be less important in these regions. Finally, ECOGPS and/or S-CLASS might have stronger effects in populations others than those with Caucasian predominance, such as the Japanese or other clinically, genetically or environmentally different cohorts.[27] Therefore, our findings cannot necessarily be generalised beyond Europe and/or North America.

To summarise, neither ECOGPS nor S-CLASS improves the ability to predict RCC-SM. Therefore, these variables may be safely omitted when risk stratification is performed in RCC patients.

Conflict of interest statement

None declared.

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