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Prognostic role of ECOG performance status in patients with urothelial carcinoma of the upper urinary tract: an international study

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Study Type – Prognosis (inception cohort series)
Level of Evidence 2a

What's known on the subject? and What does the study add?
ECOG Performance Status has gained wide popularity as an integral part of the assessment of patients with upper urinary tract carcinoma. Our findings indicate that ECOG-PS is strongly associated with perioperative and overall survival and should be considered carefully in our decision-making process.

OBJECTIVE

- To evaluate the prognostic role of ECOG Performance status (ECOG-PS) in a large multi-institutional international cohort of patients treated with radical nephroureterectomy for upper tract urothelial carcinoma.

MATERIALS AND METHODS

- Data of 427 patients treated with radical nephroureterectomy at five international institutions in Asia, Europe and Northern America were collected retrospectively from 1987 to 2008.
- Logistic and Cox regression models were used for univariable and multivariable analyses.

RESULTS

- ECOG-PS was 0 in 272 of 427 (64%) patients. The median follow-up of the whole cohort was 32 months.
- The five-year recurrence-free (RFS), cancer-specific (CSS) and overall (OS) survival estimates were 71.7%, 74.9% and 68.5%, respectively, in patients with ECOG-PS 0 compared with 60.1%, 67.8%, and 51.4% respectively, in patients with ECOG-PS ≥1 (*P* value 0.08 for RFS, 0.43 for CSS, and <0.001 for OS, respectively).
- On multivariable Cox regression analyses, ECOG-PS was not an independent predictor of either RFS (hazard ratio 1.4; $P = 0.107$) or CSS (hazard ratio 1.2; $P = 0.426$) but was an independent predictor of OS (hazard ratio 1.5; $P = 0.03$).

CONCLUSIONS

- In this large multicentre international study, ECOG-PS was not significantly associated with RFS and CSS.
- Conversely we find a strong association with survival 1-month after surgery and OS. Further research is needed to ascertain the additive prognostic role of ECOG-PS in well-designed prospective multicentre studies.

KEYWORDS

performance status, ECOG, prognosis, urinary tract cancer, urothelial carcinoma, nephroureterectomy, recurrence-free survival, cancer-specific mortality

INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) represents approximately 5% of all urothelial tumours and 10% of all renal tumours [1]. Standard treatment for high-risk UTUC consists of radical nephrouretectomy (RNU) with ipsilateral bladder cuff excision and regional lymphadenectomy [2]. Tumour stage, presence of lymphovascular invasion, lymph node metastasis and grade have been

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documented as major prognostic factors [2–10]. Invasive UTUC has a poor prognosis. The 5-year survival rates for patients with pT2 and pT3 disease are 73% and 40%, respectively; and the median survival for patients with stage T4 disease is estimated at 6 months [11]. Surgery represents the only potentially curable therapeutic intervention for these patients. Accurate prediction of survival in patients with UTUC is essential for counselling and for the selection of potential adjuvant treatments. The Eastern Cooperative Oncology Group (ECOG) performance status (ECOG-PS) was established to assess cancer patient's overall well being and functional status [12]. Since its inception, ECOG-PS has gained wide popularity and represents an integral part in the assessment of patients with various malignancies such as renal cell carcinoma or bladder cancer. To our knowledge, no studies have assessed the potential value of ECOG-PS status as a prognostic factor in patients with UTUC. We hypothesized that ECOG-PS could be helpful as a prognostic variable to predict perioperative mortality (30 days) and oncological outcomes after surgery. Therefore, we tested this hypothesis in a large multi-institutional international cohort of patients treated with RNU for UTUC.

PATIENTS AND METHODS

This was an institutional review board-approved study with all participating sites providing the necessary institutional data-sharing agreements before initiation of the study. Five academic centres worldwide provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen, and the final data set was produced for the current analysis.

The database comprised 427 patients who underwent RNU with ipsilateral bladder cuff resection between 1987 and 2008. Performance status was assigned according to the ECOG-PS classification: grade 0 for patients fully active, able to carry on all pre-disease performance without restriction; grade 1 for patients restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work; grade 2 for patients ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; grade 3 for patients capable of only limited self-care, confined to bed or chair more than 50% of waking hours; grade 4 for patients completely disabled, who cannot carry on any self-care and are totally confined to bed or chair [12]. Surgery was performed by several surgeons according to the standard criteria for RNU, i.e. extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected along with enlarged lymph nodes if abnormal on preoperative computed tomography scans or palpable intraoperatively. Extended lymphadenectomy was not routinely performed.

All surgical specimens were processed according to standard pathological procedures at each institution. Tumours were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [13]. Tumour grading was assessed according to the 1973 WHO/International Society of Urologic Pathology consensus classification [14]. Lymphovascular invasion was defined as the presence of tumour cells within an endothelium-lined space without underlying muscular walls.

For the follow-up regimen patients were generally observed every 3 to 4 months for the first year after RNU, every 6 months from the second to the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scan, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated. Disease recurrence was defined as recurrence failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not considered in the analysis of recurrence-free survival (RFS). Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or from death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e. death within 30 days of surgery) were censored at time of death for cancer-specific survival (CSS) analyses.

Pearson's chi-squared test was used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann–Whitney *U* test. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $P \leq 0.05$. All reported *P* values are two-sided. Analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

ECOG-PS was 0 in 272 of 427 (64%) patients. Table 1 shows the association between ECOG-PS and clinical and pathological features. Compared with those with ECOG-PS ≥1, patients with ECOG-PS 0 were significantly younger and more commonly men, more likely to undergo lymph node dissection (all *P* values <0.05). Moreover, the distribution of tumour grade was significantly different between the two groups ($P < 0.001$), whereas all the other pathological features were not.

The median follow-up of the whole cohort was 32 months, interquartile range (IQR) 13–76 months. At last follow-up, 119 patients (28%) had developed disease recurrence and 95 (22%) were dead of UTUC. Moreover, 55 patients (13%) experienced non cancer-related deaths. The median follow-up for patients alive at last follow-up was 46 months (IQR 16–90 months). The overall 2-year and 5-year RFS estimates were 75.7% (SE 2.2%) and 67.6% (SE 2.6%), respectively. The overall 2-year and 5-year CSS estimates were 82.2% (SE 2%) and 72.5% (SE 2.6%), respectively. The 5-year RFS and CSS estimates were 71.7% (SE 3.1%) and 74.9% (SE 3.1%), respectively,

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TABLE 1 Association of ECOG performance status with clinical and pathologic characteristics

		ECOG performance status		
	Cases (%)	0 (n = 272, 64%)	≥1 (n = 155, 36%)	P value
Age (years) (mean ± SD)	67.3 ± 10.2	64.4 ± 9.8	72.4 ± 8.8	<0.001
Gender				
Male	318 (75%)	213 (67%)	105 (33%)	0.02
Female	109 (25%)	59 (54%)	50 (46%)	
Pathological stage				
Ta	84 (20%)	55 (66%)	29 (34%)	0.102
Tis	7 (2%)	6 (86%)	1 (14%)	
T1	93 (22%)	51 (55%)	42 (45%)	
T2	19 (18%)	58 (73%)	21 (27%)	
T3	128 (30%)	77 (60%)	51 (40%)	
T4	36 (8%)	25 (70%)	11 (30%)	
Grade				
G1	54 (13%)	39 (72%)	15 (28%)	<0.001
G2	72 (17%)	22 (31%)	50 (69%)	
G3	301 (70%)	211 (70%)	90 (30%)	
Lymphovascular invasion*				
Absent	301 (73%)	190 (63%)	111 (37%)	1
Present	113 (27%)	72 (64%)	41 (36%)	
Lymph node removed (median and IQR)	3 (2–6)	3 (2–6)	3 (1–6)	0.745
Lymph node stage				
N0	124 (29%)	95 (77%)	29 (23%)	0.01
Nx	270 (63%)	155 (57%)	115 (43%)	
N+	33 (8%)	22 (67%)	11 (33%)	
Follow-up duration (months) (median and IQR)	32 (13–76)	37 (13–81)	28 (12–62)	0.07

**Missing in 13 cases.*

in patients with ECOG-PS 0 compared with 60.1% (SE 4.6%) and 67.8% (SE 4.7%), respectively, in patients with ECOG-PS ≥1 (P = 0.08 for RFS and P = 0.43 for CSS; Fig. 1).

On multivariable Cox regression analyses that included age, gender, stage, grade, lymphovascular invasion and lymph node status, ECOG-PS was not associated with either RFS (hazard ratio 1.4; P = 0.107; Table 2) or CSS (hazard ratio 1.2; P = 0.426; Table 3). Analyses were rerun after excluding 46 patients (11%) who received adjuvant chemotherapy. This resulted in consistent statistical patterns and P values.

The 2-year and 5-year overall survival (OS) estimates were 77.3% (SE 2.2%) and 62.3% (SE 2.8%), respectively. The 5-year OS rates were 68.5% (SE 3.3%) in patients with ECOG-PS 0, compared with 51.4% (SE 4.7%) in patients with ECOG-PS ≥1 (P < 0.001; Fig. 1).

On multivariable Cox regression analyses ECOG-PS was an independent predictor of OS (hazard ratio 1.5; P = 0.03) after adjusting for the effects of other covariates (Table 4).

DISCUSSION

ECOG-PS is intended to assess disease progression, how the disease affects the daily living abilities of the patient, and, whenever possible, to determine appropriate treatment and prognosis. Cancer-related causes for poor performance status may include pain from the primary tumour or metastases, pleural effusions, brain metastasis, ascites, anaemia, cachexia, weight loss, fatigue, gastrointestinal problems or paraneoplastic syndromes. The scale has been largely adopted in oncology, with kidney cancer being the urological disease where it is most commonly used. Previous studies assessed the role of ECOG-PS as a predictor of outcome in patients with UTUC undergoing chemotherapy. Specifically, Ecke *et al.* [15] reported a series of 27 patients with locally advanced UTUC who received adjuvant chemotherapy with gemcitabine, paclitaxel and cisplatin. Median survival time for patients with ECOG-PS 0 vs ≥1 were 52 vs 22 months suggesting that ECOG-PS is associated with survival in patients treated with adjuvant chemotherapy [15]. In a multicentre, multinational phase III trial including patients with locally advanced or metastatic UTUC comparing two regimens of chemotherapy, von der Maase *et al.* [16] found that PS and presence of visceral metastasis were the most important predictive factors for overall survival and time to progression. To our knowledge, the present series is the first one where the prognostic impact of ECOG-PS status was assessed in patients with UTUC undergoing RNU as a primary treatment. We found that ECOG-PS is associated with greater age and

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female gender and is a strong, independent predictor of overall survival. ECOG-PS was, however, not associated with tumour-specific features such as stage, RFS and CSS.

With regard to the cancer-related outcomes, in our series ECOG-PS failed to be associated with both RFS and CSS. This was not in agreement with the fact that ECOG-PS was found to be predictive of survival in patients with locally advanced or metastatic UTUC undergoing chemotherapy in previous studies [16] where ECOG-PS may play a role as a predictor of response to systemic treatments. The lack of a prognostic role for ECOG-PS in patients undergoing RNU as the primary treatment for UTUC might reflect the prevalent role of clinical and pathological variables including surgical technique [5,17,18], stage of the primary tumour [2], lymphovascular invasion [19], presence of lymph node metastases [8,9], tumour location [18] and tumour architecture [20]. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients [20,21], presence of concomitant carcinoma *in situ* [22]. Concomitant carcinoma *in situ* is a feature of aggressive disease in patients with organ-confined urothelial carcinoma after RNU or tumour necrosis [23,24] in determining outcomes. However, because of study design, it has to be taken into account that patients with poor PS might have not been offered surgery, which may have biased our findings. On the whole, from a clinical perspective, these findings also indicate that patients with poor ECOG-PS may benefit from radical surgery as much as the counterpart with more favourable ECOG-PS and they should be offered RNU whenever possible, despite the higher risk of perioperative mortality.

The present study has several limitations. First and foremost are the limitations inherent in retrospective analyses. Although we have performed multiple internal and external reviews of our consortium data set, we excluded patients for whom we could not obtain complete information, which could possibly create selection bias. In addition, the population in this study underwent RNU by multiple surgeons, indication and extension of lymph node dissection were not standardized, and the

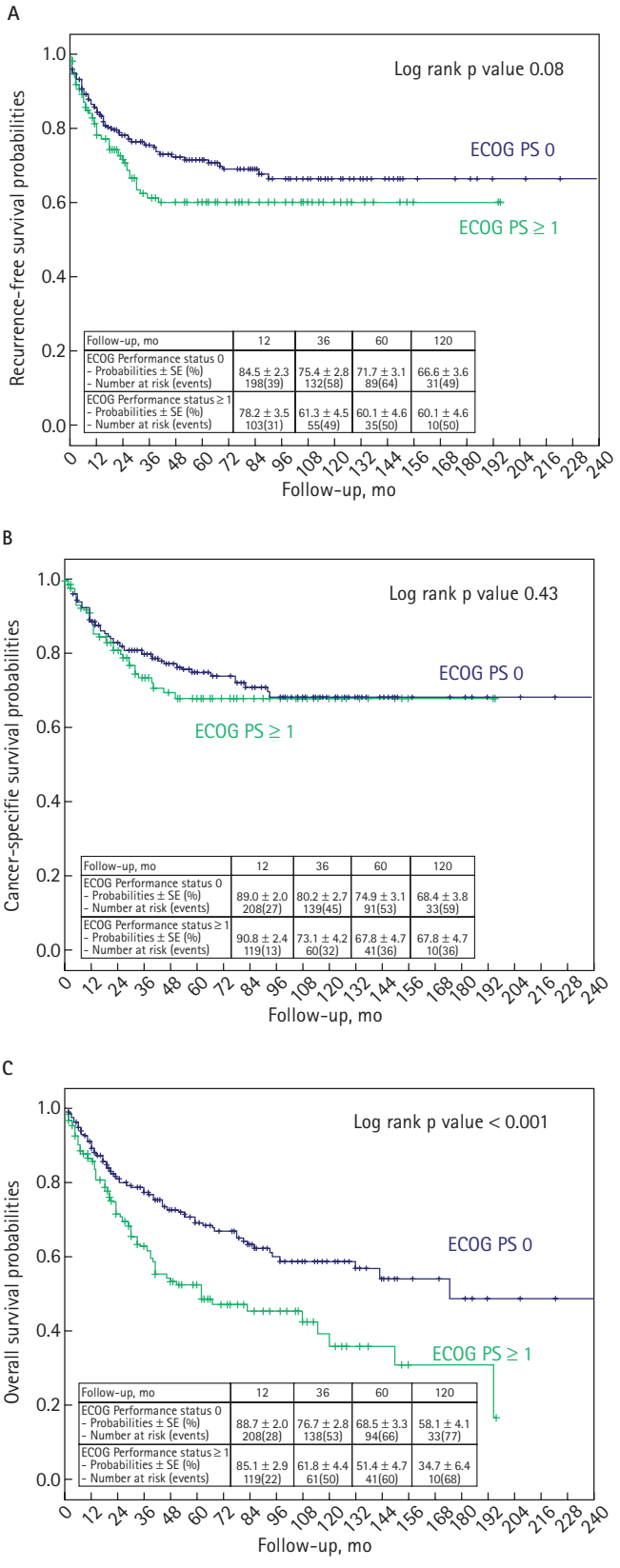

FIG. 1.
*Kaplan–Meier curves of (**A**) recurrence-free survival, (**B**) cancer-specific survival, and (**C**) overall survival stratified by ECOG Performance status in 427 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma.*

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TABLE 2 Univariable and multivariable Cox regression analysis of ECOG performance status with disease recurrence (N = 427, 119 recurrences)

	Univariable analysis			Multivariable analysis		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.0	0.9–1.03	0.140	1.0	0.9–1.03	0.317
Gender	1.5	0.9–2.1	0.05	1.2	0.8–1.8	0.339
ECOG Performance status	1.4	0.9–1.9	0.08	1.4	0.9–2.1	0.107
Stage			<0.001			<0.001
Ta/Tis	1	Referent	–	1	Referent	–
T1	1.3	0.6–3.1	0.541	1.1	0.4–2.8	0.824
T2	2.9	1.3–6.4	0.007	2.2	0.9–5.2	0.087
T3	5.1	2.5–10.3	<0.001	2.9	1.3–6.7	0.012
T4	25.7	11.9–55.7	<0.001	10.4	4.0–27.0	<0.001
Grade			<0.001			0.141
G1	1	Referent	–	1	Referent	–
G2	1.9	0.6–6.1	0.253	1.2	0.4–4.3	0.689
G3	5.6	2.0–15.1	0.001	2.2	0.7–6.5	0.160
Lymphovascular invasion	4.0	2.8–5.9	<0.001	1.9	1.3–2.9	0.002
Lymph node status			<0.001			0.362
N0	1	Referent	–	1	Referent	–
Nx	0.7	0.7–1.7	0.707	1.1	0.7–1.7	0.741
N+	5.0	2.9–8.8	<0.001	1.6	0.8–2.9	0.173

ECOG, Eastern oncology Cooperative Group; HR, hazard ratio; 95% CI, 95% confidence interval.

TABLE 3 Univariable and multivariable Cox regression analysis of ECOG performance status with cancer-specific survival (N = 427, 95 cancer-related deaths)

	Univariable analysis			Multivariable analysis		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.0	0.9–1.04	0.115	1.0	0.9–1.05	0.08
Gender	1.2	0.7–1.8	0.514	1.0	0.6–1.6	0.963
ECOG Performance status	1.2	0.8–.8	0.441	1.2	0.7–2.0	0.426
Stage			<0.001			<0.001
Ta/Tis	1	Referent	–	1	Referent	–
T1	1.4	0.5–4.3	0.541	1.6	0.4–5.7	0.482
T2	3.9	1.4–10.9	0.008	3.8	1.1–12.9	0.032
T3	7.9	3.1–20.0	<0.001	5.7	1.8–18.2	0.003
T4	45.6	17.1–121.7	<0.001	24.5	6.9–86.5	<0.001
Grade			<0.001			0.168
G1	1	Referent	–	1	Referent	–
G2	0.8	0.2–3.3	0.847	0.5	0.1–2.0	0.337
G3	4.6	1.7–12.5	0.003	1.3	0.4–3.9	0.697
Lymphovascular invasion	5.4	3.5–8.3	<0.001	2.5	1.6–4.0	<0.001
Lymph node status			<0.001			0.634
N0	1	Referent	–	1	Referent	–
Nx	1.1	0.7–1.9	0.988	1.2	0.7–2.0	0.524
N+	5.5	2.9–10.3	<0.001	1.4	0.7–2.9	0.347

ECOG, Eastern oncology Cooperative Group; HR, hazard ratio; 95% CI, 95% confidence interval.

follow-up lacked uniformity. However, all surgeons operated at selected centres with significant experience in urothelial cancer management, which might increase the external validity of the data, compared with the single-centre single-surgeon setting. Finally, data on preoperative renal function were not available in most of the patients as well as those patients with poor ECOG-PS who received treatments other than RNU, such as endourological percutaneous or retrograde management.

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TABLE 4 Univariable and multivariable Cox regression analysis of ECOG performance status with overall survival (N = 427, 150 any-cause deaths)

	Univariable analysis			Multivariable analysis		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.05	1.03–1.06	<0.001	1.04	1.02–1.06	<0.001
Gender	1.3	0.9–1.8	0.160	0.9	0.7–1.4	0.972
ECOG Performance status	1.8	1.3–1.4	<0.001	1.5	1.1–2.3	0.03
Stage			<0.001			<0.001
Ta/Tis	1	Referent	–	1	Referent	–
T1	1.1	0.6–2.0	0.821	0.8	0.4–1.7	0.576
T2	2.1	1.1–3.8	0.018	1.6	0.8–3.2	0.195
T3	3.5	2.0–5.9	<0.001	2.1	1.1–4.2	0.023
T4	17.4	9.2–32.8	<0.001	8.6	3.9–19.2	<0.001
Grade			<0.001			0.167
G1	1	Referent	–	1	Referent	–
G2	2.1	0.9–4.9	0.086	1.4	0.6–3.7	0.446
G3	3.9	1.8–8.2	0.001	2.0	0.9–4.9	0.108
Lymphovascular invasion	3.6	2.6–5.1	<0.001	2.1	1.4–3.1	<0.001
Lymph node status			<0.001			0.173
N0	1	Referent	–	1	Referent	–
Nx	1.4	0.9–2.0	0.152	1.4	0.9–2.1	0.131
N+	4.7	2.7–8.0	<0.001	1.7	0.9–3.2	0.086

ECOG, Eastern oncology Cooperative Group; HR, hazard ratio; 95% CI, 95% confidence interval.

In this large multicentre international study, ECOG-PS was not significantly associated with cancer-related outcomes (RFS and CSS), but it was a strong predictor of overall mortality. ECOG-PS should be considered in the decision-making regarding RNU for patients with UTUC. Further research is needed to ascertain the additive prognostic role of ECOG-PS in well-designed prospective multicentre studies.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **UTUC**, upper urinary tract urothelial carcinoma; **RNU**, radical ureterectomy; **ECOG–PS**, Eastern Cooperative Oncology Group performance status; **RFS**, recurrence-free survival; **CSS**, cancer-specific survival; **IQR**, interquartile range; **OS**, overall survival.

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