Survival and functional outcomes of patients with metastatic solid organ cancer admitted to the intensive care unit of a tertiary centre

Francis J Ha, Andrew J Weickhardt, Sagun Parakh, Andrew D Vincent, Neil J Glassford, Stephen Warrillow and Daryl Jones

ABSTRACT

Objective: Metastatic solid organ cancer is associated with a poor prognosis, and admission of patients with these cancers to the intensive care unit remains a dilemma. We aimed to assess outcomes in a cohort of these patients who were admitted to the ICU of a general tertiary centre.

Design, setting and patients: A retrospective observational study of patients with incurable metastatic solid organ malignancies who had unplanned admission to a tertiary hospital ICU between 1 January 2010 and 30 June 2015.

Main outcome measures: Survival outcomes up to 1 year after ICU admission, and functional outcomes as measured by Eastern Cooperative Oncology Group (ECOG) grade up to 3 months after ICU discharge. We also determined rates of advance care planning documentation.

Results: A total of 101 patients were treated in the ICU during the study period. Hospital, 30-day and 1-year mortality rates were 35%, 41% and 77%, respectively, and the median survival was 2.3 months (95% CI, 1.1–3.9 months). On multivariable analysis, lowest albumin level (hazard ratio [HR], 1.10; 95% CI, 1.04–1.15) and highest white cell count (HR, 1.03; 95% CI, 1.00–1.07) were significant, although they were marginal predictors of poorer overall survival. Higher ECOG grade showed a trend towards significance (HR, 1.60; 95% CI, 0.94–2.73; $P = 0.08$). In patients alive and assessable at 1 month, 17/31 (55%) had functionally declined. At 3 months, 15/22 surviving patients (68%) had returned to their baseline, pre-ICU admission ECOG grade. Ninety per cent had no advance care directive and two-thirds did not have a medical enduring power of attorney.

Conclusions: Survival is poor in patients with metastatic cancer after emergent ICU admission, although functional state is often recovered by 3 months in surviving patients. Albumin level, white cell count and ECOG grade are simple prognostic markers of survival.

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The number of cancer patients being admitted to the intensive care unit is increasing.[1] However, the presence of cancer remains the second most common reason for refusal of ICU admission.[2] Admitting cancer patients to the ICU, especially those with metastatic disease, involves weighing expected survival benefit against the quality of life after discharge.

There is variation between studies reporting ICU survival outcomes in patients with solid organ cancer, which may be due to inclusion of a mixed population of patients with haematological cancers and patients with or without metastatic disease.[3,4] Most studies do not report mortality in patients with metastases, a group with poorer overall prognosis,[5] and no studies have assessed the functional outcome of cancer patients after ICU admission.

Advance care planning (ACP) may assist in providing appropriate care according to patient preferences. ACP includes discussion about goals of care, resuscitation, advance care directives (ACDs) and designation of medical enduring power of attorney (MEPA).[6] There are no data reporting the prevalence of ACP uptake in Australian cancer patients, but ACP documentation is widely considered to be low among the general public and residents of aged care facilities in Australia.[7,8]

We retrospectively assessed the survival and functional status of patients with incurable metastatic disease at a major tertiary hospital to determine their outcomes after admission to the ICU. We also sought to determine the documentation of goals of care, ACDs and MEPA before admission to the ICU.

Methods

Our study was a retrospective, ethics-approved, medical record review. It included enrolment of consecutive patients aged ≥ 18 years with metastatic solid organ malignancies admitted to the ICU at a single, large, 400-bed tertiary hospital between 1 January 2010 and 30 June 2015. We included patients with unplanned ICU admission after surgery due to acute complications during the immediate perioperative period. We excluded patients with haematological malignancies, patients treated with curative intent (as adjudicated by two oncologists, A W and S P, through consensus agreement) and patients electively admitted to the ICU for routine post-operative monitoring.

We collected demographic data and data related to cancer diagnosis and ICU admission. Baseline demographic data included area of residence (regional or metropolitan), living arrangement before hospital admission, comorbidities and smoking status.

Data were also collected on functional status before ICU admission, as measured by the Eastern Cooperative Oncology Group (ECOG) grade, which grades performance from 0 (fully active; able to carry out all pre-disease performance without restriction) to 4 (completely disabled; cannot carry out any self-care; totally confined to bed or chair) or 5 (dead).[9] The last recorded outpatient ECOG status up to 4 months before ICU admission was used as the pre-ICU ECOG status.

Cancer-specific data included primary diagnosis, sites of metastases and time from diagnosis of metastatic disease to ICU admission. ICU-specific data collected within 24 hours of admission included reason for admission as determined by an intensivist at the time of admission; Acute Physiology and Chronic Health Evaluation (APACHE) II score; treatments received; and baseline biochemical test results, including albumin level and white cell count (WCC). The diagnoses of sepsis, cardiovascular instability or respiratory distress were determined by the intensivist at the time of discharge from the ICU or at death. After hospital discharge, we also collected data relating to post-hospital living arrangements and ECOG status, as documented at subsequent follow-up in the outpatient clinic or hospital admission, at 1 month (range, 1–60 days) and 3 months (range, 61–120 days).

We collected ACP documentation,[6] including pre-ICU admission resuscitation status, as well as documentation of ACDs and MEPA where present. An ACD is legal documentation outlining the patient's preferences for medical treatment and limitations of interventions at the end of life.[10] An MEPA is a legal document stating the patient's appointed legal representative to make medical decisions on their behalf if they become incapable of doing so, such as during rapid cognitive decline.[11]

Analysis

We used the Kaplan–Meier estimator to determine the median follow-up and overall survival. Factors of interest, specified before the study, were age, ECOG grade, sepsis (yes versus no), cardiovascular instability (yes versus no), respiratory distress (yes versus no), liver metastases (yes versus no), lowest albumin value in first 24 hours of admission, highest WCC in first 4 hours of admission and length of ICU stay (< 24 hours versus ≥ 24 hours).

We examined pairwise Spearman rank correlations to identify associations between factors. Cox proportional hazards models were fitted, and we assessed failures of the proportionality assumption using Schoenfeld residuals. For each factor of interest, a univariable Cox model was constructed, excluding missing data. For completeness, a full multivariable Cox model was constructed with all factors, imputing missing covariate data, using chained equation multiple imputation ($m = 50$). For comparison, we performed a univariable Cox regression with the APACHE II score as the predictor. We report the proportion of variance explained (R^2) and the concordance index (C-index) to compare Cox models. For graphical presentation, the Cox linear predictors are divided into four groups using the 16th, 50th and 84th quantiles (corresponding to the mean and mean ± 1 standard deviation of a normal distribution). Kaplan–Meier curves are presented for each group. Analyses were performed in *R*, version 3.3.1 (R Project), with statistical significance defined as $P < 0.05$.

Results

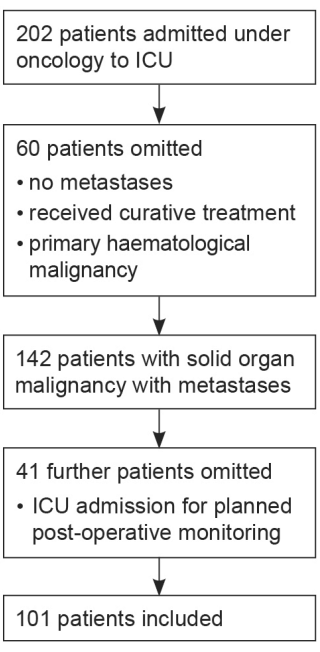
Baseline characteristics

Over the 5 and a half years, 202 oncology patients were admitted to the ICU, with 101 admitted emergently with solid organ metastatic disease (Figure 1). The median age at ICU admission was 64 years (interquartile range [IQR], 52.5–71.4 years) and 55% were male. The most common primary malignancy was lung cancer (22%), followed by upper gastrointestinal or hepatobiliary cancers (18%) (Table 1). All patients were living at home before ICU admission. Of the 73% of patients with a documented ECOG before ICU admission, 62% were assessed as ECOG grade 0–1, and 19% were assessed as ECOG grade 3–4. The median documentation time of ECOG status before ICU admission was 11 days (range, 1–108 days). The baseline demographic data for the 101 patients are summarised in Table 1.

ICU-related characteristics

The median length of time between diagnosis of metastatic disease and ICU admission was 17 months (IQR, 6–42 months). ICU admission was most commonly related to complication of therapy (47%) or underlying malignancy (38%). The most common reasons for ICU admission were respiratory distress (52%), sepsis (47%) and cardiovascular instability (45%). The median length of stay in the ICU was 27 hours (IQR, 15–69 hours). Nearly half the patients

Figure 1. Patient selection



ICU = intensive care unit.

Table 1. Baseline patient demographic data

Characteristic	Data (*n* = 101)
Median age, years (IQR)	64 (52.5–71.4)
Male, *n* (%)	55 (55%)
Residence, *n* (%)	
Regional	19 (19%)
Metropolitan	82 (82%)
Living at home before hospital admission, *n* (%)	101 (100%)
Comorbidities, *n* (%)	39 (39%)
Hypertension	8 (8%)
Ischaemic heart disease	9 (9%)
Chronic obstructive pulmonary disease	5 (5%)
Congestive cardiac failure	16 (16%)
Primary malignancy, *n* (%)	
Lung	22 (22%)
Breast	14 (14%)
Colorectal	14 (14%)
Urogenital	14 (14%)
Upper gastrointestinal or hepatobiliary	18 (18%)
Melanoma	5 (5%)
Other	14 (14%)
Site of metastases, *n* (%)	
Liver	44 (44%)
Lung	38 (38%)
Lymph node	49 (49%)
Brain	16 (16%)
Bone	41 (41%)
Adrenal gland	5 (5%)
Peritoneum	7 (7%)
Other	7 (7%)
ECOG grade pre-admission, *n* (%)	
Documented	73 (100%)
0–1	45 (62%)
2	15 (20%)
3–4	14 (19%)
Not documented	27 (27%)

IQR = interquartile range. ECOG = Eastern Cooperative Oncology Group.

Table 2. ICU-related demographics

Characteristic	Data (*n* = 101)
Broad reason for ICU admission, *n* (%)	
Underlying disease	38 (38%)
Complications of therapy	47 (47%)
Underlying comorbidities	7 (7%)
Other	19 (19%)
Specific reason for ICU admission, *n* (%)	
Unplanned post-operative monitoring	19 (19%)
Respiratory distress	53 (52%)
Altered conscious state	19 (19%)
Sepsis	47 (47%)
Cardiac arrest	1 (1%)
Cardiovascular instability	45 (45%)
Acute kidney injury	11 (11%)
Other	2 (2%)
Source of ICU admission, *n* (%)	
Emergency department	39 (39%)
Ward	25 (25%)
Operating theatre or recovery	32 (32%)
Other hospital	4 (4%)
Other hospital ICU	1 (1%)
ICU test results, median (IQR)	
APACHE II score	16.0 (12.8–19.0)
Albumin level (lowest in first 24 hours)	23.0 (20.0–26.50)
WCC (highest in first 4 hours)	9.75 (5.25–17.0)
WCC (lowest in first 4 hours)	7.5 (4.40–13.1)
Haemoglobin level (lowest)	9.10 (7.95–10.3)
Treatment received in ICU, *n* (%)	
Mechanical ventilation	25 (25%)
Non-invasive ventilation	30 (30%)
Vasopressors	43 (43%)

ICU = intensive care unit. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. WCC = white cell count.

(43%) required vasopressor support, and 25% received mechanical ventilation. Further ICU-related demographic data are summarised in Table 2.

Outcomes after ICU admission

After discharge from the ICU, the median length of hospital stay was 4 days (IQR, 1–10 days). ICU and hospital mortality rates were 16% and 35%, respectively. Thirty-day and 1-year mortality rates were 41% and 77%, respectively. In total, 87 deaths were observed, with the median survival time being 2.3 months (95% CI, 1.1–3.9 months).

In the univariable Cox regressions, a higher ECOG grade (P = 0.03), respiratory distress (P = 0.05), lowest albumin level (P = 0.002) and highest WCC (P = 0.005) were significant predictors of poorer overall survival. Sepsis (P = 0.02) and cardiovascular instability (P = 0.02) were predictors of better overall survival (Table 3). In this cohort, cardiovascular instability and sepsis (ρ = 0.52) were effectively co-linear, and both factors negatively correlated with respiratory distress (ρ = –0.42 and –0.58, respectively).

In the full multivariable Cox regression, lowest albumin level (HR, 1.10; 95% CI, 1.04–1.15) and highest WCC (HR, 1.03; 95% CI, 1.00–1.07) were the only two predictors

Table 3. Associations with survival*

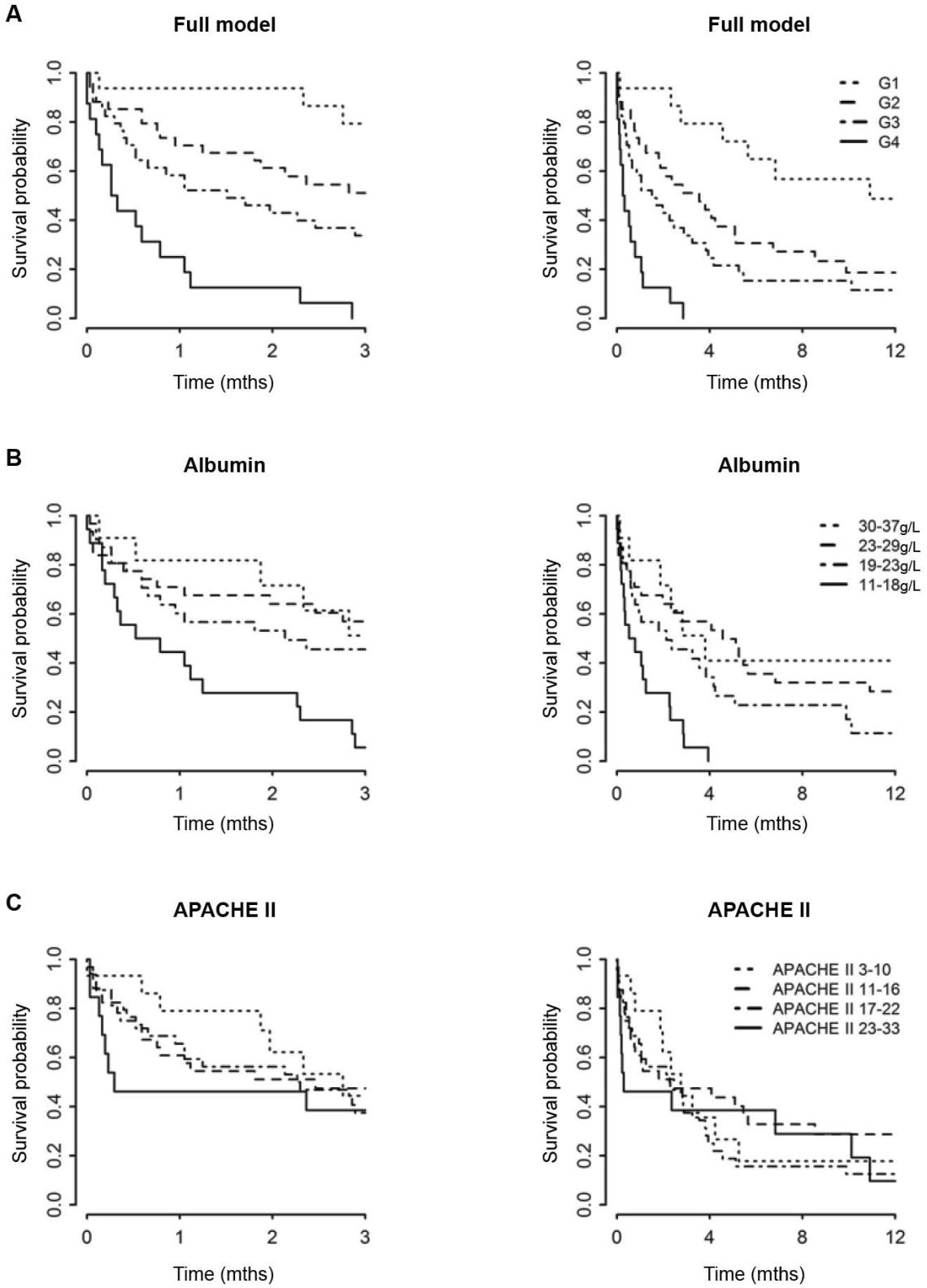
	Mortality, % (event/n)		Univariable analysis		Multivariable analysis (imputed)	
Variable	30-day	1-year	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, years						
< 65	35% (18/52)	82% (40/49)	1.00 (0.98–1.01)	0.87	0.99 (0.98–1.01)	0.58
≥ 65	42% (19/45)	90% (37/41)				
ECOG grade						
0–1	28% (12/43)	84% (31/37)	1.72 (1.04–2.85)	0.03	1.60 (0.94–2.73)	0.08
≥ 2	48% (14/29)	86% (25/29)				
Sepsis						
No	48% (25/52)	90% (44/49)	0.60 (0.39–0.94)	0.02	0.73 (0.36–1.45)	0.35
Yes	27% (12/45)	80% (33/41)				
Cardiovascular instability						
No	47% (26/55)	90% (47/52)	0.60 (0.39–0.93)	0.02	0.81 (0.43–1.52)	0.50
Yes	26% (11/42)	79% (30/38)				
Respiratory distress						
No	23% (11/47)	81% (34/42)	1.55 (1.01–2.39)	0.05	1.12 (0.59–2.13)	0.73
Yes	52% (26/50)	90% (43/48)				
Liver metastases						
No	41% (22/54)	86% (44/51)	0.84 (0.55–1.30)	0.44	0.65 (0.40–1.06)	0.08
Yes	35% (15/43)	85% (33/39)				
Lowest albumin level, first 24 hours (g/L)						
< 23	45% (18/40)	95% (35/37)	0.92 (0.88–0.97)	0.002	0.91 (0.87–0.96)	0.0008
≥ 23	31% (15/48)	77% (34/44)				
Highest WCC, first 4 hours (× 10^3/μL)						
< 10	30% (13/43)	82% (32/39)	1.04 (1.01–1.07)	0.005	1.03 (1.00–1.07)	0.03
≥ 10	44% (20/45)	88% (37/42)				
Length of ICU stay, hours						
< 24	49% (19/39)	88% (30/34)	0.70 (0.45–1.09)	0.12	0.76 (0.45–1.29)	0.30
≥ 24	31% (18/58)	84% (47/56)				
APACHE II score						
< 20	32% (22/69)	83% (52/63)	1.04 (0.99–1.08)	0.09		
≥ 20	57% (12/21)	95% (19/20)				

HR = hazard ratio. ECOG = Eastern Cooperative Oncology Group. WCC = white cell count. ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. * 30-day and 1-year mortality rates are reported for dichotomised predictors as number of events/total number of assessable patients, and univariable and multivariable Cox-estimated HRs are reported.

that maintained significance, with albumin level showing the strongest association with survival (Figure 2). In comparison, the APACHE II score was not significantly associated with survival (univariable $P = 0.09$), explaining only 3% of the variance (C-index, 0.561; SE, 0.038). Albumin level alone explained 10% of the variance (C-index, 0.609; SE, 0.038). The full multivariable model in a complete-case analysis explained 34% of the variance (C-index, 0.696; SE, 0.046).

Of the patients alive at discharge, most (88%) returned to living at home, although 11% had a decline in living arrangements requiring relocation to an assisted living facility (3%) or were discharged to a hospice (8%). Of the 35 patients alive at 1 month, 15 (43%) had an ECOG grade ≤ 1 after ICU discharge (Figure 3) and 20 did not have ECOG grade documentation during this follow-up period. Compared with their pre-ICU functional status, 17 of 31 assessable patients (55%) declined in functional status. Of patients who were alive and assessable 3 months after discharge, 15 of 22 (68%) returned to their baseline pre-ICU ECOG grade, with 13 of 24 (54%) assessed as ECOG grade ≤ 1 (Figure 3).

Figure 2. Kaplan–Meier curves for full multivariable model, albumin level and APACHE II score



APACHE = Acute Physiology and Chronic Health Evaluation. G1 = Grade 1 (85th–100th percentile). G2 = Grade 2 (51st–84th percentile). G3 = Grade 3 (17th–50th percentile). G4 = Grade 4 (1st–16th percentile).

Goals-of-care documentation and related legal orders

Most assessable patients (47/52; 90%) did not have an ACD at the time of hospital admission, and about two-thirds of patients did not have an MEPA (35/53; 66%). In patients who had their goals-of-care order documented before ICU admission, one-quarter (22/88) were not for cardiopulmonary resuscitation (CPR), intubation or non-invasive ventilation, 57% (50/88) were not for CPR but other active management was permitted, and full treatment was permitted for a minority (16/88; 18%).

Discussion

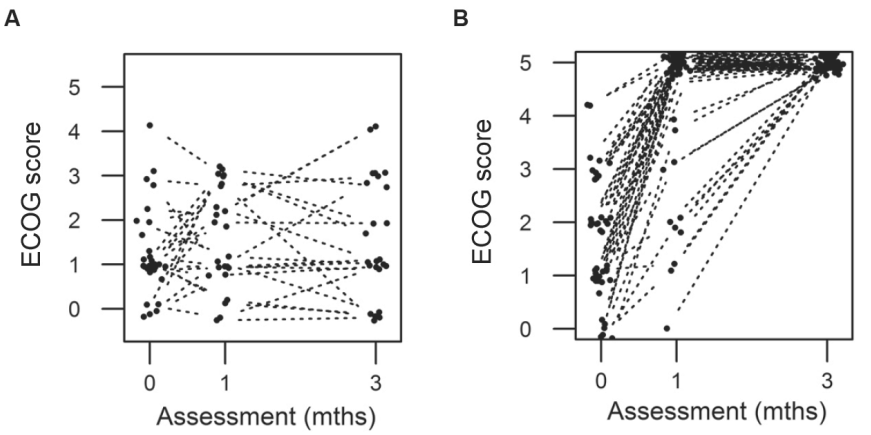
We conducted a retrospective, observational study of patients with incurable metastatic solid organ malignancies admitted to a major tertiary hospital ICU over a 5-year period. The study was conducted using a prospectively designed analysis plan, and our inclusion criteria for the period 2010–2015 resulted in a representative cohort of patients being treated in current clinical oncology practice. Our study is the first to assess survival and functional outcomes after ICU admission for patients with metastatic solid organ cancer. It is also the first to assess documentation of ACP, including goals of care, in such patients.

There was a high rate of mortality, with deaths in 41% of patients within 30 days and in 77% within 1 year. We identified a low albumin level at ICU admission and elevated WCC as being associated with increased mortality, and a higher ECOG grade showed a trend in significance. In addition, although most survivors returned home, a substantial proportion of patients declined in functional status after ICU admission. Despite these poor outcomes, there was a low rate of documentation of ACP made before admission of these patients.

An Italian study has previously assessed survival in a similar cohort with incurable metastatic solid organ malignancy, and reported a comparable 1-year mortality.[12] Interestingly, this survival outcome is similar to that of patients with solid organ cancer without metastases who are admitted to the ICU.[5,13] Studies evaluating metastasis as a predictor of survival report conflicting results regarding its role in determining suitability for ICU admission.[14,15]

A low albumin level has previously been reported as a predictor of early ICU mortality,[16] but it has not been extensively validated in patients with cancer. In patients with oesophageal cancer electively admitted to the ICU after oesophagectomy, the post-operative serum albumin level predicted in-hospital mortality.[17] Our findings extend beyond early mortality, with a low albumin level being a simple marker of overall survival in patients with cancer admitted to the ICU. A high WCC as a predictor of poorer overall survival, on multivariable analysis, has limited clinical utility alone, given the small HR and its inclusion in the APACHE II score. A higher ECOG grade showed a trend towards significance for predicting overall survival, and its association was likely limited by the lack of documentation reducing the number of observations required in the model for statistical significance. Functional status as a prognostic marker of early mortality is consistent with other studies in cancer patients.[18,19] We observe that sepsis and cardiovascular instability appear to be associated with improved survival in this cohort, compared with other reasons for admission. In the presence of febrile neutropenia, sepsis is a relatively reversible condition with appropriate use of antibiotics, inotropic support and short ICU admission. This is different from patients admitted with multiorgan failure including respiratory distress, which we found correlated with poorer survival.

Figure 3. ECOG grade at 0 months (baseline), 1 month and 3 months after ICU admission in patients (A) alive versus (B) dead at 3 months



ECOG = Eastern Cooperative Oncology Group. ICU = intensive care unit.

In patients alive and assessable after discharge, more than half (55%) had declined functionally by 1 month. However, most returned to or had improved on their baseline pre-ICU functional status by 3 months after discharge. This is consistent with studies of functional outcome in non-cancer patients after ICU admission, in whom an initial decline for up to 3 months is usually followed by a return to baseline by 6–12 months.[20]

Despite the poor prognosis of this cohort, most patients did not have a previously documented ACD or MEPA before ICU admission. Given that about one in three clinicians have identified at least one patient who had received inappropriate care in the ICU,[21] the

lack of documentation for ACP may lead to end-of-life care (EOLC) which is misaligned with the patient's priorities. Numerous factors influence the uptake of ACP in cancer patients, including a patient's fear and anxiety about EOLC discussions, the timing of such discussions and the patient's relationship with their treating clinician.[22] On average, 600 patients were seen per month in the outpatient oncology department at our institution over the study period, but only 1.7 patients per month were admitted to the ICU. Although ACP documentation does not necessarily translate to improved patient outcomes,[23] discussions between patients and the clinicians regularly involved in their care are important in minimising inappropriate interventions and improving patient quality of life in crucial periods such as ICU admission. Aggressive EOLC with ICU admission within 30 days of death is associated with relatively large differences in family-reported quality ratings for EOLC, and a lower likelihood that patients with advanced cancer received care congruent with their preferences.[24]

Our study is strengthened by a focus on patients with metastatic solid organ malignancy who were undergoing palliative treatment. As shown, even patients who are thought well enough for ICU admission have high mortality, and we have identified potential indicators of a poor response to intensive care in these patients.

Patients included in our study were treated from 2010 to 2015, and included a minority of patients treated with either targeted therapy or immunotherapy. However, the proportion of patients receiving these treatment modalities is likely to dramatically increase over the next few years, given the vastly improved results achieved in a variety of solid organ malignancies, including prolonged complete responses in patients with melanoma and lung cancer.[25,26] Whether our observations extend to this group of patients is uncertain and warrants prospective assessment. The adverse effects of immunotherapy can lead to life-threatening autoimmune disorders requiring ICU admission, and these effects can occur before patient response to treatment can be easily assessed and interpreted.[27]

Our study identified that most patients in our cohort died or declined functionally at early follow-up, but a subgroup of patients returned to their baseline functional status by 3 months. Further studies of functional outcomes after ICU discharge for patients with cancer are needed to validate our findings. In view of the suboptimal documentation of ACDs and MEPA, the barriers to ACP in patients with metastatic solid organ cancer need to be determined to develop appropriate strategies for increasing earlier uptake.

Conclusions

Survival outcomes are poor in patients with metastatic solid organ malignancy, with fewer than 23% of patients alive at 1 year. Albumin level, WCC and, potentially, functional status are important, simple predictors of overall survival. Functional outcomes are poor initially, but may improve in patients who survive beyond 3 months. Documentation for ACP is low, despite the poor prognosis for these patients.

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Competing interests

None declared.

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