ORIGINAL ARTICLE

Patients With Cancer of Unknown Primary

A retrospective analysis of 223 patients with adenocarcinoma or undifferentiated carcinoma

Harald Löffler, Joe Puthenparambil, Thomas Hielscher, Kai Neben, Alwin Krämer

SUMMARY

Background: Cancer of unknown primary (CUP) now accounts for 2–3% of all fatal cases of cancer in Germany. Histologically, most of these tumors are either adenocarcinoma or undifferentiated carcinoma. Scant data on their clinical features and prognosis are now available, and the published survival times are highly variable. In this article, we document and analyze our own experience with CUP to date.

Methods: We took all 223 patients with CUP (adenocarcinoma or undifferentiated carcinoma) whom we saw in our CUP clinic from 2006 to 2010 as an unaltered sample for retrospective analysis of clinical data and overall survival. We performed the analysis with Kaplan-Meier plotting, log-rank testing, and Cox regression.

Results: With a median follow-up time of 32.9 months, the median survival from the time of diagnosis was 16.5 months. Metastases were most commonly found in the lymph nodes, followed by the liver, bones, and lungs. The main pre-treatment prognostic variables that remained significant after adjustment for multiple testing were the Eastern Cooperative Oncology Group (ECOG) score for overall state of health and the number of organ systems involved. These variables were used to construct a practice-oriented risk stratification.

Conclusion: In patients with adeno- or undifferentiated CUP syndrome, the ECOG score and the number of organ systems involved are important risk factors.

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By definition, cancers of unknown primary origin (CUP) are histologically confirmed cancers where, when all diagnostic investigations are complete, only metastases have been found, with no evidence of a primary tumor. In terms of all cancer-related deaths in Germany in 2011, CUP was responsible for 2.1% among men and 2.5% among women (1). Older retrospective studies reported median survival at 3 to 6 months, but more recent studies of selected patients give median survival times in the order of 1 year (2–5).

Among CUPs, two special histological categories are neuroendocrine carcinomas and squamous cell carcinomas, which make up respectively 2 to 4% and 5 to 8% of all CUPs (2, 6). The former are treated according to specific protocols for neuroendocrine tumors, while squamous cell CUPs usually iaffect cervical lymph nodes and are treated in a similar way to head and neck tumors of known primary origin (2, 7). Both these subgroups have a significantly better prognosis than adenocarcinomas or undifferentiated carcinomas (which make up the great majority of all CUPs) (2, 3, 6). Generally, the standard treatment for adenocarcinoma or undifferentiated CUP is a combination of two drugs, one of them platinum-based (8), although here again, defined special cases occur that should received other, more specific protocols – but these cases make up only a small minority of this category (2, 8–10).

Current knowledge about CUP is partly based on a limited number of phase II studies, most of them small [they are summarized in (2)], so the evidence level about standard therapies must be classified as low (11). It is also based on a few case series of unselected patients (*eTable 1*), which have value, particularly for estimating prognosis, but some of which are out of date. Although no standards exist for prognosis-adjusted treatment, from the patient's point of view statements about prognosis are extremely important. For this reason, we thought it worth presenting a systematic compilation of our own experience of treating patients with CUP.

The aims of this study were to describe our patient population without selecting them for treatability (as required in treatment studies), but in terms of clinically relevant characteristics of their disease; to document their overall survival; and on this basis to identify prognostically relevant variables. Neuroendocrine and squamous cell carcinomas were excluded in order to focus on the most relevant patient group, those with

TABLE 1

Selected patient characteristics (whole study group)

Characteristic	Value	Number	%
Sex	Male	113	50.7
	Female	110	49.3
ECOG score at first diagnosis*	0	33	17.7
	1	100	53.8
	2	38	20.4
	3	15	8.1
	Not known	37	–
Histological type	Adenocarcinoma	178	79.8
	Undifferentiated carcinoma	45	20.2
Organ systems involved	Supradiaphragmatic lymph nodes	89	39.9
	Infradiaphragmatic lymph nodes	58	26.0
	Lungs	56	25.1
	Bones	58	26.0
	Liver	69	30.9
	Brain	18	8.1
	Bone marrow	1	0.4
	Pleura	14	6.3
	Peritoneum	31	13.9
	Adrenals	10	4.5
	Skin	6	2.7
	Other	16	7.2
Number of organ systems involved	1	111	49.8
	2	67	30.0
	3	31	13.9
	4	13	5.8
	5	1	0.4
First-line therapy	Platinum based	110	49.3
	Taxane based	53	23.8
	Gemcitabine based	53	23.8
	Carboplatin + paclitaxel	47	21.1
	Cisplatin + gemcitabine	19	8.5
	Gemcitabine monotherapy	17	7.6
	Radical resection	16	7.2
	Radiation	21	9.4

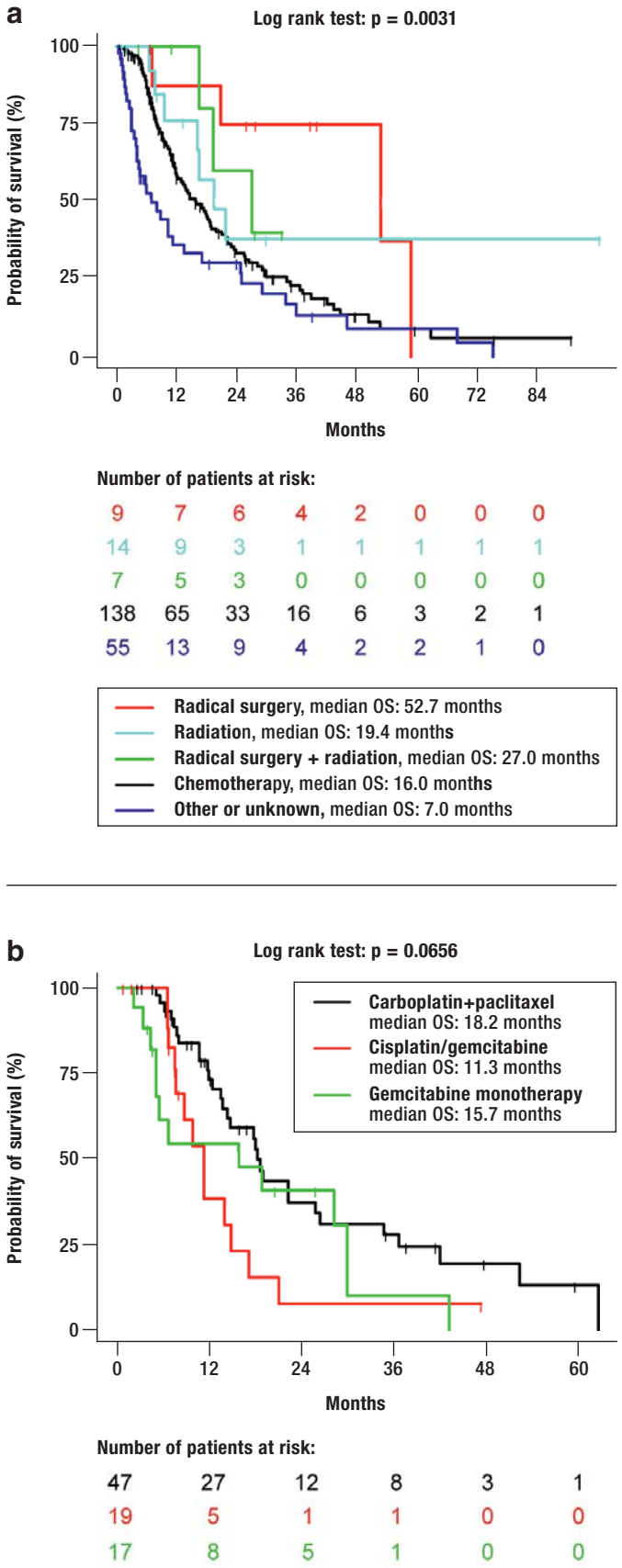
*Percentages for ECOG scores refer to those patients for whom this information was available.

adenocarcinomas and undifferentiated tumors, and to avoid distortion of the results by the biological, clinical, and prognostic features of the former two subtypes.

Methods

The patients studied were a convenience sample collected with no thoughts about representativeness and no planning of case numbers. The group included all patients with adenocarcinoma or undifferentiated CUP who presented to us (H.L., K.N., and A.K.) at the CUP outpatient clinic at the National Cancer Center (NCT, Nationales Centrum für Tumorerkrankung) in Heidelberg, Germany, during the years 2006 to 2010. Inclusion criteria were a histologically confirmed cancer diagnosis and lack of evidence of a primary tumor after completion of diagnostic investigations that

FIGURE 1



Overall survival in relation to treatment

a) Overall survival (OS) after first-line therapies (log rank test: p = 0.0031)

b) OS after generally used cytostatic therapy protocols (log rank test: p = 0.0656)

The figure indicates survival probabilities from the time of first diagnosis in dependence on first-line therapies as shown. The exact definition of the treatment groups is given in the main text; it should be noted that the group shown in dark blue includes both patients who received no treatment and those for whom no information about treatment was available. The legend within the figure shows median OS and the p-value (log rank test); values below 0.05 indicate a significant difference between groups.

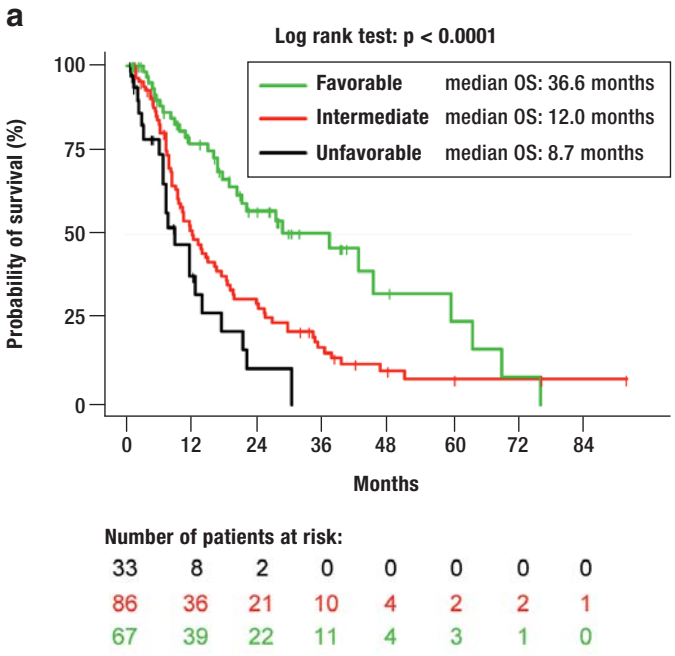
included at least cross-sectional imaging of thorax and abdomen, gastroscopy, and, for women, gynecological examination and mammography. The diagnostic classifications and all the findings included in this analysis were validated by one of us (H.L., K.N., or A.K.) as the relevant medical specialist. Neuroendocrine and squamous cell carcinomas were excluded. The group also included the cases of patients attending for a second opinion, and of patients whose relatives consulted us in the absence of the patient concerned, as long as these were consultations in person with one of us during the outpatient clinic and the cases were adequately documented by written findings and details of medical history.

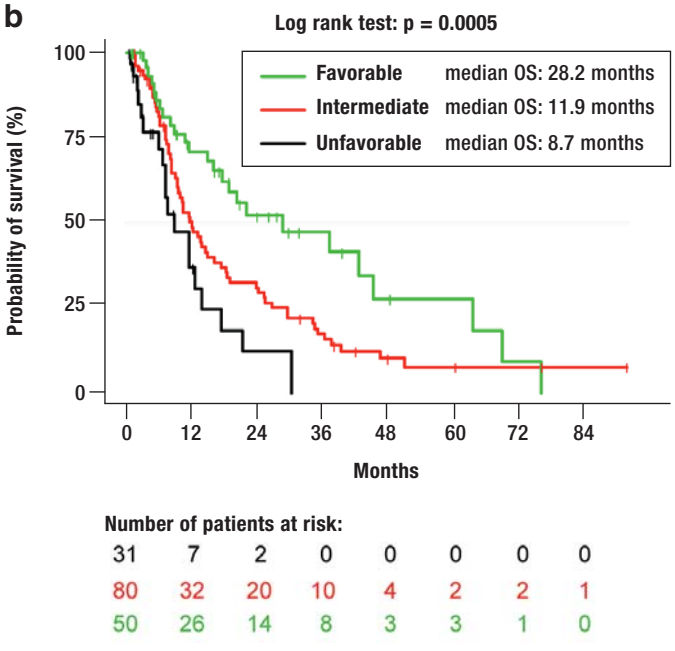
The analysis focused on clinical variables that are regularly or frequently recorded during routine care and of which it was thought possible that they might affect the prognosis. The variables recorded appear in *eTables 1* and *2*. Tumor markers were classified as raised if they exceeded the upper reference value published by the laboratory in question. Cases were followed up on the basis of the medical records and of systematic data collection from doctors at other institutions and from local residents' registration offices (*Einwohnermeldeämter*).

Overall survival was calculated from the time of first diagnosis. The distribution of survival times was estimated using the Kaplan–Meier method. In the primary analysis, hazard ratios (HR) including the 95% confidence interval (CI) of clinical factors were calculated using the univariate Cox regression model. The proportional hazards assumption was tested using the method of Grambsch and Therneau (12). To control the false discovery rate, the univariate Cox regression p-values were adjusted for multiple testing using the Benjamini–Hochberg correction (13). In individual cases, groups were additionally investigated for overall differences using the log rank test and multivariate Cox regression was carried out to correct for further characteristics. Since this was a retrospective observation study that was purely exploratory in nature, the p-values should not be interpreted as confirmatory, but as hypothesis-generating. All p-values are two-tailed. p-Values below 0.05 were regarded as statistically significant. All analyses were carried out using R 3.0.1 software (14).

A practical approach to risk stratification. The figure indicates survival probabilities from the time of first diagnosis in dependence on prognostic group
a) for the whole study group (log rank test: $p < 0.0001$)
b) for the subgroup of patients who underwent neither radical surgery nor irradiation as first-line therapy (log rank test: $p = 0.0005$)
The following prognostic groups were defined:
Favorable prognosis (green), patients with ECOG score ≤1 and only one organ system involved; unfavorable prognosis (black), patients with ECOG >1 and more than one organ system involved; intermediate prognosis (red), all other patients, i.e., those with either ECOG >1 or with more than one involved organ system. The legend within the figure shows median OS and the p-value (log rank test); values below 0.05 indicate a significant difference between groups.

FIGURE 2





Results

General patient characteristics

From 2006 to 2010, 218 patients with adenocarcinoma or undifferentiated CUP were treated or advised in the CUP outpatient clinic at the NCT in Heidelberg. In another five cases, patients' relatives attended for consultations based on written documents and medical history details, resulting in a final total of 223 patients. In 68 cases (30%) patients were treated at the NCT, while 155 patients (70%) were primarily treated elsewhere. Median age at first diagnosis was 59.7 years (range 20 to 86 years); the numbers of men and women were almost equal (*Table 1*).

Median observation time was 32.9 months, and 145 of the 223 patients died during the observation period. Median survival was 16.5 months (95% CI 12.9 to 19.9 months), with a 1-year survival rate of 57% (50% to 65%) and a 2-year survival rate of 36% (29% to 43%). Men had significantly shorter survival than women (*eFigure a*, *eTable 2*), but no age dependence was shown (*eFigure b*, *eTable 2*). Highly significant factors were the ECOG (Eastern Cooperative Oncology Group) performance score (15) (*eFigure c, eTable 2*) and the number of organ systems involved: the relatively large patient group (50% of the whole) (*Table 1*) with only one organ system involved showed a marked survival advantage (*eFigure d, eTable 2*).

Factors associated with an unfavorable prognosis were involvement of lungs, liver, or adrenals (*Table 2*). Among patients with adrenal metastases, median survival was 7.4 months, corresponding to a HR of 2.69 (1.17 to 6.22). However, in the Cox model, adrenal metastases as a risk factor were not independent of the number of organ systems involved, since nine out of ten patients with adrenal metastases had more than two involved organ systems, compared with only 17% of all other patients.

A detailed analysis in terms of tumor markers and immunohistochemical markers as risk indicators yielded little in this group of patients. Initially raised serum CA 19–9 levels (shown in 40 of 89 cases with a recorded serum CA 19–9 concentration) was associated with significantly poorer survival (*eTable 2*). For

TABLE 2

Overall survival and hazard ratios in relation to involvement of different organ systems

Organ system involved	Median survival (months)	Hazard ratio (95% CI) in comparison to patients without involvement of the same organ system	p-value	Adjusted p-value
Supradiaphragmatic lymph nodes	14.7	0.96 (0.68–1.35)	0.816	0.867
Infradiaphragmatic lymph nodes	8.6	1.25 (0.86–1.81)	0.245	0.430
Lungs	11.3	1.59 (1.11–2.28)	0.012	0.073
Bones	11.9	1.42 (0.99–2.04)	0.053	0.156
Liver	11.3	1.52 (1.09–2.13)	0.014	0.073
Brain	16.5	1.33 (0.67–2.62)	0.412	0.584
Pleura	18.6	0.95 (0.51–1.76)	0.863	0.898
Peritoneum	22.2	0.87 (0.54–1.41)	0.573	0.680
Adrenals	7.4	2.69 (1.17–6.22)	0.020	0.091

CI, confidence interval

further details, see *eTable 2*. Since a raised level of most tumor markers was prognostically unfavorable (although for most markers a significant difference was not reached because of the small number of cases), this is likely to be due to a general association between tumor mass and prognosis. Overall, especially since in the case of most tumor markers information was only available for a small proportion of the patients, the results of the present study relating to tumor markers should be interpreted with caution.

Treatments received

For CUP, the therapeutic algorithm involves first excluding defined special cases whose treatment differs from the general standard of a broad-acting palliative cytostatic combination therapy (2, 9, 10). In particular, patients with local involvement should be referred for local radical treatment, typically with curative intent – i.e., radical resection and/or irradiation. In our study, this applied to 30 patients (13%), of whom

- nine (4%) underwent resection only;
- fourteen (6%) underwent irradiation (in three cases combined with chemotherapy);
- seven (3%) underwent a combination of resection and irradiation.

The treatment algorithm also requires excluding other specific special cases, but these are rare in the group of adenocarcinomas and undifferentiated CUPs (2). For the remaining great majority of CUP patients, the standard treatment is the combination of a platinum derivative together with another cytostatic with palliative intent; the German guideline, in agreement with international recommendations, favors the combination of carboplatin and paclitaxel (9, 10, 16), which is also the first choice in our center. Another frequently used standard combination is cisplatin with gemcitabine. If a milder cytostatic therapy appears indicated, often monotherapy with gemcitabine is used, as is also preferred by ourselves in this situation. In our patient group, 138 patients (62%) received cytostatic therapy alone; for 55 patients (25%) no information about treatment received was available or no treatment was received (*Table 1*). Of the patients treated with cytostatics, the majority (110 of 138, corresponding to 80%) received a platinum-based treatment (*Table 1*).

The breakdown of overall survival according to treatment received shows that local treatment was associated with a significantly better prognosis (*Figure 1a*, *eTable 2*). Another breakdown of patients treated with cytostatics (*Figure 1b*, *eTable 2*) shows best results for the combination of carboplatin and paclitaxel, which in pairwise comparisons did significantly better than cisplatin with gemcitabine (HR for cisplatin + gemcitabine: 2.28, $p = 0.02$). However, after adjusting for risk factors (ECOG score, number of organ systems involved, etc.), the difference was no longer significant (HR: 1.17; $p = 0.78$).

A practical approach to risk stratification

Overall survival was highly significantly associated with ECOG score and number of involved organ systems, allowing easy classification of patients on the basis of these parameters into those with a favorable prognosis (ECOG ≤1 and 1 organ system involved, 67 patients, 36%), those with an intermediate prognosis (either ECOG >1 or >1 organ system involved, 86 patients, 46%), and those with an unfavorable prognosis (both ECOG >1 and >1 organ system involved, 33 patients, 18%). Within the overall study group, highly significant prognostic differences were shown between these groups (*Figure 2a*). It might be objected that the group with a favorable prognosis also contained the patients in the categories given treatment with curative intent, thus falsifying the result. However, the differences between the prognostic groups remained highly significant even after the exclusion of patients who underwent surgery and/or irradiation – even then, the favorable prognosis group with only one involved

organ system and an ECOG score of 0 or 1 (50 patients) showed a median survival of 28.2 months (*Figure 2b*).

Discussion

The results of this study in regard to the prognostic significance of the ECOG score, the number of organ systems affected, and adrenal metastases confirm similar results of earlier studies (*eTable 1*) (6, 17). The median age in our study group agrees well with that in previous publications (3–6, 17, 18), which supports the assumption that our study group was representative. One difference from older data, which usually show a predominance of male patients, is the equal numbers of men and women in our study. An obvious possible explanation of the rise in numbers of women with CUP, which has been confirmed in independent epidemiological data, is the increased tobacco consumption among women, which in the past few decades has led to a general rise in the occurrence of tobacco-related cancers in women (1, 19).

Naturally, our patient study group is not representative of the general population, because no planning was carried out to ensure that a representative sample was included. The relatively high proportion of patients (41%) with only one involved organ system and good physical performance (ECOG ≤1) suggests that some patient selection must have taken place, perhaps due to the fact that the patients most likely to attend a university center are those for whom every possible attempt at therapy seems indicated, whereas those with multiple involved organ systems and poorer physical performance are more often treated palliatively nearer home. These factors could have contributed to the fact that, at 16.5 months, the median survival in our study was better than that in most previous studies. Despite these reservations, however, we do believe that, today, for mobile and treatable patients who can be managed on an outpatient basis, a longer median survival may be expected than the 3 to 6 months shown in older studies.

One potentially useful feature of the risk stratification presented here is that it counteracts the way in which selection of the patient population at our center, as referred to above, distorts prognosis estimation, by separating out the patient groups who may be under- or over-represented. It is worth mentioning that several systems for risk stratification of patients with CUP have already been published, but have not yet come in wide use, partly because they require the use of complicated decision trees (*eTable 1*) (6, 17). Compared to these, the risk stratification method we present here is easy to use on all patients who have a complete diagnosis, without any extra work. Because our study does not contain a separate validated patient sample, however, prospective validation of the method in an independent cohort would be desirable. As a further limitation of the validity of our results, it could be objected that diagnoses were not generally confirmed by histological reference assessment, which was only done if initial classification was not sufficient; however, it must be emphasized that histological confirmation with assessment by a board-certified pathologist was obtained in every case.

A valid comparison of the efficacy of individual treatments is not possible in our study, as the lack of randomization could confound the results, e.g., different ranges of indications associated with" the choice of treatment. Our results relating to this should therefore be interpreted with caution. They do appear to confirm that the guideline standard combination treatment with carboplatin and paclitaxel should normally be offered as the first choice, and that gemcitabine monotherapy is a good alternative if carboplatin+paclitaxel appears too toxic (10). It also appears relevant that patients treated primarily with local radical procedures, especially radical resection with or without postsurgical radiotherapy, have a comparatively good prognosis. It must be emphasized that this likely does not result from the chosen mode of therapy, but rather from rational selection of patients to receive it: local radical procedures are only a rational option for locally limited disease. To this extent, the data in our study support the guideline recommendation that, for patients with locally limited disease, local radical therapy should be considered first (9, 10).

Conclusions for clinical practice

In the group of patients with adenocarcinoma or undifferentiated CUP seen at a university cancer center and presented here, median survival was between 1 and 2 years. A practical approach to risk stratification is to take together the patient's ECOG score for physical performance and the number of organ systems involved in the cancer. The guideline recommendation that patients with local involvement should be referred for a local radical procedure (surgery with or without radiation) is supported by the data, which show that these patients have a relatively good prognosis.

Conflict of interest statement
Professor Krämer received funding for the PACET-CUP study from Merck.
The other authors declare that no conflict of interest exists.

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KEY MESSAGES

- In this group of patients with adenocarcinoma or undifferentiated CUP, median overall survival from first diagnosis was 16.5 months.
- Men and women were equally affected; men had a slightly poorer prognosis, but age had no effect on prognosis.
- The most frequently involved organ system was the lymph nodes, followed by liver, bones, and lungs.
- The most important prognostic parameters were the patient's general physical condition (ECOG score) and the number of diseased organ systems.
- Patients who received local treatment (surgery with or without irradiation) had a markedly better prognosis than the rest of the group.

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A retrospective analysis of 223 patients with adenocarcinoma or undifferentiated carcinoma

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eTABLE 1

Case series of unselected patients with CUP (in chronological order)*

Reference	Study population	Results
Altman E, Cadman E: An analysis of 1539 patients with cancer of unknown primary site. Cancer 1986; 57: 120–4.	1539 patients from a single center (USA), timeframe 1922–1981	Median overall survival 5 months. Only 56% received therapy. 18% of cases not histologically confirmed. Patients with histological confirmation and who received therapy had a median survival of 7 months.
Alberts AS, Falkson G, Falkson HC, van der Merwe MP: Treatment and prognosis of metastatic carcinoma of unknown primary: analysis of 100 patients. Med Pediatr Oncol 1989; 17: 188–92.	100 patients from a single center (South Africa), timeframe 1977–1984	Median overall survival 124 days. Poor physical performance (ECOG score) was prognostically unfavorable.
Pavlidis N, Kalef-Ezra J, Briassoulis E, et al.: Evaluation of six tumor markers in patients with carcinoma of unknown primary. Med Pediatr Oncol 1994; 22: 162–7.	85 patients from three centers (Greece), timeframe 1986–1991	Aim was to study serum tumor markers. Median overall survival not stated, but the Kaplan–Meier curves provided showed it to be about 5 months. CA 19-9 and CA 15-3 levels correlated with number of metastases.
Abbruzzese JL, Abbruzzese MC, Hess KR, Raber MN, Lenzi R, Frost P: Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. J Clin Oncol 1994; 12: 1272–80	657 patients from a single center (M. D. Anderson, USA), timeframe 1987–1992	Median overall survival 11 months. The patients studied appear to be a subgroup of the cases reported on again later by the same team of authors, see next row.
Hess KR, Abbruzzese MC, Lenzi R, Raber MN, Abbruzzese JL: Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. Clin Cancer Res 1999; 5: 3403–10.	1000 patients from a single center (M. D. Anderson, USA), timeframe 1987–1994	Median overall survival 11 months. Two prognostic stratifications systems with 10 vs. 9 groups. Prognostically relevant parameters included number of organ systems involved, histological type (non-adenocarcinoma prognostically better, neuroendocrine carcinomas particularly good), and pattern of involvement (including adrenal metastases as particularly poor).
van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, Hillen HF: Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984–1992. Eur J Cancer 2002; 38: 409–13.	1285 cases from cancer registry data (Netherlands, representing approx. 1 million inhabitants), timeframe 1984–1992	1024 histologically confirmed cases, 261 exclusively clinically diagnosed cases. Histologically confirmed cases: median age 66 years, median overall survival 11 weeks, 67% received only supportive therapy. Prognostically favorable: age <50 years, lymph node involvement.
Levi F, Te VC, Erler G, Randimbison L, La Vecchia C: Epidemiology of unknown primary tumours. Eur J Cancer 2002; 38: 1810–2.	699 cases from cancer registry data from two Swiss cantons (total number of inhabitants 786 000), timeframe 1984–1993	543 histologically confirmed cases: median age 71 years, median overall survival 11 weeks. 156 exclusively clinically diagnosed cases: median age 79 years, median overall survival 6 weeks. Only prognostically more favorable histologically defined subgroup was squamous cell carcinomas with a median overall survival of 41 months.
Culine S, Kramar A, Saghatchian M, et al.: Development and validation of a prognostic model to predict the length of survival in patients with carcinomas of an unknown primary site. J Clin Oncol 2002; 20: 4679–83.	150 patients from a single center (France), timeframe 1989–1999	Median overall survival 7.5 months. Establishing a prognostic model based on poor physical condition (ECOG score) and either presence of liver metastases or raised serum LDH (these two parameters correlated to each other) as unfavorable prognostic factors.
van de Wouw AJ, Jansen RL, Griffioen AW, Hillen HF: Clinical and immunohistochemical analysis of patients with unknown primary tumour. A search for prognostic factors in UPT. Anticancer Res 2004; 24: 297–301.	70 patients from a single center (Netherlands), timeframe 1990–1996	Median overall survival 12 weeks. Unfavorable prognostic factors: age ≥60 years, ECOG score >1, number of organ systems involved >2, liver metastases, raised LDH.
Seve P, Ray-Coquard I, Trillet-Lenoir V, et al.: Low serum albumin levels and liver metastasis are powerful prognostic markers for survival in patients with carcinomas of unknown primary site. Cancer 2006; 107: 2698–705.	317 patients from a single center (Canada), timeframe 1998–2004	Median overall survival 104 days. Poor prognosis group defined by liver metastases or reduced serum albumin. ECOG score >1 also prognostically unfavorable.

Reference	Study population	Results
Ponce Lorenzo J, Segura Huerta A, Diaz Beveridge R, et al.: Carcinoma of unknown primary site: development in a single institution of a prognostic model based on clinical and serum variables. Clinical Transl Oncol 2007; 9: 452–8.	100 patients from a single center (Spain), timeframe 2002–2006	Limited to main population of CUP by exclusion of subgroups with specific therapy options. Median overall survival 4.7 months. Unfavorable prognostic factors included ECOG score >1, number of organ systems involved >2, liver metastases.
Trivanovic D, Petkovic M, Stimac D: New prognostic index to predict survival in patients with cancer of unknown primary site with unfavourable prognosis. Clin Oncol 2009; 21: 43–8.	145 patients from two centers (Croatia), timeframe 2002–2007	Limited to main population of CUP by exclusion of subgroups with specific therapy options. Median overall survival 330 days. Unfavorable prognostic factors: ECOG score >1, liver metastases, raised LDH, anemia, higher age, QT prolongation.
Thöm I, Rogers C, Andritzky B, et al.: Single-center management of 136 patients with cancer of unknown primary site (CUP syndrome) over a period of 10 years. Onkologie 2009; 32: 741–6.	136 patients from a single center (Uniklinik Hamburg-Eppendorf), timeframe 1989–1998	Median overall survival 7.9 months. Prognostic parameters: patient's general condition, sex (women had a better prognosis), mode of therapy (resection was best), Hübner prognostic group (based on tumor stage and patient's general physical condition).
Fernandez-Cotarelo MJ, Guerra-Vales JM, Colina F, de la Cruz J: Prognostic factors in cancer of unknown primary site. Tumori 2010; 96: 111–6.	265 patients from a single center (Spain), timeframe 1999–2003	Median overall survival 2.5 months. Squamous cell carcinoma was prognostically favorable. Other prognostic factors: age, serum levels of albumin and alkaline phosphatase, treatment.
Petrakis D, Pentheroudakis G, Voulgaris E, Pavlidis N: Prognostication in cancer of unknown primary (CUP): development of a prognostic algorithm in 311 cases and review of the literature. Cancer treatment reviews 2013; 39: 701–8.	311 patients from a single center (Greece), timeframe 1988–2011	Median overall survival 8 months. Establishing a prognostic model based on poor physical condition (ECOG score), leukocytosis, and visceral metastases as unfavorable prognostic factors.

*Case series were collected through a combined approach that included searching a literature database (PubMed) using relevant search terms, and mining our own literature archive for relevant studies and relevant current publications for the literature they cited. All internationally published studies on CUP, in which patients were not selected with reference to age or suitability for treatment, and which investigated overall survival and clinically relevant patient characteristics (e.g., organ systems involved, tumor markers), are listed. Studies that were restricted to rarer subgroups were not included. However, studies that excluded rarer subgroups, but did investigate at least the most frequent subcategory (adenocarcinoma) are included. Some studies included patients without histological confirmation, whose diagnosis was made on an exclusively clinical basis; this is noted above individually for the relevant studies.

eTABLE 2

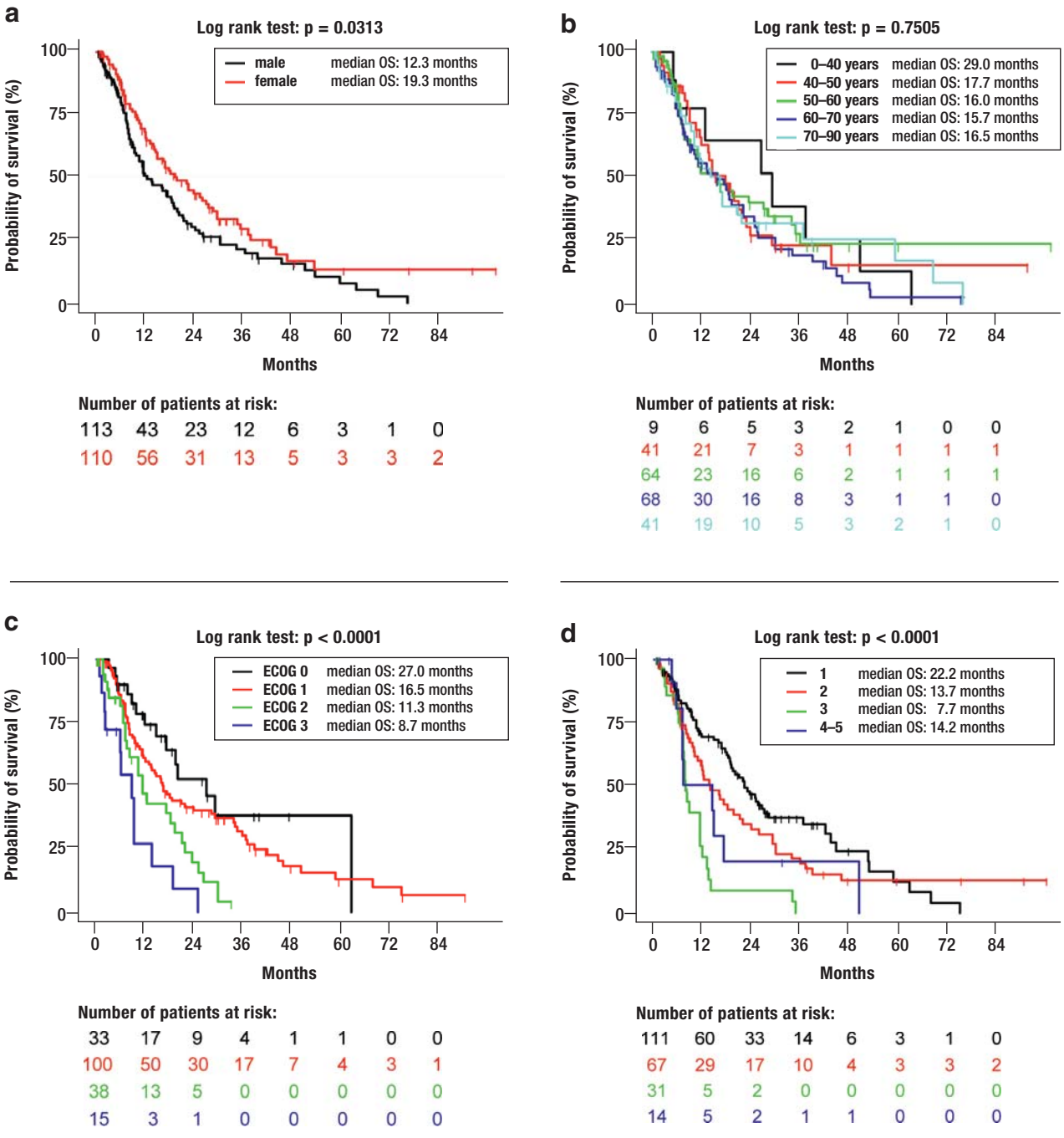
Parameters investigated and their prognostic effect on overall survival*

Parameter	N	Level	Reference	Hazard ratio	95% confidence interval		p-value	Adjusted p-value
Sex	223	Female	Male	0.70	0.50	0.97	0.0321	0.1091
ECOG at first diagnosis	186	1	0	1.42	0.79	2.53	0.2376	0.4303
		2	0	2.70	1.41	5.16	0.0028	0.0286
		3	0	4.74	2.17	10.34	<0.0001	0.0016
ECOG at first diagnosis (grouped)	186	2/3	0/1	2.36	1.58	3.51	<0.0001	0.0006
Age (regarded as a quantitative variable)	223			1.01	0.99	1.02	0.4525	0.6237
Supradiaphragmatic lymph nodes	223	Involved	Not involved	0.96	0.68	1.35	0.8159	0.8668
Infradiaphragmatic lymph nodes	223	Involved	Not involved	1.25	0.86	1.81	0.2447	0.4303
Lung metastases	223	Involved	Not involved	1.59	1.11	2.28	0.0121	0.0726
Bone metastases	223	Involved	Not involved	1.42	0.99	2.04	0.0534	0.1562
Liver metastases	223	Involved	Not involved	1.52	1.09	2.13	0.0142	0.0726
Brain metastases	223	Involved	Not involved	1.33	0.67	2.62	0.4128	0.5848
Pleural metastases	223	Involved	Not involved	0.95	0.51	1.76	0.8627	0.8979
Peritoneal metastases	223	Involved	Not involved	0.87	0.54	1.41	0.5731	0.6798
Adrenal metastases	223	Involved	Not involved	2.69	1.17	6.22	0.0202	0.0912
Skin metastases	223	Involved	Not involved	1.35	0.50	3.66	0.5590	0.6788
Other metastases	223	Involved	Not involved	1.32	0.74	2.33	0.3458	0.5186
Number of organ systems affected	223	2	1	1.34	0.92	1.95	0.1316	0.3195
		3	1	3.20	1.98	5.18	<0.0001	0.0001
		4–5	1	1.86	0.92	3.75	0.0826	0.2216
Number of organ systems affected (grouped)	223	2–5	1	1.68	1.21	2.34	0.0021	0.0269
Histological type	223	Undifferentiated	Adenocarcinoma	1.07	0.71	1.60	0.7590	0.8415
CEA (serum, regarded as a quantitative variable)	100			1.00	1.00	1.01	0.0215	0.0912
CA19–9 (serum, regarded as a quantitative variable)	89			1.00	1.00	1.00	0.0038	0.0324
NSE (serum, regarded as a quantitative variable)	35			1.35	0.92	1.99	0.1201	0.3063
CA 125 (serum, regarded as a quantitative variable)	46			1.00	0.99	1.01	0.9878	0.9878
CA 15–3 (serum, regarded as a quantitative variable)	34			1.02	0.89	1.17	0.7798	0.8461
AFP (serum, regarded as a quantitative variable)	41			1.00	0.97	1.03	0.9610	0.9802
CA 72–4 (serum, regarded as a quantitative variable)	17			1.01	1.00	1.02	0.0551	0.1562
CEA (serum, raised vs. normal)	100	Raised	Normal	1.73	1.05	2.85	0.0309	0.1091
CA 19–9 (serum, raised vs. normal)	89	Raised	Normal	2.20	1.28	3.77	0.0045	0.0324
NSE (serum, raised vs. normal)	35	Raised	Normal	1.48	0.48	4.53	0.4918	0.6600
CA 125 (serum, raised vs. normal)	46	Raised	Normal	1.61	0.65	4.02	0.3063	0.4882
CA 15–3 (serum, raised vs. normal)	34	Raised	Normal	1.22	0.47	3.16	0.6855	0.7769
AFP (serum, raised vs. normal)	41	Raised	Normal	1.25	0.46	3.37	0.6583	0.7630
CA 72–4 (serum, raised vs. normal)	17	Raised	Normal	1.83	0.47	7.11	0.3856	0.5618
CK5/6 (immunohistochemistry)	48	Positive	Negative	1.83	0.78	4.30	0.1645	0.3427
CK7 (immunohistochemistry)	161	Positive	Negative	1.17	0.70	1.95	0.5507	0.6788
CK19 (immunohistochemistry)	23	Positive	Negative	4.16	0.55	31.59	0.1680	0.3427

Parameter	N	Level	Reference	Hazard ratio	95% confidence interval		p-value	Adjusted p-value
CK20 (immunohistochemistry)	144	Positive	Negative	0.87	0.55	1.37	0.5381	0.6788
CA19.9 (immunohistochemistry)	38	Positive	Negative	0.65	0.30	1.37	0.2558	0.4349
CEA (immunohistochemistry)	29	Positive	Negative	2.23	0.76	6.60	0.1462	0.3389
CDX2 (immunohistochemistry)	76	Positive	Negative	0.60	0.25	1.40	0.2359	0.4303
TTF-1 (immunohistochemistry)	139	Positive	Negative	0.81	0.41	1.62	0.5491	0.6788
CA 125 (immunohistochemistry)	19	Positive	Negative	1.77	0.55	5.71	0.3420	0.5186
Therapies, grouped	223	Surgery	Chemo	0.36	0.13	0.99	0.0475	0.1514
		Surgery + radiation	Chemo	0.53	0.17	1.67	0.2752	0.4528
		Other	Chemo	1.63	1.11	2.39	0.0136	0.0726
		Radiation	Chemo	0.62	0.29	1.35	0.2285	0.4303
Cytostatic therapies, grouped	83	Cis+gem	Carbo+taxol	2.10	1.07	4.11	0.0303	0.1091
		Gem mono.	Carbo+taxol	1.61	0.83	3.12	0.1597	0.3427

*Univariate Cox model (proportional hazards model) with adjusted p-values for multiple comparisons. All parameters refer to the time of first diagnosis.
Abbreviations and explanations:
N, number of patients studied for the parameter in question; level, value of parameter for which the risk is shown; reference, value of parameter used for comparison;
ECOG, ECOG score (measure of general physical performance originated by the Eastern Cooperative Oncology Group, see main text) at time of first diagnosis;
surgery, radical resection alone as first-line therapy; chemo, cytostatic therapy alone as first-line therapy;
surgery + radiation, radical resection combined with radiation as first-line therapy; other, first-line therapy unknown or not surgery, radiation, or cytostatic therapy;
radiation, radiation with or without cytostatic therapy (but without surgery) as first-line therapy; cis+gem, cisplatin+gemcitabine as first-line therapy;
carbo+taxol, carboplatin+paclitaxel as first-line therapy; gem mono., gemcitabine monotherapy as first-line therapy.

eFIGURE



Overall survival (OS) in dependence on various patients characteristics

a) OS according to sex, log rank test: p = 0.03133

b) OS according to age group, log rank test: p = 0.7505

c) OS according to ECOG score, log rank test: p < 0.0001

d) OS according to number of organ systems involved, log rank test: p < 0.0001

The figure indicates survival probabilities from the time of first diagnosis in dependence on patient characteristics as shown

The legend within the figure shows median OS and the p-value (log rank test); values below 0.05 indicate a significant difference between groups.