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ORIGINAL ARTICLE

The three-month referral threshold as an independent prognostic marker of cancer-specific survival in advanced oncological disease

Supplementary Files

Table S1. Detailed inclusion and exclusion criteria, with patient numbers at each stage of the eligibility filter (from *n* = 152 to *n* = 147)

Stage	Criterion	*n*
Initially eligible patients	Adults with a confirmed oncological diagnosis and advanced locoregional or metastatic disease, admitted between May 01, 2018, and May 31, 2022	152
Exclusion criterion 1	Death within the first 72 hours of the first palliative admission (to limit the instability of hazard estimates in the initial phase)	−5
Analyzed cohort	Final cohort for all statistical analyses	147
Inclusion criterion—diagnosis confirmation	Oncological diagnosis confirmed histopathologically or by imaging through standardized protocols (CT, MRI, PET-CT)	147/147
Inclusion criterion—advanced disease	Locoregional T4 stage or documented distant metastasis, according to the contemporary TNM classification	147/147
Inclusion criterion—admission to the center	First admission to the specialized inpatient palliative service of the studied center	147/147
Inclusion criterion—complete data	Availability of data for the date of documentation of advanced disease, the date of palliative admission, ECOG status, and vital status	147/147

Notes: Cases with incomplete information on the date of documentation of advanced disease did not meet the inclusion criteria and were excluded prior to the formation of the final cohort (a priori filter; not reflected in the numbers above).
Abbreviations: CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group; MRI: Magnetic resonance imaging; PET: Positron emission tomography; TNM: Tumor–node–metastasis.

Table S2. Left-truncation Cox analysis: direct comparison with the main model for both subcohorts

Subcohort/analysis	Main HR	Truncation HR	ΔHR	*p* (truncation)
Locoregional subcohort	0.49	0.46	0.03	0.008
Metastatic subcohort	0.58	0.56	0.02	0.001
Maximum ΔHR observed	–	–	0.03	–

Notes: ΔHR = the absolute difference between the HR of the main model and the HR of the left-truncation model. A ΔHR < 0.10 is considered an indicator of minimal immortal-time bias; in the left-truncation model, the origin of time is placed at the documentation of advanced disease (t_D), unlike the main model, in which the origin is the first palliative admission (t_0); this repositioning eliminates the contribution of the "immortal" interval to the risk set.
Abbreviation: HR: Hazard ratio.

Table S3. Sensitivity analysis of the indirect component (ACME) at different hypothetical values of the mediator–outcome confounding parameter ρ

Hypothetical ρ	Estimated ACME HR	Adjusted 95% CI	Adjusted *p*	Significance
0.00 (baseline)	1.27	1.08–1.49	0.004	Yes
0.10	1.24	1.06–1.46	0.008	Yes
0.20	1.21	1.04–1.42	0.013	Yes
0.30	1.18	1.02–1.37	0.028	Yes
0.34*	1.16	1.00–1.35	0.049	Threshold
0.40	1.14	0.98–1.33	0.089	No
0.50	1.11	0.95–1.30	0.189	No

Notes: ρ = sensitivity parameter quantifying unmeasured mediator–outcome confounding[1]; ρ = 0 implies the absence of unmeasured confounding; increasing values indicate progressive confounding; the critical value *ρ = 0.34 indicates the threshold at which the indirect component loses its significance—a moderate robustness, sufficient for unmeasured confounders of small-to-medium magnitude.
Abbreviations: ACME: Average causal mediation effect; CI: Confidence interval; HR: Hazard ratio.

Table S4. Complete STROBE checklist (22 items)

Number	STROBE item	Reporting requirement	Location in the manuscript
Title and abstract			
1a	Title/abstract—indicate the study design in the title or abstract	Retrospective observational cohort study, indicated explicitly in the title and abstract	Title, Abstract (design)
1b	Title/abstract—informative and balanced abstract	Abstract structured in five sections (background, objective, methods, results, conclusion)	Abstract
Introduction			
2	Background/rationale—scientific background and rationale	Heterogeneity of definitions of "earliness"; lack of a standardized, auditable threshold	Section 1, paragraphs 1–3
3	Objectives—specific objectives with pre-specified hypotheses	Primary objective + five secondary objectives, all pre-specified	Section 1, paragraphs 5–6
Methods			
4	Design—the study design	Retrospective observational cohort, single-center	Section 2.1
5	Setting—location, period, recruitment	Centrul Medical Galaxy Med SRL, Craiova; May 2018–May 2022; follow-up to June 2025	Section 2.1

(*Cont'd...*)

Table S4. (*Continued*)

Number	STROBE item	Reporting requirement	Location in the manuscript
6	Participants—eligibility criteria, sources; follow-up methods	Detailed criteria, n = 152 to n = 147, median follow-up 26 months	Section 2.1; Table S1
7	Variables—all variables: outcome, exposure, predictors, confounders	Cancer-specific death; temporal marker ≤ 3/> 3 months; ECOG; metastatic extension	Section 2.2
8	Data sources/measurement—data sources and assessment methods	Death certificate; imaging report/MDT decision; ECOG at first admission	Section 2.2
9	Bias—efforts to address potential sources of bias	Stratum 6 (landmark + left truncation); Section 4.6 (limitations)	Sections 2.3, 4.6
10	Study size—how the sample size was determined	Consecutive cohort; post-hoc power analysis (78%)	Sections 2.1, 4.1
11	Quantitative variables—handling of quantitative variables	Ordinal ECOG locoregional; binary metastatic; temporal marker dichotomized a priori at three months	Section 2.2
12a[2,3]	Statistical methods—all statistical methods	Six pre-specified strata (Cox; Fine–Gray; Grambsch–Therneau; Imai–Keele–Tingley; RMST; Landmark + left truncation)	Section 2.3; Table 1
12b	Statistical methods—subgroups and interactions	Stratified subcohorts: Locoregional vs. metastatic	Section 2.3
12c	Statistical methods—missing data	Complete data for all 147 patients; no imputation required	Section 2.2
12d	Statistical methods—loss to follow-up	Administrative censoring on June 30, 2025; 33/147 alive at censoring	Section 2.1; Table 3
12e	Statistical methods—sensitivity analyses	Sensitivity with the ρ parameter (mediation); IPCW (RMST); left truncation	Section 2.3; Tables S2, S3
Results			
13a	Participants—numbers at each stage	152 eligible–147 included (five excluded)	Sections 2.1, 3.1; Table S1
13b	Participants—reasons for non-participation	Excluded: Five deaths within the first 72 h	Section 2.1
13c	Participants—flow diagram	Flow diagram integrated in the text and Table S1	Section 2.1; Table S1
14a	Descriptive data—demographic, clinical characteristics	Cohort characteristics stratified by the temporal marker	Tables 2, 3
14b	Descriptive data—missing data for each variable	0% missing data for the essential variables	Section 2.2

(*Cont'd...*)

Table S4. (*Continued*)

Number	STROBE item	Reporting requirement	Location in the manuscript
14c	Descriptive data—follow-up duration	Median 26 months (interquartile range 4–62; maximum 85 months)	Section 2.1; Table 3
15	Outcome data—numbers of outcome events	17 locoregional events; 92 metastatic	Tables 3, 4
16a[4]	Main results—unadjusted and adjusted estimates	Kaplan–Meier; multivariable-adjusted hazard ratio	Section 3.2; Figures 1–2; Table 4
16b	Main results—categorization of continuous variables	Temporal marker dichotomized at 3 months (a priori)	Section 2.2
16c	Main results—absolute risk translated into a relevant period	RMST in patient-months (60/24 months horizon)	Section 3.5; Table 8
17[2,3]	Other analyses—subgroups, interactions, sensitivity	Fine–Gray; Grambsch–Therneau; mediation; RMST; landmark; left truncation	Sections 3.3–3.6
Discussion			
18	Key results—summary of results	Synthesis of results in the literature context	Section 4.1
19	Limitations—limitations with potential bias direction	Seven transparent limitations with the bias direction indicated	Section 4.6
20	Interpretation—interpretation with context, evidence, mechanisms	Discussion of each methodological stratum with cautious clinical interpretation	Sections 4.1–4.5
21	Generalizability—generalizability (external validity)	Single-center study—requires multicenter validation	Sections 4.6, 4.7
Other			
22	Funding—source of funding and role of funders	No external funding	Funding

Abbreviations: ECOG: Eastern Cooperative Oncology Group; IPCW: Inverse probability of censoring weighting; RMST: Restricted mean survival time.

Table S5. Exploratory prognostic score—components and stratification (not externally validated)

Factor	Points	HR (Cox model)	Median CSS	Observation
Score components				
Referral > 3 months (the only modifiable component)	+1	0.58[a]	–	Potentially actionable at the system level
ECOG PS 4 vs. 2–3	+1	2.67	–	Characteristics of the disease at presentation
2 metastatic sites vs. 1	+1	1.94	–	Intermediate extension
≥3 metastatic sites vs. 1	+2	3.21	–	Strongest predictor in the model
Risk categories (illustrative, observed)				
Score 0–1 (low risk)	0–1	–	~10.4 months	Favorable profile
Score 2–3 (intermediate risk)	2–3	–	~4.8 months	More attentive monitoring
Score 4–5 (high risk)	4–5	–	~2.0 months	Palliative referral without delay; sole improvable element

Notes: [a]HR 0.58 = referral ≤ 3 months (protective association); + 1 point = referral > 3 months; the median CSS values are observed estimates; the score described in this section is strictly exploratory and cannot be used in clinical practice until external validation; it was derived from a single-center retrospective subcohort of 92 patients; its thresholds have not been independently validated; Its presentation here is for strictly illustrative purposes, to indicate a direction for further research.
Abbreviations: CSS: Cancer-specific survival; ECOG PS: Eastern Cooperative Oncology Group performance score; HR: Hazard ratio.

Table S6. Sensitivity analyses for the temporal threshold in the metastatic subcohort (HR adjusted for metastatic extent and ECOG status)

Sensitivity analysis	Adjusted HR	95% CI	*p*
Pre-specified threshold (≤3 months)—reference	0.58	0.41–0.82	0.002
Continuous delay (per month, linear model)	1.08	1.03–1.13	0.001
Alternative threshold ≤ 2 months	0.50	0.33–0.76	0.001
Alternative threshold ≤ 4 months	0.62	0.44–0.87	0.006
Alternative threshold ≤ 6 months	0.71	0.49–1.02	0.061
Optimal threshold (maximally selected rank stat.)	3.2 months	–	n.s.

Notes: Continuous modeling of referral delay and the alternative thresholds is presented in comparison with the pre-specified three-month threshold; the direction and significance of the association are preserved across the 2-, 3-, and 4-month thresholds; at six months, the confidence interval crosses unity due to reduced contrast between groups; the "maximally selected rank statistics" analysis does not identify an optimal threshold significantly different from the pre-specified one.
Abbreviations: CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; n.s.: Not significant.

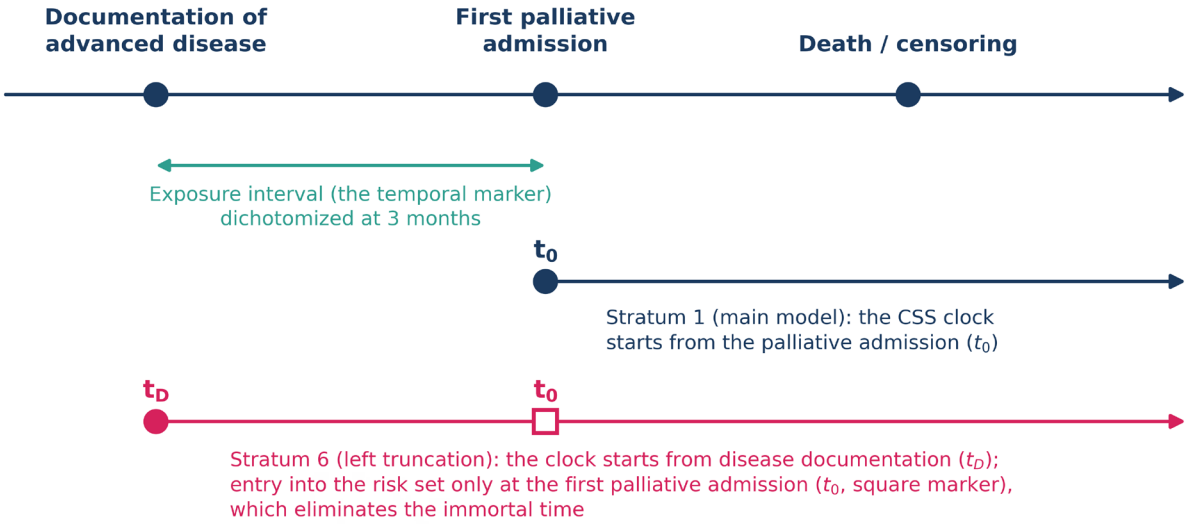

Figure S1. Schematic representation of the two temporal origins used in the analysis. The exposure interval (the temporal marker) was measured from the documentation of advanced disease (t_D) to the first palliative admission (t_0) and was dichotomized at three months. In the main model (Stratum 1) and in all baseline analyses, the cancer-specific survival clock started from the first palliative admission (t_0). In the left-truncation analysis (Stratum 6), the clock started at the documentation of advanced disease (t_D), and and the patient entered the risk set only at the time of the first palliative admission (t_0, square marker), thereby eliminating the contribution of the immortal interval to the Cox risk set.
Abbreviation: CSS: Cancer-specific survival.

References

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