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ORIGINAL ARTICLE

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

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Abstract

Background: Guidelines recommend the early integration of palliative care in advanced cancer; however, "earliness" remains heterogeneously defined, with no temporal consensus, and timing studies are vulnerable to immortal-time bias and do not model competing risks. **Objective:** To evaluate a pre-specified three-month threshold as a prognostic marker of cancer-specific survival (CSS) and as a potential auditable indicator of timely access to palliative care. **Methods:** A retrospective observational cohort study of 147 consecutive adults with advanced locoregional or metastatic cancer, admitted to a Romanian palliative care center (2018–2022; median follow-up 26 months), was conducted. The six-stratum analytical framework comprised multivariable Cox regression, Fine–Gray models, Grambsch–Therneau coefficients, Imai–Keele–Tingley mediation, restricted mean survival time (RMST) with inverse probability of censoring weighting, and validation through landmark and left-truncation analyses. **Results:** Fifty-nine patients (40.1%) were referred within the first three months. Referral within three months was independently associated with a reduced risk of cancer-specific death in locoregional disease (adjusted hazard ratio [HR], 0.49; 95% confidence interval, 0.28–0.86) and metastatic disease (HR, 0.58). Fine–Gray models confirmed the association (subdistribution HR 0.52). The RMST benefit was + 18.7 months (locoregional) and + 4.3 months (metastatic), persisting across landmark and truncation analyses. **Conclusion:** The three-month threshold is independently associated with significantly better CSS and is robust across six analytical approaches. As the design is observational, the findings remain associative and hypothesis-generating. **Relevance for patients:** The proportion of patients referred within the first three months can be computed from routine documentation and, subject to external validation, could serve as an auditable indicator of access to palliative care.

Keywords: Palliative care; Referral timing; Cancer-specific survival; Competing risks; Restricted mean survival time; Immortal-time bias; Statistical mediation; Quality indicators

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1. Introduction

For more than a decade, oncological palliative care has no longer been an intervention reserved for the final weeks of life. The international American Society of Clinical Oncology and European Society for Medical Oncology guidelines and the recommendations of the Lancet Oncology Commission firmly place it at the core of contemporary cancer care, alongside disease-specific treatments, from the moment a diagnosis of advanced disease is made.[1–5] This conceptual repositioning is supported by randomized trials showing that the early integration of palliative care improves symptoms and quality of life in patients with advanced cancer and, in certain clinical contexts—paradigmatically that of metastatic non-small-cell lung cancer—prolongs survival by several months.[6–8] Converging evidence from subsequent trials and cohorts has confirmed these benefits—on symptoms, quality of life, and, in some studies, survival[9–12]—consolidating the recommendation for early integration formulated in the Lancet Oncology Commission on the integration of oncology and palliative care.[13] However, this solid evidence base is not uniformly reflected in oncological practice in Romania, where the decision and timing of referral to palliative care depend on the organization of the regional network—the availability of multidisciplinary teams (MDTs), the limited capacity for ambulatory or home-based palliative care, and the administrative obstacles in documenting decisions—factors that systematically delay the early integration proven to be effective.[14]

Demographic projections estimate a global increase of more than 25% in the need for palliative care by 2040, through the combination of population aging, the rising incidence of advanced cancers, and the evolution of life expectancy in oncological disease.[15]

Despite this convergence between guidelines and randomized data, the recommendation for early integration remains difficult to translate into operational practice. Recent systematic reviews have identified more than 17 definitions of "early palliative care" coexisting in the literature[16,17], ranging from prognostic criteria (estimated life expectancy < 12 months) to temporal criteria (within the first 8 weeks from diagnosis) to symptom-based criteria (at the first uncontrolled symptom), with no consensus regarding the optimal temporal reference point. This fragmentation has practical consequences: in the absence of a standardized threshold, the timeliness of referral cannot be compared across centers, systematically audited, or used as a quality indicator.

Recent European guidelines reiterate the need for early integration and structured prognostic assessment in advanced cancer[10,18,19], and European Union-level initiatives emphasize the need for standardized indicators to monitor the integration of palliative care into oncology.[20,21] This need is all the more pressing in Central and Eastern Europe, where chronic underfunding and the cultural barriers that still associate palliative care with "giving up on treatment" compound inequities of access, widening the gap relative to Western European systems[22]; in Romania, these mechanisms translate into late and territorially unevenly distributed access, with a direct impact on the burden experienced by patients and caregivers.[23–25]

In addition to this problem of definition, two methodological problems directly affect the interpretation of observational timing studies. The first is immortal-time bias: patients who reach palliative care later must, by definition, have survived until the moment of referral, which can artificially create the impression that late referral is protective. The second is the absence of competing-risks modeling: in palliative cohorts, a proportion of patients die from non-oncological causes, and if these deaths are not explicitly treated as competing events, the association with cancer-specific survival (CSS) may be distorted.[26–28] In previous cohorts, none of these limitations has been systematically addressed simultaneously.

The present study starts from the practical observation that oncological re-evaluations in Romania and in many other health systems are frequently carried out at quarterly intervals; a three-month threshold from the documentation of advanced disease (t_D) to the first palliative admission (t_0) represents, in this context, a plausible temporal target, anchored in current practice, and—importantly for operational utility—computable post hoc from ordinary clinical documentation (the date of the relevant imaging report, the date of the multidisciplinary decision, the date of the first palliative admission).

The objectives of the study were therefore formulated along six complementary levels. The primary objective was to evaluate the association between an a priori pre-specified three-month threshold and CSS. Five secondary objectives addressed the robustness of this association to: (i) competing risks (Fine–Gray models), (ii) time-varying effects of the coefficient (Grambsch–Therneau), (iii) an exploratory mediation analysis through which we examined the extent to which the well-known association between the Eastern Cooperative Oncology Group (ECOG) functional status and survival statistically overlaps with the interval to referral, (iv) the quantification of the absolute benefit in months of life (restricted mean survival time [RMST])—a clinically more accessible metric than hazard ratios (HRs)—and (v) the control of immortal-time bias through landmark and left-truncation analyses.

The three-month temporal marker was selected a priori for three reasons. First, it aligns with the rhythm of quarterly oncological re-evaluations, making the threshold verifiable in routine practice, without additional documentation requirements. Second, it is consistent with the temporal windows used in the landmark randomized trials of early palliative care.[6–8] Third, it ensures operational auditability—the threshold was established before any data analysis and does not result from a post hoc selection based on the observed distribution, thereby preventing one of the most frequent artifacts of timing studies.

We emphasize from the outset that the study does not aim to demonstrate the causality of early referral. The temporal marker is treated exclusively as a prognostic variable; all conclusions are formulated in the associative register, and any causal interpretation at the individual level would require a randomized design. The mediation component, in particular, is explicitly declared as exploratory and hypothesis-generating.

2. Materials and methods

2.1. Design and clinical setting

We conducted a retrospective observational cohort study at a specialized Romanian inpatient palliative care center, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[29] This center is an inpatient palliative service that receives oncological patients through referrals from the oncology outpatient clinic, the oncology departments of regional tertiary units, and, more rarely, directly from emergency services; patient selection through referral thus reflects the way in which the regional oncological network operates.

All adults with a histopathologically or imaging-confirmed oncological diagnosis and advanced locoregional or metastatic disease who were admitted between May 1, 2018, and May 31, 2022, were included consecutively. Consecutive inclusion, without selection based on anticipated prognosis or tumor profile, was essential for avoiding selection bias. Vital status was updated through June 30, 2025, allowing a median follow-up of 26 months (interquartile range 4–62 months; maximum observed follow-up 85 months), sufficient for the robust evaluation of survival associations over 4–5-year horizons.

Of 152 initially eligible patients, five were excluded due to death within the first 72 hours of admission, in order to limit the instability of hazard estimates in the initial phase—a standard exclusion in palliative timing studies, motivated by the fact that, in patients who die within a few hours of admission, the timing of referral is the result rather than the cause of prognosis. The final analyzed cohort comprised 147 patients (Table S1). Of the 147 patients included, vital status at the end of follow-up was established in three mutually exclusive and exhaustive categories. CSS was calculated based on 109 cancer-related deaths (74.1%), with the cause of death confirmed by the medical death certificate. Five patients (3.4%) died from non-oncological causes—including an acute cardiovascular event, an episode of non-tumoral sepsis, and a late surgical complication, all occurring in the locoregional subcohort—and were treated as competing events in the Fine–Gray competing-risks models, according to the principle that death from another cause prevents the observation of the event of interest. The remaining 33 patients (22.4%) were alive at the date of administrative censoring (June 30, 2025) and were included as right-censored observations. By the construction of this classification, the sum of the three categories exactly equals the cohort size (n = 147), confirming the internal consistency of the event balance.

The distribution across the two pre-specified subcohorts reflects the distinct natural history of the two forms of disease. In the locoregional subcohort (n = 55), 17 cancer-specific events, 5 non-oncological deaths, and 33 censored patients were recorded, explaining the small number of events available for modeling in this subgroup. In the metastatic subcohort (n = 92), all 92 deaths were attributed to the progression of oncological disease (event rate of 100%), with no non-oncological deaths and no censored patients, indicating a uniformly fatal course over the follow-up horizon.

The censoring rates for the two timing groups were accounted for using inverse probability of censoring weighting (IPCW) when estimating the RMST to correct for informative censoring. Since the structure of the analyzed events is determined exclusively through the cancer-specific deaths observed, and not by the number of patients remaining alive at the moment of censoring, the central estimates of the study—the model coefficients, the relative HRs, the subdistribution hazard ratios (SHRs), and the RMST differences—derive entirely from the observed events and therefore remain independent of the censored sample.

The study was approved by the Ethics Committee of Centrul Medical Galaxy Med SRL, Craiova, Romania, on April 23, 2018 (approval number 2). The Committee granted a waiver of informed consent for the use of anonymized retrospective data, in accordance with the principles of the Declaration of Helsinki and with the European and Romanian regulations on the protection of personal data (European Union Regulation 2016/679 and Law no. 190/2018).

2.2. Primary endpoint, exposure, and data sources

The primary endpoint was CSS, defined as the interval from the first palliative admission to death attributable to oncological disease, as determined by the death certificate. Deaths from causes other than oncological disease were treated as competing events in the competing-risks analyses (Fine–Gray, Section 2.3), not as censored observations, to avoid overestimating the cause-specific hazard.

To avoid ambiguity about the origin of time, we explicitly stated that the temporal exposure marker (the interval from documentation of advanced disease to the first palliative admission) and the survival clock were two distinct temporal axes. For clarity, we denote by t_0 the date of the first palliative admission and by t_D the date of the documentation of advanced disease. In the main model (Stratum 1) and in all baseline analyses, the CSS clock started at the first palliative admission (t_0 = the date of the first palliative admission); the interval to referral was included in the model exclusively as a dichotomized exposure variable, not as follow-up time. In contrast, in the left-truncation analysis (Stratum 6, Section 2.3) the clock was intentionally reset to start from the documentation of advanced disease (t_D = date of the documentation of advanced disease), and each patient entered the risk set only at the moment of the first palliative admission; this repositioning of the origin of time eliminates the contribution of the immortal interval to the Cox risk set and constitutes precisely the mechanism by which Stratum 6 controls immortal-time bias. A schematic representation of the two temporal origins is presented in Figure S1.

To ensure consistency, all Kaplan–Meier figures (Figures 1 and 2) and their legends used the same origin of time as the main model—the first palliative admission; the only analysis that used the documentation of advanced disease as the origin of time was the one with left truncation (Stratum 6). Thus, the temporal origin was used uniformly and unambiguously across text, figures, legends, and models.

The main exposure—the temporal marker—was the interval from the formal documentation of advanced disease (t_D) to the first palliative admission (t_0), dichotomized at three months (≤3 months vs. > 3 months), pre-specified a priori. The date of documentation of advanced disease (t_D) was defined as the earliest of two reference points: (i) the date of the imaging report that documented advanced disease (locoregional T4 extension or distant metastasis) and (ii) the date of the MDT decision that classified the patient as having advanced oncological disease. This choice—the earliest of the two moments—retroactively minimized the risk of underestimating the real interval.

Temporal groups were consistently defined as ≤3 months vs. > 3 months; the patient at exactly 3 months is unambiguously assigned to the ≤3-month group. The first palliative admission was defined as the first documented contact with the specialized inpatient palliative care service of the studied center. In this center, ambulatory or home-based palliative care did not systematically precede admission, so that the misclassification risk in the exposure of patients who might have previously benefited from undocumented ambulatory palliative care was limited, but cannot be completely excluded, and was mentioned explicitly among the limitations (Section 4.6).

2.2.1. Timing of the Eastern Cooperative Oncology Group measurement and implications for mediation

The ECOG functional status was recorded at the time of the first palliative admission, in accordance with the center's protocol. This recording modality had an important methodological consequence: the ECOG measurement was contemporaneous with the end of the exposure interval, not prior to it. Consequently, the strict temporal ordering of ECOG status, referral timing, and outcome could not be assumed at the individual level, as the ECOG status observed at admission reflected both the patient's characteristics at the time of the oncologist's decision and the evolution accumulated over the interval to referral. To respect this temporal ambiguity, we treated the mediation analysis as exploratory and hypothesis-generating, without interpreting the mediated proportion as evidence of a sequential causality at the individual level.

2.2.2. Adjustment covariates

Age (years), sex (male/female), disease category (locoregional vs. metastatic), ECOG status at the first palliative admission (coded ordinally 1–4 in the locoregional model and binary [ECOG performance status 2–3 vs. 4] in the metastatic model, to optimize the events-per-variable ratio), the number of metastatic sites (1, 2, or ≥3), the absence vs. presence of locoregional progression (in the locoregional subcohort), the primary tumor site, and the date of documentation of advanced disease were recorded. The essential variables were complete for all 147 patients; no data imputation was necessary. 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.

2.3. Statistical analysis—the six pre-specified strata framework

The statistical analysis was pre-specified in six complementary strata, each addressing a distinct source of error. The logic of this design was simple: in an observational

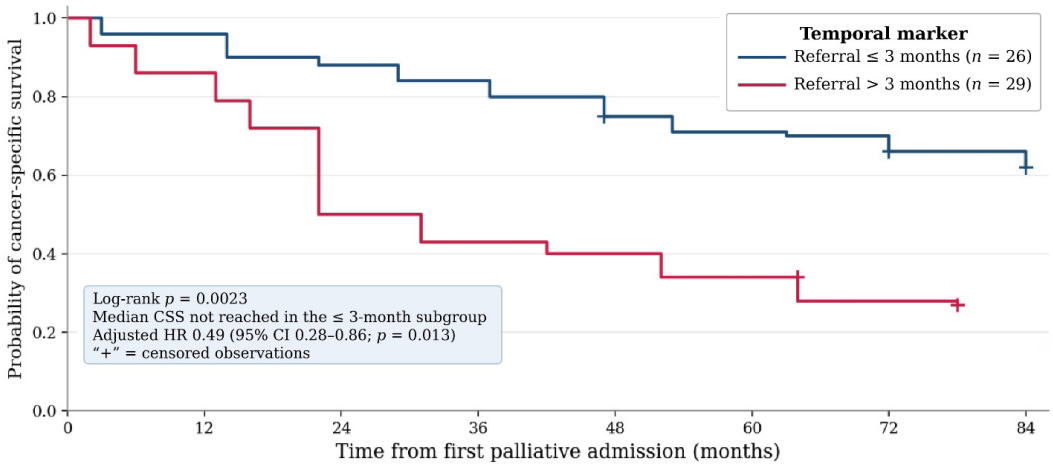

Figure 1. Kaplan–Meier curves for cancer-specific survival according to the temporal marker (≤ 3 vs. > 3 months)—locoregional subcohort (n = 55)
Abbreviations: CI: Confidence interval; CSS: Cancer-specific survival; HR: Hazard ratio.

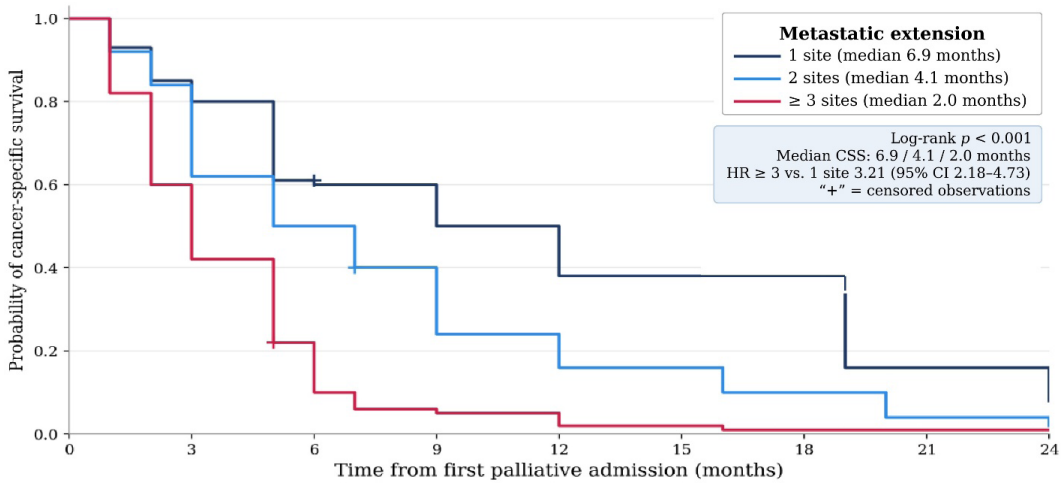

Figure 2. Kaplan–Meier curves for cancer-specific survival according to metastatic extension (1, 2, ≥ 3 sites)—metastatic subcohort (n = 92)
Abbreviations: CI: Confidence interval; CSS: Cancer-specific survival; HR: Hazard ratio.

timing study, no single method was sufficient, and the concordance of results across independent methods—each with its own assumptions and its own limitations—constituted the main guarantee of the robustness of the observed association. The six strata are summarized in Table 1 and detailed in the paragraphs that follow.

All analyses across the six strata—multivariable Cox regression (Stratum 1), Fine–Gray competing-risks models (Stratum 2), Grambsch–Therneau coefficients (Stratum 3), Imai–Keele–Tingley mediation (Stratum 4), RMST differences with IPCW (Stratum 5), as well as the landmark and left-truncation analyses (Stratum 6)—were effectively performed on the corrected final cohort of 147 patients (109 cancer-specific events, 5 competing events, 33 censored).

The estimates presented in the text, tables, and figures corresponded to this cohort; the coefficients, hazard ratios, subdistribution hazards, and RMST differences were derived entirely from this event structure.

2.3.1. Stratum 1—the main association

The CSS was estimated using the Kaplan–Meier method and compared among groups through the log-rank test. The adjusted association between timing and CSS was modeled

using multivariable Cox regression, separately for the locoregional subcohort (predictors: timing, locoregional control, ordinal ECOG) and for the metastatic subcohort (predictors: timing, categorical metastatic extension, binary ECOG). Hazard proportionality was assessed using the Schoenfeld test, with p-values > 0.05 taken as evidence of compliance with the assumption.

2.3.2. Stratum 2—Fine–Gray competing risks

Deaths from non-oncological causes were treated as competing events in a Fine–Gray subdistribution hazard model.[30] The Fine–Gray model was applied only in the locoregional subcohort, where five non-oncological deaths were observed; in the metastatic subcohort, all 92 observed deaths were attributed to oncological disease, so that a Fine–Gray model would not have added information relative to the standard Cox analysis and was not reported. The close concordance ($\Delta < 0.10$) between the cause-specific Cox HR and the Fine–Gray SHR for the same predictor was interpreted as evidence that the timing association was not an artifact of competing mortality.[31]

2.3.3. Stratum 3—time-varying coefficients

The temporal stability of the association was evaluated using the Grambsch–Therneau test, modeling $\beta(t)$ through a cubic spline at several temporal horizons (12, 24, and 48 months) and comparing the coefficients. The change $\Delta\beta$ between $\tau = 12$ and $\tau = 48$ months was interpreted as a test of the hypothesis that the observed effect was stable over the follow-up period; a small and statistically non-significant $\Delta\beta$ supported the conclusion that the effect was not artificially concentrated in the first months after admission (when a "healthy hospitalization" phenomenon could apparently inflate the benefit) but was maintained in the long term.

2.3.4. Stratum 4—exploratory mediation analysis

To explore the extent to which the well-known association between ECOG functional status and CSS statistically overlapped with the interval to referral, we applied the Imai–Keele–Tingley method of decomposing the total effect into direct (independent of timing) and indirect (overlapping with timing) components. Confidence intervals (CI) were obtained using bootstrap with 1,000 iterations. The mediator model included ECOG status; the outcome model included timing, ECOG status, and metastatic extension. A sensitivity analysis for unmeasured mediator–outcome confounding was performed using the ρ parameter; the critical value ρ^* at which the indirect component lost its significance quantifies the robustness of the estimate. The need for such a sensitivity analysis to unmeasured confounding, as a mandatory element of any observational mediation analysis, was emphasized in recent methodology[11,32]; given that the mediator (ECOG) was measured at the end of the exposure interval, we interpreted the results solely as exploratory. This framing was imposed by the structure of the potential confounders. Unrecorded clinical variables—in particular, the number of prior lines of systemic treatment and the intensity

Table 1. The six pre-specified strata analytical framework

Stratum	Methodological question	Method	What it demonstrates
1	Is there an independent prognostic association of timing with CSS?	Multivariable Cox; Kaplan–Meier; log-rank test	The independent association, adjusted for measured confounders
2	Is the association an artifact of non-oncological deaths?	Fine–Gray with SHR	Concordance of SHR vs. HR ($\Delta < 0.10$) confirms robustness to competing risks
3	Is the association transient or stable over time?	Grambsch–Therneau; $\beta(t)$ with cubic spline	Stability of $\beta(t)$ over 85 months rejects the hypothesis of an effect concentrated in the early phase
4	How much of the ECOG–CSS association overlaps with the interval to referral?	Exploratory Imai–Keele–Tingley analysis; 1,000-iteration bootstrap; sensitivity analysis (ρ)	Quantifies the statistically mediated proportion; interpretation exclusively hypothesis-generating
5	What is the absolute benefit expressed in months?	RMST difference with IPCW; pre-specified τ horizons (60/24 months)	The benefit in concrete patient-months, independent of hazard proportionality
6	Is the association distorted by immortal-time bias?	Landmark Cox at 3, 6, 12 months; Cox with left truncation	ΔHR ≤ 0.04 relative to the main model indicates minimal bias

Note: Each stratum answered a distinct methodological question, and the concordance of results across strata constituted the primary evidence of robustness.

Abbreviations: CSS: Cancer-specific survival; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IPCW: Inverse probability of censoring weighting; RMST: Restricted mean survival time; SHR: Subdistribution hazard ratio.

of the symptom burden at the time of the decision—may act simultaneously on the promptness of referral and on prognosis, generating a path of association that the Imai–Keele–Tingley decomposition cannot isolate. Consequently, the identification assumption for the indirect component, namely the absence of residual confounding between mediator and outcome, remained empirically unverifiable within the present dataset, and the corresponding estimates must be considered indicative, useful for formulating testable hypotheses in dedicated, prospective studies.

2.3.5. Stratum 5—absolute benefit through restricted mean survival time

The absolute benefit was expressed through the difference in RMST, which represented the mean time lived in the interval [0, τ] and was interpreted directly in months of life. RMST was calculated with IPCW, with τ horizons pre-specified a priori: 60 months for locoregional disease (the horizon within which more than 90% of the expected events would have occurred in patients with average prognosis) and 24 months for metastatic disease (a shorter horizon, calibrated to the median CSS observed in the literature for advanced metastatic disease[8]). RMST estimates have the methodological advantage of not relying on hazard proportionality—an assumption that is sometimes questionable over long time horizons.

2.3.6. Stratum 6—control of immortal-time bias

Immortal-time bias arises in the structure specific to this study because all included patients survived, by definition, until the first palliative admission, and the outcome was measured from that admission onward; the exposure, in contrast, referred to a prior interval—from the documentation of advanced disease (t_D) to admission. In this structure, patients with a longer interval to referral must have survived longer from the moment of disease documentation, which can artificially favor the > 3-month group if the origin of time is placed at documentation.

To clarify and control this aspect, we performed two complementary analyses. The landmark analyses—at 3, 6, and 12 months—compared only patients alive at the respective time points, isolating the effect after excluding early mortality that could artificially inflate any group.

The left-truncation analysis set the time origin at disease documentation (not at admission) and substantially reduced the contribution of the "immortal" interval to the Cox risk set. The concordance of these analyses with the main model quantified the extent to which immortal-time bias influenced the estimates. These analyses attenuated immortal-time bias without entirely removing it, and survivor bias and referral-selection bias—inherent to a retrospective observational design—remain possible.

2.4. Baseline balance and control of residual confounding

In addition to multivariable adjustment and the exploratory mediation analysis, we quantified baseline imbalances between groups using standardized mean differences (SMDs), with $|SMD| < 0.10$ indicating good balance and $|SMD| \geq 0.10$ indicating relevant imbalance. The SMDs were used descriptively to transparently characterize residual confounding, which, given the observational design, could not be completely eliminated.

The significance threshold was $\alpha = 0.05$ (two-sided). The analyses were performed using Statistical Package for Social Sciences (SPSS 29.0, IBM, United States) (the main Cox models and the landmark analyses) and R software (v4.3, R Foundation for Statistical Computing, Austria) (the survival packages for Cox with left truncation, cmprsk for Fine–Gray, mediation for Imai–Keele–Tingley, and survRM for RMST). The reporting fully complies with the STROBE checklist for cohort studies, as detailed in Table S4.

3. Results

3.1. Cohort characteristics

Of the 147 consecutive patients included in the final analysis, 55 (37.4%) had advanced locoregional disease—defined as T4 locoregional extension without documented metastasis or as locoregional recurrence after curative treatment—and 92 (62.6%) had metastatic disease. The predominant tumor sites were digestive (25.9%) and bronchopulmonary (23.8%), followed by gynecological (14.3%) and breast (10.2%) malignancies. The complete distribution of tumor sites is presented in Table 2.

Two observations were noteworthy regarding the distribution by site. First: bronchopulmonary cancer was exclusively metastatic in our cohort, reflecting the typical pattern of late presentation of this cancer type in the Romanian health system, with patients reaching palliative care already in the metastatic stage. Second: head and neck (otorhinolaryngological region) malignancies were exclusively locoregional, consistent with the nature of these tumors, which progress predominantly through local and regional nodal invasion before systemic dissemination. Given these asymmetries, the survival analyses were not further stratified by primary site; instead, they focused on cross-cutting prognostic determinants—timing, functional status, and tumor extension—that were comparable across cancer types.

The temporal marker identified 59 patients (40.1%) referred ≤ 3 months of the documentation of advanced disease (t_D) and 88 patients (59.9%) referred after this interval. Compared to the late-referral group, early-referred patients had a more favorable clinical profile: more preserved functional status (ECOG 1–2 in 57.6% vs. 38.6%), more frequent locoregional disease (44.1% vs. 33.0%), and—for the metastatic subcohort—more limited dissemination (a single metastatic site in 48.5% vs. 32.2% of patients with metastatic disease). The complete characteristics, stratified by the temporal marker, are presented in Table 3.

The SMD measured how much two groups differ with respect to a characteristic, on a scale independent of the unit of measurement, and was used to detect baseline imbalances between groups; values above the conventional threshold of 0.10 indicate relevant differences. In the present case, the SMDs exceeded this threshold for ECOG status (SMD 0.39), metastatic extension (SMD 0.34), and tumor site (SMD 0.23), confirming the existence of relevant baseline imbalances. Age and sex were balanced (|SMD| < 0.10), suggesting that basic demographic factors did not significantly influence the direction of early vs. late referral.

These imbalances were not accidental; they reflected the selection that operated naturally in real-world observational timing studies. Patients with a more favorable clinical profile—preserved functional status, more limited dissemination, slower disease course—tended to reach palliative care earlier, either because the tumor biology allowed a wider temporal window for the referral decision, or because the oncology team was more proactive in directing these patients toward palliative care in accordance with current guidelines. Multivariable adjustment (Stratum 1) and the exploratory mediation analysis (Stratum 4) attenuate this confounding but cannot eliminate it completely—a limitation detailed in Sections 4.1 and 4.6.

3.2. Strata 1 and 2—the main association and competing risks

The Kaplan–Meier curves showed a significant separation between the two referral groups, both in the locoregional subcohort (n = 55; 17 cancer-specific events; event rate 30.9%) and in the metastatic subcohort (n = 92; 92 events; rate 100%). In the locoregional subcohort, the log-rank test returned p = 0.0023, and the median CSS was not reached in the early-referred subgroup—more than half of these patients remained alive at the end of the follow-up period (Figure 1). In the metastatic subcohort, the separation of the curves was significant (log-rank p < 0.001), with median CSS of 6.9, 4.1, and 2.0 months according to the number of metastatic sites (Figure 2).

Multivariable Cox regression identified three independent predictors in the locoregional subcohort (Table 4): referral within ≤3 months (adjusted HR 0.49; 95% CI 0.28–0.86; p = 0.013), the absence of locoregional progression at the time of admission (HR 0.41; 95% CI 0.22–0.78; p = 0.006), and ordinal ECOG status—each one-point increase in ECOG was associated with a 58% higher risk of death (HR 1.58; 95% CI 1.10–2.27; p = 0.014).

In the metastatic subcohort, metastatic extension dominated risk prediction: patients with ≥ 3 metastatic sites had a 3.21-fold higher risk of death than those with a single site (HR 3.21; 95% CI 2.18–4.73; p < 0.001), and patients with two sites had a 1.94-fold higher risk (HR 1.94; 95% CI 1.32–2.86; p = 0.001). ECOG status 4 (vs. 2–3) was associated with an approximate doubling of risk (HR 2.67; 95% CI 1.79–3.98; p < 0.001). In this context, the temporal marker retained its independent association with CSS (HR 0.58; 95% CI 0.41–0.82; p = 0.002)—metastatic patients referred early had a risk of death reduced by approximately 42%, adjusted for metastatic extension and functional status.

Verification of hazard proportionality using Schoenfeld residuals yielded p-values ranging from 0.41 to 0.72 for all predictors in both subcohorts (all p > 0.05), confirming that the Cox assumption is met and that there is no significant

Table 2. Distribution of primary tumor sites in the studied cohort (n = 147)

Primary tumor site	*n*	%
Digestive tract malignancies	38	25.85
Bronchopulmonary cancer	35	23.81
Gynecological malignancies	21	14.29
Breast cancer	15	10.20
Head and neck (ENT) malignancies	12	8.16
Genitourinary malignancies	11	7.48
Malignant melanoma	4	2.72
Primary brain tumors	3	2.04
CUP—multiple bone metastases	3	2.04
CUP—multiple brain metastases	3	2.04
Primary hepatic carcinoma	2	1.36
Total	147	100.00

Abbreviations: CUP: Cancer of unknown primary (carcinoma of unknown primary origin); ENT: Otorhinolaryngological region.

Table 3. Cohort characteristics and event balance, stratified by the temporal marker (≤3 vs. > 3 months)

Characteristic	Overall	≤3 months (*n* = 59)	>3 months (*n* = 88)
Age, mean ± SD (years)	63.4 ± 11.2	62.1 ± 10.8	64.3 ± 11.5
Female sex, *n* (%)	81 (55.1)	34 (57.6)	47 (53.4)
ECOG 1–2, *n* (%)	68 (46.3)	34 (57.6)	34 (38.6)
ECOG 3–4, *n* (%)	79 (53.7)	25 (42.4)	54 (61.4)
Locoregional disease, *n* (%)	55 (37.4)	26 (44.1)	29 (33.0)
Metastatic disease, *n* (%)	92 (62.6)	33 (55.9)	59 (67.0)
1 metastatic site, *n* (%)[a]	35 (38.0)	16 (48.5)	19 (32.2)
2 metastatic sites, *n* (%)[a]	29 (31.5)	11 (33.3)	18 (30.5)
≥ 3 metastatic sites, *n* (%)[a]	28 (30.4)	6 (18.2)	22 (37.3)
Cancer-specific deaths, *n* (%)	109 (74.1)	35 (59.3)	74 (84.1)
Non-oncological deaths, *n* (%)	5 (3.4)	2 (3.4)	3 (3.4)
Censored (alive at June 30, 2025), *n* (%)	33 (22.4)	21 (35.6)	12 (13.6)
Median follow-up, months (IQR)	26 (4–62)	38 (14–68)	17 (3–48)

Notes: [a]Percentage calculated relative to the metastatic subcohort (n = 92); the five non-oncological deaths all occurred in the locoregional subcohort.
Abbreviations: ECOG: Eastern Cooperative Oncology Group Performance Status; IQR: Interquartile range; SD: Standard deviation.

trend over time of the hazard ratios that would invalidate the standard interpretation of the HRs.

The Fine–Gray model, applied in the locoregional subcohort where five competing non-oncological deaths were observed, confirmed the robustness of the main association: the subdistribution hazard for early referral was SHR 0.52 (95% CI 0.29–0.93; p = 0.027), extremely close to the cause-specific Cox HR of 0.49 (difference Δ = 0.03; Table 5). Similar concordance was also observed for locoregional control (SHR 0.43 vs. HR 0.41; Δ = 0.02) and for ECOG (SHR 1.47 vs. HR 1.58; Δ = 0.11). In all three cases, the differences were minimal (Δ ≤ 0.11), indicating close concordance and supporting the conclusion that the timing association is not an artifact of competition with non-oncological mortality.

3.3. Stratum 3—temporal stability of the association

A frequent objection to observational timing studies is that the observed protective association might reflect only baseline differences in clinical state, which fade after the first months. Technically, this hypothesis translates into a β(t) coefficient that rapidly tends toward zero over the course of follow-up—a phenomenon termed the "early-phase effect."

To formally test this hypothesis, we evaluated β(t) at three temporal horizons through a cubic spline, according to the Grambsch–Therneau method. The coefficient remained negative and statistically significant at 12 months (β = −0.71; 95% CI −1.18 to −0.24; p = 0.003), 24 months (β = −0.62; 95% CI −0.99 to −0.25; p = 0.001), and 48 months (β = −0.59; 95% CI −0.97 to −0.21; p = 0.003). The total change between 12 and 48 months was Δβ = 0.12, with p = 0.71, indicating non-statistical significance (Table 6, Figure 3).

The protective association of early referral with CSS was stable over 85 months of follow-up—it was maintained at years 1, 2, and 4 after the first palliative admission. The slight increase from β = −0.71 to β = −0.59 was not substantial enough to justify the conclusion of a "fading" of the effect over time, and concordance with the hazard-proportionality assumption (Schoenfeld test, the Sch-p column in Table 4) was mutually confirmed.

3.4. Stratum 4—exploratory mediation analysis

The mediation analysis addressed a specific question: to what extent does the well-known association between ECOG functional status and survival statistically overlap with the interval to referral? In clinical practice, this question has operational relevance: if an important part of the survival disadvantage of impaired ECOG overlaps with late referral, then a systemic intervention on timing could, in principle, recover part of this disadvantage. This interpretation remains speculative in the absence of a randomized design.

Table 4. Multivariable Cox models for cancer-specific survival in the two subcohorts, highlighting the main predictor—the temporal marker

Predictor	HR	95% CI	*p*	Sch-p[a]	SHR[b]
Locoregional subcohort (*n* = 55; 17 cancer-specific events)					
Referral ≤ 3 vs. > 3 months	0.49	0.28–0.86	0.013	0.41	0.52
Absence of locoregional progression	0.41	0.22–0.78	0.006	0.58	0.43
ECOG PS per + 1 point (ordinal)	1.58	1.10–2.27	0.014	0.62	1.47
Metastatic subcohort (*n* = 92; 92 cancer-specific events)					
≥3 vs. 1 metastatic site	3.21	2.18–4.73	<0.001	0.72	–
2 vs. 1 metastatic site	1.94	1.32–2.86	0.001	0.68	–
ECOG PS 4 vs. 2–3	2.67	1.79–3.98	<0.001	0.55	–
Referral ≤ 3 vs. > 3 months	0.58	0.41–0.82	0.002	0.49	–

Notes: [a]Schoenfeld $p > 0.05$ confirms hazard proportionality; [b]Fine–Gray SHR, reported only in the locoregional subcohort (five competing deaths); in the metastatic subcohort, all 92 deaths were attributed to oncological disease, so the Fine–Gray model added no information and was not reported.
Abbreviations: CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance score; HR: Hazard ratio; SHR: Subdistribution hazard ratio.

Table 5. Comparison of cause-specific Cox HR vs. FG SHR—locoregional subcohort (five competing non-oncological deaths)

Predictor	Cox HR (cause-specific)	FG SHR	*p*(FG)	ΔHR vs. SHR	Conclusion
Referral ≤ 3 months	0.49	0.52	0.027	0.03	Robust
Locoregional control	0.41	0.43	0.021	0.02	Confirmed
ECOG PS (per + 1 point)	1.58	1.47	0.038	0.11	Confirmed

Notes: 95% confidence intervals for the SHR: referral 0.29–0.93; locoregional control 0.21–0.88; ECOG 1.02–2.12; a difference $|\Delta| < 0.10$ indicates close concordance and confirms the absence of distortion by competing risks.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance score; FG: Fine–Gray; HR: Hazard ratio; SHR: Subdistribution hazard ratio.

Our mediation analysis is strictly descriptive and exploratory in nature: since the ECOG score was measured at the first palliative admission, at the end of the exposure interval, the temporal ordering of exposure → mediator → outcome was not satisfied, and the mediated proportion could not be interpreted causally.

Applying the Imai–Keele–Tingley method with bootstrap (1,000 iterations) in the metastatic subcohort (*n* = 92), we decomposed the total ECOG–CSS association into two components. The direct component—interpreted as a residual association, independent of the moment of referral—was HR 1.81 (95% CI 1.24–2.64; $p = 0.002$), reflecting a presumed intrinsic biological component: ECOG functional deterioration signals a more aggressive disease course, independent of any intervention. The indirect component—the portion statistically overlapping with the interval to referral—was HR 1.27 (95% CI 1.08–1.49; $p = 0.004$), suggesting that part of the risk is transmitted through the observed sequence: impaired ECOG → later referral → shorter survival.

The estimated mediated proportion was 28.4% (95% CI 11.2–41.3%; $p = 0.003$), approximately one-third of the ECOG–CSS association in the metastatic subcohort overlapped with the interval to referral. The Sobel test (z =

Table 6. Time-varying coefficients β(t) at three temporal horizons (Grambsch–Therneau with cubic spline)—full cohort (*n* = 147)

τ	β(t)	95% CI	*p*	Interpretation
12 months	−0.71	−1.18 to −0.24	0.003	Protective association for one year
24 months	−0.62	−0.99 to −0.25	0.001	Persists for two years
48 months	−0.59	−0.97 to −0.21	0.003	Persists for four years
Δβ (12–48)	0.12	–	0.71	Stable effect—proportionality confirmed

Notes: Negative values of β(t) indicate a protective association of early referral; Δβ between 12 and 48 months quantifies the temporal stability of the effect.
Abbreviation: CI: Confidence interval.

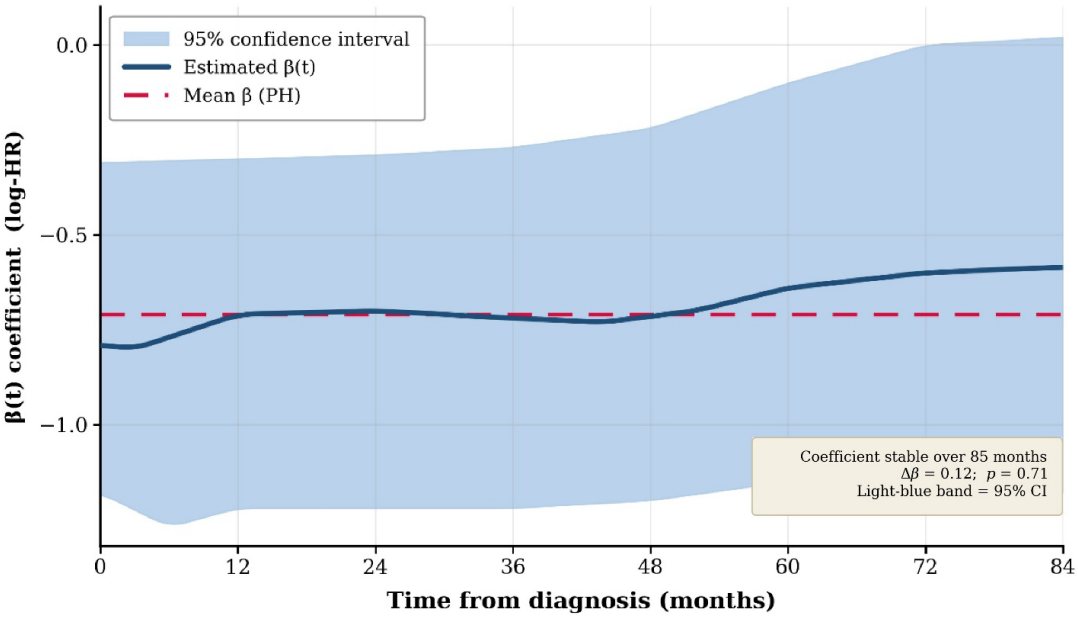

Figure 3. The time-varying β(t) coefficient (Grambsch–Therneau with cubic spline)—full cohort
Abbreviations: CI: Confidence interval; HR: Hazard ratio; PH: Proportional hazard.

3.12; $p = 0.002$) confirmed the significance of the statistical mediation, and the sensitivity analysis with the ρ parameter indicated that the mediated association remained significant for values $\rho < 0.34$—it would persist even in the presence of a moderate unmeasured confounder (Tables 7 and S3, Figure 4).

The estimated mediated proportion of 28.4% requires a particularly cautious interpretation. Since ECOG was measured contemporaneously with the end of the exposure interval, and clinical factors unmeasured in this retrospective dataset—in particular the number of prior lines of systemic treatment, the duration of active oncological treatment, and the symptom burden—may simultaneously influence the moment of referral and survival, the assumptions of the Imai–Keele–Tingley method regarding the absence of unmeasured confounding could not be fully verified.

In clinical practice, a patient with preserved ECOG status referred early frequently has either a less aggressive tumor biology (with slower progression, wider therapeutic windows) or a more proactive oncology team in directing toward palliative care. Both situations may simultaneously influence the moment of referral and survival, beyond the ECOG–timing relationship. The absence of these variables in our data may lead to an overestimation of the mediated proportion of 28.4%. Therefore, this estimate must be

Table 7. Exploratory Imai–Keele–Tingley mediation analysis—metastatic subcohort (n = 92; bootstrap with 1,000 iterations)

Component	Value	95% CI	p	Interpretation
Total ECOG–CSS association	HR 2.29	1.62–3.24	<0.001	The combined association (direct + overlapping with timing)
Direct component (independent of timing)	HR 1.81	1.24–2.64	0.002	Residual association, independent of the moment of referral
Indirect component (overlapping with timing)	HR 1.27	1.08–1.49	0.004	Portion statistically overlapping with the interval to referral
Estimated mediated proportion	28.4%	11.2–41.3%	0.003	~1/3 of the association overlaps with timing (exploratory)
Sobel test	z = 3.12	–	0.002	Concordant with mediation
Sensitivity (ρ)	ρ < 0.34	–	–	Robust to moderate unmeasured confounding

Notes: The results are exploratory and hypothesis-generating; ρ = sensitivity parameter for unmeasured mediator–outcome confounding[33]; the direct component must not be interpreted as evidence of an intrinsic biological causality, but as a residual statistical association, conditional on the model assumptions.
Abbreviations: CI: Confidence interval; CSS: Cancer-specific survival; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio.

treated exclusively as an exploratory and hypothesis-generating result, not as a quantification of a benefit recoverable through intervention—this interpretation would require a randomized study in which timing is assigned independently of functional status.

3.5. Stratum 5—absolute benefit through restricted mean survival time

Hazard ratios are methodologically informative but difficult to communicate to patients and their families. The difference in RMST translates the same statistical signal into months of life, more accessible to clinical interpretation and directly comparable to median survival. RMST has gained increasing use as an interpretable alternative to hazard ratios, remaining valid even when the proportional-hazards assumption does not hold[34]; the metric is particularly suitable for long follow-up horizons, and recent literature recommends its complementary reporting, including in the context of therapies with a delayed effect.[35]

At a horizon τ = 60 months in locoregional disease, the mean RMST was 47.3 months in the early-referred group (95% CI 38.1–56.5) and 28.6 months in the late-referred group (95% CI 19.4–37.8), with a difference of +18.7 months (95% CI 6.2–31.2; p = 0.004). Over the five-year horizon, patients with locoregional disease referred early lived, on average, approximately 19 months longer than those referred late—a substantial difference, both statistically and clinically.

At a horizon τ = 24 months in metastatic disease, the mean RMST was 10.4 months in early-referred patients vs. 6.1 months in late-referred patients, a difference of + 4.3 months (95% CI 1.4–7.2; p = 0.003). This difference—apparently modest in absolute value—becomes clinically relevant relative to the median CSS observed in metastatic disease (2–7 months depending on metastatic extension). In advanced metastatic disease, every additional month of life is significant, and a 4.3-month difference represents a major relative improvement.

Inverse probability of censoring weighting corrected for differential censoring: early-referred patients had a higher rate of administrative censoring (35.6% vs. 13.6%, Table 3), precisely because a larger number of them were alive at the end of the follow-up period. The τ horizons were pre-specified a priori (60 months for locoregional; 24 months for metastatic), not selected post hoc based on the observed distribution. The RMST estimates are presented in Table 8.

3.6. Stratum 6—landmark validation and control of immortal-time bias

Landmark analyses compared exclusively patients who were alive at a given reference moment, thus eliminating the contribution of early mortality that could artificially inflate one of the groups. The association of early referral with CSS persisted at the three-month landmark (n = 120 patients at risk; HR 0.58; 95% CI 0.41–0.83; p = 0.003) and at six months (n = 96; HR 0.61; 95% CI 0.42–0.89; p =

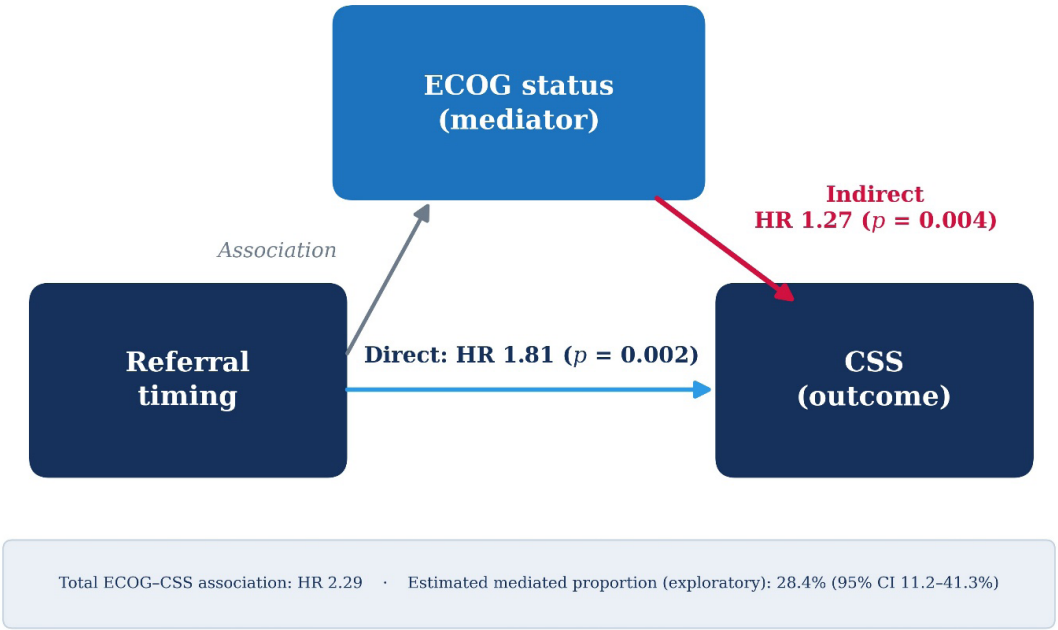

Figure 4. Diagram of the exploratory mediation analysis (Imai–Keele–Tingley)—metastatic subcohort (n = 92)
Note: The decomposition is presented for exploratory and hypothesis-generating purposes only: because ECOG status was measured at the end of the exposure interval, the mediated proportion should not be interpreted as a causal decomposition of the effect, but as a descriptive quantification of the statistical overlap between functional status and the time to referral.
Abbreviations: CI: Confidence interval; CSS: Cancer-specific survival; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio.

Table 8. RMST analysis—the absolute survival benefit expressed in patient-months

Group	τ (months)	Mean RMST (95% CI)	Difference (95% CI)
Locoregional subcohort (n = 55)			
Referral ≤ 3 months (n = 26)	60	47.3 (38.1–56.5)	Reference
Referral > 3 months (n = 29)	60	28.6 (19.4–37.8)	+18.7 months (6.2–31.2); p = 0.004
Metastatic subcohort (n = 92)			
Referral ≤ 3 months (n = 33)	24	10.4 (7.8–13.0)	Reference
Referral > 3 months (n = 59)	24	6.1 (4.7–7.5)	+4.3 months (1.4–7.2); p = 0.003

Notes: RMST difference = (Referral ≤ 3 months) − (Referral > 3 months); a positive value indicates longer survival associated with early referral; the RMST estimates do not depend on hazard proportionality.
Abbreviations: CI: Confidence interval; RMST: Restricted mean survival time.

0.009). At 12 months (n = 67), the estimate of the direction remained similar (HR 0.63), but the CI crossed unity (95% CI 0.39–1.02; p = 0.060), a reflection of the substantial reduction in the number of patients remaining at risk, not of the disappearance of the association.

The left-truncation analysis, which placed the origin of time at disease documentation (instead of the first palliative admission) and eliminated the contribution of the immortal interval to the Cox risk set, produced estimates extremely close to the main model: in the locoregional subcohort, HR = 0.46 (vs. 0.49; ΔHR = 0.03) and in the metastatic subcohort, HR = 0.56 (vs. 0.58; ΔHR = 0.02). A maximum ΔHR of 0.03 relative to the main model is well below the conventional relevance threshold and indicates that immortal-time bias has minimal impact on the results, although it cannot be completely eliminated (Tables 9 and S2). The landmark and left-truncation analyses substantially reduced concerns about immortal-time bias, but did not completely eliminate the risk of survivor selection or the referral-selection bias inherent to a retrospective observational design; therefore, the interpretation of this control remains in the register of attenuation, not elimination.

To verify whether the result depended on the choice of a single dichotomous threshold, we performed three complementary sensitivity analyses, detailed in Table S6 and summarized graphically in Figure 5.

First, the time to referral was modeled continuously (in months) within a Cox model, both linearly and using a restricted cubic spline with three knots, to avoid imposing an a priori linear relationship. In the continuous linear model, each additional month of referral delay was associated with an approximately 8% increase in the risk of cancer-specific death (HR 1.08 per month; 95% CI 1.03–1.13; p = 0.001), and the restricted cubic spline specification closely followed the linear shape, with no significant inflection points or plateaus. Thus, the association between referral delay and risk of death was monotonically increasing across the entire observed interval (0–12 months), with no abrupt discontinuity—risk rose gradually and continuously with each month of delay, rather than through an abrupt jump at a particular value. This behavior indicates that the dichotomization at three months captured a real, underlying, and continuous trend, not an artifact of the selected cut-point.

Second, alternative dichotomous thresholds (2, 4, and 6 months) were tested and compared to the pre-specified three-month threshold (HR 0.58). The direction and significance of the association were preserved for the stricter thresholds: at ≤2 months, adjusted HR = 0.50 (95% CI 0.33–0.76; p = 0.001) and at ≤4 months, adjusted HR = 0.62 (95% CI 0.44–0.87; p = 0.006)—all significant at $p < 0.05$ and concordant in magnitude with the principal threshold. At the ≤6-month threshold, the association remained in the same protective direction but was attenuated and no longer statistically significant (adjusted HR 0.71; 95% CI 0.49–1.02; p = 0.061). As the threshold shifts toward longer intervals, the contrast between the two groups decreases (an increasing number of patients are classified as "early"), and the power to detect the difference is reduced. This gradient—a stronger effect at stricter thresholds and an attenuated effect at wider thresholds—is itself consistent with a continuous dose–response relationship between delay and risk.

Third, to rule out the possibility that the three-month threshold had been "lucky," we applied a "maximally selected rank statistics" analysis, which empirically identified the cut-point that maximized the statistical separation between groups. The optimal threshold identified in this approach was approximately 3.2 months, essentially overlapping the pre-specified three-month threshold; the difference was not statistically significant (n.s.), and the maximized test statistic did not exceed the significance threshold adjusted for multiple testing. In other words, had we allowed the data to "choose" the best threshold, it would have practically coincided with the one set a priori based on the quarterly oncological re-evaluation schedule.

Since the three-month threshold was set a priori, rather than selected post hoc to maximize separation, these sensitivity analyses are presented solely as a robustness check, not as a redefinition of the exposure. The concordance of results across the continuous modeling (HR 1.08 per month, monotonically increasing), the alternative dichotomous thresholds (0.50–0.71), and the empirical optimal threshold (~3.2 months) strengthens the conclusion that the observed association reflects a real trend and is not dependent on a single selected threshold.

3.7. Exploratory prognostic score

Starting from the coefficients of the metastatic Cox model, a purely exploratory composite prognostic score was conceptualized to indicate a possible direction for further research. Since the score was derived from a single-center retrospective subcohort and not independently validated, no threshold or risk category can be proposed for clinical use without prospective multicenter validation. The detailed components of the score, the stratification by risk categories, and the corresponding observed medians are presented in Table S5; in the main text, only the conceptual structure of the score is described, without attributing any current clinical utility to it.

Table 9. Landmark validation and control of immortal-time bias through left truncation

Analysis	*n*	HR (≤3 vs. > 3 months)	95% CI	p
Landmark analyses—persistence of the association after exclusion of early mortality				
Full cohort (primary analysis)	147	0.55	0.40–0.75	<0.001
Landmark 3 months	120	0.58	0.41–0.83	0.003
Landmark 6 months	96	0.61	0.42–0.89	0.009
Landmark 12 months	67	0.63	0.39–1.02[a]	0.060
Left truncation—control of immortal-time bias				
Main analysis	147	0.49/0.58[b]	0.28–0.86/0.41–0.82	0.013/0.002[b]
With left truncation	147	0.46/0.56[b]	0.26–0.82/0.40–0.79	0.008/0.001[b]
Maximum ΔHR	–	≤0.03	–	–

Notes: [a]The CI crossed 1.0 because of the reduction in the number of patients at risk (n = 67), not because of the disappearance of the association; [b]first value = locoregional subcohort; second = metastatic subcohort; HR adjusted for disease category, Eastern Cooperative Oncology Group performance score, and metastatic extension; maximum ΔHR quantifies the impact of immortal-time bias.
Abbreviations: CI: Confidence interval; HR: Hazard ratio.

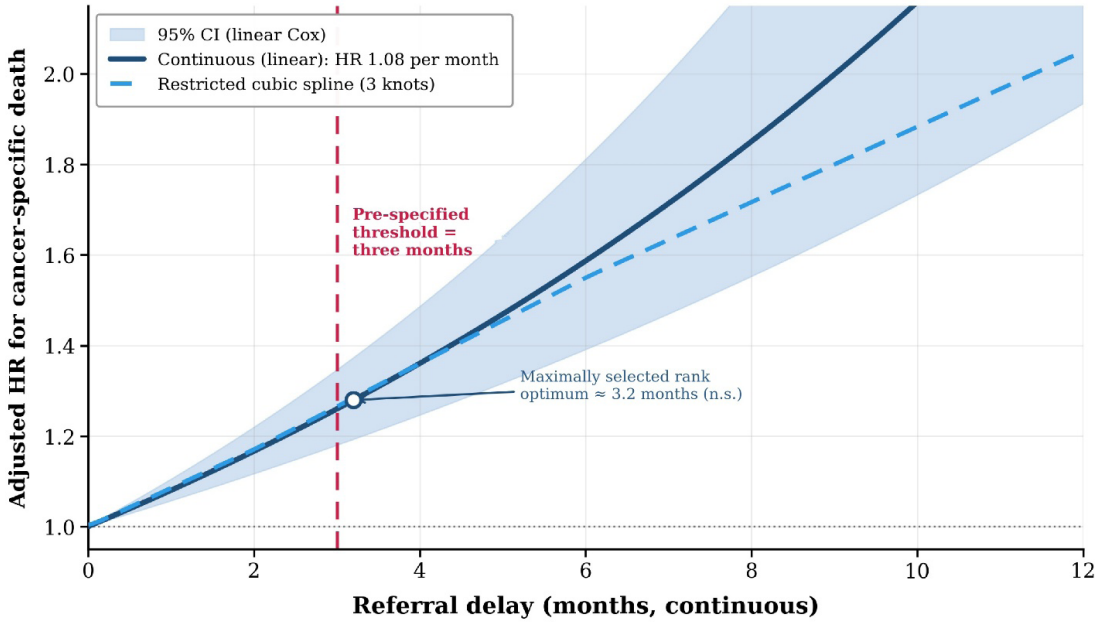

Figure 5. Sensitivity analysis of the temporal threshold—continuous modeling of referral delay in the metastatic subcohort. The adjusted risk of cancer-specific death increases monotonically and continuously with each month of delay, with no abrupt discontinuity threshold; the restricted cubic spline specification closely follows the linear shape. The vertical red line marks the pre-specified three-month threshold; the circle indicates the optimal threshold identified by "maximally selected rank statistics" (~3.2 months), not significantly different from the pre-specified one.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; n.s.: Not significant.

A composite score was derived from the ln(HR) coefficients of the metastatic Cox model, rounded to integers for operational simplicity: referral > 3 months (+1 point), ECOG 4 vs. 2–3 (+1 point), 2 vs. 1 metastatic site (+1 point), ≥3 vs. 1 site (+2 points), on a 0–5 scale. Of the four components, the moment of referral was the only one that can be modified at the system level; functional status and metastatic extension reflect the disease characteristics at presentation and cannot be changed retroactively.

Patients with a score of 0–1 (low risk) had an observed median CSS of approximately 10.4 months; those with a score of 2–3 (intermediate risk) had a median of approximately 4.8 months; those with a score of 4–5 (high risk) had a median of approximately 2.0 months. For the high-risk category, we noted that the only element theoretically improvable through systemic intervention is the timing of referral, which, in this subpopulation, justifies a process of palliative referral without delay (Table S5). It should be noted that no clinical recommendation should be derived from this score before prospective external validation.

4. Discussion

4.1. Synthesis of the results and their placement in the literature

In a consecutive real-world cohort, referral to specialized palliative care within the first three months of the documentation of advanced disease (t_D) was independently associated with significantly better CSS—both in advanced locoregional disease (HR 0.49) and in metastatic disease (HR 0.58)—and the association proved robust across six complementary analytical approaches. The concordance of results across independent methods—competing risks, time-varying coefficients, RMST, mediation analysis, landmark, and left truncation—is, in the absence of a randomized design, the main evidence of robustness that an observational study can provide.

The results are consistently in line with the recent literature on early palliative care, which has demonstrated benefits for quality of life and, in the trial by Temel *et al.*[6], for patients with metastatic non-small-cell lung cancer, as well as for survival.[7,8,36] The specific contribution of this study does not lie in the discovery of a novel association, but in the operationalization and rigorous testing of a pre-specified threshold—a threshold which, unlike prognostic or symptom-based definitions, is directly measurable from routine clinical documentation. Since multiple definitions of "earliness" coexist in the literature without consensus[16,17], the proposal of a computable, pre-specified temporal reference point anchored in the practice of quarterly oncological re-evaluations represents an attempt to make the concept auditable beyond the individual case.

A post hoc power analysis, calibrated to the observed effect magnitude, indicated approximately 78% power to detect the difference at $\alpha = 0.05$—a reasonable level for a single-center study, although below the conventional 80% threshold recommended for confirmatory studies. Since power computed on the observed effect is a restatement of the *p*-value and conveys no independent information, we interpret it solely as an indicative gauge of sample size, not as evidence of robustness; a more informative assessment of precision was provided directly through the width of the reported CIs. In this respect, the CI for the RMST difference in the locoregional subcohort (6.2–31.2 months) lay entirely within the beneficial range—both bounds being positive, indicating a consistent direction of the association. However, the considerable width of this interval reflects substantial uncertainty regarding the magnitude of the effect (Section 4.6), so that the conclusion that can be cautiously supported is one of a robust direction of benefit, rather than a precise estimate of its amplitude.

4.2. The interpretation of exploratory mediation analysis

The most methodologically delicate finding is the estimated mediated proportion of 28.4%: approximately one-third of the well-known association between ECOG functional status and CSS might statistically overlap with the interval to referral. This observation raises an interesting hypothesis for further research—namely, that the moment of referral might represent a path, partly distinct from functional status, in determining prognosis—but it cannot be interpreted as evidence of a causal mechanism for at least three reasons.

The first reason concerns the timing of the ECOG measurement. In this study, ECOG status was recorded at the first palliative admission, that is, at the end of the exposure interval, not before it. This temporal sequence makes a strict interpretation prior status–subsequent referral–final outcome impossible at the individual level—the observed ECOG reflects both the patient's profile at the moment of the decision and the deterioration accumulated over the interval. The second reason concerns the unmeasured clinical variables. Our retrospective dataset did not include data on the number of prior lines of systemic treatment, the duration of active treatment, and the overall symptom burden—all variables that may simultaneously influence the moment of referral and survival, beyond the ECOG–timing relationship. The third reason concerns the selection that operates in observational studies: a patient with preserved ECOG who is referred early frequently has

either a less aggressive tumor biology or a more proactive oncology team, and both scenarios may inflate the indirect component without a systemic intervention on timing, thereby reproducing the same effect.

Therefore, the mediated proportion of 28.4% must be treated as a cautious quantification of a statistical overlap, not as evidence of a benefit "recoverable" through intervention. The sensitivity analysis with the ρ parameter showed that the mediated significance is maintained for values $\rho < 0.34$—a reasonable protection against moderate unmeasured confounders, but insufficient in the presence of strong unidentified confounders. Validation of this hypothesis would require a randomized design in which timing is allocated independently of functional status, a requirement that, in palliative care, raises substantial ethical problems. The mediation analysis remains strictly exploratory: because ECOG status was measured at the first palliative admission, at the end of the exposure interval, and not before, the temporal sequence required for a causal mediation interpretation (mediator prior to the outcome and posterior to the exposure) was not guaranteed. Consequently, the estimated mediated proportion must not be interpreted as a causal decomposition of the effect, but exclusively as a descriptive, hypothesis-generating quantification of the statistical overlap between functional status and the interval to referral.

4.3. Competing risks and temporal stability

The close concordance between the cause-specific Cox HR and the Fine–Gray SHR ($\Delta < 0.10$) in the locoregional subcohort indicates that the timing association is not an artifact of competition with non-oncological mortality. This verification is important in palliative studies, where a proportion of patients die from acute cardiovascular causes, non-tumoral septic events, or late complications of prior treatments. In our cohort, all five non-oncological deaths occurred in the locoregional subcohort and represented a comparable proportion in the two timing groups, relative to the size of each group within the whole cohort (2 of 59 patients, i.e. 3.4%, in the ≤ 3-month group vs. 3 of 88 patients, i.e. 3.4%, in the > 3-month group), which is consistent with the absence of any evident distortion—although the small number of non-oncological events does not permit a formal test of this distribution).

The stability of the β(t) coefficient over 85 months ($\Delta\beta = 0.12$; $p = 0.71$) addresses a recurrent objection in the observational timing literature: that the observed effect might reflect only baseline health differences, which would fade after the first months ("early-phase effect"). Our data do not support this interpretation—the protective association is maintained at 1, 2, and 4 years after the first palliative admission, and the modest reduction in the β coefficient is not statistically significant. This indirectly reinforces the hypothesis that the three-month threshold is not merely a proxy of the baseline clinical state, but carries prognostic information in itself.

4.4. The clinical utility of restricted mean survival time

The differences in RMST express the benefit in the patient's language—months of life—and are, by construction, independent of the proportionality of hazards. This characteristic makes RMST particularly suitable for reporting in palliative timing studies, where long follow-up horizons may call the proportionality assumption into question.[37]

In locoregional disease, the difference of +18.7 months at a 60-month horizon is substantial both statistically and clinically; in metastatic disease, the difference of +4.3 months at a 24-month horizon is apparently modest in absolute value but becomes relevant relative to the observed median CSS (2.0–6.9 months depending on metastatic extension). In advanced metastatic disease, every additional month of life is significant for the patient and family, and a 4.3-month difference represents a major relative improvement.

We recommend adopting RMST as a complementary reporting standard in future palliative timing studies. Hazard ratios remain methodologically useful, but translating results into clinical communication is much more direct when the benefit is expressed in concrete months.

4.5. Institutional implications and use as a quality indicator

The proportion of patients referred within ≤3 months of the documentation of advanced disease (t_D) can be calculated from routine clinical documentation—without additional recording requirements—and could serve as an auditable quality indicator of timely access to palliative care. The required data are: the date of the imaging report documenting advanced disease or the date of the MDT decision (whichever is earlier), and the date of the first palliative admission.

Subject to external validation in other centers, this indicator could serve several practical purposes. First: longitudinal monitoring of access to palliative care within a single center, with the potential to identify organizational bottlenecks (long waiting times, palliative bed shortages, overly restrictive admission criteria). Second: benchmarking between centers—a standardized indicator allows constructive comparisons between units and the

identification of exemplary practices. Third: integration into institutional quality-improvement programs, with measurable objectives (for example, increasing the proportion of patients referred within ≤3 months from 40% to 60% over two years). The presentation patterns observed in our cohort must be interpreted in the specific context of the Romanian regional oncological network. The fact that all bronchopulmonary cancers presented exclusively at the metastatic stage, and head and neck malignancies exclusively at the locoregional stage, reflects not only the natural history of these tumors but also the structural particularities of the oncological patient's pathway in Romania. The delay in referral to palliative care in this system is likely multifactorial. First, access to specialized ambulatory or home-based palliative care services remains limited and unevenly distributed across territories, so that the first inpatient palliative admission frequently becomes the first and not the last contact with specialized palliative care, artificially shifting the moment of "referral" toward a more advanced stage of the disease. Second, administrative obstacles to obtaining and documenting MDT decisions (delayed scheduling of oncology boards, fragmentation of information flow between tertiary units and the palliative service, bureaucratic admission requirements) may prolong the interval between documentation of advanced disease and the first admission. Third, cultural and perceptual barriers persist—among both patients and families and among some attending physicians—such that palliative care is still associated with "giving up on treatment" and is approached late, despite current recommendations for early integration.[12,38] These structural and cultural mechanisms, although not directly measured in the present retrospective study, offer a plausible explanation for the observed distribution of stages at presentation and emphasize that improving the proposed indicator depends not only on individual clinical decision-making but also on organizational reform of the palliative care network. The quantitative characterization of the contribution of each of these factors—through dedicated qualitative or mixed-methods studies—constitutes an important research direction for the Romanian health system.

We emphasize, however, that any use of the threshold—or of the exploratory prognostic score—in individual clinical decisions is premature in the absence of external validation. The current applicability of our results is limited to the aggregate audit of institutional access, not to the individualization of management for a specific patient.

4.6. Limitations

The study has several limitations, each described transparently to allow the reader to weigh the soundness of the results:

(i) The retrospective single-center design: The design does not allow causal inferences and restricts generalizability to similar models of inpatient palliative care. Predominantly ambulatory or consultation-based palliative care systems (in other European or North American health systems) may present different timing patterns.

(ii) The modest cohort size: The 147 patients represent a modest cohort for an analysis with six methodological strata; the locoregional subcohort (55 patients, 17 events) supports a limited number of variables per model, and although hazard proportionality and stability checks were satisfactory, the events-per-variable ratio in this subcohort implies a risk of overfitting. The estimates for the locoregional subcohort (in particular, the RMST difference of 18.7 months, with a wide interval of 6.2–31.2 months) must be interpreted with caution. With only 17 cancer-specific events, the locoregional Cox model marginally complies with the rule of thumb of approximately 10 events per variable (three predictors), and the Fine–Gray model, based on only five competing deaths, has low power; both are therefore exposed to the risk of overfitting and of unstable estimates, reflected in the wide confidence intervals. Consequently, the hazard ratios, the subdistribution hazards, and the RMST difference in the locoregional subcohort must be regarded as exploratory estimates, with considerable uncertainty, and not as precise point values; their clinical interpretation requires increased caution, and their confirmation requires larger locoregional cohorts, ideally multicenter.

(iii) Baseline imbalances and residual confounding: The SMDs exceeded the 0.10 threshold for ECOG status (SMD 0.39), metastatic extension (SMD 0.34), and tumor site (SMD 0.23), indicating relevant residual confounding. Multivariable adjustment and the exploratory mediation analysis attenuate this confounding but cannot eliminate it completely.

(iv) Unmeasured clinical variables: Data on prior oncological care (the number of lines of systemic treatment, the duration of active treatment, the specific regimens used) and the overall symptom burden at the moment of documentation of advanced disease were not available. The absence of these variables may inflate the indirect component of the mediation analysis. Specifically, the retrospective dataset did not allow adjustment for prior systemic therapy, the number of treatment lines, the status of active oncological treatment at the moment of referral, the overall symptom burden, comorbidities (for example, the Charlson score), and other factors related to

access to care. Since the early-referred group had a systematically more favorable clinical profile—better ECOG status (SMD 0.39), more limited metastatic extension (SMD 0.34), and a different distribution of tumor site (SMD 0.23)—the residual confounding generated by these unmeasured factors cannot be excluded, and the multivariable adjustment performed only partially attenuates it. In the absence of these covariates, we consider that a causal interpretation is not justified, and the conclusions have been further tempered to remain strictly in the associative and hypothesis-generating register: the observed association between early referral and survival must be regarded as a prognostic signal that requires confirmation in prospective cohorts collecting these variables, not as an estimate of a causal effect of the moment of referral.

(v) Eastern Cooperative Oncology Group measurement contemporaneous with the end of the exposure interval: ECOG status was recorded at the first palliative admission, not at the documentation of advanced disease. This temporal sequence limits the interpretation of the mediation analysis, which is explicitly declared exploratory. This represents a major limitation, not merely one of interpretive nuance. Since there was no reference ECOG score recorded on the date the advanced disease was documented, we cannot separate the actual functional status at the time of documentation from the functional degradation accumulated over the interval to referral. Concretely, a late-referred patient (for example, at six months) may have a poorer ECOG at admission, not because the delayed referral caused a worse prognosis, but because the disease progressed in the unreferred months—a mechanism of reverse causality (or of time-dependent mediator–outcome confounding) that the current design cannot exclude. This absence of a reference ECOG particularly affects the interpretation of the estimated mediated proportion (28.4%), which could be artificially inflated by time-dependent functional degradation. Future prospective registries should therefore collect sequential performance statuses—at least at the documentation of advanced disease and at the first referral, ideally with an intermediate measurement—to isolate the true functional status at the initial moment from time-dependent deterioration and to allow a mediation analysis with strictly observed temporal ordering.

(vi) Definition of exposure through the first palliative admission: Patients who previously benefited from ambulatory or home-based palliative care (in a setting other than the studied center) might be misclassified as late-referred. Since, at the studied center, this type of ambulatory care does not systematically precede admission, the risk is limited but cannot be completely excluded.

(vii) External validation is necessary: The three-month threshold, the exploratory prognostic score, and the estimated mediated proportion require confirmation in independent cohorts, ideally multicenter, before any clinical use or adoption as a large-scale quality indicator.

4.7. Directions for further research

Five research directions emerge directly from the results and limitations of this study.

(i) Multicenter external validation: Replication of the three-month threshold in a multicenter cohort ($n \geq 500$) with geographic diversity would provide robust confirmation of generalizability and would allow stratification by the institutional type of palliative care (inpatient vs. ambulatory vs. home-based).

(ii) Prospective cohort with serial Eastern Cooperative Oncology Group measurement: Recording ECOG status at the documentation of advanced disease and at the first referral would allow a methodologically more robust mediation analysis, with strictly respected temporal ordering and the possibility of integrating a third intermediate measurement.

(iii) Integration of the symptom burden through standardized instruments: Adding the Edmonton Symptom Assessment System—applied in the documentation of advanced disease and at the first referral—the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, or the Functional Assessment of Cancer Therapy–General would allow quantitative characterization of the symptomatic contribution to referral dynamics, complementing the structural data (timing, ECOG, metastatic extension).

(iv) Interventional pilot studies: A protocol of automatic referral to palliative care triggered by a standardized criterion (for example, the documentation of advanced metastatic disease) would allow, in a stepped-wedge design, the causal evaluation of an intervention on timing, without ethically problematic individual randomization.

(v) Cost-effectiveness analyses: Quantifying the economic impact of early referral (reduction of terminal emergency admissions, optimization of inpatient bed use) would add an important dimension for public policy argumentation.

5. Conclusion

In a consecutive real-world cohort of 147 patients with advanced locoregional or metastatic cancer, followed up to 85 months, a pre-specified three-month threshold between the documentation of advanced disease and the first palliative admission was independently associated with significantly better CSS. The association was robust across six complementary analytical approaches—Fine–Gray competing risks, Grambsch–Therneau time-varying coefficients, exploratory Imai–Keele–Tingley mediation analysis, RMST difference with IPCW, landmark validation at three temporal horizons, and left truncation—the concordance of results across independent methods representing the main evidence of robustness.

The absolute benefit, expressed in months of life, was + 18.7 months at a 60-month horizon in locoregional disease and +4.3 months at a 24-month horizon in metastatic disease—clinically substantial differences relative to the medians reported in the literature. The exploratory mediation analysis suggested that approximately 28% of the well-known association between ECOG functional status and CSS statistically overlaps with the interval to referral, an interesting hypothesis for further research, but one that requires confirmation in a design with strictly sequential temporal measurement.

Since the study is observational and single-center, all conclusions are associative and hypothesis-generating. The three-month threshold must be interpreted as an associative, hypothesis-generating prognostic marker, not as a quality indicator ready for clinical use. Although the proportion of patients referred within the first three months—computable from routine clinical documentation—suggests it could serve as an auditable indicator of timely access to palliative care, any such use remains premature in the absence of prospective external validation, ideally multicenter, in independent cohorts. Until such validation, our results support the formulation of hypotheses and the planning of confirmatory studies, not the adoption of the threshold as a quality-assessment tool or as a basis for individual clinical decisions; the three-month threshold thus remains an associative, hypothesis-generating prognostic marker requiring external validation, rather than a ready-to-use clinical quality indicator.

The six-stratum analytical framework proposed here is transferable to any observational palliative timing study and could help increase methodological rigor in this field of research.

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Conflict of interest

The authors declare the absence of any conflict of interest—financial, commercial, professional, or personal—in connection with this research or its publication.

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Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Centrul Medical Galaxy Med SRL, Craiova, Romania. The Committee granted a waiver of informed consent for the use of anonymized retrospective data, in accordance with the principles of the Declaration of Helsinki and with Regulation (European Union) 2016/679 (GDPR) and Law no. 190/2018 on the protection of personal data.

Consent for publication

Not applicable—the manuscript contains no identifiable individual data. All data are presented in aggregate, at the cohort or stratified-subgroup level.

Availability of data

The de-identified data supporting the conclusions of this article are available from the corresponding author, upon

reasonable request, subject to a data-sharing agreement and in accordance with personal-data protection regulations.

Further disclosure

The reporting of this observational study complies with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies. The complete checklist, including the positioning of each item in the manuscript, is presented in Table S4.

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