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PD-1 inhibitor exposure, hepatic metastasis and independent prognostic factors in recurrent or metastatic esophageal cancer: a single-center retrospective cohort study

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Abstract

Background: PD-1 inhibitor-based chemoimmunotherapy is now standard first-line treatment for advanced esophageal cancer. Real-world data remain scarce, and which clinical variables still carry prognostic weight once immunotherapy is routine is not settled.

Methods: Consecutive patients with recurrent or initial metastatic esophageal cancer treated at our center, who had received at least one line of systemic therapy and had complete follow-up, were reviewed. Overall survival (OS) and progression-free survival (PFS) were both measured from the diagnosis of recurrent or metastatic disease, when first-line therapy began, and groups were compared by the log-rank test. Prognostic factors were examined by Cox regression stratified by disease setting, together with subgroup and sensitivity analyses.

Results: Seventy-eight patients were analyzed (median age 62 years; 82.1% male; 80.8% squamous; 46 initial metastatic). 53 of the 73 patients with known exposure (72.6%) had received a PD-1 inhibitor. Median follow-up was 39.4 months, median OS was 24.4 months (95% CI 17.7-32.6) and median PFS 9.3 months (95% CI 7.5-15.8). PD-1 exposure raised the objective response rate (43.4% vs 5.0%; P = 0.002) without improving OS (adjusted HR 1.39) or PFS (adjusted HR 0.78), and stricter definitions of exposure and landmark analyses left these estimates unchanged. Liver metastasis was the only variable associated with both endpoints after adjustment (OS HR 2.97, 95% CI 1.42-6.19; PFS HR 2.38, 95% CI 1.15-4.92), and the association was at least as strong among the 63 patients with squamous cell carcinoma (OS HR 4.18). PD-1 exposure was associated with longer PFS in an exploratory analysis of the 45 patients with initial metastatic disease (adjusted HR 0.36, 95% CI 0.14-0.93).

Conclusions: Among the patients with advanced esophageal squamous cell carcinoma included in our study, the median OS was 24.4 months and the median PFS was 9.3 months. Both outcomes exceeded historical real-world data for this setting, supporting the feasibility of routine clinical use of first-line chemoimmunotherapy. PD-1 exposure improved the response rate but not survival, in an observational comparison the likeliest explanation is confounding by indication. Liver metastasis was the strongest independent adverse prognostic factor and indicates the group in greatest need of new treatment options.

Keywords: esophageal cancer; esophageal squamous cell carcinoma; PD-1 inhibitor; real-world evidence; liver metastasis; metastatic burden; prognosis; survival analysis

Background

Esophageal cancer ranks ninth among malignancies and seventh among causes of cancer death worldwide, with an estimated 511,000 new cases and 445,000 deaths in 2022 [1]. Much of this burden falls on China, where approximately 224,000 new cases and 187,500 deaths were recorded in 2022 and where esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype [2, 3].

Early disease is usually asymptomatic, so about half of all patients already have distant metastases at diagnosis and more than one third develop metachronous recurrence after radical treatment of localized disease [4, 5]. Palliative chemotherapy for recurrent or metastatic disease historically produced a median overall survival (OS) of only 9 to 12 months. Over the past decade, five randomized trials (KEYNOTE-590, ORIENT-15, ESCORT-1st, JUPITER-06, and CheckMate 648)

established chemoimmunotherapy, an anti-PD-1 or anti-PD-L1 antibody combined with platinum-based chemotherapy, as the standard first-line approach, with median OS of 12.4 to 17.0 months in the experimental arms [6-10]. With the success of the GEMSTONE-304 trial, this benefit was further extended to PD-L1 inhibitors, which have since been incorporated into Chinese guidelines [11].

How far these results carry over to routine practice is still less clear. Real-world populations include older and frailer patients with comorbidity, who would not have qualified for registration trials, and also patients with more favorable biology, such as local recurrence or a limited metastatic burden, who are under-represented in trials. Single-arm and comparative real-world series have given conflicting results [12, 13], and in a non-randomized setting the comparison between PD-1-exposed and PD-1-unexposed patients is especially vulnerable to confounding by indication, since the decision to give immunotherapy is itself driven by the clinical characteristics that determine prognosis [14].

Where the metastases are located appears to matter for prognosis as well. Population-based analyses of metastatic esophageal cancer report the shortest survival in patients with bone or liver involvement and a more favorable course in those with isolated distant lymph node disease [15, 16]. The oligometastatic state, in which a limited number of lesions may be amenable to local consolidative therapy, is now widely treated as a distinct biological entity [17-19]. Experimentally, liver metastases blunt PD-1 checkpoint blockade throughout the body. Activated antigen-specific CD8+ T cells are drawn into the liver and undergo apoptosis after interacting with FasL-expressing monocyte-derived macrophages, leaving a systemic immune desert that reduces the benefit of immunotherapy independently of other biomarkers of response [20]. Whether these site-specific effects persist under modern regimens remains unknown.

We designed this study with two aims: to describe real-world OS and progression-free survival (PFS) in patients with recurrent or metastatic esophageal cancer, and to identify which clinical variables remain independently associated with survival after adjustment, with particular attention to PD-1 inhibitor exposure, metastatic site and metastatic burden.

Methods

Study design and patients

This retrospective cohort study was conducted at the First Affiliated Hospital of Xiamen University. We screened the institutional database for consecutive patients with esophageal malignancy and identified 152 who had histologically confirmed recurrent or initially metastatic disease of any histological subtype (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma or neuroendocrine carcinoma), had received at least one line of systemic therapy for recurrent or metastatic disease, and complete clinicopathological and follow-up data. Data on survival, metastatic site or treatment were missing for 74 of them, leaving 78 patients in the analysis set. Recurrent or metastatic disease was diagnosed between March 2018 and September 2024, and the data cutoff was 28 May 2025.

Data collection and variable definitions

Baseline variables abstracted from the medical records were age, sex, histological subtype, disease setting at initial diagnosis (initial metastatic disease versus recurrence after treatment of previously localized disease), sites of metastasis at the time recurrent or metastatic disease was diagnosed (liver, lung, bone, and distant nodal or other sites), the number of involved metastatic sites, receipt of radiotherapy at any point in the treatment course, the first-line regimen and number of cycles delivered, and PD-1 inhibitor exposure. Metastatic burden was derived by counting the distinct anatomical sites listed in the initial metastasis record, and two or more involved sites was treated as multi-site disease.

PD-1 inhibitor exposure was taken from the treatment record and was defined as exposure at any point during the treatment course, as originally planned. Whether a PD-1 or PD-L1 inhibitor formed part of the first-line regimen was recorded separately (58 of 78 patients), and among the patients classified as unexposed we identified those who received a PD-1 inhibitor after progression (5 of 20). Five patients treated within blinded randomized controlled trials had an exposure status that could not be determined and were excluded from all analyses comparing PD-1-exposed with PD-1-unexposed patients (n = 73 for those analyses). Programmed death-ligand 1 (PD-L1) combined positive score was recorded for only 22 patients (28.2%) and was not entered into any model, and we summarize its distribution descriptively in the Results.

Tumor response to first-line therapy had been graded by the treating physician according to RECIST version 1.1 as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) [21]. Objective response was defined as CR or PR. Three patients with discordant responses across individual lesions were classified as non-responders because at least one lesion was reported as PD.

Outcome definitions

The time origin for both endpoints was the date on which recurrent or metastatic disease was diagnosed. Also it was the date on which first-line systemic therapy for advanced disease started, and the median interval from the time origin to the first response assessment being 3.2 months. OS was defined as the interval from the time origin to death from any cause. PFS was defined as the interval from the time origin to the first documented radiological progression or death from any cause, whichever occurred first. Patients who were alive and progression-free at the last follow-up were censored at the date of last contact. Since the time origin is the start of first-line therapy and not the date of first cancer diagnosis, the disease-free interval of the 32 patients who developed metachronous recurrence does not contribute to their survival time.

Statistical analysis

Categorical variables were summarized as counts with percentages and compared using Fisher's exact test, continuous variables were summarized as median with interquartile range (IQR) and compared using the Mann-Whitney U test. OS and PFS were estimated by the Kaplan-Meier method and compared with the two-sided log-rank test, and 6-, 12-, 24- and 36-month survival probabilities were derived from the Kaplan-Meier estimates. Median follow-up was estimated by the reverse Kaplan-Meier method.

Univariable Cox proportional-hazards regression was used to screen candidate prognostic factors. A pre-specified set of clinically relevant covariates (age, sex, liver metastasis, number of metastatic sites, radiotherapy and PD-1 exposure) was entered into the multivariable model. Disease setting (initial metastatic versus recurrent) also violated the proportional-hazards assumption and was therefore entered as a stratification factor rather than as a covariate, a sensitivity analysis treating disease setting as a covariate gave similar results. The proportional-hazards assumption for the remaining covariates was verified with Schoenfeld residuals. Model discrimination was assessed with Harrell's concordance index.

In a pre-specified subgroup analysis we examined the association between PD-1 exposure and survival within strata defined by age, sex, disease setting, histology, liver metastasis and number of metastatic sites, and tested for interaction using likelihood-ratio tests. A further sensitivity analysis restricted the PD-1 comparison to the 45 patients with initial metastatic disease. In addition, the PD-1 comparison was repeated under two stricter definitions of exposure (PD-1 inhibitor as part of the first-line regimen, and exclusion from the unexposed group of patients who received a PD-1 inhibitor only after progression). Landmark analyses were performed at one, two and three months after the time origin, with patients who had progressed or died before the landmark excluded, and all multivariable models were repeated in the 63 patients with esophageal squamous cell carcinoma. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). Analyses were performed in Python 3.13 using the lifelines and SciPy packages. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies [22]. Two-sided P values below 0.05 were considered statistically significant.

Ethics approval

The study was approved by the Institutional Review Board of the First Affiliated Hospital of Xiamen University (SL-2026KY303-02). Written informed consent was waived given the retrospective design. All data were anonymized before analysis, and the study was conducted in accordance with the Declaration of Helsinki.

Results

Patient and treatment characteristics

Seventy-eight patients were analyzed. Their baseline characteristics are summarized in Table 1. The median age was 62 years (IQR 57-66, range 39-77) and 64 patients (82.1%) were male. Sixty-three patients (80.8%) had squamous cell carcinoma,and the remaining 15 comprised adenocarcinoma or adenosquamous carcinoma (4), neuroendocrine carcinoma (4) and histologically unclassified tumors (7). Forty-six patients (59.0%) had metastatic disease at initial diagnosis, and 32 (41.0%) developed local recurrence after standardized treatment.

At the time recurrent or metastatic disease was diagnosed, lung was the most frequently involved distant organ (33 patients, 42.3%), followed by liver (18 of the 77 patients with available data, 23.4%) and bone (14, 17.9%). Distant lymph node or locoregional-only involvement accounted for the remaining patients. Forty-two patients (53.8%) had two or more involved sites and 36 (46.2%) had a

single involved site. Thirty-four patients (43.6%) received radiotherapy during their treatment course. The median number of first-line systemic cycles delivered was 4 (IQR 2-6).

Of the 73 patients with determinate PD-1 inhibitor exposure, 53 (72.6%) had received a PD-1 inhibitor. The two groups differed in two respects: patients exposed to PD-1 inhibitors were less often treated for recurrent disease (30.2% versus 60.0%, P = 0.030) and less often received radiotherapy (34.0% versus 70.0%, P = 0.008). Age, sex, histology, individual metastatic sites, metastatic burden and the number of involved sites were balanced between the groups (all P > 0.10). 58 patients overall received a PD-1 or PD-L1 inhibitor as part of the first-line regimen, and 5 of the 20 patients classified as unexposed later received a PD-1 inhibitor after progression.

Survival in the overall cohort

Median follow-up for the cohort was 39.4 months. 52 patients (66.7%) had died and 60 had experienced progression or death by the data cutoff. Median OS was 24.4 months (95% CI 17.7-32.6), and the 1-, 2- and 3-year OS probabilities were 75.6% (95% CI 64.5-83.7), 51.9% (95% CI 39.9-62.6) and 34.7% (95% CI 23.4-46.3), respectively. Median PFS was 9.3 months (95% CI 7.5-15.8), with 1-, 2- and 3-year PFS probabilities of 43.6% (95% CI 32.5-54.2), 25.6% (95% CI 16.1-36.2) and 21.7% (95% CI 12.7-32.2) (Fig. 1).

Outcomes according to PD-1 inhibitor exposure

Among the 73 patients with known exposure status, median OS was 24.4 months (95% CI 17.1-32.6) in the PD-1-exposed group and 24.8 months (95% CI 6.9-63.7) in the unexposed group (unadjusted HR 1.12, 95% CI 0.59-2.11; log-rank P = 0.731; Fig. 2A). The corresponding 1- and 2-year OS probabilities were 79.2% and 51.6% versus 70.0% and 50.0%. Median PFS was 11.2 months (95% CI 8.2-17.2) versus 8.6 months (95% CI 2.9-16.8) (unadjusted HR 0.75, 95% CI 0.42-1.33; log-rank P = 0.319; Fig. 2B), with 1-year PFS probabilities of 49.1% and 35.0% respectively. Adjustment for age, sex, liver metastasis, number of metastatic sites and radiotherapy, stratified by disease setting, left these results essentially unchanged (OS HR 1.39, 95% CI 0.63-3.03, P = 0.414; PFS HR 0.78, 95% CI 0.38-1.60, P = 0.506; Table 2 and Fig. 3). Estimates were similar when exposure was restricted to first-line PD-1 use (adjusted OS HR 1.48, 95% CI 0.68-3.23, P = 0.321; adjusted PFS HR 0.85, 95% CI 0.42-1.72, P = 0.645) and when the five patients who received a PD-1 inhibitor only after progression were removed from the unexposed group (53 exposed versus 15 never exposed; adjusted OS HR 1.52, 95% CI 0.58-4.00, P = 0.400; adjusted PFS HR 0.96, 95% CI 0.42-2.21, P = 0.930). Radiotherapy was recorded for any time during the treatment course, not for the first-line period alone. Meanwhile, when we dropping it from the multivariable model changed little (adjusted OS HR 1.10, 95% CI 0.54-2.21 and PFS HR 0.62, 95% CI 0.32-1.21 for PD-1 exposure; adjusted OS HR 2.89, 95% CI 1.40-5.97 and PFS HR 2.40, 95% CI 1.16-4.93 for liver metastasis). In landmark analyses that excluded patients who had progressed or died before the landmark, the PFS estimates remained compatible with no difference (adjusted HR 0.96, 95% CI 0.48-1.93 at 1 month and 1.21, 95% CI 0.55-2.66 at 3 months).

Response to first-line therapy

Objective response to first-line therapy was documented in 26 of 78 patients (33.3%): 1 complete response and 25 partial responses, 30 patients had stable disease and 19 had progressive disease, and

the remaining three had discordant responses across individual lesions and were classified as non-responders. By PD-1 exposure, 23 of 53 exposed patients (43.4%) achieved an objective response, against 1 of 20 unexposed patients (5.0%). Otherwise, two further responders were among the five patients whose exposure status was indeterminate. The difference between the groups was significant (Fisher's exact P = 0.002; Table 1 and Fig. 5B). Individual patient timelines and best responses appear in Fig. 5.

Independent prognostic factors

On univariable analysis, liver metastasis (HR 2.22, 95% CI 1.20-4.11, P = 0.011), involvement of two or more metastatic sites (HR 2.06, 95% CI 1.16-3.63, P = 0.013) and male sex (HR 0.50, 95% CI 0.25-0.99, P = 0.046) were associated with OS, and recurrent disease showed a borderline association (HR 0.60, 95% CI 0.33-1.06, P = 0.079). For PFS, no variable reached the conventional significance threshold, although liver metastasis (HR 1.71, 95% CI 0.95-3.09, P = 0.075) and radiotherapy (HR 1.61, 95% CI 0.97-2.68, P = 0.066) approached it. Age, histological subtype, lung metastasis, bone metastasis and PD-1 exposure were not associated with either endpoint (Table 2).

In the multivariable model stratified by disease setting (n = 73), liver metastasis was the only variable independently associated with both endpoints: OS HR 2.97 (95% CI 1.42-6.19, P = 0.004) and PFS HR 2.38 (95% CI 1.15-4.92, P = 0.019). Involvement of two or more metastatic sites carried a numerically higher risk of death that did not reach significance (OS HR 1.92, 95% CI 0.95-3.87, P = 0.070). Male sex showed a borderline protective association for OS (HR 0.45, 95% CI 0.20-1.02, P = 0.056). With only 14 women in the cohort this estimate is unstable, and we report it as an exploratory observation, not as a conclusion. Age, radiotherapy and PD-1 exposure were not independently associated with either endpoint.

Subgroup and sensitivity analyses

Subgroup analyses of the PD-1 exposure effect are shown in Fig. 4 and Table 3. The association between PD-1 exposure and survival did not differ significantly across strata defined by age, sex, disease setting or histology (all interaction P > 0.30). The only stratum in which the interaction term reached or approached significance was liver metastasis (P = 0.033 for OS and P = 0.052 for PFS). Within this subgroup PD-1 exposure was associated with longer PFS (HR 0.13, 95% CI 0.02-0.76, P = 0.024), but the estimate rested on just two PD-1-unexposed patients with liver metastasis and cannot be interpreted on its own. Those estimates appear in Table 3 only, and we draw no conclusion from them. PD-1 exposure was also associated with longer PFS among patients with two or more metastatic sites (HR 0.42, 95% CI 0.18-0.97, P = 0.043) and, less clearly, among patients with initial metastatic disease (HR 0.46, 95% CI 0.20-1.08, P = 0.073).

In the sensitivity analysis restricted to the 45 patients with initial metastatic disease and known PD-1 exposure, PD-1 exposure was associated with longer PFS after adjustment for age, sex, liver metastasis and metastatic burden (HR 0.36, 95% CI 0.14-0.93, P = 0.034), with no corresponding association with OS (HR 0.92, 95% CI 0.33-2.57, P = 0.881). The number of first-line cycles delivered was not associated with OS (HR 0.96 per cycle, 95% CI 0.87-1.05, P = 0.360) or PFS (HR 0.97, 95% CI 0.88-1.07, P = 0.557).

Sensitivity analyses restricted to the 63 patients with esophageal squamous cell carcinoma gave the same picture as the main analysis. Median OS was 24.8 months and median PFS 10.5 months. Liver metastasis remained the only variable independently associated with OS (adjusted HR 4.18, 95% CI 1.63-10.71, P = 0.003) and showed no independent association with PFS (adjusted HR 1.84, 95% CI 0.81-4.22, P = 0.148). PD-1 exposure was associated with neither OS (adjusted HR 1.33, 95% CI 0.53-3.33) nor PFS (adjusted HR 0.64, 95% CI 0.28-1.46). PD-L1 combined positive score was available for 22 of 78 patients (28.2%) and could be quantified in 20, with a median score of 10 (range <1 to 80) and a score of 10 or higher in 13 of 20 (65.0%). Among these 20 patients the median score was 10.0 in the 11 who achieved an objective response and 20.0 in the 9 who did not (P = 0.541).

Discussion

In this real-world cohort of 78 patients with recurrent or metastatic esophageal cancer, most of whom received PD-1 inhibitor-based first-line therapy, median OS was 24.4 months and median PFS 9.3 months. PD-1 inhibitor exposure was accompanied by a substantially higher objective response rate (43.4% versus 5.0%) but by no difference in either survival endpoint, before or after adjustment for measured confounders. Liver metastasis was the only variable independently associated with both OS and PFS in the multivariable model, and the only factor for which the interaction with PD-1 exposure reached or approached significance.

Median OS in our cohort is considerably longer than the 12.4 to 17.0 months reported in the intention-to-treat populations of the first-line registration trials [6-11]. Both endpoints were measured from the date of diagnosis of recurrent or metastatic disease, when first-line systemic therapy started, so the disease-free interval of patients with recurrence does not distort this comparison. Part of it reflects who was included. We deliberately enrolled patients with primary metastatic disease, and metachronous recurrence, those are under-represented in trials and whose more indolent biology pushes survival estimates upward. Patients with oligometastatic had a median OS of 33.0 months against 17.1 months in those with two or more sites (log-rank P = 0.011). Post-progression therapy was not captured systematically, but 43.6% of patients received local radiotherapy at some point and later-line systemic therapy was available, both of which can lengthen OS beyond what the PFS signal alone would suggest.

The dissociation between response and survival was the most unexpected result of this study, in which PD-1-exposed patients had a much higher objective response rate (43.4% versus 5.0%) yet no detectable improvement in OS or PFS. Confounding by indication is the most likely explanation. PD-1 inhibitors were given at the physician's discretion, and the two groups were not exchangeable: exposed patients were more often treated for initial metastatic disease and less often received radiotherapy. We adjusted for these factors, but unmeasured determinants such as performance status, comorbidity, organ function and PD-L1 expression (recorded for only 22 patients) may have differed between the groups and pushed in the direction opposite to the true treatment effect. The unexposed group was also small (n = 20) and differed systematically from the exposed group. 12 patients (60.0%) were treated for recurrent disease and 14 (70.0%) had received radiotherapy, seven of them meeting both criteria. Exposure misclassification works in the same direction: 5 of the 20 patients classified as unexposed received a PD-1 inhibitor after progression, and removing them from the unexposed group left 15

patients who had never received a checkpoint inhibitor, in whom the PFS difference disappeared almost entirely (adjusted HR 0.96) while the OS estimate moved further from unity (adjusted HR 1.52).

Response rate and survival are not interchangeable endpoints in immunotherapy, where durable responses in a minority can be diluted by early progression in the majority. In this small, non-randomized setting we read our comparative estimates as showing no demonstrable benefit, not as evidence that the drug does nothing. The higher response rate is consistent with the phase 3 evidence and with the direction of effect in the initial metastatic subgroup.

Liver metastasis was the strongest adverse prognostic factor in this cohort, with a median OS of 16.1 months compared with 27.0 months in patients without hepatic involvement, an approximately threefold higher hazard of death and a more than twofold higher hazard of progression after adjustment. It was also the only variable for which the treatment interaction reached or approached significance. These findings fit population-based data showing that hepatic involvement carries one of the shortest median survival times in metastatic esophageal cancer [15], and a wider literature showing that liver metastases impair antitumor immunity throughout the body. In preclinical models, liver metastases siphon activated CD8+ T cells from the circulation and drive them into apoptosis through FasL-expressing monocyte-derived macrophages, leaving a systemic immune desert and resistance to checkpoint blockade. However, liver-directed radiotherapy can reverse this by depleting the responsible myeloid population [20]. Studies have shown that the hepatic microenvironment is also enriched in immunosuppressive myeloid cells, including tumor-associated macrophages and myeloid-derived suppressor cells, which drive T-cell exhaustion and limit the response to PD-1 blockade [23]. However, our clinical data do not reproduce this pattern. The subgroup estimates pointed in the opposite direction to the preclinical model, with a numerically favorable PFS signal in patients with liver involvement and a similar signal in those with a high metastatic burden, but both rested on very few unexposed patients (two and nine, respectively) and are fully compatible with chance. We do not read them as evidence either for or against a site-specific effect of checkpoint blockade. What our data do support is the prognostic, not predictive, importance of hepatic involvement: liver metastasis was the only variable independently associated with both endpoints, and the association was at least as strong in the 63 patients with squamous cell carcinoma (adjusted OS HR 4.18). For that reason, hepatic involvement identifies patients for whom intensification or alternative strategies, including liver-directed local therapies such as radiotherapy or interventional embolization, as well as novel combinations, are the most reasonable next step, and for whom prospective recording of PD-L1 status and myeloid populations would be most informative.

We also find that patients with two or more involved sites had roughly twice the hazard of death as those with a single site, although the association weakened after adjustment. This is in keeping with the oligometastasis paradigm [17] and with evidence from other tumor types that local consolidative therapy may prolong survival in limited metastatic disease [18, 19]. Existing research still cannot provide strong evidence to establish a role for metastasis-directed therapy in oligometastatic esophageal cancer. Our data suggest that patients with a limited burden are those most likely to benefit from such local therapies, and that the question would need to be tested prospectively. The higher-

burden stratum in which PD-1 exposure was associated with a numerically longer PFS contained only nine unexposed patients, so that estimate is unstable and should not be over-interpreted.

The strengths of this study are the complete follow-up data for every patient, pathological confirmation of all diagnoses, systematic capture of metastatic sites and treatment details, and a statistical approach that explicitly addressed the violation of the proportional-hazards assumption by disease setting. There are several limitations to this study. The design is retrospective and single-center, and the sample size is small, particularly the PD-1-unexposed group (n = 20) and subgroups such as patients with liver metastasis or women. Also, the confidence intervals are correspondingly wide, and the multivariable model, with approximately eight events per variable, is exploratory. Adverse events, including immune-related adverse events, were not captured systematically in the source records and were not analyzed, so the safety of checkpoint inhibition in this population could not be assessed. PD-1 exposure was also not randomized, so the analysis is subject to the confounding by indication described above. Residual confounding by performance status, comorbidity, nutritional status, PD-L1 expression, and liver function cannot be excluded, and neither a propensity-score nor an instrumental-variable approach was feasible given this sample size.

In this study, the treatment start date was not recorded as a separate variable, and for a small number of patients the interval between diagnosis and the first response assessment exceeded 8 months, so the exact date on which systemic therapy began may have differed slightly from the date used here. Disease setting was used as a stratification factor, and sensitivity analyses restricted to initial metastatic disease and to squamous cell carcinoma were performed. PD-L1 combined positive score was available for only 28.2% of patients and was not analyzed, and no molecular data were available, so residual confounding by PD-L1 expression cannot be excluded. Treatment regimens were heterogeneous and changed over the accrual period as the standard of care evolved, and post-progression therapies were not recorded systematically. Some patients received chemoradiotherapy with curative intent, which is not directly comparable to palliative systemic therapy, and radiotherapy was modelled as a time-fixed covariate recorded at any point during the treatment course, so a limited immortal-time bias for that covariate cannot be excluded. Though omitting radiotherapy from the model left the estimates for PD-1 exposure and liver metastasis essentially unchanged. Five patients treated within blinded trials had an indeterminate exposure status and were excluded from the comparative analyses, and one patient had a recorded progression-free survival exceeding overall survival by seven days, an internal inconsistency in the source records that we chose to report rather than to adjust. Our findings were not externally validated and require confirmation in independent, ideally multi-center and prospectively collected cohorts.

Conclusions

In this real-world cohort of patients with recurrent or metastatic esophageal cancer, median overall survival reached 24.4 months and median PFS approached 9.3 months, both measured from the start of first-line therapy for advanced disease and both longer than the benchmarks reported in first-line registration trials. PD-1 inhibitor exposure raised the objective response rate substantially but left overall and progression-free survival unchanged after adjustment. In a non-randomized comparison this dissociation most likely reflects confounding by indication, not a genuine absence of clinical

activity. Liver metastasis was the strongest independent adverse prognostic factor for both endpoints and identifies the subgroup in greatest need of new treatment options. Prospective studies are still needed, with systematic capture of PD-L1 status, performance status and immune-related adverse events and with adequate representation of PD-1-unexposed patients, to establish how much prognostic and predictive value clinical variables retain now that immunotherapy is standard.

List of abbreviations

AE: adverse event; CI: confidence interval; CPS: combined positive score; CR: complete response; ESCC: esophageal squamous cell carcinoma; HR: hazard ratio; IQR: interquartile range; M1: distant metastasis; OS: overall survival; PD: progressive disease; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Xiamen University (SL-2026KY303-02). Because of the retrospective design, the requirement for written informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable.

Availability of data and materials. The datasets generated and analyzed during the current study are not publicly available because they contain identifiable patient information, but de-identified data are available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. ZR and DYQ contributed equally to this work. ZR designed the study, performed the statistical analysis and drafted the manuscript. DYQ collected and verified the clinical data. LJC conceived and supervised the study and critically revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of the study population

Characteristic	All patients (n = 78)	PD-1 (n = 53)	No PD-1 (n = 20)	P
Age, years, median (IQR)	62.0 (57.0-66.0)	62.0 (58.0-66.0)	62.5 (51.8-66.5)	0.480
Age ≥ 65 years, n (%)	25 (32.1)	17 (32.1)	6 (30.0)	1.000
Male sex, n (%)	64 (82.1)	45 (84.9)	16 (80.0)	0.725
Recurrent disease (vs initial M1), n (%)	32 (41.0)	16 (30.2)	12 (60.0)	0.030
Squamous histology, n (%)	63 (80.8)	45 (84.9)	13 (65.0)	0.101
Liver metastasis, n (%)	18 (23.4)	15 (28.3)	2 (10.0)	0.128
Lung metastasis, n (%)	33 (42.3)	26 (49.1)	5 (25.0)	0.110
Bone metastasis, n (%)	14 (17.9)	11 (20.8)	2 (10.0)	0.493
≥ 2 metastatic sites, n (%)	42 (53.8)	30 (56.6)	9 (45.0)	0.436
Radiotherapy received, n (%)	34 (43.6)	18 (34.0)	14 (70.0)	0.008
Metastatic sites, median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	1.0 (1.0-2.0)	0.342
Objective response (CR/PR), n (%)	26 (33.3)	23 (43.4)	1 (5.0)	0.002
Deaths, n (%)	52 (66.7)	34 (64.2)	14 (70.0)	0.784

Data are median (interquartile range) or n (%). The All patients column includes all 78 patients; the PD-1 and no-PD-1 columns include the 73 patients with determinate exposure status and therefore do not sum to the All patients column. Percentages are calculated on the number of patients with available data. P values were calculated with Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Objective response was defined as complete or partial response to first-line therapy; two of the five patients with indeterminate exposure status also

achieved an objective response and are counted only in the All patients column. CR, complete response; IQR, interquartile range; M1, distant metastasis; PD-1, programmed cell death protein 1; PR, partial response.

Table 2. Univariable and multivariable Cox regression analyses for overall survival and progression-free survival

Endpoint	Variable	Univariable HR (95% CI)	Univariable P	Multivariable HR (95% CI)	Multivariable P
Overall survival	Age (per 10 years)	1.05 (0.71-1.53)	0.815	0.88 (0.55-1.39)	0.577
Overall survival	Male (vs female)	0.50 (0.25-0.99)	0.046	0.45 (0.20-1.02)	0.056
Overall survival	Recurrent (vs initial M1)	0.60 (0.33-1.06)	0.079	-	-
Overall survival	Squamous (vs non-squamous)	0.82 (0.42-1.60)	0.564	-	-
Overall survival	Liver metastasis	2.22 (1.20-4.11)	0.011	2.97 (1.42-6.19)	0.004
Overall survival	Lung metastasis	1.31 (0.76-2.26)	0.339	-	-
Overall survival	Bone metastasis	1.50 (0.72-3.12)	0.277	-	-
Overall survival	≥ 2 metastatic sites	2.06 (1.16-3.63)	0.013	1.92 (0.95-3.87)	0.070
Overall survival	Radiotherapy	1.32 (0.77-2.28)	0.318	1.57 (0.78-3.16)	0.202
Overall survival	PD-1 use	1.12 (0.59-2.11)	0.731	1.39 (0.63-3.03)	0.414
Progression-free survival	Age (per 10 years)	1.02 (0.69-1.53)	0.904	0.94 (0.61-1.44)	0.768
Progression-free survival	Male (vs female)	0.59 (0.31-1.12)	0.108	0.64 (0.30-1.36)	0.246
Progression-free survival	Recurrent (vs initial M1)	1.08 (0.65-1.82)	0.758	-	-
Progression-	Squamous (vs	0.66 (0.36-	0.189	-	-

free survival	non-squamous)	1.23)			
Progression-free survival	Liver metastasis	1.71 (0.95-3.09)	0.075	2.38 (1.15-4.92)	0.019
Progression-free survival	Lung metastasis	1.12 (0.67-1.86)	0.666	-	-
Progression-free survival	Bone metastasis	1.28 (0.65-2.55)	0.477	-	-
Progression-free survival	≥ 2 metastatic sites	1.36 (0.81-2.28)	0.249	1.20 (0.64-2.24)	0.577
Progression-free survival	Radiotherapy	1.61 (0.97-2.68)	0.066	1.66 (0.89-3.08)	0.109
Progression-free survival	PD-1 use	0.75 (0.42-1.33)	0.322	0.78 (0.38-1.60)	0.506

The multivariable model included age, sex, liver metastasis, number of metastatic sites, radiotherapy and PD-1 use, and was stratified by disease setting (initial metastatic vs recurrent); it was fitted in the 73 patients with known PD-1 exposure (48 deaths and 55 progression or death events). A dash indicates that the variable was not retained in the multivariable model. CI, confidence interval; HR, hazard ratio; M1, distant metastasis; PD-1, programmed cell death protein 1.

Table 3. Subgroup analysis of the association between PD-1 inhibitor exposure and survival

Endpoint	Subgroup	n	HR (95% CI)	P	P for interaction
Overall survival	Overall	73	1.12 (0.59-2.11)	0.731	-
Overall survival	Age < 65 years	50	1.04 (0.50-2.18)	0.910	0.927
Overall survival	Age ≥ 65 years	23	1.49 (0.40-5.51)	0.547	
Overall survival	Male	61	1.15 (0.56-2.35)	0.701	0.366
Overall survival	Female	12	1.41 (0.34-5.88)	0.636	
Overall survival	initial M1	45	1.08 (0.44-2.67)	0.861	0.502
Overall	Recurrent	28	1.03 (0.39-	0.953	

survival			2.72)		
Overall survival	Squamous	58	1.13 (0.52-2.44)	0.759	0.854
Overall survival	Non-squamous	15	1.25 (0.38-4.14)	0.718	
Overall survival	Liver metastasis present	17	0.40 (0.08-1.92)	0.254	0.033
Overall survival	Liver metastasis absent	56	1.10 (0.53-2.27)	0.797	
Overall survival	≥ 2 sites	39	1.21 (0.48-3.07)	0.684	0.145
Overall survival	1 site	34	0.94 (0.38-2.32)	0.900	
Progression-free survival	Overall	73	0.75 (0.42-1.33)	0.322	-
Progression-free survival	Age < 65 years	50	0.72 (0.36-1.44)	0.352	0.657
Progression-free survival	Age ≥ 65 years	23	0.88 (0.31-2.52)	0.819	
Progression-free survival	Male	61	0.67 (0.35-1.28)	0.224	0.313
Progression-free survival	Female	12	1.23 (0.31-4.85)	0.763	
Progression-free survival	initial M1	45	0.46 (0.20-1.08)	0.073	0.487
Progression-free survival	Recurrent	28	1.06 (0.45-2.53)	0.892	
Progression-free survival	Squamous	58	0.62 (0.31-1.25)	0.182	0.238
Progression-free survival	Non-squamous	15	1.71 (0.54-5.46)	0.365	
Progression-free survival	Liver metastasis present	17	0.13 (0.02-0.76)	0.024	0.052

Progression-free survival	Liver metastasis absent	56	0.71 (0.37-1.36)	0.302	
Progression-free survival	≥ 2 sites	39	0.42 (0.18-0.97)	0.043	0.165
Progression-free survival	1 site	34	1.12 (0.48-2.58)	0.793	

Hazard ratios are unadjusted and were estimated within each subgroup; P values are from Wald tests. P values for interaction were derived from likelihood-ratio tests comparing models with and without the PD-1 by subgroup interaction term. The subgroup of patients with liver metastasis contained only two PD-1-unexposed patients, and the corresponding estimates are not interpretable in isolation. CI, confidence interval; HR, hazard ratio; M1, distant metastasis; PD-1, programmed cell death protein 1.

Figure legends

Fig. 1 Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival in the overall cohort (n = 78). Shaded areas represent 95% confidence bands and plus signs denote censored observations. Numbers at risk are shown beneath each panel.

Fig. 2 Overall survival (A) and progression-free survival (B) according to PD-1 inhibitor exposure, in the 73 patients with known exposure status; five patients enrolled in blinded randomized trials were excluded. Hazard ratios are unadjusted and P values are from two-sided log-rank tests.

Fig. 3 Forest plot of univariable and multivariable Cox regression analyses for overall survival (A) and progression-free survival (B). The multivariable model included age (per 10 years), sex, liver metastasis, number of metastatic sites, radiotherapy and PD-1 exposure, and was stratified by disease setting (initial metastatic vs recurrent).

Fig. 4 Subgroup analyses of the association between PD-1 inhibitor exposure and overall survival (A) and progression-free survival (B). Hazard ratios are unadjusted and were estimated within each subgroup; the column on the right shows P values for interaction.

Fig. 5 (A) Individual patient timelines ordered by overall survival. Solid bars denote progression-free survival, pale bars post-progression survival, crosses progression, dots death and arrowheads censoring. (B) Best overall response to first-line therapy according to PD-1 inhibitor exposure.

Figures

Fig. 1

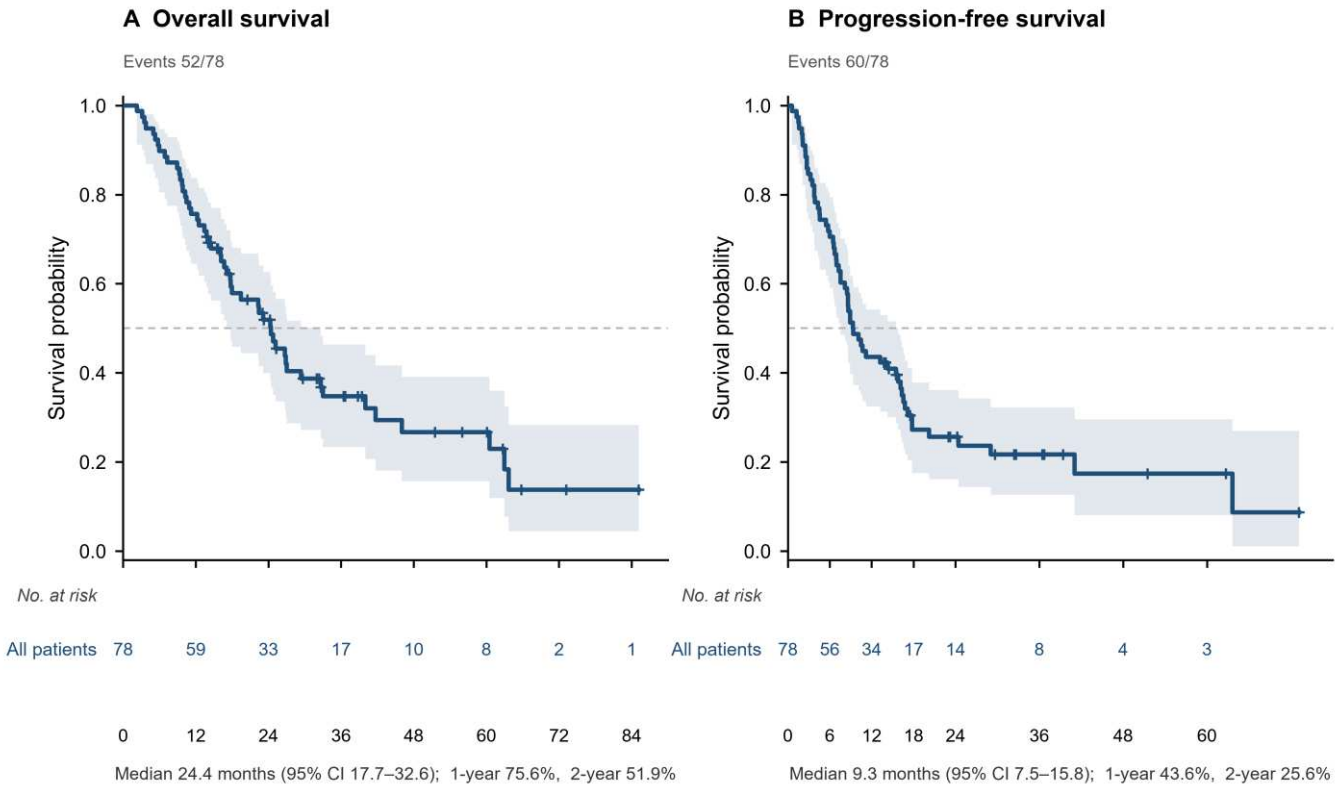


Fig. 2

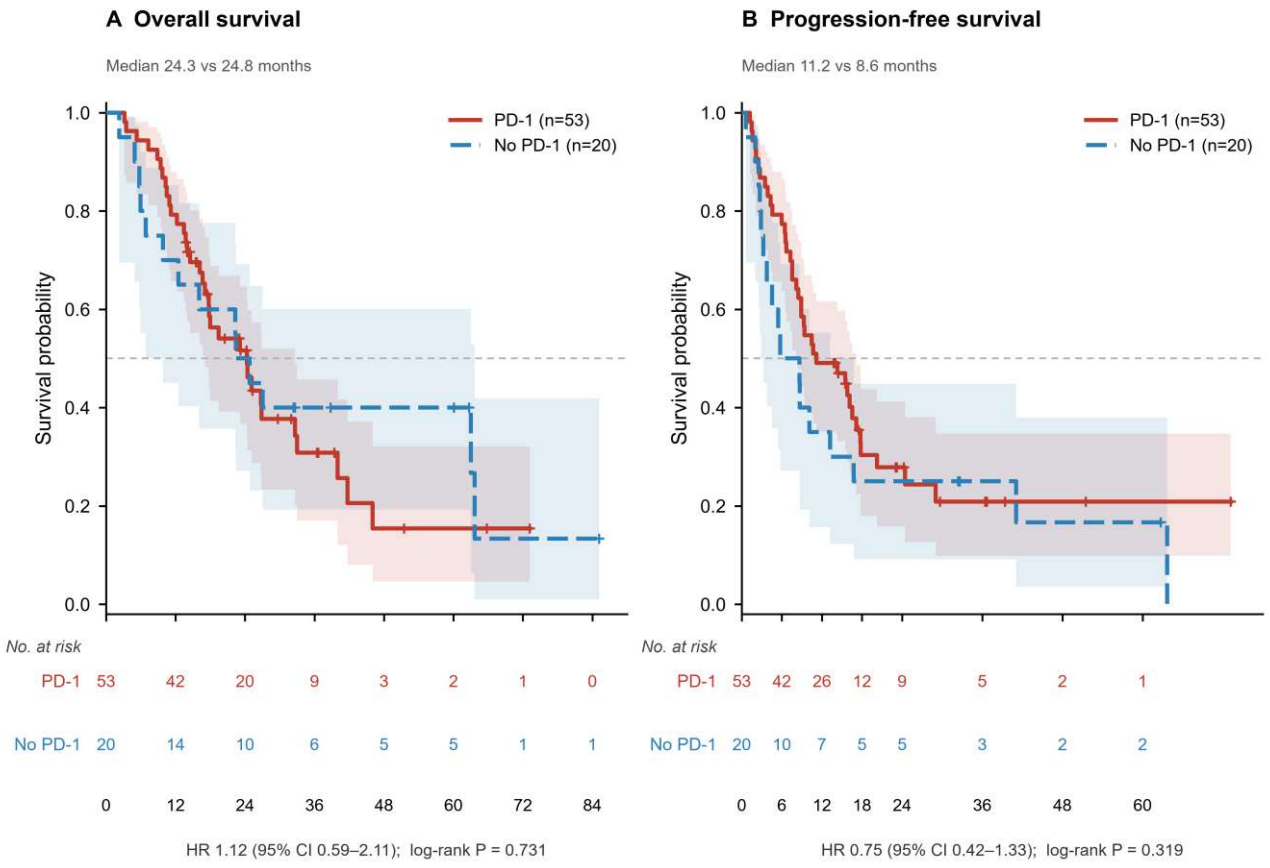
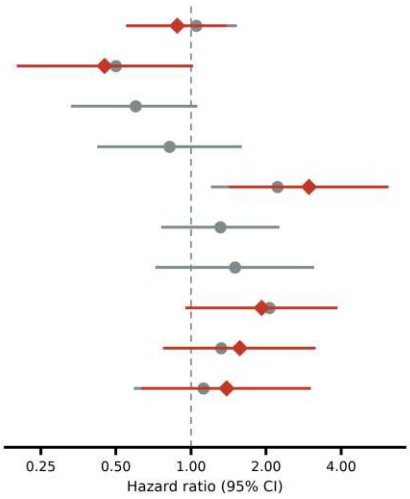

A Overall survival
Median 24.3 vs 24.8 months
PD-1 (n=53)
No PD-1 (n=20)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
No. at risk
PD-1 53 42 20 9 3 2 1 0
No PD-1 20 14 10 6 5 5 1 1
0 12 24 36 48 60 72 84
HR 1.12 (95% CI 0.59–2.11); log-rank P = 0.731
B Progression-free survival
Median 11.2 vs 8.6 months
PD-1 (n=53)
No PD-1 (n=20)
Survival probability
No. at risk
PD-1 53 42 26 12 9 5 2 1
No PD-1 20 10 7 5 5 3 2 2
0 6 12 18 24 36 48 60
HR 0.75 (95% CI 0.42–1.33); log-rank P = 0.319

Fig. 3

A **Overall survival**

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Age (per 10 years)	1.05 (0.71–1.53)	0.815	**0.88 (0.55–1.39)**	**0.577**
Male (vs female)	0.50 (0.25–0.99)	0.046	**0.45 (0.20–1.02)**	**0.056**
Recurrent (vs de-novo M1)	0.60 (0.33–1.06)	0.079	—	—
SCC (vs non-SCC)	0.82 (0.42–1.60)	0.564	—	—
Liver metastasis	2.22 (1.20–4.11)	0.011	**2.97 (1.42–6.19)**	**0.004**
Lung metastasis	1.31 (0.76–2.26)	0.339	—	—
Bone metastasis	1.50 (0.72–3.12)	0.277	—	—
≥2 metastatic sites	2.06 (1.16–3.63)	0.013	**1.92 (0.95–3.87)**	**0.070**
Radiotherapy	1.32 (0.77–2.28)	0.318	**1.57 (0.78–3.16)**	**0.202**
PD-1 use	1.12 (0.59–2.11)	0.731	**1.39 (0.63–3.03)**	**0.414**



B **Progression-free survival**

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Age (per 10 years)	1.02 (0.69–1.53)	0.904	**0.94 (0.61–1.44)**	**0.768**
Male (vs female)	0.59 (0.31–1.12)	0.108	**0.64 (0.30–1.36)**	**0.246**
Recurrent (vs de-novo M1)	1.08 (0.65–1.82)	0.758	—	—
SCC (vs non-SCC)	0.66 (0.36–1.23)	0.189	—	—
Liver metastasis	1.71 (0.95–3.09)	0.075	**2.38 (1.15–4.92)**	**0.019**
Lung metastasis	1.12 (0.67–1.86)	0.666	—	—
Bone metastasis	1.28 (0.65–2.55)	0.477	—	—
≥2 metastatic sites	1.36 (0.81–2.28)	0.249	**1.20 (0.64–2.24)**	**0.577**
Radiotherapy	1.61 (0.97–2.68)	0.066	**1.66 (0.89–3.08)**	**0.109**
PD-1 use	0.75 (0.42–1.33)	0.322	**0.78 (0.38–1.60)**	**0.506**

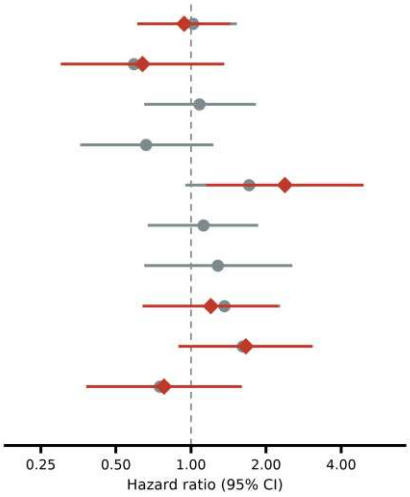
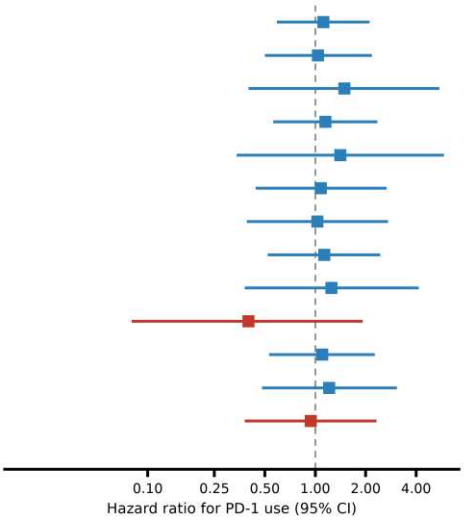


Fig. 4

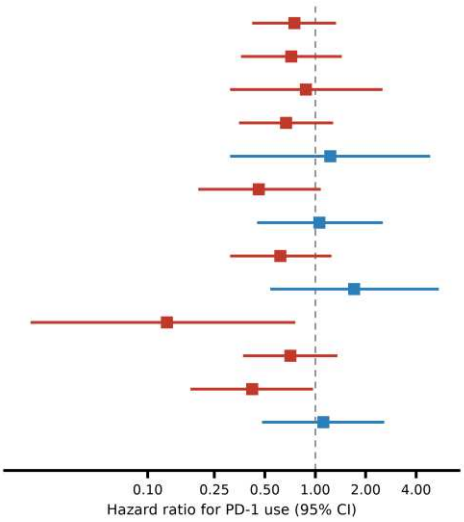
A **Overall survival**

Subgroup	n	Events	HR (95% CI)
Overall	73	48	1.12 (0.59–2.11)
Age <65	50	35	1.04 (0.50–2.18)
Age ≥65	23	13	1.49 (0.40–5.51)
Male	61	39	1.15 (0.56–2.35)
Female	12	9	1.41 (0.34–5.88)
De-novo M1	45	31	1.08 (0.44–2.67)
Recurrent	28	17	1.03 (0.39–2.72)
SCC	58	37	1.13 (0.52–2.44)
Non-SCC	15	11	1.25 (0.38–4.14)
Liver met +	17	14	0.40 (0.08–1.92)
Liver met −	56	34	1.10 (0.53–2.27)
≥2 sites	39	26	1.21 (0.48–3.07)
1 site	34	22	0.94 (0.38–2.32)



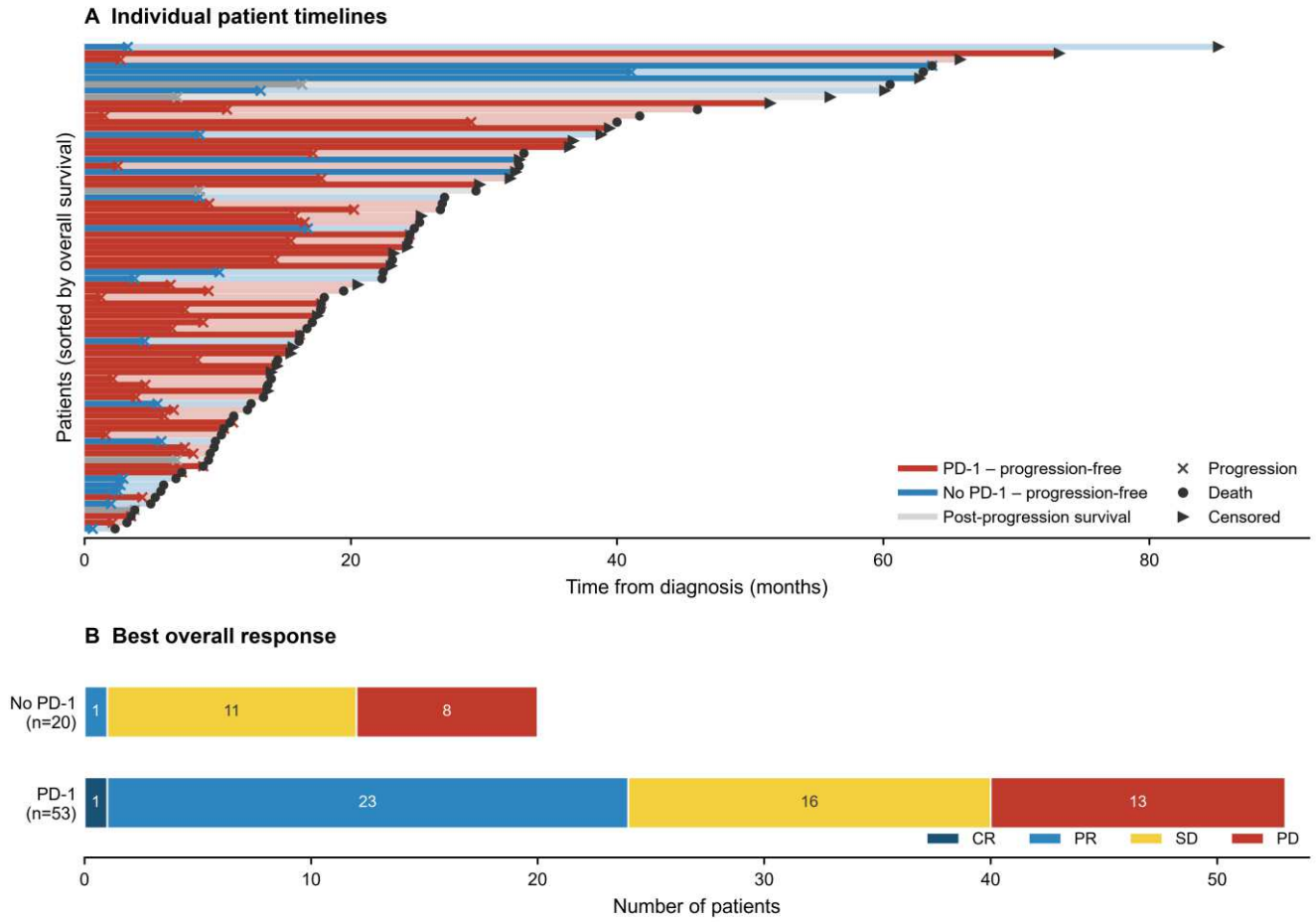
B **Progression-free survival**

Subgroup	n	Events	HR (95% CI)
Overall	73	55	0.75 (0.42–1.33)
Age <65	50	38	0.72 (0.36–1.44)
Age ≥65	23	17	0.88 (0.31–2.52)
Male	61	45	0.67 (0.35–1.28)
Female	12	10	1.23 (0.31–4.85)
De-novo M1	45	34	0.46 (0.20–1.08)
Recurrent	28	21	1.06 (0.45–2.53)
SCC	58	42	0.62 (0.31–1.25)
Non-SCC	15	13	1.71 (0.54–5.46)
Liver met +	17	15	0.13 (0.02–0.76)
Liver met −	56	40	0.71 (0.37–1.36)
≥2 sites	39	29	0.42 (0.18–0.97)
1 site	34	26	1.12 (0.48–2.58)



HR < 1 (favours PD-1) HR > 1 (favours no PD-1)

Fig. 5


A Individual patient timelines
Patients (sorted by overall survival)
PD-1 – progression-free
No PD-1 – progression-free
Post-progression survival
Progression
Death
Censored
0
20
40
60
80
Time from diagnosis (months)
B Best overall response
No PD-1 (n=20)
1
11
8
PD-1 (n=53)
1
23
16
13
CR
PR
SD
PD
0
10
20
30
40
50
Number of patients