Effect of baseline cancer pain on the efficacy of immunotherapy in lung cancer patients

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Background: Cancer pain is a common symptom in cancer patients. However, few reports have evaluated the effect of baseline cancer pain on the efficacy of immunotherapy in lung cancer patients. The aim of this retrospective study is to reveal the effect of baseline cancer pain on the prognosis of lung cancer patients receiving immunotherapy.

Methods: We retrospectively reviewed the medical records of lung cancer patients who received immunotherapy at Zhejiang Cancer Hospital and were included 280 patients with or without baseline cancer pain. Propensity score matching (PSM) was used to minimize potential selection bias. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier estimation and log-rank tests. Cox proportional hazard regression analysis was performed to identify factors associated with survival independence.

Results: The median PFS and OS of the patients with baseline cancer pain were significantly shorter than that of patients without baseline cancer pain (PFS: 3.1 *vs.* 6.5 months, P=0.001; OS: 16.5 *vs.* 31.2 months, P<0.001). PSM also included 27 patients with or without breakthrough pain. Patients with breakthrough pain had significantly shorter median PFS and OS than those without breakthrough pain (PFS: 1.9 *vs.* 4.2 months, P=0.001; OS: 9.9 *vs.* 18.7 months, P=0.012). Cox analysis results implicated breakthrough pain as an independent prognostic factor for immunotherapy.

Conclusions: Baseline cancer pain is a negative prognostic factor for lung cancer patients receiving immunotherapy. Patients with baseline cancer pain may have a worse survival prognosis if they develop breakthrough pain.

Keywords: Baseline cancer pain; breakthrough pain; immune checkpoint inhibitors (ICIs); efficacy; lung cancer

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Introduction

Cancer pain is one of the most prevalent signs of the disease and one of the consequences that patients fear the most (1). There is growing evidence in oncology that quality of life and survival are associated with early and effective palliative care, including pain management (2). The incidence of pain in patients with newly diagnosed and advanced cancer is approximately 24% to 60% and approximately 62% to 86%, respectively. The pain is severe in one-third of the patients (1,3-5). Previous studies (6,7) stated that 90% of individuals with lung cancer will experience cancer pain during the illness, which will reduce immunity (8).

Recently, immune checkpoint inhibitors (ICIs) have been rapidly developed. ICIs can activate the anti-cancer function of depleted T cells and have substantial survival benefits in a variety of malignant tumor patients (9,10), with a significant effect in treating lung cancer. Widely used ICIs mainly include inhibitors of cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed death-ligand 1 (PD-L1) (11). ICIs are promising immunotherapy drugs that can achieve satisfactory efficacy for different tumor types, different treatment pathways, different drug combinations, and different treatment regimens (12). However, only 20% to 30% of patients benefit from ICI monotherapy (13,14). Even in melanoma patients, who display the highest

response rates to ICI, only a few patients achieve lasting remission, and 60% to 70% of patients do not have any discernible response to anti-PD-1 therapy, which has the effect of immune tolerance. In addition, other factors affect immunotherapy, such as toxic superposition of non-small cell lung cancer (NSCLC), drug toxicity, special population, and other problems (9,10,15,16). The efficacy of ICIs in studies of the Eastern Cooperative Oncology Group (ECOG) is reportedly affected by a variety of factors, such as PD-L1 expression, smoking history, radiotherapy, ECOG performance status (PS) (17-20), and concomitant medications (21). However, no reports have assessed whether baseline cancer pain has an effect on survival outcomes among patients with lung cancer who received ICIs.

The aim of this retrospective study was to determine the effect of baseline cancer pain on the prognosis of individuals with lung cancer who were treated with ICIs. In addition, we explored the impact of breakthrough pain on prognosis. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-375/rc).

Methods

Patients

The medical records of patients with persistent lung cancer who received ICI treatment in Zhejiang Cancer Hospital from January 1, 2000, to December 31, 2022, were retrospectively evaluated. We included 280 lung cancer patients. All patients met the following criteria: (I) 18 years of age or older; (II) tumor stage IIIB or IV lung cancer according to the American Joint Committee on Cancer (AJCC) eighth edition of tumor-node-metastasis (TNM) staging of lung cancer; (III) baseline cancer pain in cancer pain group and no baseline cancer pain in non-cancer pain group; and (V) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, having at least one lesion that could be radiographically measured. Patients with non-advanced lung cancer and those with incomplete information were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee at Zhejiang Cancer Hospital (No. IRB-2023-120) and individual consent for this retrospective analysis was waived.

Highlight box

Key findings
- Baseline cancer pain affects the efficacy of immune checkpoint inhibitors, and eruptive pain is an independent prognostic factor for immunotherapy.

What is known and what is new?
- Immunotherapy has significantly improved the prognosis of lung cancer. However, it is unclear whether baseline cancer pain has an effect on immunotherapy.
- In addition to evaluating the effect of baseline cancer pain on immunotherapy, we analyzed for the first time the impact of breakthrough pain on immunotherapy outcomes.

What is the implication, and what should change now?
- Survival time is shorter with immunotherapy in patients with baseline cancer pain, and outbreak pain affects the prognosis of immunotherapy. Larger cohort studies are needed to further investigate their effectiveness.

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Assessments

Baseline cancer pain was defined as a type of tumor-related pain present in the initiation phase of immunotherapy. The pain intensity of patients was assessed on a digital rating scale [i.e., Numerical Rating Scale (NRS) 0–10]. We provided each patient with a digital rating scale at each visit to help us understand when and how far their pain occurred. Cancer pain was divided into three categories: somatic pain (37.5%), neuropathic pain (31.3%), visceral pain (8.3%), and mixed pain (22.9%) (Table S1).

RECIST version 1.1 criteria were used to determine progression-free survival (PFS) (defined as the duration between initiation of immunotherapy and disease progression or all-cause mortality) and overall survival (OS) (measured from the onset of diagnosis of advanced cancer to death, loss to follow-up, or the date of last follow-up, whichever occurred first). Secondary endpoints included overall response rate (ORR), frequency of patients who obtained partial response (PR) or complete response (CR) at two consecutive evaluations at least 4 weeks apart. The responses to immunotherapy were also determined using RECIST version 1.1. Patients were followed up until December 31, 2022.

Statistical analyses

The analyses were performed using Solutions Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 9 (GraphPad Software, Inc., San Diego, CA, USA). Propensity score matching (PSM) was performed to limit potential selection bias. A logistic regression model was established based on the following covariates to calculate the propensity score: age, sex, ECOG PS, presence or absence of lung-related surgery, histological type, smoking history, PD-L1 expression, combined medication, line of treatments with ICIs, adverse reactions, and types of ICIs. Patients with baseline cancer pain were matched with patients without baseline cancer pain using a 1:1 Greedy algorithm (caliper =0.2). Differences in continuous and categorical variables were evaluated with the Wilcoxon rank-sum and Fisher's exact test, respectively. Survival curves were estimated using the Kaplan-Meier method. Cox regression analysis was employed to compute the hazard ratio (HR) and 95% confidence interval (CI) for PFS and OS. A P value of <0.05 was considered statistically significant.

Results

Patient characteristics

The 280 patients identified in this research included 133 with baseline cancer pain and 147 without baseline cancer pain. In the cancer pain group, this pain was mild (NRS: 1–3) in 47 patients (35.3%) and moderate to severe (NRS ≥4) in 86 patients (64.7%). After PSM, 48 patients with baseline cancer pain and 48 patients without baseline cancer pain were selected. Before matching, in the group with baseline cancer pain, fewer patients were positive for PD-L1 (17.3% vs. 31.3%; P=0.011), PS was worse (PS ≥2 patients: 21.8% vs. 2.7%; P<0.001), and fewer patients had undergone lung-related surgery (20.3% vs. 64.6%; P<0.001), compared to patients without baseline cancer pain. Immunotherapy regimens also differed in these patients (immunochemotherapy, 38.3% vs. 53.7%; immunotherapy plus targeted therapy, 13.6% vs. 15.0%; immune monotherapy, 48.1% vs. 31.3%). PSM was performed to balance confounding covariates between the two groups. The resulting two groups of patients were matched age, sex, ECOG PS, presence or absence of lung-related surgery, histological type, smoking history, PD-L1 expression, combined medication, lines of ICI treatments, types of ICIs, and adverse reactions (Table 1).

Of the 133 patients with baseline cancer pain, 61 developed breakthrough pain during immunotherapy. PSM was used to match patients with breakthrough pain. After matching, 27 patients with breakthrough pain and 27 patients without breakthrough pain were selected. Most patients with baseline cancer pain had ≤2 pain sites (93.8%), a small number of patients felt pain at a level ≥3 (6.3%), and 19 patients (39.6%) experienced breakthrough pain during cancer pain (Table S1).

Relationship between pain and efficacy

CR was achieved in none of the 48 patients with baseline cancer pain and in one (2.1%) of the patients without baseline cancer pain. PR was achieved in seven (14.6%) of the 48 patients with baseline cancer pain and 15 (31.3%) of the patients without baseline cancer pain. The ORR of lung cancer patients with baseline cancer pain was significantly shorter than that of lung cancer patients without baseline cancer pain (14.6% vs. 33.3%; P=0.031; Table S2).

The median PFS of lung cancer patients with baseline cancer pain was significantly shorter than that of lung

Table 1 Patient characteristics before and after PSM

Characteristics	Before PSM			After PSM		
	Cancer pain (+) (n=133)	Cancer pain (–) (n=147)	P value	Cancer pain (+) (n=48)	Cancer pain (–) (n=48)	P value
Age (years)			0.35			1.000
≥65	38	49		16	16	
<65	95	98		32	32	
PS			<0.001*			1.000
0–1	104	143		44	45	
2–4	29	4		4	3	
Sex			0.063			0.378
Male	110	108		31	35	
Female	23	39		17	13	
Smoking history			0.135			0.414
Yes	97	95		22	26	
No	36	52		26	22	
ICIs line of treatments			0.898			0.145
1	45	50		10	13	
2	50	60		27	16	
3	26	24		8	13	
>3	12	13		3	6	
Histological types			0.789			0.268
SCC	13	13		2	6	
Non-SCC	120	134		46	42	
PD-L1 expression			0.011*			0.601
Positive	23	46		10	8	
Negative	110	101		38	40	
EGFR/ALK mutation			0.124			1.000
Positive	24	16		10	9	
Negative	109	131		38	39	
Lung surgery			<0.001*			0.838
Yes	27	95		25	26	
No	106	52		23	22	
Combined medication			0.013*			0.172
ICIs + chemotherapy	51	79		15	24	
ICIs + targeting	18	22		9	7	
ICIs	64	46		24	17	

Table 1 *(continued)*

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Table 1 *(continued)*

Characteristics	Before PSM			After PSM		
	Cancer pain (+) (n=133)	Cancer pain (–) (n=147)	P value	Cancer pain (+) (n=48)	Cancer pain (–) (n=48)	P value
Adverse reactions			0.058			1.000
Yes	59	49		18	18	
No	74	98		30	30	
ICIs types			0.931			0.627
PD-1	111	125		39	40	
PD-L1	15	15		4	6	
CTLA-4	4	5		2	1	
NE	3	2		3	1	

*, P<0.05. PSM, propensity score matching; PS, performance status; ICIs, immune checkpoint inhibitors; SCC, squamous cell carcinoma; PD-L1, programmed cell death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-1, programmed cell death 1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; NE, not evaluable.
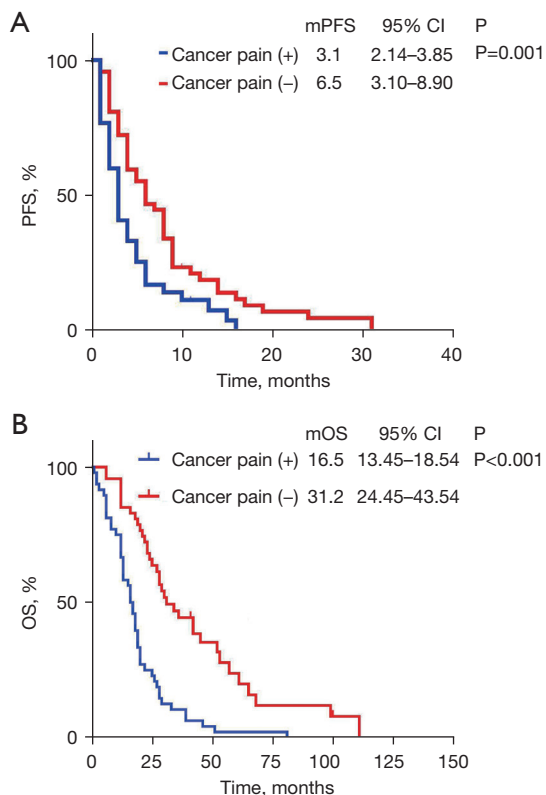

Figure 1 Survival analysis of 96 patients with lung carcinoma treated with immunotherapy after propensity score matching. (A) PFS curves of patients with or without baseline cancer pain. (B) OS curves of patients with or without baseline cancer pain. CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival.

cancer patients without baseline cancer pain (3.1, 95% CI: 2.14–3.85 *vs.* 6.5, 95% CI: 3.10–8.90 months; P=0.001; *Figure 1A*). The median OS of lung cancer patients with baseline cancer pain was significantly shorter than that of lung cancer patients without baseline cancer pain (16.5, 95% CI: 13.45–18.54 *vs.* 31.2, 95% CI: 24.45–43.54 months; P<0.001; *Figure 1B*).

The median PFS of patients with baseline cancer pain who presented with breakthrough pain was significantly shorter than that of patients with baseline cancer pain without breakthrough pain (1.9, 95% CI: 1.31–2.63 *vs.* 4.2, 95% CI: 2.60–5.79 months; P=0.001; *Figure 2A*).

The median OS of patients with baseline cancer pain who presented with breakthrough pain was significantly shorter than that of patients with cancer pain without breakthrough pain (9.9, 95% CI: 6.85–11.14 *vs.* 18.7, 95% CI: 11.21–24.78 months; P=0.012; *Figure 2B*).

Survival outcomes according to patient characteristics

In univariable analyses, several features displayed meaningful P values. These included age, PS value, lung surgery, EGFR/ALK mutation positive, PD-L1 expression, lines of ICI treatments, medication with combined ICIs, and breakthrough pain (*Table 2*). Multivariate analysis performed on these data revealed that breakthrough pain, age, and lines of ICI treatments are independent prognostic factor for OS (HR =2.296, 95% CI: 1.215–4.336, P=0.010; HR =0.533, 95% CI: 0.289–0.984, P=0.044; HR =0.165,
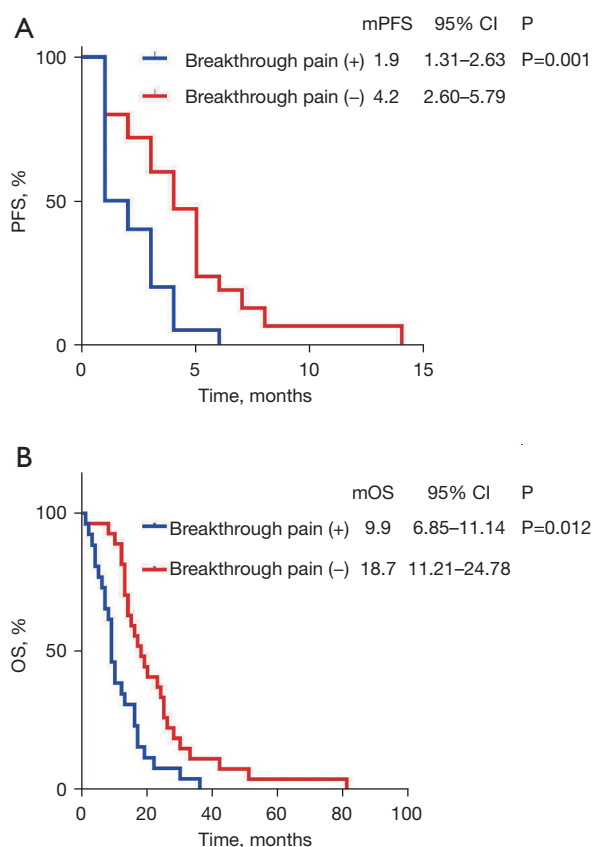
Figure 2 Survival analysis of 27 patients with lung carcinoma with breakthrough pain after propensity score matching. (A) PFS curves of patients with or without breakthrough pain. (B) OS curves of patients with or without breakthrough pain. CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival.

95% CI: 0.073–0.372, P<0.001, respectively; *Figure 3*), but not with PFS.

Discussion

Our results demonstrate that baseline cancer pain is a negative prognostic factor for lung cancer patients receiving immunotherapy. Patients with baseline cancer pain may have a worse survival prognosis if they develop breakthrough pain. As far as we know, this is the first research to assess the result of baseline cancer pain on survival in lung cancer patients treated with ICIs. Furthermore, this is also the initial investigation of the impact of breakthrough cancer pain on survival among patients with lung cancer who received ICIs.

People with cancer pain often use opioids and nonsteroidal drugs for pain relief. According to the treatment guidelines for cancer pain, the drugs used to relieve mild cancer pain are non-steroidal anti-inflammatory drugs (NSAIDs), with opioids used to treat moderate to severe cancer pain (22). It has been reported that opioid users respond less to ICI treatment than non-opioid users [odds ratio (OR) =0.49, 95% CI: 0.37–0.65; P<0.001] (23). Taniguchi *et al.* reported that patients with opioid use displayed significantly shorter median PFS (1.17 *vs.* 2.07 months, P=0.002) and OS (4.20 *vs.* 9.57 months, P=0.018) than patients without opioid use (24). Miura *et al.* (25) further investigated the effect of concomitant drugs on clinical outcomes in patients with advanced NSCLC with ICIs. The authors identified opioid use as an independent risk factor (time-to-treatment failure: HR =1.39, P=0.021, OS: HR =1.54; P=0.007), and described that patient who used opioids had a shorter median OS (5.7 *vs.* 15.9 months; P<0.001). NSAIDs were shown to have an impact on OS and PFS of patients who received ICI treatment in one study (26), while other studies did not discover a meaningful connection between NSAIDs and ICIs concerning OS and PFS (23,27). Our study featured a slight difference in survival time; the OS we observed was longer than in other studies. The difference is mainly due to two factors. First, our OS was defined as the time from the onset of late diagnosis to the time of death, while OS was previously defined as the time from the start of initiation of the immune drug to the death of the patient. Second, our study included a variety of immunotherapy regimens, including immunotherapy combinations. Cancer pain has an immunosuppressive effect (8,28). Animal studies provide direct evidence that natural killer (NK) cells play a key role in controlling metastasis (29), conclusive evidence from humans suggests that low perioperative NK activity is associated with higher rates of cancer recurrence and mortality in lung cancer patients (30), taking into account acute pain also inhibits NK activity, Cancer pain suppresses immune function by reducing the activity of NK cells (31). ICIs enhance the anti-tumor activity of immune cells by inhibiting immune checkpoints. They have opposite effects on the immune system, so cancer pain may have a negative impact on immunotherapy efficacy. However, there has been a lack of previous studies that directly examine the relationship between baseline cancer pain and ICIs. Our findings reveal that patients with baseline cancer pain had shorter median PFS and median OS than those without baseline cancer pain (3.1 *vs.* 6.5 months, P=0.001; 16.5 *vs.*

Table 2 Univariate analysis of patients with baseline cancer pain

Characteristics	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Sex (male vs. female)	0.781 (0.579–1.052)	0.104	0.869 (0.540–1.398)	0.562
Age (<65 vs. ≥65 years)	0.991 (0.761–1.291)	0.947	1.597 (1.061–2.402)	0.025*
PS (0–1 vs. 2–4)	1.687 (1.134–2.510)	0.010*	1.490 (0.965–2.301)	0.072*
Smoking history (yes vs. no)	1.173 (0.900–1.529)	0.237	1.125 (0.740–1.170)	0.583
Lung surgery (yes vs. no)	0.871 (0.681–1.114)	0.272	0.574 (0.350–0.943)	0.028*
Histological types (SCC vs. non-SCC)	0.912 (0.594–1.401)	0.675	1.478 (0.826–2.643)	0.210
EGFR/ALK mutation (positive vs. negative)	1.532 (1.087–2.158)	0.015*	0.738 (0.449–1.214)	0.232
PD-L1 mutation (positive vs. negative)	0.657 (0.491–0.880)	0.005*	1.213 (0.745–1.973)	0.437
Treatment				
ICIs line of treatments (1 vs. ≥2)	1.523 (1.172–1.979)	0.002*	3.034 (2.001–4.599)	<0.001*
ICIs combined medication (yes vs. no)	0.541 (0.372–0.785)	0.001*	0.805 (0.556–1.167)	0.252
ICIs types (anti-PD-1 vs. others)	0.936 (0.586–1.494)	0.782	1.321 (0.805–2.166)	0.271
Adverse reactions (yes vs. no)	1.069 (0.833–1.371)	0.601	1.260 (0.870–1.823)	0.221
Cancer pain				
Pain property neuropathic pain (yes vs. no)	0.859 (0.316–2.337)	0.766	0.877 (0.277–2.777)	0.824
Degree of pain (<4 vs. ≥4)	1.428 (0.974–2.093)	0.068	0.963 (0.660–1.405)	0.844
Number of pain sites (≤2 vs. >2)	1.626 (0.846–3.129)	0.145	1.212 (0.647–2.268)	0.549
Breakthrough pain (yes vs. no)	1.843 (1.276–2.661)	0.001*	1.659 (1.139–2.415)	0.008*
Breakthrough pain frequency (<3 vs. ≥3)	1.146 (0.710–1.848)	0.577	1.018 (0.637–1.627)	0.941
Dose of opioid (≤10 vs. >10 mg q12h)	1.198 (0.835–1.720)	0.326	1.273 (0.880–1.842)	0.201

*, P<0.05. The data are HR and 95% CI values for PFS and OS from all patients. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PS, performance status; SCC, squamous cell carcinoma; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed cell death-ligand 1; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death 1.

31.2 months, P<0.001). These findings indicate that patients who receive ICIs with baseline cancer pain may have a worse survival.

Breakthrough pain is a distinct pain state and common in patients with cancer pain (32). After PSM, survival curve analysis of 54 patients with breakthrough pain revealed worse survival outcomes of patients with breakthrough pain. Patients with breakthrough pain had shorter median PFS and median OS than patients without breakthrough pain (1.9 vs. 4.2 months, P=0.001; 9.9 vs. 18.7 months, P=0.012). In addition, multivariable analyses revealed that breakthrough pain was an independent prognostic factor (HR =2.296, 95% CI: 1.215–4.336, P=0.010).

Our study has some limitations. First, the study was retrospective and the information provided by medical records is limited. Although we performed PSM analysis to balance confounders, our sample size was also small. Therefore, this PSM analysis may not be optimal. In addition, our study included lung carcinoma with small cells. Small cell lung cancer is not sensitive to immunotherapy in this situation. In addition, more disease may have more pain, and patients with cancer pain may have a higher tumor burden. We did not conduct PSM for comorbidities and underlying conditions, which may also be factors affecting patient efficacy and survival, and need to be further explored in the future (33). This may have affected the findings.
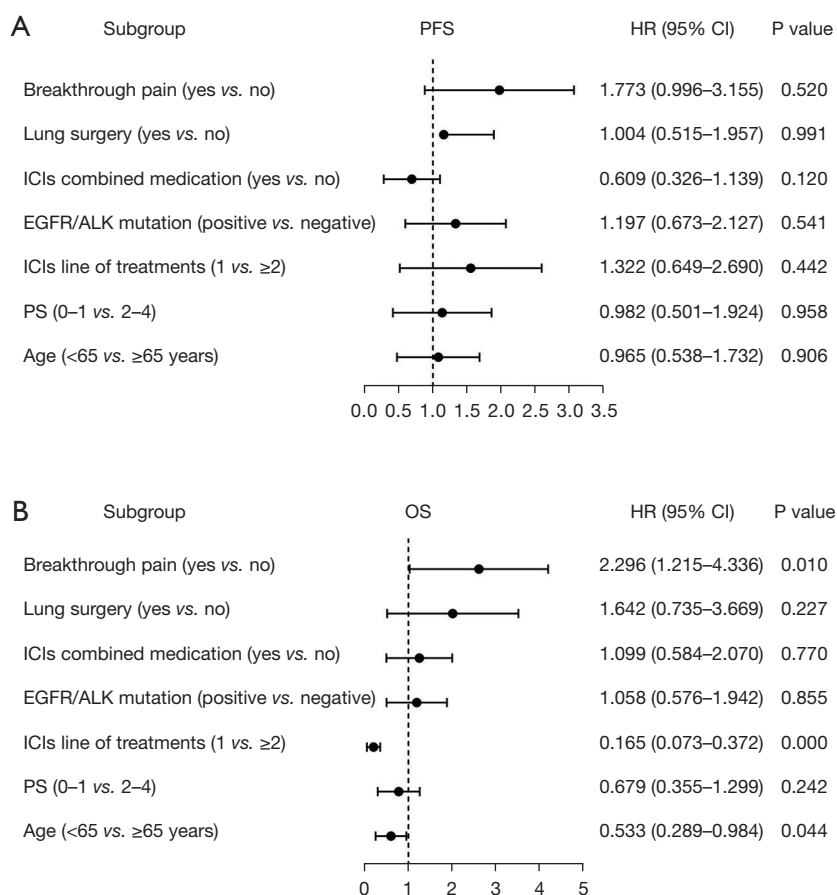
Figure 3 HR and 95% CI for PFS and OS in all patients. PFS, progression-free survival; PS, performance status; HR, hazard ratio; CI, confidence interval; ICIs, immune checkpoint inhibitors; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; OS, overall survival.

Conclusions

Patients with baseline cancer pain have worse survival. Patients with baseline cancer pain who develop breakthrough pain have a worse response to immunotherapy. Breakthrough pain is an independent prognostic factor of immunotherapy.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-375/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-375/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee at Zhejiang Cancer Hospital (No. IRB-2023-120) and individual consent for this retrospective analysis was waived.

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Table S1 Characteristics of cancer pain after PSM

Cancer pain characteristics	Proportion (%)	Number
Pain property		
Somatic pain	37.5	18
Neuropathic pain	31.3	15
Visceral pain	8.3	4
Mixed pain	22.9	11
Pain sites		
≤2	93.8	45
≥3	6.3	3
Breakthrough pain		
Yes	39.6	19
No	60.4	29

PSM, propensity score matching.

Table S2 Effect of Immunotherapy (after PSM)

Response	Group	
	Cancer pain (+) (n=48)	Cancer pain (–) (n=48)
CR	0	1
PR	7	15
SD	24	24
PD	14	8
NE	3	0
ORR (%)	14.58	33.33

PSM, propensity score matching; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate.