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## 非小细胞肺癌骨转移的临床与预后分析

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**[摘要]** **目的:**总结非小细胞肺癌骨转移的临床特点,探讨影响其预后的相关因素。**方法:**总结1999年4月—2006年6月上海市胸科医院住院治疗的174例非小细胞肺癌骨转移患者的临床资料, Kaplan-Meier法估计患者1、2年生存率,单因素分析(Log-rank检验)筛选患者预后的影响因素,多因素分析(COX逐步回归模型)进一步确认独立危险因素。**结果:**非小细胞肺癌骨转移好发部位依次为胸部(38.1%)、脊柱(32.8%)、骨盆(16.3%)、四肢(8.7%)和颅骨(4.1%),其中肋骨(30.7%)、腰椎(17.3%)、胸椎(13.1%)分列前3位。中位生存时间为10.73个月, Kaplan-Meier生存分析结果显示1年、2年生存率分别为47.1%、17.8%。单因素分析显示:PS评分、骨痛、单纯骨转移、单发骨转移、血清碱性磷酸酶(AKP)、血清乳酸酶(LDH)、CEA水平与预后相关( $P < 0.05$ );多因素分析显示:PS评分、单纯骨转移、单发骨转移为非小细胞肺癌骨转移预后的独立影响因素。**结论:**非小细胞肺癌骨转移好发于胸部(肋骨)、脊柱(腰椎/胸椎)、骨盆(髌骨)等;PS评分、单纯骨转移、单发骨转移可能对患者预后影响较大。

**[关键词]** 骨转移;非小细胞肺癌;骨相关事件

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### Clinical and prognostic analysis of bone metastases of non-small-cell lung cancer

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**[ABSTRACT]** **Objective:** To study the clinical features and prognostic factors of bone metastases of non-small-cell lung cancer. **Methods:** The clinical data of 174 patients with bone metastases of non-small-cell lung cancer, who were treated in our hospital during April 1999 to June 2006, were retrospectively analyzed. Kaplan-Meier analysis was used to estimate the 1- and 2-year survival rates of patients. Log-rank test was used to screen the factors influencing the survival of patients and Cox regression was used to further confirm the independent factors. **Results:** The predilection sites of bone metastases of non-small-cell lung cancer were chest (38.1%), spine (32.8%), pelvis (16.3%), extremities (8.7%), and skull (4.1%), with the ribs (30.7%), lumbar vertebrae (17.3%), and thoracic vertebra (13.1%) ranking the top three. The median survival time of the 174 patients was 10.73 months; Kaplan-Meier analysis showed that the 1- and 2-year survival rates were 47.1% and 17.8%, respectively. It was also showed that the PS Score, bone pain, asymptomatic bone metastases, solitary bone metastasis, serum AKP, LDH, and CEA were associated with the prognosis of patients ( $P < 0.05$ ). Multivariate analysis showed that PS score, solitary bone metastasis and single bone metastasis were the independent factors of prognosis. **Conclusion:** The predilection sites of bone metastasis of non-small-cell lung cancer include chest part (ribs), spine (lumbar/thoracic vertebrae), pelvis (ilium), etc. PS score, asymptomatic bone metastases, and solitary bone metastasis have great influence on the prognoses of patients.

**[KEY WORDS]** bone metastasis; non-small-cell lung carcinoma; skeletal-related events

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肺癌是目前全球癌症发病率和病死率均居首位的恶性肿瘤,极易远处转移。以骨转移常见,发生率为30%~40%,多以溶骨性破坏为主,主要表现为顽

固性疼痛、功能障碍、病理性骨折、脊髓压迫症及高钙血症等,严重影响患者的生活质量,预后较差<sup>[1]</sup>。目前缺乏对其预后影响因素的全面分析,无法有效

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地进行预后评估和采取针对性的治疗措施。因此,本研究回顾性分析了1999年4月—2006年6月上海市胸科医院住院治疗的174例非小细胞肺癌骨转移患者的临床资料,总结其临床特点,探讨影响其预后生存期的相关因素。

### 1 资料和方法

1.1 入选标准 (1)经细胞学或组织学确诊的非小细胞肺癌。(2)骨转移诊断标准<sup>[2]</sup>:骨扫描提示多发骨转移;骨扫描阳性同时经CT或MRI或X线任一证实;骨扫描阳性同时有临床症状,如局部疼痛或压痛,病理性骨折,截瘫者;PET-CT提示骨转移者。骨转移诊断标准中符合其中1条即入选。

1.2 临床资料 174例入选患者,男117例,女57例,年龄29~85岁,中位年龄61岁。72例患者吸烟≥400年支,102例患者吸烟<400年支。病理类型:腺癌119例,鳞癌32例,腺鳞癌7例,低分化癌或混有腺癌、鳞癌、低分化癌16例。ECOG体能状态(PS)评分:1分患者163例,PS评分≥2分患者11例;80例患者(46.0%)确诊时存在骨痛;141例

(81.0%)患者接受化学药物治疗,107例(61.5%)患者使用双膦酸盐治疗;48例患者接受骨放射性治疗。

1.3 随访 采用电话形式随访,生存期自确诊肺癌日期开始计算,至死亡日期或最后随访日期为止,存活时间以月表示。

1.4 统计学处理 采用SPSS 10.0 统计分析软件进行统计分析。以患者中位生存期及1年、2年生存率为预后观察指标。Kaplan-Meier法估计患者1年、2年的生存率,单因素分析采用Log-rank检验,多因素分析采用COX逐步回归模型。

### 2 结果

2.1 骨转移的分布特点 根据参考文献<sup>[3]</sup>将人体骨骼分为5个区,(1)胸部:包括锁骨、肋骨、肩胛骨、胸骨;(2)脊柱:颈椎、胸椎、腰椎;(3)骨盆:髌骨、坐骨、耻骨、骶骨;(4)肢体:上肢、下肢;(5)颅骨。本组骨转移好发部位(表1)依次为胸部(38.1%)、脊柱(32.8%)、骨盆(16.3%)、四肢(8.7%)和颅骨(4.1%);其中肋骨(30.7%)、腰椎(17.3%)、胸椎(13.1%)分列前3位。

表1 骨转移部位的分布  
Tab 1 Distribution of bone metastasis sites

Pathological type	N	Anatomic region					Total
		Thoracic	Vertebral	Pelvic	Limb	Skull	
Adeno	119	116	97	50	28	14	305(70.0)
Squamous	32	24	29	12	7	3	75(17.2)
Adenosquamous	7	6	3	3	0	0	12(2.8)
Other	16	20	14	6	3	1	44(10.1)
Total	174	166(38.1)	143(32.8)	71(16.3)	38(8.7)	18(4.1)	436

2.2 骨相关事件 骨相关事件<sup>[4]</sup>(skeletal related events,SREs)指病理性骨折、脊髓压迫、骨放射治疗(因缓解骨痛或防治病理性骨折、脊髓压迫)、骨科手术及高钙血症。174例患者中,44例(25.3%)患者病程中发生骨相关事件。在骨相关事件中,骨放射治疗48例,病理性骨折2例,脊髓压迫3例,无骨科手术。34例患者发生1次骨相关事件,10例患者发生2次骨相关事件。

### 2.3 预后因素分析

2.3.1 总体生存情况 174例患者的中位生存时间为10.73个月,1年、2年生存率分别为47.1%、17.8%。

2.3.2 单因素分析结果 单因素分析显示:ECOG PS评分( $P=0.003$ )和有无骨痛( $P=0.031$ )与非小细胞肺癌骨转移患者的预后相关。性别、年龄、吸烟指

数、病理类型、T分期、N分期、骨相关事件与预后关系不大(表2)。单纯骨转移组的中位生存期高于多脏器转移组( $P=0.034$ ),单发骨转移组的中位生存期和生存率亦高于多发骨转移组( $P=0.023$ )。血清碱性磷酸酶(AKP)、血清乳酸酶(LDH)、癌胚抗原CEA水平升高组的生存期明显低于相应的低值组( $P<0.05$ )。化疗周期、双膦酸盐的应用及局部骨放疗均与肺癌骨转移患者的预后关系不大(表3)。

2.3.3 多因素分析结果 多因素分析结果(表4)显示:ECOG PS评分、单纯骨转移、单发骨转移是非小细胞肺癌骨转移患者预后的独立影响因素。PS评分1分患者生存期优于PS评分≥2分的患者( $P=0.030$ ),多脏器转移患者生存期较单纯骨转移患者短( $P=0.017$ ),多发骨转移患者的生存期短( $P=0.021$ )。

表2 肺癌骨转移临床特征对预后的影响

Tab 2 Clinical features and prognostic analysis of lung cancer with bone metastases

Prognostic factors	n	MST(month)	Survival rate(%)		$\chi^2$	P value
			1 year	2 year		
Gender					2.08	0.150
Male	117	9.73	42.74	17.09		
Female	57	12.57	56.14	19.30		
Age					1.44	0.178
$\leq 60$	87	11.03	47.13	12.64		
$> 60$	87	10.70	47.13	22.99		
Smoking					1.65	0.199
$< 400$	102	12.57	53.92	17.65		
$\geq 400$	72	7.70	37.50	18.06		
Pathological type					0.50	0.919
Adeno	119	10.67	47.06	35.71		
Squamous	32	12.97	56.25	21.87		
Adenosquamous	7	7.53	28.57	14.29		
Other	16	7.13	37.50	18.75		
ECOG PS score					9.11	0.003
1	163	11.27	48.47	19.02		
$\geq 2$	11	5.10	27.27	0.00		
T-stage					0.84	0.359
T <sub>1</sub> -T <sub>2</sub>	103	11.30	48.54	20.39		
T <sub>3</sub> -T <sub>4</sub>	71	10.43	45.07	14.08		
N-stage					1.04	0.308
N <sub>0</sub> -N <sub>1</sub>	29	14.07	58.62	41.18		
N <sub>2</sub> -N <sub>3</sub>	145	10.60	44.83	16.55		
Bone pain					5.73	0.031
Yes	80	7.57	38.75	16.25		
No	94	12.70	54.26	19.15		
SREs					0.12	0.732
Yes	44	11.03	46.92	17.69		
No	130	11.30	47.73	18.18		
Number of SREs					2.62	0.106
1	34	12.67	60.00	40.00		
2	10	8.90	44.12	11.76		

SREs; Skeletal related events; MST: Median survival time

### 3 讨论

本研究结果发现,肺癌合并骨转移患者的中位生存时间为10.73个月,1年生存率为47.1%,2年生存率为17.8%,与以往研究<sup>[1-3]</sup>类似,骨转移灶以胸部(肋骨)、脊柱(腰椎/胸椎)多见,其次为骨盆、四肢、头颅。Ohashi等<sup>[5]</sup>研究提示初始的ECOG PS评分是非小细胞肺癌患者预后因素之一。本研究多因素分析结果亦提示PS评分是影响非小细胞肺癌骨转移的独立影响因素( $P=0.030$ ),可能与患者伴进行性脏器功能减退及多种并发症有关。Albain等<sup>[6]</sup>研究表明转移器官的数量可影响生存期,单个脏器转移的生存期长于多脏器转移;单纯骨转移、单发骨转移是非小细胞肺癌骨转移预后的有益因素,

与本研究结果基本吻合。

本研究单因素分析结果显示低血清AKP、LDH、CEA水平是预后有益的因素,与Vinolas等<sup>[7]</sup>研究结果类似,提示对临床上出现血清AKP、LDH、CEA升高应给予骨扫描检查。但进一步的多因素分析并未发现其具有统计学意义,具体机制仍有待进一步探讨。单因素分析显示无骨痛症状患者的中位生存期高于有骨痛症状的患者( $P=0.031$ ),与Merrick等<sup>[8]</sup>研究结果一致。本研究中有SREs组的生存期与无SREs组无统计学差异( $P=0.072$ ),与Tsuya等<sup>[9]</sup>的研究结果基本一致。然而仅发生1次SREs患者的中位生存期优于发生2次SREs的患者,但差异未达统计学意义,这可能与样本量不足有关。

表 3 肺癌骨转移特点、血清肿瘤学指标、治疗措施对患者预后的影响

Tab 3 Effect of metastatic characteristics, laboratory parameters, and therapeutic measures on prognosis of patients

Prognostic factors	n	MST(month)	Survival rate(%)		$\chi^2$	P value
			1 year	2 year		
Metastatic characteristic						
Solitary bone metastasis					5.48	0.034
Yes	99	12.97	55.56	22.22		
No	75	8.30	36.00	12.00		
Single bone metastasis					5.62	0.023
Yes	42	15.43	59.52	26.19		
No	132	10.26	43.18	15.15		
Weight-bearing bone metastases					0.05	0.997
Yes	130	11.45	47.58	17.74		
No	44	10.57	43.24	16.22		
Laboratory indicators						
AKP					4.50	0.038
$\geq 150$ U/L	27	6.43	33.33	7.41		
$< 150$ U/L	120	11.27	48.33	17.50		
LDH					5.31	0.021
$< 245$ U/L	91	12.70	52.75	19.78		
$\geq 245$ U/L	56	7.37	33.93	8.93		
Serum CEA					4.45	0.031
$< 5$ ng/ml	29	12.87	60.00	26.67		
$\geq 5$ ng/ml	40	11.30	46.34	7.32		
Serum NSE					0.82	0.366
$< 20$ ng/ml	56	16.87	53.85	15.38		
$\geq 20$ ng/ml	13	12.40	51.79	14.29		
Serum CYFRA21-1					0.52	0.469
$< 3.3$ ng/ml	24	14.23	58.33	8.33		
$\geq 3.3$ ng/ml	45	11.27	48.89	17.78		
Therapeutic factors						
Cycle of chemotherapy					3.74	0.081
$\geq 3$	127	11.28	51.18	22.83		
$< 3$	47	11.65	36.17	4.26		
Bisphosphonates					2.07	0.122
Yes	107	11.67	48.60	20.56		
No	67	10.86	44.78	13.43		
Radiotherapy					0.27	0.438
Yes	48	11.71	48.78	19.51		
No	126	11.24	46.62	17.29		

AKP: Alkline phosphatase; LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; NSE: Neurosecretion enzyme

表 4 多因素分析非小细胞肺癌骨转移患者预后的影响因素

Tab 4 Prognostic analysis of non-small-cell lung cancer with bone metastasis by COX regression model

	$\beta$ value	P value	OR	95% CI	
				Low	High
ECOG PS	1.338	0.030	2.812	1.135	3.801
Solitary bone metastasis	0.639	0.017	1.895	1.123	3.200
Single bone metastasis	0.714	0.021	2.042	1.114	3.741

本研究中使用双膦酸盐组与未使用双膦酸盐治疗的患者生存期无统计学差异( $P=0.122$ )。Lipton等<sup>[10]</sup>研究显示唑来膦酸可使骨转移患者NTx水平恢复或维持正常水平,SREs的发生风险下降,生存期同时也得到延长。这种生存获益可能与双膦酸盐可延缓威胁生命的SREs的发生<sup>[11]</sup>以及唑来膦酸潜在抗肿瘤活性<sup>[12-13]</sup>有关。唑来膦酸可通过抑制肿瘤细胞与矿化骨粘连,抑制肿瘤细胞侵袭、增殖和诱导肿瘤细胞凋亡来发挥直接抗肿瘤作用;唑来膦酸的间接抗肿瘤作用包括抑制血管形成<sup>[14]</sup>和免疫调节作用<sup>[15]</sup>;另外唑来膦酸可影响骨转移过程,抑制骨转移的形成和减少骨肿瘤负荷<sup>[16]</sup>以及预防骨转移发生<sup>[17]</sup>的作用。

综上所述,骨是肺癌常见的转移部位,PS评分、单发骨转移和单纯骨转移影响患者的预后生存期,双膦酸盐的早期应用效果仍有待进一步的研究证实。

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