



· 论 著 ·

# 锝 [ $^{99}\text{Tc}$ ] 亚甲基二膦酸盐注射液单药及联合 $^{89}\text{SrCl}_2$ 治疗骨转移瘤效果的meta分析

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[摘要] 背景与目的: 骨转移瘤是常见的肿瘤骨转移疾病, 且患者预后较差, 常会合并多种严重并发症, 包括骨痛、骨折、脊髓压迫等骨相关事件 (skeletal-related event, SRE), 影响患者的生活质量。放射性核素治疗对骨转移患者具有较好的效果, 可以明显地缓解骨痛。本研究旨在评价锝 [ $^{99}\text{Tc}$ ] 亚甲基二膦酸盐注射液 ( $^{99}\text{Tc}$ -MDP) 单用或联合氯化锶 ( $^{89}\text{SrCl}_2$ ) 治疗骨转移瘤的疗效。方法: 数据库检索公开发表在2000年1月—2022年7月的关于 $^{99}\text{Tc}$ -MDP联合 $^{89}\text{SrCl}_2$ 及单用 $^{99}\text{Tc}$ -MDP治疗骨转移瘤疗效的研究报道, 对所有纳入的文献进行资料提取和质量评价, 采用Revman 5.3软件进行meta分析。结果: 27篇文献符合纳入标准, 共2 564例患者纳入本研究。结果显示, 与 $^{89}\text{SrCl}_2$ 单药组比较,  $^{99}\text{Tc}$ -MDP联合 $^{89}\text{SrCl}_2$ 可提高骨转移瘤患者的骨痛缓解率 (RR=1.22, 95% CI: 1.18~1.27,  $P<0.001$ ), 骨转移灶愈合率 (RR=1.35, 95% CI: 1.25~1.47,  $P<0.001$ ); 单用 $^{99}\text{Tc}$ -MDP与 $^{89}\text{SrCl}_2$ 单药组相比, 骨痛缓解率 (RR=0.98, 95% CI: 0.90~1.06,  $P=0.57$ ) 及骨转移灶愈合率 (RR=0.93, 95% CI: 0.82~1.06,  $P=0.27$ ), 差异无统计学意义。 $^{99}\text{Tc}$ -MDP单用或联合 $^{89}\text{SrCl}_2$ 治疗的常见不良反应为白细胞、血小板计数降低, 但单用或者联合使用不良反应发生率差异无统计学意义 (单用 $^{89}\text{SrCl}_2$  vs  $^{99}\text{Tc}$ -MDP联合 $^{89}\text{SrCl}_2$ : RR=0.83, 95% CI: 0.53~1.30,  $P=0.42$ ; 单用 $^{89}\text{SrCl}_2$  vs 单用 $^{99}\text{Tc}$ -MDP: RR=0.93, 95% CI: 0.76~1.13,  $P=0.45$ )。结论:  $^{99}\text{Tc}$ -MDP联合 $^{89}\text{SrCl}_2$ 治疗能够有效地缓解骨转移瘤患者的疼痛, 其骨转移瘤的骨痛缓解率及骨转移灶愈合率均优于 $^{89}\text{SrCl}_2$ 单药治疗组, 且不良反应未明显增加。由于本研究在纳入文献质量及数量等方面存在局限性, 故今后需要更高质量的随机对照研究验证。

[关键词] 骨转移瘤; 锝 [ $^{99}\text{Tc}$ ] 亚甲基二膦酸盐注射液; 氯化锶; Meta分析

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**A meta-analysis of the efficacy of  $^{99}\text{Tc}$ -MDP alone and in combination with  $^{89}\text{SrCl}_2$  in the treatment of bone metastases** CHEN Man<sup>1</sup>, ZENG Feiyan<sup>1</sup>, LI Qingqing<sup>1</sup>, LI Hongdan<sup>1</sup>, LIN Yansong<sup>2</sup>, FENG Ping<sup>1</sup> (1. National Medical Products Administration Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, Institute of Clinical Trials, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China; 2. Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China)

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[Abstract] **Background and purpose:** Bone metastatic tumor is a common disease of tumor bone metastasis, and the prognosis of patients is poor, with a variety of serious complications, including bone pain, fracture, spinal cord compression and other skeletal related events, affecting the quality of life of patients. At present, radionuclide therapy still has positive clinical effects in patients with bone metastasis, and it still plays an important role in relieving bone pain. This study aimed to evaluate the efficacy of technetium [ $^{99}\text{Tc}$ ] methylene diphosphonate injection ( $^{99}\text{Tc}$ -MDP) alone or in combination with strontium chloride ( $^{89}\text{SrCl}_2$ ) in the treatment of bone metastases. **Methods:** Databases were used to search for studies published between January 2000 and July 2022 on the efficacy of

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<sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub> and <sup>99</sup>Tc-MDP alone in the treatment of bone metastases. All included literature was extracted and evaluated for quality, and Meta-analysis was performed using RevMan 5.3 software. **Results:** Twenty-seven publications met the inclusion criteria, and a total of 2564 patients were included in this study. The results demonstrated that <sup>99</sup>Tc-MDP combined with <sup>89</sup>SrCl<sub>2</sub> improved bone pain relief (RR=1.22, 95% CI: 1.18-1.27, *P*<0.001) and bone metastasis healing (RR=1.35, 95% CI: 1.25-1.47, *P*<0.001). However, when compared with <sup>89</sup>SrCl<sub>2</sub> alone, it could not be concluded that <sup>99</sup>Tc-MDP alone increased the rate of bone pain relief (RR=0.98, 95% CI: 0.90-1.06, *P*=0.57) and bone metastasis healing (RR=0.93, 95% CI: 0.82-1.06, *P*=0.27), and the difference between the two groups was not statistically significant. The common adverse effects of <sup>99</sup>Tc-MDP treatment alone or in combination with <sup>89</sup>SrCl<sub>2</sub> were decreased leukocyte and platelet counts, however, the difference in the incidence of adverse effects between <sup>99</sup>Tc-MDP treatment alone and in combination with <sup>89</sup>SrCl<sub>2</sub> was not statistically significant (<sup>89</sup>SrCl<sub>2</sub> vs <sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub>: RR=0.83, 95% CI: 0.53-1.30, *P*=0.42; <sup>89</sup>SrCl<sub>2</sub> vs <sup>99</sup>Tc-MDP: RR=0.93, 95% CI: 0.76-1.13, *P*=0.45). **Conclusion:** <sup>99</sup>Tc-MDP combined with <sup>89</sup>SrCl<sub>2</sub> treatment was effective in relieving pain in patients with bone metastases, and the bone pain relief rate and bone metastasis healing rate of <sup>99</sup>Tc-MDP combined with <sup>89</sup>SrCl<sub>2</sub> treatment for bone metastases were better compared with the <sup>89</sup>SrCl<sub>2</sub> monotherapy group, with no significant increase in adverse reactions after typical dosing. Due to the limitations of the quality and quantity of literature included in this study, higher quality randomized controlled studies are needed.

[ **Key Words** ] Bone metastasis; <sup>99</sup>Tc-MDP; <sup>89</sup>SrCl<sub>2</sub>; Meta-analysis

骨转移瘤是许多恶性肿瘤常见的骨转移疾病, 不同肿瘤的骨转移发生率不一, 70%~80%的骨转移发生于乳腺癌、前列腺癌、肺癌等原发癌症<sup>[1-3]</sup>。肿瘤骨转移后患者预后较差, 易合并多种严重并发症, 包括骨痛、骨折、脊髓压迫等骨相关事件 (skeletal-related event, SRE), 对患者的生活质量产生显著影响<sup>[3]</sup>。因此缓解骨转移瘤患者骨痛, 降低骨折发生风险, 提高患者的生活质量对患者远期生存具有重要意义。

目前放射性核素治疗方式在临床中仍具有积极的效果, 指南<sup>[4]</sup>和专家共识<sup>[1]</sup>推荐其可用于肿瘤骨转移的非手术治疗中, 其在骨痛缓解方面发挥着重要作用。氯化锶 (<sup>89</sup>SrCl<sub>2</sub>) 主要用于全身性骨转移瘤的治疗, 其能够在骨肿瘤病灶浓聚, 在病灶部位发射β射线, 集中照射病变部位, 抑制并杀灭肿瘤细胞, 从而起到缓解骨痛、抑制骨转移灶扩张的作用, 在乳腺癌、肝癌等骨转移瘤中都得到广泛应用<sup>[4-7]</sup>。尽管<sup>89</sup>Sr能够杀死肿瘤细胞、抑制转移灶, 但肿瘤细胞导致的骨破坏及骨折风险仍然存在。锝 [<sup>99</sup>Tc] 亚甲基二膦酸盐 (<sup>99</sup>Tc-MDP) 为我国原研核素药品, 能够靶向到达骨破坏区域, 抑制破骨同时能够促进成骨, 从而修复骨侵蚀, 缓解骨痛, 降低骨折的发生率<sup>[8-9]</sup>。<sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>能够有效地缓解骨转移瘤患者骨痛及缩小转移灶, 且联合应用的效果优于单用<sup>89</sup>Sr, 联合用药也不增加不良反

应。尽管有2篇文献<sup>[10-11]</sup>对<sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的效果进行了系统评价或meta分析, 但均未全面评估其在骨痛缓解、骨转移灶及不良反应等方面的有效性及安全性, 且时间久远, 不能满足现有循证医学证据要求, 因此有必要重新检索临床用药报道, 并采用meta分析的方法客观评价<sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>与单用<sup>89</sup>SrCl<sub>2</sub>、单用<sup>99</sup>Tc-MDP治疗恶性转移性骨肿瘤的有效性和安全性, 从而为临床医师提供更全面且更具体的参考。

## 1 资料和方法

### 1.1 检索策略

计算机检索中国知识基础设施工程即中国知网数据库 (CNKI)、万方数据库 (Wanfang Data)、维普期刊数据库 (VIP)、Cochrane数据库、PubMed数据库、Web of Science数据库及Embase数据库中公开发表有关<sup>99</sup>Tc-MDP治疗骨转移瘤效果的研究报道, 检索时限为2000年1月1日—2022年7月1日。中文主题检索词为“<sup>99</sup>Tc-MDP”、“锝 [<sup>99</sup>Tc] 亚甲基二膦酸盐”、“<sup>89</sup>Sr”、“<sup>89</sup>SrCl<sub>2</sub>”、“氯化锶”、“<sup>89</sup>锶”、“锶”、“二氯化锶”、“骨转移”、“骨转移瘤”、“肿瘤骨转移”、“继发性骨肿瘤”。英文检索词为

“Technetium [ $^{99}\text{Tc}$ ] methylenediphosphonate injection”、“ $^{99}\text{Tc-MDP}$ ”、“ $^{89}\text{SrCl}_2$ ”、“ $^{89}\text{Sr}$ ”、“Sr”、“strontium-89 chloride”、“bone metastasis/skeletal metastasis”、“osseous metastases/bony metastases”、“metastatic cancer”。例如CNKI数据库检索式：SU% (“ $^{99}\text{Tc-MDP}$ ” + “锝 [ $^{99}\text{Tc}$ ] 亚甲基二膦酸盐” + “ $^{99}\text{Tc-MDP}$ ”) AND SU% (“骨转移” + “骨转移癌” + “肿瘤骨转移”) AND SU% (“ $^{89}\text{Sr}$ ” + “ $^{89}\text{SrCl}_2$ ” + “氯化锶” + “89 锶” + “锶” + “二氯化锶”)。

## 1.2 文献纳入和排除标准

### 1.2.1 研究类型

收集国内外在2001年1月1日—2022年7月1日公开发表的关于 $^{99}\text{Tc-MDP}$ 治疗骨转移瘤疗效的文献，研究类型为干预性研究，研究内容是 $^{99}\text{Tc-MDP}$ 单用或联合 $^{89}\text{SrCl}_2$ 治疗骨转移瘤的疗效，不限制发表语种，对于重复发表或有重叠的文章或研究，则纳入最新的或数据完整的研究。

### 1.2.2 研究对象

恶性肿瘤伴有骨转移的患者，经病理学检查证实所有的肿瘤为原发且均通过单光子发射计算机断层成像 (single photon emission computed tomography, SPECT) 全身显像、计算机断层成像 (computed tomography, CT) 或X光片证实骨转移诊断。

### 1.2.3 受试者纳入和排除标准

纳入标准：① 受试者年龄大于等于18周岁；② 明确为癌症骨转移患者；③ 使用 $^{99}\text{Tc-MDP}$ 进行骨转移止痛治疗，且设置有对照组；④ 使用 $^{89}\text{SrCl}_2$ 进行骨转移止痛治疗，且设置有对照组。

排除标准：① 患者处于化疗期；② 给药干预的同时使用唑来膦酸或其他止痛药物如阿片类药物、非甾体类抗炎药。

### 1.2.4 干预措施

将骨转移瘤患者随机分为2组或3组， $^{99}\text{Tc-MDP}$ 组接受 $^{99}\text{Tc-MDP}$ 单独治疗，联合用药组接受 $^{99}\text{Tc-MDP}$ 与核素 $^{89}\text{SrCl}_2$ 治疗， $^{89}\text{SrCl}_2$ 组接受 $^{89}\text{SrCl}_2$ 治疗，采用静脉注射或静脉滴注的方式给药。

### 1.2.5 结局指标

① 骨痛缓解率。即各组内骨骼疼痛消失或部分缓解患者所占百分比。依据中华人民共和国卫生健康委医政司颁布的《核医学诊断与治疗规范》，骨骼疼痛反应分3级标准：I级为显效，即所有部位的骨痛消失；II级为有效，即50%以上部位骨痛消失或骨痛明显减轻，必要时服用少量止痛药；III级为无效，即疼痛不减轻或无任何改善<sup>[12]</sup>。② 骨转移灶愈合率。即在各组内骨显像结果显示转移灶完全或部分消失患者所占百分比。全身骨显像评价标准：I级为显效，即骨显像检查结果证实所有转移病灶消失；II级为有效，即骨显像检查结果证实转移灶部分消失或缩小，摄取浓度低；III级为无效，即骨骼显像检查显示转移病灶无变化或有新病灶出现<sup>[12]</sup>。将II级、I级计入总有效率。

## 1.3 文献筛选和资料提取

将从数据库检索所得文献导入参考文献管理软件EndNote X9中，2名研究者根据纳入、排除标准进行筛选。仔细阅读全文提取资料，内容包括作者、发表时间、研究对象、干预措施、干预时间、结局指标和不良反应等。收集数据由2名研究者独立完成并相互核对，如有分歧，则沟通解决，若仍不能解决，则交由第3名研究者判断。

## 1.4 文献质量评价

所有文献的质量评价由2名研究者独立完成，采用Cochrane系统评价手册推荐的偏倚风险评估工具<sup>[13]</sup>对所有纳入文献进行方法学质量评价。评价内容包括随机方法、分配隐藏、盲法、不完整资料偏倚、选择性报告偏倚和其他偏倚<sup>[14]</sup>。当两人评价文献出现分歧时由第三人参与讨论解决，最后决定文献质量，低质量文献不予纳入。

## 1.5 统计学处理

在临床同质的前提下进行合并分析，统计效应量用相对危险度 (relative risk, RR) 及95%置信区间 (confidence intervals, CI) 表示。各研究间进行异质性检验，当研究间无统计学异质性

( $P \geq 0.1$ ,  $I^2 \leq 50\%$ ) 时, 采用固定效应模型。如各研究间存在统计学异质性 ( $P < 0.1$ ,  $I^2 > 50\%$ ), 分析造成异质性的因素, 根据其因素对各研究进行亚组分析; 若难以判断异质性的产生原因, 则采用随机效应模型进行合并分析。敏感性分析采用依次剔除1篇文献后再进行效应量合并分析。发表偏倚采用漏斗图分析, 对于不适合进行meta分析的文献采用描述性方法进行分析。采用Revman 5.3软件 (Cochrane协作网所提供) 对所有数据进行统计学分析。

## 2 结 果

### 2.1 文献检索结果

按检索策略检索初步获得245篇文献, 其中

包括177篇中文文献, 68篇英文文献。使用软件EndNote X9去除89篇重复文献, 仔细阅读文献标题和摘要进行初筛, 获得中文文献64篇。阅读剩余文献全文, 最终27篇文献<sup>[15-41]</sup>符合纳入排除标准, 共2 564例患者, 均进行meta分析, 详细文献检索情况见图1。各研究均描述了患者数量、性别、年龄、原发肿瘤类型等基本信息, 各研究骨转移瘤治疗结局指标计数资料均采用骨痛缓解率 (%) 或骨转移灶愈合率 (%) 表示, 组间比较采用 $\chi^2$ 检验。各研究<sup>89</sup>SrCl<sub>2</sub>用法大致相同, <sup>99</sup>Tc-MDP用法在各组间略有差异, 体现在用药间隔时间及疗程上。纳入文献基本情况见表1。

### 2.2 方法学质量评价

依照Cochrane偏倚风险评估工具<sup>[13]</sup>对所有纳入的文献进行质量等级评价。① 随机序列生

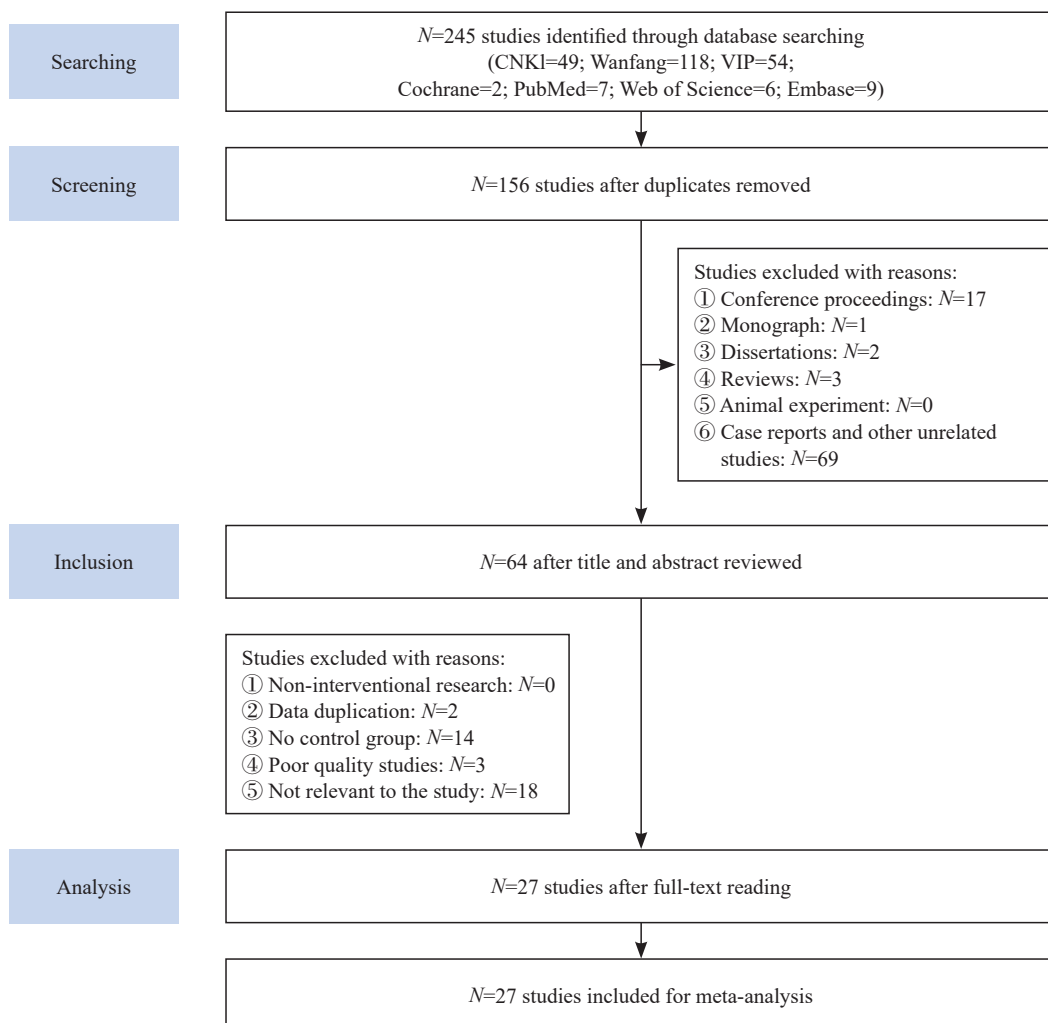


图 1 文献筛选流程

Fig. 1 Literature screening flowchart

成：4篇文献（14.8%）描述了采用随机数字表法进行随机，评估为低风险；其余23篇（85.2%）文献未详细描述随机方法，评估为不清楚。② 分配隐藏：27篇文献（100.0%）未详细说明分配隐藏方案，评估为不清楚。③ 对患者、试验人员实施盲法：27篇文献（100.0%）未描述方法的实施，评估为不清楚；④ 对结局评估者实施盲法：27篇文献（100.0%）未描述是否对结局评价者实

施盲法，评估为不清楚；⑤ 不完整结果数据：27篇文献（100.0%）均无缺失数据，评估为低风险；⑥ 选择性报告：27篇文献（100.0%）报告了所有期望的结果，评估为低风险；⑦ 其他偏倚：13篇文献（48.1%）详细描述了基线情况，评估为低风险；其余14篇（51.9%）未对患者基线情况进行描述，评估为不清楚。评价结果见图2。

表1 纳入文献基本情况

Tab. 1 Characteristics of included studies

Study/published year	Cancer	Evaluation	Group	Mean age/ year	Gender (female)	Case n	Treatment	AE
Sang S B, et al [28] 2001	Lung cancer, prostate cancer, breast cancer, nasopharyngeal cancer, rectal cancer, and cancers of unknown origin	Rate of relief of bone pain and healing of bone metastases	$^{89}\text{SrCl}_2$	55.0	41.2%	38	$^{89}\text{SrCl}_2$ 150 MBq, 5 patients received a second injection, all with an interval of more than 3-6 months	White blood cells and platelets decreased slightly in some patients, most of which occurred 4-8 weeks after treatment, but they all recovered to the pre-treatment level during follow-up. Transient pain intensification occurred in very few patients after treatment, and most of them disappeared after 3 to 7 days of treatment
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$			30	$^{89}\text{SrCl}_2$ 150 MBq, $^{99}\text{Tc-MDP}$ 200 mg/d, 5d as a course, 2-3 courses	
Zhong G P, et al [39] 2002	Prostate cancer, kidney cancer, bladder cancer, testicular cancer	Rate of relief of bone pain and healing of bone metastases	$^{89}\text{SrCl}_2$	60.9	15.2%	16	$^{89}\text{SrCl}_2$ 1.48-2.22 MBq/kg	Transient bone pain was aggravated in some patients after treatment, which was relieved with painkillers and gradually alleviated 2-4 days later. A small number of cases showed hematological grade I to II toxic reactions. White blood cell count and platelet count decreased 1-2 weeks later, and decreased to the lowest level (lower limit of normal value) in 1 month, then gradually recovered to the pre-treatment level within 2-5 weeks
			$^{99}\text{Tc-MDP}$			9	$^{99}\text{Tc-MDP}$ 200 mg/d, 5 d as a course. The second course of treatment was performed at an interval of 10 d, 4 courses	
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$			8	One course of $^{99}\text{Tc-MDP}$ by intravenous drip, followed by one dose of $^{89}\text{SrCl}_2$ by intravenous injection after 3 to 5 d	
Mo Y, et al [24] 2004	Breast cancer, lung cancer, prostate cancer and other malignancies	Rate of relief of bone pain	$^{89}\text{SrCl}_2$	56.0	41.2%	51	$^{89}\text{SrCl}_2$ 111-148 MBq (3-4 mci), every 3 to 6 months	No serious toxic and side effects were observed in both groups. After treatment with $^{89}\text{SrCl}_2$ , a small number of patients showed inhibition of bone marrow hematopoietic function, manifested by decreased white blood cell and platelet counts. It will return to normal in about 4 to 6 weeks. There was no obvious damage to liver and kidney function
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$			54	$^{89}\text{SrCl}_2$ 111-148 MBq (3-4 mci), every 3 to 6 months; $^{99}\text{Tc-MDP}$ 200 mg/d, 5 d as a course	

表1 (续)

Study/published year	Cancer	Evaluation	Group	Mean age/ year	Gender (female)	Case <i>n</i>	Treatment	AE
Li J G, et al <sup>[20]</sup> 2004	Breast cancer, lung cancer, prostate cancer, esophageal cancer, cardiac cancer, cervical cancer, nasopharyngeal cancer, rectal cancer, liver cancer and others	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	Male 56.5 Female 50.5	46.2%	55	<sup>89</sup> SrCl <sub>2</sub> 130-174 MBq	In terms of liver function, 14 patients showed increased single index
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>				51	<sup>89</sup> SrCl <sub>2</sub> 130-174 MBq. After 20 d, injecting <sup>99</sup> Tc-MDP 200 mg intravenously for more than 3 h, 5 days as a course of treatment; or 3 h intravenously for 10 days as a course of treatment. One course of treatment per month for 2 to 3 consecutive courses.
Shi G Q, et al <sup>[30]</sup> 2006	Prostate cancer, lung cancer, breast cancer, rectal cancer and malignancies of unknown primary	Rate of relief of bone pain	<sup>89</sup> SrCl <sub>2</sub>	62.3	33.3%	24	<sup>89</sup> SrCl <sub>2</sub> 2.6 MBq/kg.	In blood images, mildly affected: 18, moderately affected: 4, severely affected: 2
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	58.6	20.8%	24	<sup>89</sup> SrCl <sub>2</sub> 2.6 MBq/kg; <sup>99</sup> Tc-MDP 5 mg/d	In blood images, mildly affected: 17, moderately affected: 4, severely affected: 3
Shi F, et al <sup>[29]</sup> 2006	Breast cancer, lung cancer, prostate cancer, and other malignancies  Breast cancer, lung cancer, nasopharyngeal cancer and other malignant tumors.	Rate of relief of bone pain	<sup>89</sup> SrCl <sub>2</sub>	50.0	40.8%	71	<sup>89</sup> SrCl <sub>2</sub> 1.48-2.22 MBq/kg (40-60 uci)	No serious side effects were observed. Bone pain was aggravated in a small number of patients 2-4 days after treatment, but no special treatment was done. A few patients showed inhibition of bone marrow hematopoietic function, leukocyte and platelet decline, about 4-6 weeks later returned to normal, no significant damage to liver and kidney function
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	47.0	55.4%	74	<sup>89</sup> SrCl <sub>2</sub> 1.48-2.22 MBq/kg (40-60 uci); <sup>99</sup> Tc-MDP 200 mg/d, 5 days for a course	
Ren H, et al <sup>[27]</sup> 2008	Lung cancer, breast cancer, prostate cancer, rectal cancer, stomach cancer  Lung cancer, breast cancer, prostate cancer, rectal cancer, stomach cancer, ovarian cancer.	Rate of relief of bone pain	<sup>89</sup> SrCl <sub>2</sub>	67.2	38.7%	31	<sup>89</sup> SrCl <sub>2</sub> 1.48-2.22 MBq/kg, once every 3 months	In the two groups, 22.5% and 24.2% of the cases had grade I - II leukopenia, and 16.1% and 21.2% of the cases had grade I - II thrombocytopenia, respectively. There was no statistically significant difference between the two groups. Hematological toxicity usually appears at 4-6 weeks and recovers after 2-3 weeks, mainly as platelet and leukocyte reduction
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	63.6	48.5%	33	<sup>89</sup> SrCl <sub>2</sub> 1.48-2.22 MBq/kg, once every three months; <sup>99</sup> Tc-MDP 11mg/d, 7 days for a course of treatment, once a month	
Guan R G, et al <sup>[18]</sup> 2008	Lung cancer, breast cancer, nasopharyngeal cancer, prostate cancer  Lung cancer, breast cancer, nasopharyngeal cancer, cervical cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	46.0	48.1%	27	<sup>89</sup> SrCl <sub>2</sub> 111-148 MBq	Only 2 patients developed skeletal depression, transient hypoleucopenia, toxicity evaluation was II degree, untreated, spontaneous recovery after 2 weeks
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	47.0	58.6%	29	<sup>89</sup> SrCl <sub>2</sub> 111-148 MBq. After 3 d, injecting <sup>99</sup> Tc-MDP 20 mg intravenously once a day for 5 d, followed by <sup>99</sup> Tc-MDP 5mg intravenously for 15 d	

表1 (续)

Study/published year	Cancer	Evaluation	Group	Mean age/year	Gender (female)	Case n	Treatment	AE	
Wang J F, et al [31] 2009	61 cases of breast cancer, 52 cases of prostate cancer, 45 cases of lung cancer, thyroid cancer, nasopharyngeal cancer, rectal cancer	Rate of relief of bone pain and healing of bone metastases	$^{89}\text{SrCl}_2$	53.0	41.2%	45	$^{89}\text{SrCl}_2$ 148 MBq	After treatment, a small number of patients felt general fatigue, nausea and other symptoms, some patients slightly decreased, a very small number of patients showed transient pain exacerbation after treatment	
			$^{99}\text{Tc-MDP}$				38		$^{99}\text{Tc-MDP}$ 200 mg/d, 5 days for a course, once a month, for 2-3 courses
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$				82		$^{89}\text{SrCl}_2$ 148 MBq; $^{99}\text{Tc-MDP}$ 200 mg/d, 5 days for a course, once a month, for 2-3 courses
Zhang J H, et al [35] 2010	Breast cancer, lung cancer, nasopharyngeal cancer, and other tumors	Rate of relief of bone pain	$^{89}\text{SrCl}_2$	52.0	61.7%	60	$^{89}\text{SrCl}_2$ 111-148 MBq (3-4 mci) every 3-6 months	There was no significant difference between the groups	
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$	49.0	57.4%	61	$^{89}\text{SrCl}_2$ 111-148 MBq (3-4 mci) every 3-6 months; $^{99}\text{Tc-MDP}$ 200 mg/d, 5 days for a course		
Ning S F, et al [26] 2010	Lung cancer, breast cancer, prostate cancer, nasopharyngeal cancer, rectal cancer, stomach cancer, uterine cancer	Rate of relief of bone pain	$^{89}\text{SrCl}_2$	66.3	44.6%	65	$^{89}\text{SrCl}_2$ 1.48-2.22 MBq/kg, every 3 months	In the two groups, 20% and 22.6% of the cases showed mild to moderate leukopenia, and 15.4% and 17% of the cases showed mild to moderate thrombocytopenia. Single decline was more common, and one case in both groups had severe leukopenia and thrombocytopenia	
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$	61.5	52.8%	53	$^{89}\text{SrCl}_2$ 1.48-2.22 MBq/kg, every 3 months; $^{99}\text{Tc-MDP}$ 15 mg/d, 10 days for a course		
Zhu W R, et al [40] 2011	Prostate cancer	Rate of relief of bone pain and healing of bone metastases	$^{89}\text{SrCl}_2$	63.2 ± 7.6	0.0%	46	$^{89}\text{SrCl}_2$ 148-185 MBq	There were no adverse reactions in the two groups	
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$			49	$^{89}\text{SrCl}_2$ 148-185 MBq; $^{99}\text{Tc-MDP}$ 22 mg/d, 10 days for a course, for 3-5 courses		
Chen M, et al [15] 2011	Breast cancer	Rate of relief of bone pain	$^{89}\text{SrCl}_2$	43.5	100.0%	45	$^{89}\text{SrCl}_2$ 1.48-2.22 MBq/kg (40-60 uCi)/kg	Leukocytosis of grade 1 in 4 cases and grade 2 in 1 case; Grade 1 thrombocytopenia in 5 patients	
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$			42	$^{89}\text{SrCl}_2$ 1.48-2.22 MBq/kg (40-60 uCi)/kg; $^{99}\text{Tc-MDP}$ 5 mg/d, 15 days for a course	Leukocytosis of grade 1 in 3 cases; 2 cases of grade 1 thrombocytopenia	
Dong Z F, et al [16] 2012	Lung squamous cell carcinoma, lung adenocarcinoma, small cell lung cancer, lung adeno-squamous cell carcinoma	Rate of relief of bone pain and healing of bone metastases	$^{89}\text{SrCl}_2$	50.0	25.7%	33	$^{89}\text{Sr}$ 1.48 × 10 <sup>8</sup> Bq	Hematotoxic reaction (17 cases of degree 1, 3 cases of degree 2, 0 cases of degree 3)	
			$^{99}\text{Tc-MDP}+^{89}\text{SrCl}_2$	52.0	33.3%	30	$^{89}\text{Sr}$ 1.48 × 10 <sup>8</sup> Bq; $^{99}\text{Tc-MDP}$ 25 mg/d, 15 days for a course	Hemotoxic reaction (11 cases of degree 1, 2 cases of degree 2, 0 cases of degree 3)	
Ning J H, et al [25] 2014	Lung cancer, breast cancer, prostate cancer, stomach cancer, bladder cancer, nasopharyngeal cancer	Rate of relief of bone pain and healing of bone metastases	$^{89}\text{SrCl}_2$	56.0	44.4%	54	$^{89}\text{Sr}$ 4 mci	Aggravation of bone pain occurred in 18 cases	

表1 (续)

Study/published year	Cancer	Evaluation	Group	Mean age/year	Gender (female)	Case n	Treatment	AE
			<sup>99m</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>			54	<sup>89</sup> Sr 4 mci; <sup>99m</sup> Tc-MDP 22 mg/d, 10 days for a course, for 3 courses	Aggravation of bone pain occurred in 12 cases
Zhu W R, et al [40] 2015	Breast cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	61.5	Not described	42	<sup>89</sup> SrCl <sub>2</sub> 1.48-2.22 MBq/kg	There were no adverse reactions in the two groups
			<sup>99m</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>			45	<sup>89</sup> SrCl <sub>2</sub> 1.48-2.22 MBq/kg; <sup>99m</sup> Tc-MDP 22 mg/d, 10 days for a course, for 3 courses	
Yang J, et al [34] 2015	Prostate cancer, lung cancer, breast cancer	Rate of relief of bone pain	<sup>89</sup> SrCl <sub>2</sub>	56.0 ± 13.3	27.6%	63	<sup>89</sup> SrCl <sub>2</sub> 148 MBq (4 mci)	The bone pain of 3 patients worsened 3-7 days after treatment, and was self-alleviated 1 week later. White blood cells and platelets decreased for 4-6 weeks and recovered to normal. There were no significant changes in liver and kidney function
			<sup>99m</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>			64	<sup>89</sup> SrCl <sub>2</sub> 148 MBq (4 mci); <sup>99m</sup> Tc-MDP 33 mg/d, for 5 days	
Xie C H, et al [32] 2015	Lung cancer, stomach cancer, breast cancer, and other malignancies	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	55.1 ± 6.3	47.6%	63	<sup>89</sup> SrCl <sub>2</sub> 2.22 MBq/kg	Leukopenia and thrombocytopenia: 5 patients, elevated transaminase: 3 patients, fever, nausea, vomiting and other symptoms: 5 patients
			<sup>99m</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	56.7 ± 6.9	44.4%	63	<sup>89</sup> SrCl <sub>2</sub> 2.22 MBq/kg; <sup>99m</sup> Tc-MDP 200 mg/d, 5 days for a course, once a month, for 2-3 courses	Leukopenia and thrombocytopenia: 3 patients, elevated transaminase: 4 patients, fever, nausea, vomiting and other symptoms: 9 patients
Liu H C, et al [32] 2015	Breast cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	56.4 ± 13.8	100.0%	30	<sup>89</sup> SrCl <sub>2</sub> 1.48-1.85 MBq/kg	Leukocyte and/or platelet decreased in 5 cases
			<sup>99m</sup> Tc-MDP	51.6 ± 11.7		22	<sup>99m</sup> Tc-MDP 16.5 mg/d, 6 days for a course, once a month, for 2-3 courses	No adverse reaction
			<sup>99m</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	54.1 ± 12.1		28	<sup>89</sup> SrCl <sub>2</sub> 1.48-1.85 MBq/kg; <sup>99m</sup> Tc-MDP 16.5 mg/d, 6 days for a course, once a month, for 2-3 courses	Leukocyte and/or platelet decreased in 4 cases
Xu R S, et al [33] 2016	Prostate cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	71.5	0.0%	47	<sup>89</sup> SrCl <sub>2</sub> 148 MBq	Most of the patients showed transient decrease in WBC and PLT, which could recover to normal by itself. 4 patients showed low white blood cell count, which recovered to normal after symptomatic treatment
			<sup>99m</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>			50	<sup>89</sup> SrCl <sub>2</sub> 148 MBq; <sup>99m</sup> Tc-MDP 1 time/d for 10 d for 1 cycle. 1 cycle of treatment per month, 3 times in a row for 1 course of treatment	
Huang Y, et al [19] 2017	Prostate cancer, lung cancer, breast cancer, endometrial cancer, nasopharyngeal cancer, liver cancer, rectal cancer, and other types of malignant tumors	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	62.1 ± 13.2	35.1%	111	<sup>89</sup> SrCl <sub>2</sub> 4 mci/d, 10 days for a course, for 3 courses	Pain: 18 cases; leukopenia: 22 cases; thrombocytopenia: 17 cases; allergic reaction: 8 cases; gastrointestinal reaction: 2 cases



表1 (续)

Study/published year	Cancer	Evaluation	Group	Mean age/year	Gender (female)	Case <i>n</i>	Treatment	AE
			<sup>99</sup> Tc-MDP	59.7 ± 13.7	35.4%	130	<sup>99</sup> Tc-MDP 5.5 mg/d, 5 days for a course, for 3 courses	Pain: 22 cases; leukopenia: 28 cases; thrombocytopenia: 20 cases; allergic reaction: 7 cases; gastrointestinal reaction: 5 cases
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	62.1 ± 13.2	31.3%	160	<sup>89</sup> SrCl <sub>2</sub> 4 mci/d, 10 days for a course, for 3 courses; <sup>99</sup> Tc-MDP 22 mg/d, 10 days for a course, for 3 courses	Pain: 13 cases; leukopenia: 14 cases; thrombocytopenia: 10 cases; allergic reaction: 5 cases; gastrointestinal reaction: 1 case
Zhao D D, et al [38] 2017	Left breast cancer, right breast cancer	Rate of relief of bone pain	<sup>89</sup> SrCl <sub>2</sub>	51.1 ± 7.2	Not described	42	<sup>89</sup> SrCl <sub>2</sub> 1.48-1.85 MBq/kg	Thrombocytopenia: 3 cases; leukopenia: 4 cases
	Left breast cancer, right breast cancer, bilateral breast cancer		<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	50.0 ± 6.9		44	<sup>89</sup> SrCl <sub>2</sub> 1.48-1.85 MBq/kg; <sup>99</sup> Tc-MDP 100 mg/d, 6 days for a course, once a month, for 3 courses	Thrombocytopenia: 4 cases; leukopenia: 6 cases
Zhang W, et al [37] 2019	Prostate cancer, lung cancer, breast cancer, endometrial cancer, liver cancer, nasopharyngeal cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	55.6 ± 3.3	42.3%	26	<sup>89</sup> SrCl <sub>2</sub> 4 mci/d, 10 days for a course	4 cases (pain, leukopenia, thrombocytopenia, allergic reaction, gastrointestinal reaction)
			<sup>99</sup> Tc-MDP	56.3 ± 3.5	38.5%	26	<sup>99</sup> Tc-MDP 5.5 mg/d, intravenously, 5 days for a course	3 cases (pain, leukopenia, thrombocytopenia, allergic reaction, gastrointestinal reaction)
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	57.6 ± 3.1	42.3%	26	<sup>89</sup> SrCl <sub>2</sub> 4 mci/d, 10 days for a course; <sup>99</sup> Tc-MDP 5.5 mg/d, intravenously, 5 days for a course	4 cases (pain, leukopenia, thrombocytopenia, allergic reaction, gastrointestinal reaction)
Zhang J Y, et al [36] 2019	Breast cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	50.48 ± 8.1	100.0%	35	<sup>89</sup> SrCl <sub>2</sub> 48-1.85 MBq/kg.	Fever (2 cases), nausea (1 case), vomiting (1 case), elevated serum creatinine (0 cases), abnormal blood calcium (2 cases), hematotoxicity (6 cases of grade 1, 3 cases of grade 2, and 0 cases of grade 3)
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	48.81 ± 8.0		35	<sup>89</sup> SrCl <sub>2</sub> 48-1.85 MBq/kg; <sup>99</sup> Tc-MDP 11 mg/d, 10 days for a course	Fever (1 case), nausea and vomiting (1 case), elevated serum creatinine (1 case), abnormal blood calcium (3 cases), hematotoxicity (5 cases of grade 1, 2 cases of grade 2, 0 cases of grade 3)
Liu L, et al [23] 2019	Unspecified	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	56.8 ± 6.7	46.7%	60	<sup>89</sup> SrCl <sub>2</sub> 14.8 × 10 <sup>7</sup> /time	No adverse reaction
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	55.9 ± 7.0	43.3%	60	<sup>89</sup> SrCl <sub>2</sub> 14.8 × 10 <sup>7</sup> /time; <sup>99</sup> Tc-MDP 200 mg/d, 5 days for a course	

表1 (续)

Study/published year	Cancer	Evaluation	Group	Mean age/year	Gender (female)	Case n	Treatment	AE
Liu J G, et al [22] 2020	Prostate, breast, lung, stomach, and other cancers	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	58.2 ± 12.0	45.9%	37	<sup>89</sup> SrCl <sub>2</sub> 4mci, every 3-6 months	Leukocyte and platelet: 3 patients (with varying degrees), among which 1 patient received radiotherapy before treatment, 1 patient received chemotherapy before treatment, and 1 patient showed mild elevation of alanine aminotransferase in 3-4 weeks, which was reduced to normal after symptomatic treatment
			<sup>99</sup> Tc-MDP	59.3 ± 12.0	48.3%	29	<sup>99</sup> Tc-MDP 22 mg/d, 5 days for a course, once a month, for 2-3 courses	No adverse reaction
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	58.9 ± 12.0	48.3%	29	<sup>99</sup> Tc-MDP 22 mg/d, 5 days for a course, once a month, for 2-3 courses; <sup>89</sup> SrCl <sub>2</sub> 4 mci, every 3 to 6 months	Leukocyte and platelet: 3 patients (with varying degrees), among which 1 patient received radiotherapy before treatment, 1 patient received chemotherapy before treatment, and 1 patient showed mild elevation of alanine aminotransferase in 3-4 weeks, which was reduced to normal after symptomatic treatment
Fu Y J, et al [17] 2020	Prostate cancer	Rate of relief of bone pain and healing of bone metastases	<sup>89</sup> SrCl <sub>2</sub>	68.41 ± 7.2	0.0%	38	<sup>89</sup> SrCl <sub>2</sub> 1.48 MBq/kg	5.26% (2/38): anemic in 1 case; myelosuppression in 1 case
			<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub>	69.04 ± 6.9		39	<sup>89</sup> SrCl <sub>2</sub> 1.48 MBq/kg; <sup>99</sup> Tc-MDP, 20 days for a course, for 1 course	12.82% (5/39): poor appetite in 2 cases; fatigue in 1 case; phlebitis in 1 case; skin redness and swelling in 1 case

AE: Adverse event.

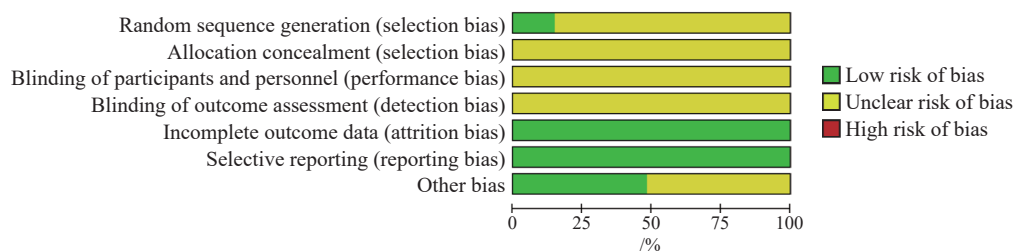


图2 纳入研究的方法学质量评价

Fig. 2 Evaluation of methodological quality of included studies

## 2.3 <sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤效果meta分析结果

### 2.3.1 骨痛缓解率

27篇文献<sup>[15-41]</sup>均报道了患者骨痛缓解情况,以骨痛缓解率作为评价疗效的主要指标,共2 564例患者。纳入的各研究间无统计学异质

性( $P=0.26$ ,  $I^2=14\%$ ),故采用固定效应模型分析,结果显示,<sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>治疗组的骨痛缓解率高于<sup>89</sup>SrCl<sub>2</sub>单药组,合并效应量显示其差异有统计学意义( $RR=1.22$ , 95% CI: 1.18~1.27,  $P<0.001$ ,图3)。

2.3.2 骨转移灶愈合率

共有18篇文献<sup>[16-23, 25, 28, 31-33, 36, 37, 39-41]</sup>均报道了患者骨转移灶愈合情况，以骨转移灶愈合率作为评价疗效的指标，共1 663例患者。纳入各研究间异质性差异无统计学意义 ( $P=0.07$ ,

$I^2=35%$ )，故采用固定效应模型分析，结果显示，<sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>治疗组的骨转移灶愈合率高于<sup>89</sup>SrCl<sub>2</sub>单药组，其差异有统计学意义 (RR=1.35, 95% CI: 1.25~1.47,  $P<0.001$ , 图4)。

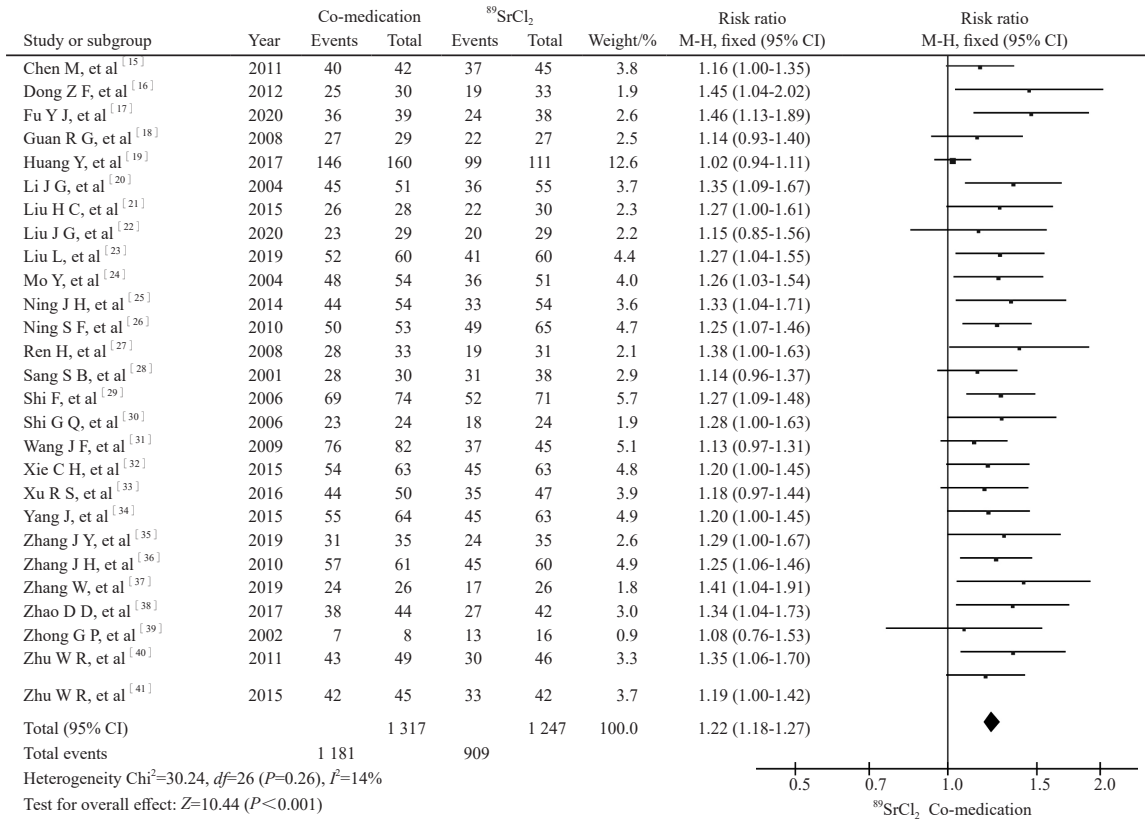


图3 联合用药与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移癌的骨痛缓解率森林图

Fig. 3 Forest plot comparing bone pain relief between <sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub> and <sup>89</sup>SrCl<sub>2</sub> alone group

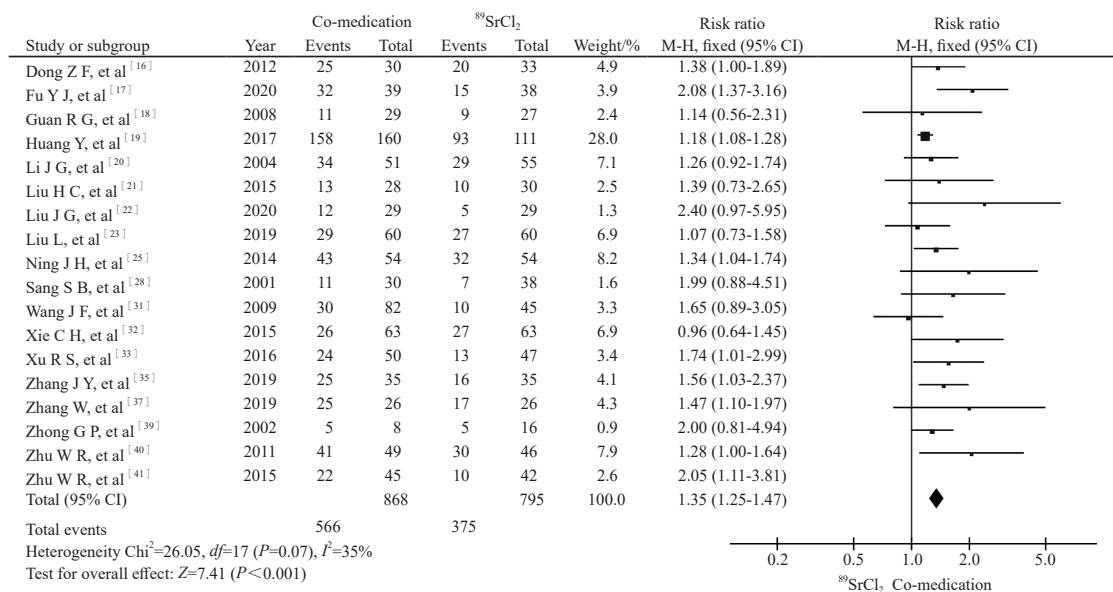


图4 联合用药与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移癌的骨转移灶愈合率森林图

Fig. 4 Forest plot comparing healing rate of bone metastases between <sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub> and <sup>89</sup>SrCl<sub>2</sub> alone group

## 2.4 单用<sup>99m</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤效果分析

### 2.4.1 骨痛缓解率

6篇文献<sup>[19, 21, 22, 31, 37, 39]</sup>报道了患者骨痛缓解情况, 以骨痛缓解率作为评价疗效的主要指标, 共519例患者。纳入各研究异质性差异无统计学意义 ( $P=0.87, I^2=0\%$ ), 故采用固定效应模型分析, 结果显示, <sup>99m</sup>Tc-MDP组的骨痛缓解率与<sup>89</sup>SrCl<sub>2</sub>单药组差异无统计学意义。合并效应量显示其差异无统计学意义 ( $RR=0.98, 95\% CI: 0.90\sim 1.06, P=0.57$ , 图5)。

### 2.4.2 骨转移灶愈合率

6篇文献<sup>[19, 21-22, 31, 37, 39]</sup>均报道了患者骨转移灶愈合情况, 以骨转移灶愈合率作为评价疗效的指标, 共519例患者。纳入各研究间异质性差异无统计学意义 ( $P=0.31, I^2=17\%$ ), 故采用固定效应模型分析, 结果显示, <sup>99m</sup>Tc-MDP组的骨转移灶愈合率与<sup>89</sup>SrCl<sub>2</sub>单药组差异无统计学意义, 合并效应量显示其差异无统计学意义 ( $RR=0.93, 95\% CI: 0.82\sim 1.06, P=0.27$ , 图6)。

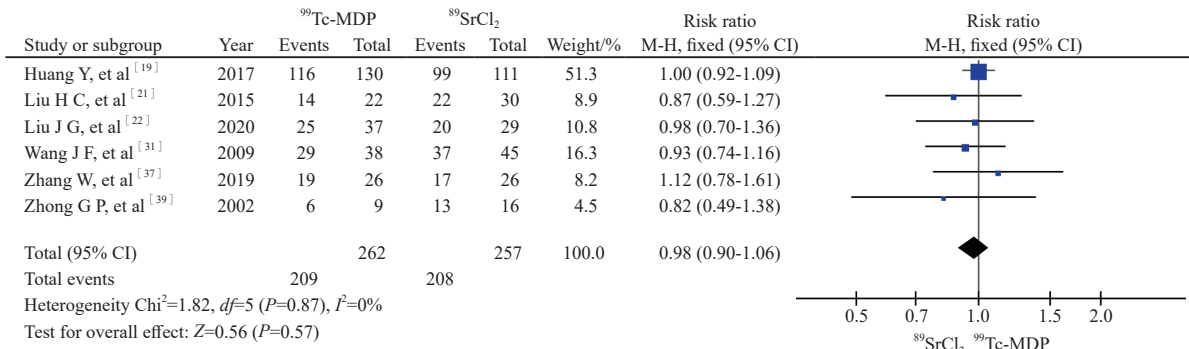


图5 单用<sup>99m</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的骨痛缓解率森林图

Fig. 5 Forest plot comparing bone pain relief between <sup>99m</sup>Tc-MDP alone and <sup>89</sup>SrCl<sub>2</sub> alone group

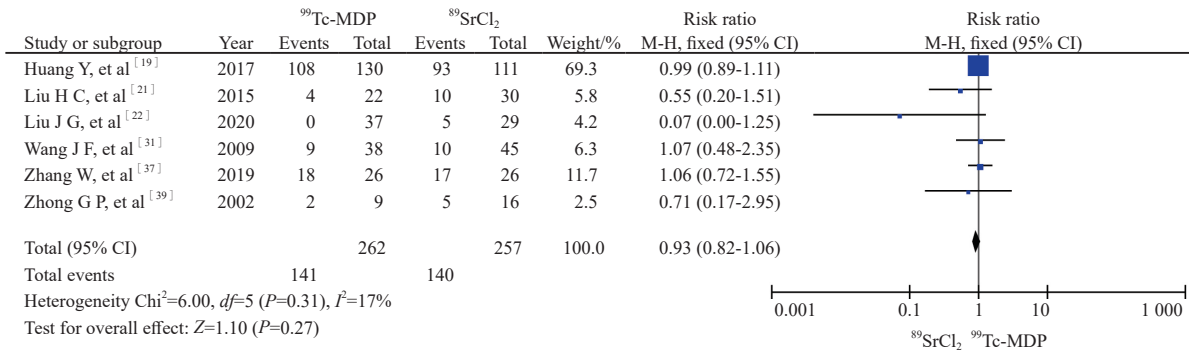


图6 单用<sup>99m</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的骨转移灶愈合率森林图

Fig. 6 Forest plot comparing healing rate of bone metastases between <sup>99m</sup>Tc-MDP alone and <sup>89</sup>SrCl<sub>2</sub> alone group

## 2.5 不良反应

### 2.5.1 不良反应总体情况

共有26篇文献<sup>[15-22, 24-36, 42]</sup>报道了患者用药后不良反应情况, 主要不良反应是白细胞计数下降、血小板计数下降、骨痛闪耀/加重以及胃肠道反应, 其中9篇研究提到白细胞、血小板计数下降治疗4~8周后可恢复至治疗前水平; 7篇研

究提及少数患者治疗后出现一过性骨痛加剧, 服用止痛药后3天内缓解或不予特殊处理7 d左右可自行缓解; 2篇研究报道单用<sup>99m</sup>Tc-MDP组患者无不良反应发生; 10篇研究提到各组间不良反应发生率差异无统计学意义 ( $P>0.05$ ); 其余部分研究报道到了恶心、呕吐、纳差、静脉炎等个例出现的不良反应, 均在治疗后自行好转。

### 2.5.2 <sup>99</sup>Tc-MDP联合<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的不良 反应Meta分析结果

共13篇研究<sup>[15-17, 19, 21-22, 25, 30, 32, 36-38, 40]</sup>报道了联合用药组和<sup>89</sup>SrCl<sub>2</sub>单药组不良反应总例数，以不良反应率作为评价不良反应的指标，

共1 191例患者，纳入研究各组间存在异质性（ $P < 0.001$ ， $I^2 = 89\%$ ），故选用随机效应模型。结果显示，联合用药组的不良反应发生率与<sup>89</sup>SrCl<sub>2</sub>单药组差异无统计学意义（RR=0.83，95% CI: 0.53~1.30， $P=0.42$ ，图7）。

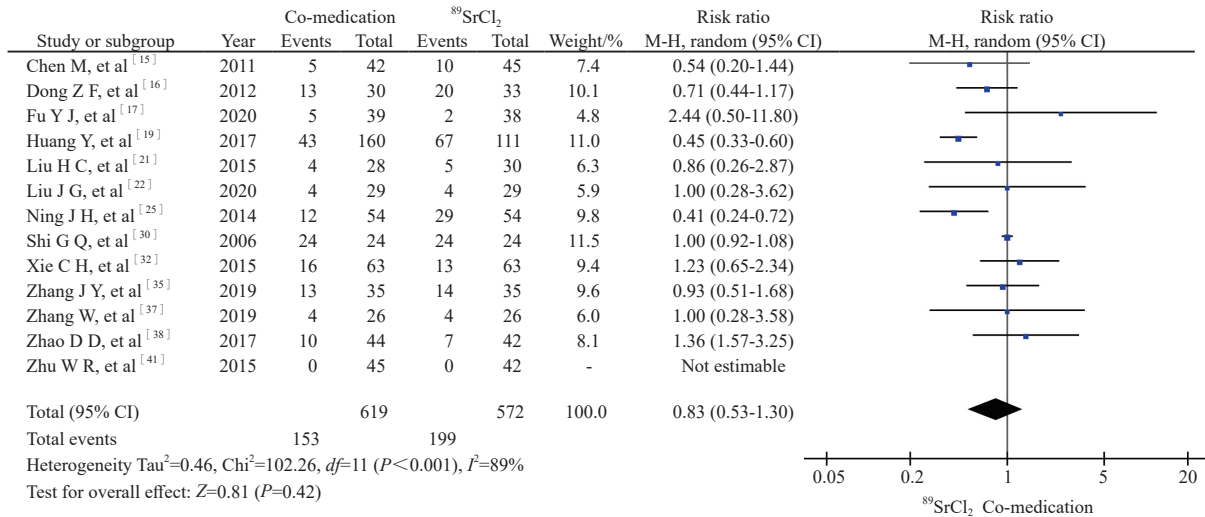


图7 联合用药与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的不良  
反应率森林图

Fig. 7 Forest plot comparing AEs between <sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub> and <sup>89</sup>SrCl<sub>2</sub> alone group

### 2.5.3 单用<sup>99</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤 的不良反应Meta分析结果

共4篇研究<sup>[19, 21-22, 37]</sup>报道了<sup>99</sup>Tc-MDP组和<sup>89</sup>SrCl<sub>2</sub>单药组不良反应总例数，以不良反应率作为评价不良反应的指标，共411例患者，

各研究间异质性差异无统计学意义（ $P = 0.11$ ， $I^2 = 50\%$ ），故采用固定效应模型，结果显示，<sup>99</sup>Tc-MDP组的不良反应发生率与<sup>89</sup>SrCl<sub>2</sub>单药组差异无统计学意义（RR = 0.93，95% CI: 0.76~1.13， $P=0.45$ ，图8）。

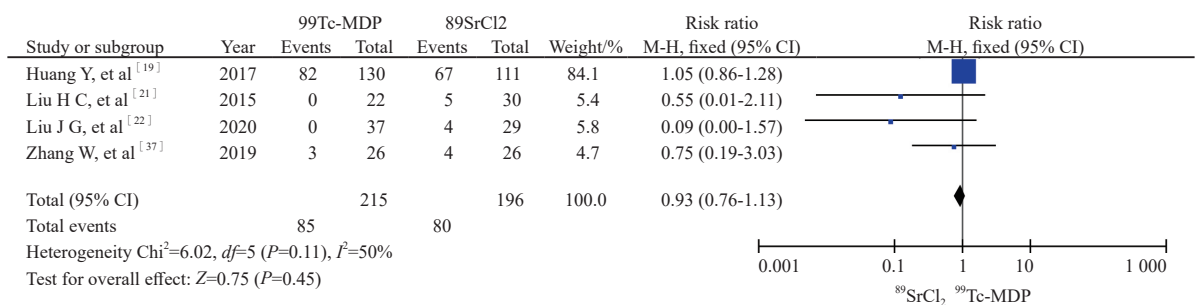


图8 单用<sup>99</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的不良  
反应率森林图

Fig. 8 Forest plot comparing AEs between <sup>99</sup>Tc-MDP alone and <sup>89</sup>SrCl<sub>2</sub> alone group

## 2.6 发表偏倚评估

以骨痛缓解率和骨转移灶愈合率为指标（纳入文献较多）绘制漏斗图。结果显示，所有研究漏斗图显示各散点几乎均匀分布在轴线两侧。总体来看，本研究纳入的文献存在较小的发表偏倚

可能性，结果较可靠（图9~12）。

## 2.7 敏感性分析

通过逐一剔除单个文献对研究结局进行敏感性分析。剔除前后结果无明显改变，表明meta分析合并结果基本稳定（表2）。

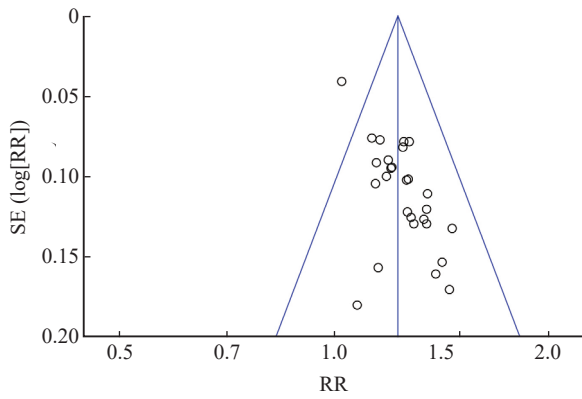


图9 联合用药与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的骨痛缓解率漏斗图  
**Fig. 9 Funnel plot of literature included in bone pain relief comparing between <sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub> and <sup>89</sup>SrCl<sub>2</sub> alone group**

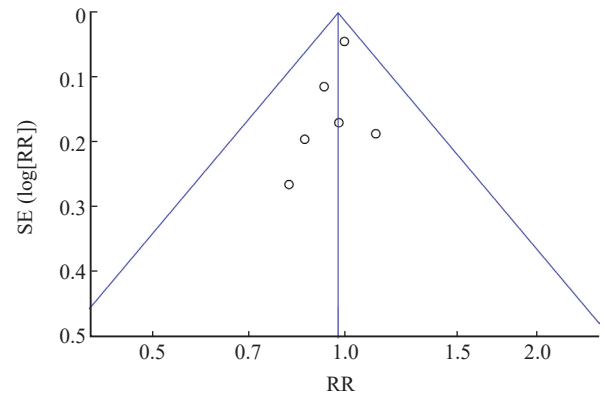


图11 单用<sup>99</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的骨痛缓解率漏斗图  
**Fig. 11 Funnel plot of literature included in bone pain relief comparing between <sup>99</sup>Tc-MDP alone and <sup>89</sup>SrCl<sub>2</sub> alone group**

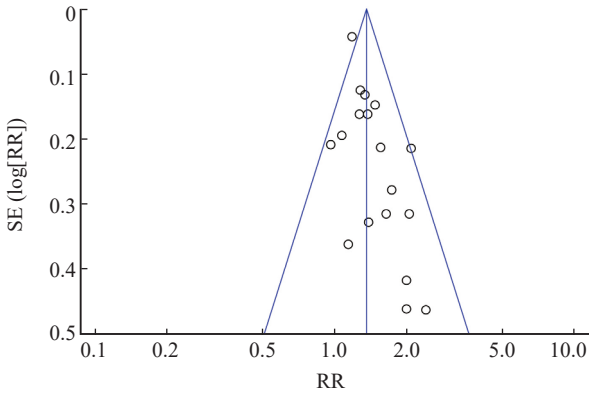


图10 联合用药与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的骨转移灶愈合率漏斗图

**Fig. 10 Funnel plot of literature included in healing rate of bone metastases comparing between <sup>99</sup>Tc-MDP in combination with <sup>89</sup>SrCl<sub>2</sub> and <sup>89</sup>SrCl<sub>2</sub> alone group**

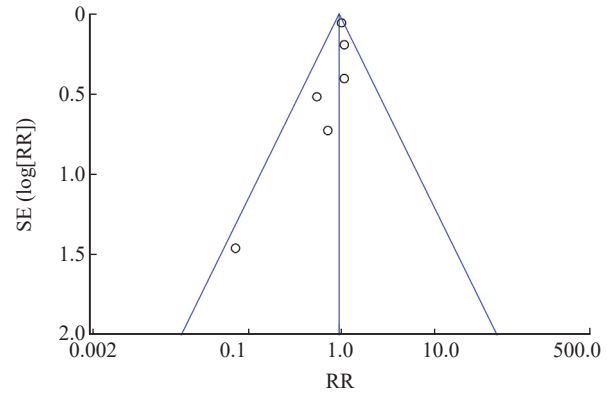


图12 单用<sup>99</sup>Tc-MDP与单用<sup>89</sup>SrCl<sub>2</sub>治疗骨转移瘤的骨转移灶愈合率漏斗图

**Fig. 12 Funnel plot of literature included in healing rate of bone metastases comparing between <sup>99</sup>Tc-MDP alone and <sup>89</sup>SrCl<sub>2</sub> alone group**

表2 敏感性分析结果

Tab. 2 Results of sensitivity analysis

Outcome	Before exclusion			After exclusion*		
	RR	95% CI	P value	RR	95% CI	P value
<sup>99</sup> Tc-MDP+ <sup>89</sup> SrCl <sub>2</sub> vs <sup>89</sup> SrCl <sub>2</sub>						
Bone pain relief rate	1.22	1.18-1.27	<0.001	1.22-1.25	1.17-1.31	<0.001
Bone metastases healing rate	1.35	1.25-1.47	<0.001	1.33-1.42	1.22-1.58	<0.001
Adverse reaction rate	0.83	0.53-1.30	0.42	0.76-0.89	0.47-1.41	0.08-0.59
<sup>99</sup> Tc-MDP vs <sup>89</sup> SrCl <sub>2</sub>						
Bone pain relief rate	0.98	0.90-1.06	0.57	0.95-0.99	0.82-1.10	0.40-0.76
Bone metastases healing rate	0.93	0.82-1.06	0.27	0.80-0.97	0.57-1.12	0.19-0.63
Adverse reaction rate	0.93	0.76-1.13	0.45	0.29-0.98	0.10-1.20	0.03-0.82

\*: The interval between the minimum and maximum value of the statistical indicator after exclusion.

### 3 讨 论

肿瘤细胞转移后能够诱导破骨性或成骨性细胞的病理学改变,临床中使用骨靶向药物如双磷酸盐、PANKL抑制剂和骨靶向放射性药物进行治疗具有较好效果。 $^{99}\text{Tc-MDP}$ 作为放射性核素治疗药物具有骨靶向性,通过靶向到达骨破坏区域抑制破骨细胞的活性来抑制肿瘤细胞转移后对骨的破坏,同时增加成骨细胞活性促进成骨,从而平衡骨代谢来缓解肿瘤骨转移患者的疼痛及骨量丢失。在临床中, $^{99}\text{Tc-MDP}$ 常作为联合 $^{89}\text{SrCl}_2$ 用药的选择,以期快速缓解患者疼痛和控制转移灶,但相较于单用 $^{99}\text{Tc-MDP}$ 或单用 $^{89}\text{SrCl}_2$ ,其安全性和有效性未能得到全面验证。本文旨在分析 $^{99}\text{Tc-MDP}$ 联合 $^{89}\text{SrCl}_2$ 相较于单用 $^{99}\text{Tc-MDP}$ 或单用 $^{89}\text{SrCl}_2$ 的有效性安全性。

相较于王洪良等<sup>[11]</sup>所进行的关于 $^{89}\text{SrCl}_2$ 联合 $^{99}\text{Tc-MDP}$ 治疗骨转移瘤效果的meta分析,本文纳入了单用 $^{99}\text{Tc-MDP}$ 治疗的数据进行对比分析,其结果更能支持二者联合应用对于骨转移瘤治疗的协同作用。对于不同病理学类型的肿瘤而言,宁尚峰等<sup>[26]</sup>提到联合组在肺癌、乳腺癌、鼻咽癌、直肠癌等方面优于 $^{89}\text{SrCl}_2$ 组,而对于前列腺癌两组治疗均佳,但证据不充分,需进一步临床验证和分析。除了刘琳等<sup>[23]</sup>的研究,其他26篇研究都报道了用药后的不良反应,从观察结果来看, $^{99}\text{Tc-MDP}$ 不论是联合 $^{89}\text{SrCl}_2$ 还是单独应用后,只有少数患者用药后发生不良反应,大多可自行好转或对症治疗数日内好转,均未出现严重的不良反应。在刘建国等<sup>[22]</sup>的研究中,个别发生不良反应的患者曾在治疗前接受过放疗或化疗,因此白细胞、血小板下降及一过性骨痛加剧等不良反应可能是由放射性核素类药物引起,也可能是其他治疗方式导致或者疾病本身的症状。钟甘平等<sup>[39]</sup>的研究中提到联合用药可以减少 $^{89}\text{SrCl}_2$ 治疗中一过性骨痛加重的情况发生。因此可以认为, $^{99}\text{Tc-MDP}$ 联合 $^{89}\text{SrCl}_2$ 或单独用于治疗骨转移瘤具有较高的安全性。

综上所述, $^{99}\text{Tc-MDP}$ 与 $^{89}\text{SrCl}_2$ 之间在治疗骨转移瘤方面具有协同作用, $^{99}\text{Tc-MDP}$ 与 $^{89}\text{SrCl}_2$ 联

合可提高恶性肿瘤骨转移患者的治疗效果和生存质量,而单用 $^{99}\text{Tc-MDP}$ 则在提高恶性肿瘤骨转移治疗有效率方面无明显作用,不论是联合治疗或是单独治疗,其安全性都值得肯定。本研究结果存在以下不足之处:①部分研究未说明分组是否随机、是否采用盲法,无法排除分配和实施的偏倚;②因 $^{99}\text{Tc-MDP}$ 为国产原研药,纳入文献均为中文文献,纳入的原始研究结果不能很好地代表所有人群;③纳入病例的特征(性别比例、人数、年龄、原发肿瘤类型等)不完全一致;④随访时间不一致。因此,期待未来进行大样本随机对照临床试验以得出更为准确可信的结论,并提供更多的循证医学依据。

**利益冲突声明:**所有作者均声明不存在利益冲突。

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