DOI:10.16781/j.0258-879x.2016.01.0005

·论　著·

单中心中国初诊前列腺癌患者骨转移预测因素分析

唐　亮[1,2△]，高　旭[1△]，许传亮[1]，陈国强[2]，王　燕[1]，王海峰[1]，孙颖浩[1*]
1. 第二军医大学长海医院泌尿外科，上海 200433
2. 龙岩市第二医院泌尿外科，龙岩 364000

[摘要]　**目的**　界定国人初诊前列腺癌患者骨转移高危因素，初步确定骨转移极低风险患者特征。**方法**　收集2010年至2015年在第二军医大学长海医院初次确诊的496例前列腺癌患者的临床资料。所有患者确诊后均行^{99m}Tc MDP注射的全身骨骼ECT扫描。分析所有患者确诊时的年龄、穿刺前末次前列腺特异抗原(PSA)、临床T分期、前列腺穿刺Gleason评分及骨扫描、相应MRI/CT结果。用单因素及多因素logistic回归方法得出预测骨转移的相关临床指标。**结果**　496例患者中，81例(16.3%)存在骨转移。骨转移组与无骨转移组的年龄无差异，但骨转移组患者PSA水平大于无骨转移组($P<0.001$)。随着PSA水平、临床T分期或穿刺Gleason评分升高，骨转移风险增大($P<0.001$)。单因素logistic回归分析显示，穿刺前PSA>20 ng/mL、临床T分期为T3～T4和活检Gleason评分≥8是骨转移的影响因素。多因素logistic回归显示，PSA>50 ng/mL和活检Gleason评分≥8是骨转移的独立预测因素。初诊PSA≤20 ng/mL且Gleason评分≤6的79例前列腺癌患者无一例出现骨转移。**结论**　初诊PSA≤20 ng/mL且Gleason评分≤6的中国前列腺癌患者骨转移发生率非常低，这部分患者在初诊时不需要行骨扫描检查。

[关键词]　前列腺肿瘤；骨转移；前列腺特异抗原；危险因素
[中图分类号]　R 737.25　　[文献标志码]　A　　[文章编号]　0258-879X(2016)01-0005-05

Independent predictors of bone metastases at the initial stage of prostate cancer diagnosis: a single center analysis in Chinese patients

TANG Liang[1,2△], GAO Xu[1△], XU Chuan-liang[1], CHEN Guo-qiang[2], WANG Yan[1], WANG Hai-feng[1], SUN Ying-hao[1*]
1. Department of Urology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China
2. Department of Urology, Second Hospital of Longyan City, Longyan 364000, Fujian, China

[**Abstract**]　**Objective**　To indentify the high risk factors of bone metastasis in Chinese patients at the initial stage of prostate cancer (PCa) diagnosis, so as to elucidate the characteristics of patients with very low risk of bone metastasis at the initial stage of prostate cancer. **Methods**　A consecutive series of 496 patients with newly diagnosed PCa between 2010 and 2015 were enrolled in the present study. All the patients were subjected to ECT scan for presence of bone metastasis (BM) using total-body ^{99m}Tc MDP scintigraphy regardless of baseline PCa characteristics. Factors including the age of diagnosis, prostate specific antigen (PSA) level at diagnosis, Gleason score, clinical T stage, bone scan and CT/MRI results were analyzed. Univariate and multivariate logistic regression analyses were performed to identify the predictors of bone metastases. **Results**　Of the 496 patients, 81 patients (16.3%) had bone metastases. The PSA levels of patients with BM were significantly higher than those without BM ($P<0.001$). The mean age of the patients with BM was not significantly older than that of the patients without BM. Patients with higher PSA level, clinical T stage or Gleason score showed a significantly higher risk of BM ($P<0.001$). Univariate logistic regression analysis showed that PSA>20 ng/mL at diagnosis, clinical stage at T3-T4 and Gleason score≥8 were the risk factors of bone metastasis in PCa patients. The multivariate analysis showed that the PSA level>50 ng/mL and the Gleason score≥8 were the independent predictors of bone metastases. No bone metastasis was found in 79 patients with PSA≤20 ng/mL and at the same time with Gleason score≤6. **Conclusion**　The bone metastases rate is very low in Chinese patients with a PSA level ≤20 ng/mL and at the same time with Gleason score≤6, so a bone scan is not necessary as a routine

[收稿日期]　2015-11-23　　[接受日期]　2015-12-31
[基金项目]　国家自然科学基金(81172076). Supported by National Natural Science Foundation of China(81172076).
[作者简介]　唐　亮，博士，主治医师. E-mail: ebaytldf@163.com; 高　旭，博士，教授. E-mail: gaoxu.changhai@gmail.com
△共同第一作者(Co-first authors).
*通信作者(Corresponding author). Tel: 021-31161719, E-mail: sunyh@medmail.com.cn

for these patients with newly diagnosed prostate cancer.

[**Key words**] prostatic neoplasms; bone metastasis; prostate-specific antigen; risk factors

[Acad J Sec Mil Med Univ, 2016, 37(1): 5-9]

在全球范围内，前列腺癌发病率在男性恶性肿瘤中排名第二[1]。中国前列腺癌的发病率较西方国家低[2]，但近年来已成为发病增长最迅速的恶性肿瘤[3-4]，一此研究报道转移性前列腺癌在初诊患者比例超过 20%[5]。近年来随着前列腺特异抗原(PSA)在前列腺癌诊疗中的应用，器官局限性前列腺癌的患者比例增加，初诊患者中骨转移比例降低[6-7]，特别是我国初诊前列腺癌患者骨转移比例在降低[8]。2014 年 NCCN 指南中推荐对临床 T1 期前列腺癌并且 PSA≥20 ng/mL 或临床分期 T2 且 PSA≥10 ng/mL 或 Gleason score≥8 或临床 T3、T4 期前列腺癌患者行骨扫描检查[9]。AUA 指南推荐无症状患者穿刺 Gleason 评分＞7 或者 PSA＞20 ng/mL 的患者行骨扫描[10]。近期 Briganti 等[11]应用分类与回归树分析方法对初次确诊前列腺癌患者的临床资料进行分析，发现 Gleason 评分＞7 分的患者或活检 Gleason 评分≤7 但 PSA ＞10 ng/mL，并且临床分期 T2～T4 的患者需要行骨骼 ECT 扫描。中国泌尿外科协会指南中指出，一旦前列腺癌确诊，即推荐骨骼 ECT 扫描，特别是 PSA≥20 ng/mL 或 Gleason 评分＞7 的患者[12]。

由此可见，各个指南或者权威文献中得出的结论并不完全一致，但其中 PSA≥20 ng/mL 以及 Gleason 评分≥8 是比较常见的划分界限。中国人群前列腺癌发生率及病死率均低于白种人[13-14]，中国人群前列腺癌有其自身特点，国外指南可能并不适合中国人初诊患者。本研究通过对中国初诊前列腺癌患者的临床相关资料进行单因素及多因素 logistic 回归分析，旨在找到与骨转移相关的预测指标，同时找到骨转移发生率极低的患者特征。

1　材料和方法

1.1　*数据来源*　2010 年至 2015 年在第二军医大学长海医院初次确诊为前列腺癌的患者 496 例。所有患者均行骨 ECT 扫描检查(^{99m}Tc MDP)。收集患者的年龄、穿刺前末次 PSA、临床 T 分期和穿刺 Gleason 评分等数据。临床 T 分期按照 2002 UICC TNM 分期标准[15]，患者在进行骨扫描检查时均未接受内分泌治疗。患者数据来源于长海医院前列腺癌数据库[16]。本研究经长海医院伦理委员会批准，所有患者均签署知情同意书(但不涉及研究的具体目的和方法)。

1.2　*骨转移诊断标准*　所有骨骼 ECT 扫描均由经验丰富的医生进行读片、撰写报告。若骨骼 ECT 不能确定是否存在骨转移，则进一步行 CT/MRI 明确有无骨转移。骨 ECT 中骨转移通常表现为单发或多发非对称区域内放射性浓聚，这些改变在排除骨退变或者先前骨骼创伤后即可诊断为骨转移[17]。根据诊断结果将患者分为骨转移与无骨转移组。

1.3　*统计学处理*　统计软件采用 SPSS 20.0 (SPSS, Chicago, IL, USA)。年龄和 PSA 水平以中位数(范围)表示。两组间年龄、PSA 水平差异采用 Kruskal-Wallis 平均方差分析，分类变量(PSA、临床 T 分期、Gleason 评分)采用 χ^2 检验。对可能的影响因素进行单因素及多因素 logistic 回归分析，评价骨转移阳性患者的预测指标。检验水准(α)为 0.05。

2　结　果

2.1　*两组一般资料比较*　2010 年至 2015 年长海医院确诊为前列腺癌的患者共 496 例，其中 392 例(79.0%)患者骨扫描结果为阴性。余 104 例患者(21.0%)中，49 例患者骨扫描结果为确定有骨转移，55 例患者提示为骨转移可疑。采用 CT、MRI 对这 55 例患者进行进一步检查，确定 32 例患者存在骨转移，另外 23 例患者则排除了骨转移。因此，总共 81 例患者(16.3%)通过 ECT 或 MRI/CT 确定初诊时存在骨转移。所有纳入患者按照骨转移与无骨转移分组后的情况见表 1，骨转移组与无骨转移组的年龄差异无统计学意义(P=0.562)，但骨转移组患者临床 T 分期、穿刺前末次 PSA 水平和活检 Gleason 评分高于无骨转移组(P<0.001)。

2.2　*骨转移预测指标分析*　单因素 logistic 回归分析显示，穿刺前 PSA＞20 ng/mL、临床 T 分期为 T3～T4和活检 Gleason 评分≥8 是骨转移的影响因素；通过多因素 logistic 回归显示，PSA＞50 ng/mL 和活检 Gleason 评分≥8 是骨转移的独立预测因素(表 2)。

表 1　骨转移和无骨转移两组患者基本资料及临床特征比较

Tab 1　Comparison of baseline data and clinical characteristics of bone metastasis and non-bone metastasis groups

Index	Total N=496	Non-bone metastasis n=415	Bone metastasis n=81	P value
Age (year), median(range)	69.0(47-89)	69.0(47-89)	69.5(47-86)	0.562
Clinical stage n(%)				<0.001
T_1	212(100.0)	194(91.5)	18(8.5)	
T_2	191(100.0)	164(85.9)	27(14.1)	
T_3	60(100.0)	43(71.7)	17(28.3)	
T_4	33(100.0)	14(42.4)	19(57.6)	
PSA ρ_B/(ng·mL^{-1}), median(range)	19.3(0.4-4 348.0)	16.0(0.4-999.0)	94.1(5.0-4 348.6)	<0.001
PSA n(%)				<0.001
≤10 ng·mL^{-1}	122(100.0)	117(95.9)	5(4.1)	
>10 and ≤20 ng·mL^{-1}	131(100.0)	123(92.4)	8(6.1)	
>20 and ≤50 ng·mL^{-1}	125(100.0)	111(88.8)	14(11.2)	
>50 and ≤100 ng·mL^{-1}	64(100.0)	43(67.2)	21(32.8)	
>100 ng·mL^{-1}	54(100.0)	21(38.9)	33(61.1)	
Biopsy Gleason score n(%)				<0.001
≤6	118(100.0)	112(94.9)	6(5.1)	
3+4	100(100.0)	98(98.0)	2(2.0)	
4+3	81(100.0)	72(88.9)	9(11.1)	
8-10	197(100.0)	133(67.5)	64(32.5)	

PSA: Prostate-specific antigen

表 2　前列腺癌骨转移单因素和多因素 logistic 回归分析结果

Tab 2　Univariate and multivariate logistic analysis results of bone metastasis of prostate cancer

Factor	Univariate analysis		Multivariate analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
PSA				
≤10 ng·mL^{-1}	Reference			Reference
>10 and ≤20 ng·mL^{-1}	1.522(0.484,4.786)	0.472	1.245(0.379,4.083)	0.718
>20 and ≤50 ng·mL^{-1}	2.951(1.029,8.465)	0.044	1.963(0.655,5.885)	0.228
>50 and ≤100 ng·mL^{-1}	11.428(4.055,32.304)	0.000	5.620(1.847,17.098)	0.002
>100 ng·mL^{-1}	36.771(12.880,104.978)	0.000	14.793(4.637,47.199)	0.000
Biopsy Gleason score				
≤6	Reference			Reference
3+4	0.381(0.075,1.931)	0.224	0.430(0.082,2.250)	0.318
4+3	2.629(0.916,7.550)	0.072	1.638(0.515,5.213)	0.403
8-10	8.982(3.749,21.521)	0.000	4.360(1.676,11.339)	0.003
Clinical stage				
T_1	Reference			Reference
T_2	1.774(0.944,3.337)	0.075	0.810(0.389,1.686)	0.573
T_3	4.261(2.032,8.936)	0.000	0.814(0.326,2.036)	0.660
T_4	16.581(7.094,38.755)	0.000	2.109(0.728,6.113)	0.169
Age	1.010(0.978,1.042)	0.552	1.008(0.972,1.047)	0.659

PSA: Prostate-specific antigen

2.3　*骨转移极低风险患者特征分析*　本次研究的患者数据显示，初诊 PSA≤20 ng/mL 且 Gleason 评分≤6 的中国前列腺癌患者共计 79 例，无一例出现骨转移。此外，有 73 例患者活检 Gleason 评分=3+4且 PSA≤20 ng/mL，这部分患者中也仅有 2 例患者出现骨转移。

3　讨　论

近年来随着 PSA 在前列腺癌诊疗中的应用，器官局限性前列腺癌的患者比例增加，我国初诊前列腺癌患者骨转移比例在降低[8]。对于这些骨转移风险很低的患者来说，^{99m}Tc MDP 骨扫描就成为一种费时且价格不菲的检查，导致医疗资源浪费，同时该检查还对患者造成一定程度放射性损害，因此找到与骨转移相关的预测指标，界定骨转移发生率极低的患者特征具有重要意义。全球范围内有不少文献报道了关于初诊前列腺癌患者骨转移发生率及预测因素，所得结论不尽相同[18-24]。Lee 等[18]纳入病例的骨转移发生率与本研究相近，通过多因素回归分析得出穿刺前末次 PSA、临床 T 分期、肿瘤病理分级为骨转移的独立预测因素。Kosuda 等[24]认为，穿刺前末次 PSA≤10 ng/mL 或者 Gleason 评分≤6 的患者初次确诊时不需行骨扫描检查，PSA、Gleason 评分为独立预测因素。本研究通过单因素 logistic 回归分析得出穿刺前末次 PSA、穿刺 Gleason 评分、临床 T 分期(TNM 2002)为骨转移的影响因素，多因素 logistic 回归发现穿刺前末次 PSA>50 ng/mL 和 Gleason 评分≥8 为骨转移的独立预测因素。Tanaka 等[25]回顾性分析了 857 例日本初诊前列腺癌患者数据，通过多因素回归分析得出 PSA>50 ng/mL 和 Gleason 评分≥4+3 为骨转移独立预测因素。本研究中独立预测因素的 Gleason 评分较 Tanaka 等[25]研究结果略高，但 PSA 浓度均>50 ng/mL。

通过本次回顾性分析发现，对于初诊 PSA≤20 ng/mL且 Gleason 评分≤6 的中国前列腺癌患者是不需行骨扫描检查的。本研究中初诊 PSA≤20 ng/mL 且 Gleason 评分≤6 的 79 例中国前列腺癌患者无一例出现骨转移；另有 73 例 Gleason 评分=3+4 且 PSA≤20 ng/mL 的患者，也仅有 2 例患者出现了骨转移。但为了更加严格地排除初诊骨转移患者，我们将穿刺前末次 PSA≤20 ng/mL 且穿刺 Gleason 评分≤6 定为初诊患者无需行骨扫描的界值。同时，对于穿刺前末次 PSA>50 ng/mL 或 Gleason 评分≥8 的患者，应当高度怀疑骨转移。

应当注意的是，有文献报道，对前列腺穿刺病理进行复审时，会有一部分病理报告与第 1 次读片结果有差别[26]。因此，严格且准确的病理读片报告是初诊患者排除骨转移的重要前提条件。

[参 考 文 献]

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013[J]. CA Cancer J Clin, 2013,63:11-30.

[2] Center M M, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates[J]. Eur Uurol,2012,61:1079-1092.

[3] 全国肿瘤防治研究办公室卫生部疾病预防控制局. 中国肿瘤登记年报 2004[M]. 北京：中国协和医科大学出版社，2008.

[4] 赫　捷，陈万青. 2012 中国肿瘤登记年报[M]. 北京：军事医学科学出版社，2013.

[5] Lai M H, Luk W H, Chan J C. Predicting bone scan findings using sPSA in patients newly diagnosed of prostate cancer: feasibility in Asian population[J]. Urol Oncol,2011,29:275-279.

[6] Gallina A, Chun F K, Suardi N, Eastham J A, Perrotte P, Graefen M, et al. Comparison of stage migration patterns between Europe and the USA: an analysis of 11 350 men treated with radical prostatectomy for prostate cancer[J]. BJU Int, 2008, 101:1513-1518.

[7] Ryan C J, Elkin E P, Small E J, Duchane J, Carroll P. Reduced incidence of bony metastasis at initial prostate cancer diagnosis: data from CaPSURE[J]. Urol Oncol,2006,24:396-402.

[8] Wang Y, Guo J, Xu L, Zhao N, Xu Z, Wang H, et al. Should bone scan be performed in Chinese prostate cancer patients at the time of diagnosis[J]. Urol Int, 2013,91:160-164.

[9] Clinical recommendations [EB/OL]. [2015-12-25] *http://www.nccn.org/professionals/physician_gls/f_guidelines.asp*

[10] Thompson I, Thrasher J B, Aus G, Burnett A L, Canby-Hagino E D, Cookson M S, et al. Guideline for the management of clinically localized prostate cancer: 2007 update[J]. J Urol ,2007,177:2106-2131.

[11] Briganti A, Passoni N, Ferrari M, Capitanio U, Suardi N, Gallina A, et al. When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines

and proposal of a novel risk stratification tool[J]. Eur Urol,2010, 7:551-558.

[12] 那彦群,叶章群,孙颖浩,孙　光. 中国泌尿外科疾病诊断治疗指南[M]. 北京:人民卫生出版社,2014: 64.

[13] Meng E, Sun G H, Wu S T, Chuang F P, Lee S S, Yu D S, et al. Value of prostate-specific antigen in the staging of Taiwanese patients with newly diagnosed prostate cancer[J]. Arch Androl, 2003,49:471-474.

[14] Farkas A, Marcella S, Rhoads G G. Ethnic and racial differences in prostate cancer incidence and mortality [J]. Ethn Dis, 2000,10:69-75.

[15] Sobin L H, Wittekind C H. TNM classification of malignant tumors[M]. 6th ed. New York: Wiley-Liss Inc., 2002.

[16] 高　旭，王海峰，王　燕，许传亮,孙颖浩. 基于浏览器/服务器架构的前列腺癌数据库的构建和临床应用[J]. 中华泌尿外科杂志,2015,36: 694-698.

[17] Hricak H, Choyke P L, Eberhardt S C, Leibel S A, Scardino P T. Imaging prostate cancer: a multidisciplinary perspective[J]. Radiology,2007,243: 28-53.

[18] Lee N, Fawaaz R, Olsson C A, Benson M C, Petrylak D P, Schiff P B, et al. Which patients with newly diagnosed prostate cancer need a radionuclide bone scan An analysis based on 631 patients[J]. Int J Radiat Oncol Biol Phys,2000,48:1443-1446.

[19] Ataus S, Citçi A, Alici B, Onder A U, Sönmezoğlu K, Erözenci A, et al. The value of serum prostate specific antigen and other parameters in detecting bone metastases in prostate cancer[J]. Int Urol Nephrol, 1999,31:481-489.

[20] Lin K, Szabo Z, Chin B B, Civelek A C. The value of a baseline bone scan in patients with newly diagnosed prostate cancer[J]. Clin Nucl Med,1999,24:579-582.

[21] Lorente J A, Valenzuela H, Morote J, Gelabert A. Serum bone alkaline phosphatase levels enhance the clinical utility of prostate specific antigen in the staging of newly diagnosed prostate cancer patients[J]. Eur J Nucl Med,1999,26:625-632.

[22] Bruwer G, Heyns C F, Allen F J. Influence of local tumour stage and grade on reliability of serum prostate-specific antigen in predicting skeletal metastases in patients with adenocarcinoma of the prostate[J]. Eur Urol,1999,35:223-227.

[23] Salonia A, Gallina A, Camerota T C, Picchio M, Freschi M, DaPozzo L F, et al. Bone metastases are infrequent in patients with newly diagnosed prostate cancer: analysis of their clinical and pathologic features [J]. Urology,2006,68:362-366.

[24] Kosuda S, Yoshimura I, Aizawa T, Koizumi K, Akakura K, Kuyama J, et al. Can initial prostate specific antigen determinations eliminate the need for bone scans in patients with newly diagnosed prostate carcinoma A multicenter retrospective study in Japan [J]. Cancer, 2002, 94:964-972.

[25] Tanaka N, Fujimoto K, Shinkai T, Nakai Y, Kuwada M, Anai S, et al. Bone scan can be spared in asymptomatic prostate cancer patients with PSA of ≤ 20 ng/mL and Gleason score of ≤6 at the initial stage of diagnosis[J]. Jpn J Clin Oncol, 2011, 41:1209-1213.

[26] Brimo F, Schultz L, Epstein J I. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy[J]. J Urol, 2010,184:126-130.

[本文编辑] 孙　岩