中国骨质疏松杂志 2013年3月第19卷第3期 Chin J Osteoporos, March 2013, Vol 19, No. 3
Published online www. wanfangdate. com. cn doi:10. 3969/j. issn. 1006-7108. 2013. 03. 009

·临床研究·

前列腺癌雄激素剥夺治疗与骨质丢失

吴燕华 刘伟 郝文科(审)

中图分类号：R737.25 **文献标识码**：A **文章编号**：1006-7108(2013)03-0233-06

摘要：**目的** 前列腺癌是男性泌尿系统常见的恶性肿瘤之一。我国前列腺癌的发病率在迅速上升。目前绝大多数患者采取雄激素剥夺治疗，与化疗相比，雄激素剥夺治疗的毒副作用较轻，更容易被患者接受，但仍会引起一系列的不良反应，本文将对前列腺癌雄激素剥夺治疗后骨质丢失的情况及防治策略进行综述。

关键词：前列腺癌；雄激素剥夺治疗；雄激素；骨质丢失

Androgen deprivation therapy for prostate cancer and bone loss *WU Yanhua, LIU Wei, HAO Wenke.*

Guangdong People's Hospital, Guangzhou 510080, China
Corresponding author: WU Yanhua, Email: sunny4666@163.com

Abstract: Prostate cancer is one of the common malignant tumors of the urinary system in the male. The incidence of prostate cancer in China is rising rapidly. At present, the vast majority of patients are receiving androgen deprivation therapy (ADT). Compared with chemotherapy, ADT has less toxic side effect, and it is more likely to be accepted by patients. However, ADT causes a range of adverse reactions. This paper reviews the risk of bone loss after ADT and the prevention and treatment strategies in patients with prostate cancer.

Key words: Prostate cancer; Androgen deprivation therapy; Androgen; Bone loss

前列腺癌(Prostate cancer)是老年男性常见的恶性肿瘤。在西方国家，前列腺癌的发病率占男性恶性肿瘤的第一位及男性肿瘤患者主要死亡原因的第二位[1,2]。虽然我国的发病率明显低于西方国家，但随着人口老龄化的加重、人们生活水平的提高、饮食结构的改变及诊断手段的提高，国内前列腺癌的发病率亦呈逐渐增高的趋势。由于前列腺癌的早期诊断和治疗手段的进步，前列腺癌的生存率越来越高。有研究显示，所有分期的前列腺癌患者5年相对生存率由1986年的80%增高到2007年的98.8%[3]。2010年美国癌症学会资料显示，局限或局灶前列腺癌的患者5年总体存活率达到100%，而已发生转移的前列腺癌患者的5年总体存活率亦达到31%[4]。

1 雄激素剥夺治疗是前列腺癌重要的治疗手段

前列腺癌的发生和进展依赖于雄激素(androgen)。雄激素是男性性激素，包括睾酮、脱氢表雄酮、雄烯二酮、雄烯二醇和双氢睾酮等类固醇激素，其中主要是睾酮(testosterone)和双氢睾酮(dihydrotestosterone, DHT)。90~95%的雄激素由睾丸分泌，剩余5%~10%由肾上腺分泌。睾酮是人体循环中主要的雄激素，而双氢睾酮作用更强，它与雄激素受体的亲和力较睾酮高5倍。睾酮进入前列腺细胞后，90%在5α-还原酶作用下转换成双氢睾酮[5]。雄激素受体(androgen receptor, AR)是一种雄激素活化转录因子，属于核受体超家族。双氢睾酮与雄激素受体结合，诱导雄激素受体与热休克蛋白分离而促进雄激素受体磷酸化。磷酸化的雄激素受体二聚化，进而转位至细胞核，结合到靶基因启动子区域的雄激素反应元件，辅助活化因子和辅助抑制因子结合到雄激素受体复合体，促进或抑制前列腺癌细胞中调控生长和生存的靶基因，最终影响前列腺癌细胞的发生和进展[6]。因此，减少或抑制雄激素的作用是阻断前列腺癌发生和发展的重要手段。

作者单位：510080 广州，广东省医学科学院，广东省老年医学研究所
通讯作者：吴燕华，Email：sunny4666@163.com

雄激素剥夺治疗(androgen deprivation therapy, ADT)是指通过减少睾酮分泌或阻断雄激素受体而使前列腺癌细胞雄激素受体失活,包括去势治疗(castration)、抗雄激素治疗和二者结合[7]。

1941 年,Huggins 和 Hodges 首先证实雄激素抑制治疗对转移性前列腺癌的有效性[8]。此后,ADT 成为治疗晚期前列腺癌的主要手段。早期 ADT 包括睾丸切除术(orchiectomy)或雌激素疗法。睾丸切除术对患者生理结构完整性和心理影响较大,且作用不可逆,而雌激素疗法对心血管不良反应较多等缺点,因此,近 20 年来促性腺激素释放激素激动剂(gonadotropin-releasing hormone [GnRH] agonists)逐渐取代睾丸切除术和雌激素疗法成为最常用的 ADT 方法。

GnRH 激动剂早期刺激 GnRH 受体,引起促黄体生成激素(luteinizing hormone, LH)和卵泡刺激素(follicle-stimulating hormone, FSH)明显升高,进而导致睾酮显著升高。GnRH 激动剂诱导的过度刺激破坏固有的 LH 释放脉冲调控,导致受体失敏或下调,最后抑制 LH 和 FSH 分泌,降低睾酮达到去势水平(即睾酮≤50 ng/dl)。但是,这种早期睾酮水平的明显增高可以刺激前列腺癌细胞生长,进而加重患者症状,如骨转移患者出现疼痛加剧[9]。目前临床使用的 GnRH 激动剂有亮丙瑞林(Leuprolide)、戈舍瑞林(Goserelin)、曲普瑞林(Triptorelin)和布舍瑞林(Buserelin)。

新近报道的 GnRH 拮抗剂(GnRH antagonists)则提供了另一种雄激素剥夺的方法。它的作用更直接,竞争性结合并阻断脑垂体 GnRH 受体,直接阻断 LH 和 FSH 的分泌,快速抑制睾酮产生。因此,它不产生 GnRH 激动剂早期的冲击效应[10]。目前供临床使用的 GnRH 拮抗剂有 Degarelix 和阿巴瑞克(Abarelix)。

目前报道的其他激素类制剂有:酮康唑(Ketoconazole)和阿比特龙(Abiraterone):通过抑制肾上腺 17-α-羟化酶/17, 20-裂解酶(CYP17A1)而减少肾上腺睾酮分泌。氟他胺(Flutamide)和度他雄胺(Dutasteride):抑制前列腺 5α-还原酶,降低睾酮转化成双氢睾酮。雄激素受体拮抗剂:与 GnRH 激动剂联用降低睾酮的冲击效应,包括甾体类抗雄激素:环丙孕酮(Cyroterone);非甾体类抗雄激素:比卡鲁胺(Bicalutamide),氟他胺(Flutamide),尼鲁米特(Nilutamide)和 MDV3100[9]。

ADT 可以提高前列腺癌患者无病生存率和总体生存率,在前列腺癌的治疗中具有重要地位,因此,近 20 年 ADT 的应用越来越广泛[11, 12]。ADT 是晚期或转移性前列腺癌治疗的首要方法。它可以减少晚期前列腺癌患者肿瘤相关事件,如脊髓压迫、骨外转移、病理性骨折和尿路梗阻,而延迟接受 ADT 患者的死亡率高于早期接受 ADT 患者[13, 14]。ADT 也是中危或高危早期前列腺癌患者手术或放射治疗的辅助治疗手段。对局灶进展或高危的局灶前列腺癌患者,ADT 联合放疗能控制局部病变,减少转移发生,提高无病生存率和总体生存率[15, 16]。ADT 还是早期前列腺癌患者手术或放疗后复发的补救措施。

虽然 ADT 给前列腺癌患者带来许多益处,但是 ADT 引起的雄激素下降不可避免会导致各种不良反应,如生活质量下降、贫血、认知改变、肥胖、血脂变化、胰岛素抵抗、糖尿病、冠心病、骨质丢失、骨折等。近年来,ADT 引起的骨质疏松和骨折风险越来越受到关注。

2 雄激素剥夺治疗引起骨质丢失

骨质疏松(osteoporosis)和前列腺癌都是年龄相关性疾病。前列腺癌诊断和死亡的中位年龄分别为 67 岁和 80 岁,而超过 70% 的前列腺癌患者年龄大于 65 岁,存在骨质疏松和脆性骨折的风险。正常男性中年后骨质丢失速率约每年 0.5% ~1.0%[17],而接受 ADT 的患者骨质丢失速率为每年 1% ~4.6%[18]。这表明 ADT 引起的骨质丢失较正常的年龄相关骨质丢失更迅速,更严重。因此,ADT 引起骨质丢失的防治越来越受到重视。

目前研究表明,ADT 降低骨密度(bone mineral density, BMD),增加骨骼脆性,使骨折(fracture)发生风险增高。

前列腺癌患者接受 ADT 1 年后 BMD 减少,在髋部、脊椎和桡骨远端 BMD 分别减少 2% ~4%、2% ~5% 和 5.3%[21-24]。Smith 等研究显示非转移性前列腺癌患者接受亮丙瑞林治疗 1 年后 BMD 下降 2.5%[25]。Greenspan 等发现非转移性前列腺癌患者接受短期(<6 个月)ADT 1 年后,髋部、股骨粗隆、桡骨、全身和后前位脊柱 BMD 分别减少 2.5%、2.4%、2.6%、3.3% 和 1.5%;而接受长期(≥6 个月)ADT 1 年后,桡骨 BMD 减少 2.0%[26]。一项对 390 例前列腺癌患者随访 10 年的研究显示,接受 ADT 患者骨质疏松发生率为 80%,未接受 ADT 者为 35.4%[27]。另一项 Meta 分析显示,接受 ADT 的

前列腺癌患者总体BMD及髋部BMD均低于未接受ADT患者;而且接受ADT患者骨质疏松发生率高于未接受ADT患者,接受ADT患者发生骨质疏松的风险均高于未接受ADT患者和健康对照人群,汇总危险比分别为1.30和2.26;该研究还显示,腰椎BMD和髋部BMD与ADT时间呈负相关[28]。非转移性前列腺癌患者不论接受连续或间断ADT,在治疗开始后6至12个月即出现BMD下降[29,30]。另有报道接受连续ADT患者2年后骨质丢失超过10%,每年腰椎、髋部和股骨颈BMD下降分别为1.4%~4.6%,0.6%~3.3%和0.7%~3.9%[18,31]。Lee等研究显示与接受间断ADT患者比较,接受连续ADT患者发生骨质疏松的总体优势比为2.14,提示间断ADT对骨质疏松的不良影响较连续ADT低,而且连续ADT持续时间越长,BMD下降更快[32]。上述研究表明ADT使前列腺癌患者BMD下降,骨质疏松发生率和发生风险增加。但上述随访时间多数仅限于1年,仅有少数随访超过治疗后2年;而间断ADT对BMD下降的长期效应目前尚不清楚。因此,将来研究需要更多关注更长时间ADT对骨质疏松的影响。

Shahinian等研究显示接受ADT的前列腺癌者骨折发生率高于未接受ADT者,分别为19.4%和12.5%[33]。Dickman等研究显示18,000例接受睾丸切除术前列腺癌患者,10年后股骨颈骨折发生率为12%,而普通人群为5%[34]。另一项研究回顾性分析了395例前列腺癌患者资料,平均随访时间为66个月,7%患者出现脆性骨折[32]。Oefelein等报道接受ADT的前列腺癌患者5年和10年的骨折发生率分别为13%和33%[35]。Smith等研究一项大型队列研究显示,与匹配对照组比较,GnRH激动剂使用组临床骨折、椎骨骨折和髋部骨折的危险比分别为1.21、1.18和1.76[36]。Taylor等回顾分析显示接受ADT的前列腺癌患者与未接受ADT患者比较,总体骨折风险增加23%[37]。Manitoba等研究显示目前和既往接受ADT的患者骨折的校正优势比分别为1.71和2.42[38]。Ontario研究显示,采用ADT的患者继发骨折的校正危险比为1.65[39]。另一项超过50,000例前列腺癌患者的研究显示,使用超过9次剂量GnRH激动剂的患者骨折相对危险度为1.45,与睾丸切除术组相当[33]。上述研究表明,ADT使前列腺癌患者骨折发生率和骨折风险增高,而且随着ADT时间的延长,骨折的风险更高。但上述研究仅局限于骨折,未对病理性骨折或骨质疏松性骨折进行分层,也没有与BMD进行相关分析。

ADT引起骨质疏松的机制,与ADT后低雄激素水平有关。在不同的年龄阶段,雄激素对骨起着不同的作用:青春期,雄激素可促进骨骼生长、骨矿物质的沉积;成年后,雄激素通过促进骨形成和抑制骨吸收,并与其他骨代谢调节激素共同维持骨量和调节骨代谢,在男性骨稳态的维持中发挥重要作用。(1)雄激素与成骨细胞上的受体结合,影响成骨细胞的增殖、分化,促进细胞因子、生长因子的分泌及基质蛋白(包括胶原蛋白、骨钙素、成骨蛋白等)的合成,在骨代谢中起调节和相互平衡的作用。(2)雄激素具有抑制骨吸收的作用,进而维持骨骼的结构完整性[19],可抑制骨质吸收刺激因子如甲状旁腺素、白细胞介素1、白细胞介素6的作用。(3)成骨细胞与破骨细胞上有雌激素受体,骨骼也是雌激素重要靶器官,睾酮在脂肪和骨髓通过P450芳香酶的作用转化为雌激素,以雌激素为介导对骨起作用。前列腺癌患者接受ADT后引起循环中睾酮水平下降,进而使睾酮转化成雌二醇的数量减少,亦使体内雌激素水平下降,从而抑制骨形成,促进骨再吸收,最终导致骨质丢失[5,20]。

3 雄激素剥夺治疗引起骨质丢失的临床表现与评估

3.1 ADT引起骨质丢失的临床表现

ADT导致的骨质丢失较难被早期意识到,骨质丢失较轻者,可无症状,仅在X线摄片或BMD测量时被发现,较重患者常诉有腰背疼痛、乏力和全身骨痛。其中骨痛通常是弥漫性,区别于骨转移灶引起的疼痛,没有固定的压痛点。另外,患者可因轻微活动、创伤、弯腰、负重、挤压或摔倒发生骨折。多发生于脊柱、髋部和前臂等。

3.2 ADT引起骨质丢失的评估

双能量X射线吸收计量法(dual-energy x-ray absorptiometry, DEXA)是目前应用最广的测定BMD的方法。世界卫生组织(WHO)采纳基于DEXA方法的T值(T score)系统作为参照标准对骨质疏松和骨量减少(osteopenia)进行诊断[40]。骨质疏松和骨量减少的定义为:以年轻健康女性为参照人群,T值小于-2.5个标准差为骨质疏松;T值大于-2.5个标准差而小于-1个标准差为骨量减少。

已有报道建议对接受超过6个月长期ADT的患者行DEXA扫描,但随访间隔目前尚未达成统一意见。有报道建议监测治疗前,治疗后12个月(治

疗前 BMD 正常者)或 6 个月(治疗前骨量减少者)的 BMD[41]。另一报道建议每 24 个月监测 BMD,对于存在其他加速骨质丢失危险因素者每 18 个月监测 1 次[42]。

其他技术如定量计算机断层摄影术(CT)、X 线照相、定量超声和核磁共振成像(MRI)等,能了解骨密度和结构,但主要用于科研,不作为诊断标准。

为了更好评估骨质疏松性骨折的其他危险因素,WHO 提供了骨折风险评估工具(Fracture Risk Assessment Tool, FRAX)用于评估 10 年后髋部骨折和任何骨质疏松性骨折的风险。该工具纳入了性别、年龄、体重指数、既往骨折病史、双亲髋部骨折、长期使用皮质激素、类风湿性关节炎(或骨质疏松的继发性因素,包括 ADT 的使用)、吸烟、饮酒和股骨颈 BMD 状态等相关临床指标。另有组织提出简化半定量系统(CAROC)用于评估 10 年后骨折风险分层。10 年主要骨质疏松性骨折风险分层有三层:低风险(<10%),中风险(10% ~20%)和高风险(>20%)。当 10 年主要骨质疏松骨折风险超过 20% 时需要开始治疗。虽然目前尚未制定有关 ADT 相关骨丢失的风险评估方法,但是上述骨折风险评估方法结合骨密度检查对 ADT 引起骨质疏松的防治措施制定具有重要意义[43, 44]。

4 ADT 引起骨质疏松和骨折的防治

骨质丢失引起的骨质疏松及骨折使患者躯体功能和生活质量下降,而且增加患者住院率和死亡率,使患者医疗费用提高。因此,对 ADT 引起骨质丢失的评估和防治是临床医师特别是老年科医师需要关注的重点。目前 ADT 引起骨质疏松的防治措施包括改变生活方式和药物干预。

4.1 改变生活方式

改变生活方式的措施包括:戒烟、戒酒和运动。负重练习和肌肉增强运动已证实能增加骨质疏松患者的骨密度,减少骨折风险。专家建议接受 ADT 患者应定期参加运动,如抵抗训练和负重练习[43-47]。

4.2 药物干预

目前有多种有效的药物用于预防和治疗 ADT 引起的骨质疏松。

4.2.1 补充钙剂和维生素 D:钙离子和维生素 D 是维持正常骨骼内环境平衡的重要。钙剂和维生素 D 已证实能增加骨密度,降低骨折风险。NCCN 指南建议所有接受 ADT 患者每日需补充钙剂(500mg 元素钙)和维生素 D(800IU)。另有报道每日补充钙剂(1500mg 元素钙)和维生素 D(800IU)对治疗 ADT 引起的骨量减少和骨质疏松有效[43-47]。

4.2.2 双膦酸盐(Bisphosphonate):双膦酸盐包括口服制剂:如阿仑膦酸(alendronate)和利塞膦酸(risedronate);静脉制剂:如帕米膦酸(pamidronate)和唑来膦酸(zolendronic acid)。它通过抑制破骨细胞活性而减少骨再吸收,是目前治疗男性骨质疏松的常用药物之一。目前研究表明双膦酸盐能有效预防前列腺癌患者 ADT 引起的骨质丢失。相关临床指南建议对于接受 ADT 的前列腺癌高危患者或 ADT 过程中出现骨质丢失的患者,双膦酸盐可用于预防骨质疏松。

多项研究显示对于接受 ADT 的非转移性前列腺癌患者,帕米膦酸、阿仑膦酸或唑来膦酸能有效减少 1 年后骨质丢失,增加骨密度[48-50]。由于目前多数研究随访时间不长,故有关双膦酸盐能否预防骨折发生目前仍不清楚。

4.2.3 Denosumab:Denosumab 是一种单克隆抗体,拮抗核因子 κB 配体受体活化因子,抑制破骨细胞的分化和活化。近来研究表明在接受 ADT 的非转移性前列腺癌患者中,Denosumab 可以增加所有部位的骨密度,降低新发椎骨骨折的发生率[43-47]。

4.2.4 降钙素(Calcitonin):鲑降钙素可以抑制骨再吸收,是不能耐受其他治疗的男性骨质疏松患者的二线治疗药物[43]。

4.2.5 选择性雌激素受体调节物(selective estrogen receptor modulators, SERMS):已有研究表明对于接受 ADT 的前列腺癌患者,雷洛昔芬(Raloxifene)可增加骨密度,降低椎骨骨折风险。另有报道托瑞米芬(Toremifene)对接受 ADT 的前列腺癌患者的骨骼健康具有有益作用[43-47]。

综上所述,ADT 是前列腺癌治疗的重要手段。ADT 明显增加前列腺癌患者骨质疏松和骨折的风险,ADT 引起的骨质疏松和骨折的防治需引起临床医师,特别是老年科医师的重视。

【参考文献】

[1] Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011, 61: 212-236.

[2] Eastham JA, Evans CP, Zietman A. What is the optimal management of high risk, clinically localized prostate cancer? Urol Oncol. 2010, 28: 557-567.

[3] SEER. Surveillance, Epidemiology and End Results (SEER):

Stat Fact Sheets: Prostate Cancer. 2008.

[4] American Cancer Society. Facts and Figures 2010. Available from: http: //www. cancer. org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-and-figures-2010.

[5] Sue A. Brown, Theresa A. Guise. Cancer treatment-related bone disease. Crit Rev Eukaryot Gene Expr. 2009, 19(1): 47-60.

[6] Chuu CP, Kokontis JM, Hiipakka RA, et al. Androgens as therapy for androgen receptor-positive castration-resistant prostate cancer. J Biomed Sci. 2011, 18(1): 63-73.

[7] Loblaw DA, Mendelson DS, Talcott JA, et al. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol. 2004, 22(14): 2927-2941.

[8] Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer J Clin 1972, 22: 232-240.

[9] Choi S, Lee AK. Efficacy and safety of gonadotropin-releasing hormone agonists used in the treatment of prostate cancer. Drug Healthc Patient Saf. 2011, 3: 107-119.

[10] Laurent Boccon-Gibod, Egbert van der Meulen, Bo-Eric Persson. An update on the use of gonadotropin-releasing hormone antagonists in prostate cancer. Ther Adv Urol. 2011, 3(3): 127-140.

[11] Barry MJ, Delorenzo MA, Walker-Corkery ES, et al. The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. BJU Int. 2006, 98(5): 973-978.

[12] Shahinian VB, Kuo YF, Freeman JL, et al. Increasing use of gonadotropinreleasing hormone agonists for the treatment of localized prostate carcinoma. Cancer. 2005, 103(8): 1615-1624.

[13] Mottet N, Bellmunt J, Bolla M, et al. EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer. Eur Urol. 2011, 59(4): 572-583.

[14] NCCN. NCCN Clinical Practice Guidelines in Oncologyt. Prostate cancer. National Comprehensive Cancer Network: Fort Washington, PA, 2011.

[15] Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011, 378(9809): 2104-2111.

[16] Payne H, Mason M. Androgen deprivation therapy as adjuvant/neoadjuvant to radiotherapy for high-risk localised and locally advanced prostate cancer: recent developments. Br J Cancer. 2011, 105(11): 1628-1634.

[17] Higano CS. Understanding treatments for bone loss and bone metastases in patients with prostate cancer: a practical review and guide for the clinician. Urol Clin North Am. 2004, 31: 331-352.

[18] Higano CS. Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? Nat Clin Pract Urol. 2008, 5(1): 24-34.

[19] Leder BZ, LeBlanc KM, Schoenfeld DA, et al. Differential effects of androgens and estrogens on bone turnover in normal men. J Clin Endocrinol MeTab. 2003, 88(1): 204-210.

[20] Saylor PJ, Smith MR. Bone health and prostate cancer. Prostate Cancer Prostatic Dis. 2010, 13(1): 20-27.

[21] Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med. 2001, 345(13): 948-955.

[22] Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003, 169(6): 2008-2012.

[23] Maillefert JF, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol. 1999, 161(4): 1219-1222.

[24] Mittan D, Lee S, Miller E, et al. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol MeTab. 2002, 87(8): 3656-3661.

[25] Smith MR, Goode M, Zietman AL, et al. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol. 2004, 22(13): 2546-2553.

[26] Greenspan SL, Coates P, Sereika SM, et al. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endocrinol MeTab. 2005, 90(12): 6410-6417.

[27] Morote J, Morin JP, Orsola A, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology. 2007, 69(3): 500-504.

[28] Ary Serpa Neto, Marcos Tobias-Machado, Marcos AP Esteves, et al. A systematic review and meta-analysis of bone metabolism in prostate adenocarcinoma. BMC Urol. 2010, 10: 9-18.

[29] Galvão DA, Spry NA, Taaffe DR, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008, 102(1): 44-47.

[30] Maillefert JF, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol. 1999, 161(4): 1219-1222.

[31] Ross RW, Small EJ. Osteoporosis in men treated with androgen deprivation therapy for prostate cancer. J Urol. 2002, 167(5): 1952-1956.

[32] Malcolm JB, Derweesh IH, Kincade MC, et al. Osteoporosis and fractures after androgen deprivation initiation for prostate cancer. Can J Urol. 2007, 14(3): 3551-3559.

[33] Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005, 352(2): 154-164.

[34] Dickman PW, Adolfsson JAN, Astrom K, et al. Hip fractures in

men with prostate cancer treated with orchiectomy. J Urol. 2004, 172(6 Pt 1): 2208-2212.

[35] Oefelein MG, Ricchuiti V, Conrad W, et al. Skeletal fracture associated with androgen suppression induced osteoporosis: the clinical incidence and risk factors for patients with prostate cancer. J Urol. 2001, 166(5): 1724-1728.

[36] Smith MR, Boyce SP, Moyneur E, et al. Risk of clinical fracture after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol. 2006, 175(1): 136-139.

[37] Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer. 2009, 115(11): 2388-2399.

[38] Lau YK, Lee E, Prior HJ, et al. Fracture risk in androgen deprivation therapy: a Canadian population based analysis. Can J Urol. 2009, 16(6): 4908-4914.

[39] Alibhai SM, Duong-Hua M, Sutradhar R, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol. 2009, 27(21): 3452-3458.

[40] Kanis JA, McCloskey EV, Johansson H, et al. A reference standard for the description of osteoporosis. Bone. 2008, 42(3): 467-475.

[41] Edmonton, AB. Prostate Cancer. Clinical practice guideline GU-004. Alberta Health Services: 2007.

[42] Wood L, Wilke D, Rendon R, et al. on behalf of the Genitourinary Cancer Site Team. Guidelines for the Management of Prostate Cancer. Halifax, NS: Cancer Care Nova Scotia; 2005.

[43] Lee CE, Leslie WD, Czaykowski P, et al. A comprehensive bone-health management approach for men with prostate cancer receiving androgen deprivation therapy. Curr Oncol. 2011, 18(4): e163-e172.

[44] VanderWalde A, Hurria A. Aging and osteoporosis in breast and prostate cancer. CA Cancer J Clin. 2011, 61(3): 139-156.

[45] Body JJ. Prevention and treatment of side-effects of systemic treatment: bone loss. Ann Oncol. 2010, 21(S7): vii180-vii185.

[46] Brufsky AM. Cancer treatment-induced bone loss: pathophysiology and clinical perspectives. Oncologist. 2008, 13(2): 187-195.

[47] Mohile SG, Mustian K, Bylow K, et al. Management of complications of androgen deprivation therapy in the older man. Crit Rev Oncol Hematol. 2009, 70(3): 235-255.

[48] Brufsky AM. Cancer treatment-induced bone loss: pathophysiology and clinical perspectives. Oncologist. 2008, 13(2): 187-195.

[49] Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw. 2010, 8(2): 162-200.

[50] Kapoor A, Gupta A, Desai N, et al. Effect of zoledronic Acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. Prostate Cancer. 2011, 2011: 156-164.

(收稿日期:2012-03-30)

(上接第 296 页)

【参考文献】

[1] Gambacciani M, Vacca F. Postmenopausal osteop-orosis and hormone replacement therapy. Minerva Med. 2004, 95: 507-520.

[2] 王建华,张智海,钟平,等. 北京女性骨质疏松患病率调查分析. 航空航天医药,2008,19(2):85.86.

[3] 马宗军,王一农,马宁,等. 宁夏地区回族正常人群骨密度及骨质疏松患病率研究. 中国骨质疏松杂志,2008,14(4):254-257.

[4] BuehbinderR, OsborneRH, EbelingPR, et al. ARandomizedTrial of Vertebroplasty for Painful Osteoporotie Vertebral Fractures. The new england journal of medicine,2009;361(6):557-568.

[5] 陈小花,陈雪娥,张丽. 指导及协助病人翻身的研究. 现代护理,2005,11(18):1505.

[6] 韦军民. 老年外科病人的围术期营养支持. 临床外科杂志,2008,16(12):798.

[7] 杨述华. 骨科并发症防治. 北京:人民卫生出版社,2008:171-174.

[8] Munoz-Torres M, Alonso G, Raya MP. Calcitonin therapy in osteoporosis. Treat Endocrinol. 2004, 3: 117-132.

[9] Mehta NM, Malootian A, Gilligan JP. Calcitonin for osteoporosis and bone pain. Curr Pharm Des. 2003, 9: 2659-2676.

[10] 袁皓瑜,袁晓群,刘加吾,等. 2006~2007 年株洲市芦淞区伤害流行病学研究. 实用预防医学,2009,16(2):352-354.

[11] 袁皓瑜,危胜平,王国良,等. 依托项目平台,实现基层疾控科研跨越. 中华疾病控制杂志,2010,14(4):365-366.

[12] Hoesel LM, Pausch M, Schnettle R, et al. The impact of osteoporosis on the classification of hip and wrist fractures. Med Sci Monit,2008,14(3):1-8.

[13] Tuck SP, Datta HK. Osteoporosis in the aging male: treatment options. Clin Inter Aging,2007;2(4):521-536.

[14] 张盘德, 冯彦林, 张自茂. 佛山地区中老年人骨密度测定及骨质疏松患病率分析. 中国骨质疏松杂志,2008,14(8):567-569.

[15] 张毅,曾平,李宁华. 北京崇文区中老年原发性骨质疏松症的发生及其影响因素:分层多阶段整群抽样调查. 中国组织工程研究与临床康复, 2007,11(27):5332-5335.

[16] 马宗军,王一农,马宁,等. 宁夏地区回族正常人群骨密度及骨质疏松患病率研究. 中国骨质疏松杂志,2008,14(4):254-257.

(收稿日期: 2012-10-31)

前列腺癌雄激素剥夺治疗与骨质丢失

作者： 吴燕华， 刘伟， WU Yanhua， LIU Wei
作者单位： 510080广州,广东省医学科学院,广东省老年医学研究所
刊名： 中国骨质疏松杂志ISTIC
英文刊名： Chinese Journal of Osteoporosis
年，卷(期)： 2013,19(3)

参考文献(50条)

1. Siegel R;Ward E;Brawley O Cancer statistics,2011:the impact of eliminating socioeconomic and racial disparities on premature cancer deaths 2011

2. Eastham JA;Evans CP;Zietman A What is the optimal management of high risk,clinically localized prostate cancer 2010

3. SEER Surveillance,Epidemiology and End Results (SEER):Stat Fact Sheets:Prostate Cancer 2008

4. American Cancer Society Facts and Figures 2010 2010

5. Sue A.Brown;Theresa A.Guise Cancer treatment-related bone disease 2009(01)

6. Chuu CP;Kokontis JM;Hiipakka RA Androgens as therapy for androgen receptor-positive castration-resistant prostate cancer 2011(01)

7. Loblaw DA;Mendelson DS;Talcott JA American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic,recurrent,or progressive prostate cancer 2004(14)

8. Hug,gins C;Hodges CV Studies on prostatic cancer.I.The effect of castration,of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate 1972

9. Choi S;Lee AK Efficacy and safety of gonadotropin-releasing hormone agonists used in the treatment of prostate cancer 2011

10. Laurent Boccon-Gibod;Egbert van der Meulen;Bo-Eric Persson An update on the use of gonadotropin-releasing hormone antagonists in prostate cancer 2011(03)

11. Barry M J;Delorenzo MA;Walker-Corkery ES The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing:a populationbased cohort study 2006(05)

12. Shahinian VB;Kuo YF;Freeman JL Increasing use of gonadotropinreleasing hormone agonists for the treatment of localized prostate carcinoma 2005(08)

13. Mottet N;Bellmunt J;Bolla M EAU Guidelines on Prostate Cancer.Part Ⅱ:Treatment of Advanced,Relapsing,and Castration-Resistant Prostate Cancer 2011(04)

14. NCCN NCCN Clinical Practice Guidelines in Oncologyt 2011

15. Warde P;Mason M;Ding K Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer:a randomised,phase 3 trial 2011(9809)

16. Payne H;Mason M Androgen deprivation therapy as adjuvant/neoadjuvant to radiotherapy for high-risk localised and locally advanced prostate cancer:recent developments 2011(11)

17. Higano CS Understanding treatments for bone loss and bone metastases in patients with prostate cancer:a practical review and guide for the clinician 2004

18. Higano CS Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer:what do we really know 2008(01)

19. Leder BZ;LeBlanc KM;Schoenfeld DA Differential effects of androgens and estrogens on bone turnover in normal men 2003(01)

20. Saylor PJ;Smith MR Bone health and prostate cancer 2010(01)

21. Smith MR;McGovern FJ;Zietman AL Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer 2001(13)

22. Smith MR;Eastham J;Gleason DM Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer 2003(06)

23. Maillefert JF;Sibilia J;Michel F Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma 1999(04)

24. Mittan D;Lee S;Miller E Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs 2002(08)

25. Smith MR;Goode M;Zietman AL Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer:effects on bone mineral density and body composition 2004(13)

26. Greenspan SL;Coates P;Sereika SM Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer 2005(12)

27. Morote J;Morin JP;Orsola A Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer 2007(03)

28. Ary Serpa Neto;Marcos Tobias-Machado;Marcos AP Esteves A systematic review and meta-analysis of bone metabolism in prostate adenocarcinoma 2010

29. Galv(a)o DA;Spry NA;Taaffe DR Changes in muscle,fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer 2008(01)

30. Maillefert JF;Sibilia J;Michel F Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma 1999(04)

31. Ross RW;Small EJ Osteoporosis in men treated with androgen deprivation therapy for prostate cancer 2002(05)

32. Malcolm JB;Derweesh IH;Kincade MC Osteoporosis and fractures after androgen deprivation initiation for prostate cancer 2007(03)

33. Shahinian VB;Kuo YF;Freeman JL;Goodwin JS Risk of fracture after androgen deprivation for prostate cancer 2005(02)

34. Dickman PW;Adolfsson JAN;Astrom K Hip fractures in men with prostate cancer treated with orchiectomy 2004(6 Pt 1)

35. Oefelein MG;Ricchuiti V;Conrad W Skeletal fracture associated with androgen suppression induced osteoporosis:the clinical incidence and risk factors for patients with prostate cancer 2001(05)

36. Smith MR;Boyce SP;Moyneur E Risk of clinical fracture after gonadotropin-releasing hormone agonist therapy for prostate cancer 2006(01)

37. Taylor LG;Canfield SE;Du XL Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer 2009(11)

38. Lau YK;Lee E;Prior H J Fracture risk in androgen deprivation therapy:a Canadian population based analysis 2009(06)

39. Alibhai SM;Duong-Hua M;Sutradhar R Impact of androgen deprivation therapy on cardiovascular disease and diabetes 2009(21)

40. Kanis JA;McCloskey EV;Johansson H A reference standard for the description of osteoporosis 2008(03)

41. Edmonton,AB Prostate Cancer.Clinical practice guideline GU-004 2007

42. Wood L;Wilke D;Rendon R on behalf of the Genitourinary Cancer Site Team 2005

43. Lee CE;Leslie WD;Czaykowski P A comprehensive bone-health management approach for men with prostate cancer receiving androgen deprivation therapy 2011(04)

44. VanderWalde A;Hurria A Aging and osteoporosis in breast and prostate cancer 2011(03)

45. Body JJ Prevention and treatment of side-effects of systemic treatment:bone loss 2010(z7)

46. Brufsky AM Cancer treatment-induced bone loss:pathophysiology and clinical perspectives 2008(02)

47. Mohile SG;Mustian K;Bylow K Management of complications of androgen deprivation therapy in the older man 2009(03)

48. Brufsky AM Cancer treatment-induced bone loss:pathophysiology and clinical perspectives 2008(02)

49.Mohler J;Bahnson RR;Boston B NCCN clinical practice guidelines in oncology:prostate cancer 2010(02)

50.Kapoor A;Gupta A;Desai N Effect of zoledronic Acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog 2011