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## 作为局限性前列腺癌患者预后标志物的前列腺特异性抗原密度

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**绪论。**在改善前列腺癌患者治疗结果的领域中,最重要的任务是按风险组正确分层。现代分层系统不能为所有前列腺癌患者提供充分的风险评估。用于预测特定患者前列腺癌临床病程的算法的进一步开发可以积极影响疾病的病程和结果。

**目的:**前列腺特异性抗原(pPSA)密度在接受激素联合放射治疗的局限性前列腺癌患者中的临床和预后价值测定。

**材料与amp;方法。**在1996年1月至2007年7月期间接受联合激素放射治疗的272例局限性前列腺癌患者中,评估了pPSA参数对肿瘤特异性生存率以及肿瘤过程的临床和形态学参数的影响。

**结果。**pPSA指标的高度临床意义已得到证实。PPSA的增加与血清PSA浓度的增加、PSA倍增时间的减少以及肿瘤分化的减少相关。pPSA的预后价值在接受联合激素放射治疗的局限性前列腺癌患者中得到证实。使用ROC分析,确定pPSA指数的阈值为 $0.36 \text{ ng}/(\text{ml}/\text{cm}^3)$ ,超过该阈值与肿瘤特异性生存水平的统计学显著降低相关。曲线下面积为0.703 (95% CI 0.236 - 0.434;  $p < 0.001$ )。随着pPSA值的增加,肿瘤特异性死亡和复发的风险也会增加。

**结论。**pPSA参数是一种可靠的前列腺癌生物标志物,具有很高的临床和预后意义,其使用与引入昂贵且繁琐的实验室和仪器诊断方法无关。

**关键词:**前列腺癌;肿瘤特异性生存率;前列腺特异性抗原;PSA;PSA密度。

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# Prostate-specific antigen density as a prognostic marker in patients with localized prostate cancer

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**BACKGROUND:** The most important task in the field of improving the results of treatment of patients with prostate cancer (PCa) is their correct stratification by risk groups. Modern stratification systems do not fully provide an adequate risk assessment for all patients with prostate cancer. Further development of algorithms for predicting the clinical course of prostate cancer for a particular patient can positively affect the course and outcome of the disease.

**AIM:** Determination of the clinical and prognostic value of the density of prostate-specific antigen (PSAD) in patients with localized prostate cancer who underwent combined external beam radiation with androgen deprivation therapy.

**MATERIALS AND METHODS:** The effect of the PSAD parameter on the tumor-specific survival rates, as well as the clinical and morphological parameters of the tumor process, was assessed in 272 patients with localized prostate cancer who underwent combined external beam radiation with androgen deprivation therapy from January 1996 to July 2007.

**RESULTS:** The high clinical significance of the PSAD indicator has been demonstrated. An increase in PSAD correlated with an increase in serum PSA concentration, a decrease in PSA doubling time, and a decrease in tumor differentiation. The prognostic value of PSAD was confirmed in patients with localized prostate cancer who received combined hormone-radiation therapy. Using ROC-analysis, the threshold value of the PSAD index was determined –  $0.36 \text{ ng / ml / cm}^3$ , the excess of which was associated with a statistically significant decrease in the level of tumor-specific survival. The area under the curve was 0.703 (95% CI 0.236–0.434;  $p < 0.001$ ). The risk of tumor-specific mortality and recurrence increased as the PSAD value increased.

**CONCLUSION:** The PSAD parameter is a reliable biomarker of prostate cancer with high rates of clinical and prognostic significance, the use of which is not associated with the introduction of costly and cumbersome methods of laboratory and instrumental diagnostics.

**Keywords:** prostate cancer; cancer-specific survival; prostate specific antigen; PCa; PCa density.

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# Плотность простатспецифического антигена как прогностический маркер у больных локализованным раком предстательной железы

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**Введение.** Важнейшая задача в области улучшения результатов лечения больных раком предстательной железы — это их правильная стратификация по группам риска. Современные системы стратификации не позволяют в полной мере обеспечить адекватную оценку риска для всех больных раком предстательной железы. Дальнейшее развитие алгоритмов прогнозирования клинического течения рака предстательной железы для конкретного больного может положительным образом повлиять на течение и исход заболевания.

**Цель.** Определение клинического и прогностического значения плотности простатспецифического антигена (пПСА) у больных локализованным раком предстательной железы, перенесших комбинированное гормоно-лучевое лечение.

**Материалы и методы.** Проведена оценка влияния параметра пПСА на показатели опухоль-специфической выживаемости, а также клинико-морфологические параметры опухолевого процесса у 272 пациентов с локализованным раком предстательной железы, получавших комбинированное гормоно-лучевое лечение в период с января 1996 г. по июль 2007 г.

**Результаты.** Продемонстрирована высокая клиническая значимость показателя пПСА. Повышение пПСА коррелировало с увеличением концентрации сывороточного ПСА, снижением времени удвоения ПСА, уменьшением дифференцировки опухоли. Подтверждено прогностическое значение пПСА у пациентов с локализованным раком предстательной железы, получавших комбинированное гормоно-лучевое лечение. С помощью ROC-анализа определено пороговое значение показателя пПСА — 0,36 нг/(мл·см<sup>3</sup>), превышение которого было связано со статистически значимым снижением уровня опухоль-специфической выживаемости. Площадь под кривой составила 0,703 (95 % ДИ 0,236–0,434;  $p < 0,001$ ). Риск опухоль-специфической смертности и возникновения рецидива возрастает по мере увеличения показателя пПСА.

**Заключение.** Параметр пПСА является надежным биомаркером рака предстательной железы с высокими показателями клинической и прогностической значимости, использование которого не связано с внедрением затратных и обременительных методов лабораторной и инструментальной диагностики.

**Ключевые слова:** рак предстательной железы; опухоль-специфическая выживаемость; простатический специфический антиген; ПСА; плотность ПСА.

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## 绪论

俄罗斯前列腺癌(PC)在恶性肿瘤发病率结构中排名第二,在60岁以上的男性中,排名第一[1]。尽管仪器和实验室诊断方法得到了发展,但对局部前列腺癌患者的疾病分期的准确预测仍远非完美。预测是根据直肠指检数据、血清前列腺特异性抗原(PSA)的初始浓度和前列腺活检(PC)的组织学检查结果。根据格里森量表确定的肿瘤分化程度,活检中肿瘤的百分比,以及神经周围浸润灶的存在[2-4]。在预测和选择最佳治疗方法的过程中,肿瘤恶性程度是一个决定性因素,因为在所有参数中,只有肿瘤分化程度与疾病结果显著相关[5]。同时,PSA水平和直肠指检结果(不考虑其他临床数据)不是重要的预后因素,因为它们可能是由于与肿瘤病变无关的原因[6]。然而,活检结果不能全面评估前列腺癌的特征,如肿瘤病灶的大小、位置和形态。格里森指数是根据对潜在异质性肿瘤部位的评估结果确定的,因此与术后大修复研究相比,不允许准确评估病变的整个体积和侵袭性[7]。治疗方法的选择在很大程度上是基于这样的假设,即根据初次活检结果得出的肿瘤特征反映了其真正的恶性程度。在这方面在格里森量表上分配总分的错误可能导致这样一个事实,即患有惰性肿瘤的患者将接受过度治疗,而患有侵袭性肿瘤的患者将得不到充分的治疗,这将对疾病的结局产生负面影响。准确评估肿瘤过程的特征将有助于区分适合主动监测的患者和需要根治治疗的患者,更好地评估疾病进一步进展的风险。

尽管实践中使用的一组临床和病理参数在大多数情况下提供了可接受的风险分层,但它远非完美,这使得难以在每个特定病例中选择最佳治疗方法[8]。这种情况需要确定前列腺癌的新预后生物标志物[9]。

PSA密度(pPSA)定义为血清PSA与前列腺体积的比率。该指标最初用于评估基线血清PSA浓度 $<10\text{ ng/ml}$ 的患者患前列腺癌的风险[10]。已知良性前列腺增生(BPH)中血清PSA浓度的增加与胰腺腺体成分的体积增加有关,即血清PSA浓度的增加与胰腺的体积。在前列腺癌中,PSA水平

的升高是由于肿瘤的侵袭性,其扩散导致破坏器官的腺泡血管结构,PSA的分泌直接进入体循环。在前列腺癌患者中,pPSA值与肿瘤成分和前列腺体积相关。因此,测定pPSA可以评估前列腺癌患者前列腺增生对血清PSA浓度的影响。

研究的目的是确定pPSA在接受联合激素放疗的局限性前列腺癌患者中的临床和预后价值。

## 材料与方法

1996年1月至2007年7月期间,随后进行动态观察回顾性研究包括272名局限性前列腺癌(cT1-T2N0M0)患者在俄罗斯A.M.Granova(RNTRSRKHT)放射学和外科技术科学中心接受联合激素放射治疗。治疗开始时患者的平均年龄为 $66.5\pm 6.8$ 岁。对于纳入研究的患者,有关于检查和治疗结果的所有必要信息。在这些患者中,评估了pPSA参数对肿瘤特异性生存指标的影响,以及肿瘤过程的临床和形态学参数。

在所有患者中,pPSA指数计算为基线血清PSA浓度与前列腺体积的比率。后者通过超声检查(US)或胰腺磁共振成像的结果进行评估。纳入研究的患者的pPSA值在 $0.004$ 至 $6.5\text{ ng/(ml}\cdot\text{cm}^3)$ 范围内变化,中值pPSA值为 $0.45\text{ ng/(ml}\cdot\text{cm}^3)$ (95%CI 0.41-0.52)。根据格里森量表对196例(72.1%)患者的肿瘤病理特征进行了评估。在98名(50.0%)患者中检测到高度分化的肿瘤(格里森评分 $\leq 6$ ),在67名(34.1%)患者中,格里森评分为7,在31名(15.8%)患者中—范围为8-10。研究组患者的PSA倍增时间参数值范围为0.7至833.33个月中值为36.66个月(95%可信区间26.84-40.00)。

所有前列腺癌患者均接受激素联合放射治疗。靶器官区域(胰腺和精囊)的平均总聚焦剂量为 $67.01\pm 5.6\text{ Gy}$ 。使用促性腺激素释放激素激动剂和/或抗雄激素药物进行激素治疗。部分患者为了达到睾酮去势水平,进行了双侧睾丸切除术。

使用计算机程序Statistica 10 En(Stat-Soft, Inc.)使用 $t$ 检验、 $\chi^2$ -Pearson检验、Fisher精确方法( $F$ 检验)、 $U$ -Mann-Whitney检验、ROC-绘制ROC曲线的分析方法(Receiver

operating characteristic)。差异在 $p < 0.05$ 有显著性。文中指标的平均值以标准差 ( $M \pm \sigma$ ) 表示。

### 结果

在研究的第一阶段, 评估了纳入研究的患者的肿瘤特异性生存率。在观察期内, 48人因潜在疾病的进展而死亡(表1)。

从表1的单变量分析结果可以看出, 存活和死亡患者在前列腺肿瘤组织的组织学分化上存在显著差异。因此, 在幸存的患者中, 高度分化的肿瘤 ( $p < 0.0001$ ) 明显更常被检测到, 而在已故的前列腺癌中, 低分化形式 ( $p < 0.05$ ) 被检测到。与死者相比, 存活患者组的基线血清PSA水平显著降低—分别为15.06和22.45ng/ml, ( $p = 0.0001$ )。PSA倍增时间也存在显著差异。该指标在存活患者组中显著更高—36.66个月。相比之下, 7.56个月。在已故患者中 ( $p < 0.01$ )。这些组的患者在pPSA值上有统计学显著差异。存活患者组的中位pPSA值为0.42ng/(ml·cm<sup>3</sup>), 而因基础疾病进展而死亡的患者组中pPSA值为0.66 ng/(ml·cm<sup>3</sup>) ( $p < 0.0001$ )。

根据治疗后PSA复发的检测, 对患者的pPSA值进行分析。肿瘤复发52例。确诊复发患者的中位pPSA为0.74ng/(ml·cm<sup>3</sup>) (95%CI 0.63 - 0.93), 无复发患者的pPSA中位数为0.41 ng/(ml·cm<sup>3</sup>) (95%CI 0, 35-0.46) ( $p < 0.001$ )。

在第二阶段, 确定参数的阈值, 其过量与肿瘤特异性存活率的统计学显著降低相关。为了确定参数的阈值, 使用了ROC分析方法(图1, 表2)。

根据得到的数据, pPSA的阈值为0.36ng/(ml·cm<sup>3</sup>), 敏感性和特异性水平分别为89.58%和46.43%。

在研究的下一阶段, 我们使用ROC分析方法获得的pPSA阈值将患者分为“低”和“高”pPSA组(表3)。

来自“低”pPSA 组的患者显著更可能患有高度分化的前列腺癌, 而“中度分化”的肿瘤在“高”pPSA组中显著更可能被发现。“低”pPSA组的基线血清PSA浓度显著降低。我们还发现PSA倍增时间随着pPSA的降低而增加。在图2显示了评估前列腺癌患者的肿瘤特异性存活率的结果, 取决于pPSA的值。

表.1. 存活和死亡前列腺癌患者的主要临床和形态学参数 ( $n=272$ )

Table 1. Main clinical and morphological parameters in surviving and deceased patients with prostate cancer ( $n = 272$ )

指标	存活患者 ( $n=224$ )	已故患者 ( $n=48$ )	$p$
年龄, 岁 ( $Me, 95\%CI$ )	67.75, 67.14 - 68.67	66.87, 65.61 - 67.85	$>0.05^*$
观察时间, 月 ( $Me, 95\%CI$ )	147.0, 139.0 - 156.2	75.5, 63.7 - 100.0	$<0.0001^*$
基线PSA水平, ng/ml ( $Me, 95\%CI$ )	15.06, 13.08 - 17.57	22.45, 18.81 - 28.21	$0.0001^*$
pPSA, ng/(ml·cm <sup>3</sup> ) ( $Me, 95\%CI$ )	0.42, 0.36 - 0.46	0.66, 0.57 - 0.90	$<0.0001^*$
PSA倍增时间, 月 ( $Me, 95\%CI$ )	36.66, 30.46 - 40.00	7.56, 1.21 - 36.66	$<0.01^*$
格里森评分:			
• $<7$	93(41.5%)	5(10.4%)	$<0.0001^{**}$
• 7	54(24.1%)	13(27.0%)	$>0.05^{**}$
• $>7$	20(8.9%)	11(22.9%)	$<0.05^{***}$
• 未知	57(25.4%)	19(39.5%)	$<0.05^{**}$
局部照射的总焦点剂量, Gy ( $Me, 95\%CI$ )	68.0, 66.00 - 68.00	66.0, 66.00 - 68.00	$>0.05^*$

注: PSA—前列腺特异性抗原,  $Me$ —中位数, 95%CI—95%置信区间。\* $U$ —惠特尼检验。\*\* $\chi^2$ 皮尔逊检验。\*\*\* $F$ 检验 (Fisher精确检验)。

表.2. 局部前列腺癌患者前列腺特异性抗原密度值的ROC曲线表征

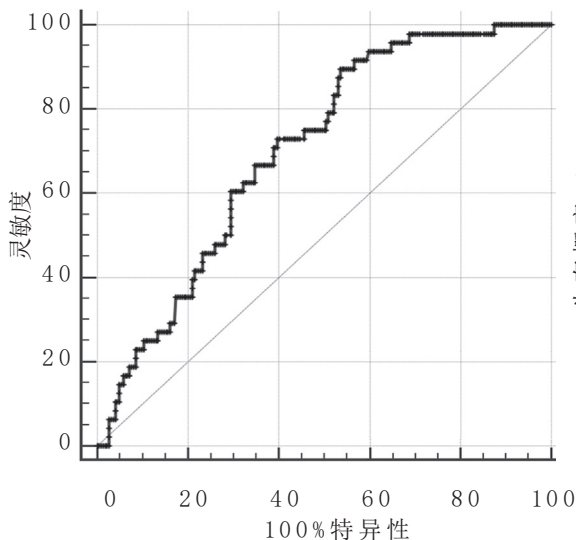
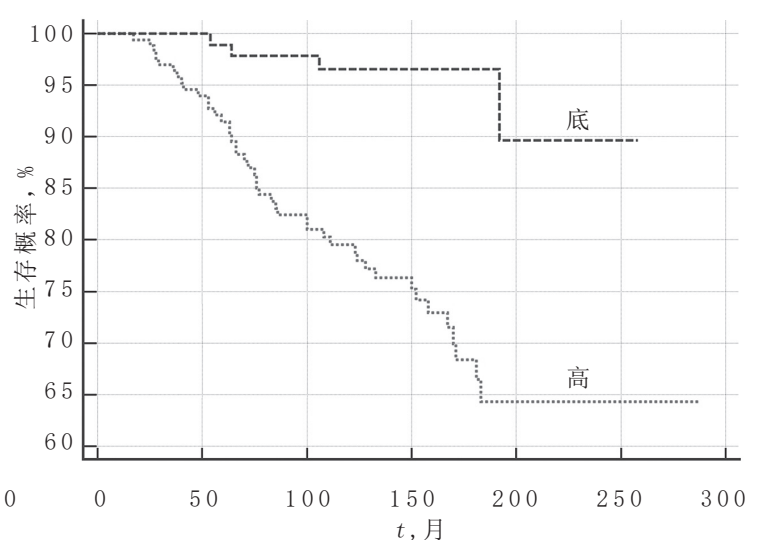
Table 2. Characteristic of ROC-curve of values of the density of prostate-specific antigen in patients with localized prostate cancer

ROC曲线下面积	根均方误差	$p$	最优准则	95%CI	
				底线	上限
0.703	0.0363	$<0.0001$	0.3601	0.2360	0.4345

**表.3.** 前列腺癌患者的临床和形态学参数取决于前列腺特异性抗原的密度值 ( $n=272$ )**Table 3.** Clinical and morphological parameters in patients with prostate cancer depending on values of the density of prostate-specific antigen ( $n = 272$ )

分析特征	“低” pPSA ( $n=101$ )	“高” pPSA ( $n=171$ )	<i>p</i>
年龄, 岁 ( <i>Me</i> , 95%CI)	68.33, 67.21–69.56	66.92, 64.92–67.65	>0.05*
基线PSA水平, ng/ml ( <i>Me</i> , 95%CI)	9.8, 8.00–11.30	23.00, 20.35–26.07	<0.0001*
PSA 倍增时间, 月 ( <i>Me</i> , 95%CI)	40.00, 36.66–47.73	24.60, 13.97–36.66	<0.001*
C 格里森评分:			
• <7	63(62.3%)	35(20.4%)	<0.0001**
• 7	14(13.8%)	53(30.9%)	<0.01**
• >7	9(8.3%)	22(12.8%)	>0.05***
• 未知	15(14.8%)	61(35.6%)	<0.001**

注: PSA—前列腺特异性抗原, *Me*—中位数, 95%CI—95%置信区间。\**U*—惠特尼检验。\*\* $\chi^2$ 皮尔逊检验。\*\*\**F*检验 (Fisher 精确检验)。

**图.1.** 局限性前列腺癌患者前列腺特异性抗原密度值的ROC分析结果**Fig. 1.** Results of ROC-analysis of values of the density of prostate-specific antigen in patients with localized prostate cancer**图.2.** 具有“高”和“低”密度前列腺特异性抗原的局限性前列腺癌患者的肿瘤特异性存活率**Fig. 2.** Cancer-specific survival prostate cancer patients with “high” and “low” density of prostate-specific antigen

由于随访期间存活者的累积比例未低于50%，因此未达到中位肿瘤特异性存活率。“低” pPSA组的平均肿瘤特异性生存期为247.21个月 (95% CI 236.27–258.15个月)，在“高” pPSA组中—222.64个月 (95% CI 206.29–238.98个月)。“低”和“高” pPSA组局部前列腺癌患者的一年肿瘤特异性生存率达到100%，五年—98.9±1.0和91.5±2.1%，十年—96.6±1.9和79.6±3.2%分别。与“低” pPSA组相比，“高” pPSA组患者的相对死亡风险增加了3.6倍 (95%可信区间2.0139–6.4446)。因此，在局限

性前列腺癌患者中，pPSA值越低，肿瘤特异性生存率越高。

## 讨论

众所周知，胰腺恶性肿瘤组织每单位体积释放到体循环中的PSA约为胰腺良性组织的10倍[1]。与大多数发达国家不同，随着基于血清PSA筛查的引入，新诊断前列腺癌的病例数量增加，死亡人数减少[12]。在俄罗斯，我们观察到该疾病的死亡率稳步上升[10]。1992年，M.C.Benson和合著者[13]提出pPSA的概念是为了中和前列腺体积对血清PSA水平的影响。随后，几项研究的结

果表明, pPSA值高于0.15 ng/(ml·cm<sup>3</sup>)与PCa检测概率显著提高相关[14-16]。

本研究是少数致力于研究局限性前列腺癌患者pPSa值与激素放射治疗结果之间关系的研究之一[17-19]。我们已经证明, 在这组患者中, 该参数具有很高的临床和预后意义。因此, 我们现在pPSA值较高的患者中, 肿瘤的组织分化程度较低, 初始血清PSA水平较高, PSA倍增时间也较短, 这表明肿瘤生长率较高。我们还证明, 具有高pPSA的局限性前列腺癌患者在治疗后有较高的肿瘤特异性死亡率和复发风险。

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## 结论

所得结果表明, pPSA是前列腺癌的可靠生物标志物, 具有较高的临床和预后意义, 其使用与引入昂贵且繁琐的实验室和仪器诊断方法无关。

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