

【临床研究】

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the risk factors affecting the prognosis of patients with prostate cancer after radical prostatectomy were analyzed by logistic regression analysis. The predictive values of serum PSA and AMACR levels for poor prognosis of patients with prostate cancer after radical prostatectomy were analyzed by receiver operating characteristic (ROC) curve. **Results** The levels of serum PSA and AMACR of patients with prostate cancer after radical prostatectomy were significantly lower than those before operation ($P<0.05$). There was no significant difference in age, BMI, maximum tumor diameter, prostate volume and pathological type between the poor prognosis group and the good prognosis group ($P>0.05$). The proportion of TNM stage III – IV, the proportion of lymph node metastasis, the proportion of low differentiation, the proportion of Gleason score ≥ 7 , the proportion of incisional margin positive and the preoperative serum PSA and AMACR levels in the poor prognosis group were significantly higher than those in the good prognosis group ($P<0.05$). Logistic analysis showed that TNM stage III – IV, lymph node metastasis, low degree of differentiation, high Gleason score, incisional margin positive and high serum PSA and AMACR levels were risk factors for poor prognosis of prostate cancer patients after radical prostatectomy ($P<0.05$). ROC analysis showed that the area under the curve (AUC) of serum PSA and AMACR in predicting poor prognosis of patients with prostate cancer after radical prostatectomy was 0.796 and 0.824, respectively; and the AUC of combined PSA and AMACR in predicting poor prognosis of patients with prostate cancer after radical prostatectomy was 0.916. The AUC of combination of serum PSA and AMACR levels in predicting poor prognosis of patients with prostate cancer after radical prostatectomy was significantly greater than that of the serum PSA and AMACR alone ($P<0.05$). **Conclusion** Abnormal increase of serum PSA and AMACR levels is a risk factor for poor prognosis of patients with prostate cancer after radical prostatectomy. The combined detection of serum PSA and AMACR levels has a high predictive value for the poor prognosis of patients with prostate cancer after radical prostatectomy.

Key words: prostate specific antigen; alpha-methylacyl coenzyme A racemase; radical prostatectomy; prognosis

前列腺癌是一种中老年男性常见的恶性肿瘤,患病率呈逐年上升趋势,其致死率位居世界第三,严重危及男性生命健康^[1-2]。目前,前列腺根治术是临床治疗前列腺癌最为有效的方法,但患者术后具有一定的复发、死亡风险,预后较差^[3]。及早、有效地预测患者前列腺癌根治术后的预后情况,并给予相关干预措施,有助于延长患者生存时间,改善其生活质量。血清前列腺特异性抗原 (prostate specific antigen, PSA) 是临床筛查前列腺癌的常用指标,其水平高低与癌症的发生及发展密切相关^[4]。α-甲酰辅酶 A 消旋酶 (alpha-methylacyl coenzyme A racemase, AMACR) 是一种基因编码蛋白,在前列腺癌组织及癌前病变组织中存在不同程度的表达,正常前列腺组织中含量极少,是临床诊断前列腺癌的常用标志物^[5-6]。本研究旨在分析血清 PSA、AMACR 水平在前列腺癌根治术前后的变化及其与预后的相关性,以期前列腺癌患者根治术后预后的预测提供生物学指标。

1 资料与方法

1.1 一般资料

选择 2017 年 1 月至 2020 年 1 月于驻马店市中心医院行前列腺癌根治术的 128 例前列腺癌患者为研究对象,年龄 61 ~ 83 (70.46 ± 8.73) 岁,体质指数 (body mass index, BMI) 18.07 ~ 24.38 (22.01 ± 1.76) kg · m⁻²,前列腺体积 24 ~ 46 (34.94 ±

9.14) mL,肿瘤最大径 3 ~ 6 (4.87 ± 0.61) cm。病例纳入标准:(1)符合前列腺癌的诊断标准^[7],并经穿刺活检证实;(2)接受前列腺癌根治术治疗;(3)术前未接受免疫治疗、放化疗等相关治疗方式;(4)预计生存期不低于 10 a;(5)患者和(或)家属知情同意并签署同意书。排除标准:(1)伴有凝血、免疫等功能障碍者;(2)对手术、麻醉不耐受者;(3)伴有淋巴结转移的前列腺癌 C 期患者及盆腔淋巴结转移的前列腺癌 D 期患者;(4)合并前列腺增生及其他恶性肿瘤;(5)存在严重的心、肝、肾等重要脏器功能障碍。本研究获得医院医学伦理委员会审核批准。

1.2 手术方法

所有患者入院后行前列腺癌根治术治疗:患者取仰卧位,行全身麻醉。于患者脐下缘切—2 cm 切口,建立气腹,使气腹压维持在 14 mm Hg (1 mm Hg = 0.133 kPa);在脐下 2 横指左右的右侧腹直肌旁作一切口,置入 10 mm Trocar,并于左侧腹直肌旁及髂前上棘内侧 2 横指各作一切口,并置入 5 mm Trocar,于脐下缘切口置入 12 mm Trocar;腹腔镜下暴露髂外静脉,游离闭孔神经及闭孔动、静脉,切除上述组织周围的淋巴组织,分离耻骨后间隙至前列腺尖处,切开膀胱颈及尿道前后壁,游离精囊及输精管,显露膀胱后间隙,保留前列腺两侧的神血管,暴露尿道壁,并切开尿道壁,充分游离前列腺,彻底切除前列腺癌组织。术后常规给予抗生素治疗。

1.3 预后判断及分组

患者术后均通过电话、微信等方式随访 3 a 或随访至患者死亡,定期对患者进行复查,记录患者生存及复发情况。通过前列腺核磁、骨扫描等方式检测患者复发情况。根据患者预后分组,3 a 内患者死亡或前列腺癌复发纳入预后不良组,3 a 内无复发患者纳入预后良好组。

1.4 观察指标

(1)基本资料:收集患者的年龄、BMI、肿瘤最大径、前列腺体积、病理类型、淋巴结转移、远处转移、TNM 分期、分化程度、Gleason 评分、切缘。(2)PSA 和 AMACR 水平:分别于术前及术后 7 d,抽取患者空腹静脉血 5 mL,静置 0.5 h 后,1 500 r·min⁻¹离心 10 min,留取血清;采用酶联免疫吸附法测定血清 PSA、AMACR 水平,检测试剂盒均购自武汉华美生物工程有限公司,严格按试剂盒说明书进行操作^[8-9]。

1.5 统计学处理

应用 SPSS 22.0 软件进行数据统计与分析。计量资料以均数±标准差($\bar{x} \pm s$)表示,2 组间比较采用 *t* 检验;计数资料以例数和百分率表示,2 组间比较采用 χ^2 检验;采用 logistic 回归分析影响前列腺癌根治术后患者预后的危险因素;绘制受试者操作特征(receiver operating characteristic, ROC)曲线,分析血清 PSA、AMACR 水平对前列腺癌根治术后患者预后不良的预测价值;*P* < 0.05 为差异有统计学意义。

2 结果

2.1 手术前后患者血清 PSA、AMACR 水平比较

患者术后血清 PSA、AMACR 水平显著低于术前,差异有统计学意义(*P* < 0.05);结果见表 1。

表 1 手术前后患者血清 PSA、AMACR 水平比较
Tab.1 Comparison of serum PSA and AMACR levels of patients before and after operation ($\bar{x} \pm s$)

| 组别 | <i>n</i> | PSA/($\mu\text{g} \cdot \text{L}^{-1}$) | AMACR/($\text{mg} \cdot \text{L}^{-1}$) |
|----------|----------|---|---|
| 术前 | 128 | 55.45 ± 14.38 | 42.37 ± 8.17 |
| 术后 7 d | 128 | 13.47 ± 5.14 | 21.81 ± 7.04 |
| <i>t</i> | | 31.101 | 21.568 |
| <i>P</i> | | < 0.001 | < 0.001 |

2.2 前列腺癌根治术后患者预后影响因素单因素分析

预后不良组与预后良好组患者的年龄、BMI、肿瘤最大径、前列腺体积、病理类型比较差异无统计学意义(*P* > 0.05);预后不良组患者 TNM 分期Ⅲ~Ⅳ期占比、淋巴结转移占比、肿瘤低分化占比、Gleason 评分≥7 分占比、切缘阳性占比及术前血清 PSA、AMACR 水平显著高于预后良好组,差异有统计学意义(*P* < 0.05);结果见表 2。

表 2 前列腺癌患者根治术后预后影响因素单因素分析
Tab.2 Single factor analysis of prognostic factors after radical prostatectomy for prostate cancer patients

| 因素 | 预后不良组 (<i>n</i> = 31) | 预后良好组 (<i>n</i> = 97) | χ^2 | <i>P</i> |
|---|---------------------------|---------------------------|----------|----------|
| 年龄/岁 | 69.95 ± 10.14 | 71.35 ± 10.76 | 0.639 | 0.524 |
| BMI/($\text{kg} \cdot \text{m}^{-2}$) | 21.86 ± 1.63 | 22.18 ± 1.54 | 0.993 | 0.323 |
| TNM 分期 | | | | |
| Ⅰ~Ⅱ期/例(%) | 10(32.26) | 52(53.61) | 4.288 | 0.038 |
| Ⅲ~Ⅳ期/例(%) | 21(67.74) | 45(46.39) | | |
| 肿瘤最大径/cm | 4.92 ± 0.55 | 4.73 ± 0.49 | 1.824 | 0.071 |
| 前列腺体积/mL | 35.07 ± 9.32 | 33.82 ± 9.11 | 0.661 | 0.510 |
| 病理类型 | | | | |
| 腺泡腺癌/例(%) | 28(90.32) | 90(92.78) | 0.924 | 0.921 |
| 导管内癌/例(%) | 1(3.23) | 4(4.12) | | |
| 导管腺癌/例(%) | 1(3.23) | 1(1.03) | | |
| 其他/例(%) | 1(3.23) | 2(2.06) | | |
| 淋巴结转移 | | | | |
| 否/例(%) | 19(61.29) | 36(37.11) | 5.604 | 0.018 |
| 是/例(%) | 12(38.71) | 61(62.89) | | |
| 肿瘤分化程度 | | | | |
| 低分化/例(%) | 24(77.42) | 53(54.64) | 5.086 | 0.024 |
| 中、高分化/例(%) | 7(22.58) | 44(45.36) | | |
| Gleason 评分 | | | | |
| ≥7 分/例(%) | 22(70.97) | 48(49.48) | 4.375 | 0.036 |
| <7 分/例(%) | 9(29.03) | 49(50.52) | | |
| 切缘 | | | | |
| 阳性/例(%) | 8(25.81) | 10(10.31) | 4.669 | 0.031 |
| 阴性/例(%) | 23(74.19) | 87(89.69) | | |
| 术前血清 PSA 水平/($\mu\text{g} \cdot \text{L}^{-1}$) | 57.01 ± 12.73 | 43.65 ± 11.51 | 5.482 | < 0.001 |
| 术前血清 AMACR 水平/($\text{mg} \cdot \text{L}^{-1}$) | 46.14 ± 9.91 | 31.47 ± 9.28 | 7.537 | < 0.001 |

2.3 前列腺癌根治术后患者预后危险因素 logistic 回归分析

Logistic 回归分析结果显示,TNM 分期Ⅲ~Ⅳ期、淋巴结转移、低分化程度、高 Gleason 评分、切缘阳性及高血清 PSA、AMACR 水平是影响前列腺癌根治术后患者预后不良的危险因素(*P* < 0.05);结果见表 3。

表 3 前列腺癌根治术后患者预后危险因素 logistic 分析
Tab.3 Logistic analysis of risk factors for prognosis of patients with prostate cancer after radical prostatectomy

| 因素 | β | SE | Wald χ^2 | <i>P</i> | 比值比 | 95% 置信区间 | |
|--------------|---------|-------|---------------|----------|-------|----------|-------|
| | | | | | | 上限 | 下限 |
| TNM 分期Ⅲ~Ⅳ期 | 0.835 | 0.247 | 11.428 | < 0.001 | 2.305 | 1.826 | 2.784 |
| 淋巴结转移 | 0.774 | 0.281 | 7.587 | < 0.001 | 2.168 | 1.690 | 2.647 |
| 低分化程度 | 0.781 | 0.270 | 8.367 | < 0.001 | 2.184 | 1.686 | 2.681 |
| 高 Gleason 评分 | 0.817 | 0.253 | 10.428 | < 0.001 | 2.264 | 1.754 | 2.773 |
| 切缘阳性 | 0.806 | 0.266 | 9.181 | < 0.001 | 2.239 | 1.773 | 2.705 |
| 高 PSA 水平 | 0.858 | 0.244 | 12.365 | < 0.001 | 2.358 | 1.784 | 2.933 |
| 高 AMACR 水平 | 0.842 | 0.259 | 10.569 | < 0.001 | 2.321 | 1.766 | 2.876 |

2.4 血清 PSA、AMACR 水平对前列腺癌根治术后患者预后不良的预测价值。

血清 PSA 预测前列腺癌根治术后患者预后不良的曲线下面积(area under curve, AUC)为 0.796,95% 置信区间为 0.698~0.836,截断值为 50.19 $\mu\text{g} \cdot \text{L}^{-1}$,灵敏度为 72.58%,特异度为 85.31% (*P* < 0.001);血

清 AMACR 预测前列腺癌根治术后患者预后不良的 AUC 为 0.824,95% 置信区间为 0.742 ~ 0.904,截断值为 40.13 mg · L⁻¹,灵敏度为 86.14%,特异度为 78.63% ($P < 0.001$);血清 PSA 与 AMACR 水平联合预测前列腺癌根治术后患者预后不良的 AUC 为 0.916,95% 置信区间为 0.817 ~ 0.991,灵敏度为 94.17%,特异度为 86.88% ($P < 0.001$);血清 PSA 与 AMACR 水平联合预测前列腺癌根治术后患者预后不良的 AUC 显著大于二者单独预测 ($P < 0.05$)。结果见图 1。

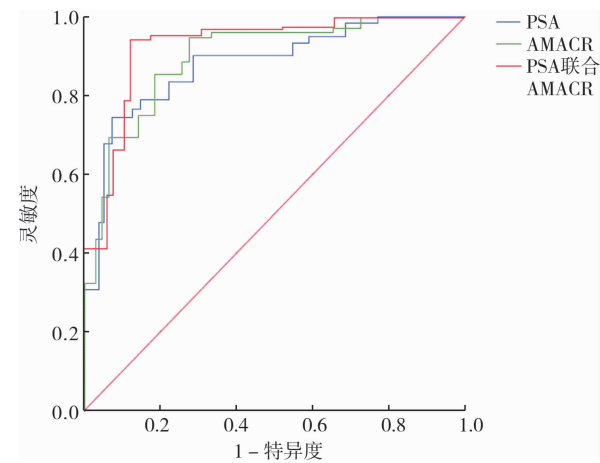


图 1 血清 PSA、AMACR 水平预测前列腺癌根治术后患者预后不良的 ROC 曲线

Fig.1 ROC curve of serum PSA and AMACR levels in predicting poor prognosis of prostate cancer patients after radical prostatectomy

3 讨论

前列腺癌是一类最为常见的泌尿系统恶性肿瘤,好发于前列腺外周带,多见于中老年男性;疾病早期患者大多无明显症状,随病情进展,患者可出现下尿路梗阻症状,严重者可出现尿潴留、尿失禁等,若出现骨转移,可导致脊髓压迫、剧烈骨痛、病理性骨折等,对患者身体健康及生活质量造成严重影响^[10-12]。目前,临床多通过手术治疗前列腺癌患者,其中前列腺癌根治术是临床治疗前列腺癌最为有效的方式,而腹腔镜下手术相较于传统手术具有出血量少、术后恢复快等优势,被广泛用于临床治疗^[13-14]。但前列腺癌患者在术后仍存在较高的复发率及病死率,预后情况较差。因此,可靠、有效地预测前列腺癌患者根治术后预后,对改善患者生活质量、提高生存率极为重要。

PSA 是一种由前列腺上皮细胞分泌的单链糖蛋白,具有较高的前列腺组织特异性,是临床鉴别诊断前列腺癌的常用血清标志物^[15]。前列腺导管腔、腺泡与血液循环间存在组织屏障;正常情况下,PSA 可

经导管分泌至精液中,精液中 PSA 水平是血清中的 100 万倍;而患有前列腺癌时,癌细胞增殖、生长可破坏这一组织屏障,导致大量 PSA 渗透至血液中,致使血清 PSA 水平大幅度增高^[16-17]。有研究报道,血清 PSA 水平与前列腺癌的病理改变密切相关,可用于评估前列腺癌病情进展及预后评价^[18]。AMACR 属胞质蛋白,在前列腺癌组织中呈过度表达,但在血清中含量较少,其结构及功能与前列腺癌的发生与发展密切相关^[19-20]。本研究结果显示,前列腺癌患者术后血清 PSA、AMACR 水平显著低于术前,预后不良组患者 TNM 分期Ⅲ ~ Ⅳ期占比、淋巴结转移占比、肿瘤低分化占比、Gleason 评分 ≥ 7 分占比、切缘阳性占比及术前血清 PSA、AMACR 水平显著高于预后良好组,TNM 分期Ⅲ ~ Ⅳ、淋巴结转移、低分化程度、高 Gleason 评分、切缘阳性及血清 PSA、AMACR 水平是前列腺癌患者根治术后预后不良的危险因素,与赖飞等^[21]结果相符。这说明,前列腺根治术用于治疗前列腺癌可有效清除体内肿瘤病灶,TNM 分期Ⅲ ~ Ⅳ期、淋巴结转移、低分化肿瘤、Gleason 评分 ≥ 7 分、切缘阳性、血清 PSA、AMACR 水平异常升高可提示患者术后复发、死亡风险较高,临床需密切关注患者术后恢复情况并给予相应干预措施。

本研究结果显示,血清 PSA、AMACR 水平预测前列腺癌根治术后患者预后不良的 AUC 分别为 0.796、0.824;这说明,血清 PSA、AMACR 水平对前列腺癌根治术后患者预后有一定的预测价值。此外,血清 PSA 和 AMACR 水平联合预测前列腺癌根治术后患者预后不良的 AUC 为 0.916,血清 PSA 和 AMACR 水平联合预测前列腺癌根治术后患者预后不良的 AUC 显著大于二者单独预测。这可能是因为:前列腺癌组织中 AMACR 释放入血量较少,并受检测方法、技术及环境等因素的影响,影响临床检测的准确度;部分正常组织、其他上皮癌亦可分泌少量 AMACR,自身免疫性疾病也可影响血清 AMACR 水平,临床检测时特异性较低;血清 PSA 水平易受饮酒、饮食、感冒发热、夫妻生活等多种因素影响;因此,血清 PSA 和 AMACR 水平联合检测可降低误差率,提高对前列腺癌根治术后患者预后的预测价值。

4 结论

TNM 分期Ⅲ ~ Ⅳ期、淋巴结转移、肿瘤低分化程度、Gleason 评分 ≥ 7 分、切缘阳性、血清 PSA、AMACR 水平异常升高可提示患者术后复发风险较高;血清 PSA、AMACR 水平对前列腺癌根治术后患

者预后有一定的预测价值,二者联合检测可降低误差率,提高对前列腺癌根治术后患者预后的预测价值,具有较高的临床参考价值。

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