·综　述·

根治性前列腺切除术后Gleason评分升级的研究进展

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摘要：Gleason评分对于前列腺癌风险评估、治疗决策制定和预后判断有重要价值，而前列腺穿刺活检与根治性前列腺切除术（radical prostatectomy，RP）后病理的Gleason评分常存在差异，且主要表现为评分升级，这严重影响了临床决策的制定及预后判断。本文回顾近年国内外相关文献，对RP后Gleason评分升级相关因素的研究进展作一综述，旨在为患者提供更加精准的风险评估和最佳的个体化治疗方案，最终改善患者预后，提高生存质量。

关键词：前列腺肿瘤；穿刺活检；Gleason评分
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GLOBOCAN 2020数据显示，全球前列腺癌（prostate cancer，PCa）患病率居男性恶性肿瘤第2位，病死率居第5位[1]。与欧美发达地区相比，我国前列腺癌患病率较低，但近年呈显著上升趋势。前列腺穿刺活检是目前唯一能够获取前列腺癌确诊信息的临床检测手段[2]，穿刺病理提供的Gleason评分对于疾病风险评估、治疗决策制定和判断预后有着重要的意义。由于病理分级错误、肿瘤异质性或抽样误差等原因，临床中前列腺穿刺活检与根治性前列腺切除术后病理的Gleason评分常存在差异，且主要表现为评分升级。这不仅影响了诊治策略的选择，且Gleason评分升级与根治性前列腺切除术（radical prostatectomy，RP）后手术切缘阳性、包膜外或精囊侵犯、生化复发等不良预后相关[3]。本文回顾近年国内外相关文献，对根治性前列腺切除术后Gleason评分升级相关因素的研究进展作一综述。

1　年龄、体质量指数（body mass index，BMI）对Gleason评分升级的影响

国外研究表明[4-6]，年龄被认为是术后病理Gleason评分升级的重要危险因素。WANG等[7]对17个临床研究共纳入48 590例前列腺癌患者的荟萃分析显示，年龄是RP后Gleason评分升级的独立预测因素（*OR*=1.04，95%*CI* 1.03～1.05，*P*<0.01），即年龄每增加1岁，升级的风险增加4%，这与既往报道相似[5]。值得注意的是，国内多数研究[8-11]显示，年龄与术后Gleason评分升级无明显相关性，这可能与纳入样本量不足和人群构成不同相关。最近有研究[12]发现，多参数磁共振成像（multiparameter magnetic resonance imaging，mpMRI）引导下系统联合靶向穿刺活检术消除了年龄增长和升级风险增加之间的联系，既往研究中报道的年龄对Gleason评分升级的影响，可能是由于MRI前时代的诊断偏移和领先时间偏移导致。肥胖是前列腺癌不良病理及疾病进展的影响因素，有研究表明肥胖与RP后的Gleason评分升级有关[13]。HE等[9]研究中发现，肥胖患者发生Gleason评分升级的风险是非肥胖患者的2.6倍。刘奥等[8]研究结果表明，BMI>28 kg/m^{2}可作为Gleason评分升级的独立影响因素（*OR*=2.54，95%*CI* 1.15～5.62，*P*=0.021）。笔者认为，充分考虑年龄、BMI因素，可以提示更准确的风险分层，并且有助于前列腺癌患者更佳治疗决策的选择。

2　临床指标对Gleason评分升级的影响

2.1 前列腺特异性抗原（prostate specific antigen，PSA）、前列腺体积（prostate volume，PV）、前列腺特异抗原密度（prostate specific antigen density，PSAD）、前列腺健康指数（prostate health index，PHI）　PSA、PSAD是前列腺癌筛查、诊断、预测危险程度及预后的重要参考指标。一项荟萃分析[14]

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结果表明，PSA水平是Gleason评分升级的独立预测因子，较高的PSA水平与升级风险增加显著相关。还有研究[15]显示，PSA每增加1个单位，升级的风险提高2%。KIM等[16]发现较小的PV、更大的肿瘤体积是Gleason评分升级的独立预测因素，而RP后肿瘤体积百分比与Gleason评分升级呈负相关，这提示肿瘤生物学因素和抽样误差在Gleason评分升级中都发挥了作用，由较小的腺体发展而来的癌症可能具有更强的侵袭性。SIM等[17]发现PSAD≥0.26 ng/（ml·cm^3）、PSA≥7.63 ng/ml、PV≤25.1 cm^3是Gleason评分升级的预测因素，ROC曲线下面积（area under the curve，AUC）分别为0.765、0.721、0.639，在ROC曲线的比较中，PSAD较PV有更好的预测Gleason评分升高的效能，差异有统计学意义（P=0.05）。然而国内的许多研究[8,10]结果未能证实PSA和（或）PSAD与术后Gleason评分升高存在相关性。血清前列腺特异性抗原同源异构体2（isoform[−2]prostate specific antigen，p2PSA）是PSA的前体（prostate precursor of specific antigen，proPSA）的截短形式，由p2PSA经计算得到其衍生指标PHI。NOVAK等[18]研究结果显示，与PSA相比，PHI是术后Gleason评分升级的更强预测因子（AUC=64.8 *vs* AUC=57.4，P<0.05），PHI值越高，Gleason评分升级的风险就越高。KIM等[19]研究结果表明，PHI≥55（OR=3.64，95% CI 1.05～12.68，P=0.042）是Gleason评分升级的独立预测因素。另外，PHI水平对预测前列腺癌的侵袭性和根治性前列腺切除术后不良病理有着重要作用。

2.2 *炎性细胞*　肿瘤微环境中的炎性反应，已被广泛认为是决定肿瘤形成过程，促进肿瘤细胞增殖、迁移和存活的关键，因此炎性反应指标可以反映肿瘤进展和免疫系统的状态。GOKCE等[20]发现较高的中性粒细胞与淋巴细胞比值（neutrophil to lymphocyte ratio，NLR）与较高的前列腺癌穿刺活检Gleason评分相关。另一项研究[21]显示，NLR是低风险前列腺癌患者Gleason评分升级和BCR的预测因子。ÖZSOY等[22]研究同样表明NLR≥3患者穿刺活检Gleason评分较高的可能性更大，且与RP后Gleason评分升级显著相关（OR=1.39，P<0.001）。FERRO等[23]对260例接受RP的意大利患者进行回顾性研究，结果表明中性粒细胞与淋巴细胞比值、血小板与淋巴细胞比值（platelets to lymphocyte ratio，PLR）、嗜酸性粒细胞与淋巴细胞比值（eosinophil to lymphocyte ratio，ELR）是Gleason评分升级的预测因子。然而，在一项多种族前瞻性研究[24]中，没有发现NLR、PLR与Gleason评分升级具有相关性。这些炎性指标成本低廉且易于测量，对于是否能够或较好地预测Gleason评分升级的作用，未来值得在更大的人群中进一步研究。

3　穿刺相关因素对Gleason评分升级的影响

3.1 *穿刺方式、穿刺至RP间隔时间*　超声引导下经会阴或直肠途径的系统穿刺是目前主要穿刺方式，而与影像学更加紧密结合的精准靶向穿刺（targeted biopsy，TB）技术也日趋普遍开展。XU等[25]研究表明，穿刺方式是Gleason评分升级的独立预测因素（P=0.001），系统穿刺较靶向穿刺出现Gleason评分升级的可能性更大。KAYANO等[26]通过多因素Logistic回归分析，证实了系统穿刺是Gleason评分升级的独立危险因素（OR=2.64，95% CI 1.11～6.28，P=0.024）；与系统穿刺相比，融合靶向穿刺与较低的Gleason评分升级率、活检和最终病理间的一致性相关。EVANS等[27]研究结果显示，经会阴穿刺活检与RP后的Gleason评分一致性优于经直肠穿刺，这可能与经会阴穿刺覆盖范围较广而能获取更多的前列腺癌好发部位可疑组织相关；此研究还发现，较长的穿刺至RP间隔时间可以预测Gleason评分升级，这与之前研究[28]结果一致，而间隔时间>6～9个月会增加Gleason评分升级、生化复发和手术切缘阳性风险，甚至影响患者预后。但应该警惕的是，少数患者会在短期监测内出现Gleason评分升高[29]。

3.2 *穿刺针数、穿刺阳性针数及穿刺阳性针数百分比、肿瘤组织长度（肿瘤百分比）、穿刺长度*　目前最佳的前列腺穿刺针数尚未有定论，多数研究[29]认为足够穿刺针数可以提高RP后Gleason评分一致性，降低评分升高的风险；同时有研究表明，穿刺阳性针数及穿刺阳性针数百分比越大，Gleason评分升高可能性越大[30-31]。SEISEN等[32]发现采用6、12和21针前列腺穿刺活检时，RP后Gleason评分升级率分别为71.3%、50.1%和48.7%，结果表明穿刺>12针是Gleason评分升级的独立保护因素（OR=0.696，95% CI 0.49～0.99，P=0.041）；此外，每针肿瘤组织长度>5 mm是Gleason评分升级最强危险因素（OR=2.938，95% CI 2.17～3.98，P<0.001）。SONG等[33]研究结果显示，穿刺阳性针数>2及最大肿瘤百分比>20%与Gleason评分升级显著相关。REIS等[34]发现穿刺长度是活检Gleason评分被低估

的独立危险因素，长度增加1 mm，Gleason评分升级风险降低89.9%（*OR*=0.10，95%*CI* 0.01～0.99，*P*=0.049），表明更长的活检长度会降低采样不准确性，进而获得更准确的Gleason评分。

4 前列腺影像报告和数据系统（prostate imaging reporting and data system，PI-RADS）对Gleason评分升级的影响

PI-RADS是对前列腺影像学表现进行分级和评分，为前列腺癌的诊断提供了一种半定量的量化标准。朱良勇等[35]研究结果表明，PI-RADS评分与Gleason评分呈正相关性；同时PI-RADS评分越高，活检病理为Gleason评分3+3=6的患者RP后病理升级的可能性越大。SONG等[33]分析443例前列腺癌患者发现，PI-RADS评分1～3分的患者157例、PI-RADS评分4～5分的患者286例，分别有54.1%、74.1%的患者发生Gleason评分升级，高PI-RADS评分患者较低PI-RADS评分患者Gleason评分升级风险增加（*P*<0.001）。ALQAHTANI等[36]对纳入322例前列腺癌患者的研究表明，PI-RADS评分显著提高了MRI扫描对Gleason评分升级的预测能力（*OR*=0.014，95% *CI*0.006～0.034，*P*=0.001）。同样，另一项研究[19]结果表明，PI-RADS病变≥4（*OR*=7.03，95%*CI* 1.68～29.51，*P*=0.018）是RP后病理Gleason评分升级的独立预测因素。基于mpMRI的PI-RADS评分对前列腺癌穿刺活检Gleason评分及RP后病理Gleason评分变化具有预测作用，可作为术前影像学工具来确定风险分层，并帮助患者就治疗决策和疾病预后提供咨询。

5 其他因素及预测模型建立

郑祥义等[37]分析了330例前列腺穿刺Gleason评分3+3=6分的前列腺癌患者数据，165例（50.0%）发生了病理级组上调，临床分期≥T_{2b}期（*OR*=7.158）为RP后ISUP级组上调的独立危险因素。国内研究[8,10]表明，穿刺病理ISUP级组是RP后ISUP级组升高的独立预测因素，穿刺病理ISUP级组≤2的患者RP后出现ISUP级组升高的可能性较大。这说明较低的ISUP分级分组（或穿刺Gleason评分）、临床分期≥T_{2b}期的患者RP后出现病理升级的风险增大。目前，越来越多由不同影响因素组合构建的预测RP后病理升级的列线图模型被开发报道[8,15,38]，在内部验证中均显示出良好的预测性能，但多数未在外部数据集或其他队列中测试，构建的模型实际性能有待基于庞大人群的前瞻性多中心研究进一步验证。

6 小结

影响前列腺穿刺活检与RP后Gleason评分升级的因素众多，部分因素尚存在争议，各因素间可能存在交互作用，一些潜在的可能有意义的因素尚未被纳入研究，未来更多的大规模、多中心前瞻性研究有望进一步阐明影响Gleason评分升级的预测因素。临床上结合多项预测因素进行综合评估，能够增加泌尿科医生在临床决策方面的信心，为前列腺癌患者提供更加精确全面的风险评估及最佳的个体化治疗方案，最终改善患者预后，提高生存质量。

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(下转第 76 页)

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(上接第 72 页)

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