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局限期前列腺癌治疗方式的研究进展

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[摘 要] 局限期前列腺癌(localized prostate cancer，LPC)患者一般具有较长生存时间，因此，如何选择适当的治疗措施减少复发风险的同时尽量提高患者生存质量便显得尤为重要。手术、放疗和内分泌治疗是局限期前列腺癌常见的治疗方式，新技术的出现不仅提高局限期PC疗效，同时显著降低治疗风险，提高患者生存质量。

[关键词] 局限期前列腺癌；疗效；治疗相关并发症；生存质量

Progress in therapy method in patients with prostatic cancer

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Abstract Patients with localized prostate cancer (PC) generally have a longer survival time, therefore, how to choose the appropriate treatment measures to reduce the risk of recurrence while as far as possible to improve the quality of life of patients will be particularly important. Surgery, radiotherapy and endocrinotherapy are the common treatment methods for localized PC. New technology helps improve the effect of localized PC, significantly reduce the risk, and improve the patients' quality of life.

Keywords localized prostate cancer; curative effect; treatment-related complications; quality of life

近年来前列腺癌(prostatic cancer，PC)的发病率呈逐年升高趋势[1]。与其他癌症不同，很大一部分局限期PC患者，尤其是预期生存期小于10年的高龄且低危患者，并不能从积极治疗中获益[1]。即使预期生存期大于10年的患者，也仅推荐处于中或高危组进行治疗性干预[2]。局限期PC治疗易造成医疗浪费，并且可能给患者带来不必要的负担(精神、身体、经济等)。相比周围侵犯和远处转移PC，局限期PC治疗决策更注重如何降低手术及放疗并发症的发生及减轻雄激素阻断治疗(androgen deprivation therapy，ADT)的不良反应。美国医学会对局限期PC治疗方案的研究高度重视，并列为25个优先研究项目之一[3]。目前，国内局限期PC治疗方案相关研究较少。本文旨在收集手术、放射治疗及ADT治疗局限期PC的疗效、并发症和生存质量相关数据，兼顾化疗以资临床参考。

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1 手术、放射治疗

1.1 疗效

Bill-Axelson等[4]组织的SPCG-4试验中，将695名局限期PC患者分为PC根治组与观察组。与观察组相比，根治性PC切除术不但能使局限期PC患者实现总生存期获益，而且能够降低PC转移风险。Wallis等[5]的Meta分析结果提示根治性PC切除术可使局限期前列腺癌总生存期明显延长，并且高于体外照射治疗及体外照射联合近距离照射治疗。综上，手术治疗可使PC患者实现生存获益。

虽然早期研究[6]结果支持手术较放疗在延长患者生存期上具有优势，但因后续未进行扩大样本验证及医疗相关概念的更换[前列腺特异抗原(prostate-specific antigen，PSA)水平被作为PC分期因素之一]，目前出现了大量与其相悖的研究结果。近期一项名为ProtecT的临床试验[7]将1 643名患者随机分为主动监测和根治性PC切除及放疗3组，结果PC特异性病死率差异无统计学意义(P=0.48)，总病死率差异亦无统计学意义(P=0.87)。Lennernäs等[8]的研究共入组89例PC(分期为局限期和局部晚期)患者，随机分为手术组与放疗组(体外照射+近距离照射+ADT)，2组具有相近的总病死率与PC特异性病死率。Zelefsky等[9]研究发现接受调强放疗的患者与接受根治性PC切除术的患者，无论是治疗疗效还是不良反应差异均无统计学意义。无独有偶，PC Gleason评分(GS评分)较高的患者，手术及外照射放疗联合ADT治疗较单独治疗方案(外照射治疗、近距离放疗、ADT治疗)未见总生存期获益，但接受放疗联合ADT治疗的患者表现出了更低的转移率[10]。该结论为前列腺癌治疗提供了2a级的治疗证据[11]。

1.2 相关并发症

ProtecT研究[12]发现手术治疗常见并发症为尿失禁和阴茎勃起功能障碍，外照射治疗后常见并发症为尿道梗阻和胃肠功能紊乱。

1.2.1 尿失禁、阴茎勃起功能障碍

在SPCG-4试验[13]中发现：相对于观察组，手术治疗组尿失禁和阴茎勃起障碍的发生风险明显增加。另一项PC研究中[14]纳入了3 533名患者，其中1 655人患有局限期PC，并且在确诊后的1年内接受了手术或放疗，在第2年和第5年的随访中，接受手术治疗的患者倾向于患有尿失禁和阴茎勃起功能障碍，而接受放疗的患者常伴有肠道功能紊乱，随访15年，除接受放射治疗的患者仍然较高比例出现肠道功能紊乱外，其他并发症出现比例差异均无统计学意义，而值得注意的是，此时绝大多数入组患者出现了阴茎勃起功能障碍。Gilberti等[15]发现随访过程中，接受近距离照射患者排尿功能在治疗后6个月时总体劣于同期接受手术治疗患者，但阴茎勃起功能总体优于手术治疗患者，2组泌尿生殖系统功能差异在接受治疗的5年后消失。

1.2.2 肠道功能障碍

受放射野的影响，放疗对肠道功能及前列腺附近器官影响非常大，尤其对直肠附近区域的正常组织[16]。放疗并发症会对一部分患者生存质量造成长久影响[16]。相比之下，接受PC根治性切除术患者的胃肠道症状比接受外照射治疗的患者要轻得多。

1.2.3 二重肿瘤

近期一项关于局限期PC的临床研究[18]中发现：与手术治疗相比，接受放疗的患者具有较高的二重肿瘤发生率[标准化发病率(standard incidence rate，SIR)=2.0，95%CI 1.7~2.3]，并且该风险可持续影响患者40~65年(SIR=3.5，95%CI 2.3~4.7)。一项包含了21项临床研究及555 873名患者的Meta分析[19]进一步证实了上述研究结果，并且发现：二重肿瘤的发生部位与放射野有关，常见的有膀胱癌、直肠癌、结肠癌。

1.2.4 其他并发症

因根治性切除术大多完整保留了术区基底组织，故治疗后组织慢性缺血的发生风险明显低于接受放疗的患者[20]。放疗相关并发症一般较重并且恢复困难，常常导致慢性器官功能障碍[21]。并且，放疗是PC患者发生骨折风险的独立危险因素[22]。接受放疗的局限期PC患者，冠状动脉疾病、心肌疾病以及心源性猝死的发生比例较高[22]。这可能与放疗常与ADT治疗联合有关，尚需扩大样本进一步研究证实。

1.3 患者生存质量

因手术及放疗(±ADT)会使局限期PC患者获得明显的生存获益，并且疗效相当，所以，治疗方式的选择上更加注重治疗后患者生存质量获益情况。在名为ProtecT的实验中，接受手术治疗与接受放疗的患者相比，身体状态、精神状态以及焦虑、抑郁的发生率并没有差别[12]。Lennernäs等[8]和Gilberti等[15]研究发现：接受放疗的患者与接受根治性PC手术治疗患者相比，生存质量相关指标差异没有统计学意义，但上述PC的相关治

疗，却降低了患者配偶的生存质量[23]。

2 ADT 在局限期 PC 治疗中的评价

除非患者强烈要求，否则，对于局限期PC患者不主张单纯应用ADT[24]。

虽然PC根治术前新辅助ADT具有降低临床分期、肿瘤GS评分、提高手术切除率、不良反应小于新辅助化疗等优势，但与基于多西他赛的新辅助化疗方案相比，后者却显示出较明显的总生存期获益[25]。

ADT常与放疗联合使用以延长总生存期[26-28]。局限期PC患者放疗联合长期ADT(2~3年)总生存期获益明显优于短期ADT治疗(6个月)[29]。局限期PC患者放疗联合短期ADT治疗(16周)足以达到延长患者总生存期效果，但该临床试验纳入的3组患者ADT治疗时间均较短(分别为16周，28周与36周)，由于无法明确继续延长ADT治疗时间是否有利于提高总生存时间，可能造成研究结论的片面性[30]。

ADT可能导致骨质异常、心血管系统疾病、糖尿病、性功能障碍、认知障碍等疾病[31]。其中，性功能障碍发生率可达90%[32]。ADT可使阴茎长度缩短[33]，睾丸缩小[34]，这会给患者带来很大心理压力，并且使其对治疗方案依从性下降。在为期1年的观察中[35]发现：ADT着实给患者带来了很大的精神压力，并且生存质量明显降低，但是，在疗效上并没有比仅仅接受对症治疗的患者更有优势。

近期，1项针对局部治疗同时联合ADT的研究[22]发现：入组患者的心血管事件与骨事件发生率并没有高于对照组。处于中高危组的局限期PC患者，长期ADT(24个月)比短期治疗(4个月)的心血管事件发生率明显增加[36]。PC患者接受ADT不会增加其心血管疾病相关死亡风险[37]。辅助ADT可以增加放疗后患者肠道损害风险[16,38]，并且加重PC根治术患者泌尿系统损伤程度[39]。虽然，放疗前予以为期8周的新辅助ADT可以增加患者总生存期[30]，但同时明显增加了这部分患者性功能障碍风险[40]。

3 结语

局限期PC患者经手术与放疗(±ADT)可以获得近似疗效。手术治疗常见并发症为尿失禁和阴茎勃起功能障碍，外照射治疗后常见并发症为尿道梗阻和胃肠功能紊乱，此外，放疗可增加患者罹患二重肿瘤风险。放疗对其他系统(循环系统、骨骼等)影响需扩大样本进一步证实。ADT与放疗联合使用可增加局限期PC患者总生存期，但同时增加了骨质异常、心血管系统疾病、糖尿病、性功能障碍、认知障碍、泌尿及消化系统损伤等并发症发生风险。根治性PC切除术前基于多西他赛的新辅助化疗较新辅助ADT具有更高的总生存期获益。随着神经保留PC切除术的不断完善[41]和神经-血管冰冻切片实验的不断进展[42]，达芬奇机器人手术预后不断改善。此外，调强放射治疗(intensity modulated radiation therapy，IMRT)及立体定向大分割放疗技术不断更新，使得三维立体照射与超精准放疗得以应用于临床治疗。这些新技术不仅提高了局限期PC疗效，同时显著降低了治疗风险，提高患者生存质量。由于治疗手段不断完善，局限期PC相关诊疗数据仍需扩大样本进一步研究完善。

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