·荟萃分析·

冷冻消融对高危与局部复发前列腺癌疗效的荟萃分析

梁轩 杨雪玲 郭志

【摘要】 **目的** 采用荟萃分析方法系统评价冷冻消融术对高危与局部复发前列腺癌的治疗效果及预后。**方法** 在 PubMed 等数据库检索自建库至 2016 年 3 月关于高危与局部复发前列腺癌冷冻消融治疗及放疗文献，筛选文献并提取所纳入文献患者的 5 年无生化复发率等相关信息。选取 Stata ver. 11 软件运用随机效应模型合并 5 年无生化复发率（bDFS）及其 95% 可信区间。**结果** 补救冷冻 5 年 bDFS 45%（95% *CI* 0.43 ~ 0.47），补救放疗 5 年 bDFS 45%（95% *CI* 0.44 ~ 0.47）。高危冷冻 5 年 bDFS 66%（95% *CI* 0.64 ~ 0.67），高危放疗和高危单 EBRT 5 年 bDFS 分别为 61%（95% *CI* 0.60 ~ 0.63）和 54%（95% *CI* 0.52 ~ 0.56）。**结论** 接受补救性治疗的局部复发前列腺癌患者，冷冻消融与放疗 5 年 bDFS 接近。对于高危前列腺癌，冷冻消融治疗对比传统单纯 EBRT 放疗显示出明显的优势。

【关键词】 前列腺肿瘤； 冷冻疗法； 消融技术

Effect on cryoablation of high-risk and locally recurrent prostate cancer: a Meta-analysis *Liang Xuan*, Yang Xueling, Guo Zhi. * Department of Ultrasound, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China*

Corresponding author: Guo Zhi, Department of Ultrasound, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China, Email: cjr. guozhi @ vip. 163. com

【**Abstract**】 **Objective** To discuss the curative effect and prognosis of cryoablation to high-risk and locally recurrent prostate cancer patients. **Methods** Cryoablation related publications and relevant references were searched for potential pertinent articles until March, 2016. Articles were selected according to the exclusion criteria, Stata ver. 11 was used to perform the statistical analysis. **Results** 5-year biochemical disease-free survival of salvage ablation for prostate cancer was 45% (95% *CI* 0.43 – 0.47), in salvage radiotherapy of 45% (95% *CI* 0.44 – 0.47). The 5-year biochemical disease-free survival of high-risk prostate cancer cryoablation was 66% (95% *CI* 0.64 – 0.67). The result of high-risk prostate cancer radiotherapy and EBRT were respectively 61% (95% *CI* 0.60 – 0.63) and 54% (95% *CI* 0.52 – 0.56). **Conclusions** The five-year biochemical recurrence of salvage cryoablation is similar to salvage radiotherapy. For high-risk prostate cancer, cryoablation shows an advantage than traditional EBRT radiation.

【**Key words**】 Prostatic neoplasms; Cryotherapy; Ablation techniques

Hernandez 等[1]提出的 D′amico 危险分级依据血清 PSA 水平、Gleason 评分及临床分期将前列腺癌（PCa）患者分为高、中、低危 3 个危险等级。英国泌尿外科医师协会的一项调查显示，新发 PCa 至少 30% 属于高危患者，Shao 等[2]的研究也得到了相近的结果。对于高危 PCa 不能耐受手术的部分患者，相对较高的复发率及不良反应发生率常预后不佳。即使是中低危 PCa 患者，初次治疗后，仍有部分患者出现局部复发，需接受补救性治疗。在我国，以中晚期患者居多，对于补救治疗的选择尤为重要。然而，对冷冻消融治疗的肯定停滞于临床证据的不足，本文旨在系统评价冷冻消融对高危及局部复发的 PCa 患者的临床疗效及预后。

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作者单位：300060 天津医科大学肿瘤医院超声诊疗科 国家肿瘤临床医学研究中心 天津市“肿瘤防治”重点实验室；天津市恶性肿瘤临床医学研究中心（梁轩），介入治疗科（杨雪玲、郭志）

通信作者：郭志，Email：cjr. guozhi@ vip. 163. com

对象与方法

1. 检索策略：两位研究者分别独立对 PubMed, Medline, EmBase, LiLACS 和 Central 数据库上公开发表于的所有相关文献（截止到 2016 年 3 月）进行检索。检索词主要包括“prostate cancer”“cryoablation”及“radiotherapy”。

2. 纳入及排除标准：（1）入选研究必须是前瞻性或回顾性临床研究。（2）入选的研究必须包含有效的患者无生化复发率（bDFS）信息。生化复发的界定需符合 ASTRO（1999）标准、Phoenix（2006）标准或血清非 0 值，补救放疗组选取根治手术后复发标准。（3）高危组研究对象选择需符合 D′Amico 标准，并且为初治患者。（4）补救冷冻组研究对象选取单纯放疗失败患者。（5）补救放疗组中，对术后辅助放疗的患者予以排除。（6）接受术后长程激素治疗及化疗、生物治疗的患者需要被排除。

3. 数据收集：提取所纳入文献信息包括：第一作者，论文的发表时间，样本量，随访时间，患者年龄，肿瘤分期，治疗方式，治疗前血清 PSA 水平，接受治疗后 bDFS，此外，对于补救冷冻及高危冷冻组的研究，追加提取了不良反应发生率。

4. 统计学方法：采用 Stata ver. 11（Stata Corp, College Station, TX）统计软件合并各纳入实验中接受治疗后 bDFS 以及 95% 可信区间。采用 Q 检验来评估 Meta 分析所纳入的试验之间的异质性，用 I^2 值来量化数据异质性。在 Q 检验中，$P<0.10$，认为研究之间存在异质性，采用随机效应模型，用 *Begg* 及 *Egger* 检验是否存在偏倚，各组 P 值均 >0.05，不存在发表偏倚。

结　果

1. 纳入文献的一般情况：根据检索策略共获得冷冻相关文献 763 篇，放疗相关文献 15 111 篇。严格遵循纳入文献标准筛选后，本研究筛选出 75 个临床研究[3-78]，包括 16 739 例 PCa 患者。各组均含有部分患者接受了治疗前的短程辅助激素治疗，但接受治疗前或治疗后长程激素治疗、化疗及生物治疗的患者是不包括在内的。补救冷冻组中所报道患者 5 年 bDFS 为 25% ~59%，其中最低值由 Ismail 等[5]研究得到，Pisters 等[7]的研究关于补救手术与补救冷冻之间的对比，选取其中 56 例接受补救冷冻治疗的患者及其生化复发信息。Spiess 等[8]的研究中有 8.2% 的患者接受了术前激素治疗，Chin 等[3]的试验中 71 例患者补救冷冻手术前接受了化学去势（ADT）治疗，Ahmad 等[10]和 Spiess 等[8]的研究则排除了所有接受激素治疗的病例。补救放疗组 5 年 bDFS 19.0% ~81.8%，最高的 bDFS 发生在 Briganti 等[46]的研究中，该研究对比了术后辅助放疗与观察等待后复发补救放疗之间的关系，本研究选取了其中补救组的 390 例患者信息，而 Catton 等[17]提供了 19% 的最低 bDFS，Ost 等[44]多个研究同样筛选了其中补救组的信息。高危冷冻组中 5 年 bDFS 浮动在 42.7% ~89.0%，Ward 等[25]在对 366 例 T3 期 PCa 患者冷冻治疗研究中，得出了 42.7% 的结果，其中 31.4% 患者接受了激素治疗，而 Bahn 等[50]报道了高危组患者接受冷冻消融治疗后 5 年 bDFS 达到了 89%，同时也有 91.5% 的患者接受了术前激素治疗。Bahn 等[50]、Levy 等[55]、Dhar 等[56]各研究中均选取了各研究中高危组患者，并对应摘取了高危组患者的生存信息。Donnelly 等[49]的实验中，通过 TRUS 选取前列腺 >45 g 的 26 例患者，予以术前短程低剂量 ADT 治疗。Bolla 等[60]几个研究中设置了接受治疗后联合激素治疗的对照组，予以排除。Dearnaley 等[70]和 Cahlon 等[72]对所有高危患者都进行了放疗前新辅助内分泌治疗的预处理。接受所有种类放疗的患者 5 年无生化复发率浮动在 39.0% ~84.2%。在所有研究中，内外联合的治疗方式得到 61% ~94% 的结果，而单纯 EBRT 的结果则为 34.4% ~79.0%。

2. 单个率的荟萃分析：合并后得到补救冷冻及补救放疗患者 5 年 bDFS 分别为 45%（95% *CI* 0.43 ~0.47）（图 1）及 45%（95% *CI* 0.44 ~0.47）（图 2）。高危冷冻患者 5 年 bDFS 为 66%（95% *CI* 0.64 ~0.67）（图 3），高危 PCa 患者接受放疗 5 年 bDFS 61%（95% *CI* 0.60 ~0.63）（图 4），而接受单纯 EBRT 的高危患者 5 年 bDFS 54%（95% *CI* 0.52 ~0.56）（图 5）。

讨　论

最新一项研究显示，从 COLD 筛选出的 279 个注册患者，得到 5 年 bDFS 58.9%，中位随访 21.6 个月[78]。而 2013 年 Ward 等[58]的一项针对 T3 患者冷冻治疗的研究中，5 年 bDFS 率为 51.9%，本试验中所纳入的数据补救冷冻 5 年 bDFS 25% ~59%，高危患者冷冻 5 年 bDFS 42.7% ~89.0%。这些数据的浮动可能来源于各个研究组患者病情及所接受治疗的差异，但是一个不可忽视的问题就是试验终

点和生化进展标准的不统一。

关于冷冻消融不良反应，并未做数据合并。由于很多研究只纳入了某个研究组，而报道中对于不良反应的描述多数为全部患者的发生情况，并且短期随访的研究中不良反应可能还未出现，这可能影响最后合并的结果。不同研究者提供的不良反应发生率也显示了冷冻消融的术后不良反应低的特点。

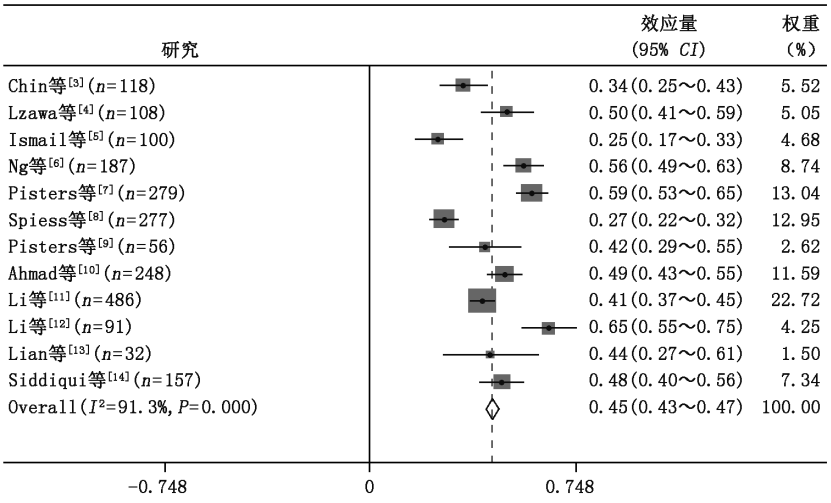

图 1　补救冷冻患者 5 年 bDFS 森林图

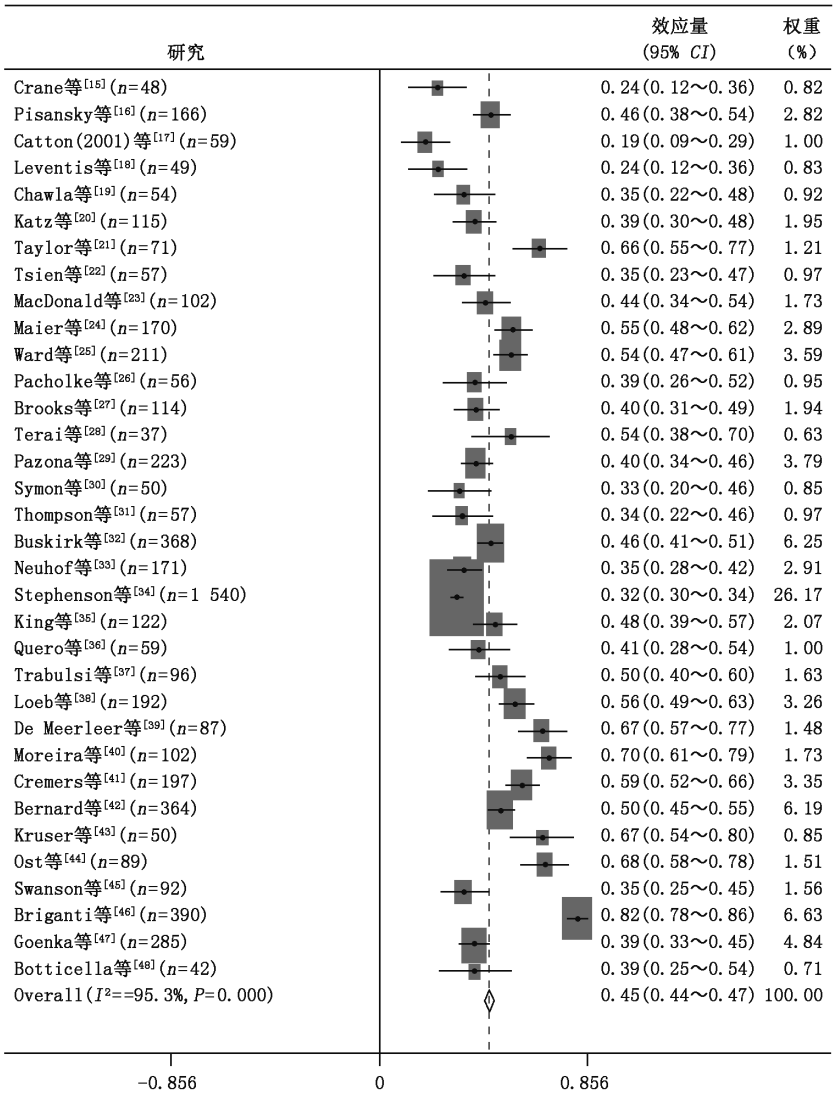

图 2　补救放疗患者 5 年 bDFS 森林图

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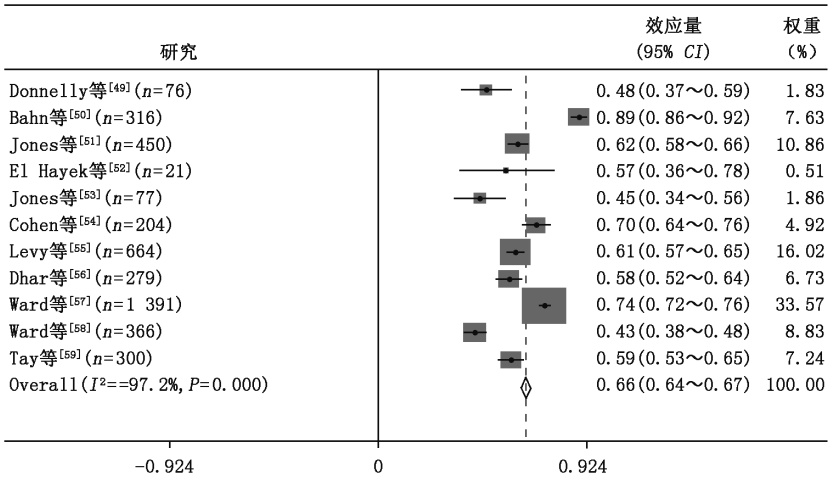

图 3　高危冷冻患者 5 年 bDFS 森林图

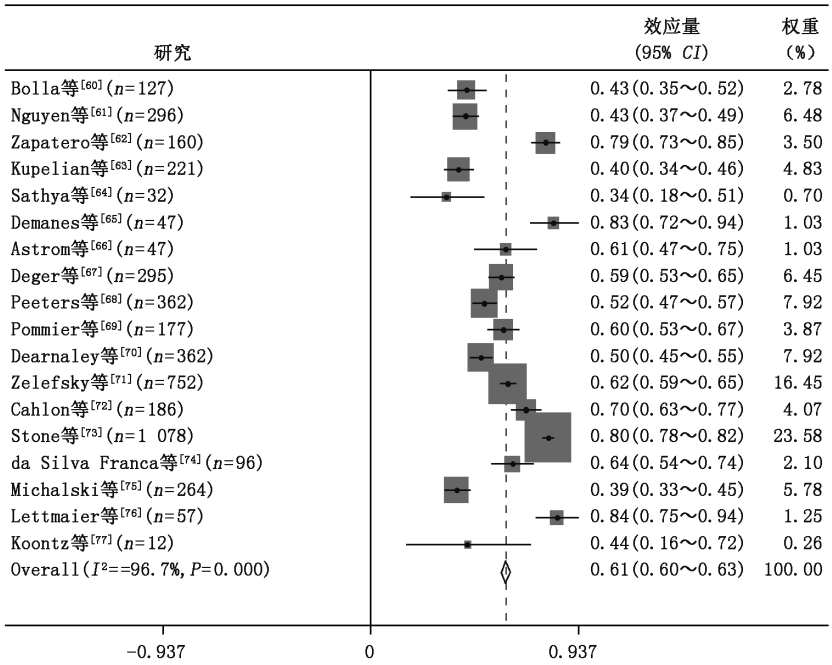

图 4　高危放疗患者 5 年 bDFS 森林图

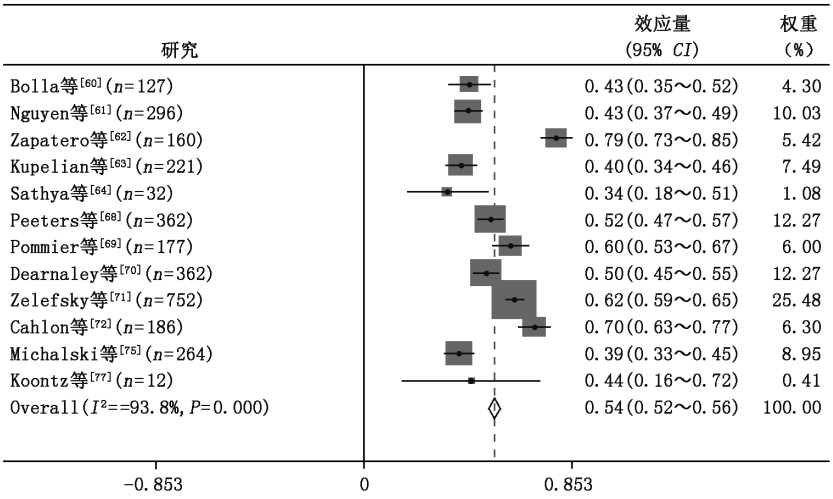

图 5　高危单纯 EBRT 患者 5 年 bDFS 森林图

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