

根治性放疗与根治性手术治疗肌层浸润性膀胱癌的 Meta 分析

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摘要: [目的] 系统评价根治性放疗与根治性手术治疗膀胱癌临床效果。[方法] 应用 ENDNOTE 软件全面检索 Pubmed (1973~2013 年) 数据库, 对符合纳入标准的临床对照试验, 采用 RevMan 4.3 软件进行 Meta 分析。对于无对照临床研究资料, 采用同质合并分析。[结果] 共纳入 6 个临床对照试验, 共 1 264 例患者, Meta 分析结果显示, 根治性放疗与根治性手术切除治疗膀胱癌患者的 5 年生存率无统计学差异 ($P=0.36$), 合并比值比 (OR) 为 1.10 (95%CI: 0.86~1.40)。18 篇无对照临床研究共纳入根治性放疗治疗膀胱癌患者 1 749 例, 多数文献采用全膀胱放疗 40~60Gy, 联合以顺铂为基础的化疗方案, 完全反应率达到 65% 以上, 平均 5 年总生存率在 50% 以上, 最低为 37%, 最高可达 82%。[结论] 根治性放疗不会降低膀胱癌患者生存率, 且能维持正常膀胱功能, 提高了患者生存质量。

关键词: 膀胱癌; 根治性手术; 根治性放疗; 生存率; Meta 分析

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A Meta-analysis of Radical Radiotherapy or Radical Cystectomy for Patients with Bladder Cancer Muscle Invaded

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Abstract: [Purpose] To investigate the response of radical cystectomy or radical radiotherapy for patients with bladder cancer muscle invaded. [Methods] The trails (randomized controlled trails and uncontrolled clinical trials) in Pubmed (1973~2013) were searched by ENDNOTE software. Meta-analysis was performed on the results of homogenous studies by RevMan 4.3. [Results] Six controlled clinical trials (1264 patients) were enrolled. The Meta-analysis results showed no statistical difference of 5-year survival between radical radiotherapy treatment group and radical surgery group (OR = 1.10, 95%CI: 0.86~1.40, $P=0.36$). Eighteen clinical uncontrolled trials (1749 patients underwent by radical radiotherapy) were enrolled, most of the patients underwent radical radiotherapy (40~60Gy) and combined with cisplatin based chemotherapy. The complete response rate achieved 65%, the average 5-year survival was more than 50% (37%~82%). [Conclusions] Radical radiotherapy will not reduce the survival rate in patients with bladder cancer muscle invaded. And it can maintain the normal bladder function and improve quality of life.

Key words: bladder cancer; radical cystectomy; radical radiotherapy; survival; Meta-analysis

膀胱肿瘤是泌尿系统最常见的肿瘤之一, 约有 60% 的患者诊断为膀胱癌时已侵犯肌层^[1]。对于局部肌层浸润性膀胱癌的最适宜首次治疗方法一直存在争议, 现阶段我国大多数泌尿科医生倾向于根治性手术治疗, 但是手术毕竟是一种破坏性治疗手段, 具有较多并发症, 尤其是丧失排尿功能。而在英国和加拿大等地, 对于膀胱癌患者更多的推行保留膀胱功能的治疗策略, 主要是通过根治性放疗和密切的

随访, 其 5 年生存率可达 40%^[2]。我们对迄今发表的临床对照试验采用 Cochrane 系统评价的方法进行分析, 阐明根治性放疗治疗肌层浸润性膀胱癌效果及安全性, 以期为临床治疗肌层浸润性膀胱癌提供依据。

1 资料与方法

1.1 纳入标准

研究类型: 公开发表的临床对照试验和临床病

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例系列报告。

研究对象：经临床确诊的肌层浸润性膀胱癌患者。

干预措施：试验中病例首次接受膀胱癌根治术或根治性放疗治疗。

排除标准：原始文献无明确结局及随访截止时间；所有病例的基本情况未叙述清楚；影像学或膀胱镜等辅助检查证实病灶未侵袭膀胱肌层；临床证据已有远处转移。

主要结局指标：长期生存率，完全反应率。

1.2 检索策略

按 Cochrane 协作网卵巢肿瘤研究组的要求,应用 ENDNOTE 软件全面检索 Pubmed(1973~2013)数据库。检索词为:bladder cancer;bladder neoplasm; radiotherapy and cystectomy, 并列多种医学主题词,任何新的术语都会重新用于检索策略,仔细浏览和鉴定检索结果,下载相关文献仔细阅读全文。并认真浏览其参考文献发现有价值的文献再次进行检索,并查看“related articles”。

1.3 资料提取

2 位评价员独立通过浏览标题、摘要选择相关文献,然后查找并阅读全文,根据上述纳入标准对文献的研究设计、患者纳入、干预措施及观察结果进行评价,筛选试验。最终,评价员通过讨论决定入选文献。

1.4 RCT 质量评价

纳入随机对照试验的方法学质量采用 Cochrane Reviewer'Handbook 4.2.6 随机对照试验的质量评价标准进行评价:根据随机方法、盲法、分配隐藏等标

准评价纳入研究的质量。如果试验报告的资料不可使用,将进一步与作者联系后决定是否剔除该试验。

1.5 统计学处理

采用 Cochrane 协作网提供的 RevMan4.3 软件进行 Meta 分析。计数资料采用比值比(OR)及其 95% CI 为疗效分析统计量。分析纳入研究间的统计学异质性,当 $F>50\%$ 时,可认为研究结果间的统计学异质性较大,进一步分析异质性产生的原因,若无明显临床异质性,可采用随机效应模型进行 Meta 分析;反之,进行描述性分析。

2 结 果

2.1 临床对照文献的基本特征

共纳入 6 篇关于膀胱癌根治性手术或根治性放疗治疗膀胱癌患者的临床对照研究^[3-8],共 1 264 例患者。纳入文献病例局部病灶分期多为 T₂~T₄ 期,行根治性放疗的患者平均年龄略高于膀胱癌根治术的患者(Table 1)。

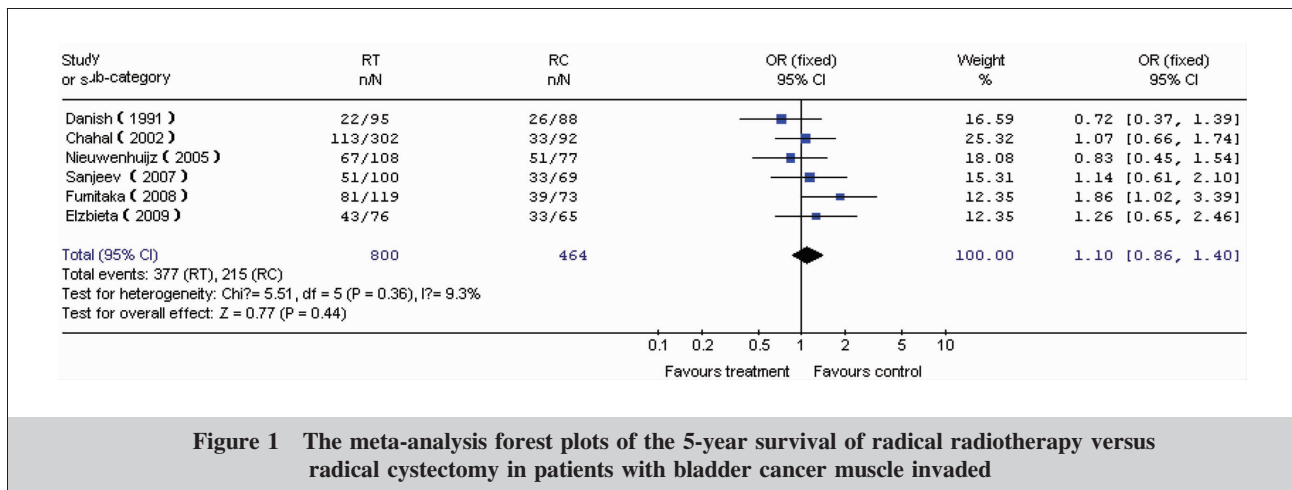
2.2 5 年总生存率比较

纳入文献亚组内异质性检验结果显示各亚组内纳入文献不存在统计学异质性($P>0.05$),并且纳入全部文献异质性检验结果显示无统计学异质性 ($P>0.05$),故选择固定效应模型。6 篇临床对照研究 Meta 分析结果显示根治性放疗和根治性膀胱切除术治疗肌层浸润性膀胱癌患者 5 年总生存率差异无统计学意义($P=0.36$),合并比值比(OR)为 1.10(95%CI:0.86~1.40)。Figure 1。

Table 1 Features of included randomized controlled trails

Literature	Year	Treatment*	Average age (years)	N	TNM stage	5-yr survival(n)	Follow-up period(year)
3	1991	RT	70	95	T ₂ ~T _{4a}	23%(22)	1983~1986
		RC	65	88		29%(26)	
4	2003	RT	71	302	T ₂ ~T ₄	37%(113)	1993~1996
		RC	66	92		35%(33)	
5	2009	RT	68	76	T ₁ ~T ₂	56%(43)	1991~2001
		RC	63	65		50%(33)	
6	2009	RT	70	119	T ₂ ~T ₄	68%(81)	1997~2007
		RC	67	73		53%(39)	1983~1997
7	2008	RT	75	100	T ₂ ~T ₄	51%(51)	1996~2000
		RC	68	69		47%(33)	
8	2005	RT	63	108	T ₁ ~T ₂	62%(67)	1988~2000
		RC	63	77		66%(51)	

Note:*, RT: radiotherapy; RC: cystectomy



2.3 发表偏倚

漏斗图上点分布基本呈倒置的漏斗状，未见明显发表偏倚。

2.4 临床病例系列研究评价

剔除重复病例报告和信息不全的文献，本研究最终纳入 18 篇临床病例系列研究^[9-25]。所有文献都是回顾性研究，共纳入根治性放疗治疗肌层浸润性膀胱癌患者 1 749 例，治疗时平均年龄在 70（65~74）岁左右，分期多为 T₂₋₄N₀M₀，绝大多数病例的治疗方法是全膀胱放疗联合以顺铂为基础的化疗方案。标准的放疗计划是包括全膀胱和肿瘤边缘 2~3cm，初始放疗剂量 40~60Gy，然后根据患者反应情况酌

情对肿瘤边缘加量。根治性放疗联合化疗治疗肌层浸润性膀胱癌的患者完全反应率达到 65%，平均 5 年生存率在 50%左右，最低为 37%，最高为 82%（Table 2）。

3 讨 论

在过去 30 年，许多医学中心报告了膀胱癌患者根治性手术后令人鼓舞的 5 年生存率^[26,27]。但是膀胱癌在老年人群中的发病率逐渐增高，而老年患者体力状态差，或合并其他疾病而不能耐受手术。Henningsohn 等^[28]指出膀胱替代手术后严重影响患

Table 2 Features and survivals of included uncontrolled clinical trials

Literature	Year	Average age (year)	N	TNM stage	Treatment	RR (%)	Overall survival (year)
9	1996	68	91	T ₂₋₄ N _x M ₀	Bladder 39.6Gy+ Cisplatin /MCV	75	62%(4)
10	1997	74	56	T ₂₋₄ N ₀ M ₀	Bladder 40Gy+ Cisplatin /MCV	50	55%(5)
11	1997	73	106	T ₂₋₄ N ₀ M ₀	Bladder 40Gy+ Cisplatin /MCV	66	52%(5)
12	1998	73	21	T ₂₋₃ N _x M ₀	Pelvic 40~60Gy +M-VAC	80	37%(5)
13	1998	71	46	T ₂₋₄ N _x M ₀	Bladder 50Gy+ Cisplatin /5-Fu	65	53%(3)
14	1998	69	184	T ₂₋₄ N ₀ M ₀	Bladder 45~54Gy+ Cisplatin or Carboplatin	80	56%(5)
15	1998	68	61	T ₂₋₄ N _x M ₀	Bladder 39.6Gy+ Cisplatin /MCV	61	48%(5)
16	1999	70	67	T ₂₋₄ N _x M ₀	Bladder 550Gy+ Carboplatin	92	55%(5)
17	2000	65	34	T ₂₋₄ N ₀ M ₀	Bladder 44Gy+ Cisplatin /5-Fu	67	83%(3)
18	2001	68	31	T ₂₋₄ N _x M ₀	Bladder 55Gy+ MMC/5-FU	74	65%(1)
19	2002	67	326	T ₂₋₄ N ₀ M ₀	Bladder 54Gy+ Cisplatin /5-Fu	72	42%(10)
20	1983	72	52	T ₂₋₄ N _x M ₀	Pelvic 64.8Gy+ Cisplatin /MCV	74	61%(3)
21	2004	65	77	T ₂₋₄ N ₀ M ₀	Bladder 69 Gy+ Cisplatin /5-Fu	90	58%(5)
22	2009	74	50	T ₂₋₄ N _x M ₀	Bladder 64.3Gy+ Cisplatin / Taxol	87	79%(2)
23	2006	72	113	T ₂₋₄ N ₀ M ₀	Bladder 64~64Gy+ Cisplatin	70	50%(5)
24	2007	73	24	T ₂₋₄ N ₀ M ₀	Bladder 40Gy+ Cisplatin / Epirubicin	42	82%(5)
25	2010	74	75	T ₂₋₄ N _x M ₀	Pelvic 50~70Gy	65	57%(3)

者的胃肠道功能和性功能,而且泌尿系统的感染增加,感觉功能减退。现代肿瘤治疗的新观念改变了对肿瘤根治手术的根本态度,对于肿瘤的治疗不仅要达到控制疾病的目的,还要注重治疗后及长期生活质量。因此,根治性放疗要成为膀胱癌患者另一可行的选择,在不降低生存期的前提下同时保持患者良好的泌尿生殖功能。

尽管有很多关于根治性放疗治疗膀胱癌预后良好的报告,但是外科医生依然怀疑保留膀胱会降低患者的生存期。本文研究发现根治性放疗和根治性手术治疗肌层浸润性膀胱癌后生存率差异无统计学意义。对于膀胱癌患者,根治性放疗作为首选治疗是安全的,且没有降低患者的生存率。这与之前的很多比较两种首选的根治性治疗手段结果是一致的,均报告两者间生存率无显著性差异^[7,8,29-31]。在最近的一篇Cochrane数据库系统评价文献中,Shelley等^[32]分析了3篇临床对照文献共包括439例病例,随机分为手术组221例,根治性放疗组218例,对其无特定疾病生存率分析结果显示虽然手术组的3年生存率高于根治性放疗组,但是两组的5年生存率无显著性差异。而且本研究所纳入的18篇临床病例研究根治性放疗联合化疗治疗肌层浸润性膀胱癌的患者完全反应率达到65%,而且80%以上的患者治疗后能保留功能良好的自身膀胱,这与其他很多研究的结果也是一致的^[5,33-35]。此外,在治疗肌层浸润性膀胱癌存在一个主要问题是有40%~60%的患者在诊断后1~2年会出现远处转移^[36]。微小病灶转移被认为在处理局部病灶的同时已经存在,通过有效的全身系统化疗能显著提高患者的生存率^[37]。本研究纳入的近期病例报告治疗方法也均是全膀胱放疗和联合化疗方案,因此建议在将根治性放疗作为初始治疗时,同步配合应用全身系统化疗方案。而且治疗后应严格进行常规的膀胱镜定期复查,可以早期发现局部复发行补救根治术,延长患者的生存期。

膀胱癌在老年人群中的发病率逐渐增高,而老年患者体力状态差,或存在其他疾病而不能耐受手术,因此应该推荐根治性放疗作为老年膀胱癌患者的首次治疗手段。根治性放疗不会降低患者的生存期,且能维持正常膀胱功能,提高了患者生存质量。而且根治性放疗后需定期行膀胱镜检查,早期发现局部复发可行补救根治术,延长患者的生存期。

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