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·临床研究·

干扰素辅助治疗肝癌随机对照试验的 Meta 分析

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[摘 要] **目的**:用 Meta 分析的方法定量评价干扰素辅助治疗肝癌的效果。**方法**:计算机检索 EMbase、PubMed、Cochrane 图书馆、中国生物医学文献数据库、中国期刊全文数据库(CNKI)、维普中文科技期刊数据库,收集有关干扰素辅助治疗肝癌的随机对照试验(randomized controlled trial,RCT),两名评价者单独评价纳入研究的方法学质量并提取资料,用 Cochrane 协作网提供的 RevMan5.0 软件进行 Meta 分析。**结果**:共纳入 8 篇 RCTs,共计 836 例患者。Meta 分析结果显示,肝癌患者接受基础治疗后,干扰素辅助治疗组在复发率方面与安慰剂组相比,差异有统计学意义[RR=0.86,95% CI(0.77,0.96),$P<0.05$];两组在病死率方面的差异也有统计学意义[RR=0.64,95% CI(0.54,0.76),$P<0.05$]。**结论**:干扰素辅助治疗可以降低肝癌患者的病死率和复发率,但远期疗效尚待大样本、高质量的 RCTs 进一步证实。

[关键词] 干扰素;肝癌;辅助治疗;随机对照试验;Meta 分析
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Adjuvant treatment with interferon for patients with hepatocellular carcinoma: A Meta analysis based on randomized controlled trials

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[**Abstract**] **Objective**: To quantitatively assess the efficacy of interferon (IFN) in the adjuvant treatment for patients with hepatocellular carcinoma (HCC) using Meta analysis. **Methods**: Randomized controlled trials (RCTs) of adjuvant treatment with interferon for patients with HCC were searched in Embase, Medline, Cochrane Library, Chinese biomedicine literature database, Chinese Scientific Journals full-text database, and Chinese Journal full-text databases. Two reviewers independently assessed the quality of included studies and extracted data. Meta analysis was carried out using Review Manager (version 5.0) provided by Cochrane Collaboration. **Results**: Eight RCTs totaling 836 patients were included. Meta analysis showed that the adjuvant treatment with IFN significantly reduced the recurrence rate after curative treatment of HCC, with a pooled risk ratio of 0.86 (95 percent confidence interval 0.77 to 0.96); the effect on reduction in mortality rate was still significant with a pooled risk ratio of 0.64 (95 percent confidence interval 0.54 to 0.76). **Conclusion**: IFN has a beneficial effect on both mortality rate and tumour recurrence, and the results still need to be confirmed by RCTs of high quality and large sample size.

[**Key words**] interferon; hepatocellular carcinoma; adjuvant treatment; randomized controlled trial; Meta analysis
[Chin J Cancer Biother, 2012, 19(1): 81-86]

原发性肝癌(hepatocellular carcinoma,HCC)是常见的恶性肿瘤之一,其发病率在全世界居恶性肿瘤第 6 位,而病死率却居第 3 位,每年至少约有 60 万人死于肝癌[1]。肝癌高发区主要集中在非洲撒哈拉及东南亚,这与当地的病毒性肝炎发病高密切相关[2]。由于肝癌恶性程度高、发病隐匿、早期诊断率低,多数患者首诊时已处于局部晚期或发生转

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移[3]。因此,只有 10% ~30% 的新发病例可接受根治性治疗,如手术、肝移植等[4]。由于高昂的费用和严格的选择标准,使得肝移植只能适合一小部分患者,因此绝大多数患者接受手术切除和肝动脉化疗栓塞术(transarterial chemoembolization,TACE)治疗[5]。接受手术切除和 TACE 的患者术后 3 年内局部肿瘤的复发率常超过 50%,这也是患者死亡的主要原因[6]。在我国,肝癌患者常携带乙型肝炎病毒(hepatitis B virus, HBV)和丙型肝炎病毒(hepatitis C virus, HCV),鉴于干扰素可以抑制 HBV 和 HCV 复制,同时还可杀伤癌细胞,多数学者认为干扰素可以减低肝癌患者治疗后的复发率[7-8],但各随机对照试验(randomized controlled trial,RCT)的结论尚不一致[9-15]。因此,本研究拟用循证医学的原理和方法,全面收集干扰素辅助治疗肝癌的 RCTs,并进行 Meta 分析,为临床实践提供循证医学证据。

1　材料与方法

1.1　纳入标准和排除标准

1.1.1　研究类型　RCT。

1.1.2　研究对象　纳入标准:(1)细胞学或病理学证实为原发性肝癌患者,且携带有 HBV 或 HCV;(2)试验组和对照组均接受手术切除或 TACE;(3)试验组接受干扰素,对照组接受安慰剂;(4)重要器官功能基本正常。排除标准:(1)排除对生物制品有过敏史及过敏体质的患者;(2)排除孕妇及哺乳期妇女。

1.1.3　干预措施　(1)试验组接受干扰素;(2)对照组接受安慰剂。

1.1.4　测量指标　病死率、复发率

1.2　文献检索

1.2.1　检索词　英文检索词:hepatocellular carcinoma, liver cancer, interferon, adjuvant treatment, liver resection, liver ablation, transarterial chemoembolization,TACE。中文检索词:肝癌、肝脏肿瘤、干扰素、辅助治疗、手术、切除术、化疗栓塞等。

1.2.2　计算机检索　Cochrane Library(2011 第 2 期),PubMed (1966-01 至 2011-04),EMbase (1974-01 至 2011-04),CBM(1978-01 至 2011-04),维普中文科技期刊全文数据库(1989-01 至 2011-04),中国期刊全文数据库(CNKI,1994-01 至 2011-04)。同时辅以手工检索和 Google 网络检索,并在参考资料中追踪查阅相关文献,末次检索日期为 2011 年 4 月 10 日。文献语种不限制。

1.3　文献筛选及资料提取

两位研究者独立筛选文献,对有分歧而难以确定其是否纳入的文献通过讨论解决。两位研究人员按预先设计的表格独立地对符合纳入标准的试验进行资料提取,填写资料提取表格,并交叉核对提取的资料,缺乏的资料尽量与作者联系予以补充。

1.4　文献质量评价

研究的方法学质量评价采用 Cochrane 系统评价手册的方法进行测量。质量评价包括以下 4 个方面:(1) 随机方法是否正确;(2)是否采用分配方案隐藏(concealment of allocation);(3)是否采用盲法;(4)是否描述了失访、退出的发生情况。如果有退出或失访情况,是否进行了意向性分析(intention to treat analysis,ITT)[16]。评价结果分为 3 级:A 级,所有评价指标均为“正确或充分”,发生各种偏倚的可能性最小;B 级,有 1 项或 1 项以上指标描述不清楚或部分满足,发生偏倚的可能性为中等;C 级,任意一项或多项完全不满足或未使用,有发生偏倚的高度可能性。两位研究者独立评价文献质量,如遇分歧而难以确定时通过讨论或联系原文作者确定。

1.5　统计学处理

采用 Cochrane 协作网提供的 RevMan 5.0 统计软件进行 Meta 分析。首先进行异质性分析,并根据临床异质性和方法学异质性进行亚组分析,当亚组内各研究间无统计学异质性($I^2 \leqslant 50\%$,$P \geqslant 0.1$)时,采用固定效应模型对各研究进行 Meta 分析;反之,如各研究间存在统计学异质性($I^2 \geqslant 50\%$,$P < 0.1$),若无明显临床异质性时,可采用随机效应模型进行分析,并慎重解释研究结果。计数资料采用风险比(risk ratio,RR),计量资料采用 WMD,区间估计均采用 95% 可信区间 (confidence interval,CI)。如存在明显的临床和方法学异质性时,则采用描述性分析。当纳入足够多的研究时,则进行漏斗图分析,观察是否存在发表偏倚。

2　结　果

2.1　文献检索结果

初检文献 495 篇,通过阅读题名、摘要,排除文献 402 篇,剩余 93 文献通过阅读全文来筛选,最终纳入 8 篇 RCTs 进行 Meta 分析。文献筛查流程见图 1。纳入各研究试验组和对照组基线具有可比性。共有 836 例患者纳入,其中干扰素组 436 例患者,安慰组 400 例患者;最短的随访时间范围为 24.8 个月,最长的为 7.1 年。

2.2　纳入试验的方法学质量评价

根据 Cochrane 文献的评价标准,纳入试验的方

法学质量评价见表 2。

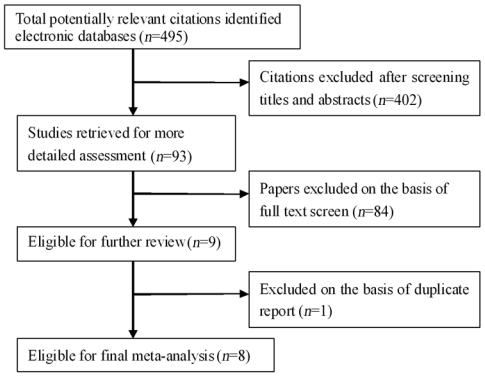

图 1 文献筛查流程图

Fig. 1 Literature screening flowchart

2.3 干扰素辅助治疗对肝癌复发率的影响

纳入的 8 篇研究均报道了肝癌复发率,Meta 分析结果显示:原发性肝癌患者接受基础治疗后,与安慰剂组相比,干扰素辅助治疗组在复发率[RR = 0.86,95% CI(0.77,0.96)]方面差异有统计学意义,提示干扰素组复发的风险低于安慰剂组。纳入研究间无异质性(I^2 =0%,P =0.54),结果见图 2。

为进一步验证上述结果,按照患者接受的基础治疗的类型进行亚组分析。Meta 分析结果显示,对于接受根治性手术切除的患者,干扰素组和安慰剂辅助治疗组肝癌在复发率方面差异有统计学意义[HR = 0.88,95% CI(0.78,1.00)],纳入研究间无异质性(I^2 = 4%,P = 0.39);对于接受 TACE 的患者而言,两组在复发率方面差异亦有统计学意义[HR = 0.81,95% CI (0.66,0.99)],纳入研究间有异质性(I^2 = 0%,P = 0.78)。提示干扰素辅助治疗可以降低原发性肝癌的复发率。

表 1 纳入研究的基本特征

Tab. 1 Characteristics of included studies

Study	Intervention	Patients' characteristic	Follow-up (month)
Ikeda K (2000)[9]	10 patients received natural IFN-β 6×10^6 twice a week for 36 months	20 patients with HCV infection and treatment with surgical resection or percutaneous ethanol injection	25.0
Kubo S (2000)[10]	15 patients received 6×10^6 IFN-α intramuscularly every day for 2 weeks, then three times weekly for 14 weeks, and finally twice weekly for 88 weeks	30 men with HCV infection and curative surgical resection	60.0
Shiratori Y (2003)[11]	49 patients received 6×10^6 IFN-α intramuscularly three times weekly for 48 weeks	74 patients with compensated cirrhosis owing to HCV after curative ablation of a maximum of 3 HCC lesions with percutaneous ethanol injection	85.2
Lin SM (2004)[12]	11 patients received 3×10^6 IFN-α 2b intramuscularly three times weekly for 24 months	30 patients after non-surgical treatment (TACE or percutaneous acetic acid injection) of HCV	27.0
Sun HC (2006)[13]	118 patients received 3×10^6 IFN-α intramuscularly twice a week for 2 weeks and then 5×10^6 three times weekly for 18 months	236 patients after curative resection of HBV related HCC	36.5
Mazzaferro V (2006)[14]	76 patients received 3×10^6 IFN-α 2b three times weekly for 48 weeks	150 patients after curative resection of HCV-related or HCV and HBV-related	45.0
Lo CM (2007)[15]	40 patients received $10\times10^6/m^2$ IFN-α 2b subcutaneously three times weekly for 16 weeks	80 patients after curative resection of HBV-related HCC	30.0
Li M (2009)[17]	108 patients received IFN-α 2b 3×10^6 three times a week by intramuscular injection one week	216 patients after TACE treatment of hepatitis B virus HBV related unresectable HCC	24.8

表 2　纳入研究的质量评价

Tab. 2　Assessment quality of included studies

Study	Randomization	Allocation concealment	Blinding	Lost of follow up	ITT	Grade
Ikeda K(2000)[9]	Unclear	Unclear	Unclear	Yes	Yes	B
Kubo S (2000)[10]	Adequate	Unclear	Unclear	Yes	Yes	B
Shiratori Y (2003) [11]	Adequate	Unclear	Unclear	Yes	Yes	B
Lin SM (2004)[12]	Unclear	Unclear	Unclear	Yes	Yes	B
Sun HC (2006) [13]	Adequate	Adequate	Unclear	Yes	Yes	B
Mazzaferro V(2006) [14]	Adequate	Unclear	Unclear	Yes	Yes	B
Lo CM (2007)[15]	Adequate	Adequate	Unclear	Yes	Yes	B
Li M (2009)[17]	Adequate	Adequate	Unclear	Yes	Yes	B

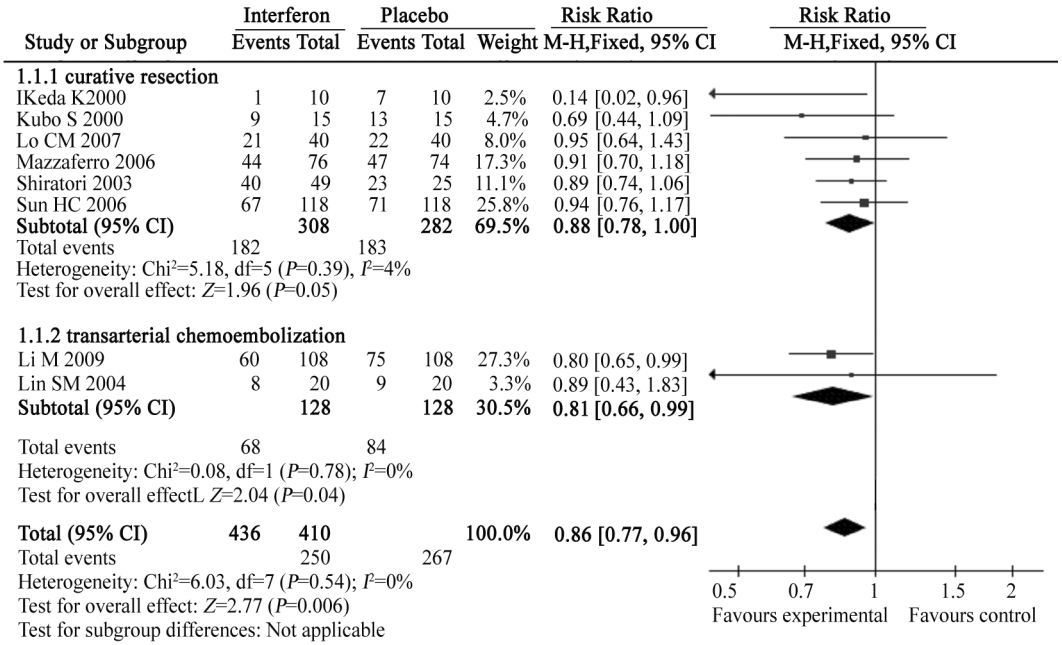

图 2　干扰素辅助治疗肝癌患者复发率的 Meta 分析

Fig. 2　Meta analysis of recurrence rate of hepatocellular carcinoma patients after adjuvant treatment with interferon

2.4　干扰素辅助治疗对肝癌病死率的影响

有 7 篇研究均报道了肝癌患者治疗后的病死率,Meta 分析结果显示:原发性肝癌患者接受基础治疗后,与安慰剂组相比,干扰素辅助治疗组在病死率[RR = 0.64,95% CI(0.54,0.76)]方面差异有统计学意义,提示干扰素组发生死亡的风险低于安慰剂组。纳入研究间无异质性(I^2 = 0%,P = 0.90)。结果见图 3。

按照患者接受基础治疗的类型进行亚组分析,对于接受根治性手术切除的患者,Meta 分析结果显示:干扰素组和安慰剂辅助治疗组肝癌患者在病死率[RR = 0.66,95% CI(0.53,0.82)]方面差异有统计学意义,纳入研究间无异质性(I^2 = 0%,P = 0.85);对于接受 TACE 的患者而言,两组在病死率[RR = 0.61,95% CI(0.47,0.81)]方面差异亦有统计学意义,纳入研究间无异质性(I^2 = 0%,P = 0.41)。提示干扰素辅助治疗可以降低原发性肝癌患者的病死率。

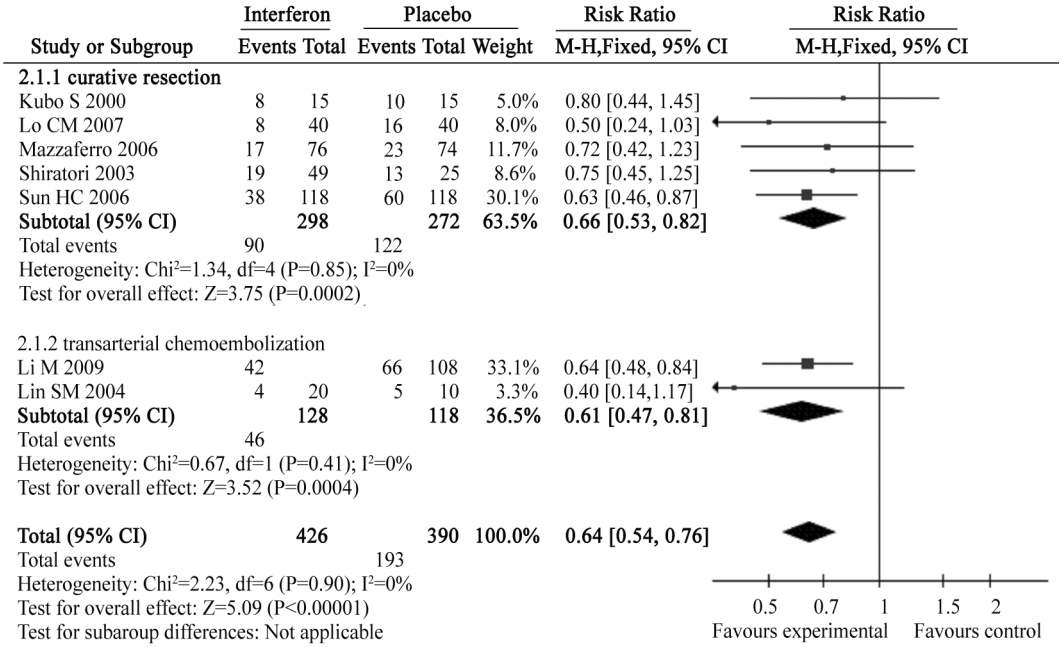

图 3　干扰素辅助治疗肝癌患者病死率的 Meta 分析

Fig. 3　Meta analysis of mortality rate of hepatocellular carcinoma patients after adjuvant treatment with interferon

3　讨　论

本研究用 Meta 分析的方法评价了干扰素在原发性肝癌辅助治疗中的价值,纳入研究中的患者均携带 HBV 或 HCV。Meta 分析结果提示,对于接受手术切除或 TACE 治疗后的肝癌患者,干扰素辅助治疗可以使患者受益;与安慰剂组相比,干扰素患者复发率减低了 14%,病死率降低了 36%。纳入研究对干扰素的安全性报道较少,只有 2 篇文献[12,15]报道,干扰素常见的不良反应为发热、畏寒、肌肉痛、头痛,严重不良反应的发生率在 8% ~24%。干扰素辅助治疗肝癌的机制尚不清楚。

干扰素具有抗病毒、抗细胞增殖、抗血管生成及免疫调节等多种生物学功能,已被广泛应用于多种疾病的治疗中[7-8]。体外实验[18]表明,IFN-α 能够抑制人脐静脉血管内皮细胞的增殖,并且其抑制作用随着 IFN-α 的剂量和作用时间延长而增强。体内实验[19]显示,IFN-α 治疗后肿瘤直径明显减小,且微血管密度亦明显低于对照组。由此可以推测,IFN-α 可能通过抑制肿瘤的血管新生、抗细胞增殖起到抗肿瘤作用。干扰素的上述生物学特性可能解释干其使原发性肝癌患者受益的原因。

本研究纳入的研究均为 RCT,其中 2 篇研究未描述具体的随机方法,只有 3 篇研究报道了采用分配方案隐藏,其余原文均未报道,所以选择性偏倚的可能性大。纳入各研究均未报道是否实施盲法,所以本研究所纳入文献测量偏倚和实施偏倚的可能性很大。信息联系没有得到作者回应,因此无法判断是否存在报道性偏倚和其他潜在的偏倚。建议以后的研究都能按照临床试验报告的统一标准(consolidated standards of reporting trials,CONSORT)全面报道研究结果[20]。

本研究也存在以下局限性:(1)纳入研究虽均为 RCT,各研究样本量均较小,且各研究结论不一致,进行 Meta 分析可以增加样本量,提高检验效能,但也可能会受制于其潜在的偏倚;(2)纳入研究患者的基本特征不全相同,影响肝癌预后的因素主要有临床分期、病理类型、治疗方法、瘤体的大小、肝功能的状态、机体的免疫能力,这些因素也可能会影响 Meta 分析结果;(3)纳入研究干扰素的剂量和疗程各不相同,干扰素的类型不全一致,由于纳入研究数量有限,无法进行亚组分析和敏感性分析,这可能会影响结果的稳定性;(4)纳入研究报道的测量指标多为复发率和病死率,很少有研究评价总生存期(overall survival,OS)和无疾病进展生存期(progression free survival,PFS)等终点指标,建议以后的研究应该关注其远期疗效。

本研究表明,干扰素辅助治疗可以降低肝癌患者病死率和复发率,其远期疗效尚待大样本的随机对照试验进一步证实。

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