

经动脉化疗栓塞结合经皮微波凝固治疗肝癌的实验和临床研究

申宝忠,刘 岩,李任飞,杨 光,于友涛,董宝玮,梁 萍

申宝忠,刘岩,李任飞,杨光,于友涛,哈尔滨医科大学第三临床医学院放射科 黑龙江省哈尔滨市 150040
董宝玮,梁萍,中国人民解放军总医院 北京市 100853
申宝忠,男,1961-01-02生,黑龙江省齐齐哈尔市人,汉族,1984年哈尔滨医科大学本科毕业,1999年哈尔滨医科大学硕士研究生毕业,教授,主任医师,主要从事消化系统的影像诊断及介入治疗研究。
哈尔滨市科委基金资助课题, NO.2002AA9CS151-2
项目负责人:申宝忠,150040,黑龙江省哈尔滨市哈平路150号,哈尔滨医科大学第三临床医学院。 shenbzh@hotmail.com
电话:0451-6623347 传真:0451-6623347
收稿日期:2002-10-07 接受日期:2002-10-29

Effects of intraarterial chemoembolization combined with percutaneous microwave coagulation on hepatocellular carcinoma: a clinical and experimental study

Bao-Zhong Shen, Yan Liu, Ren-Fei Li, Guang Yang, You-Tao Yu, Bao-Wei Dong, Ping Liang

Bao-Zhong Shen, Yan Liu, Ren-Fei Li, Guang Yang, You-Tao Yu, Department of Radiology, Third Affiliated Hospital, Harbin Medical University, Harbin 150040, Heilongjiang Province, China
Bao-Wei Dong, Ping Liang, Department of Ultrasound, Chinese PLA General Hospital, Beijing, 100853
Supported by the Natural Scientific Foundation of Harbin City, NO. 2002AA9CS151-2
Correspondence to: Dr. Bao-Zhong Shen, Department of Radiology, Third Affiliated Hospital, Harbin Medical University, 150 Haping Road, Harbin 150040, Heilongjiang Province, China. shenbzh@hotmail.com
Received: 2002-10-07 Accepted: 2002-10-29

Abstract

AIM: To evaluate the role of microwave coagulation for liver cancer after occlusion of hepatic artery in animal experiment and clinical study.

METHODS: Total 24 suitable hepatic lobes of ten dogs were separated into two groups. Microwave coagulation alone (control group) or after hepatic artery occlusion (experiment group) was performed respectively. The power of irradiation was 50 W and the duration was 300 and 400 seconds. Clinically, 25 patients with hepatocellular carcinoma (30 nodules) were treated with PMCT after TACE. The TACE was performed 1-3 times and PMCT 1-2 times totally in every patients.

RESULTS: In animal experiment, the coagulated area was elliptic in control group and was elliptic or round in experimental group. The volume of coagulated tissue in experimental group was 3.8 times bigger than that in control. Clinically, all the lesions in contrast-enhanced CT showed slight enhancement or no enhancement after treatment. Intratumoral blood flow decreased significantly in 6 patients and disappeared

in 20 patients. In 19 patients with elevated α -fetoprotein, the level decreased in all patients and was normalized in 14. There were no significant side-effects.

CONCLUSION: PMCT after TACE can significantly enlarge the necrosis volume of microwave coagulation, and promote the efficacy of treatment for hepatocellular carcinoma.

Shen BZ, Liu Y, Li RF, Yang G, Yu YT, Dong BW, Liang P. Effects of intraarterial chemoembolization combined with percutaneous microwave coagulation on hepatocellular carcinoma: a clinical and experimental study. *Shijie Huaren Xiaohua Zazhi* 2003;11(3):268-271

摘要

目的: 通过动物实验和临床研究评价经动脉化疗栓塞(TACE)+经皮微波凝固(PMCT)在肝癌治疗中的作用。

方法: 活体实验狗10只,取其中24个肝叶分别行TACE+PMCT和单纯PMCT,微波输出功率50 W,时间为300和400 s,比较两组动物肝脏凝固范围的大小和形态。另原发性肝癌25例(30个结节)行TACE+PMCT治疗,TACE治疗1-3次,PMCT治疗1-2次。

结果: 动物实验中,非栓塞组组织凝固区多为椭圆形。栓塞+微波组组织凝固区为椭圆形或近球形,凝固灶体积较前者平均增大3.8倍。临床CT复查,所有术前强化的病灶动脉期强化明显减弱或消失。6例患者再次血管造影表现为肿瘤血供明显减弱,20例表现为肿瘤血供消失。19例AFP升高的患者均出现AFP下降,14例达正常范围。未出现明显并发症。

结论: TACE后行PMCT可明显增大组织凝固范围,提高肝癌治疗的疗效。

申宝忠,刘岩,李任飞,杨光,于友涛,董宝玮,梁萍. 经动脉化疗栓塞结合经皮微波凝固治疗肝癌的实验和临床研究. *世界华人消化杂志* 2003;11(3):268-271
<http://www.wjgnet.com/1009-3079/11/268.htm>

0 引言

微波凝固治疗肝癌(HCC),可产生完全,局部组织坏死。我们通过阻断肿瘤供血血管,减低血流所引起的冷却效应,观察经动脉化疗栓塞(TACE)后经皮微波凝固治疗(PMCT)的范围和形态,并在实验的基础上应用于临床,总结TACE+PMCT在治疗HCC中的作用。

1 材料和方法

1.1 材料 选择成年狗 10 条, 全麻后进行实验. 共选择其中 24 个肝叶行微波凝固. (1) 栓塞组开腹后经胃十二指肠动脉逆行插管至肝固有动脉, 注入碘化油和明胶海绵碎屑, 栓塞肝动脉 级分支后, 于栓塞叶段行微波凝固; (2) 非栓塞组于与栓塞相应的叶段直接行微波凝固, 进针深度与栓塞组相同. 微波(2 450 Hz)天线长度为 27 mm, 输出功率 50 和 60 W, 加热时间 300 或 400 s. 实验结束后取肝组织剖开, 观察凝固灶的大小及形态, 并观察其镜下病理改变.

1.2 方法 HCC 患者 25 例, 男 22 例, 女 3 例, 年龄 35-63(平均 49)岁. 肿瘤最大径 2.9-8.2(平均 5.2 cm), 单发结节 21 例, 4 例为 2-3 个结节, 肝功能为 Child A, B 级. TACE 方案均采用动脉灌注 Epi-ADM 50 mg, 5-Fu DR 1 000 mg, 丝裂霉素 20 mg+ 碘化油 10-20 mL 栓塞肿瘤血管, 明胶海绵碎屑或明胶海绵条栓塞至肿瘤供血动脉完全消失. TACE 后 2-3 d, 局部麻醉后行超声引导下 PMCT 治疗, 依据肿瘤大小穿刺 1-5 针, 2-10 点微波凝固治疗, 对于直径 < 6 cm 的肿瘤, 我们使微波凝固后的强回声将肿瘤完全覆盖. 直径 > 6 cm 的肿瘤, 由于患者承受能力的限制, 则着重对肿瘤的周边及碘化油充盈缺损区行微波凝固. 术后检查肝功能变化, 并行 CT 增强扫描, 数字减影、超声及 AFP 检查. 根据复查结果, 行补充 TACE 或 PMCT 治疗, 治疗间隔时间 1-3 mo. 本组患者 TACE 治疗 1-3 次, PMCT 治疗 1-2 次.

统计学处理 样本均数 t 检验.

2 结果

2.1 动物实验 肝组织微波凝固后肉眼观呈现以天线为长轴的轮廓清晰的椭球体, 由中心向外依次分为中心区, 凝固区, 充血反应区三层. 单纯微波凝固组 中心区 宽约 5 mm, 呈黑褐色焦带状; 凝固区 位于碳化区的外周, 呈灰褐色, 质硬, 紧邻中心区含微孔; 充血反应区位于凝固坏死区的外周, 宽约 3 mm, 呈红色. 充血反应区的外围可见一条宽约 1 mm 的暗红色出血带(图 1). 栓塞+微波凝固组 中心区 宽约 5 mm, 成黑褐色焦带状; 凝固区 呈灰白色, 质硬, 气化明显; 充血反应区宽约 8 mm, 呈淡红色, 有时其外可见不明显的暗红色出血带.(图 2)凝固时间 400 s 时, 中心碳化区及周围气化较凝固时间 300 s 时明显. 光镜下中心区表现为黑褐色无结构碳化区; 凝固区肝组织正常结构消失, 肝细胞分界不清, 细胞膜结构不清, 呈重度凝固变性, HE 染色呈深红色(图 3); 反应区表现为肝细胞变性, 但程度较轻, 可见血管充血(图 4). 单纯微波凝固治疗单电极在肝组织内形成长径 25-33 mm, 短径 10-22 mm 的凝固灶, 栓塞后可形成长径 33-44 mm, 短径 24-33 mm 的凝固灶, 有显著性差别($P < 0.05$). 栓塞后平均长径增大 1.3 倍, 短径增大 1.7 倍, 体积(按公式 $V = \frac{4}{3} \pi r_{\text{短轴}}^2 r_{\text{长轴}}$ 粗略计算)增大 3.8 倍. 微波输出时间 400 s 时形成的凝

固灶略大于输出时间 300 s 时所形成的凝固灶, 但在统计学上无显著差别($P > 0.05$).

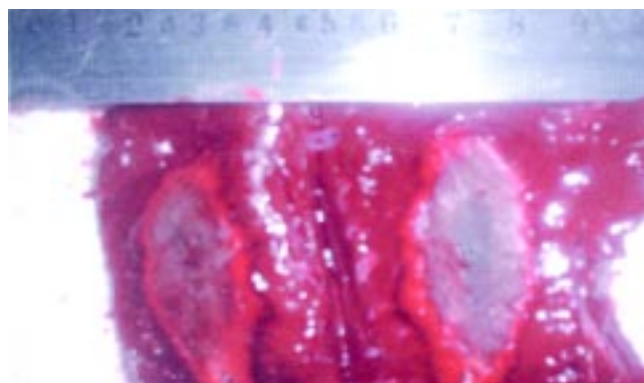


图1 单电极单纯微波凝固 微波输出功率 50 W, 输出时间 300 s. 中央为黑褐色碳化区, 其外部为灰褐色凝固区(29 × 15 × 15 mm), 外周为 3 mm 宽红色反应区.

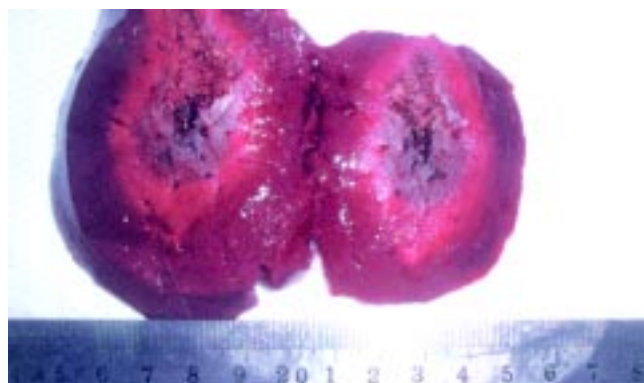


图2 栓塞后单电极微波凝固微波输出功率 50 W, 输出时间 300 s. 中央为黑褐色碳化区, 其外部为灰褐色凝固区(40 × 27 × 27 mm), 气孔明显, 外周为 7 mm 宽淡红色反应区.

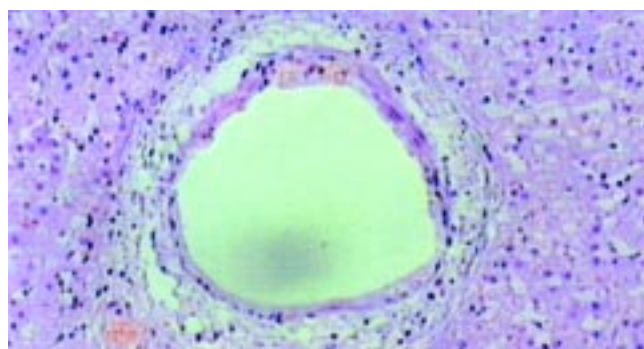


图3 凝固区: 针孔旁以纤维化为主(中心碳化已脱落), 周围细胞变性, 呈疏松改变. 肝细胞无明显界限, 变性重. 个别小血管扩张充血.

2.2 临床研究 首次治疗至今为 6-11(平均 9 mo), 所有患者均存活. CT 扫描见 20 % 的病灶缩小 50 % 以上, 27 缩小 25-50 %, 33 % 缩小 25 % 以内, 3 例病灶大小无明显变化, 3 例病灶增大, 2 例患者在其他叶段内出现新病灶. CT 增强扫描, 坏死区表现为无强化的低密度影, 增强区表示肿瘤残留或复发. 24 个病灶(80 %) 坏死完全. 治疗前 16 个结节为低回声, 8 个为高回声, 6 个为混杂回声, TACE 后 2-3 d 超声检查, 碘化油沉积良好的肿瘤区显示为高回声, 肿瘤周边可见

约3 mm 环形低回声区, PMCT 治疗过程中显示为围绕微波天线周围不断扩大的强回声区. 24 h 后强回声消失, 凝固灶内血流信号消失. 治疗前 16 例原发性肝癌的患者表现为 AFP 增高, 为 30-4 580 ug, 治疗后所有患者均表现为 AFP 值减低, 其中 10 例降为正常值 ($< 20 \text{ ug/L}$). 21 例术前血管造影肿瘤染色较明显的患者, 9 例于首次 TACE+PMCT 后 30-45 d 血管造影检查表现为肿瘤染色完全消失, 7 例经过 2-3 次 TACE 及 1-2 次 PMCT 后肿瘤染色完全消失, 5 例可见肿瘤染色较治疗前明显减少(图 5,6). 术后出现发热反应 19 例, 达 37.2-38.7, 其中 16 例于 5 d 内消失, 其余 3 例 20 d 内消失, 22 例患者在 PMCT 后出现在上腹痛, 均于术后 1 wk 内缓解. 所有患者均于术后 1 wk 内出现转氨酶一过性升高, 1 例穿刺点处皮肤轻度烧伤. 2 例自觉右上腹部皮区痛觉敏感(考虑为肋间神经损伤), 未见针道肿瘤细胞种植, 无胆道损伤、出血、周边脏器损伤、门脉血栓、气胸等严重并发症, 2 例出现腹水, 经治疗后消失.

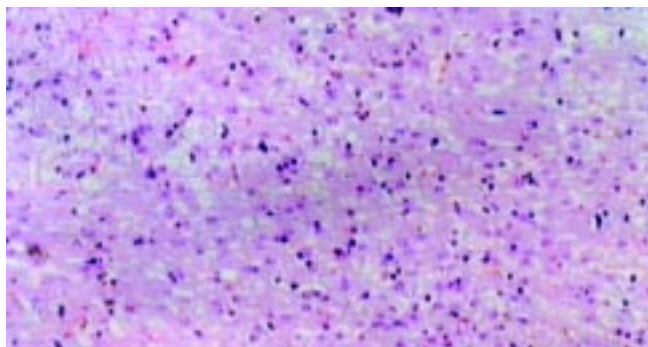


图 4 反应区:肝正常结构消失,肝细胞呈轻度变性,胞间可见点状出血.

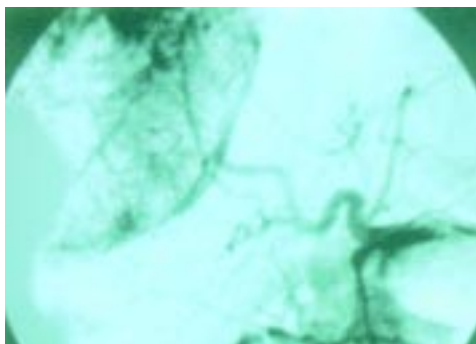


图 5 治疗前肿瘤血管造影显示肿瘤内血供丰富.

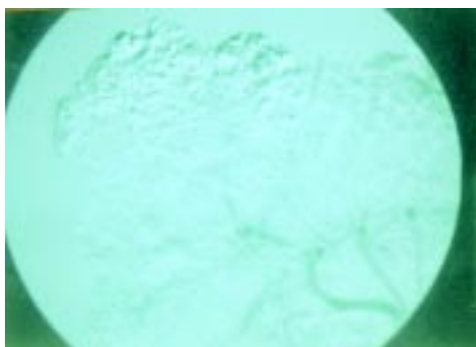


图 6 2 次 TACE+1 次 PMCT 治疗后显示肿瘤血供完全消失.

3 讨论

经皮微波凝固治疗(PMCT)是目前 HCC 介入治疗的重要方法之一^[1-12], 但单纯 PMCT 只适合治疗直径 $< 2 \text{ cm}$ 的肝脏肿瘤^[7,8,11-21].

为了减少引起肿瘤结节及其周边组织坏死和治疗较大肿瘤所需的电极数目, 需要增大单电极的凝固范围. 实验研究表明, 相同条件下, 活体动物肝脏的微波凝固范围小于离体肝脏的微波凝固范围, 说明血流引起的散热效应可使微波凝固范围缩小^[22].

Rossi et al^[23]临床研究报道用球囊导管或明胶海绵颗粒阻塞肿瘤供血动脉后可使单电极射频消融的凝固体积由 8 cm^3 增大到 $22-87 \text{ cm}^3$. TACE 可使肿瘤供血动脉阻塞, 清除了肝动脉血流的冷却效应, 同时碘化油还可以通过大量的动脉-门静脉交通支到达肿瘤周边的门静脉, 暂时性地减少了肿瘤周边门静脉的血流, 这样也减少了门静脉所致的血流吸热效应^[24]. 同时, TACE 术后 2-3 d 内肿瘤组织及其周边组织的水肿也可使对微波的阻抗降低, 使凝固范围增大^[25-27].

通过动物实验可见, TACE 后单级微波凝固的范围可明显增大. 但相同输出功率及时间时, 同一组内凝固灶的大小及形态变化较大, 说明影响凝固灶大小的因素除了肝动脉的血流外, 还有其他因素, 如门脉、肝静脉血流, 肿瘤的位置等. 肝内肿瘤多为球形生长, 因此, 使微波凝固范围在空间形态上接近于球形是提高治疗疗效的关键. 从本实验看, 栓塞后的凝固灶形态更接近于球形, 是治疗的理想形态.

通过 TACE+PMCT 治疗直径 $< 3 \text{ cm}$ 的肝脏肿瘤, 取得了满意效果^[14,27], 但有关这方面的文献, 尤其是治疗更大的肿瘤尚少有报道. 本临床研究中, 肿瘤治疗的近期有效率及缓解率都高于文献报道的单纯 TACE 和单纯 PMCT 治疗^[7-12,28]. 肿瘤体积过大、分化程度低、形状不规则、周边小结节的存在以及治疗过程中为避免周围大的肝内管状系统和重要脏器的损伤而减轻治疗力度是肿瘤治疗不彻底和局部复发的主要原因. 本研究未出现与治疗相关的严重并发症^[19,29-32], 主要预防措施是在进针过程中保证穿刺路线上无大的肝内管状系统及重要脏器, 退针过程中使用天线的余热加热穿刺防止针道转移等.

TACE 结合 PMCT 治疗肝脏肿瘤可以充分发挥二种治疗的优势, 使肿瘤的坏死率增高, 通过 TACE 可以使影像学不能发现的隐匿病变也得到有效的治疗, 减少单纯 PMCT 治疗的失误率. 而且和单纯 PMCT 相比, 联合治疗可使所需植入的微波天线数目和治疗次数减少, 从而减少了并发症的发生.

4 参考文献

- 1 Hamazaki K, Fujiwara T, Asakawa T, Ikeda Y, Matsumoto M, Murashima N, Akura Y. A long-term survivor undergoing microwave coagulation therapy for hepatocellular carcinoma located just above the main trunk of right hepatic vein. *Gan To Kagaku Ryoho* 2002;29:143-147

- 2 Shibata T, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, Konishi J. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology* 2002;223:304-307
- 3 Georgiades CS, Ramsey DE, Solomon S, Geschwind JF. New non-surgical therapies in the treatment of hepatocellular carcinoma. *Tech Vasc Interv Radiol* 2001;4:193-199
- 4 Beppu T, Ishiko T, Doi K, Matsuda T, Maeda T, Ishihara K, Ogata K, Ogawa M. A promising new treatment strategy for advanced hepatocellular carcinoma--"multi-ablation therapy" consisting of radio-frequency ablation (RFA), microwave coagulation therapy (MCT) and ethanol injection therapy (EIT). *Gan To Kagaku Ryoho* 2001;28:1583-1586
- 5 Midorikawa T, Kumada K, Kikuchi H, Ishibashi K, Yagi H. Microwave coagulation therapy for hepatocellular carcinoma. *J Hepatobil Pancreat Surg* 2000;7:252-259
- 6 Horigome H, Nomura T, Nakao H, Saso K, Takahashi Y. Treatment of solitary small hepatocellular carcinoma: consideration of hepatic functional reserve and mode of recurrence. *Hepatogastroenterology* 2000;47:507-511
- 7 Ohmoto K, Tsuduki M, Shibata N, Takesue M, Kunieda T, Yamamoto S. Percutaneous microwave coagulation therapy for hepatocellular carcinoma located on the surface of the liver. *Am J Roentgenol* 1999;173:1231-1233
- 8 Tabuse K, Tsuji T. Indication of percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Gan To Kagaku Ryoho* 1999;26:1684-1688
- 9 Seki T, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, Yamashiki N, Okamura A, Inoue K. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer* 1999;85:1694-1702
- 10 Beppu T, Ogawa M, Matsuda T, Ohara C, Hirota M. Efficacy of microwave coagulation therapy (MCT) in patients with liver tumors. *Gan To Kagaku Ryoho* 1998;25:1358-1361
- 11 Dong B, Liang P, Yu X. US-guided microwave in the treatment of liver cancer: experimental study and preliminary clinical application. *Zhonghua Yixue Zazhi* 1996;76:87-91
- 12 Murakami R, Yoshimatsu S, Yamashita Y, Matsukawa T, Takahashi M, Sagara K. Treatment of hepatocellular carcinoma: value of percutaneous microwave coagulation. *Am J Roentgenol* 1995;164:1159-1164
- 13 Asahara T, Nakahara H, Fukuda T, Nakatani T, Yano M, Hino H, Okamoto Y, Katayama K, Itamoto T, Ono E, Dohi K, Kitamoto M, Nakanishi T. Percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Hiroshima J Med Sci* 1998;47:151-155
- 14 Itamoto T, Asahara T, Kohashi T, Katayama S, Fukuda S, Nakatani T. Percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Gan To Kagaku Ryoho* 1999;26:1841-1844
- 15 Chen Y, Chen H, Wu M, Zhou W, Wei G, Wang P, Li X. Curative effect of percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Zhonghua Zhongliu Zazhi* 2002;24:65-67
- 16 Itamoto T, Katayama K, Fukuda S, Fukuda T, Yano M, Nakahara H, Okamoto Y, Sugino K, Marubayashi S, Asahara T. Percutaneous microwave coagulation therapy for primary or recurrent hepatocellular carcinoma: long-term results. *Hepatogastroenterology* 2001;48:1401-1405
- 17 Lu MD, Chen JW, Xie XY, Liu L, Huang XQ, Liang LJ, Huang JF. Hepatocellular carcinoma: US-guided percutaneous microwave coagulation therapy. *Radiology* 2001;221:167-172
- 18 Okuda K, Nakashima O, Imamura I, Imamura M, Aoyagi S. Indication and limitation of microwave coagulation therapy for stage IV-A hepatocellular carcinoma. *Gan To Kagaku Ryoho* 2000;27:1501-1508
- 19 Ohmoto K, Miyake I, Tsuduki M, Shibata N, Takesue M. Percutaneous microwave coagulation therapy for unresectable hepatocellular carcinoma. *Hepatogastroenterology* 1999;46:2894-2900
- 20 Horigome H, Nomura T, Saso K, Itoh M. Standards for selecting percutaneous ethanol injection therapy or percutaneous microwave coagulation therapy for solitary small hepatocellular carcinoma: consideration of local recurrence. *Am J Gastroenterol* 1999;94:1914-1917
- 21 Matsukawa T, Yamashita Y, Arakawa A, Nishiharu T, Urata J. Percutaneous microwave coagulation therapy in liver tumors. A 3-year experience. *Acta Radiol* 1997;38:410-415
- 22 Seki T, Wakabayashi M, Nakagawa T. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer* 1994;74:817-825
- 23 Rossi S, Garbagnati F, Lencioni R. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. *Radiology* 2000;217:119-126
- 24 Kan Z, Sato M, Ivancev K. Distribution and effect of iodized poppyseed oil in the liver after hepatic artery embolization: experimental study in several animal species. *Radiology* 1993;186:861-866
- 25 Stigsson L, Ekelund L, Jonsson N, Sjogren HO. Transcatheter arterial embolization of experimental hepatic tumours in the rat. *Acta Radiol Diagn (Stockh)* 1979;20:422-432
- 26 Ishida T, Murakami T, Shibata T, Inoue Y, Takamura M, Niinobu T, Sato T, Nakamura H. Percutaneous microwave tumor coagulation for hepatocellular carcinomas with interruption of segmental hepatic blood flow. *J Vasc Interv Radiol* 2002;13:185-191
- 27 Seki T, Tamai T, Nakagawa T, Imamura M, Nishimura A, Yamashiki N, Ikeda K, Inoue K. Combination therapy with transcatheter arterial chemoembolization and percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Cancer* 2000;89:1245-1251
- 28 董宝玮, 梁萍, 于小玲. 超声引导下微波治疗肝癌的实验研究及临床初步应用. *中华医学杂志* 1996;76:87-91
- 29 Takahashi Y, Shibata T, Shimano T, Kitada M, Niinobu T, Ikeda K, Takami M, Inoue Y, Ishida T. A case report of intra-thoracic biliary fistula after percutaneous microwave coagulation therapy. *Gan To Kagaku Ryoho* 2000;27:1850-1853
- 30 Kojima Y, Suzuki S, Sakaguchi T, Tsuchiya Y, Okamoto K, Kurachi K, Okumura T, Igarashi T, Takehara Y, Nakamura S. Portal vein thrombosis caused by microwave coagulation therapy for hepatocellular carcinoma: report of a case. *Surg Today* 2000;30:844-848
- 31 Sato M, Tokui K, Watanabe Y, Lee T, Kohtani T. Generalized intraperitoneal seeding of hepatocellular carcinoma after microwave coagulation therapy: a case report. *Hepatogastroenterology* 1999;46:2561-2564
- 32 Shimada S, Hirota M, Beppu T, Matsuda T, Hayashi N. Complications and management of microwave coagulation therapy for primary and metastatic liver tumors. *Surg Today* 1998;28:1130-1137