**Effect of Huaier Granule on Recurrence after Curative Resection of HCC:**

**A Multicenter, Randomized Clinical Trial**

Qian Chen, PhD, MD1#; Chang Shu, PhD2,3,4#; Arian D. Laurence, PhD, MD 5; Yan Chen, PhD, MD 3,6,7; Bao-Gang Peng, MD5; Zuo-Jun Zhen, MD6; Jian-Qiang Cai, MD7; Yi-Tao Ding, MD8; Le-Qun Li, MD9; Yu-Bao Zhang, MD10; Qi-Chang Zheng, MD11; Ge-Liang Xu, MD12; Bo Li, MD13; Wei-Ping Zhou, MD14; Shou-Wang Cai, MD15; Xi-Yan Wang, MD16; Hao Wen, MD17; Xin-Yu Peng, MD18; Xue-Wen Zhang, MD19; Chao-Liu Dai, MD20; Ping Bie, MD21; Bao-Cai Xing, MD22; Zhi-Ren Fu, MD23; Lian-Xin Liu, MD24; Yi Mu, MD25; Ling Zhang, MD26; Qi-Shun Zhang, MD27; Bin Jiang, MD28; Hai-Xin Qian, MD29; Yi-Jun Wang, MD30; Jing-Feng Liu, MD31; Xi-Hu Qin, MD32; Qiang Li, MD33; Ping Yin, PhD2\*; Zhi-Wei Zhang, MD 3,6,7\*; Xiao-Ping Chen, MD, FACS 3,6,7\*

Author affliations:1Division of Gastroenterology, Department of Internal Medicine at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST), Wuhan, China; 2Department of Epidemiology and Biostatistics and State Key Laboratory of Environment Health, School of Public Health, Tongji Medical College, HUST, Wuhan, China; 3Hepatic Surgery Centre at Tongji Hospital, Tongji Medical College, HUST, Wuhan, China; 4Surgery administrator office at Tongji Hospital, Tongji Medical College, Hust, Wuhan, China; 5Hematology Department, The Newcastle upon Tyne Hospitals NHS Foundation Trust at Freeman Hospital, Newcastle, UK; 6Key Laboratory of Organ Transplantation, Ministry of Education and Ministry of Public Health, Wuhan, China; 7Hubei Province for the Clinical Medicine Research Center of Hepatic Surgery, Wuhan, China; 8Surgery Department, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; 9Surgery Department, First People’s Hospital, Foshan, China; 10Surgery Department, Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China; 11Surgery Department, Nanjing Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing, China; 12Surgery Department, Cancer Hospital Affiliated to Guangxi Medical University, Nanning, China; 13Surgery Department, Third Affiliated Hospital of Harbin Medical University, Harbin, China; 14Surgery Department, Wuhan Union Hospital of HUST, Wuhan, China; 15Surgery Department, Shengli Hospital Affiliated to Anhui Medical University, Hefei, China; 16Surgery Department, West China Hospital of Sichuan University, Chengdu, China; 17Surgery Department, Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China; 18Surgery Department, Chinese PLA General Hospital of Medical School of Chinese PLA, Beijing, China; 19Surgery Department, Cancer Hospital Affiliated to Xinjiang Medical University, Urumqi, China; 20Surgery Department, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China; 21Surgery Department, First Affiliated Hospital of Shihezi University School of Medicine, Shihezi, China; 22Surgery Department, China and Japan Union Hospital of Jilin Hospital, Changchun, China; 23Surgery Department, Shengjing Hospital of China Medial University, Shenyang, China; 24Surgery Department, Southwest University Hospital, Chongqing, China; 25Surgery Department, Beijing Cancer Hospital, Beijing, China; 26Surgery Department, Shanghai Changzheng Hospital, Shanghai, China; 27Surgery Department, First Affiliated Hospital of Harbin Medical University, Harbin, China; 28Surgery Department, Beijing Ditan Hospital Affiliated to Capital Medical University, Beijing, China; 29Surgery Department, Henan Cancer Hospital Affiliated to Zhengzhou University, Zhengzhou, China; 30Surgery Department, Guangxi Liuzhou Worker’s Hospital, Liuzhou, China; 31Surgery Department, Taihe Hospital Affiliated to Hubei University of Medicine, Shiyan, China; 32Surgery Department, First Affiliated Hospital of Suzhou Medical University, Suzhou, China; 33Surgery Department, Tianjin No.3 Hospital, Tianjin, China; 34Surgery Branch at the Hospital of Infectious and Contagious Diseases Affiliated to Fujian Medical University, Fuzhou, China; 35Surgery Department, Third People’s Hospital of Changzhou, Changzhou, China; 36Surgery Department, Tianjin Medical University Cancer Institute and Hospital (TMUCIH), Tianjin, China.

\*Corresponding author: Professor Ping Ying, Zhi-Wei Zhang and Xiao-Ping Chen, Tongji Hospital of Tongji Medical College of HUST, Jie Fang Avenue 1095, Wuhan 430030, P.R. China; Tel: +86 27-83663500; Fax: +86 27-83663500

Chen Q# and Shu C# : contributed equally to this manuscript.

Correspondence to Email: Yin P (pingyin2000@126.com); Zhang Z-W (zwzhang@tjh.tjmu.edu.cn); Chen X-P (chenxpchenxp@163.com).

**Supplemental Material**

Site distribution and patient number were as follows: Tongji Hospital of HUST (69), Wuhan; Southwest University Hospital (25), Chongqing; the First Affiliated Hospital of Harbin Medical University (23), Harbin; the Third Affiliated Hospital of Harbin Medical University (44), Harbin; Shengli Hospital Affiliated to Anhui Medical University (36), Hefei; Taihe Hospital Affiliated to Hubei University of Medicine (20), Shiyan; Wuhan Union Hospital of HUST (39), Wuhan; Cancer Hospital Affiliated to Xinjiang Medical University (27), Urumqi; the First Affiliated Hospital of Shihezi University School of Medicine (26), Shihezi; Cancer Hospital of Chinese Academy of Medical Sciences (51), Beijing; Cancer Hospital Affiliated to Guangxi Medical University (45), Nanning; the First Affiliated Hospital of Suzhou Medical University (19), Suzhou; Guangxi Liuzhou Worker’s Hospital (22), Liuzhou; the First Affiliated Hospital of Sun Yat-Sen University (77), Guangzhou; Chinese Arsenal and Police (Wujing) General Hospital (6), Beijing; the First Affiliated Hospital of Xinjiang Medical University (27), Urumqi; the First People’s Hospital (53), Foshan; the Second People’s Hospital (4), Shenzhen; Tanjin No.3 Hospital (17), Tianjin; Beijing Ditan Hospital Affiliated to Capital Medical University (23), Beijing; Hubei Cancer Hospital (2), Wuhan; China and Japan Union Hospital of Jilin Hospital (25), Changchun; Shengjing Hospital of China Medial University (25), Shenyang; Chinese PLA General Hospital of Medical School of Chinese PLA (32), Beijing; West China Hospital of Sichuan University (36), Chengdu; Nanjing Drum Tower Hospital Affiliated to Nanjing University Medical School (45), Nanjing; the Second Xiangya Hospital of Central South University (9), Changsha; Shanghai Changzheng Hospital (23), Shanghai; Beijing Cancer Hospital (24), Beijing; Henan Cancer Hospital Affiliated to Zhengzhou University (22), Zhengzhou; the Second Affiliated Hospital of Zhejiang University School of Medicine (4), Hangzhou; Hospital of Infectious and Contagious Diseases Affiliated to Fujian Medical University (16), Fuzhou; Shanghai Eastern Hepatobiliary Surgery Hospital (34), Shanghai; Tianjin Medical University Cancer Institute & Hospital (TMUCIH) (13), Tianjin; the Affiliated Hospital of Guizhou Medical University (6), Guiyang; Fujian Cancer Hospital (9), Fuzhou; Changzhou TCM Hospital (1), Changzhou; Lingzhe Cancer Hospital (7), Lingzhe; Third People’s Hospital of Changzhou (16), Changzhou.

**Supplementary Table 1.** Schoenfeld residual test for assessment of proportional hazard assumption

|  |  |  |  |
| --- | --- | --- | --- |
|  | RFS | OS | ERFS |
| Correlation coefficient | -0.006 | -0.056 | 0.058 |
| *P*-value | 0.9002 | 0.6732 | 0.4981 |

**Supplementary Table 2.** Baseline disease characteristics between Huaier and control groups

|  |  |  |  |
| --- | --- | --- | --- |
|  | Huaier group (N=686) | Control group (N=316) | *P*-value |
| BMI | 23.78±3.56 | 23.44±3.30 | 0.1901 |
| ALT (U/L) | 45.82±58.59 | 49.30±80.11 | 0.4941 |
| AST (U/L) | 41.21±45.87 | 44.83±55.85 | 0.3212 |
| Total bilirubin (umol/L) | 16.29±25.02 | 14.33±6.40 | 0.0565 |
| Haemoglobin (g/L) | 142.10±22.15 | 139.90±18.10 | 0.1030 |
| Blood platelet count (109/L) | 161.90±69.91 | 152.20±66.38 | 0.0393 |
| Absolute neutrophil count (109/L) | 3.90±2.41 | 3.72±2.13 | 0.2224 |
| Serum creatinine (umol/L) | 74.00±22.91 | 74.52±21.68 | 0.7380 |

The levels of BMI, ALT, AST, total bilirubin, haemoglobin, platelet count, neutrophil count, and serum creatinine were compared between Huaier and control groups at the time of randomization. Data represent the means ± SD. P values were calculated using unpaired Student's t test. *P* < 0.05 was considered as a statistical significance.

**Supplementary Table 3.** CMH-*X*2 test for comparison of local recurrence between Huaier and control groups.

|  |  |  |
| --- | --- | --- |
|  | Huaier（N=686） | Control（N=316） |
| Recurrence-free, n(%) | 472 (68.80) | 191 (60.44) |
| Intrahepatic recurrence\*, n(%) | 214 (31.20) | 125 (39.56) |
| CMH-χ2 | 6.7502 |
| *P* | .0094 |
| Difference, 95% CI | 8.36 (1.95,14.77) |

 \*: Among those with local recurrence, 15 patients in Huaier group and 7 patients in control group had both intrahepatic and extrahepatic recurrence, respectively.

**Supplementary Table 4.** Breslow-Day test for the homogeneity across centers on recurrence, death, and extrahepatic recurrence

