Preventive treatments for recurrence after curative resection of hepatocellular carcinoma - A literature review of randomized control trials

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Abstract
To review the inhibitory effect of preventive approaches on recurrence after operation in patients with hepatocellular carcinoma (HCC), we summarized all available publications reporting randomized control trial indexed in PubMed. The treatment approaches presented above included pre-operative transcatheter arterial chemoembolization (TACE), post-operative TACE, systemic or locoregional chemotherapy, immunotherapy, Interferons and acyclic retinoic acid. Although no standard treatment has been established, several approaches presented promising results, which were both effective and tolerable in post-operative patients. Pre-operative TACE was not effective on prolonging survivals, while post-operative TACE was shown with both disease-free survival and overall survival benefits in some papers, however, it was also questioned by others. Systemic chemotherapy was generally not effective on prolonging survival but also poorly tolerated for its significant toxicities. Adoptive immunotherapy using LAK cells was proved to be beneficial to patients’ survival in a recent paper. Interferon α and Interferon β can inhibit recurrence in HCC patients with HCV infection background, though the mechanism is not fully understood. Acyclic retinoic acid was shown to decrease multi-centric recurrence after operation, which was reported by only one group. In conclusion, several adjuvant approaches have been studied for their efficacy on recurrence in HCC patients in randomized control trials; however, multi-centric randomized control trial is still needed for further evaluation on their efficacy and systemic or local toxicities; in addition, new adjuvant treatment should be investigated to provide more effective and tolerable methods for the patients with HCC after operation.

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INTRODUCTION
Over the last two decades, the surgical techniques and peri-operative care have been improved, and the operative death (within 30 days after operation) decreased to 2.5%[11], the 5-year overall survival after curative resection of hepatocellular carcinoma (HCC) increased to 25%[12] or 46.7%[22]. However, HCC is far from a curable disease because of high recurrence rate, the 5-year recurrence rate after curative resection was 38%[11] and 61.5%[22], the 5-year disease-free survival was 16%[3] or 38.6%[41] after curative resection of HCC, and the recurrence resulted in most deaths after resection[5].

People have tried a number of approaches to prevent recurrence, however, only a few of them were designed as randomized control trial (RCT), which provide evidence-based results for those treatment modalities. In this paper, the authors summarized those results from randomized control trials, attempting to find a more suitable treatment modality for prevention of recurrence.

IMPORTANT ISSUES RELATED TO EVALUATION OF EFFICACY OF PREVENTION
It is difficult to compare the results among different RCTs because of different study settings and patient collection; therefore, several important issues should be addressed in evaluation of efficacy of prevention of HCC recurrence.

The definition of “curative resection”
The most important issue is the definition of “curative resection” of HCC, because, the definition will greatly affect the recurrence rate. There is no consensus on this definition in the literature. Some authors described it as “complete removal of tumor tissues”[6]; others prefer to “complete removal of tumor tissues plus a clear resection margin ≥ 1 cm on pathological examination”[7]. And some authors used a strict criterion, in which negative findings by angiography followed by Lipiodol-CT and ultrasound one or two months after resection were also included[8]. The 1 year disease-free survival was 43.0 % by the first criteria[6], and 59.1 % by the second[7], and 69 % by the third[8]. The different definitions of curative resection and their results are listed in Table 1.

Bias in patient collection
The clinicopathological characteristics of patients enrolled in a study also influence the results. For example, tumor size, which was regarded as the age of tumor, affects the recurrence rates and survival after operation, thereafter, has great impact on the results (Table 1).

Origins of recurrence
The origin of recurrence can be divided into two sources, uni-centric and multi-centric origins[9], which could be discriminated by genetic markers, such as HBV integration sites[9,10] or p53 mutation types[11]. Uni-centric origin can also be named as intrahepatic metastatic recurrence or residual tumor, which means metastatic lesion spread from the primary main tumor, and left in the remnant liver. However, multi-centric recurrence is a newly developed lesion in the cirrhotic background. Generally two kinds of recurrences can be roughly divided according to the time of appearance. Twelve months[12] or 3-years[13] were set as a parameter to distinguish them by...
different authors. A study may be needed to clarify the percentage of uni-centric and multi-centric recurrence by different set point.

Most preventive procedures are targeting the metastatic recurrence, which are used to control the residual tumor cells in the liver. Therefore, 1, 2, 3-year disease-free survival or recurrence rates are used to evaluate the efficacy of preventive procedures targeting metastatic recurrence; however, if a preventive procedure is targeting the multi-centric origin recurrence, 3 or 5-year disease-free survival or recurrence rate should be noticed.

Table 1 showed the overall survival and disease free survival are better when the tumor size decreases, and when a stricter criteria for curative resection was applied. Therefore, when evaluating a preventive treatment targeting residual tumors, it is suggested that a subgroup of patient with more invasive HCC should be enrolled. On the other hand, a subgroup of patient with less invasive HCC or selected by stricter criteria for curative resection should be recruited to investigate a preventive treatment targeting secondary HCC appearance.

**Table 1** The important issues related to evaluation of efficacy of prevention of recurrence

| Authors       | Average tumor size | Definition of curative resection | 1 year RR | 1 year DFS | 1 year OS |
|---------------|--------------------|----------------------------------|-----------|-----------|----------|
| Kubo[4][44]   | 2.6 cm             | Yes                              | 25%       | NA        | 92%      |
| Lau[77]       | 3.8 cm             | Yes                              | NA        | 59.1%     | 86.4%    |
| Tang[123]     | <5 cm, complete tumor capsule, without portal vein involvement | Yes | No       | No        | 6.5%     |
| Poor[12]      | >5 cm              | Yes                              | 46%       | NA        | 55.5%    |
| Izumi[14][4]  | >5 cm              | Yes                              | 51.7%     | 43.0%     | 81.0%    |
| Lai[6]        | 10.4 cm            | Yes                              | 20-30%    | 69.0%     | 75%*     |

RR: recurrence rate; DFS: disease free survival; OS: overall survival; NA: data not available.
*estimated according to the authors’ paper.

**Table 2** Summary of RCTs to evaluate the efficacy of pre- and post-operative TACE on prevention of recurrence

| Authors     | Tumor factors | Treatment protocol | Sample size (Tx/ Ctl) | Observation time | DFS (Tx vs Ctl) | OS (Tx vs Ctl) | Conclusions |
|-------------|---------------|--------------------|-----------------------|------------------|----------------|----------------|--------------|
| Wu[16]      | >10 cm; resectable | Pre-operative TACE | 52 (24/ 28)          | 2-10 years       | 3-year         | 3-year         | Harmful     |
|              |               |                    |                       |                  | 39% vs 46%    | 31% vs 62%    |             |
| Yamasaki[19][20] | 2-5 cm; Single with vessel involvement or intrahepatic spreading | Pre-operative TACE | 97 (50/ 47)          | 4-6.6 years      | 3-year         | NA            | Not effective |
|              |               |                    |                       |                  | 39.1% vs 31.1%| NA            |             |
|              |               |                    |                       |                  | 32% vs 11.7%  | 56.6% vs 53.4%|             |
| Izumi[16]   |               | Post-operative TACE | 50 (23/ 27)          | 28.7 months (median) | 3-year         | 3-year         | Postpone recurrence but change over all survival |
|              |               |                    |                       |                  | 32% vs 40%    | 56% vs 67%    |             |
| Lai[15]     | Negative in lipiodol CT, angiography and ultrasound one month after operation | Post-operative TACE | 66 (30/ 36)          | Median 28.3 months | 3-year         | 3-year         | Harmful     |
|              |               |                    |                       |                  | 3-year vs 48% | 65% vs 67%    |             |
| Lai[17]     | Surgical margin ≥1 cm | Post-operative TACE | 43 (21/ 22)          | 14.1-69.7 months (40mg/ m²×8) | 3-year         | 3-year         | Beneficial |
|              |               |                    |                       |                  | 74.5% vs 36% | 84.4% vs 46.3%|             |

L: lipiodol; M: mitomycin; A: adriamycin, G: gelfoam; C: cis-platin; Tx: treatment; Ctl: control; DFS: disease free survival; OS: overall survival.
*estimated according to the figure in authors’ paper.

Wu et al have studied the effect of pre-operative TACE (preTACE) on resectability and curability in management of huge resectable HCC. Although preTACE induced tumor shrinkage as expected, the shrinkage of tumor didn’t result in an easy operation, on the contrary, the preTACE group had a longer operative time, more blood loss, more extra-hepatic metastasis, higher possibility of invading adjacent organs by tumors and removal of adjacent organs; furthermore, the disease-free survival (DFS) in preTACE group was not statistically different with that in the control group, the overall survival (OS) was even worse than that in control group. The author suggested that preTACE delayed the resection, which may leave tumor more time to develop intra-hepatic or distant metastasis; in addition, preTACE can’t eliminate tumor cells completely, therefore, preTACE for resectable huge HCC was not recommended.

In another study by Yamasaki et al, the efficacy of preTACE on small HCC was tested. The results confirmed that preTACE induced necrosis in tumor, but the results demonstrated again that it didn’t improve the DFS, because preTACE was not capable to inhibit the intrahepatocirrhotic micrometastatic lesions and tumor thrombus in microvessel.

The first RCT study on post-operative TACE (postTACE) was reported by Izumi et al in 1994. The authors enrolled 50 patients after curative resection of HCC with blood vessel involvement or intra-hepatic spreadings. The results showed that both DFS rate and DFS time were higher in postTACE group than those in control group. However, 1 and 3-year OS rates were similar in both groups (58.8 % vs 63.5 %; 30.5 % vs 20.4 %).
more than 1 cm; the median survival time in postTACE was shorter than that in the control group (644.5±129.4 days vs 759.9±137.5 day, P<0.05). The authors concluded that postTACE may postpone but not eliminate the recurrence (60.9% vs 81.5%, P=0.106) [16].

In another RCT reported by Lau et al, the authors used 20mg/m²-Lipiodol instead of conventional Lipiodol. The result showed that postTACE improved DFS and OS, decreased recurrence without major side-effects [17]. This is the only one RCT reporting a positive result for postTACE treatment. The authors suggested more effective agents should be used in postTACE.

However, in Lai et al’s study of postTACE, although the preventive treatment protocol was more aggressive than Izumi’s study, the result was even worse. The recurrence rate and extrahepatic metastasis rate were higher in postTACE group (recurrence rate: 23/30 vs 17/36, P=0.01) extrahepatic metastasis rate: 11/30 vs 5/36, P=0.03; 3-year DFS in postTACE group was lower than that in the control group (18% vs 48%, P=0.04). The OS in postTACE group was worse than that in the control group, especially in the first two years, but the difference was not statistically significant. Therefore, the authors concluded postTACE is harmful to patients after curative resection of HCC [18].

The reason of why conflicting results came from different RCTs is the selection of patients. Lai et al’s group of patients was selected by a highly rigorous standard; the rationale of preventive treatment was not solid enough to protect this group of patient with interventional treatment like postTACE. However, in Izumi and Lau’s studies, the authors selected a group of patients with more possibility of recurrence (invasive cancer or large cancer), so the results turned out to be effective.

In summary, preTACE is not helpful in terms of decreasing recurrence after resection of resectable HCC. PostTACE is only beneficial to the patients with invasive HCC, but not effective or even harmful to the patients after a “real” curative resection.

Systemic or locoregional chemotherapy

Systemic chemotherapy is generally not effective in most cases with HCC [19], only a few papers showed a favorable results of systemic chemotherapy [19]. Here is a summary of RCTs studying post-operative systemic and locoregional chemotherapy (Table 3).

### Table 3 Summary of locoregional or systemic chemotherapy for prevention of recurrence

| Authors            | Entry criteria | Treatment protocol | Sample size (Tx/ Ctrl) | Observation time | DFS (Tx vs Ctl) | OS (Tx vs Ctl) | Conclusions                           |
|--------------------|----------------|--------------------|------------------------|------------------|----------------|----------------|---------------------------------------|
| Yamamoto [20]      | Liver cancer study group of Japan for UICC stage II HCC | HCFU 200mg, bid      | 67 (32/ 35)            | 6-10 years       | Stage I cirrhosis 62% vs 32% | Stage I cirrhosis 79% vs 70% | Beneficial only to patients with Stage I liver dys function |
| Kohno [21]         | NA             | UFT 300mg, qd vs UFT 300mg, qd+IA (ia, 40mg/ m², once) | 88 (40/ 48)          | NA               | Stage I cirrhosis 0% vs 0% | Stage I cirrhosis 59% vs 57% | N.A. Not effective |
| Ono [22]           | NA             | A 40mg/m² ia and 40mg/m² iv every 3 months for 2 years, and HCFU 300mg qd for 2 years | 56 (29/ 27)          | 24 months       | NA              | N.A.            | N.A. Not effective, with poor tolerance |
| Ueno [23]          | NA             | CDDP 50-80mg and MMC 10mg ia, 2-3 times | 21 (12/ 10)          | >1 year          | 70% vs 20%     | N.A.            | Beneficial |

NA: not available; A: Adriamycin or Epirubicin; ia: intraarterially; iv: intravenously; DFS: disease free survival; OS: overall survival.

*Holz conf: exact excision of a solitary tumor, less than 5 cm in diameter, with a tumor capsule and no vascular invasion to the first or second branches of the portal vein, or for other stage II tumors, complete removal with a surgical margin from the tumor edge of more than 1 cm;*  
*see the original paper;*  
*estimated according to the figure in authors’ paper.*

Yamamoto et al studied systemic chemotherapy using HCFU 200 mg bid as a adjuvant treatment for the patients after curative resection of HCC. The result showed that systemic chemotherapy was effective in a subgroup of patients with mild cirrhosis and good liver function, but not effective in a subgroup of patients with severe cirrhosis and poor liver function. The authors discussed that systemic chemotherapy inhibited the growth of micro-metastatic lesions existing before operation or multi-centric carcinogenesis after operation, but jeopardized liver function as well, which resulted a negative effect on both OS and DFS, especially in patients with poor liver function reserved [20].

Kohno et al studied the result of an aggressive treatment combining systemic and one course of transcatheter arterial chemotherapy (TAC). There was no obvious side-effect of this treatment. However, the results showed this combination treatment did not improve the 3 and 5-year OS and DFS compared with the control group with UFT treatment alone, and another control group without any specific treatment [21].

Ono et al’s treatment protocol was even more aggressive with combining systemic and multiple courses of TAC, however, the result was still negative. Furthermore, very aggressive protocol was intolerable to most enrolled patients, and too many cases withdrew from this study [22].

Ueno et al’s study showed multiple courses of TAC improved DFS after curative resection of HCC. The flaw of this study is too small sample size [23].

A recent meta-analysis also showed that systemic chemotherapy was not effective or even harmful as an adjuvant treatment in patients after resection of HCC [24]. Another meta-analysis showed that TAE (transcatheter arterial embolization) improved OS after resection of HCC compared with TAC, and no evidence showing TACE was more effective than TAE [25], which implied a very limited benefit of locoregional chemotherapy introduced by TACE overtopping TAE alone.

From the above data, it is suggested that systemic or locoregional chemotherapy didn’t inhibit the recurrence, and the tolerance was another important factor influencing the results.

**Post-operative adoptive immunotherapy**

Post-operative active or adoptive immunotherapy became a very attractive cancer treatment modality in early 1990s.
because of a series of successful animal experiments[26]; however, it turned out to be not so effective as expected in a number of clinical trials[27-29]. At the same time, several clinical trials have been set up to test the effect of adoptive immunotherapy on recurrence in patients with HCC in early 1990s. The followings are a summary of these RCTs (Table 4).

Une et al’s study compared the effect of locoregional chemotherapy with locoregional chemotherapy plus systemic immunotherapy on recurrence after curative resection of HCC. The results showed that locoregional chemotherapy plus systemic immunotherapy decreased recurrence rate[30]. However, Kawata et al, reported from the same institution and used almost identical treatment settings, demonstrated immunomunotherapy didn’t present any survival benefit to the patients, although in a subgroup of patients with negative surgical margin (≥1 cm), the immunochemotherapy group had a better disease-free survival rate than the chemotherapy group[31]. The reason of the difference might come from the different observation time.

Lygidakis et al employed a protocol combining pre-operative and post-operative locoregional chemotherapy with systemic immunotherapy to prevent post-operative recurrence in HCC patients. The results showed this protocol decreased recurrence[32].

In Takayama’s study, which had a more than 5-year observation time, presented a clear survival benefit from systemic immunotherapy to prevent post-operative recurrence in HCC patients. The results showed that locoregional chemotherapy plus systemic immunotherapy decreased recurrence rate[33]. However, in Kubo et al’s study, the decrease of recurrence rate was associated with neither clearance of HCV nor normalization of serum ALT level, the actual reason was unknown, but the authors suggested that it might depend on direct antitumor effects or inhibition of carcinogenesis by HCV. Therefore, the mechanism of IFN’s effect on recurrence remains to be investigated further[14,36]. Recently, our data on doctors’ presetting, therefore different treatment modalities may affect the long term results[1].

In general, the immunotherapy may inhibit recurrence in patients after resection of HCC, especially in the first several years after operation, with a good tolerance. However, it needs more randomized control trial to confirm, and more powerful agents need to be discovered.

### Post-operative Interferon (IFN) treatment

The rationale of post-operative IFN treatment came from the several findings in HCV related HCC. First, a lower incidence of HCC was observed in many studies when IFN was used to clear HCV viremia[33]; second, recurrence after curative resection of HCC developed from multicentric origin, which was closely related to the HCC viremia status[14]. Third, IFN had anti-cancer effect on the early stage tumors, like micrometastatic lesions[34]. The following is the summary of post-operative IFN treatment (Table 5).

Ikeda et al’s results showed that, although the recurrence curve increased similarly in both groups in the first two years, but it remained the same in treatment group after that, which suggested that the effect of IFNβ on prevention of recurrence was not through direct inhibition of tumor cells per se, but depended on the clearance of HCV viremia, implying the mechanism of IFNα is through inhibition of multicentric recurrence. However, in Kubo et al’s study, the decrease of recurrence rate was associated with neither clearance of HCV nor normalization of serum ALT level, the actual reason was unknown, but the authors suggested that it might depend on direct antitumor effects or inhibition of carcinogenesis by HCV. Therefore, the mechanism of IFN’s effect on recurrence remains to be investigated further[14,36].

### Table 4 A summary of RCT results of adoptive immunotherapy to prevent recurrence

| Authors      | Entry criteria | Treatment protocol | Sample size | Observation time | DFS Tx vs Ctl | OS Tx vs Ctl | Conclusions |
|--------------|---------------|--------------------|-------------|-----------------|---------------|-------------|-------------|
| Une[30]     | NA            | A ia vs A+LAK and IL2 ia | 24(12/ 12)  | NA              | 50% vs 8.3%  | NA          | Beneficial  |
| Kawata[31]  | NA            | A ia vs A+H2L2+LAK ia | 24(12/ 12)  | NA              | NS            | NA          | Not beneficial |
| Lygidakis[32] | NA          | No Tx vs Chemoimmunotherapy | 40(20/ 20)   | NA              | Recurrence: Q’ 18 vs 7/ 17 | NA | Beneficial |
| Takayama[33] | Completely remove; histologically negative in surgical margin | LAK IV at the 2nd, 3rd, 4th, 12th, 24th week after operation | 155 (76/ 79) | >5 years | 3-year 46% vs 39% 5-year 68% vs 62% 5-year 37% vs 22% | Beneficial |

ia: intra-arterially; iv: intravenously; NA: not available; NS: not significant; DFS: disease free survival; OS: overall survival; Tx: treatment; Ctl: control; LAK: lymphokine activated killer cells; NA: not available.

### Table 5 Summary of RCTs of Interferon treatment

| Authors      | Entry criteria | Tx protocol | Sample size | Observation time | DFS Tx vs Ctl | OS Tx vs Ctl | Conclusions |
|--------------|---------------|-------------|-------------|-----------------|---------------|-------------|-------------|
| Ikeda[34]    | Complete remove by resection or PEI | IFNβ 6MU im bw×36 months | 20(10/ 10)  | 2-34.6 months | 1 year 0% vs 62.9% Recurrence 9’ 15 vs 13’ 15 P=0.041 | NA | Beneficial |
| Kubo[14,36]  | Complete remove, negative in CT scan 3-4 weeks after operation | IFNα 6MU bw×2 weeks then bw×14 weeks then bw×8 weeks | 30(15/ 15)  | 1817 days (Tx) and 1487 (Ctl) | 0.014 | NA | Beneficial |

### Table 6 Summary of RCTs of acyclic retinoic acid

| Authors      | Entry criteria | Tx protocol | Sample size | Observation time | Recurrence Tx vs Ctl | OS Tx vs Ctl | Conclusions |
|--------------|---------------|-------------|-------------|-----------------|----------------------|-------------|-------------|
| Muto[32,33]  | Complete removal by resection or PEI, negative in postoperative Ultrasound or CT | ARA 300mg, bid | 89(44/ 45) | 62 months (Median) | 27% vs 49% (P=0.04) | 6 year | Beneficial |

Tx: treatment; Ctl: control; OS: overall survival.
suggested anti-angiogenesis instead of the anti-proliferation property of IFNα involving in antitumor effect in animal models, and it may act through regulation of VEGF expression. A randomized control trial in HBV related HCC patients after curative resection was also conducted to test the effect of IFNα on recurrence in the authors’ institution, the interim results showed that long-term IFNα treatment improved disease-free survival of patients through direct antitumor effect, which was not associated with serum conversion of HBsAg.

**Acyclic retinoid acid**

Retinoid acid is a inducer of differentiation. All-trans retinoic acid (ARA), and showed long term ARA treatment improvement in OS and DFS.[17,33] A further study revealed the mechanism of ARA treatment was through inhibition of second primary liver cancer recurrence after curative resection of HCC have been evaluated by RCT. Although no standard treatment has been proven to be effective to all patients, several approaches presented promising results, which were both effective and tolerable in post-operative patients. Generally systemic and locoregional chemotherapy or combined with embolization was not as effective as expected, meanwhile the side-effects, such as downstaging of liver function was noticed in this treatment; however, biological treatment approaches showed a better outcome, but need more evidence before being accepted widely.

**SUMMARY**

A number of preventive treatment protocols to inhibiting recurrence after curative resection of HCC have been evaluated by RCT. Although no standard treatment has been proven to be effective to all patients, several approaches presented promising results, which were both effective and tolerable in post-operative patients. Generally systemic and locoregional chemotherapy or combined with embolization was not as effective as expected, meanwhile the side-effects, such as downstaging of liver function was noticed in this treatment; however, biological treatment approaches showed a better outcome, but need more evidence before being accepted widely.

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