Strategies to prevent recurrence after curative resection of HCC

Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine

Kang Mo Kim
Case 1

- 83/M, anti HCV(+), HCV RNA(+)
- 2006. 2. 2. AFP: 130 ng/mL
- 2006. 2. 15.
- S6 segmentectomy
HEPATOCELLULAR CARCINOMA, 6.5X 6X 5.3CM, EXPANDING NODULAR TYPE, TRABECULAR TYPE, HEPATIC AND CLEAR CELL TYPES, EDMONDSON-STEINER GRADE 4/3

1) necrosis (5%)
2) hemorrhage/ peliosis
3) fatty change (10%)
4) VASCULAR INVASION
5) no bile duct invasion
6) partial fibrous capsule
7) TUMOR CAPSULAR INVASION
8) septum formation
9) no Glisson capsule invasion
10) no satellite nodule
11) no involvement of surgical resection margin (less than 1mm)
• 2006. 5. 17. AFP: 4.3 ng/mL → RFA #1

• 2006. 6. 28. AFP: 6.8 ng/mL → RFA #2
• 2007. 5. 14. AFP: 413 ng/mL → RFA #3

• 2007. 7. 18. AFP: 3850 ng/mL → conservative Mx

• Intrahepatic HCC recurrence at 3 month after resection
Case 2

- 45/M, HBsAg(+)  
- 2006. 2. 22. AFP: 62.8 ng/mL  
- 2006. 3. 10.  
- Rt anterior segmentectomy
HEPATOCELLULAR CARCINOMA, 3.5x 3x 2cm, MULTINODULAR CONFLUENT TYPE, EDMONDSON-STEINER GRADE 3/3,
1) no necrosis.
2) no hemorrhage/ peliosis.
3) fatty change (70%).
4) no vascular invasion.
5) no bile duct invasion.
6) partial fibrous capsule.
7) no tumor capsular invasion.
8) septum formation.
9) no Glisson capsule invasion.
10) no satellite nodule.
11) no involvement of surgical resection margin.
- Micro and micronodular cirrhosis
2006. 8. 4. AFP: 5.1 ng/mL

2008. 7. 25. AFP: 1.5 ng/mL, PIVKA-2: 15 mAU/mL
• 2008. 9. 12. RFA for recurrent HCC
• 2009. 4. 6. AFP: 5.0 ng/mL

• Intrahepatic HCC recurrence at 2 year 4 month after resection
High HCC recurrence after curative resection

- Cumulative 5 yr recurrence rate: 60-75%
- Usually intrahepatic recurrence: 78-96%

**Recurrence after RFA?**

- Recurrence dependent to the skill of practitioner
- Debate on indication of RFA
  - HCC size (3-5 cm), number (1-3개), location, acceptable margin? (1 cm)
Strategies to prevent recurrence after curative resection

- **Definition of curative resection**
  - Complete removal of tumor tissues
  - + clear resection margin ≥ 1 cm on pathology
  - + negative findings by angiography followed by Lipiodol-CT and ultrasound 1-2 months after resection

- **Origin of intrahepatic recurrence**
  - ✓ Intrahepatic metastasis or remnant tumor
  - ✓ Multicentric occurrence
    - • Cloning of PCR of integrated HBV DNA
    - • Time to recurrence (1-2 years)
Post-op intrahepatic HCC recurrence

- Early recurrence (<1 year)
  - Risk factor: microscopic venous invasion, satellite nodule, multiple tumor, large tumor (>5 cm)
  - Intrahepatic metastasis or remnant tumor
  - More invasive HCC, more aggressive biology?

- Late recurrence (>1 year)
  - Risk factor: cirrhosis, high ALT, active inflammation
  - Multicentric occurrence
- 126/246 (51%) HCC recurrence (median F/U: 37 months)
- Risk factors
  for early recurrence: prev. tumor rupture, venous invasion
  for late recurrence: cirrhosis
Prognosis according to time to recurrence

- Poorer Survival in patients with early recurrence


290/577 resected HCC (4.5 yr) AMC data (2009)
Strategies to prevent intrahepatic HCC recurrence after curative resection

- Prevention of intrahepatic metastasis (early recurrence)
  - Preoperative TACE
  - Postoperative TACE
  - Systemic or locoregional chemotherapy
  - Postoperative adoptive immunotherapy

- Prevention of multicentric occurrence (late recurrence)
  - Postoperative interferon treatment
  - Acyclic retinoid acid

- Other strategies
Preoperative TACE

- Rationale: reduce tumor size, induce tumor necrosis, prevent tumor dissemination, down-staging
  - Yamasaki S, Jpn J Cancer Res 1996;87:206-211
    - 97 Patients, 2-5 cm single HCC, No difference in DFS
    - 52 Patients, >10 cm resectable HCC
    - Similar DFS, worse OS with preop TACE

- Preop TACE results in delayed surgery and difficulty in the treatment of recurrent lesions in large HCC
  - NOT recommended for resectable HCC as routine procedure
  - Efficacy in down-staging of initially unresectable HCC?
Postoperative TACE

  - 50 Patients, vessel invasion or multiple HCC
  - Improved DFS but similar OS with postop TAC+lipiodol
  - 43 Patients, multiple HCC in 30%, postop $^{131}$I-lipiodol
- Insignificant DFS ($p=0.578$) and OS ($p=0.06$) after 8 yr
Postoperative TACE

  - 66 Patients, postop TAC with lipiodol + IV epirubicin
  - worse DFS ($p=0.04$) and similar OS ($p=0.1$) with adjuvant Tx

- No RCT for postop TACE with gelfoam embolization
- May have benefit in patients with high risk of recurrence
  
  Large tumor, vascular invasion, satellite nodule
Systemic or locoregional chemotherapy

- **Ono T, et al.** Cancer 2001;91:2378-2385
  - Meta-analysis of postop systemic chemoTx +/- TAC
  - No benefit in DFS and OS, worse DFS in cirrhotic patients

  - 21 Patients with moderate hepatitis activity
  - Improved DFS with TAC

- Generally not recommended
- Limited benefit of TAC in high risk patients
Postoperative adoptive immunotherapy

  - 150 Pts, postop LAK cell transfusion X5, median F/U: 4.4 yr
  - Improved DFS but not significantly longer OS with treatment

  - Adoptive immunotherapy may eliminate micrometastasis not multicentric occurrence
Postoperative interferon treatment

- HCV related HCC
  - 20 Pts, postop IFN-β 6 MIU X2/wk for 36 months
  - IFN-β reduced early recurrence
  - Biochemical and virologic improvement was not associated with the recurrence rate
  - IFN may have a direct antitumor effect on clinically undetectable HCC
Postoperative interferon treatment

- HCV related HCC
  - 30 Pts, postop IFN-α 6 MIU X2/wk for 104 weeks
  - IFN-α reduced late recurrence and improved OS
  - IFN reduces multicentric recurrence by causing remission of active hepatitis
Postoperative interferon treatment

- HBV related HCC
  - 236 Pts, postop IFN-α 5 MU X3/wk for 18 months
  - No difference in DFS and prolonged OS with IFN treatment
  - HBeAg or HBV DNA was not checked, larger tumor in control

\[ P = 0.1425 \]

\[ P = 0.0003 \]
Acyclic retinoid

- Analogues of vitamin A, polyprenoic acid (acyclic retinoid)
- Chemoprevention - inhibit promotion of carcinogenesis
- 89 Patients, mainly HCV related, postop polyprenoic acid 300 mg bid for 12 months
- Reduced late recurrence significantly
Other strategies

- Anticipation of recurrence by tumor biology
  - DNA aneuploidy, proliferating cell nuclear antigen (PCNA), high tumor microvessel density, reduced E-cadherin expression
  - Different study populations
  - Lack of consistent and objective methodology

  - Gene expression profile in adjacent liver tissue
  - Correlation with late recurrence and prognosis
Strategies to prevent intrahepatic HCC recurrence after curative resection

- Prevention of intrahepatic metastasis (early recurrence)
  - **Preoperative TACE**
    - Not recommended for resectable HCC
    - Possible role in down-staging for unresectable HCC
  - **Postoperative TACE**
    - Possible role in invasive HCC (multiple, large, vessel invasive HCC)
    - Unresolved issue for standard procedure and adequate candidates
Strategies to prevent intrahepatic HCC recurrence after curative resection

- Prevention of intrahepatic metastasis (early recurrence)
  - Systemic or locoregional chemotherapy
    - Not recommended
  - Postoperative adoptive immunotherapy
    - Need further study, high cost
  - Postoperative interferon treatment
    - Possible role in HCV related HCC
  - Close F/U is mandatory in invasive HCC
    (1→2→3 months F/U with LDCT and tumor marker)
Strategies to prevent intrahepatic HCC recurrence after curative resection

- Prevention of multicentric occurrence (late recurrence)
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  - Possible role in HCV related HCC
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Strategies to prevent intrahepatic HCC recurrence after curative resection
- conclusion -

• Postop TACE in high risk HCC patients
• Adoptive immunotherapy for early recurrence
• Acyclic retinoid acid for late recurrence
• IFN treatment in HCV related HCC
• Antiviral therapy in HBV related HCC?
→ Need further RCT
Thank you for your attention