Japan-Korea Collaborative Research of Hepato-Biliary-Pancreatic Surgery

Category: **Liver**

Director: Masanori Kwon (Kansai Medical University)

Secretary: Masaki Kaibori (Kansai Medical University)

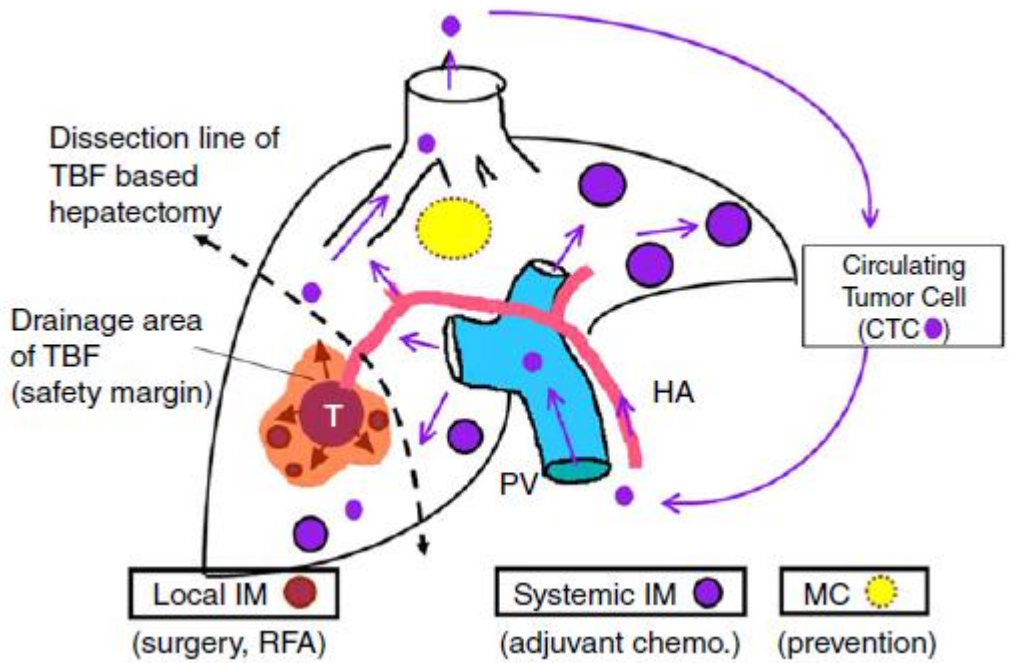
Comparison of anatomic and nonanatomic hepatic resection for hepatocellular carcinoma.

-Proposal of retrospective study-

Background

The long-term outcome after resection of hepatocellular carcinoma is influenced by factors related to the tumor and the underlying liver disease. The choice between anatomic resection versus nonanatomic resection for HCC is controversial. In Japan, anatomic resection for HBV-, HCV-, or Non B and C (NBC)-related HCC is mainly used today. **HBV-related HCC** is majority than HCV- or NBC-related HCC in **Korea**. In **Japan**, **HCV-related HCC** is about 60%, HBV- and NBC-related HCC is about 20%, respectively.

Which procedure is justified anatomic resection or nonanatomic resection for hepatocellular carcinoma in Korea or Japan?



Review of article

Dig Dis Sci (2011) 56:1626–1633
DOI 10.1007/s10620-010-1482-0

REVIEW

Survival After Anatomic Resection Versus Nonanatomic Resection for Hepatocellular Carcinoma: A Meta-Analysis

Jinggui Chen · Kai Huang · Jianghong Wu · Huiyan Zhu · Yingqiang Shi · Yanong Wang · Guangfa Zhao

Langenbecks Arch Surg (2011) 396:1109–1117
DOI 10.1007/s00423-011-0784-9

SYSTEMATIC REVIEW AND META-ANALYSIS

Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma

Yanming Zhou · Donghui Xu · Lupeng Wu · Bin Li

Disease-free survival

Review: Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma
Comparison: 01 AR Group Versus NAR Group for HCC
Outcome: 02 Disease-free survival

Study or sub-category	AR n/N	NAR n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Capussotti 2005	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hasegawa 2005	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Kaibori 2006	9/34	26/213		11.81	2.59 [1.09, 6.15]
Regimbeau 2002	13/30	9/34		9.11	2.12 [0.74, 6.07]
Ueno 2008	23/52	18/64		13.55	2.03 [0.94, 4.39]
Wakai 2006	41/95	15/63		14.92	2.43 [1.20, 4.93]
Yamashita 2007	109/201	50/120		21.61	1.66 [1.05, 2.62]
Total (95% CI)	732	600		100.00	1.78 [1.22, 2.59]

Total events: 290 (AR), 145 (NAR)
Test for heterogeneity: Chi?= 11.22, df = 6 (P = 0.08), I?= 46.5%
Test for overall effect: Z = 3.01 (P = 0.003)

0.1 0.2 0.5 1 2 5 10
Favours NAR Favours AR

Review: Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma
Comparison: 01 anatomic resection versus nonanatomic resection
Outcome: 14 5 years disease-free survival

Study or sub-category	AR group n/N	NAR group n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Regimbeau 2002	16/30	9/34		3.15	2.43 [0.85, 6.93]
Hasegawa 2005	53/156	9/54		6.17	2.87 [1.17, 6.44]
Kaibori 2006	9/34	26/213		3.68	2.59 [1.09, 6.15]
Cho 2007	54/99	20/69		7.49	2.94 [1.53, 5.45]
Wakai 2007	41/95	15/63		7.17	2.43 [1.20, 4.93]
Yamashita 2007	109/201	50/110		20.26	1.63 [1.03, 2.57]
Hanehira 2008	23/45	33/64		10.62	0.83 [0.39, 1.78]
Ueno 2008	23/52	17/64		5.94	2.19 [1.01, 4.78]
Tanaka 2009	59/128	16/79		7.46	3.37 [1.78, 6.45]
Kamiyama 2010	85/169	37/153		12.86	3.49 [2.16, 5.62]
Kang 2010	40/140	5/21		4.44	1.51 [0.42, 3.51]
Yamazaki 2010	44/111	24/98		10.76	2.02 [1.11, 3.68]
Total (95% CI)	1270	1081		100.00	2.24 [1.85, 2.72]

Total events: 557 (AR group), 281 (NAR group)
Test for heterogeneity: χ2 = 15.67, df = 11 (P = 0.15), I?= 30.7%
Test for overall effect: Z = 8.28 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10
Favours AR group Favours NAR group

Overall survival

Review: Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma
Comparison: 01 AR Group Versus NAR Group for HCC
Outcome: 01 Overall survival

Study or sub-category	AR n/N	NAR n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Capussotti 2005	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 0.40, 1.45]
Hasegawa 2005	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 1.87, 6.85]
Kaibori 2006	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 0.47, 2.02]
Regimbeau 2002	16/30	12/34		7.86	2.10 [0.77, 5.72]
Tanaka 2008	45/93	26/42		10.92	0.73 [0.34, 1.55]
Ueno 2008	34/52	35/64		10.97	1.57 [0.74, 3.33]
Wakai 2006	64/95	37/63		12.47	1.45 [0.75, 2.81]
Yamashita 2007	153/201	89/120		14.97	1.11 [0.66, 1.87]
Zipparo 2002	7/18	10/28		5.98	1.15 [0.34, 3.89]
Total (95% CI)	833	670		100.00	1.31 [0.92, 1.85]

Total events: 496 (AR), 363 (NAR)
Test for heterogeneity: Chi?= 16.41, df = 8 (P = 0.04), I?= 51.2%
Test for overall effect: Z = 1.50 (P = 0.13)

0.1 0.2 0.5 1 2 5 10
Favours NAR Favours AR

Review: Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma
Comparison: 01 anatomic resection versus nonanatomic resection
Outcome: 11 5-years overall survival

Study or sub-category	AR group n/N	NAR group n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Yamamoto 2001	40/90	64/114		8.52	1.66 [0.88, 3.77]
Regimbeau 2002	16/30	12/34		5.89	2.10 [0.77, 5.72]
Hasegawa 2005	103/156	19/54		8.01	3.58 [1.87, 6.85]
Kaibori 2006	18/34	114/213		7.59	0.98 [0.47, 2.02]
Cho 2007	65/95	34/63		8.15	1.97 [1.05, 3.69]
Wakai 2007	64/95	37/63		7.94	1.45 [0.75, 2.81]
Yamashita 2007	152/201	89/120		8.88	1.08 [0.64, 1.82]
Hanashima 2008	27/49	42/64		7.25	0.64 [0.30, 1.38]
Tanaka 2008	45/93	26/42		7.28	0.73 [0.34, 1.55]
Ueno 2008	35/52	36/64		7.26	1.60 [0.75, 3.43]
Kamiyama 2010	148/169	86/153		8.63	5.49 [3.16, 9.59]
Kang 2010	67/146	3/21		6.26	1.13 [0.45, 2.86]
Yamazaki 2010	75/111	47/92		8.54	2.68 [1.51, 4.74]
Total (95% CI)	1315	1105		100.00	1.63 [1.16, 2.32]

Total events: 879 (AR group), 615 (NAR group)
Test for heterogeneity: χ2 = 42.18, df = 12 (P < 0.0001), I^2= 71.5%
Test for overall effect: Z = 2.74 (P = 0.006)

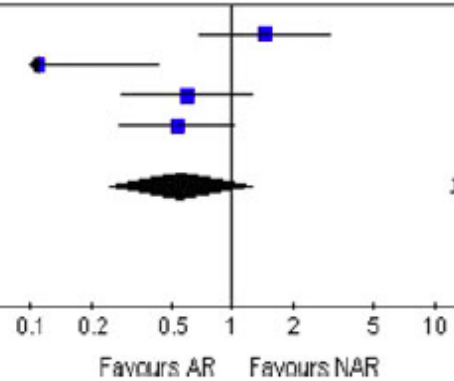
0.1 0.2 0.5 1 2 5 10
Favours AR group Favours NAR group

Review: Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma
Comparison: 01 AR Group Versus NAR Group for HCC
Outcome: 03 Local recurrence

Local recurrence

Study or sub-category	AR n/N	NAR n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Kaibori 2006	21/34	112/213		27.12	1.46 [0.69, 3.06]
Regimbeau 2002	3/30	17/34		17.45	0.11 [0.03, 0.44]
Tanaka 2006	39/83	25/42		26.95	0.60 [0.28, 1.28]
Wakai 2006	49/95	42/63		28.48	0.53 [0.28, 1.03]
Total (95% CI)	242	352		100.00	0.55 [0.25, 1.23]

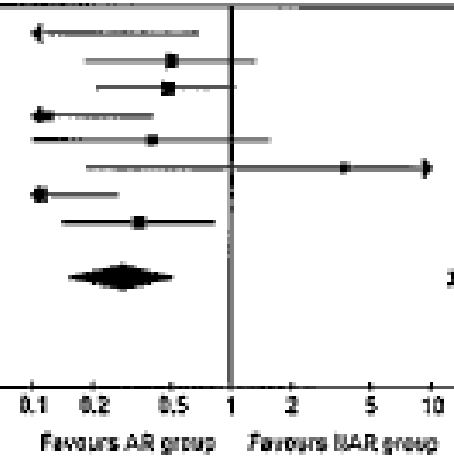
Total events: 112 (AR), 196 (NAR)
Test for heterogeneity: Chi?= 11.35, df = 3 (P = 0.010), I?= 73.6%
Test for overall effect: Z = 1.45 (P = 0.15)



Review: Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma
Comparison: 01 Efficacy
Outcome: 12 Local intrahepatic recurrence

Study or sub-category	AR group n/N	NAR group n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Regimbeau 2002	1/28	10/32		5.85	0.08 [0.01, 0.69]
Kaibori 2006	5/34	85/213		15.34	0.50 [0.19, 1.34]
Wakai 2007	14/93	16/55		18.20	0.48 [0.21, 1.07]
Kobayashi 2008	3/106	25/127		15.43	0.12 [0.03, 0.41]
Nanashima 2008	3/49	5/64		10.99	0.49 [0.10, 1.56]
Tanaka 2008	2/83	6/42		3.31	3.70 [0.15, 73.23]
Tanaka 2009	7/129	27/75		16.07	0.11 [0.03, 0.27]
Yamazaki 2010	8/111	18/58		17.03	0.35 [0.14, 0.85]
Total (95% CI)	632	714		100.00	0.28 [0.16, 0.50]

Total events: 44 (AR group), 180 (NAR group)
Test for heterogeneity: χ2 = 13.53, df = 7 (P = 0.06), I?2= 48.3%
Test for overall effect: Z = 4.28 (P < 0.0001)



Abstract

Background and Objectives To compare the effect on survival of anatomic resection (AR) versus nonanatomic resection (NAR) in patients with hepatocellular carcinoma (HCC) from all published comparative studies in the literature.

Methods Databases, including Pubmed, Embase, the Cochrane Library, Ovid, and Web of Science, were searched to identify studies comparing AR with NAR for HCC. In this meta-analysis, primary end points were the overall survival and disease-free survival; the secondary end point was local recurrence rate. The meta-analysis was performed by use of RevMan 4.2.

Results Nine comparative studies comprising 1,503 patients (833 AR and 670 NAR) were identified. In the combined results, disease-free survival was significantly higher in the AR group than in the NAR group (OR 1.78, 95% CI 1.22–2.59, $P = 0.003$; heterogeneity $P = 0.08$). Overall survival (OR 1.31, 95% CI 0.92–1.85, $P = 0.13$; heterogeneity $P = 0.04$) did not suggest any significant difference between AR and NAR. No statistically significant difference was found for local recurrence rate between the two resection methods (OR 0.55, 95% CI 0.25–1.23, $P = 0.15$; heterogeneity $P = 0.010$).

Conclusions Anatomic resection is associated with better disease-free survival than nonanatomic resection. Because heterogeneity was detected, caution is needed in interpretation of the results. Better designed, adequately powered studies are required to address this issue.

Abstract

Purpose The choice between anatomic resection (AR) versus nonanatomic resection (NAR) for hepatocellular carcinoma (HCC) is controversial. This study is a meta-analysis of the available evidence.

Methods A systematic review and meta-analysis of trials comparing AR with NAR for HCC published from 1985 to 2009 in PubMed and Medline database, Cochrane database, Embase database, and Science Citation index were conducted. Overall survival, disease-free survival, and local recurrence rate were considered as primary outcomes. Pooled effect was calculated using either the fixed effects model or random effects model.

Results Sixteen nonrandomized studies involving 2,917 patients were analyzed; 1,577 patients were in the AR group, and 1,340 were in the NAR group. Patients in the AR group were characterized by lower prevalence of cirrhosis and hepatitis virus infection, more favorable hepatic function, and larger tumor size compared with patients in the NAR group. AR provided a better 5-year overall survival than NAR (OR, 1.63; 95% CI, 1.15–2.32). Local recurrence (OR, 0.28; 95% CI, 0.16–0.50) and early (≤2 years) recurrence (OR, 0.55; 95 CI, 0.34–0.89) were all significantly lower in the AR group. AR improved disease-free survival significantly at 3 years (OR, 2.09; 95% CI, 1.52–2.88) and 5 years (OR, 2.24; 95% CI, 1.85–2.72). No differences were found between the two groups with respect to postoperative morbidity, mortality, and length of hospital stay.

Conclusions AR was superior to NAR in terms of better survival and preventing local recurrence for the treatment of HCC.

Two papers reported from Korea

Revisiting the role of nonanatomic resection of small (< 4 cm) and single hepatocellular carcinoma in patients with well-preserved liver function.

Kang CM, Choi GH, Kim DH, Choi SB, Kim KS, Choi JS, Lee WJ.

J Surg Res. 2010 May 1;160(1):81-9.

Conclusion. Our study showed that nonanatomic resection has no adverse effects on the oncologic outcomes of single and small (≤4 cm) HCC in patients with well-preserved liver function (Child-Pugh class A).

PATIENTS AND MATERIALS

Patient Population and Selection

From March 1998 to January 2005, 353 consecutive patients underwent resection of HCC at the Department of Surgery, Yonsei University College of Medicine, Seoul, Korea. Curative resection was defined as complete removal of the tumor with a clear microscopic margin and no residual tumors as demonstrated on routine imaging studies, such as computed tomography (CT) scans or chest X-rays, 1 month after hepatectomy. Of the 353 patients who underwent resection, 186 were excluded from the study for one or more of the following reasons: tumor size greater than 4 cm, multiple tumors, severely impaired liver function (Child-Pugh classes B and C), palliative positive margin resection, concurrent extrahepatic metastasis at operation, or the presence of a ruptured tumor. Ultimately, 167 patients (125 male and 42 female aged from 26 to 72 years; mean ± standard deviation, 52.2 ± 9.8 years) were included in this study. Among them, 127 patients were positive for HBs Ag, and 18 were negative for anti-HBs Ag. Sixteen patients were anti-HCV positive.

Anatomic versus non-anatomic resection for small single hepatocellular carcinomas.

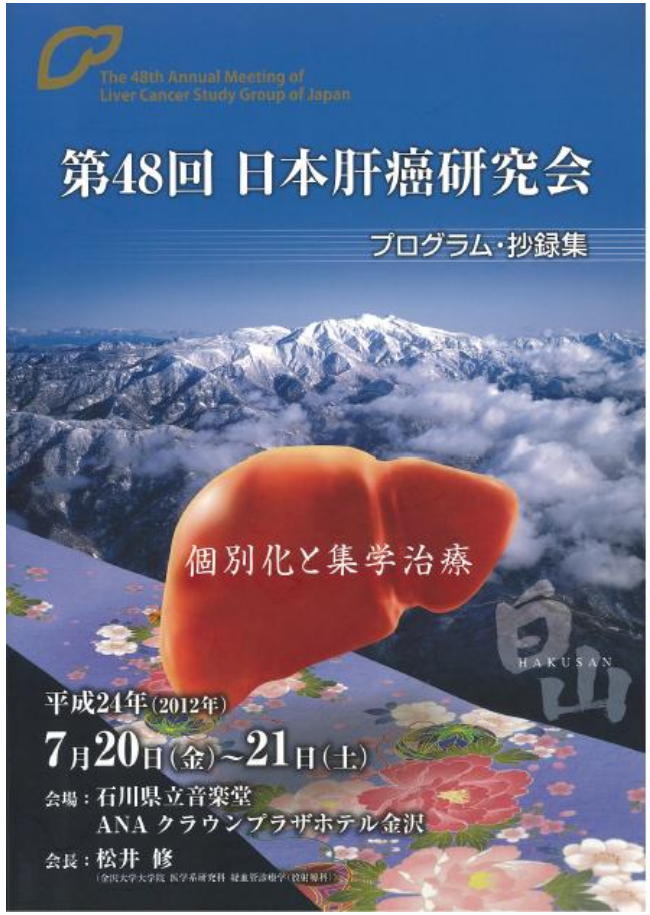
Cho YB, Lee KU, Lee HW, Cho EH, Yang SH, Cho JY, Yi NJ, Suh KS.

Hepatogastroenterology. 2007;54(78):1766-9

The 48th annual meeting of the liver cancer study group of Japan

Symposium

Evaluation of anatomic resection for HCC



Chairpersons

Tadatoshi Takayama: Nippon University

Susumu Eguchi: Nagasaki University

What is the reason why liver surgeons have different expert opinions?

1) on the definition of anatomic resection

2) on the indication of tumor characteristics for surgery

Unification of retrospective study

1. HCC, solitary, and the maximum tumor diameter of 2 –5 cm
2. ICGR15: 0 – 29%
3. The operation period between 2001 – 2010

The retrospective studies at eight high volume centers in Japan

Total case was 1,284

Patient's background

	Anatomic resection	Non-anatomic resection
Age (yrs)	68 (66-69)	68 (65-70)
T.Bil (mg/dl)	0.7 (0.5-0.8)	0.7 (0.5-0.8)
TP (g/dl)	7.2 (7.0-7.6)	7.1 (7.0-7.4)
Alb (g/dl)	4.0 (3.8-4.4)	3.9 (3.8-4.0)
PT (%)	90 (82-100)	88 (80-97)
ICGR15 (%)	12.7 (11.0-15.0)	14.6 (12.7-19.0)
Plt (/mm^3)	14.9 (12.5-16.1)	13.3 (11.0-17.8)
Child Pugh A (%)	97 (70-100)	96 (76-100)
HCV (%)	60 (30-67)	62 (50-71)
Tumor diameter (mm)	32 (28-36)	28 (25-30)
AFP (ng/ml)	11 (9-14)	14 (9-18)
DCP (mAu/ml)	47 (39-222)	52 (30-136)

ICGR15,Plt, and tumor diameter were significantly different in more than 3 institutes of all 8 institutes

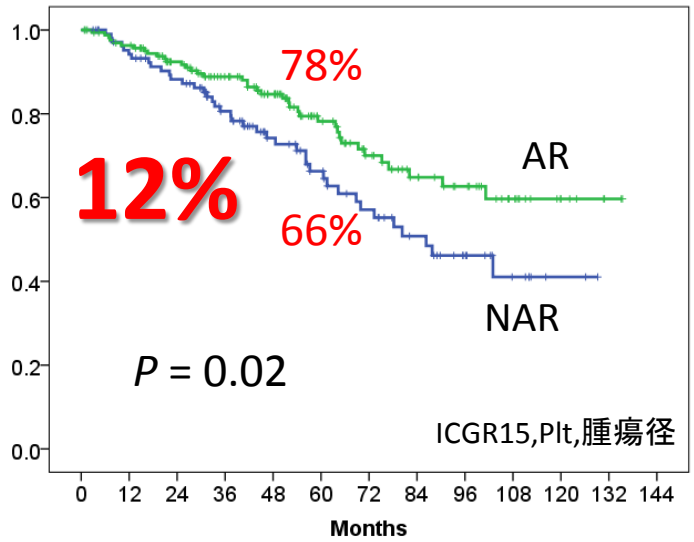
Perioperative characteristics

	Anatomic resection	Non-anatomic resection
Operative blood loss (ml)	736 (200-1000)	600 (270-810)
Ischemic time (min)	53 (32-90)	43 (22-65)
sm+ (%)	9 (0-37)	11 (2-39)
vp (%)	26 (8-69)	17 (6-67)
im (%)	8 (2-13)	6 (0-17)
LC (%)	36 (7-42)	44 (22-72)
Morbidity (%)	26 (4-41)	17 (1-46)
Mortality (%)	0 (0-1)	0 (0-1)
Postoperative hospital stay (%)	15 (14-23)	15 (13-23)

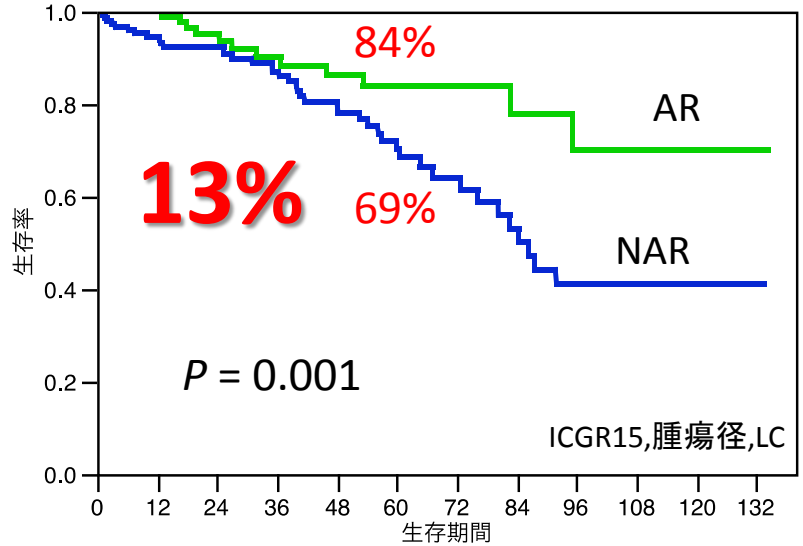
Opearive blood loss, ischemic time, and present of VP were significantly different in more than 3 institutes of all 8 institutes

Overall survival（Anatomic resection was effective）

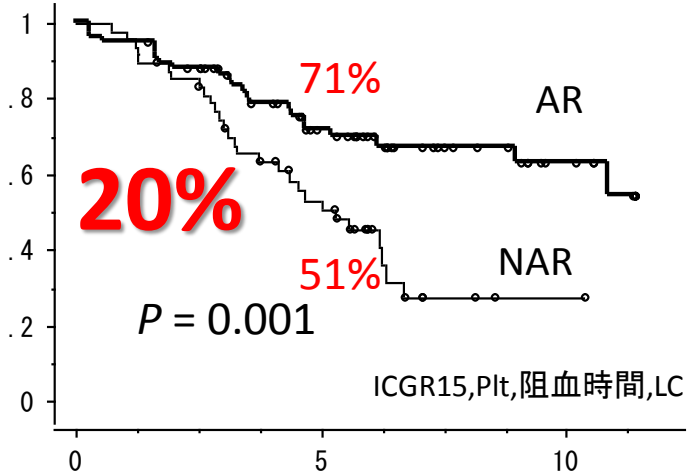
Tokyo University（Dr. Kishi）



Tokyo Women University（Dr. Katagiri）

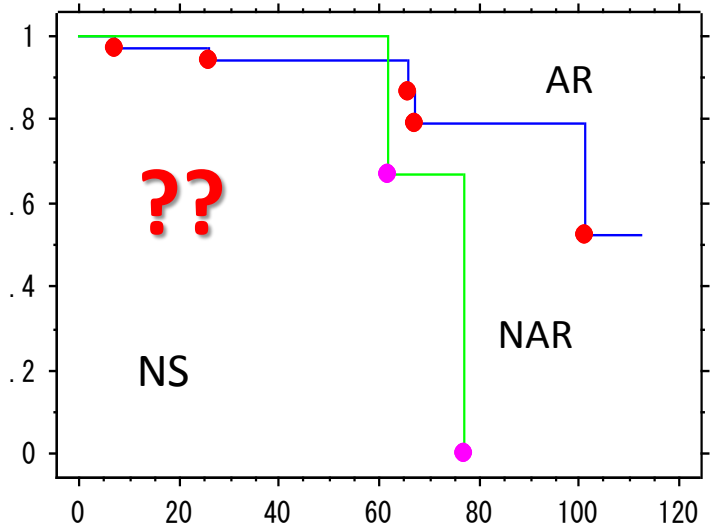


Jyuso city Hospital（Dr. Yamazaki）

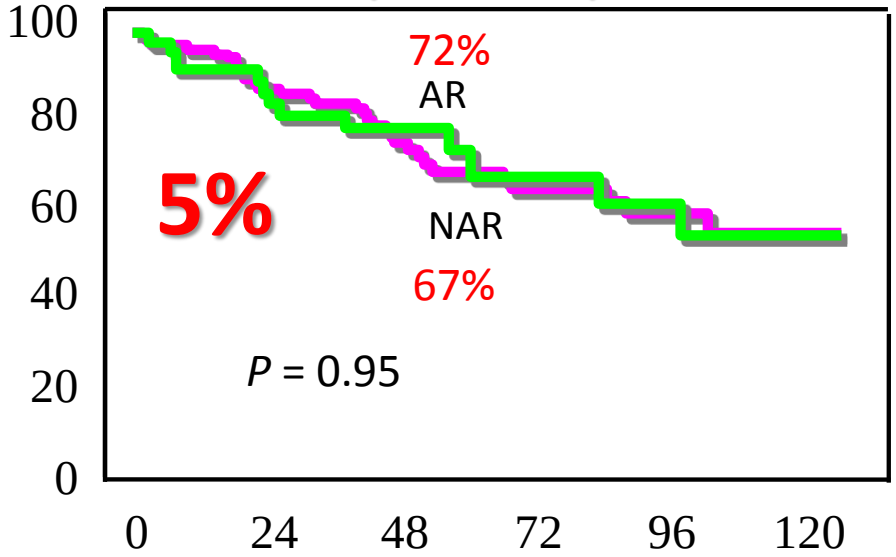


Overall survival（Anatomic resection was not effective）

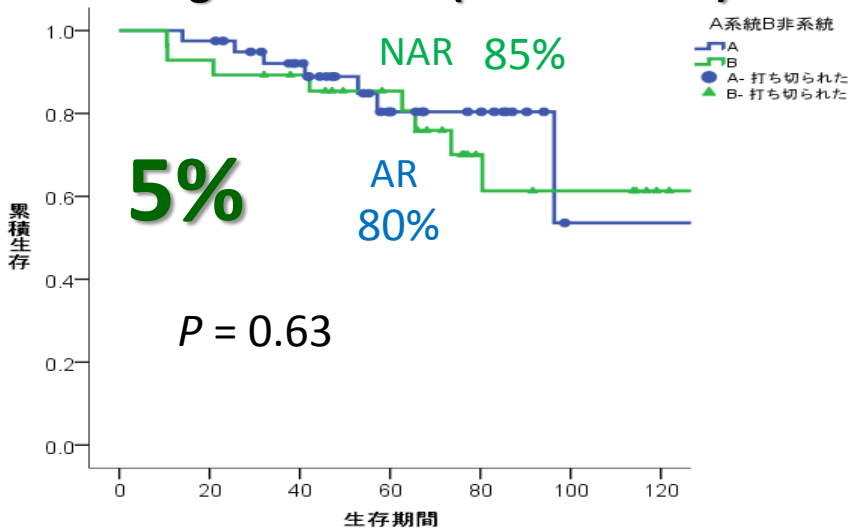
Kyoto Prefectural University of Medicine (Dr. Ochiai)



Kansai Medical University (Dr. Kaibori)

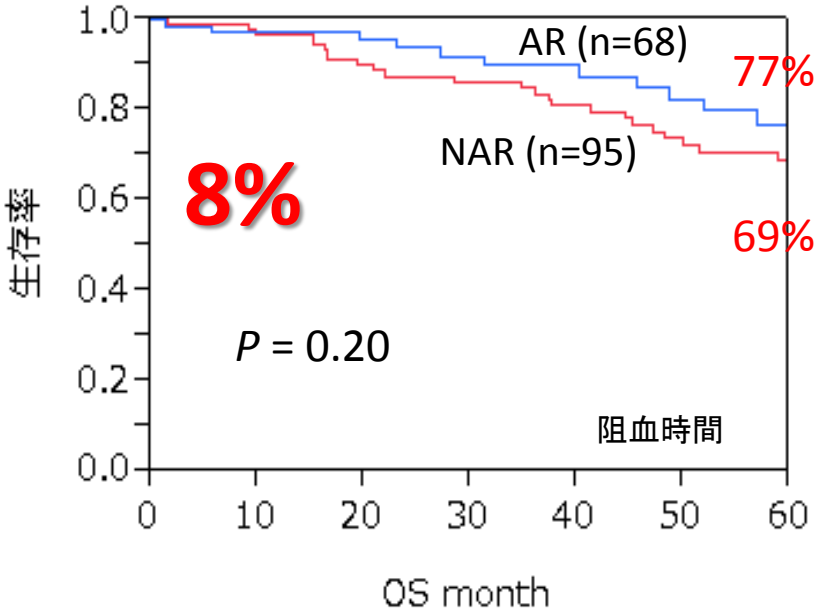


Nagasaki Unive (Dr. Takatsuki)

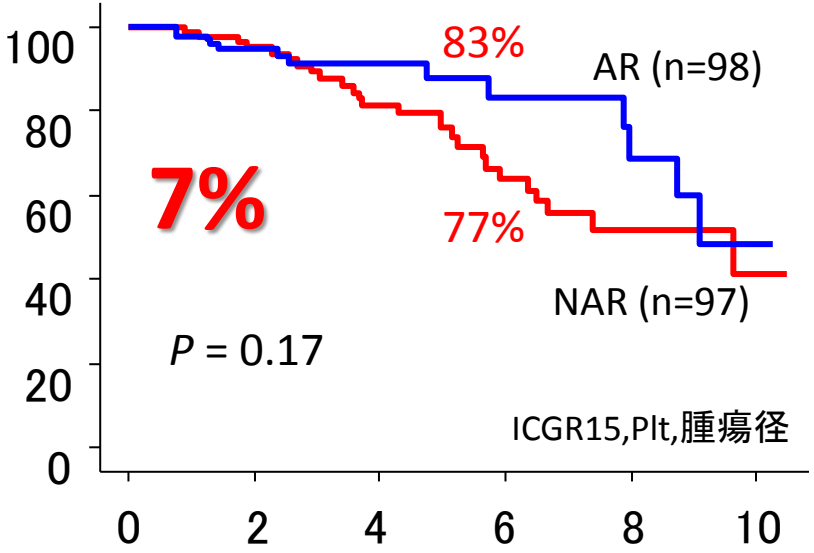


Overall survival（Anatomic resection was effective or not effective?）

Hiroshima Universitu (Dr. Kobayashi)



Hirosihima Red cross Hospital (Dr. Yamashita)



Results

1. More better preoperative function and larger tumors in anatomic resection.
2. More larger of operative blood loss and longer ischemic time during the operation in anatomic resection.
3. Better overall survival in 5 of 8 high volume centers in anatomic resection.

Inclusion criteria
The definition of anatomic resection

Classification according to the Brisbane terminology proposed by Strasberg et al.

Strasberg SM, Belghiti J, Clavn P-A, et al. The Brisbane 2000 terminology of liver anatomy and resection. Terminology Committee of the International Hepato-Pancreato-Biliary Association. HPB 2000; 2: 333-339.

Anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory.

Anatomic resection procedures were classified as **hemihepatectomy** (right hemihepatectomy was defined as resection of Couinaud subsegments V–VIII, and left hemihepatectomy was defined as resection of subsegments II–IV), **extended hemihepatectomy** (hemihepatectomy plus removal of additional contiguous segments), **sectionectomy** (resection of two Couinaud subsegments), or **segmentectomy (resection of one Couinaud subsegment)**.

All **non-anatomic procedures** were classified as **limited resection**, which was performed for both peripheral and central tumors. Peripheral tumors and tumors with extrahepatic growth were treated by partial hepatectomy, because this method was able to achieve a resection margin wider than 1 cm. Conversely, central tumors located near the hepatic hilum or major vessels were treated by enucleation, because it was too difficult or dangerous to remove enough of the liver to obtain an adequate margin.

Inclusion criteria

1. Curative resection of HCC (HBV, HCV, and NBC-related HCC) between 2006-2010

2. Object of procedure in anatomic resection:

- **Extended hemihepatectomy**
- **Hemihepatectomy**
- **Sectionectomy**
- **Segmentectomy**

3. Solitary tumor and a maximum tumor diameter up to 50mm (pathological findings)

4. ICGR15 $\leqq$ 15%

Objective and endpoints

Objective

Anatomic resection for patients with HCC is associated with better DFS and OS than non-anatomic resection.

First endpoint

Disease-free Survival

Secondary endpoint

Overall Survival

Rate of local recurrence

*Analysis of subclassification in HBV, HCV, NBC-HCC

Data collection is high volume centers from 5 to 10 insitutes in Japan and Korea, respectively

Japan-Korea Collaborative Research of Hepato-Biliary-Pancreatic Surgery

Category: **Liver**

Director: Masanori Kwon (Kansai Medical University)
Secretary: Masaki Kaibori (Kansai Medical University)

Treatment strategy for resectable synchronous colorectal liver metastases

-Proposal of retrospective study-

Background

Fifteen percent to twenty-five percent of patients affected by colorectal cancer presents with liver metastases at diagnosis. In resectable cases, surgery is the only potentially curative treatment and achieves survival rates up to 50% at 5 years.

The optimal surgical strategy for treatment of patients with synchronous colorectal liver metastases remains controversial. A variety of management including colorectal resection, liver resection, chemotherapy, and staged resection are recommended. However, there are few reports about the clinical benefit.

Back ground

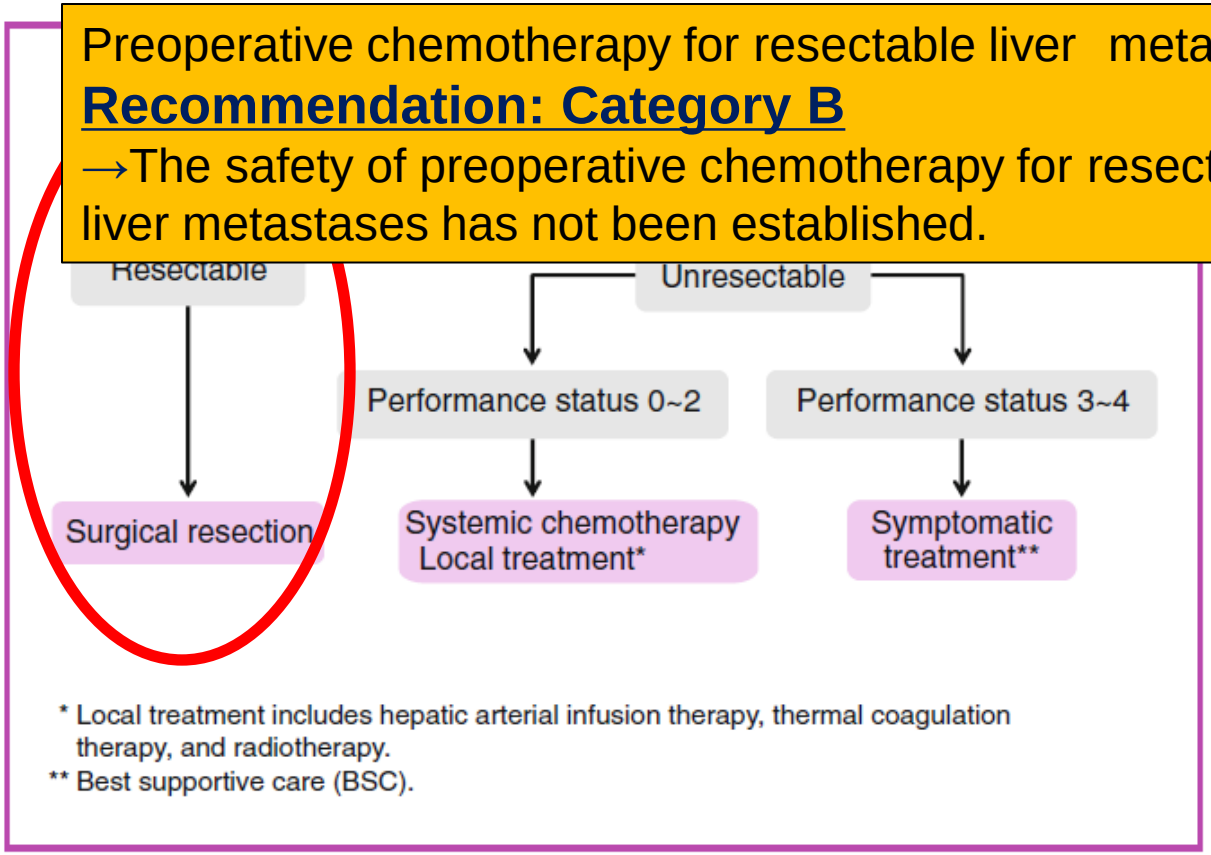
Japanese Society for Cancer of the Colon and Rectum(JSCCR)guidelines 2010 for the treatment of colorectal cancer

Treatment strategies for hematogenous metastases

Preoperative chemotherapy for resectable liver metastases

Recommendation: Category B

→The safety of preoperative chemotherapy for resectable liver metastases has not been established.



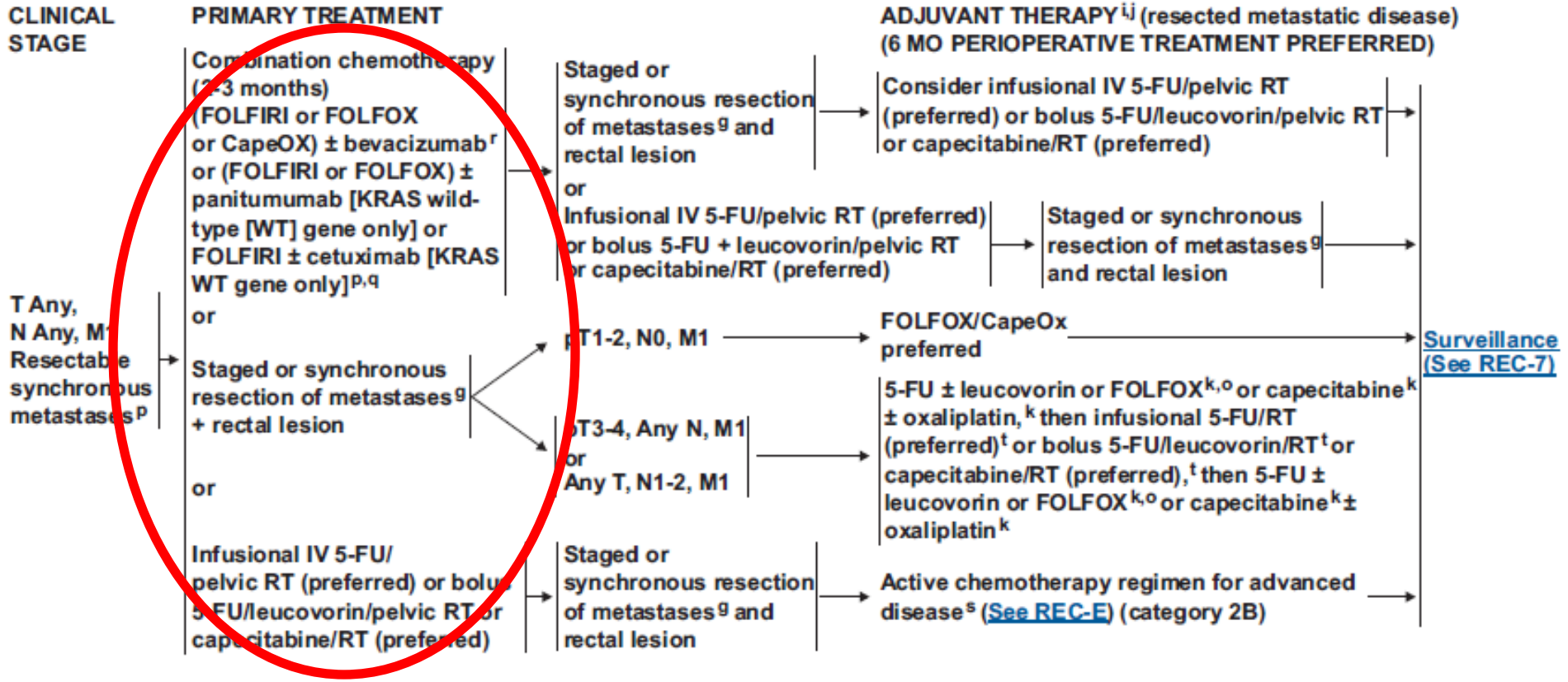
- Treatment of liver metastases is broadly divided into hepatectomy, systemic chemotherapy, hepatic arterial infusion therapy, and thermal coagulation therapy.

y is recommended for liver metastases
ve resection is possible.
y consists of systematic resection and
systematic) resection.

riteria for hepatectomy
t is capable of tolerating surgery,
(2) the primary tumor has been controlled or can be controlled,
(3) the metastatic liver tumor can be completely resected,
(4) there are no extrahepatic metastases or they can be controlled,
(5) the function of the remaining liver will be adequate.

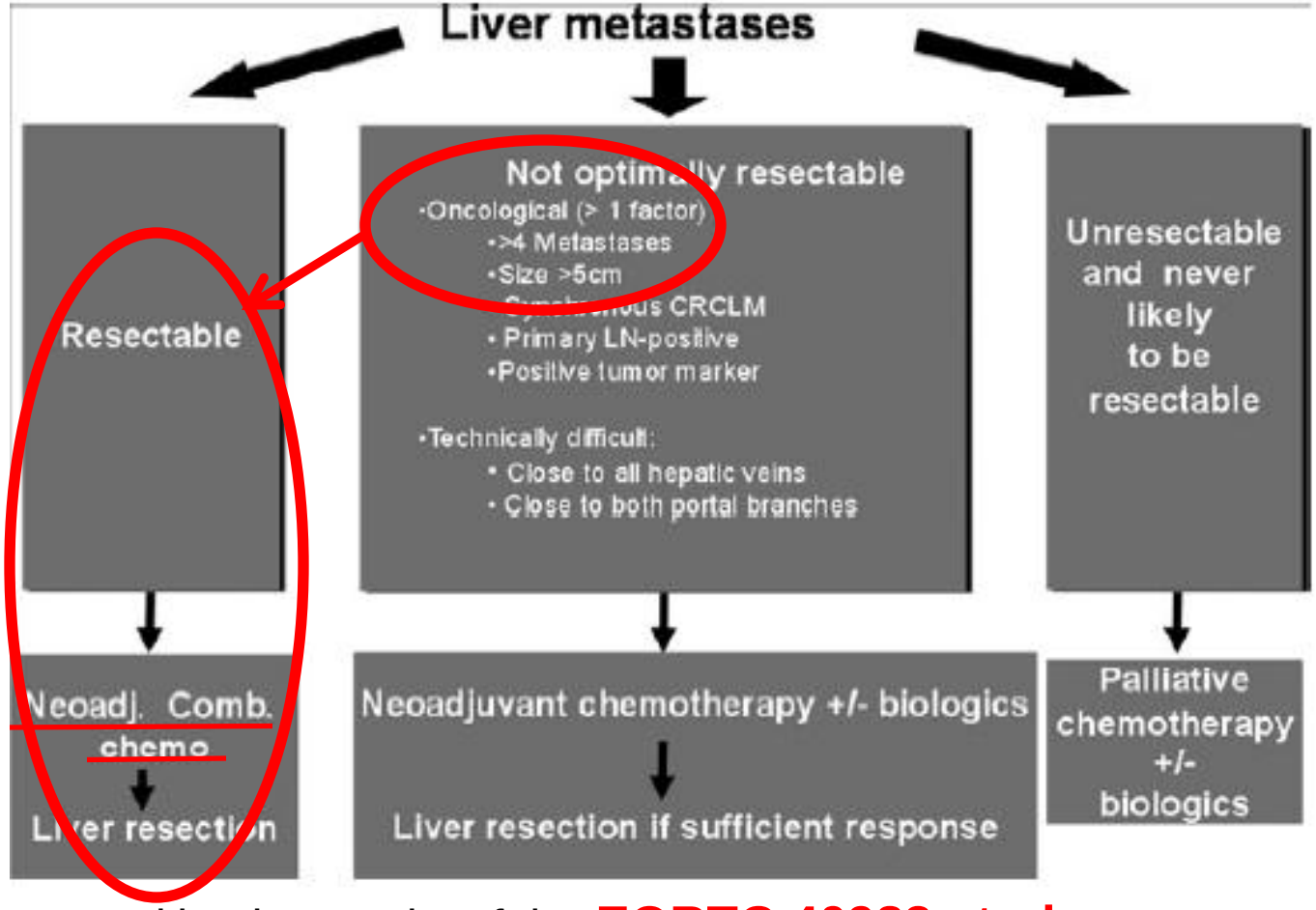
- Systemic chemotherapy and hepatic arterial infusion therapy, either alone or in combination, are considered for patients with unresectable liver metastases whose general condition can be maintained at a certain level or higher (PS 0 to PS 2).
- Thermal coagulation therapy consists of microwave coagulation therapy (MCT) and radiofrequency ablation (RFA).
- If the patient's general condition is poor (PS $\geq$ 3), best supportive care (BSC) is provided.

NCCN guideline



g See Principles of Surgery (REC-B).
i See Principles of Adjuvant Therapy (REC-C).
j See Principles of Radiation Therapy (REC-D).
k The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.
o An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.
p Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.
q There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.
r The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
s FOLFOXIRI is not recommended in this setting.
t RT is only recommended for patients at increased risk for pelvic recurrence.

Recommendation from Europe an expert panel : liver metastases



This is supported by the results of the **EORTC 40983 study**
PFS rate at 3 years 8.1% [hazard ratio (HR) = 0.77; P = 0.041]
support the use of neoadjuvant protocols for resectable metastases.

BUD···

Primary Endpoint : ITT non meet

Review of article

There was few review manuscripts regarding synchronous colorectal liver metastases

Resectable synchronous colorectal liver metastases

~~chemotherapy alone?~~

We deleted Chemotherapy alone group due to few cases

Neo adjuvant?

Adjuvant?

Surgery only?

Resectable synchronous colorectal liver metastases

Definition of 'resectable'

Number of tumors $\leqq$ 4 metastases
and
Maximum tumor size $\leqq$ 5cm
and
Tumor surgical margin was negative
(means as technically was not difficult)

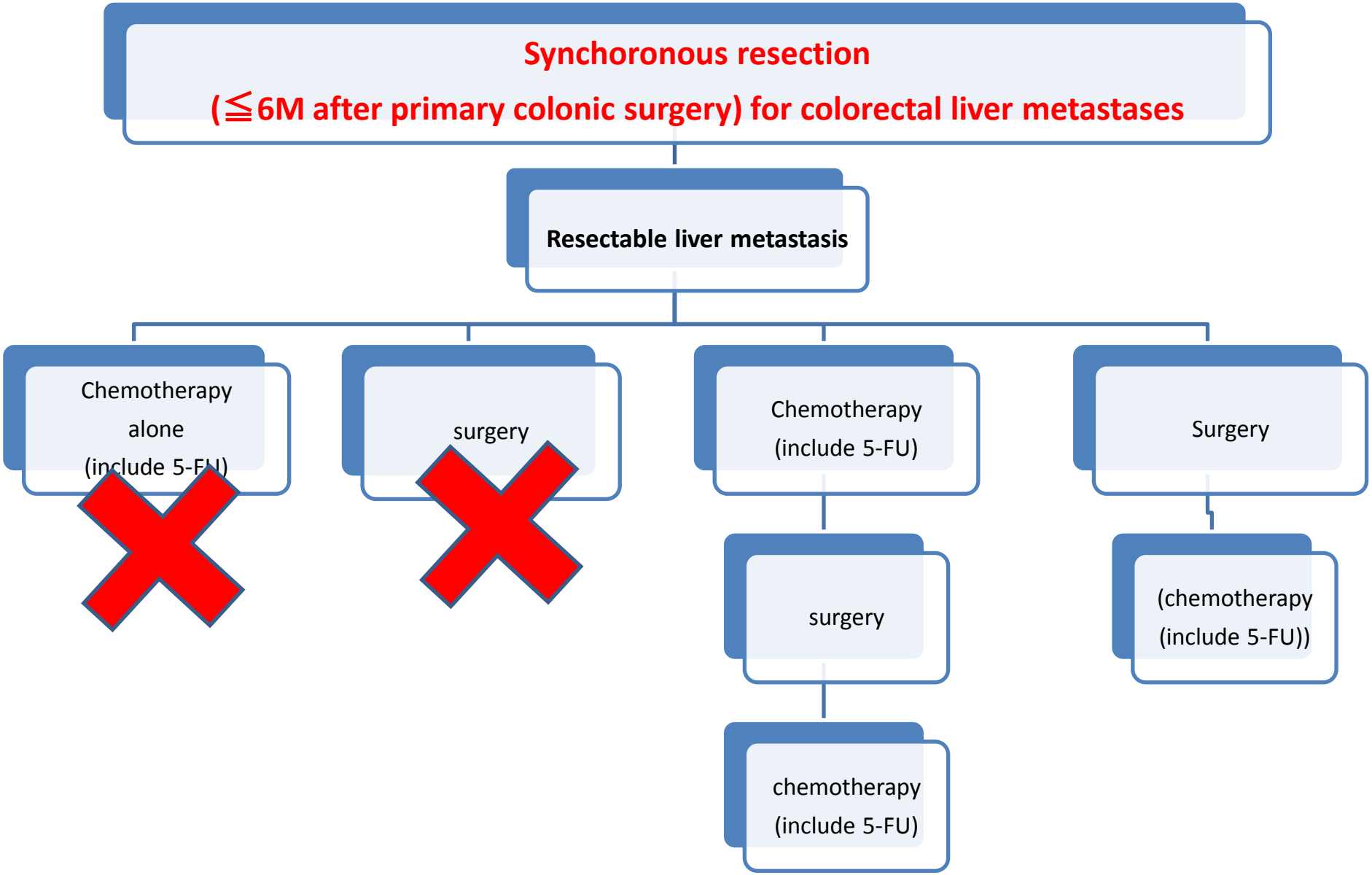
Inclusion criteria

1. R0 resection of synchronous liver metastases between 2006-2012.

1. Below than 4 metastases and 5 cm of a maximum tumor diameter.

2. Synchronous resection (≦6M after primary colonic surgery) for colorectal liver metastases without concurrent operation with primary colonic surgery.

Inclusion criteria



Patient flow diagram:2006～2012

Objective and endpoints

Objective

Demonstrate that neo-adjuvant chemotherapy combined with surgery is a better treatment than surgery with adjuvant chemotherapy.

First endpoint

Progression-free Survival

Secondary endpoint

Response rate

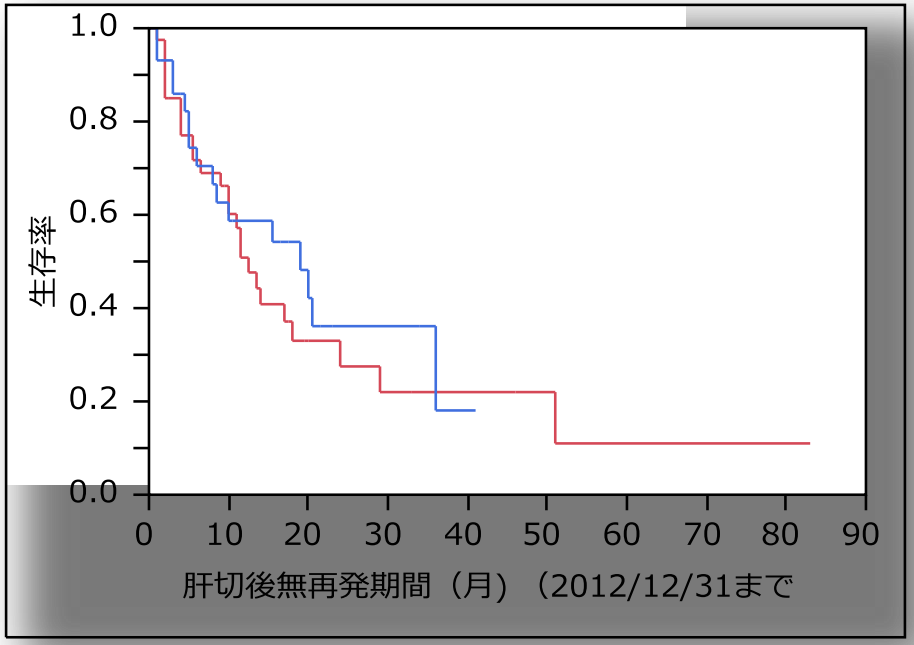
Rate of recurrence

Safety

Data collection is high volume centers from 5 to 10 insitutes in Korea and Japan, respectively

Results (Kansai Medical University)

PFS

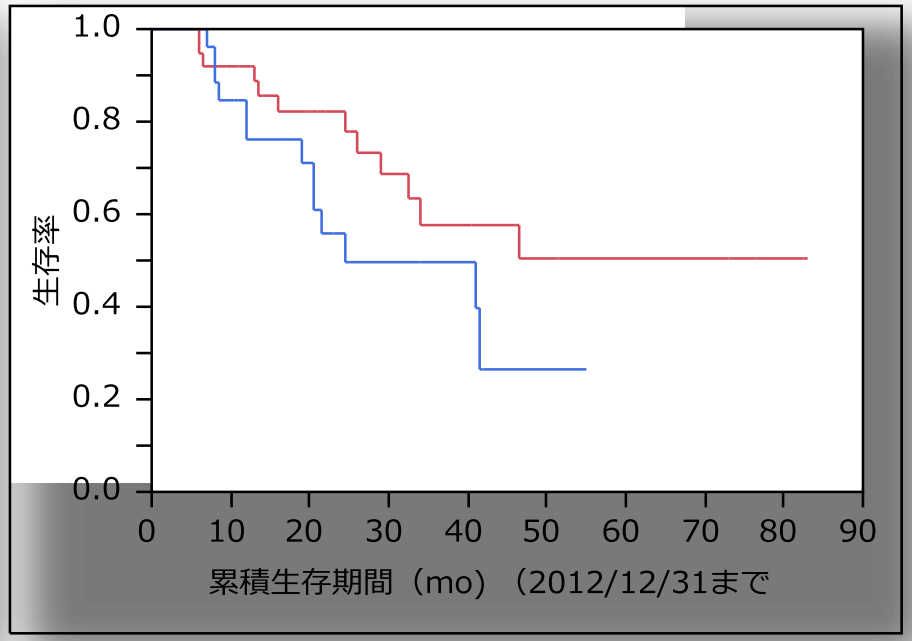


CT_OPE_CT n=26 17.5M

OPE_CT n=16 18M

Loglank p=0.5961

OS



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OPE_CT n=16 24M

Loglank p=0.1009