

HEP DART 2005

frontiers in drug development for viral hepatitis

Current therapies and needs

Eddie Cheung

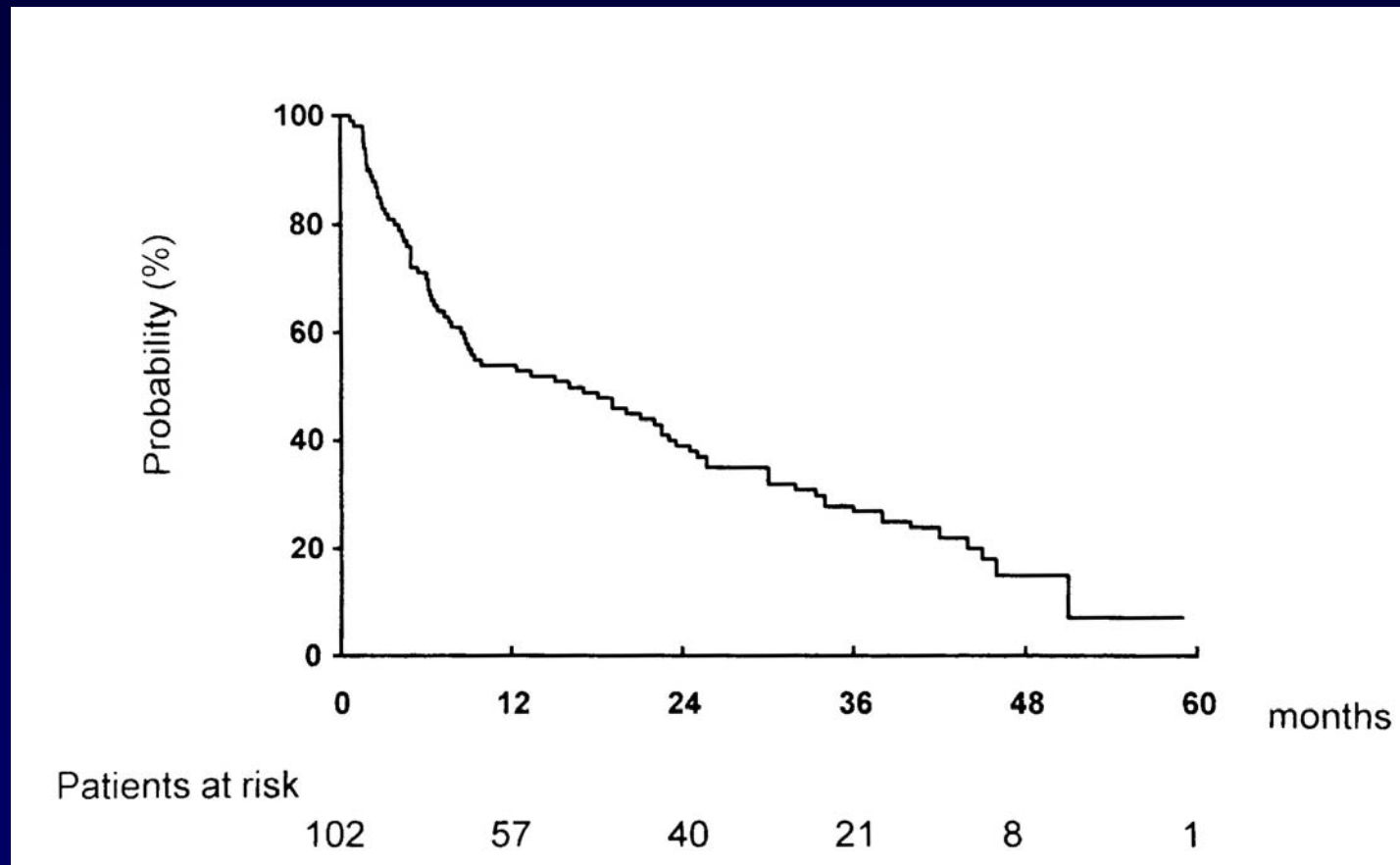
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Current Treatment and Need for Hepatocellular Carcinoma

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Actuarial Survival of Patients with Untreated HCC



Llovet JM et al, Hepatology 1999;29:62

Management of HCC

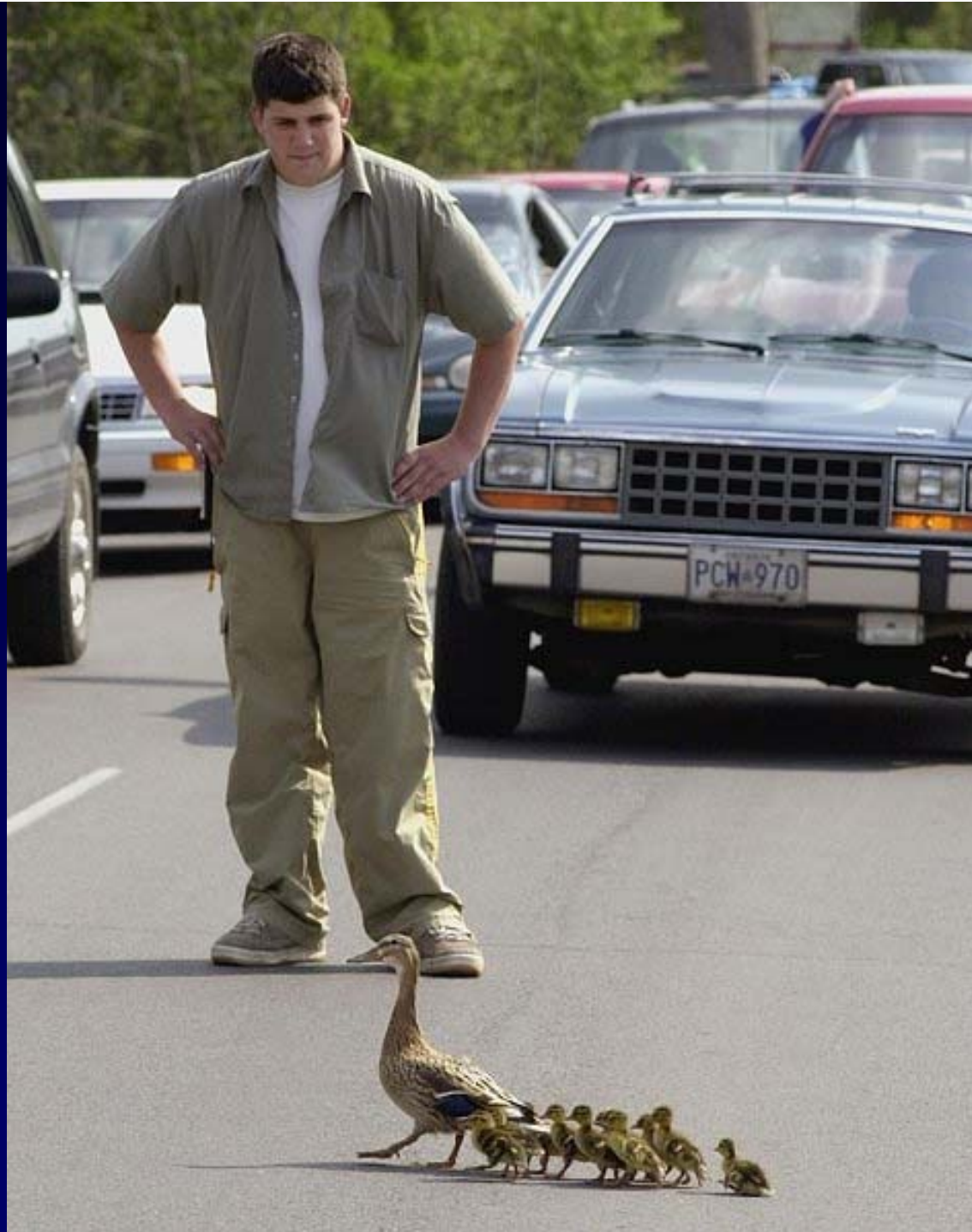
- Liver transplantation
 - Resection
 - Tumor ablation
 - Radiofrequency thermal ablation
 - Alcohol injection
 - Chemoembolization
 - Cryoablation
 - Regional radiation – yttrium beads
 - Chemotherapy
 - Regional
 - Systemic, interferon
 - Tamoxifen
- “Radical”**
- “Potentially curative”**

Management of Hepatocellular Carcinoma

Liver Transplantation

- Good results in well selected patients
 - diameter <5cm
 - no more than 3 nodules
 - no extra-hepatic spread

(Milan criteria)
- Lower rates of recurrence than with resection
- About 10% qualify for listing
 - Long waiting time
 - What to do while waiting?



Outcomes of Liver Transplantation for HCC within Milan Criteria

Author	N.	Recurrence (%)	5 yr survival (%)
Mazzaferro	48	8	75
Ismail	45	11	74
Llovet	79	4	75
Jonas	120	16	71

Management of Hepatocellular Carcinoma

Resection

- Less than 5% patients resectable
- Factors affecting resectability:
 - Size < 5cm
 - number of tumors
 - involvement of major structures
 - hepatic function
 - no extra-hepatic spread
 - no portal hypertension
- Requires experienced surgical and supporting team
- 5 year survival 60%
- 3 year recurrence 45 – 60%

Resection vs. Liver Transplant

- 1990 – 1999, Barcelona
- 138 patients with cirrhosis and HCC
85 OLT and 53 resection
- Child's A and B

	<u>OLT</u>	<u>Resection</u>
1, 3, 5-year survival	84, 74, 62%	83, 57, 50%
1, 3, 5-year disease-free	83, 72, 60%	70, 44, 31%

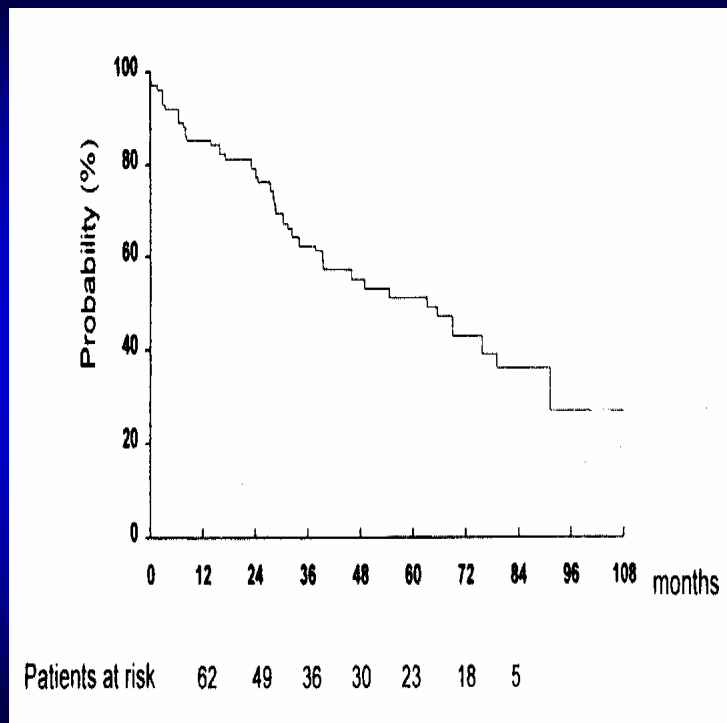
J Am Coll Surg 2000

- BUT 23% patients become ineligible for OLT with a median wait time of 6 months.
- 2 yr- ITT survival decrease from 85% to <60%

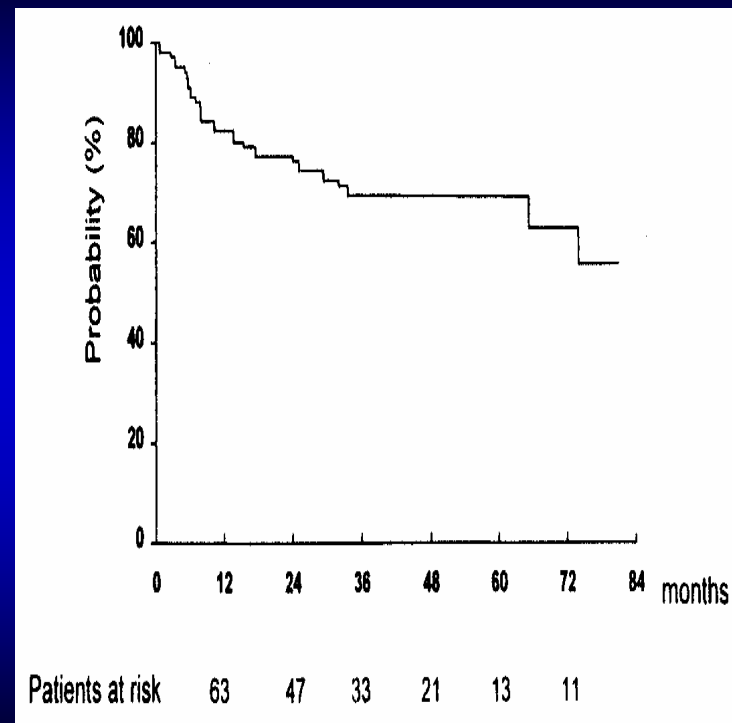
Llovet Hepatology 1999

Survival of Patients with HCC

Resection (n = 77)



Liver Transplantation (n = 87)



Ethanol Injection for HCC

- Relatively safe and well tolerated
 - Method: ultrasound guided
 1 to 2 treatments
 up to 6 injections
 1 to 5ml each
 - Survival comparable to resection
 - Limited effect on tumors >4cm
 - Can also use hot saline and acetic acid
-

Percutaneous Ethanol Injection

207 patients with cirrhosis + HCC < 5 cm

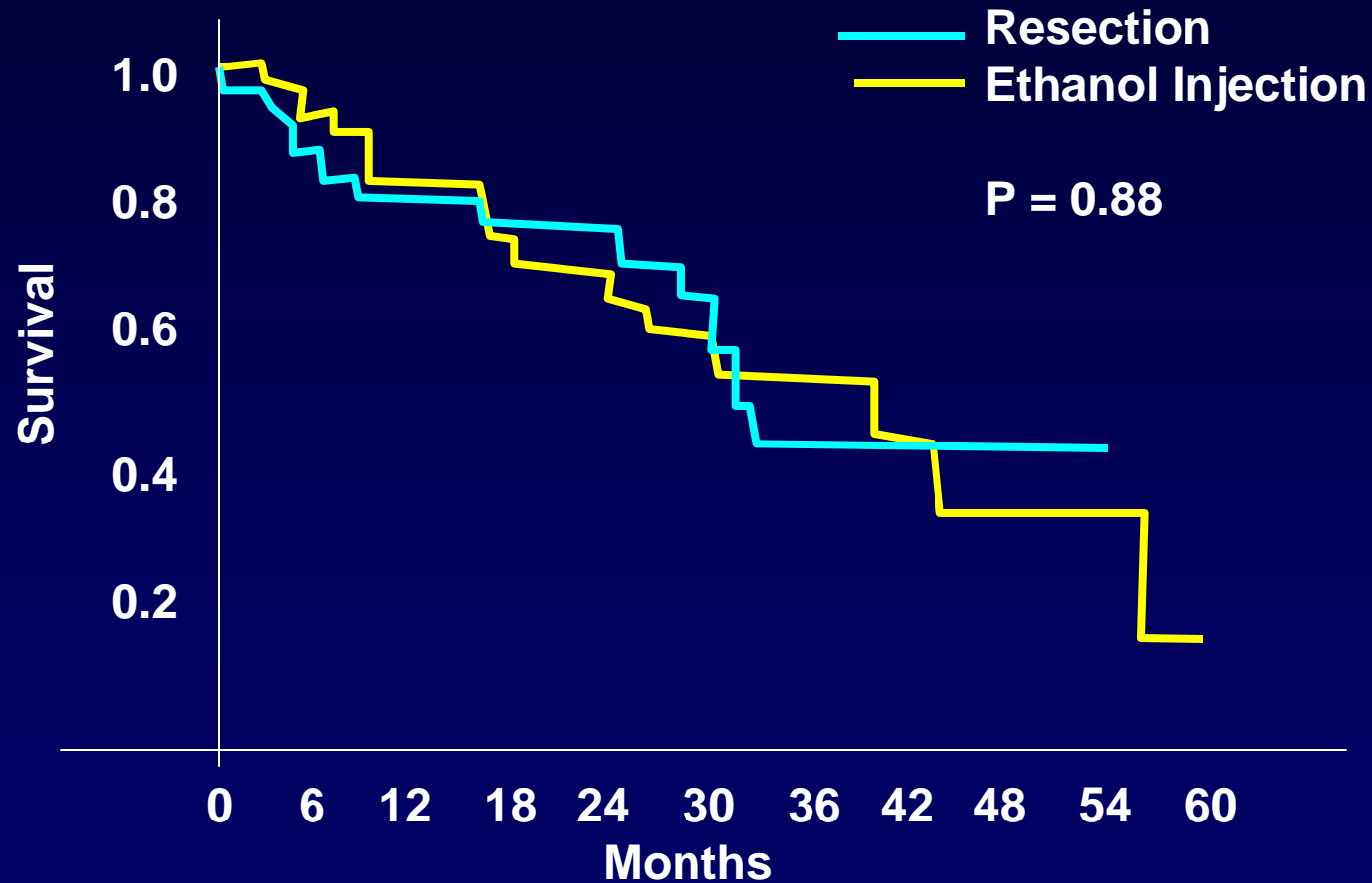
- **100% Ethanol**
- **Follow up was 25 months**
- **No complications**
- **4.3 sessions per patient**

88% complete necrosis

1,2,3-year survival rates: 90,80,63%

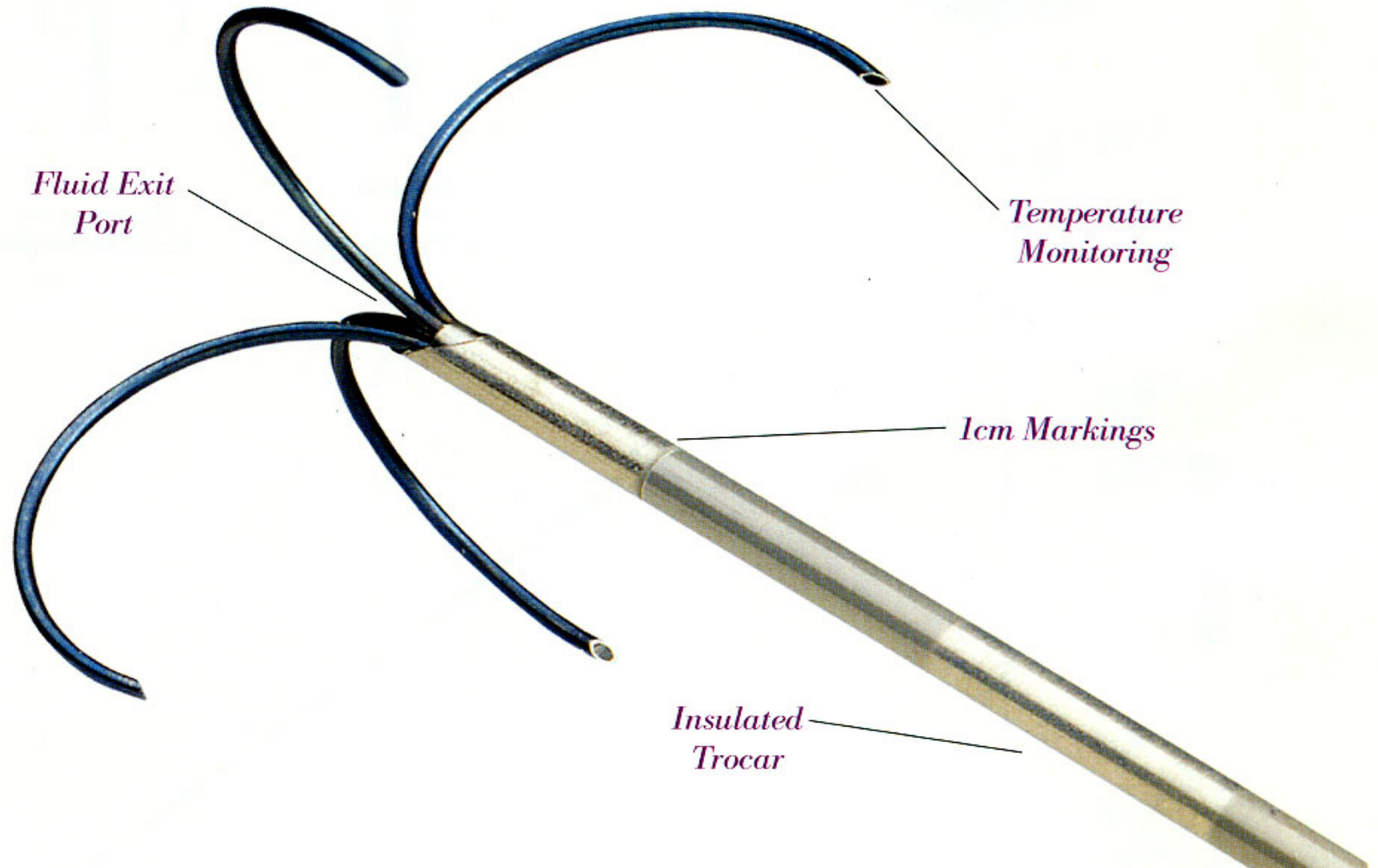
Hepatocellular Carcinoma

Resection vs. Ethanol Injection

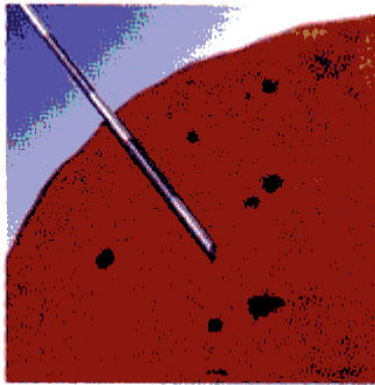


Castells et al, 1993

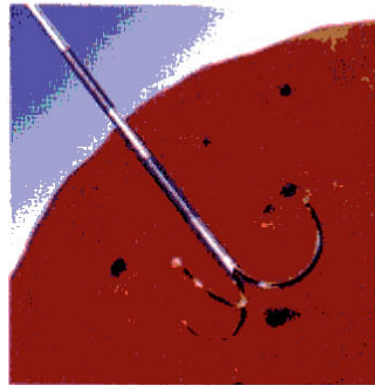
Radiofrequency Ablation



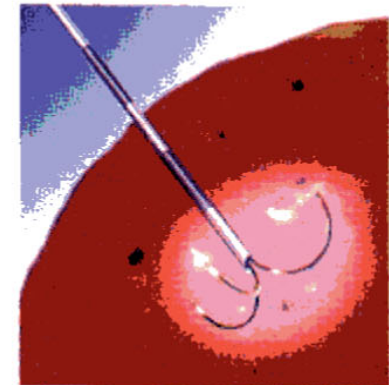
Radiofrequency Ablation



Introduction



Deployment



RF Ablation

Radio-Frequency Ablation

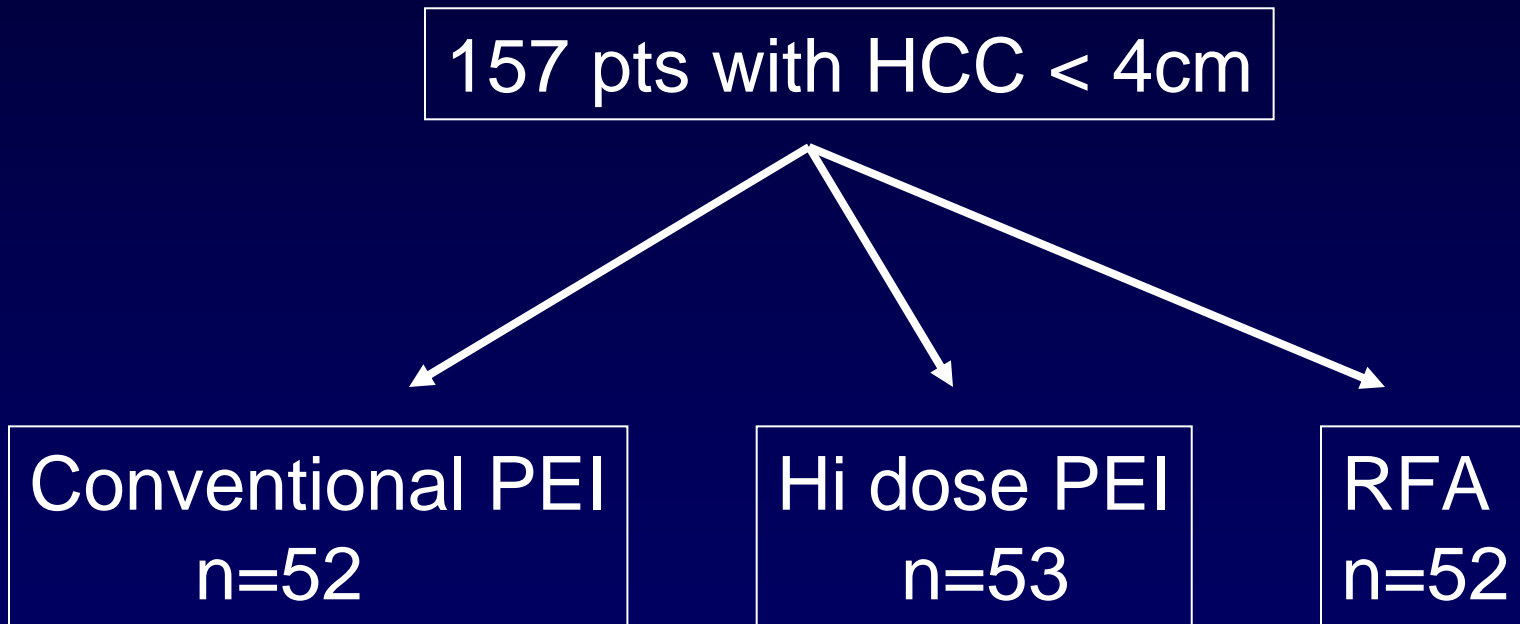


Pre-treatment



2 months post-treatment

Radiofrequency Ablation vs. Ethanol Injection



Lin et al. 2004

Radiofrequency Ablation vs. Ethanol Injection

	PEI	HD-PEI	RFA
Complete necrosis	88%	92%	96%
Progression (3yrs)	40.4%	26.4%	15.3%
Survival (3 yrs)	57.6%	60.3%	71.1%

Lin et al. 2004

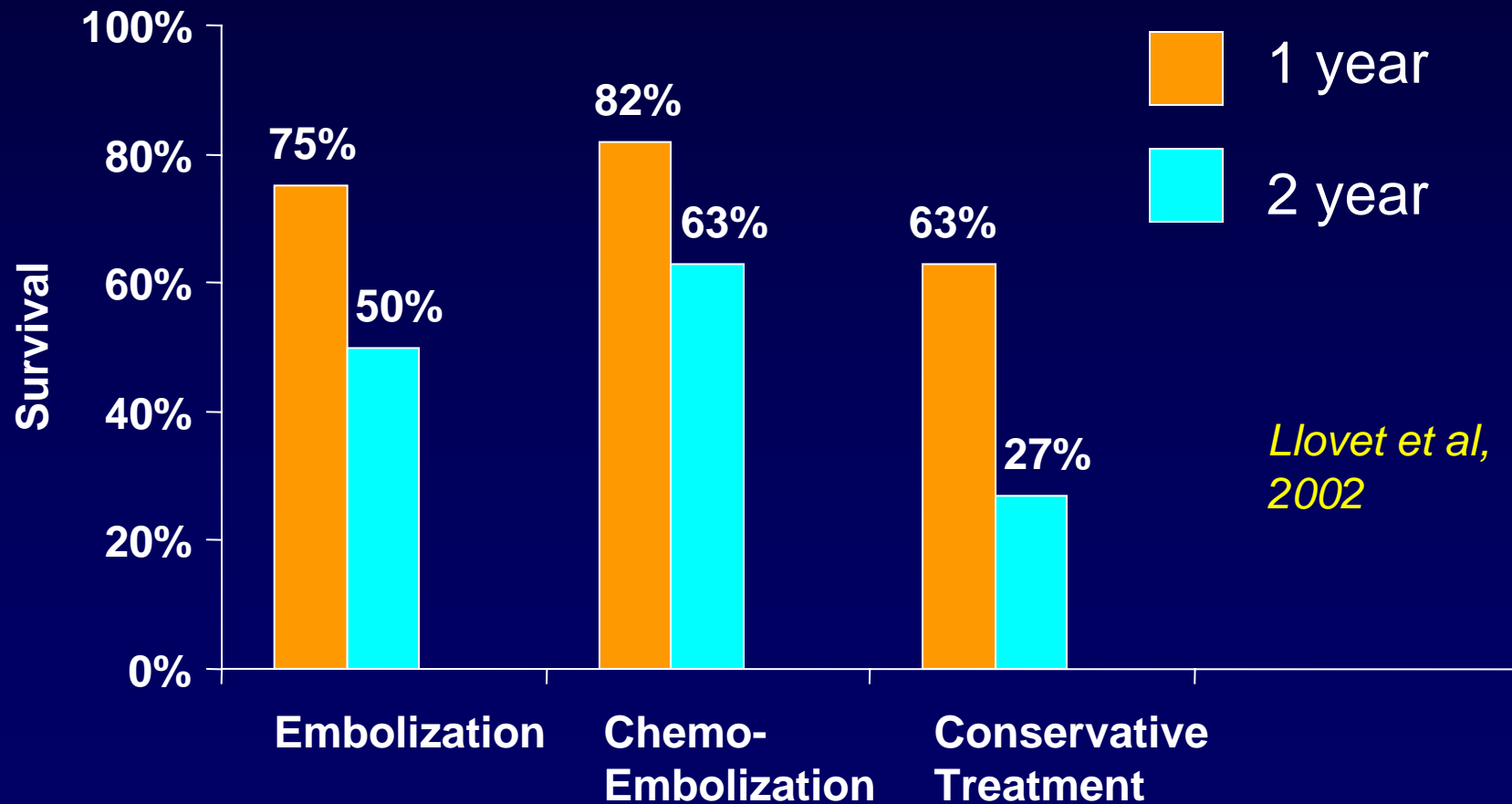
Radiofrequency (RFA) vs. Percutaneous Ethanol Injection (PEI)

	RFA n=52	PEI n=60
Complete necrosis	47 (90%)	48 (80%)
Mean no. of sessions	1.2	4.8

Radiology 1999; 210:655

- RFA - More expensive, more complications, more seeding.
- PEI - More sessions, less effective for tumors ≥ 2 cm.

Chemoembolization for Unresectable HCC



Transarterial Chemoembolization

Meta-analysis of 7 randomized controlled trials

2 yr survival: 41% (19-63%) vs. 27% (11-50%)

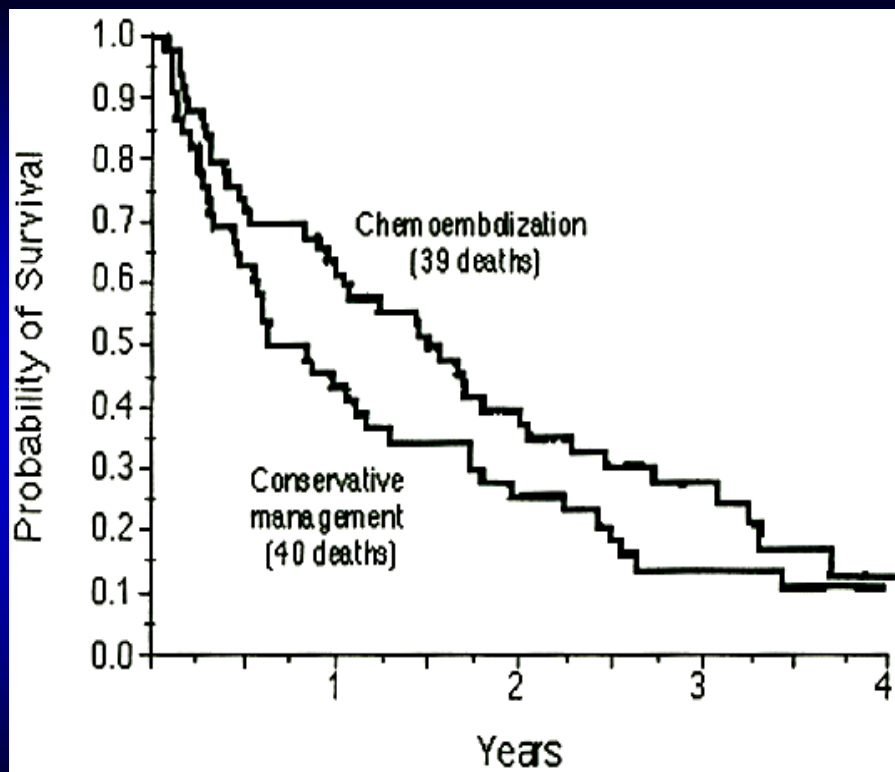
Treatment response: 35% (16-61%)

Average no. of sessions: 1-4.5

Risks:

- Infection
- Tumor lysis syndrome
- Hepatic failure

Transarterial Chemoembolization



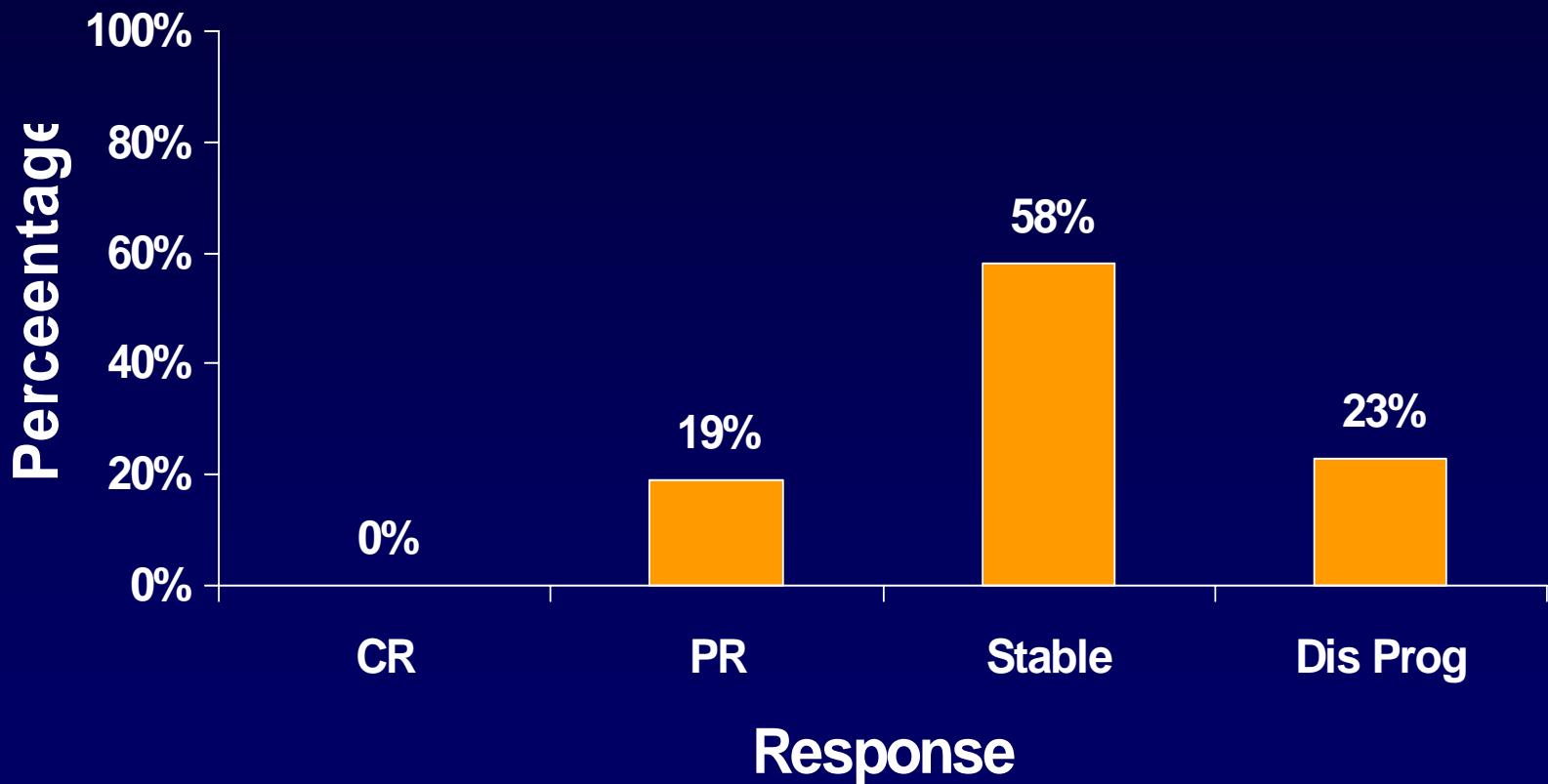
86 patients with HCC:

- No change in survival
- Tumor decrease size with TACE
- 33% liver failure
- 84% Post-embolization Syndrome

Radiation Therapy

- HCC does appear to be radio-sensitive
- Brachytherapy with ^{90}Y -labelled microspheres being tested
- Novel means are being developed to apply external beam radiation therapy to HCC

Use of ^{90}Y ttrium Microspheres (Therasphere) to Treat 36 Patients with HCC



Carr, B. 2002

Management of Hepatocellular Carcinoma

Chemotherapy

- Palliative, not curative
- Regional (intra-arterial) better than systemic
- Resistant to many agents

Chemotherapy for HCC

Thymitaq

(thymidylate synthase inhibitor)

Phase III Trial for
Unresectable HCC

Thymitaq

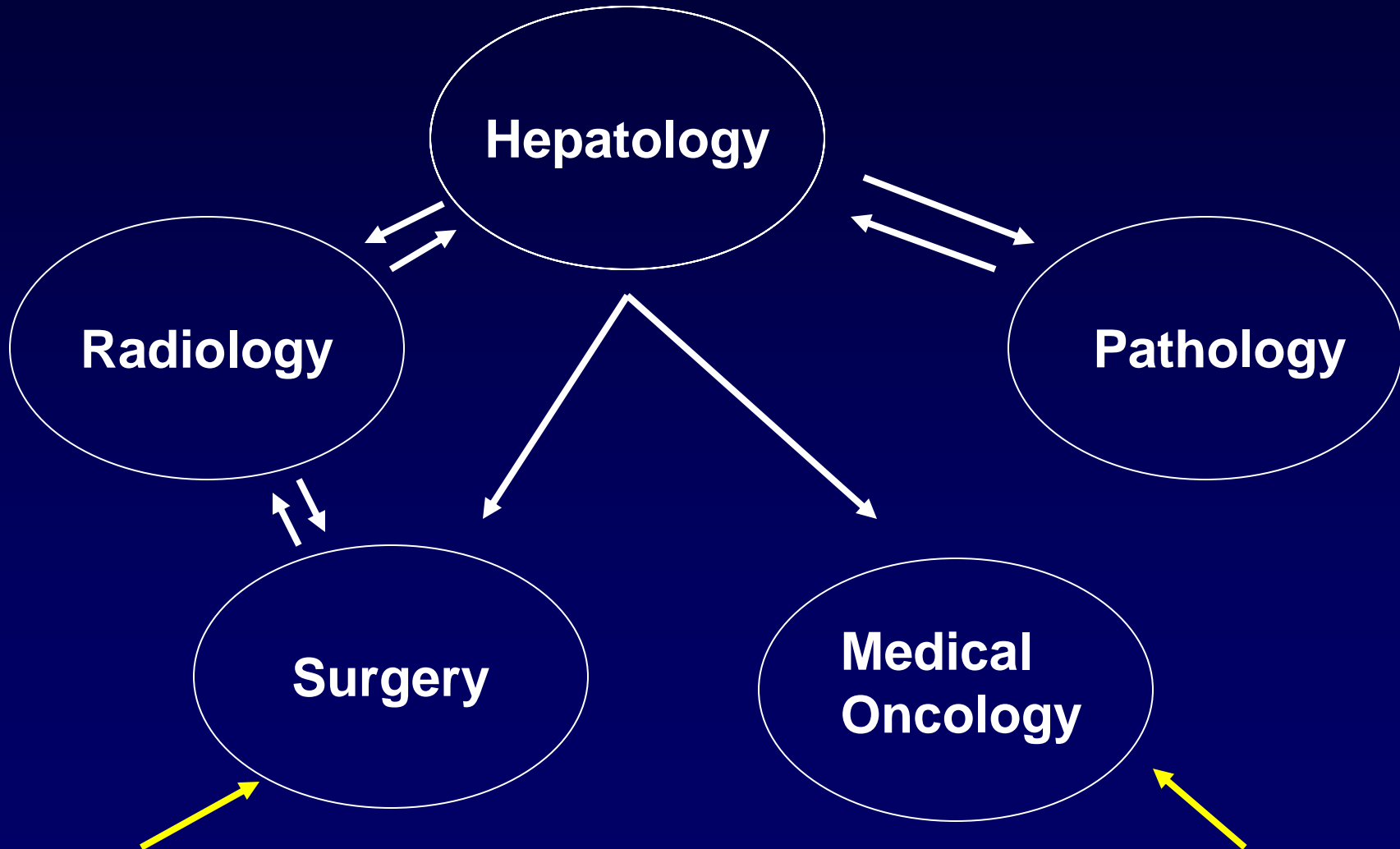
Adriamycin

Overall survival

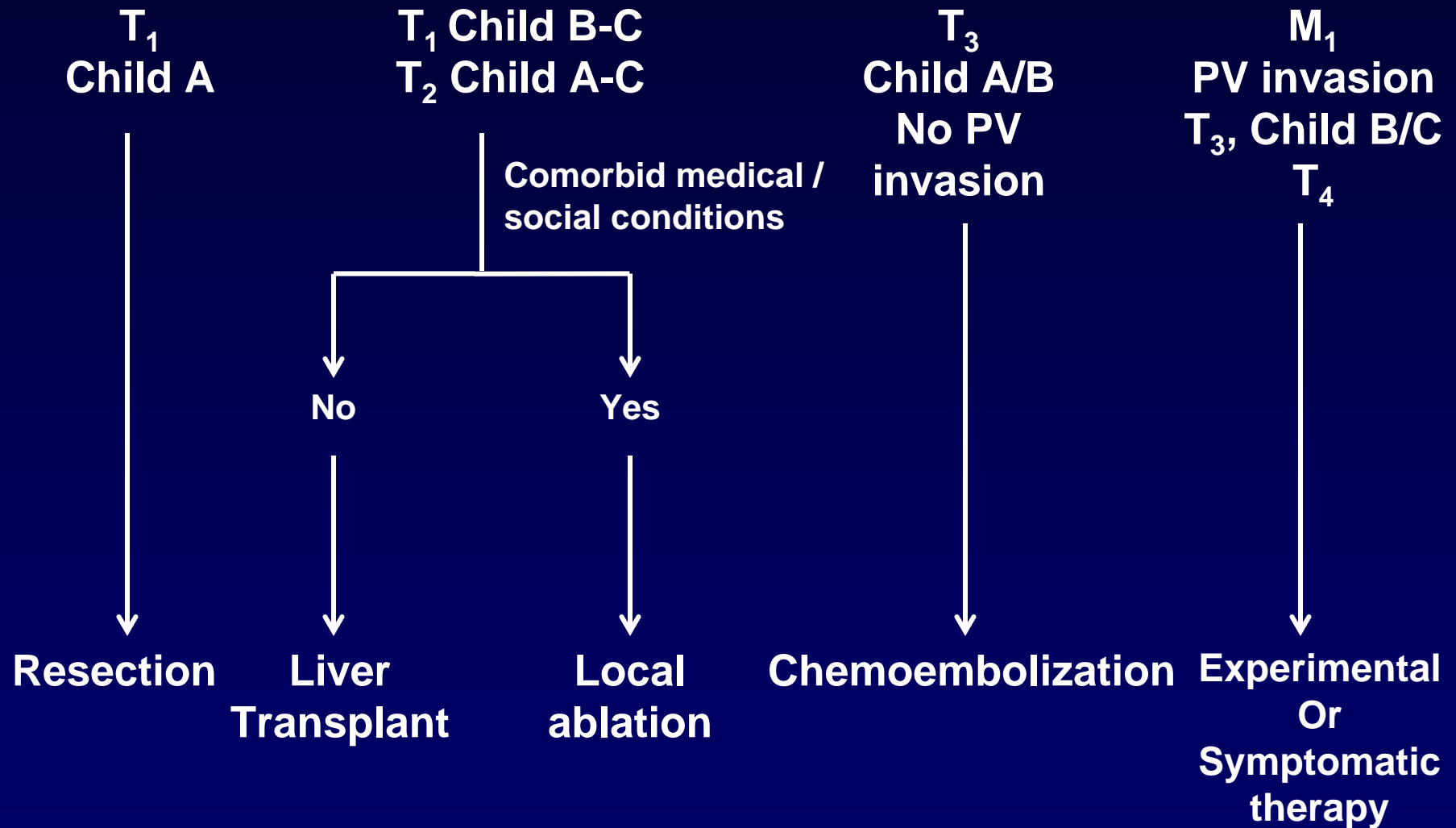
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graph TD; A[Phase III Trial for Unresectable HCC] --> B[Thymitaq]; A --> C[Adriamycin]; B --> D[Overall survival]; C --> D;
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Multidisciplinary Management of HCC

New patient referrals



Treatment Algorithm for HCC



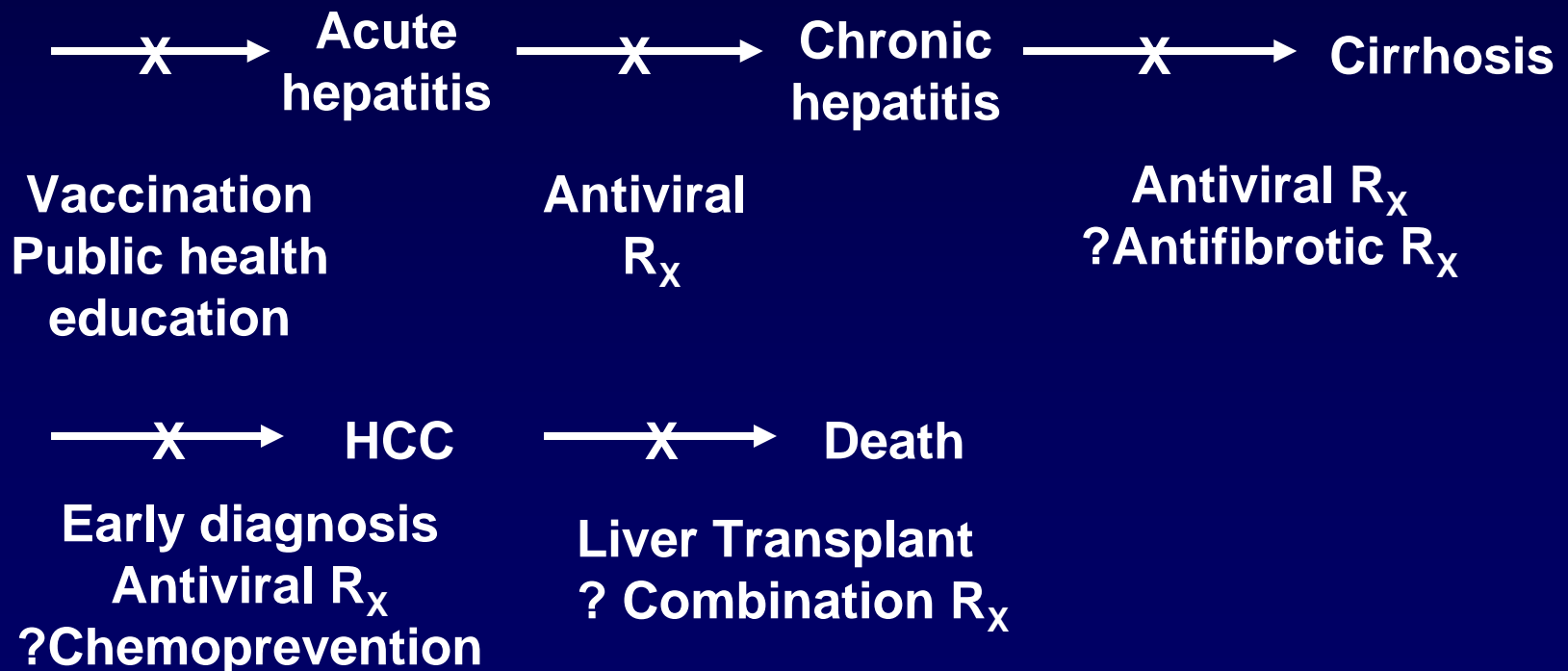
Modified from Llovet J et al, Liver Transpl 2004;100 S115



Prevention of HCC

- Hepatitis B vaccine
- Antiviral therapy against hepatitis
- Chemoprevention

Prevention and Treatment of Pre-Malignant Conditions

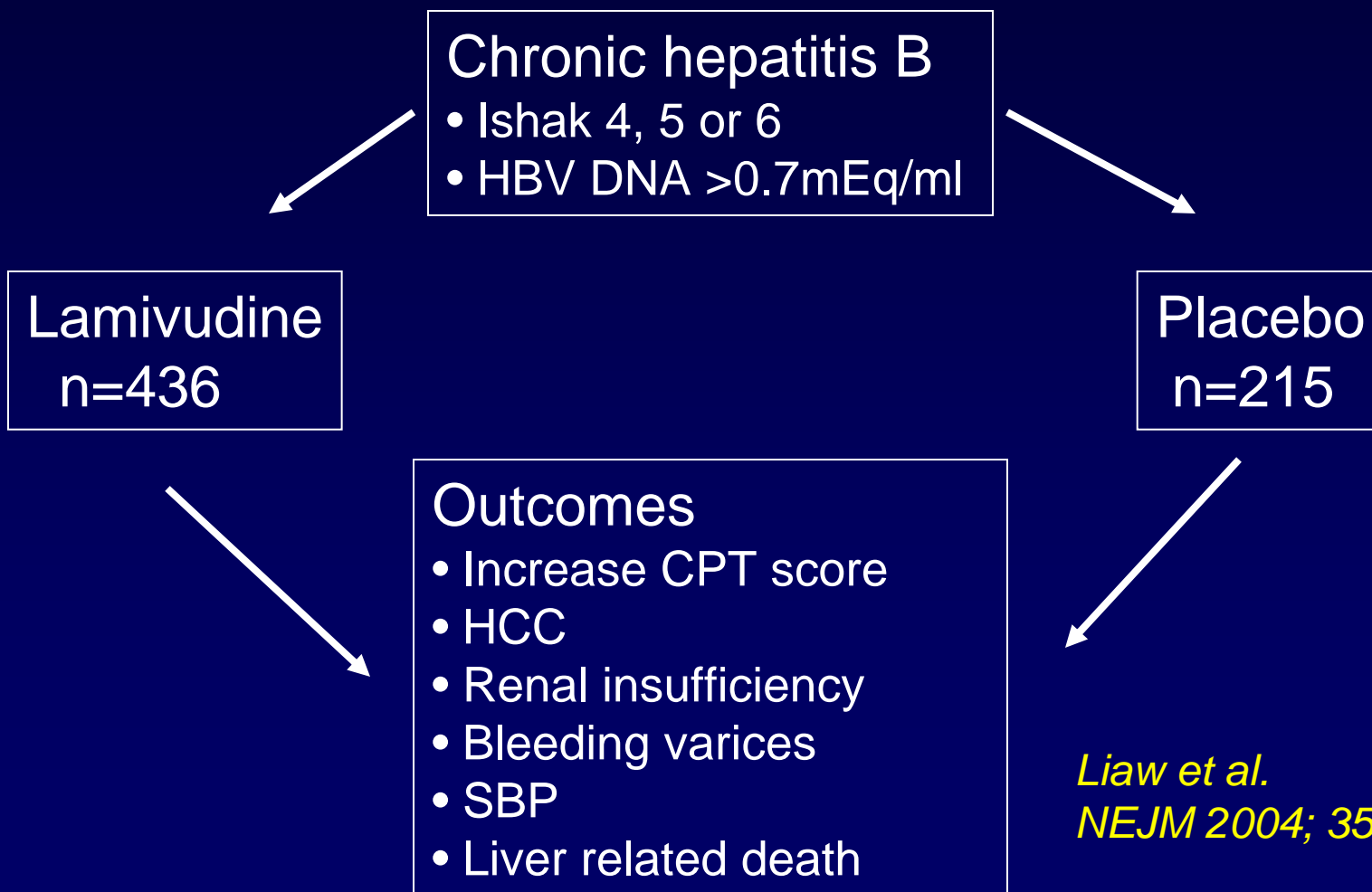


HCC Among Children 6-14 years in Taiwan

Year	HCC per 100,000 population
1981 - 1986	0.7
1986 - 1990	0.57
1990 - 1994	0.36
1996 - 1999	0.19

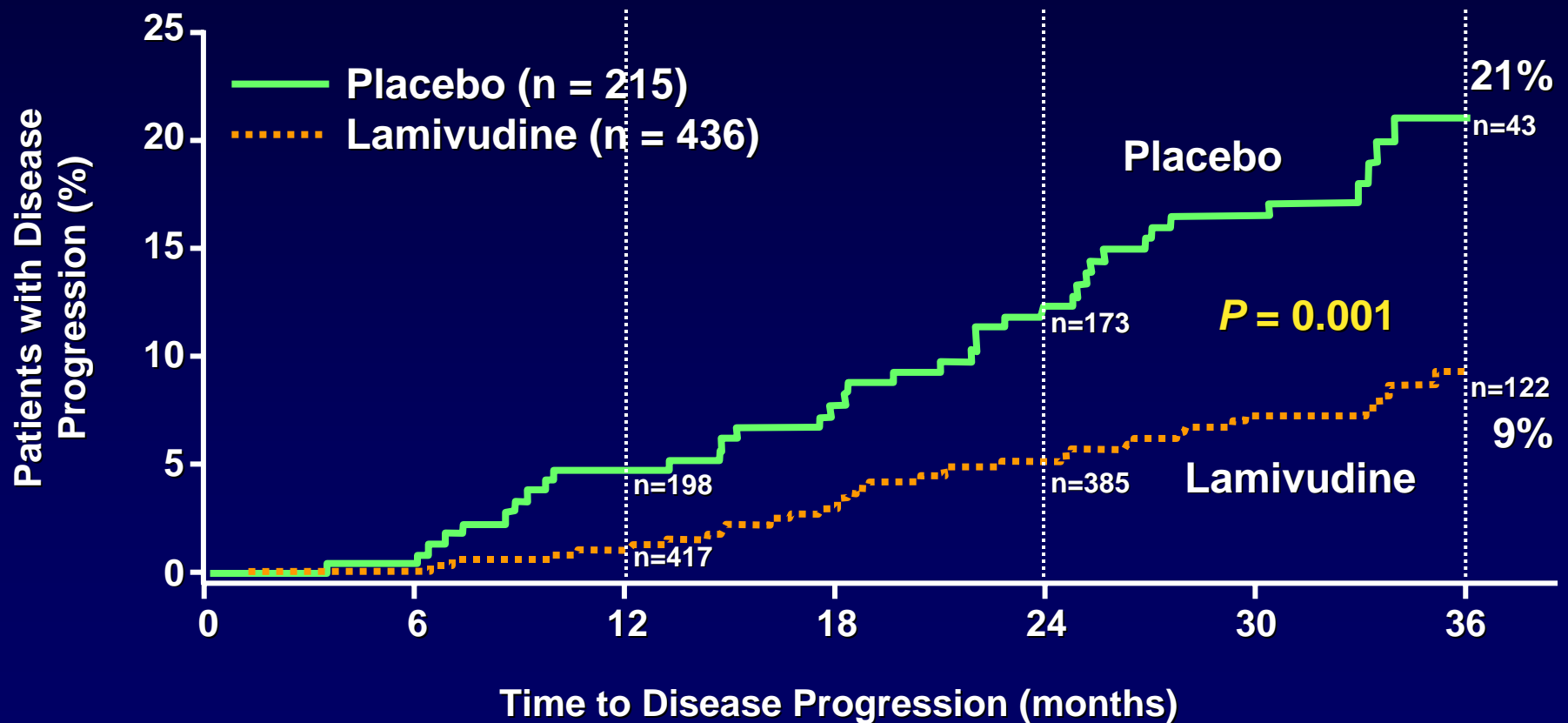
*Chang et al 1997, updated by
personal communication 2002*

Lamivudine for chronic hepatitis B and advanced liver disease



*Liaw et al.
NEJM 2004; 351:1521-31*

Time to Disease Progression on Treatment and Off-Treatment Follow-Up



Hepatocellular Carcinoma

- Incidence increasing in the U.S.
- Most patients diagnosed at advanced stages
- < 10% patients have surgically resectable tumors
- No official guidelines on HCC surveillance
- AFP - poor sensitivity (40-60%) and specificity (80-90%) in HCC surveillance, accuracy increase when combined with ultrasound
- No randomized controlled trial of HCC surveillance
- Cost-effectiveness of HCC surveillance and impact on survival unclear

HCC - Future Directions

Development of more effective treatment for HCC

- **Early diagnosis**
- **Combination Rx**
 - Tumor resection/ablation**
 - Chemoprevention for recurrent tumor**
 - Antiviral Rx**
- **Novel Rx**
 - Gene therapy / immunotherapy / anti-angiogenesis Rx**
- **Liver transplantation**

HCC - Early detection

- **Screening for high risk groups**
Chronic HBV/HCV infection, hemochromatosis
Population vs targeted screening
- **Surveillance of high risk groups**
Who, how often, what test(s)?
Age, gender, cirrhotic vs non-cirrhotic,
family history
AFP, other tumor markers, genetic markers
US, other imaging modalities
- **Confirmation of diagnosis**
Imaging CT/MRI/?PET Scan
Biopsy - yes or no

