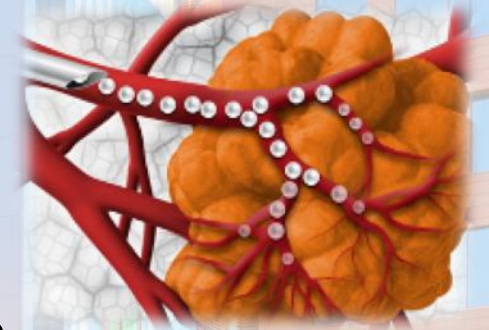
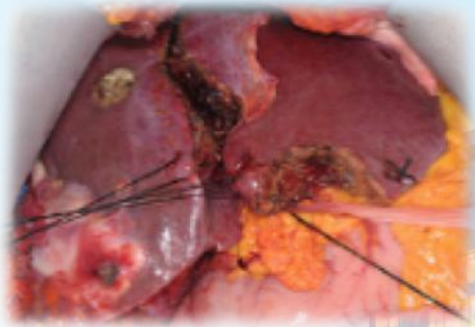


New Treatment Modalities in HCC



Güralp Onur Ceyhan

Acibadem Mehmet Ali Aydınlar University, Istanbul, Turkey

**6th Congress of the Mediterranean Multidisciplinary Oncology Forum &
3rd International Congress on Oncological Sciences**



28.11. – 01.12.2019, Antalya, Turkey





ACIBADEM
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HCC - Reality 2019

Estimated New Cases

| | | | Males | Females | | | |
|-----------------------|----------------|-------------|---|--|-----------------------|---------|-----|
| Prostate | 174,650 | 20% |  |  | Breast | 268,600 | 30% |
| Lung & bronchus | 116,440 | 13% | | | Lung & bronchus | 111,710 | 13% |
| Colon & rectum | 78,500 | 9% | | | Colon & rectum | 67,100 | 8% |
| Urinary bladder | 61,700 | 7% | | | Uterine corpus | 61,880 | 7% |
| Melanoma of the skin | 57,220 | 7% | | | Melanoma of the skin | 39,260 | 4% |
| Kidney & renal pelvis | 44,120 | 5% | | | Thyroid | 37,810 | 4% |
| Non-Hodgkin lymphoma | 41,090 | 5% | | | Non-Hodgkin lymphoma | 33,110 | 4% |
| Oral cavity & pharynx | 38,140 | 4% | | | Kidney & renal pelvis | 29,700 | 3% |
| Leukemia | 35,920 | 4% | | | Pancreas | 26,830 | 3% |
| Pancreas | 29,940 | 3% | | | Leukemia | 25,860 | 3% |
| All Sites | 870,970 | 100% | All Sites | 891,480 | 100% | | |

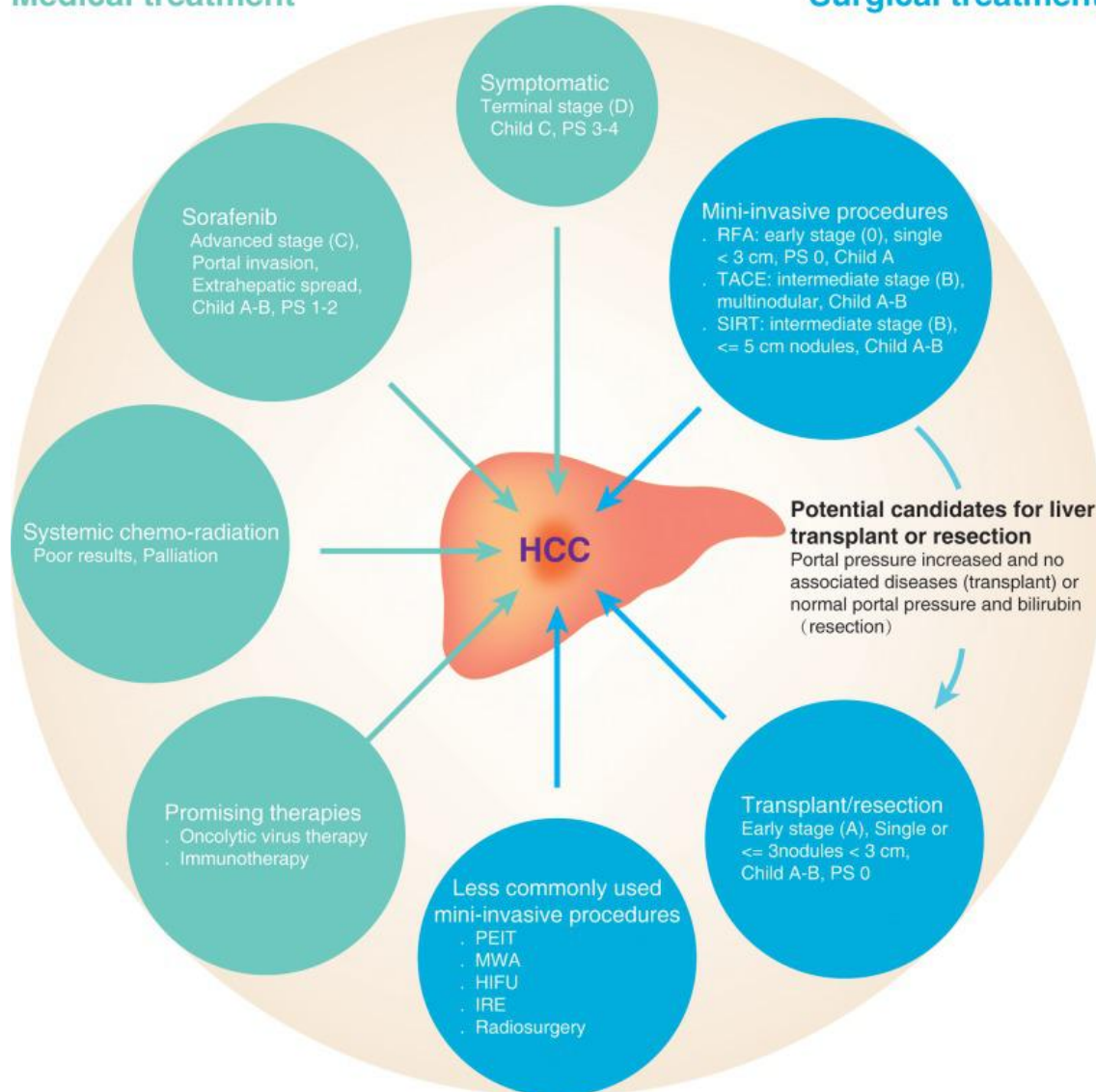
Estimated Deaths

| | | | Males | Females | | | |
|--------------------------------|----------------|-------------|--|---|--------------------------------|--------|-----|
| Lung & bronchus | 76,650 | 24% |  |  | Lung & bronchus | 66,020 | 23% |
| Prostate | 31,620 | 10% | | | Breast | 41,760 | 15% |
| Colon & rectum | 27,640 | 9% | | | Colon & rectum | 23,380 | 8% |
| Pancreas | 23,800 | 7% | | | Pancreas | 21,950 | 8% |
| Liver & intrahepatic bile duct | 21,600 | 7% | | | Ovary | 13,980 | 5% |
| Leukemia | 13,150 | 4% | | | Uterine corpus | 12,160 | 4% |
| Esophagus | 13,020 | 4% | | | Liver & intrahepatic bile duct | 10,180 | 4% |
| Urinary bladder | 12,870 | 4% | | | Leukemia | 9,690 | 3% |
| Non-Hodgkin lymphoma | 11,510 | 4% | | | Non-Hodgkin lymphoma | 8,460 | 3% |
| Brain & other nervous system | 9,910 | 3% | | | Brain & other nervous system | 7,850 | 3% |
| All Sites | 321,670 | 100% | All Sites | 285,210 | 100% | | |

HCC - Reality 2019

Medical treatment

Surgical treatment



Interdisciplinary team approach

**Radiation
Therapy**

**Interventional
Radiology**

Surgery

**Nuclear
Medicine**

Gastroenterology - Oncology

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma[☆]

Non-cirrhotic liver:

Recommendations

- Surgical resection is recommended as treatment of choice in patients with HCC arising on a non-cirrhotic liver (evidence low; recommendation strong).

Depending on:

- Liver function
- Portal hypertension
- Extent of hepatectomy
- Future liver remnant
- Patient's performance & co-morbidities

J Hepatol 2018



Surgery vs. Liver Tx in HCC

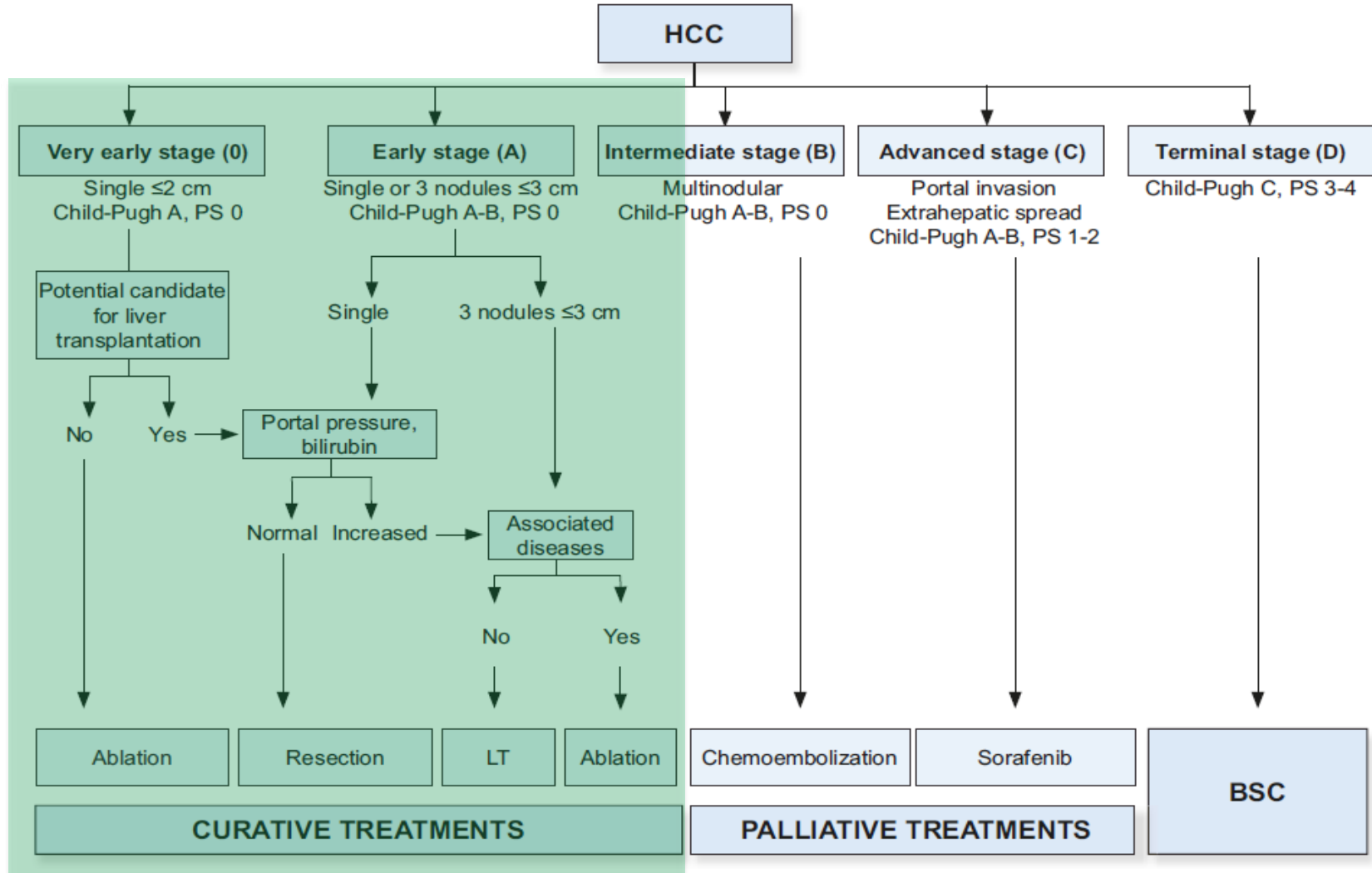
Cirrhotic liver:

Table 1 Details of expanded criteria

| Title | Year published | Criteria description |
|--------------|----------------|--|
| Milan (2) | 1996 | 1 lesion ≤ 5 cm, or 3 lesions ≤ 3 cm each |
| UCSF (3) | 2001 | 1 lesion ≤ 6.5 cm, or 2-3 lesions ≤ 4.5 cm each, with a total tumor diameter ≤ 8 cm |
| Navarro (4) | 2001 | 1 lesion ≤ 6 cm, or 2-3 lesions ≤ 5 cm each |
| Valencia (5) | 2008 | 1-3 lesions ≤ 5 cm each, total tumor diameter ≤ 10 cm |
| Hangzhou (6) | 2008 | Total tumor diameter ≤ 8 cm, AFP ≤ 400 ng/mL |

BCLC Algorithm in cirrhotic HCC

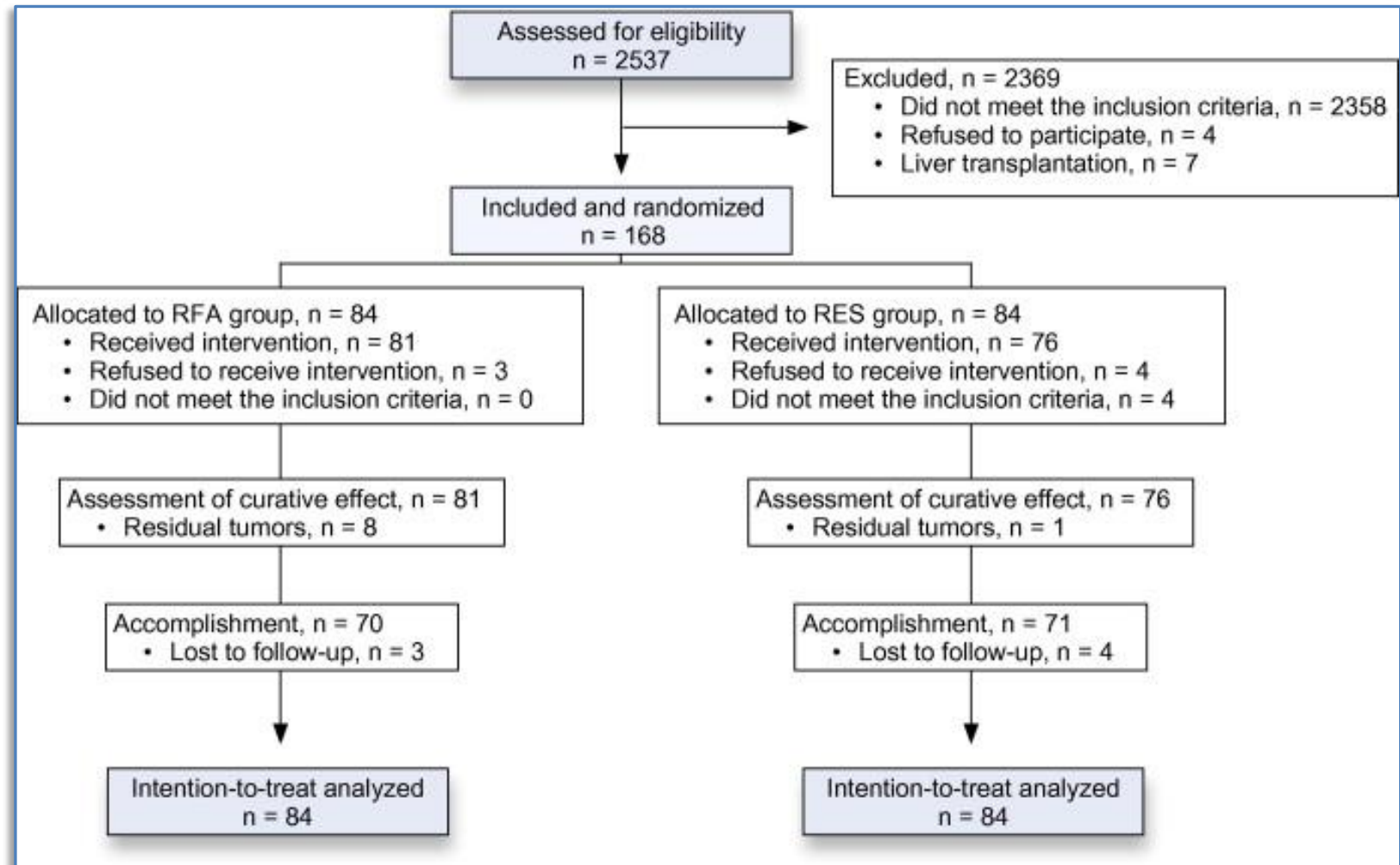
JOURNAL OF HEPATOLOGY



BACKGROUND

Resection vs. RFA in HCC – Patients

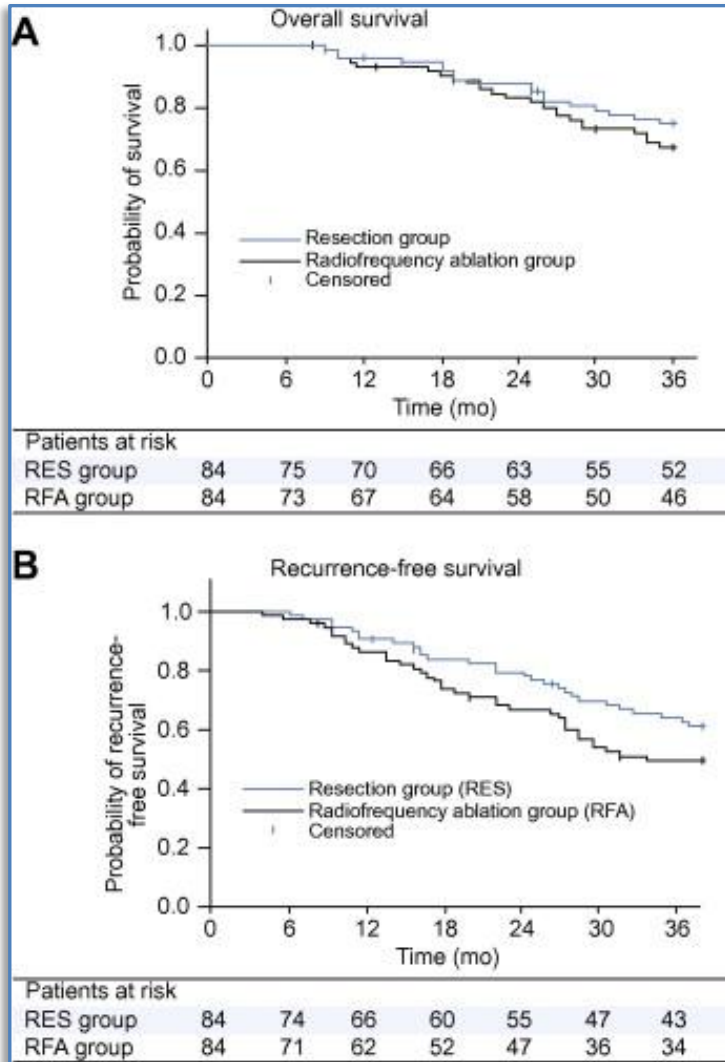
RCT (1:1) – 168 patients, 1 HCC < 4cm



Feng et al, J Hepatol 2012

Resection vs. RFA in HCC – Patients

RCT (1:1) – 168 patients, 1 HCC < 4cm

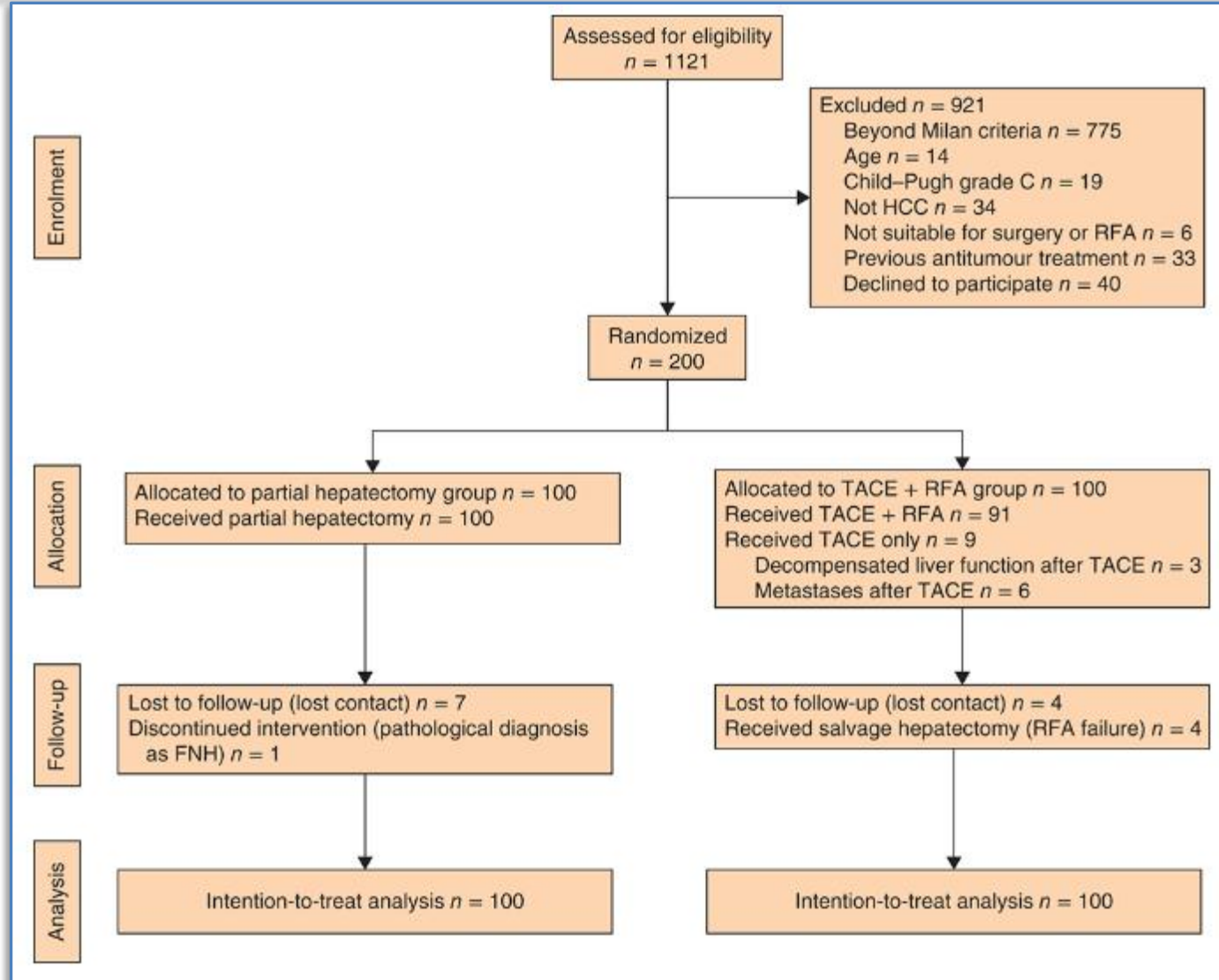


| n = 168 | RES | RFA |
|---------------------|------|------|
| 1-y survival | 96 | 93.1 |
| 2-y survival | 87.6 | 83.1 |
| 3-y survival | 74.8 | 67.2 |
| 5-y survival (2014) | ? | ? |

Feng et al, J Hepatol 2012

Resection vs. TACE/RFA in HCC

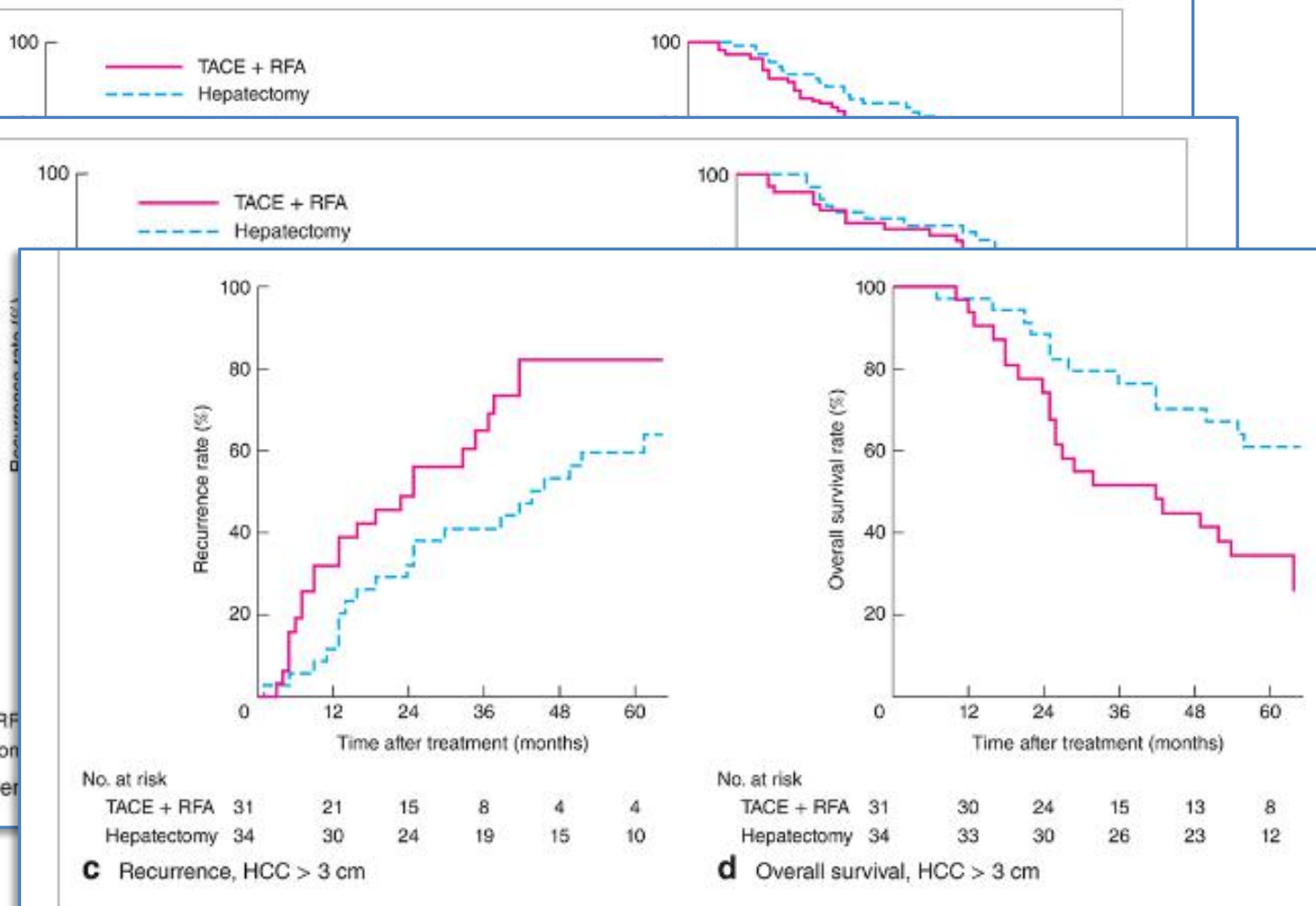
RCT (1:1) – 200 patients, *Milan - Criteria*



Resection vs. TACE/RFA in HCC

RCT (1:1) – 200 patients, Milan - Criteria

BACKGROUND



Liu et al. Br J Surg 2016



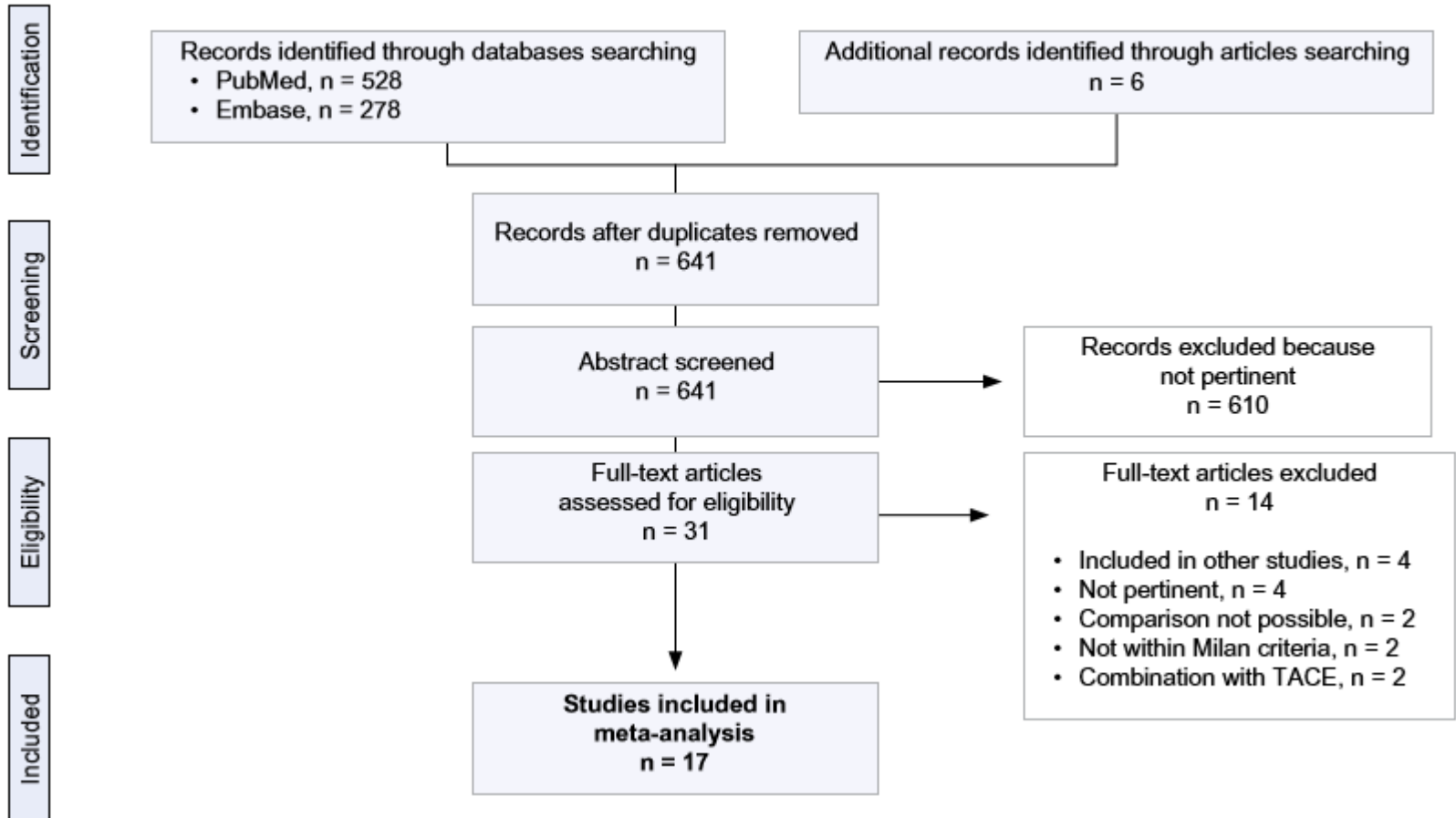
ACIBADEM
MEHMET ALI AYDINLAR
UNIVERSITY



Resection vs. RFA in HCC

Metaanalysis – 1000 Patients

JOURNAL OF HEPATOLOGY



Cuccetti et al, J Hepatol 2013



Resection vs. RFA in HCC

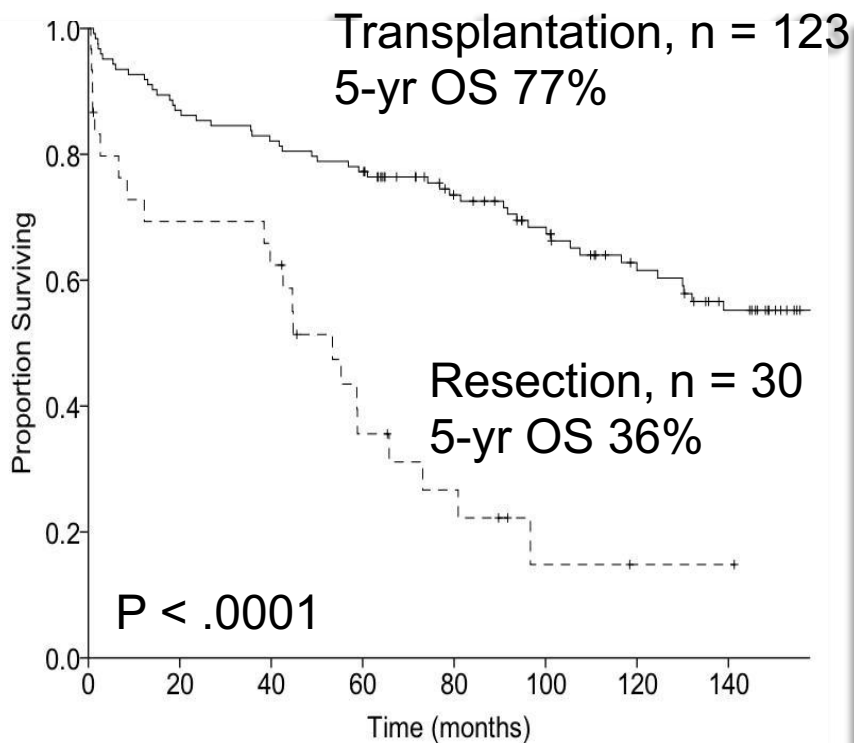
Resection – Survival benefit single lesion > 2cm

| | HR (n = 1000) | RFA (n = 1000) | p value | Effect size |
|---|---------------|----------------|---------|-------------|
| All Milan | | | | |
| Life-expectancy (yr) | 6.97 (0.44) | 6.61 (0.52) | <0.001 | 0.747 |
| Proportion optimal strategy (%)* | 70.3 | 29.7 | <0.001 | 0.889 |
| Costs (€) | 9841 (720) | 5627 (535) | <0.001 | 6.643 |
| Quality-adjusted life-expectancy (QALY) | 5.10 (0.41) | 4.80 (0.45) | <0.001 | 0.697 |
| Cost-effectiveness (€/QALY) | 1938 (179) | 1181 (137) | <0.001 | 4.749 |
| Single nodule ≤2 cm | | | | |
| Life-expectancy (yr) | 8.18 (0.80) | 8.28 (0.72) | <0.001 | -0.131 |
| Proportion optimal strategy (%)* | 47.3 | 52.7 | 0.016 | -0.108 |
| Costs (€) | 10,465 (820) | 6499 (614) | <0.001 | 5.475 |
| Quality-adjusted life-expectancy (QALY) | 5.97 (0.64) | 6.04 (0.60) | 0.006 | -0.113 |
| Cost-effectiveness (€/QALY) | 1768 (180) | 1083 (120) | <0.001 | 4.478 |
| Single nodule ≤3 cm | | | | |
| Life-expectancy (yr) | 7.96 (0.37) | 6.82 (0.42) | <0.001 | 2.880 |
| Proportion optimal strategy (%)* | 97.7 | 2.3 | <0.001 | 6.364 |
| Costs (€) | 10,292 (832) | 5494 (510) | <0.001 | 6.953 |
| Quality-adjusted life-expectancy (QALY) | 5.86 (0.43) | 4.98 (0.40) | <0.001 | 2.119 |
| Cost-effectiveness (€/QALY) | 1762 (176) | 1108 (122) | <0.001 | 4.319 |
| Single nodule 3.1-5.0 cm | | | | |
| Life-expectancy (yr) | 6.16 (0.73) | 4.61 (0.36) | <0.001 | 2.693 |
| Proportion optimal strategy (%)* | 97.8 | 2.2 | <0.001 | 6.517 |
| Costs (€) | 9326 (753) | 4503 (377) | <0.001 | 8.099 |
| Quality-adjusted life-expectancy (QALY) | 4.50 (0.56) | 3.35 (0.31) | <0.001 | 2.541 |
| Cost-effectiveness (€/QALY) | 2097 (246) | 1356 (145) | <0.001 | 3.670 |
| Two-three nodules ≤3 cm | | | | |
| Life-expectancy (yr) | 5.36 (0.71) | 5.39 (1.22) | 0.404 | -0.030 |
| Proportion optimal strategy (%)* | 48.6 | 51.4 | 0.211 | -0.056 |
| Costs (€) | 8936 (767) | 4774 (627) | <0.001 | 5.941 |
| Quality-adjusted life-expectancy (QALY) | 3.95 (0.54) | 3.99 (0.88) | 0.186 | -0.055 |
| Cost-effectiveness (€/QALY) | 2293 (287) | 1235 (219) | <0.001 | 4.145 |

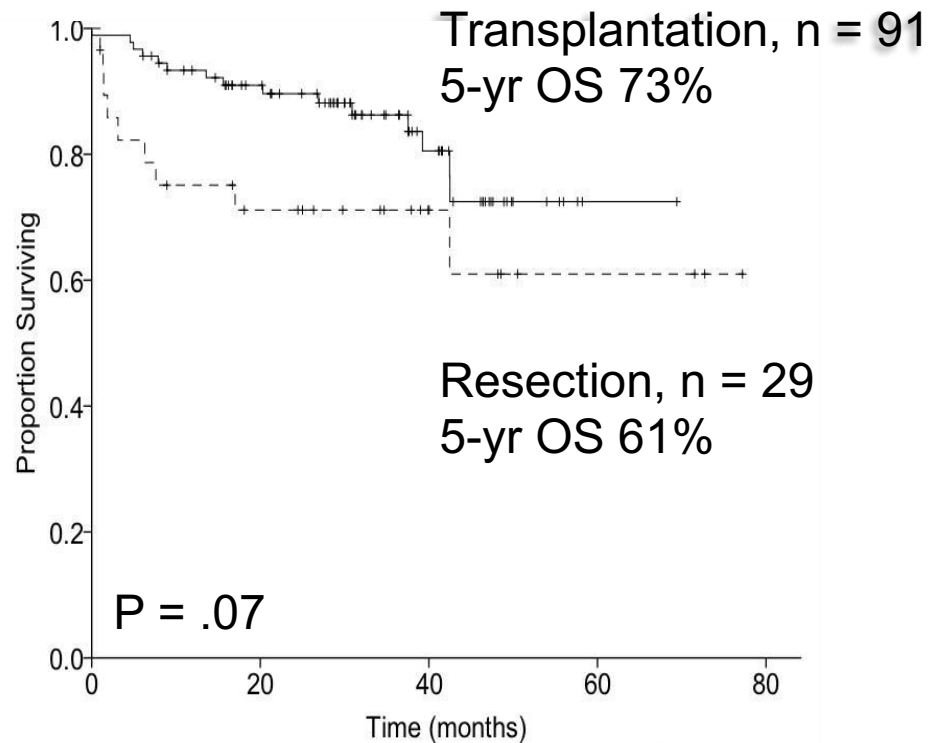
Cuccetti et al, J Hepatol 2013

Resection vs. Transplantation (HCC within Milan)

BACKGROUND



Era 1989 – 2004



Era 2005 – 2011

Andreou et al., J Gastrointestinal Surg 2018

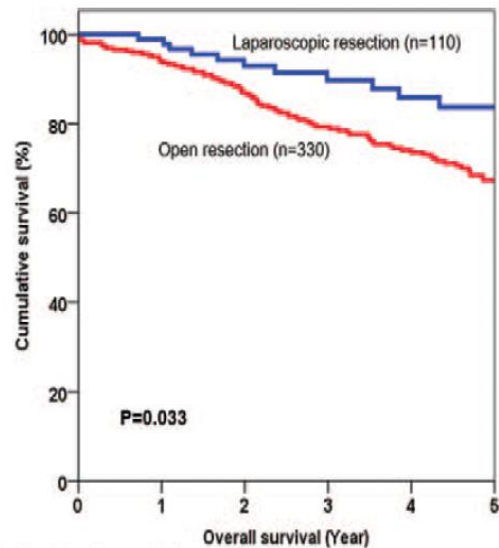


Lap. Liver resection in cirrhotic HCC

1:3 Propensity score matching 110 (lap) vs. 330 (open)

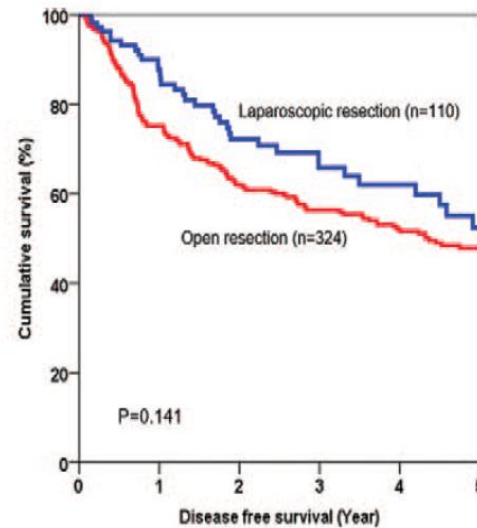
Lap. Liver Surgery:

- Bloodloss
- Hospital Stay
- Morbidity
- 30-d Mortalität



No. of patients at risk:

| | 0 | 1 | 2 | 3 | 4 | 5 |
|------------------------------|-----|-----|-----|-----|-----|-----|
| Laparoscopic Liver Resection | 110 | 90 | 69 | 53 | 42 | 32 |
| Open Liver Resection | 330 | 281 | 237 | 190 | 157 | 124 |



No. of patients at risk:

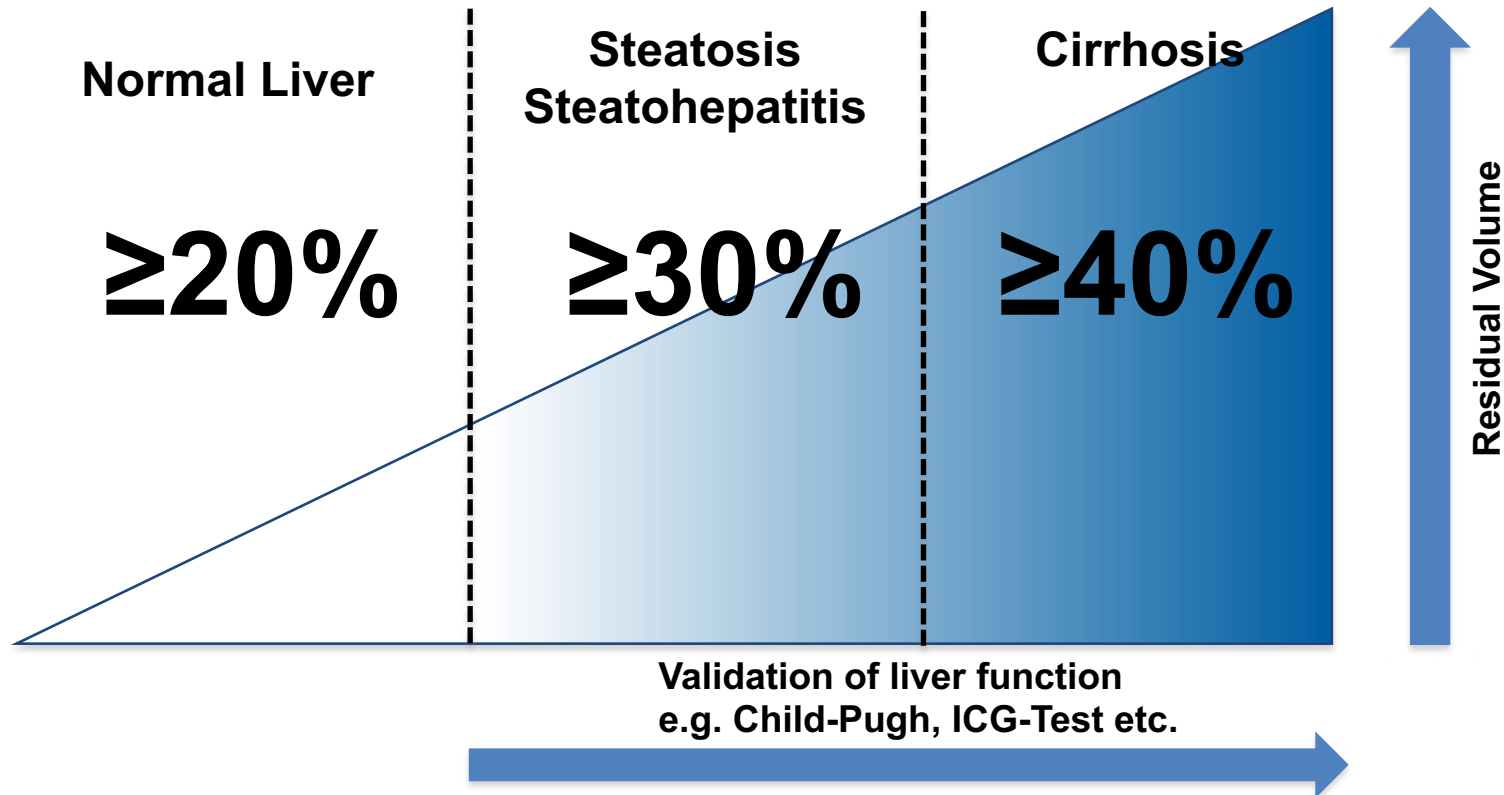
| | 0 | 1 | 2 | 3 | 4 | 5 |
|------------------------------|-----|-----|-----|-----|-----|----|
| Laparoscopic Liver Resection | 110 | 79 | 53 | 38 | 29 | 20 |
| Open Liver Resection | 324 | 221 | 163 | 128 | 106 | 82 |

Improvement of Surgical Outcome in cirrhotic HCC patients via laparoscopic resection

Cheung et al. Ann Surg 2016, Sotiropoulos et al. Metaanalysis 2017

Required liver volume for resection

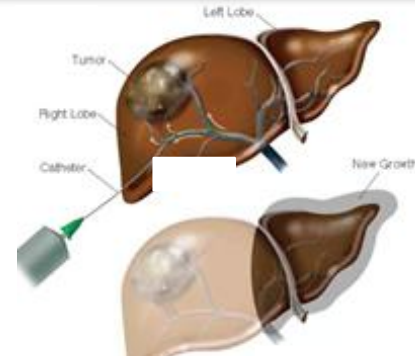
Liver volume needed depending on state of the liver



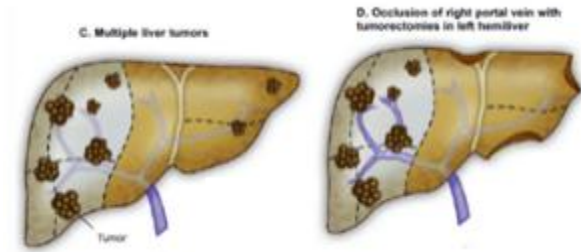
Asencio JM et al., J Hepatobiliary Pancreat Sci 2014;
Guglielmi A et al., Dig Surg 2012

Options to increase resectability rate

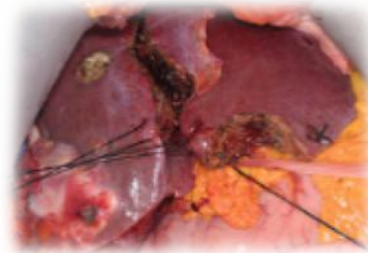
1. PV & HV Embolisation



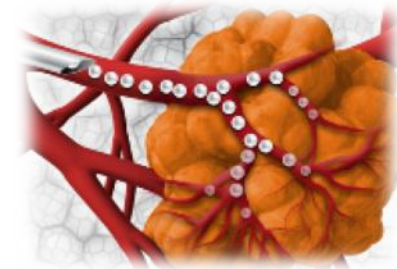
2. Portal vein ligation



3. ALPPS

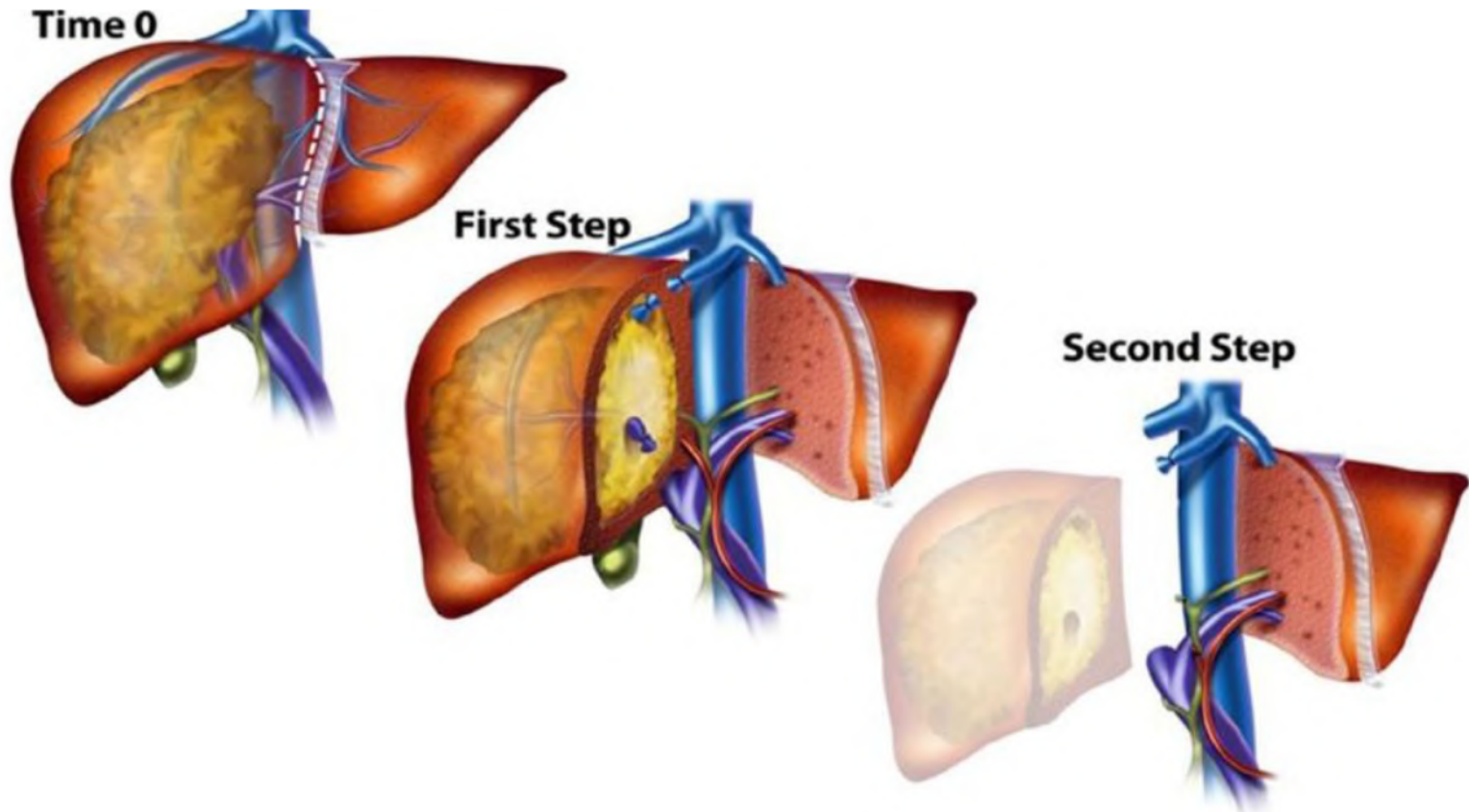


4. SIRT/TARE

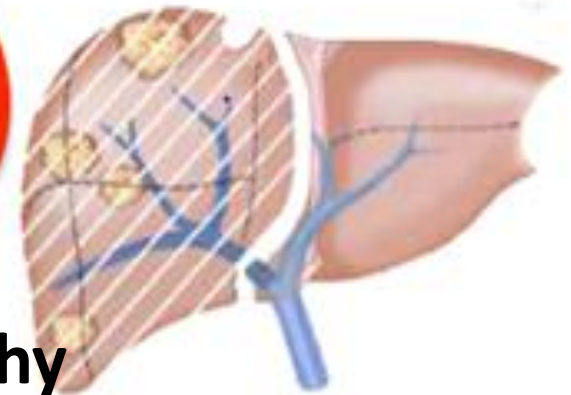
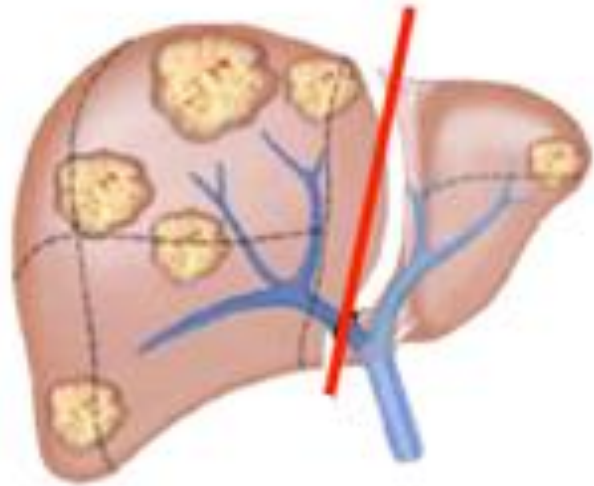


Increase of resectability by ALPPS

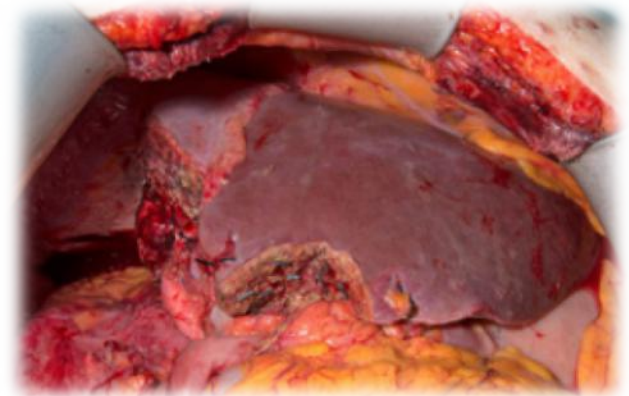
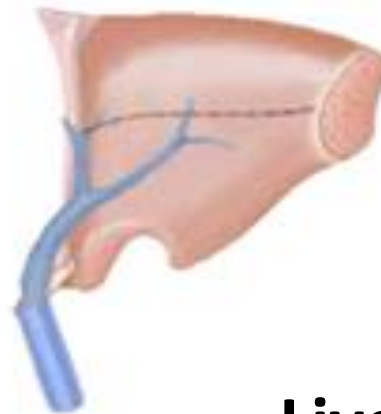
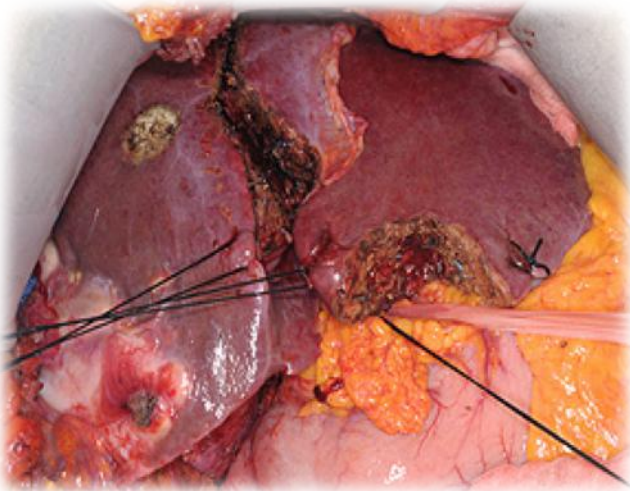
Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy



ALPPS – Surgical technique



Hypertrophy



Liver resection

ALPPS – First description

Right Portal Vein Ligation Combined With In Situ Splitting Induces Rapid Left Lateral Liver Lobe Hypertrophy Enabling 2-Stage Extended Right Hepatic Resection in Small-for-Size Settings

Andreas A. Schnitzbauer, MD, Sven A. Lang, MD,* Holger Goessmann, MD,† Silvio Nadalin, MD,§ Janine Baumgart, MD,|| Stefan A. Farkas, MD,* Stefan Fichtner-Feigl, MD,* Thomas Lorf, MD,¶ Armin Goralcyk, MD,¶ Rüdiger Hörbelt, MD,# Alexander Kroemer, MD,* Martin Loss, MD,* Petra Rümmele, MD,‡ Marcus N. Scherer, MD,* Winfried Padberg, MD,# Alfred Königsrainer, MD,§ Hauke Lang, MD,|| Aiman Obed, MD,¶ and Hans J. Schlitt, MD**

Retrospective Analysis

CRLM n = 14

Other entities n = 11

Waiting period:

9 days (range = 5 – 28 days)

CT volumetry left lateral lobe

Before: 310 ml (range: 197 – 444 mL)

After: 536 ml (range: 273 – 881 mL)

Volume increase = 74% (range: 21% to 192%)

Schnitzbauer et al. Annals of Surgery 2012



Case presentation ALPPS

58 year-old male patient

HCC of the right liver (Seg. V)

Unilocular, 3.2 cm large lesion

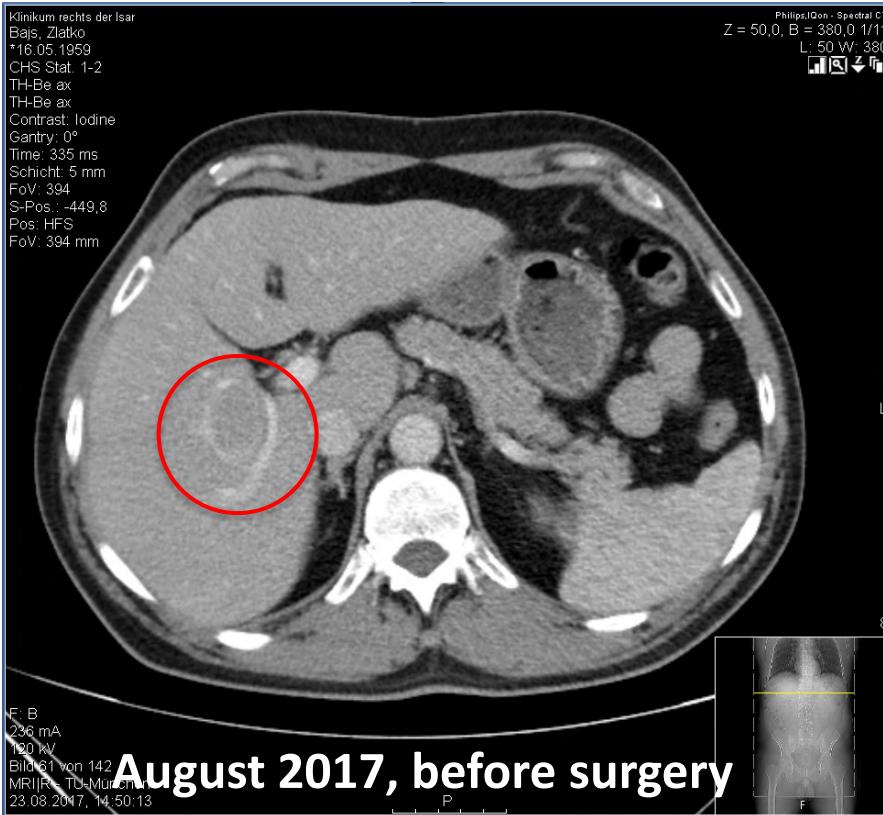
Relevant secondary diagnoses:

- Hepatitis C
- Diabetes mellitus II
- Arterial hypertension

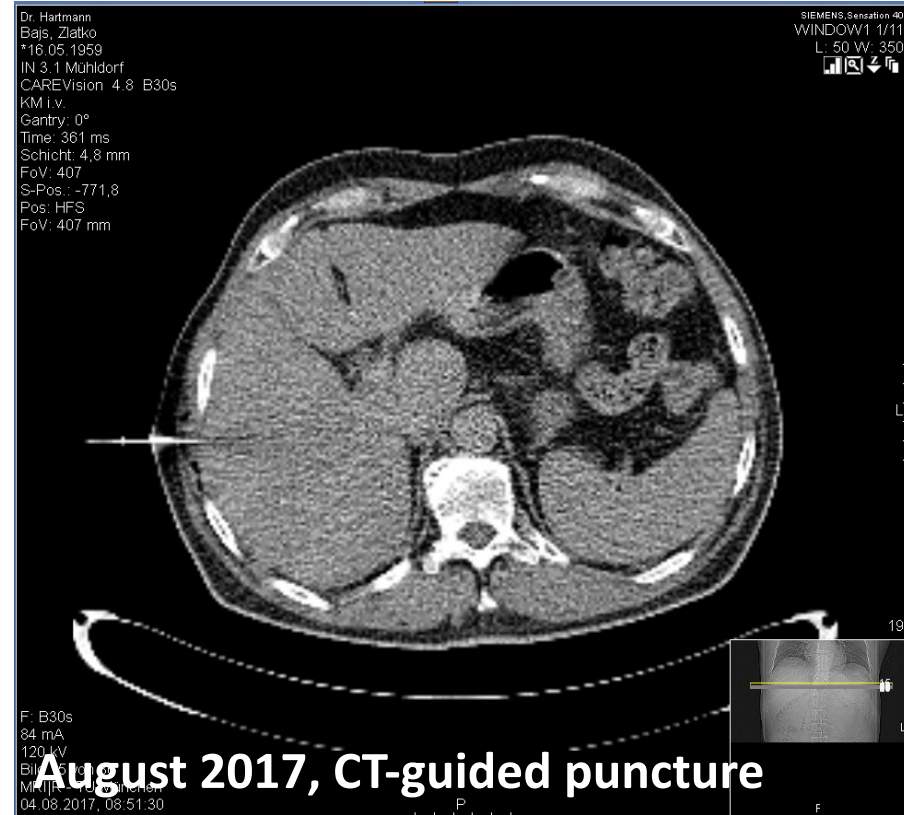
Interdisciplinary tumor board consent September 2017

--> Primary resection by right hemihepatectomy

3. Case presentation ALPPS



August 2017, before surgery



August 2017, CT-guided puncture

CT-guided puncture for histology of central single site lesion

Planned surgical approach: Right Hemihepatectomy

3. Case presentation ALPPS

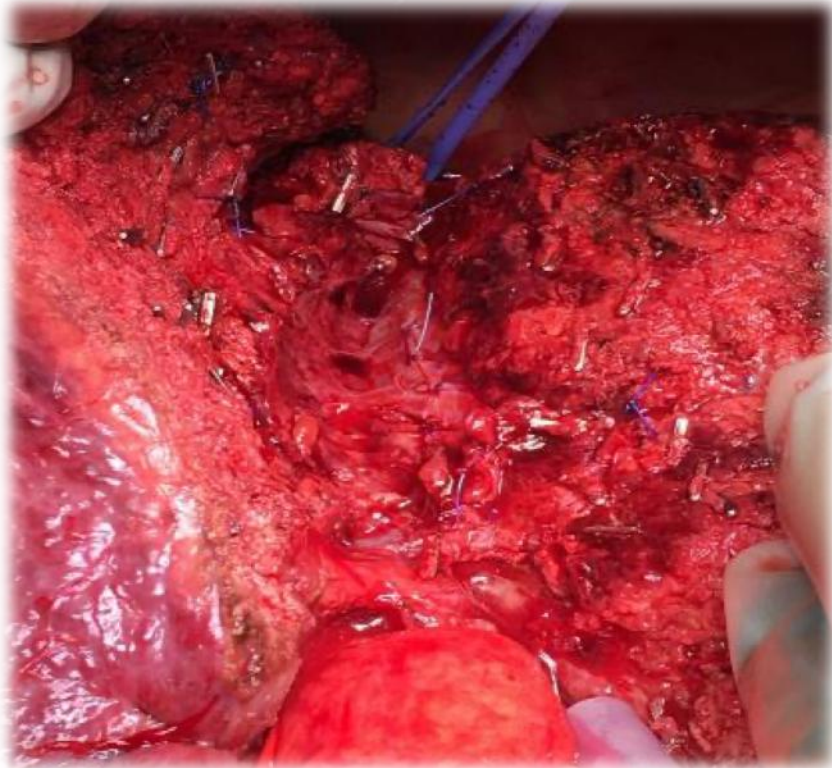
CT scan with volumetry preoperatively

| Leber | | | | |
|---------------------|-----|------------------------|------------------------|--------------------------|
| Leber: | 31% | Volumen | | % des Gesamtvol. |
| Leber funktionell | | 1525.9 cm ³ | | 98.1% |
| Leber insgesamt | | 1555.8 cm ³ | | 100.0% |
| Segmente | | | | |
| Segmente: | 50% | Funktionelles Volumen | | % des funktionellen Vol. |
| Segment 1 | 50% | 4.3 cm ³ | | 0.3% |
| Segment 2 | 50% | 181.9 cm ³ | 331.1 cm ³ | 11.9% |
| Segment 3 | 50% | 149.1 cm ³ | | 9.8% |
| Segment 4 | 50% | 164.8 cm ³ | | 10.8% |
| Segment 5 | 50% | 156.3 cm ³ | 340.2 cm ³ | 10.2% |
| Segment 8 | 50% | 183.8 cm ³ | | 12.0% |
| Segment 6 | 50% | 338.9 cm ³ | 683.0 cm ³ | 22.2% |
| Segment 7 | 50% | 344.1 cm ³ | | 22.6% |
| | | | 495.9 cm ³ | 32.5% |
| | | | 1023.2 cm ³ | 67.1% |
| Gefäße | | | | |
| Gefäße: | 50% | Volumen | | % des Gesamtvol. |
| Pfortader | 0% | 8.3 cm ³ | 29.9 cm ³ | 0.5% |
| Nicht klassifiziert | 0% | 21.6 cm ³ | | 1.4% |

Functional volume **left liver** 495,9 cm³, Percentage of funct. vol. **32.5 %**

Functional volume **right liver** 1,023.2 cm³, Percentage of funct. vol. **67,1 %**

3. Case presentation ALPPS



Intraoperative challenges:

- **Unexpected liver cirrhosis**
- **Relative small size of the left liver**

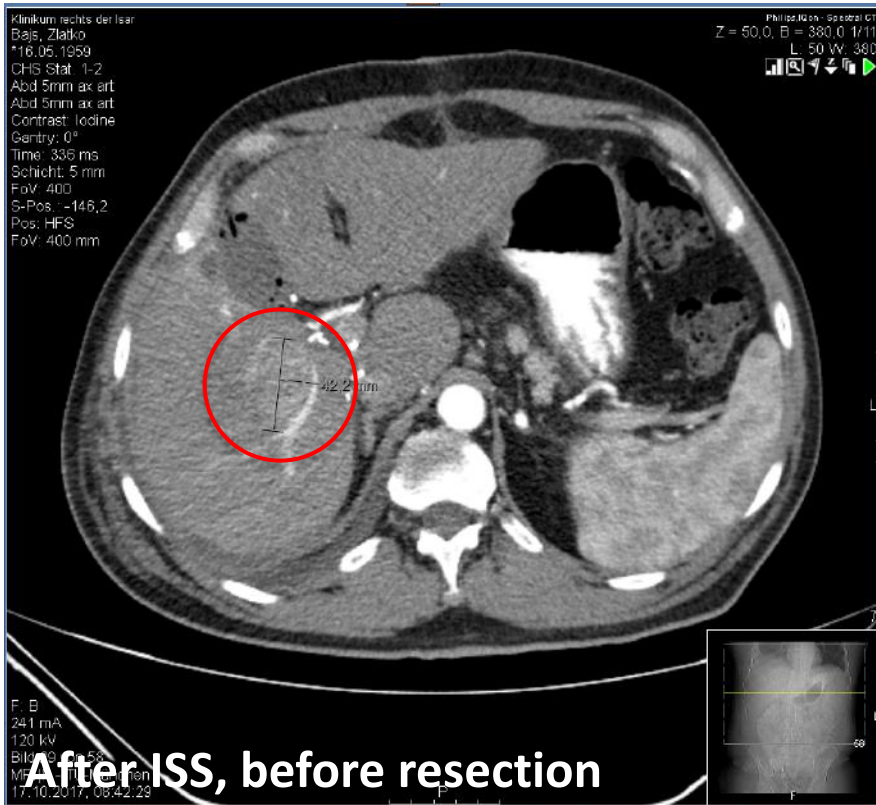
Individual approach

→ **ALPPS-Procedure**

In-situ split of the liver with ligation of the right portal vein and cholecystectomy (ALPPS procedure) on October 10, 2017

3. Case presentation ALPPS

Case presentation



CT scan with volumetry on postoperative day 7 after ALPPS

3. Case presentation ALPPS

CT scan with volumetry on postoperative day 7 after in-situ split of the liver with ligation of the right portal vein for induction of hypertrophy

| Leber | | | |
|--------------------------|-----|------------------------|----------------------|
| Leber: | 31% | Volumen | % des Gesamtvolumens |
| Leber funktionell | | 1660.3 cm ³ | |
| Leber insgesamt | | 1672.9 cm ³ | |
| Segmente | | | |
| Segmente: | 50% | Funktionelles Volumen | % des Gesamtvolumens |
| Lateraler linker Lappen | 50% | 563.6 cm ³ | |
| Medialer linker Lappen | 50% | 210.4 cm ³ | |
| Medialer rechter Lappen | 50% | | |
| Lateraler rechter Lappen | 50% | | |
| Gefäße | | | |

Increase of the left cirrhotic liver volume from 32.5% to 46.6% within only 7 days!



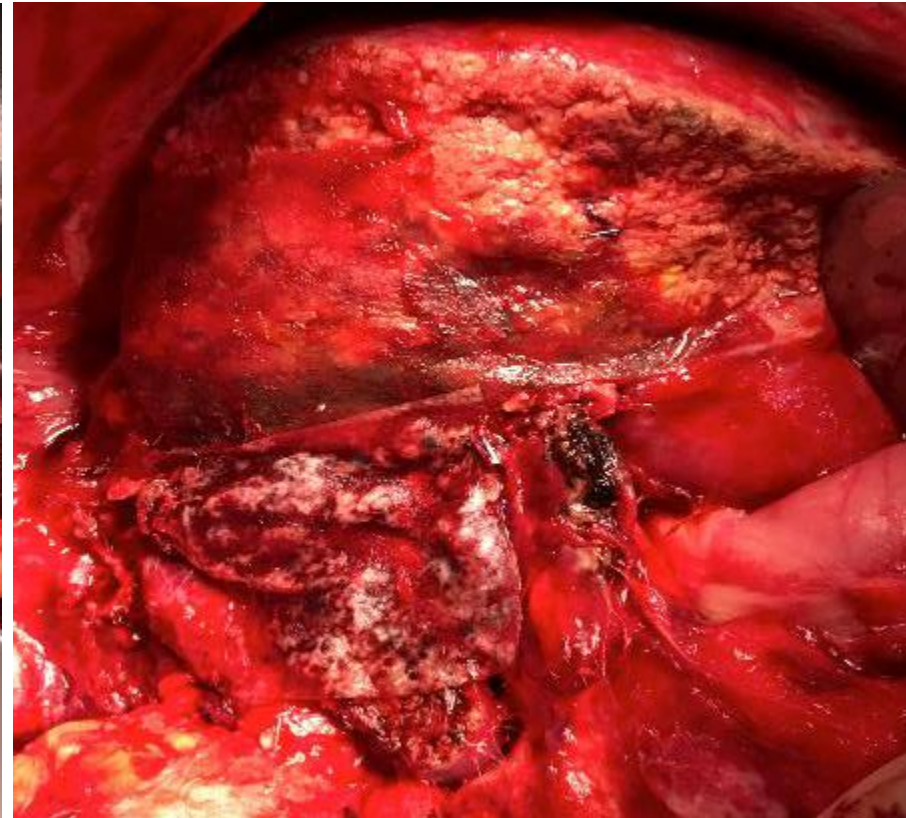
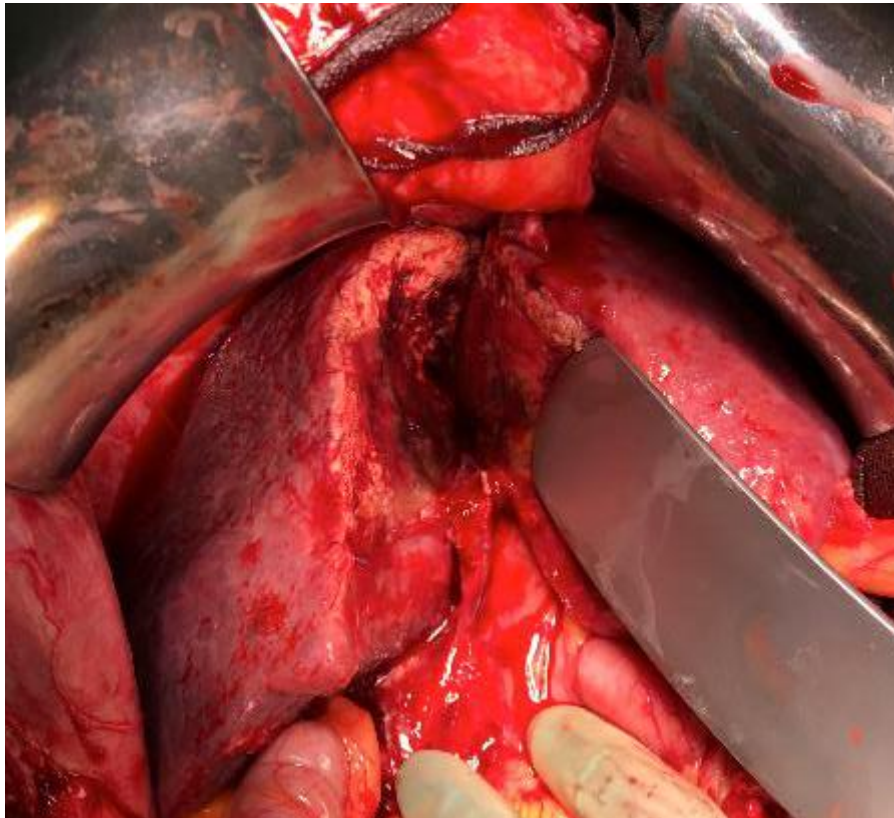
Volume **left liver** 774 cm³

Percentage of functional volume **46.6 %**

Functional volume **right liver** 886.3 cm³

Percentage of functional volume **53.4 %**

3. Case presentation ALPPS



Completion right hepatectomy after ALPPS procedure

(after 10 days) on October 20, 2017

Two-Stage-Hepatectomy vs. ALPPS

Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases

R. Adam^{1,2,4}, K. Imai^{1,2,5}, C. Castro Benitez^{1,2,4}, M.-A. Allard^{1,2,4}, E. Vibert^{1,3,4}, A. Sa Cunha^{1,2,4}, D. Cherqui^{1,3,4}, H. Baba⁵ and D. Castaing^{1,3,4}

All consecutive patients 2010-2014 with TSH or ALPPS

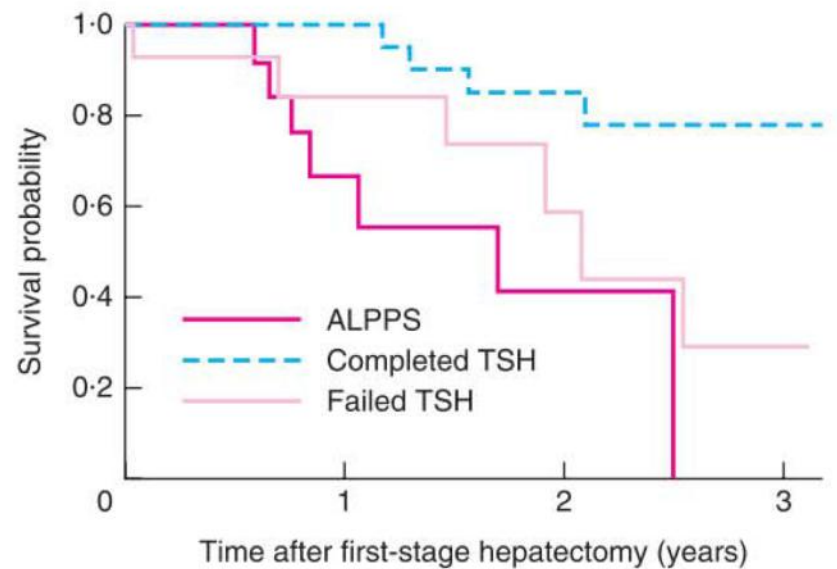
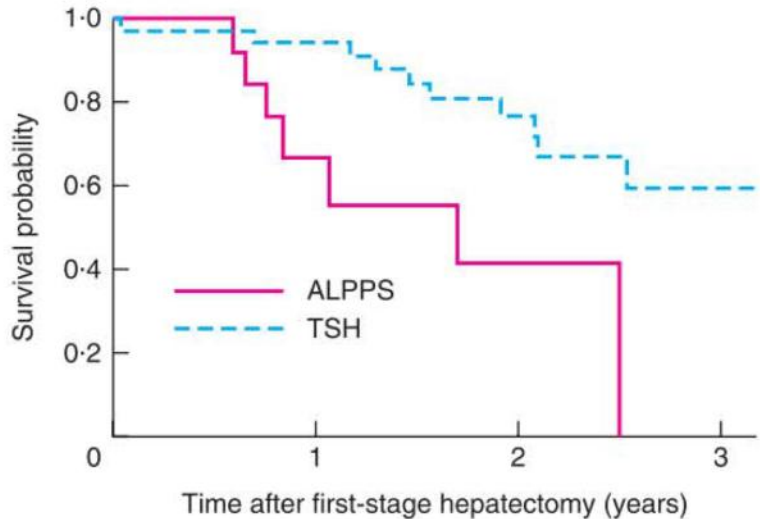
41 TSH (15 not completed) vs. 17 ALPPS (all completed)

- **90d mortality** TSH 5% vs. 0% ALPPS (n.s.)
- **Clavien Dindo ≥ 3** TSH 39% vs. 41 ALPPS (n.s.)
- **Blood loss** TSH 500ml vs. 1000ml ALPPS (p<0.02)

Adam R et al., BJS 2016



Two-Stage-Hepatectomy vs. ALPPS



| No. at risk | 0 | 1 | 2 | 3 |
|-------------|----|----|----|---|
| ALPPS | 17 | 6 | 2 | 0 |
| TSH | 41 | 31 | 16 | 5 |

Completion of the ALPPS procedure is safe, but does not lead to a better oncological outcome!!!

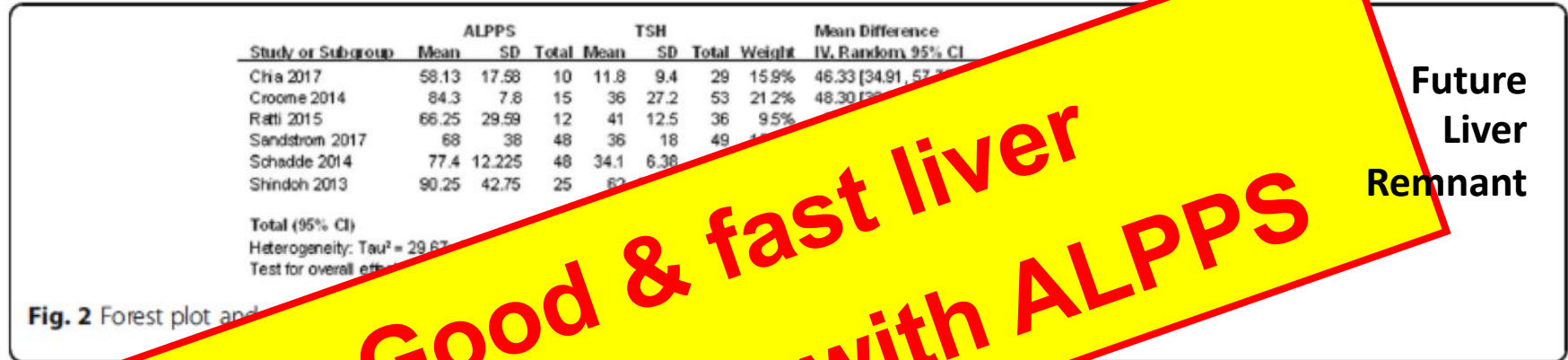
Adam R et al., BJS 2016

Two-Stage-Hepatectomy vs. ALPPS

Meta-Analysis

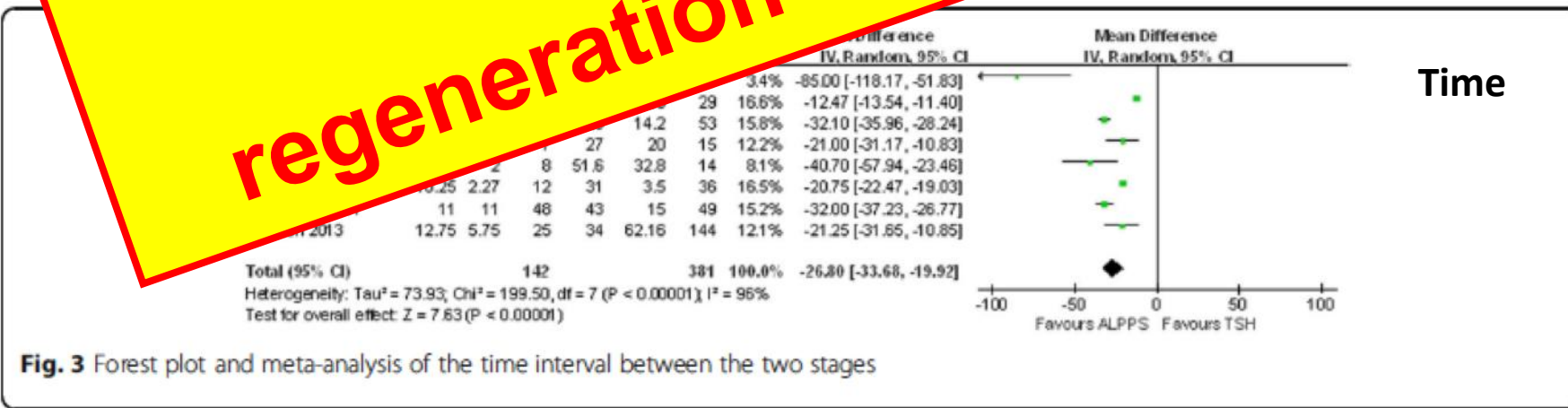
10 studies, 719 patients

Background



Future Liver Remnant

Good & fast liver regeneration with ALPPS



Time

Two-Stage-Hepatectomy vs. ALPPS

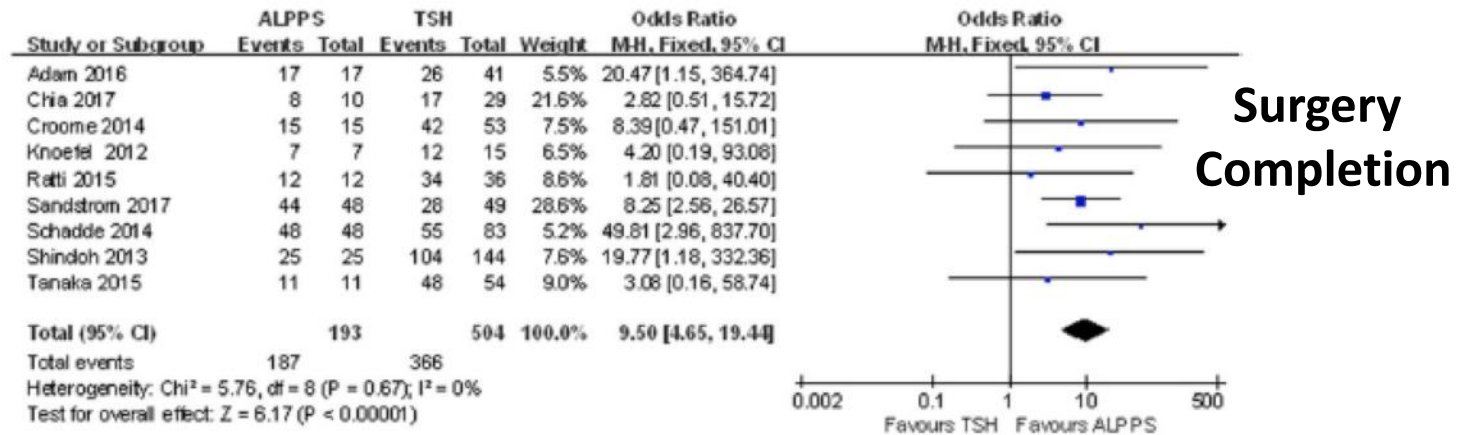


Fig. 4 Forest plot and meta-analysis of the second surgery completion rate

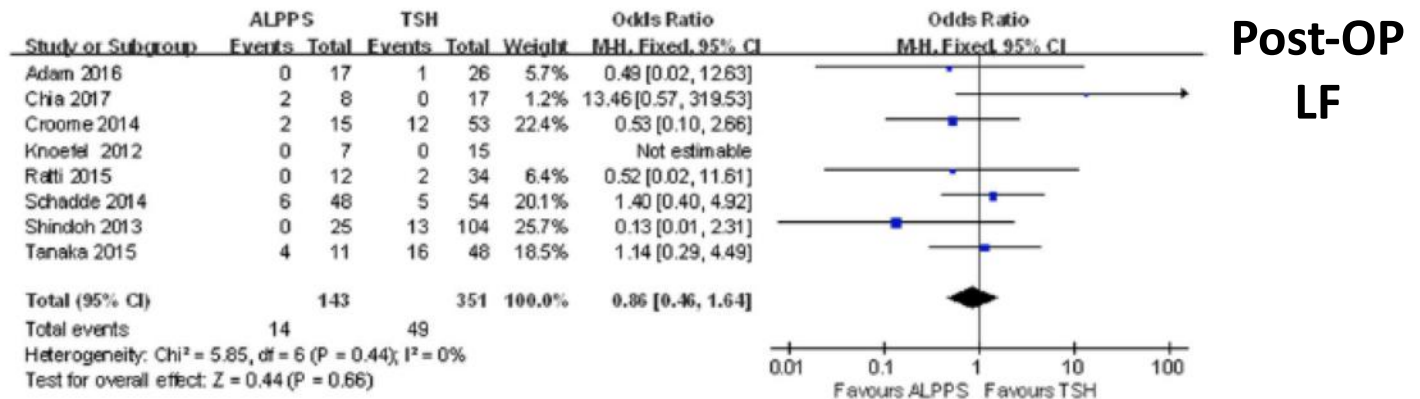


Fig. 9 Forest plot and meta-analysis of the postoperative liver failure rate in patients after stage 2 operation

Two-Stage-Hepatectomy vs. ALPPS

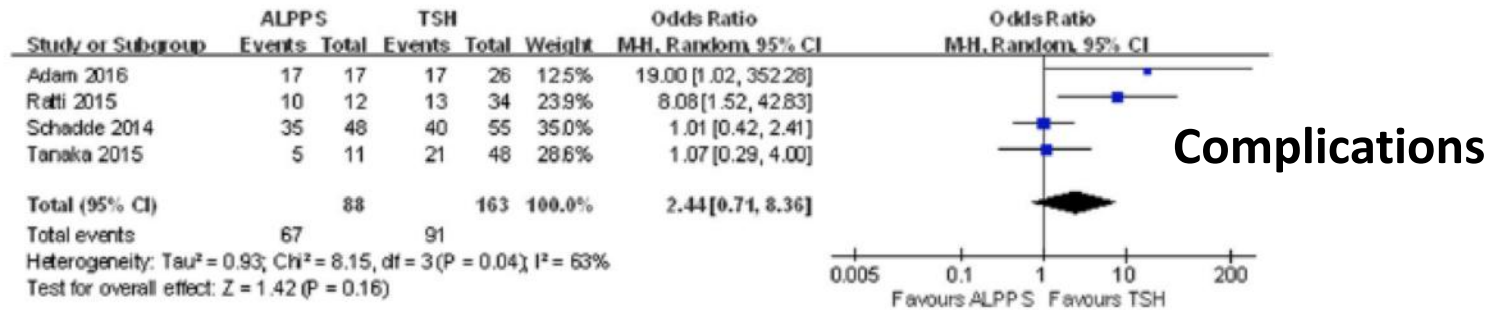


Fig. 7 Forest plot analysis of postoperative complications in patients after stage 2 operation

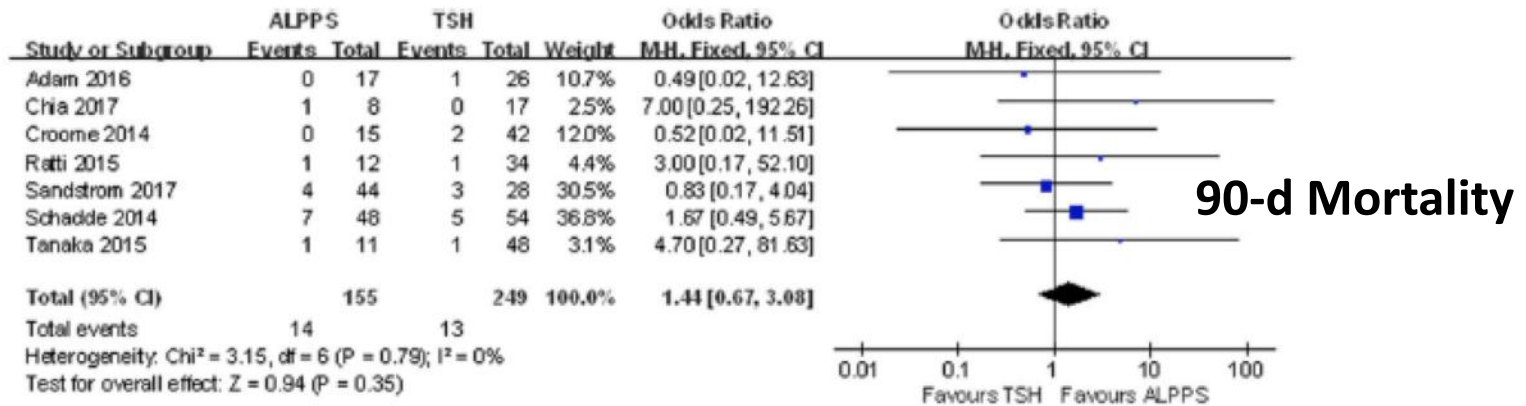


Fig. 14 Forest plot and meta-analysis of 90-day mortality after stage 2 operation

Zhou Z. et al., World J Surg Oncol 2017

Two-Stage-Hepatectomy vs. ALPPS

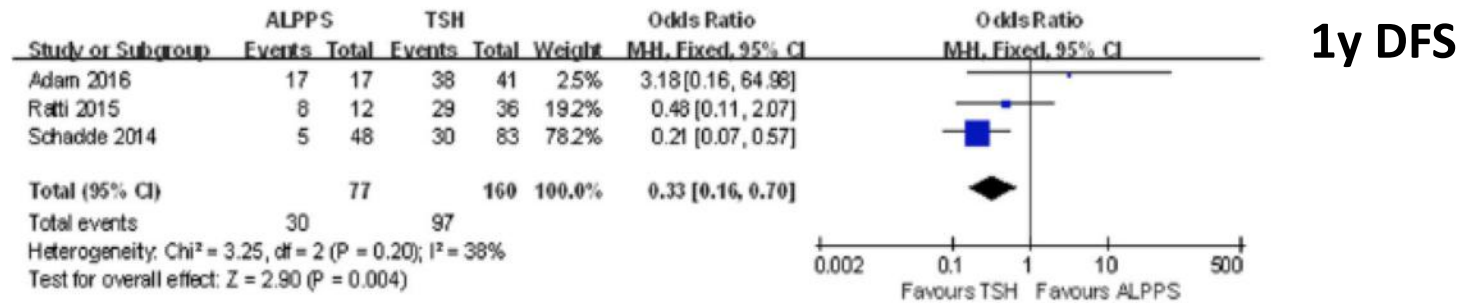


Fig. 13 Forest plot and meta-analysis of 1-year disease-free survival

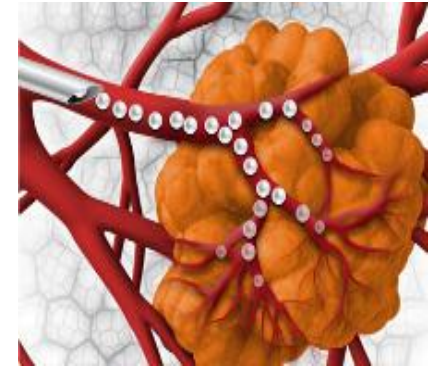
Completion of the ALPPS procedure is safe, but does not lead to a better oncological outcome!!!

Due to its speed no biological selection is possible...

Zhou Z. et al., World J Surg Oncol 2017

Selective internal radiation therapy

- **SIRT** a form of radiation therapy
- Also called **radioembolization** as it combines radiotherapy with embolization.
- **Microspheres of radioactive material** are injected into arteries that supply the tumor.



| Agents | Explanation |
|------------------------------|--|
| Resin with bound yttrium | SIR-Spheres, Diameter 20-60 μm , Activity per particle 50 Bq, Number of microspheres injected 40-80 million |
| Glass with yttrium in matrix | Therapheres, Diameter 20-30 μm , Activity per particle 25000 Bq, Number of microspheres injected 1.2 million |

Kennedy et al. Int J Radiat Oncol Biol Phys 2007

Approach SIRT for liver hypertrophy

A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90

Jin-Yao Teo¹, John C. Allen Jr.², David C. Ng³, Su-Pin Choo⁴, David W.M. Tai⁴, Jason P.E. Chang⁵, Foong-Khoon Cheah⁶, Pierce K.H. Chow^{1,2} & Brian K.P. Goh^{1,2}

¹Department of Hepatopancreatobiliary and Transplantation Surgery, Singapore General Hospital, ²Duke-NUS Graduate Medical School Singapore, ³Department of Nuclear Medicine, Singapore General Hospital, ⁴Division of Medical Oncology, National Cancer Center Singapore, ⁵Department of Gastroenterology and Hepatology, and ⁶Department of Radiology, Singapore General Hospital, Singapore

Aim: Systematic review of the literature to analyse **contralateral liver hypertrophy after unilobar SIRT**

- **7 retrospective studies reporting on 312 patients** for HCC (n = 215), CCC (n = 12), liver metastasis (n = 85)

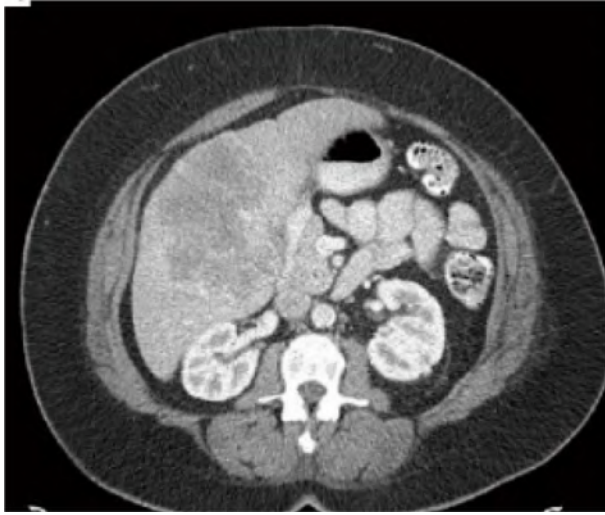
Teo et al., HPB 2016



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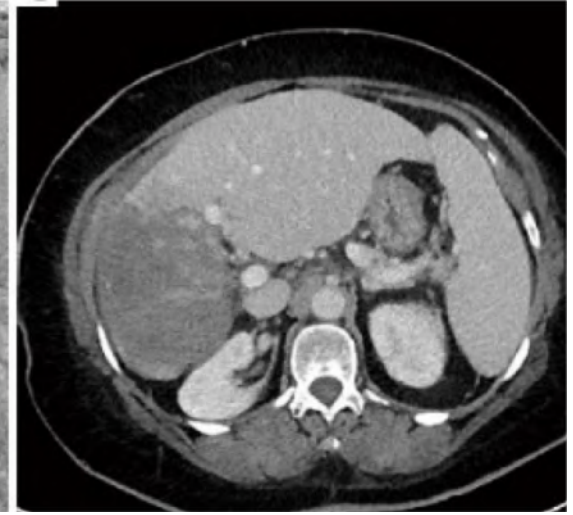
Approach SIRT for liver hypertrophy



CT prior to SIRT



Angiogram of SIRT



CT 3 years after SIRT

**SIRT significantly increased
liver hypertrophy**

Wang et al J Gastrointest Oncol 2017

Approach SIRT for liver hyp... hypertrophy

| Paper | Number of patients | Age | Pathology treated | SIRT | to treatment | Percentage hypertrophy (mean/median (range)) |
|---|--------------------|-----|---------------------------------|----------------------|------------------------------|--|
| Ahmadzadehfar et al. 2013 Germany ¹³ | 24 | M | | | Mean 44 days, median 36 days | Mean 47%, median 34% |
| | | | 67 HCC, 8 IHC, 8 CRC metastases | Glass microspheres | 23 right, 11 left | |
| | | | | 4 resin microspheres | Single | |
| Theysohn et al. 2013 Germany ¹⁶ | 45 | | | | | Mean 45% |
| | | | | | Single MRI | Median 46 days (27-79 days) |
| Teo et al. 2016 Singapore | | | | | Single CT | Median 5 months |
| | | | | Resin microspheres | Right lobe | Single |

Liver hypertrophy after SIRT up to 29-57%, but it takes longer...!!

Attractive: longlasting intrahepatic oncological therapy in the waiting time...!!

Background

CONCLUSION

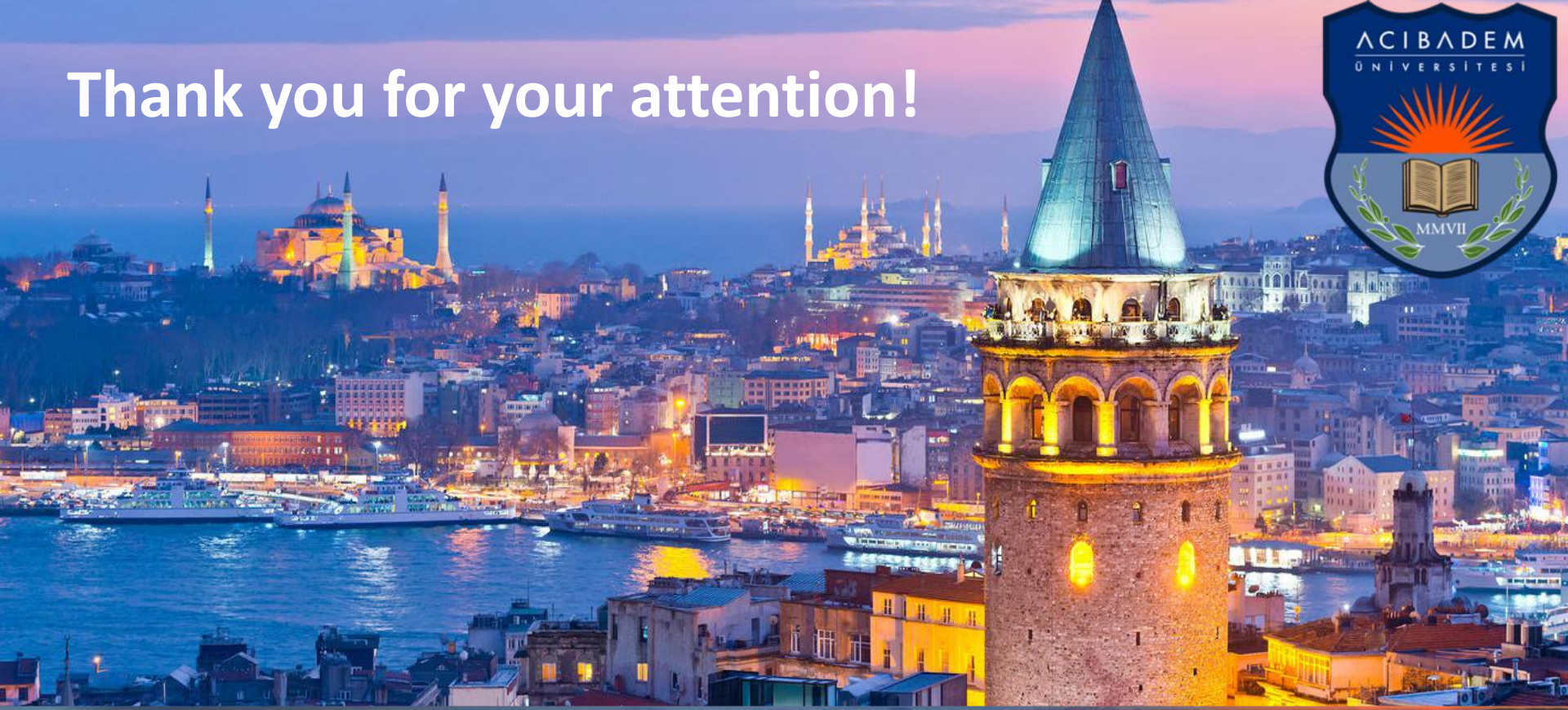
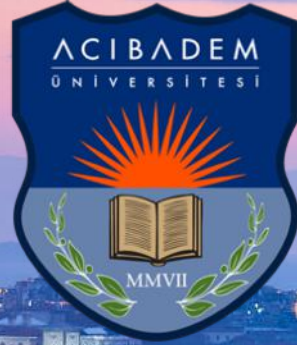
Liver transplantation is still the standard therapeutic option in advanced chronic

Due to lack of organs –
surgery is arising as a good
bridging therapy option...!

Disciplinary approach
Importance of surgery is steadily
increasing...



Thank you for your attention!



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