Current trends in liver transplantation

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Head of abdominal surgery
Professor
Geneva University Hospitals
University of Geneva

Lausanne, January 2019
Current trends

Swiss donors

Geneva recipients

DCD and machine perfusion

Transplant oncology

swisstransplant.org
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Dead on arrival (irreversible cardiac arrest on the street)</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Type II</td>
<td>Unsuccessful resuscitation (includes patients brought into the emergency room while being resuscitated by the ambulance crew)</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Type III</td>
<td>Imminent cardiac arrest in intensive care (ventilator switch-off)</td>
<td>Controlled</td>
</tr>
<tr>
<td>Type IV</td>
<td>Cardiac arrest during or after the brain death diagnostic procedure</td>
<td>Controlled</td>
</tr>
<tr>
<td>Type V</td>
<td>Unexpected cardiac arrest in intensive care</td>
<td>Uncontrolled</td>
</tr>
</tbody>
</table>
DCD – Maastricht 3 protocole National (sans ECMO-R)
(Un centre ne peut exiger d'un autre centre le recourt à l'ECMO)

Ischémie chaude fonctionnelle
Max 120 minutes

Phase d'hypotension
~ 100 min

PAM < 50 mmHg
(2 min consécutives)

Phase d'arrêt circulatoire
~ 20 min

Temps d'attente
5 min

Max
Foie : 40 min + ~ 20 min ≤ 60 min
Pancréas : 30 min + ~ 20 min ≤ 50 min
Poumons :
Reins :

Ischémie froide
Max
Foie + pancréas : 8 heures
Poumons :
Reins : 18 heures

Arrêt du traitement, y compris extubation

Arrêt circulatoire

Perfusion froide

Asystolie
ETT

Constatation de la Mort cérébrale
2 médecins (ASSM)

Transplantation
• DCD donors now represent 27% of the donors in Switzerland
• At increased risk of delayed graft function
  (≈20-30% without machine perfusion)
• At increased risk of ischemic cholangiopathy
  (≈30% without machine perfusion)
Donor:
- Age < 70 years,
- BMI < 25-30
- Functional warm ischemia: < 30 min
- No chronic liver disease (steatosis < 20%)
- AST/ALT < 4N et/ou profil +++
- Heparine +++
- CIT < 8h +++

Recipient:
- Age < 66 years
- First transplant,
- No major co-morbidity or prior surgery
- MELD < 25
Machine perfusion

- HOPE: Hypothermic Oxygenated Perfusion
- NMP: Normothermic Machine Perfusion
- NRP: Normothermic Regional Perfusion (ECMO in donor)
HOPE for human liver grafts obtained from donors after cardiac death

Philipp Dutkowski¹, Andrea Schlegel¹, Michelle de Oliveira¹, Beat Müllhaup², Fabienne M.²

First Comparison of Hypothermic Oxygenated Liver Donation

Static Cold Storage of Human Donation

Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death

R. van Rijn¹, N. Karimian¹, A. P. M. Matron¹, L. C. Burlage¹, A. C. Westerkamp¹, A. P. van den Berg³, R. H. J. de Kleine¹, M. T. de Boer¹, T. Lissen¹ and R. J. Porte¹

UNOS, United Network for Organ Sharing; UW, University of Wisconsin

Received 01 May 2014, revised 21 July 2014 and

Research Article
Hypothermic machine perfusion in human

- Standard donors
- Perfusion after static preservation
- Dual (arterial and portal) perfusion
- Non-oxygenated perfusate
- 20 liver grafts

Guarrera et al. AJT 2010
Hypothermic machine perfusion in human

![Graph showing AST (U/ml) vs. POC (Postoperative Days) for HMP and CS.](image)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Machine perfusion (HMP)</th>
<th>Cold storage (CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary nonfunction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Early allograft dysfunction</td>
<td>1* (5%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Vascular complications (total)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic artery stenosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Biliary complications (total)</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Guarrera et al. AJT 2010
Hypothermic machine perfusion in human (marginal donors)

<table>
<thead>
<tr>
<th></th>
<th>Machine perfusion</th>
<th>Cold storage</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>31</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Primary nonfunction</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0.612</td>
</tr>
<tr>
<td>Early allograft dysfunction</td>
<td>6 (19%)</td>
<td>9 (30%)</td>
<td>0.384</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAT</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0.612</td>
</tr>
<tr>
<td>PVT</td>
<td>2 (6%)</td>
<td>0</td>
<td>0.492</td>
</tr>
<tr>
<td>Biliary complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile leak</td>
<td>1 (3%)</td>
<td>3 (10%)</td>
<td>0.354</td>
</tr>
<tr>
<td>Biliary stricture</td>
<td>3 (10%)</td>
<td>10 (33%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>2 (6%)</td>
<td>7 (23%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3 (10%)</td>
<td>8 (27%)</td>
<td>0.106</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>4 (13%)</td>
<td>5 (17%)</td>
<td>0.732</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>13.6 ± 10.9</td>
<td>20.1 ± 11.1</td>
<td>0.001</td>
</tr>
<tr>
<td>One year survival</td>
<td>26/31 (83.8%)</td>
<td>24/30 (80.0%)</td>
<td>0.761</td>
</tr>
</tbody>
</table>
HOPE in human

- DCD donors (n=8)
- Similar outcomes as with standard donors
- Median follow-up: 8 months
HOPE-treated DCD livers (n=25) vs. cold-stored DCD livers (n=25)

- ↓ peak ALT (1239 vs. 2065 U/L, p<0.02)
- ↓ IH cholangiopathy (0 vs. 22%, p<0.015)
- ↓ biliary complications (20 vs. 46%, p<0.042)
- ↓ graft failure, retransplant (0 vs. 18%, p<0.05)
- 1-year graft survival (90 vs. 69%, p<0.035)
Dual HOPE-treated DCD livers (n=10) vs. cold-stored DCD livers (n=20)
**Normothermic machine perfusion**

Recreate physiological environment

- Deliver oxygen
- Physiological temperature
- Provide nutrients

→ Allow normal metabolic activity
→ Avoid ischemia-reperfusion
→ Assess viability +++

Imber Cj, Am J Transpl 2002
St Peter SD, Br J Surg 2002
Reddy SP, Transplantation 2004
Normothermic machine perfusion

Testing the liver (>30g vs. <20g)

Sutton et al. PLOS one 2014
Op den Dries et al. AJT 2013
Normothermic machine perfusion of standard livers vs. cold-storage

Bral et al. AJT 2016
Selzner et al. Liver Transplant 2016
Ravikumar et al. AJT 2016
Randomized clinical trial: normothermic machine perfusion of standard livers vs. cold-storage

Number of livers randomized: $n = 335$

- Excluded $n = 1$
  (randomized in error: R&D not in place)

Allocated to NMP
$n = 170$

- Included $n = 137$
  - Excluded $n = 33$
    - DCD did not proceed $n = 17$
    - Non-consented recipient $n = 6$
    - Non-eligible donor organ $n = 8$
    - Other reasons $n = 2$

  Successfully transplanted $n = 121$
  Discarded $n = 16$

Allocated to SCS
$n = 164$

- Included $n = 133$
  - Excluded $n = 31$
    - DCD did not proceed $n = 20$
    - Non-consented recipient $n = 6$
    - Non-eligible donor organ $n = 4$
    - Other reasons $n = 1$

  Successfully transplanted $n = 101$
  Discarded $n = 32$

Nasralla et al. Nature 2018
Randomized clinical trial normothermic machine perfusion of standard livers vs. cold-storage

- DCD and DBD donors
- 50% ↓ peak ALT
- 50% ↓ organ discard
- 54% ↑ preservation time
- Similar bile duct complications, and graft and patient survival

Nasralla et al. Nature 2018
Warm vs. cold perfusion techniques to rescue rodent liver grafts

Andrea Schlegel, Philipp Kron, Rolf Graf, Philipp Dutkowski†, Pierre-Alain Clavien* †

Department of Surgery, University Hospital Zurich, Swiss HPB and Transplant Center, Zurich, Switzerland

Journal of Hepatology 2014 vol. 61  1267–1275
Normothermic Regional Perfusion

- Less expensive
- Can be applied early
DCD-Maastricht 3 protocole National avec ECMO régionale
(Un centre ne peut exiger d'un autre centre le recours à l'ECMO)

Ischémie chaude fonctionnelle
Max 120 minutes

Phase d'hypotension
~ 100 min
PAM < 50 mmHg
(2 min consécutives)

Temps d'attente
5 min

Max
Foie : 40 min + ~ 20 min ≤ 60 min
Pancréas : 30 min + ~ 20 min ≤ 50 min
Poumons : ≤ 120 min
Reins : ≤ 120 min

Min: 120 min Max: 240 min

Ischémie froide
Max 18 heures

Arrêt circulatoire
Canulation
Perfusion froide
Transplantation

Arrêt du traitement, y compris extubation
Normothermic Regional Perfusion (NRP)

Improving the Outcomes of Organs Obtained From Circulatory Death Donors Using Abdominal Normothermic Perfusion

E. Miñambres¹, B. Suberviola², B. Domínguez-Gil³, E. Rodrigo⁴, J. C. Ruiz-San Millan⁵, J. C. Rodríguez-San Juan⁶ and M. A. Baltazar²

In Situ Normothermic Regional Perfusion for Controlled Donation After Circulatory Death—The United Kingdom Experience

G. C. Oniscu¹*, L. V. Randle², P. Muiesan³, A. J. Butler⁴, J. S. Currie¹, M. T. P. R. Perera³, J. L. Forsythe¹ and C. J. E. Watson²

Abdominal regional in-situ perfusion in donor after circulatory determination of death donors

Amelia J. Hessheimer, Juan C. García-Valdecasas, and Constantino Fondevila

Purpose of review
Provide an overview regarding the current state of abdominal regional perfusion (ARP) in donors after circulatory determination of death (DCD) organ transplantation, including the principles behind ARP functions and the most recent results of its clinical application.

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doi: 10.1111/ajt.14214

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doi: 10.1111/ajt.12927

DCD/machine perfusion
Normothermic Regional Perfusion (NRP): UK DCD score

<table>
<thead>
<tr>
<th>Risk category</th>
<th>DCD NRP transplants</th>
<th>Ischaemic cholangiopathy</th>
<th>Primary non-function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High risk</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Futile transplants</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DCD, donation after circulatory death; NRP, normothermic regional perfusion.

16% 27%

Schlegel et al. J Hepatol 2018
Oniscu et al. J Hepatol 2018
Current strategy in Geneva

- DCD donor in Geneva
  → NRP (normothermic regional perfusion)
- Liver of a DCD donor offered to Geneva
  → Cold storage to Geneva followed by HOPE (hypothermic oxygenated perfusion)
Current trends

Swiss donors

Geneva recipients

Transplant oncology
Transplant oncology

• Primary liver cancer
  • Hepatocellular carcinoma
  • Intrahepatic cholangiocarcinoma
  • Combined hepatocellular-cholangiocarcinoma
  • Hepatic epithelioid hemangioendothelioma
  • Hepatoblastoma
• Bile duct cancer
  • Perihilar cholangiocarcinoma
• Secondary liver cancer
  • Colorectal liver metastases
  • Neuroendocrine tumor (NET) liver metastases
Transplantation for HCC

• Recipient characteristics
• Donor characteristics
Transplantation for cancer: HCC

- HCC unique ≤5 cm
- ≤3 HCC ≤3 cm
• Milan (1 HCC ≤5 cm; ≤3 HCCs ≤3 cm)
• Up-to-Seven (size + number ≤7)
• Total Tumor Volume (TTV ≤115 cm³)
• ASAN (size ≤5 cm, number ≤6)
• …
HCC biology

Doubling volume time (3 months)
Morphology

- Milan (1 HCC ≤5 cm; ≤3 HCCs ≤3 cm)
- Up-to-Seven (size + number ≤7)
- Total Tumor Volume (TTV ≤115 cm³)
- ASAN (size ≤5 cm, number ≤6)
- ...

Biology

- AFP
- DCP
- FDG uptake
- microvascular invasion
- HCC grade
- ...

Tx4Cancer
AFP model

<table>
<thead>
<tr>
<th>Variables</th>
<th>β coefficient</th>
<th>Hazard ratio</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Largest diameter, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3–6</td>
<td>0.272</td>
<td>1.31</td>
<td>1</td>
</tr>
<tr>
<td>&gt;6</td>
<td>1.347</td>
<td>3.84</td>
<td>4</td>
</tr>
<tr>
<td>Number of nodules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥4</td>
<td>0.696</td>
<td>2.01</td>
<td>2</td>
</tr>
<tr>
<td>AFP level, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>100–1000</td>
<td>0.668</td>
<td>1.95</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>0.945</td>
<td>2.57</td>
<td>3</td>
</tr>
</tbody>
</table>

Pinero et al. Liver Int 2016
Notarpace et al. J Hepatol 2016
Duvoux et al. Gastroenterology 2012
Total Tumor Volume /AFP

TTV ≤115 cm³
AFP ≤400 ng/ml

P=0.34

Toso et al. Hepatology 2015
Toso et al. Hepatology 2009
Toso et al. Liver Transplantation 2008
Downstaging patients outside transplant criteria
Inclusion criteria:
- single HCC ≤8 cm
- bifocal HCC ≤5 cm
- 3 to 6 HCCs ≤4 cm, and
  maximum total diameter of 12 cm

Downstaging success:
- within Milan criteria
- AFP <400 ng/ml
- stability for >3 months
Inclusion criteria:
• no restriction

Downstaging success:
• within TTV/AFP
• stability for >3 months

Downstaging: morphology

Survival since transplantation (months)

Patients alive without recurrence

n=0.258

Toso et al. Transplant Int 2018
Downstaging: biology

Listing AFP - last AFP
- under 400 ng/ml-under 400 ng/ml (n=1721)
- over400 ng/ml-under 400 ng/ml (n=86)
Waiting time should be

- Long enough to avoid transplanting patients with early and aggressive recurrences
- Not too long, in order to transplant (and save) patients with more indolent recurrences
- > 3 months

Toso et al. Transplant Int 2018
Too early for transplantation?

Transplantable HCC

- **TT_Dr**: HCC after Downstaging or Recurrent HCC < 2 years after curative treatment of any HCC
- **TT_PR**: Partial Response still vital tumor present after bridge therapy
- **TT_UT**: Un-Treatable but transplantable HCC due to severe ascites, not captured by MELD
- **TT_FR**: HCC >T1 at First presentation or Recurrent HCC >2 years after curative treatment
- **TT0_NT**: Sustained complete response (No residual tumor) after treatment of an NT (non-transplantable) HCC
- **TT1**: Single vital HCC ≤2cm (T1)
- **TT0_L**: No residual tumor after Loco-regional embolotherapies for a HCC
- **TT0_C**: No residual tumor after Curative treatment of a HCC

Cillo et al. AJT 2015
Mazzaferro Hepatology 2016
Key messages

HCC:
• Historical criteria can be expended (one HCC ≤6 cm)
• Historical criteria should be refined (AFP ≤ 400-1000 ng/ml)
• Downstaging works
• Some patients may be too early for transplantation
Transplant oncology

- Primary liver cancer
  - Hepatocellular carcinoma
  - Intrahepatic cholangiocarcinoma
  - Combined hepatocellular-cholangiocarcinoma
  - Hepatic epithelioid hemangioendothelioma
  - Hepatoblastoma
- Bile duct cancer
  - Perihilar cholangiocarcinoma
- Secondary liver cancer
  - Colorectal liver metastases
  - Neuroendocrine tumor (NET) liver metastases
“Very early” intra-hepatic cholangiocarcinoma

- Retrospective multi-centric Spanish study
- 29 transplantations for intra-hepatic cholangiocarcinoma
- Risk of recurrence associated with:
  - size
  - tumor volume
  - microscopic vascular invasion
  - poor degree of differentiation
“Very early” intra-hepatic cholangiocarcinoma

- 15 “very early” (single lesion ≤2 cm)
- 33 more advanced
- Risk of recurrence associated with:
  - microscopic vascular invasion
  - poor degree of differentiation
Key messages

Intrahepatic cholangiocarcinoma:
• Transplantation for very early lesions (single ≤2 cm)
• Avoid micro-vascular invasion and poor differentiation
Transplant oncology

- Primary liver cancer
  - Hepatocellular carcinoma
  - Intrahepatic cholangiocarcinoma
  - Combined hepatocellular-cholangiocarcinoma
  - Hepatic epithelioid hemangioendothelioma
  - Hepatoblastoma
- Bile duct cancer
  - Perihilar cholangiocarcinoma
- Secondary liver cancer
  - Colorectal liver metastases
  - Neuroendocrine tumor (NET) liver metastases
Historical liver transplantation for CRLM

- 1983-1989
- 17 patients

18 months median survival

Mulhbacher et al. Transplant Proc 1991
Liver transplantation for CRLM

Things have changed
• Improved chemotherapy
• Improved transplantation
• Immunosuppression better tailored for oncological indications
Liver transplantation for CRLM in Oslo

N=21 patients

27 months median follow-up
Better than chemotherapy

Overall survival

Months

SECA (N=21)

P < 0.001

Nordic VII (N=47)

Recurrence in almost all patients (20/21)
# Patient characteristics

<table>
<thead>
<tr>
<th>Patients (number)</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, min-max)</td>
<td>56 (38-73)</td>
</tr>
<tr>
<td>Gender</td>
<td>female:6/ male:6</td>
</tr>
<tr>
<td>Location of primary cancer (%)</td>
<td></td>
</tr>
<tr>
<td>colon</td>
<td>11 (92)</td>
</tr>
<tr>
<td>rectum</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Pathological staging of primary cancer (%)</td>
<td></td>
</tr>
<tr>
<td>T0*</td>
<td>1 (8)</td>
</tr>
<tr>
<td>T2</td>
<td>1 (8)</td>
</tr>
<tr>
<td>T3</td>
<td>8 (67)</td>
</tr>
<tr>
<td>T4</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Node status of primary cancer (%)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>5 (42)</td>
</tr>
<tr>
<td>N1</td>
<td>5 (42)</td>
</tr>
<tr>
<td>N2</td>
<td>2 (16)</td>
</tr>
</tbody>
</table>

- Lisbon, n=8
- Coimbra, n=2
- Paris, n=1
- Geneva, n=1

Toso et al. Liver transplantation 2017
Peri-operative management

- Planned transplant in a long-term onco-surgical management, n=6
- Compassionate: up-front transplantations, n=2
- Compassionate: emergency transplantations, n=3
- Compassionate: IVC invasion discovered during transplant, n=1

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of chemotherapy courses (min-max)</td>
<td>2 (0-4)</td>
<td></td>
</tr>
<tr>
<td>Pre-transplant neo-adjuvant chemotherapy (%)</td>
<td>11 (92)</td>
<td></td>
</tr>
<tr>
<td>Response to pre-transplant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>partial response</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>stable diseases or progression</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median number of liver resections (min-max)</td>
<td>1 (0-3)</td>
<td></td>
</tr>
</tbody>
</table>
5 patients alive and free of cancer 7, 43, 47, 48, and 108 months after transplantation.
P=0.019

Proportion of patients alive and free of cancer

Time since transplantation (month)
Key messages

CRLM:
• Disease-free survival can be achieved
• Favorable factors include a long time between diagnosis and transplant, a low CEA, and “planned” indication
• This indication should be further explored
The future of liver transplantation is bright! 😊

Thank you!
Prof. Ph. Compagnon

You for your excellent daily collaboration and for your attention today