

Expanding Liver Transplantation for Cancer Indications

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Disclosures: None relevant to this presentation



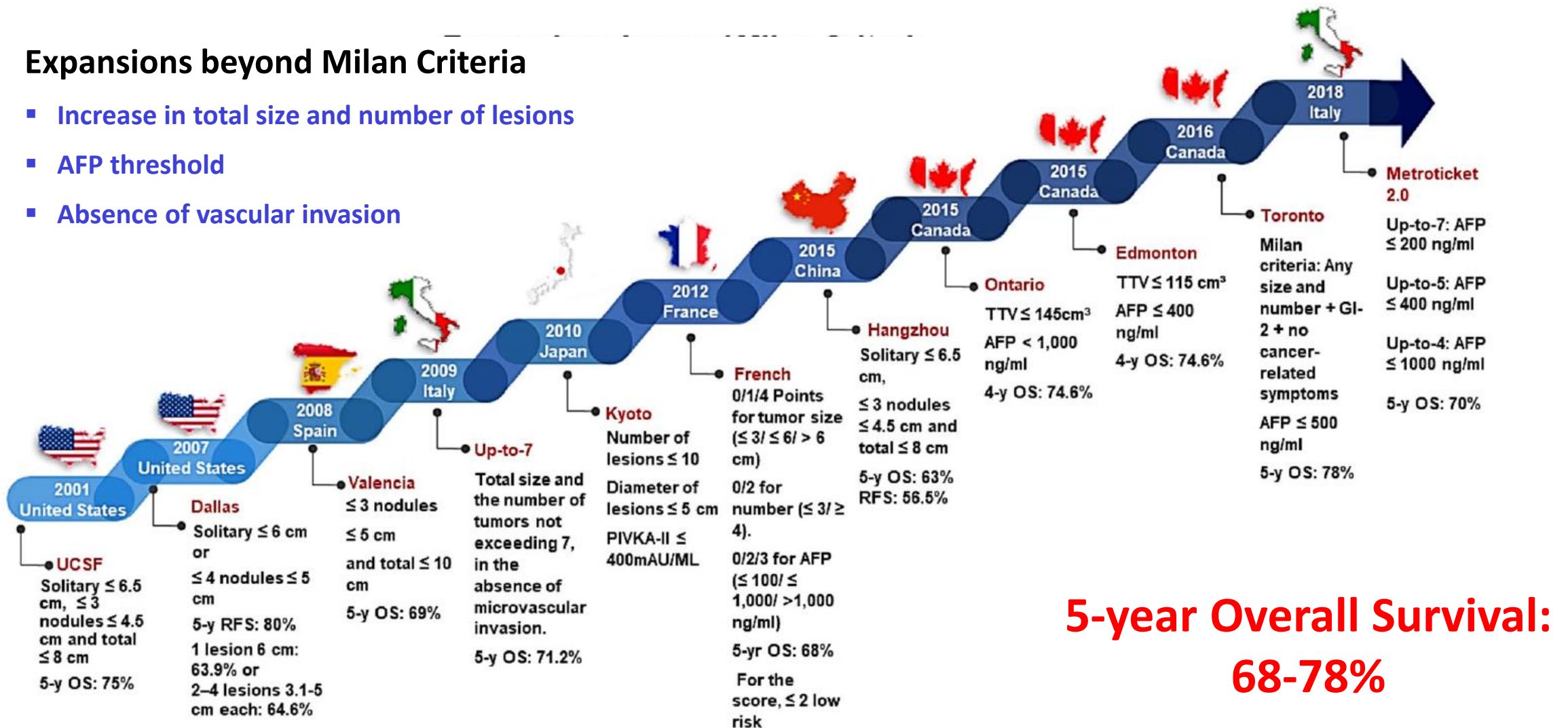
Transplant as Part of Oncologic Treatment Outline

- HCC: beyond Milan and UCSF criteria –
 - Downstaging “all comers”
 - Emerging role of ICI in downstaging
- Cholangiocarcinoma: small iCCA
- Colorectal cancer (CRC) metastases

Pushing the Limits on HCC for LT

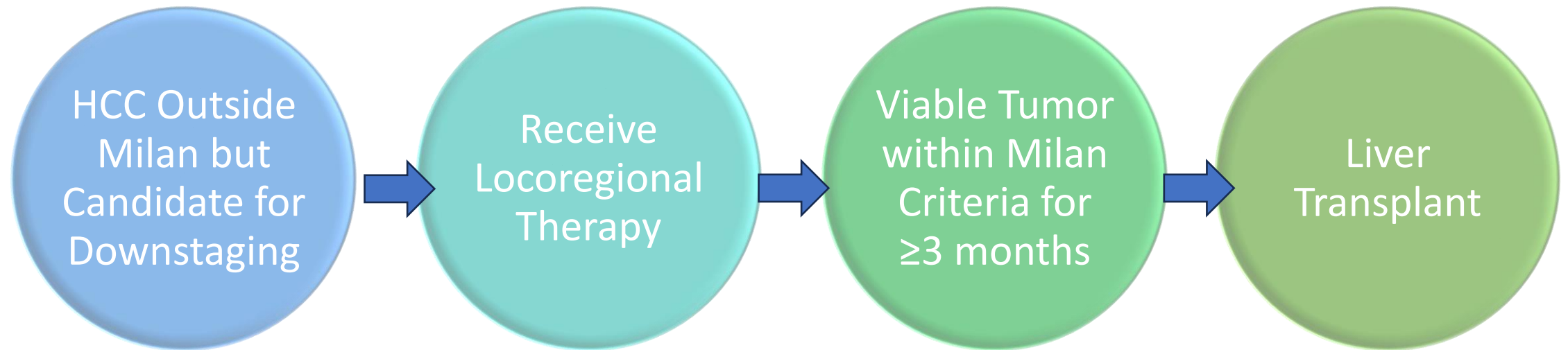
Expansions beyond Milan Criteria

- Increase in total size and number of lesions
- AFP threshold
- Absence of vascular invasion



**5-year Overall Survival:
68-78%**

Downstaging to Milan



UNOS-DS criteria:

- 1 lesion > 5 cm and < 8 cm
- 2 to 3 lesions each < 5 cm
- 4 to 5 lesions each < 3 cm with a total tumor diameter of < 8 cm
- Absence of vascular invasion and extrahepatic disease

All-Comers criteria

- Any size or number
- Absence of vascular invasion and extrahepatic disease

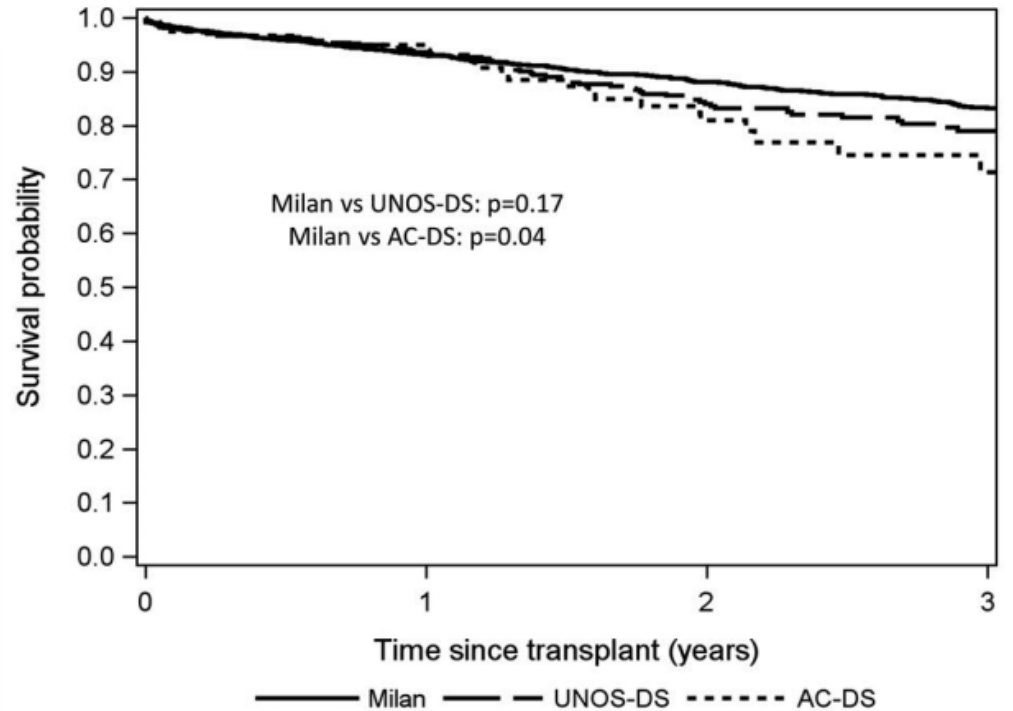
Milan Criteria

- 1 lesion \leq 5 cm
- Up to 3 lesions, all \leq 3 cm
- Absence of vascular invasion and extrahepatic disease

Downstaging Outcomes Acceptable

Retrospective analysis of the UNOS database of 3,819 patients who underwent LT from 2012 to 2015
 N=3276 always within Milan, N=422 UNOS-DS and N=121 AC-DS

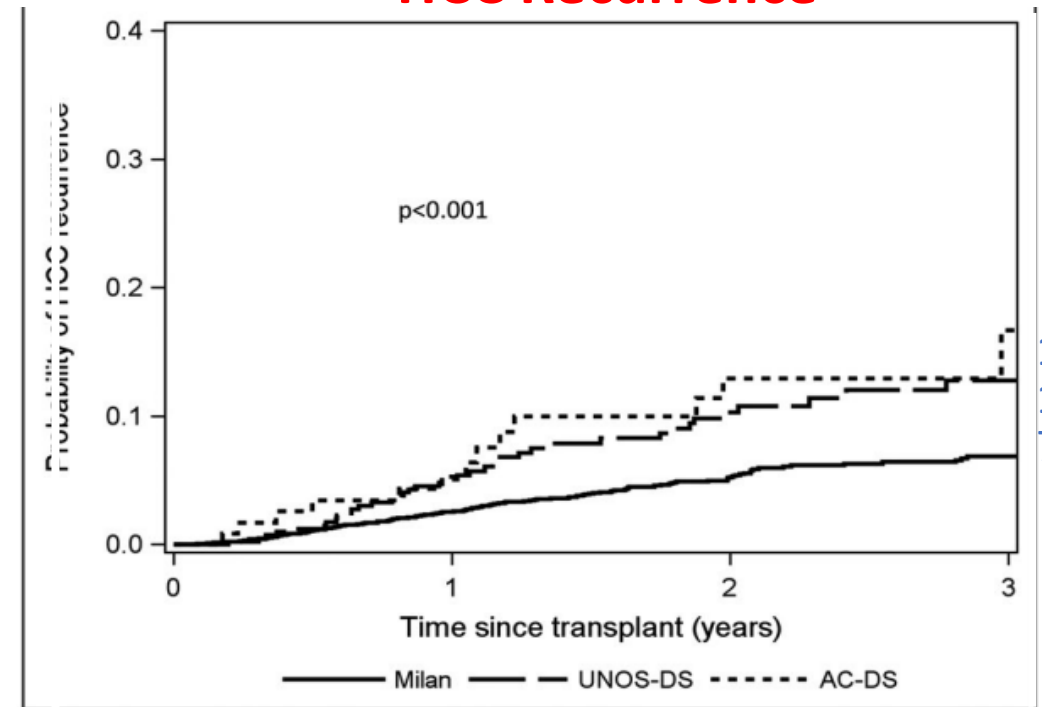
Overall Survival



82%
 79%
 71%

Milan	3276	2575	1380	441
UNOS-DS	422	352	207	97
AC-DS	121	103	56	22

HCC Recurrence



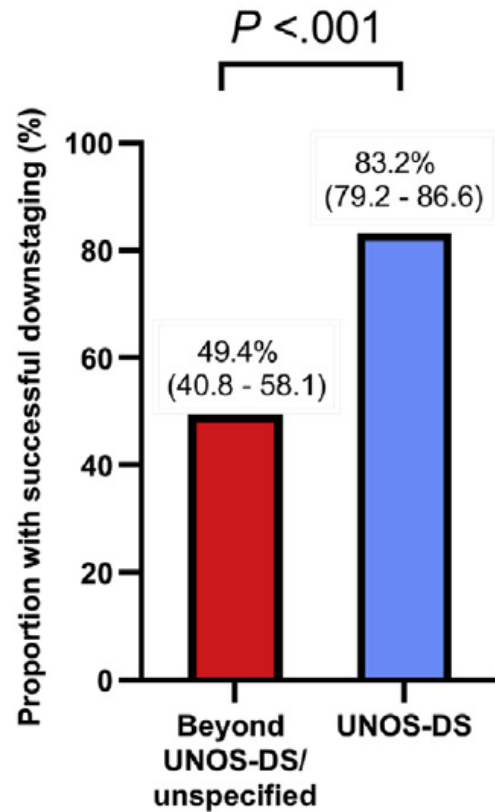
17%
 13%
 7%

Milan	3276	2535	1348	429
UNOS-DS	422	339	198	92
AC-DS	121	99	53	22

Outcomes: UNOS-DS Criteria vs All-Comers

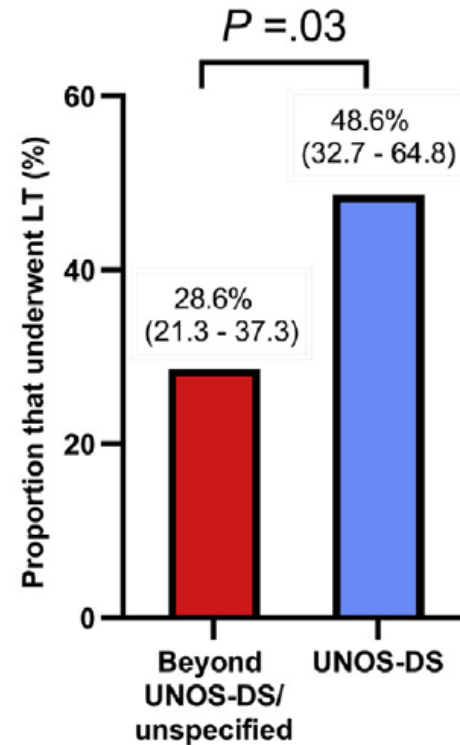
Meta-analysis: 25 papers involving 3997 patients

Successful downstaging



N= 1505 399

Received liver transplant

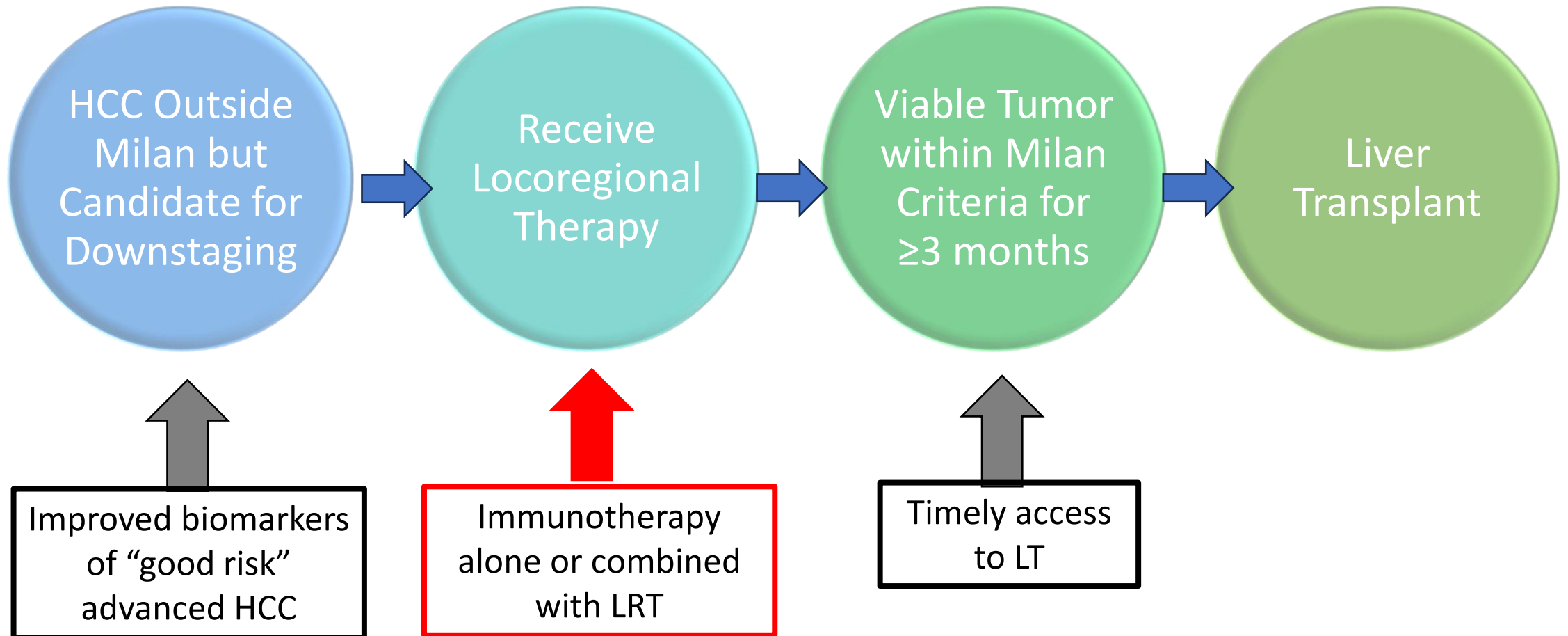


N= 1387 399

All-comers have lower rates of success in DS and receiving LT

Improving Success of DS with More HCC

Advanced



ICI as Neoadjuvant Strategy Pre-LT: Some Safety Issues

N=59 patients reported

Author	Year	Number of Patients	Underlying Liver Disease	Milan Criteria	ICI	ICI Duration	Other Pre-transplant Treatments	Time Interval between last ICI and LT	Rejection	Recurrence
Tabrizian <i>et al.</i> [34]	2021	9	5 HBV; 2 HCV; 1 NASH; 1 None	6 Yes 3 No	Nivolumab	2-32 cycles	Chemo- and Radioembolization, Ablation, Radiation	4 weeks	1 mild rejection due to low Tacrolimus levels	No
Schnickel <i>et al.</i> [35 [■]]	2022	5	4 HCV; 1 HBV	Unknown	Nivolumab	8-18 months	No	10 days - 83 months	1 Acute hepatic necrosis (14 POD), Graft loss, Re-transplant successful	No
Wang <i>et al.</i> [40]	2023	16	14 HBV; 2 ALD	No	2 Nivolumab 7 Pembrolizumab. 4 Sintilimab 2 Camrelizumab 1 Multiple	1 - 27 Cycles	Yes	1 - 184 days	9 Acute liver rejection	5 Yes
Dave <i>et al.</i> [39 [■]]	2022	6	4 HCV; 1 HBV; 1 NASH	Unknown	Nivolumab	Unknown	2 Loco-regional treatments	105 days	2 rejections; Graft loss, Re-transplant successful	Unknown

11/36 (31%): severe rejection and 1 acute hepatic necrosis;
2 graft losses (6%) requiring re-LT

Unresolved Issues for Expanding HCC Eligibility to “All Comers”

- Patient selection, including use of biomarkers
- Defining the most effective and safe treatment combinations, including use of ICI
- Determining the appropriate interval between ICI administration and liver transplantation (experts recommend ≥ 2 months currently)
- Accessing LT in a timely fashion
- Optimization of IMS to minimize rejection or other negative outcomes

Several prospective clinical trials with ICI are underway –

MEDI4736 NCT05027425 (US)

PLENTY202001 NCT05185505 (US, China)

Immuno XXL NCT05879328 (Italy)

Liver Transplant for iCCA

Current standard: Resection and regional lymph node resection

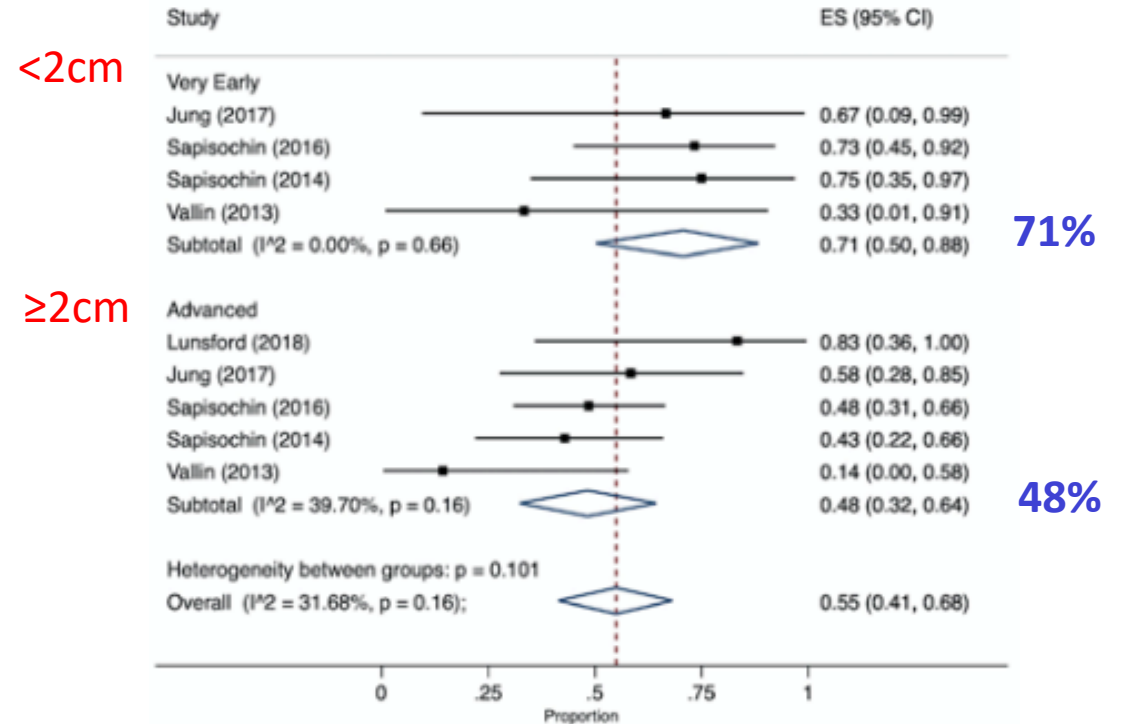
- **25-40% 5-year OS**

Early studies of LT for iCCA had poor outcomes ---contraindication to LT

LT: More recent series with better patient selection have acceptable survival rates

- **50-70% 5-year OS**

5-year overall survival



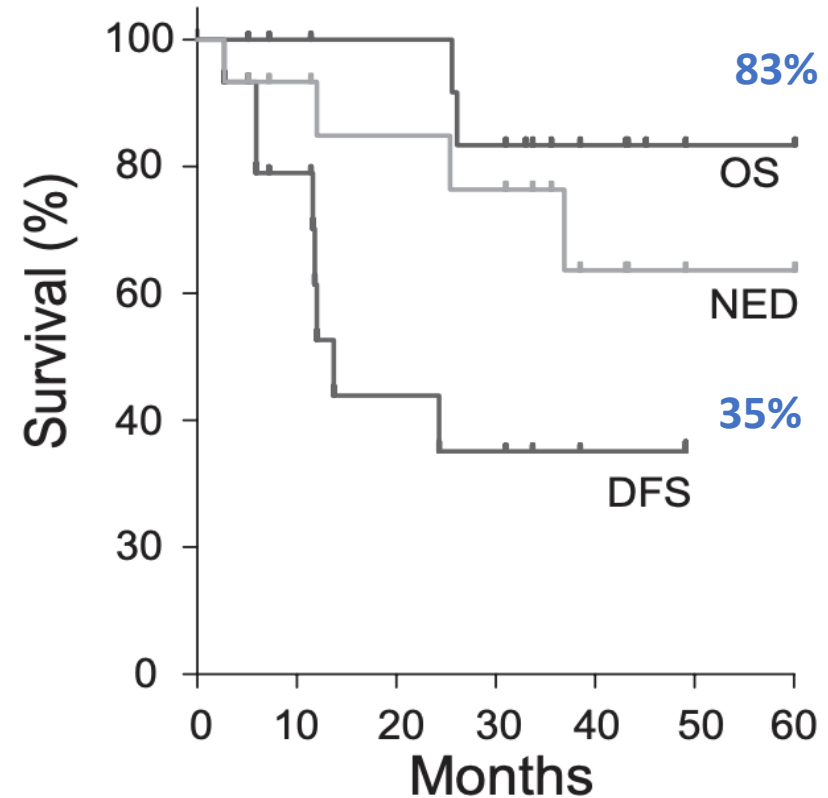
Several prospective studies underway

Liver Transplant for CRC Metastases

Oslo University First Prospective Study

Key Inclusion criteria:

- Liver-only metastases (by CT, MRI, PET)
- Relapse of liver metastases after second liver resection or liver metastases not eligible for curative liver resection
- Received first-line treatment
- Before start of chemotherapy, no lesion >10 cm, if more than 30 lesions, all <5 cm
- At least 10% response (RECIST-criteria) on chemotherapy or least 20% response after TACE (DEB-IRI) or by 90Y-spheres
- Time from CRC diagnosis to liver transplant was required to be more than 1 year.



SECA-II

Months	0	6	12	18	24	30	36	42	48	54	60
OS	15	14	12	12	12	10	6	5	2	1	2
DFS	15	11	6	5	5	4	2	1	1	0	0
NED	15	13	11	9	9	9	5	4	2	1	1

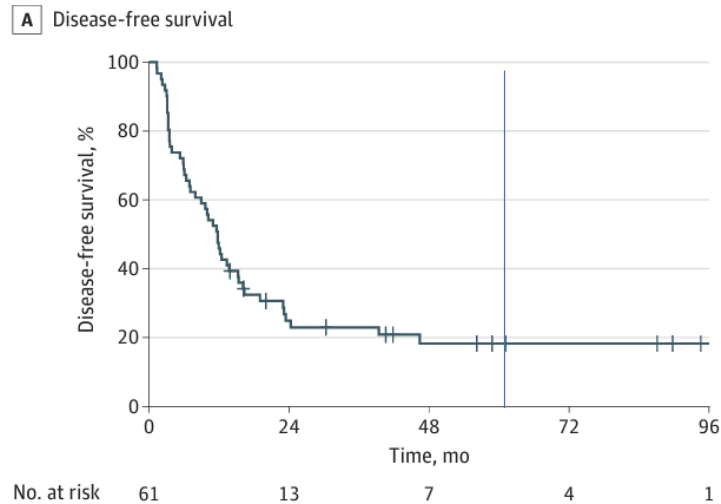
OS: overall survival

NED: No evidence of recurrent disease

DFS: disease free survival

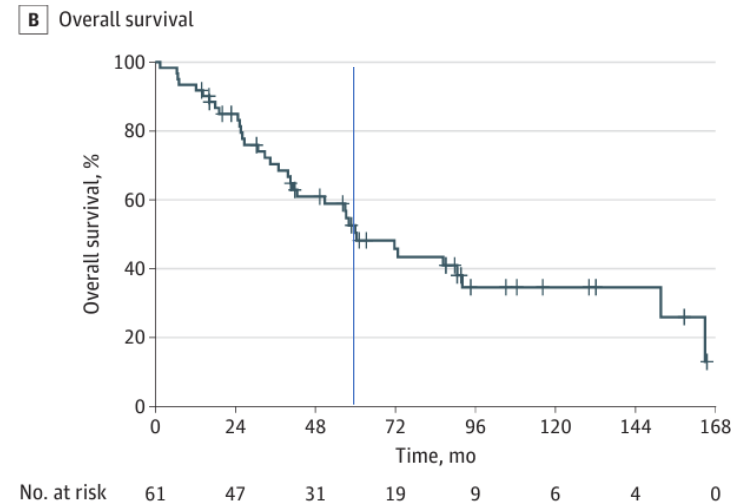
CRC Mets: Need to Optimize Patient Selection

Median DFS 11.8 mos (95% CI 9.3-14.2)



Most recurrences are within first 2 years

Median OS 60.3 mos (95% CI 44.3-76.5)



5-year OS survival at limits as acceptability for LT

- Largest lesion <5.5 cm
- Partial or stable disease in response to chemotherapy
- CEA <80 ug/L
- PET-MTV volume <70cm³
- <9 metastases
- Time from diagnosis to LT of ≥3 years


FCRS 0-2 or Oslo score 0-2

- *Also: 1 point for: tumors >5.5 cm, CEA over 80 ug/L, surgery of the primary <2 years before the LT, and progression of metastases at the time of LT*
- *Fong: 1 point for: node-positive primary, disease-free interval <12 mos, >1 tumor, size >5 cm, CEA >200 ng/mL*

Transplant Oncology

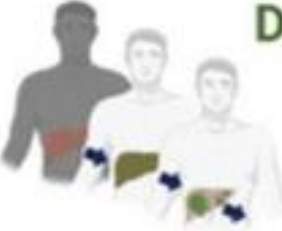
Innovative solutions for liver grafts

- Expanded indications for cancer will **worsen donor organ shortage**
- Increasing the donor supply will be a necessary for transplant oncology to be embraced widely



Marginal Grafts

- ▲ Doesn't affect the waiting list mortality
- ▲ Whole livers
- ▼ Low-quality grafts, may increase complications
- ▼ Oncological risk?





Domino Transplantation

- ▲ Good quality organs
- ▲ Scarcity of domino organs
- ▼ May affect the waiting list mortality
- ▼ Risk of getting the donor's disease



Living Donor Livers

- ▲ Excellent quality organs,
- ▲ Facilitates sequencing of treatment
- ▼ Donor risks.
- ▼ High technical complexity



Machine perfusion

- ▲ Reduces cold ischemia time
- ▲ Allows organ testing and selection
- ▲ Increased preservation time for staging
- ▼ High cost, low availability

Future Transplant Oncology

Advanced HCC, iCCA and CRC mets

- “All comers” HCC and small iCCA are yielding acceptable transplant outcomes (OS \geq 70% at 5 years)
- CRC mets and larger iCCA borderline (OS ~50% at 5 years)
- Combinations of LRT and systemic therapy as neoadjuvant therapy will offer more options to downstage and reducing recurrence
 - ICI require careful management to avoid rejection
- Defining optimal window between DS success and LT is necessary with more timing access to organs
- From oncologic perspective, lower overall survival rates would be acceptable but need to consider consequences to those with non-cancer indications on waiting list