

EFFECTIVENESS OF LOCOREGIONAL
THERAPY BEFORE LIVER
TRANSPLANTATION FOR LIVER CANCER

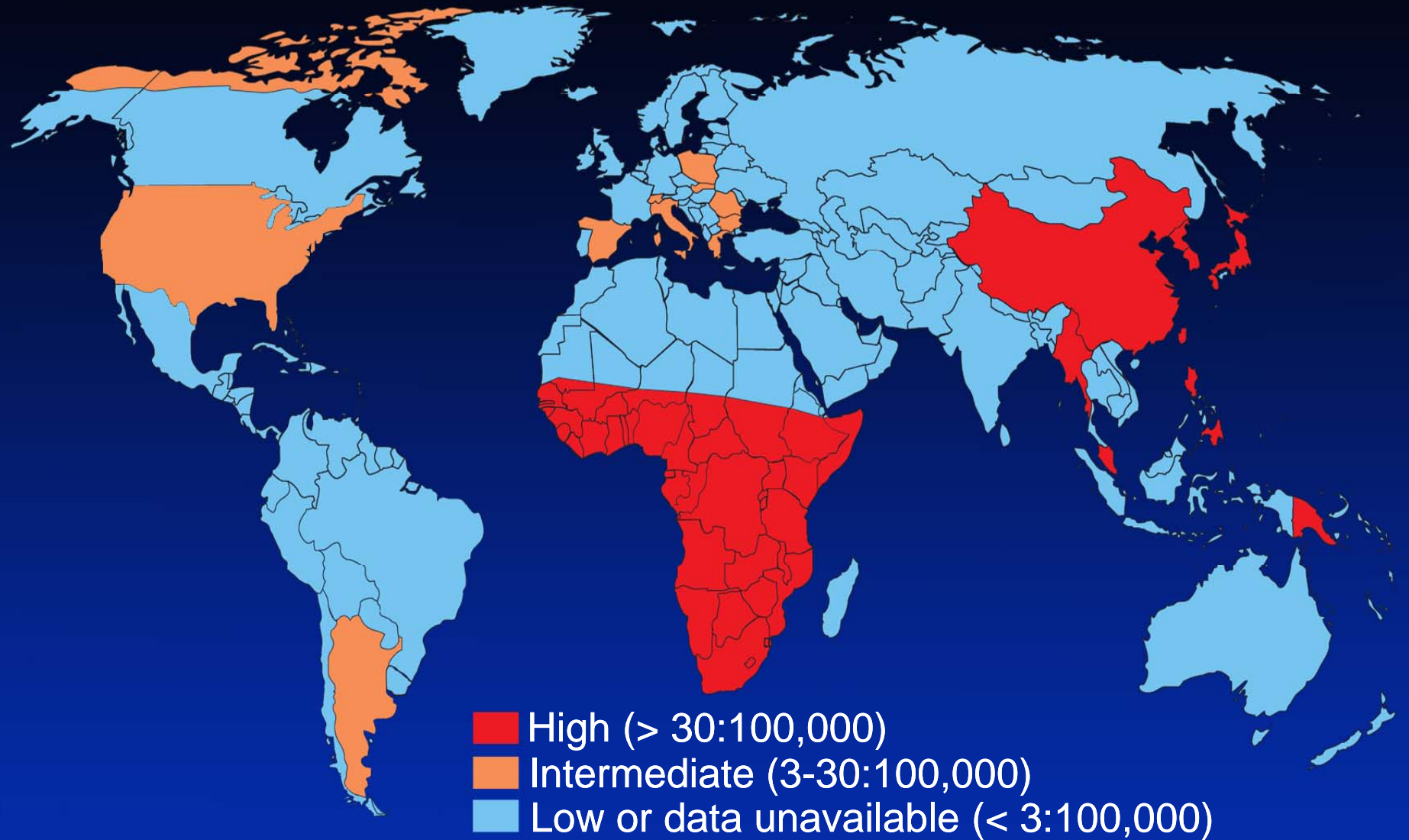
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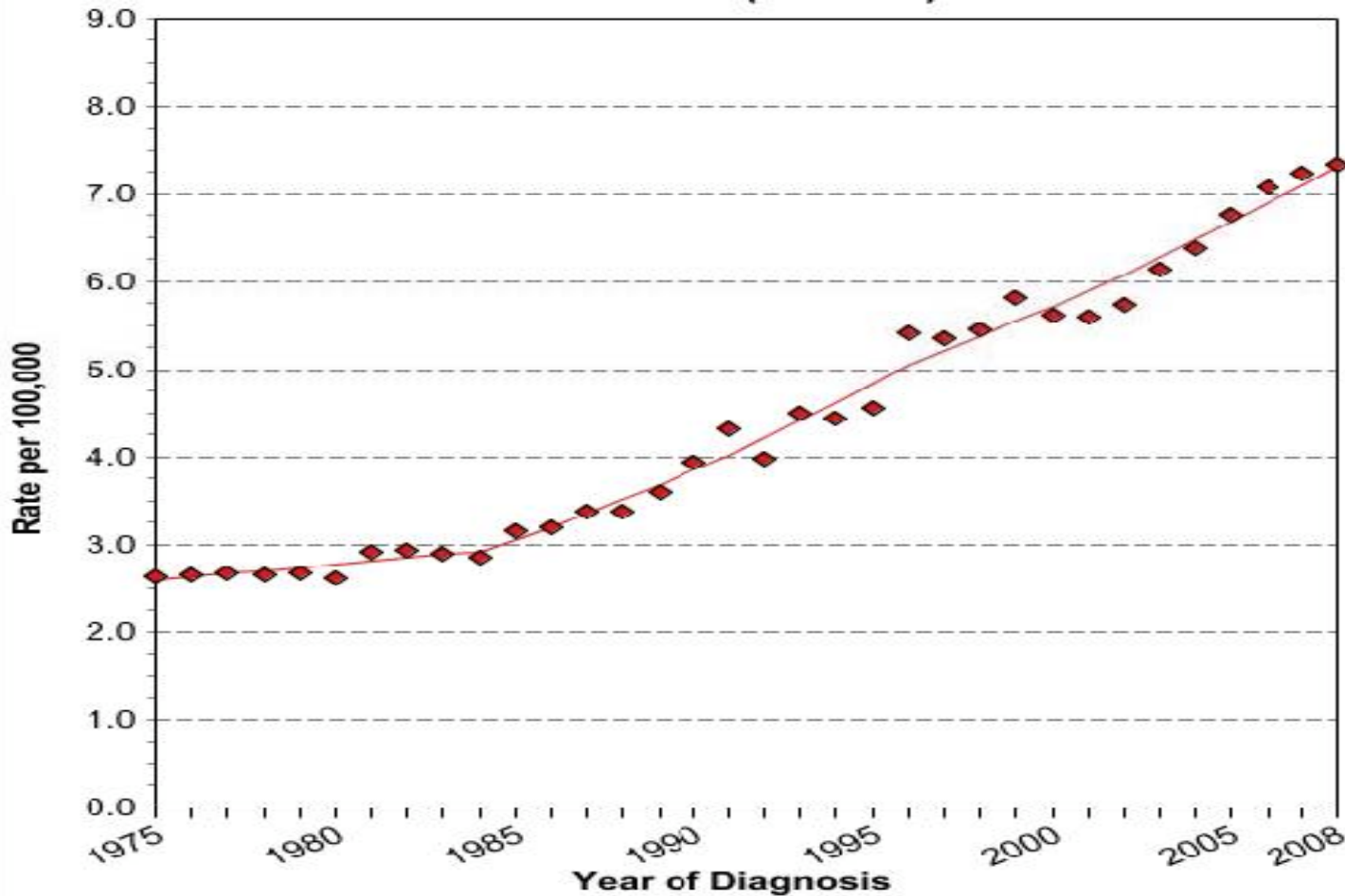
Liver cancer

- Hepatocellular carcinoma
- Most common primary malignancy of liver
- 5th most common cancer diagnosed world wide

Worldwide Incidence of Hepatocellular Carcinoma



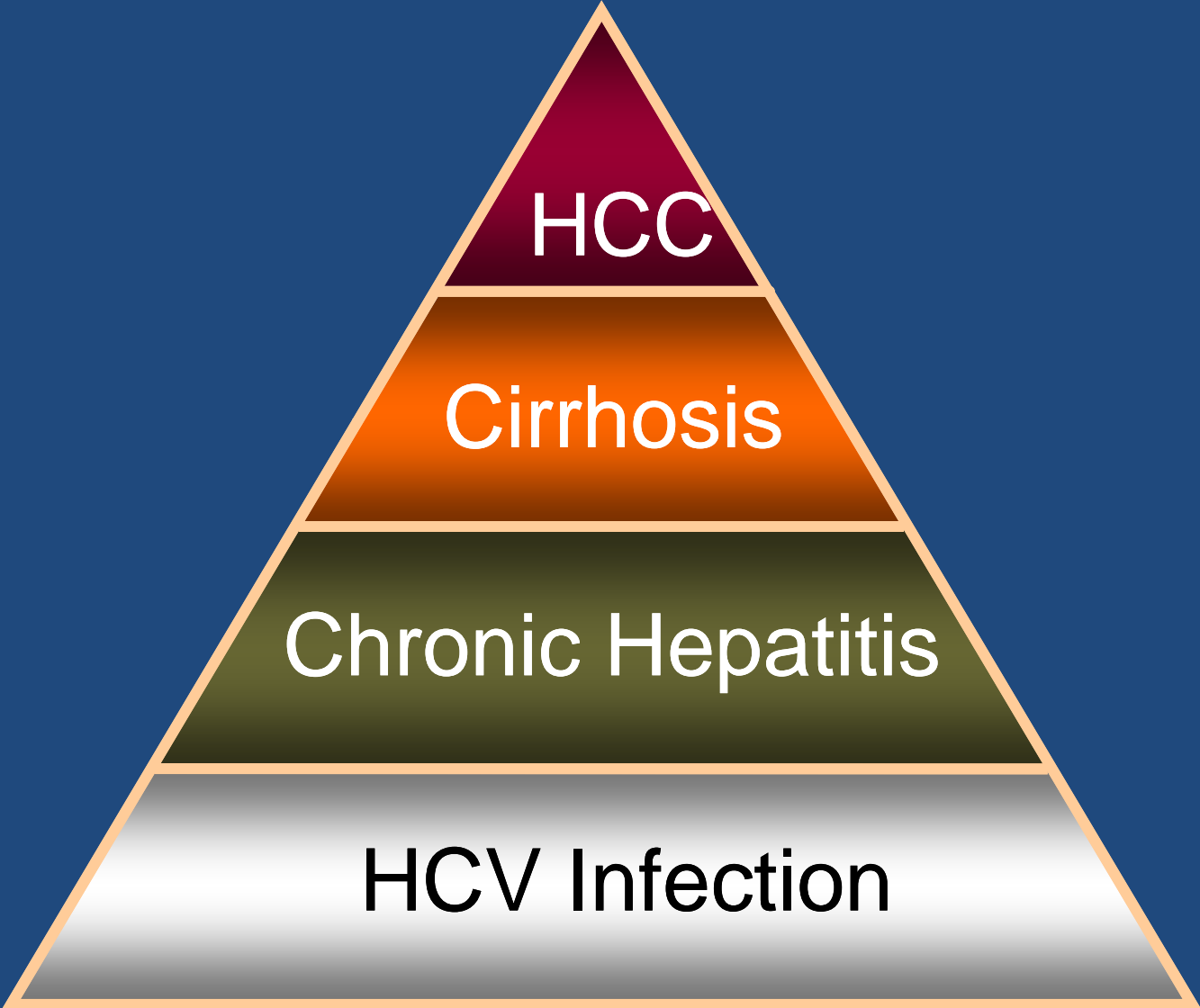
**Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Both Sexes
1975-2008 (SEER 9)**



Liver cancer

Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program.

HCC Epidemiology



25 years

A yellow double-headed vertical arrow is positioned to the right of the pyramid, spanning the height of the top three layers (Chronic Hepatitis, Cirrhosis, and HCC). The text "25 years" is centered next to the arrow, indicating the time interval between the stages it covers.

Causes

Chronic liver disease → Cirrhosis → Cancer

- Chronic Hepatitis C
- Chronic Hepatitis B
- Cirrhosis – alcohol and other chronic liver disease
- Dietary Aflatoxin exposure

Liver Cancer

- Untreated survival is 6-12 months
- Overall 5 year survival is 14%
- US – 9th leading cause cancer related mortality
- 2010 – 19,600 deaths
- Treatment of choice – Liver transplant

Criteria for Liver Transplant

- Milan criteria
- Single Nodule < 5cm, Max of Three nodules, each < 3cm
- Universally accepted
- Some centers – use expanded criteria

Problem -?

- Shortage of organs
- Long waiting time
- Tumor progression – high drop out rate

Locoregional treatment

- Done while waiting for liver transplantation
- Chemoembolization, radiofrequency ablation
- Objective
 - Decrease Drop out rate
 - Improve post-transplant outcomes
 - Downstage tumor

Locoregional Treatment

- No randomized studies
- Retrospective , cohort studies
- Results are controversial
- Resource intensive procedures
- Most studies focus on survival
- Paucity of data on drop out rate, recurrence

Objective

Study Effectiveness of locoregional treatment
before liver transplantation for liver cancer
using national database

Significance

- Better define role of locoregional therapy
- Better use of health care resources

Data

- United Network for Organ Sharing (UNOS)
- Private organization under contract with federal government
- Data requested for liver cancer 2002-2010

Inclusion Criteria

- Listed for transplant for Liver cancer
- Age > 18 years
- Deceased donor transplant
- No prior organ transplantation
- No marginal donor
- Donor age < 10 or > 75 years

Patient population

- 13011 patients registered for liver transplant for liver cancer
- After exclusion criteria & missing information
 - 1) Tumor within criteria - 10,968
 - 1) Tumor beyond criteria - 582

Specific Aim #1

- For tumor Within Criteria
- Effect of locoregional treatment
 - Drop out rate
 - Post transplant survival
 - Post-transplant tumor recurrence

Analysis

- Kaplan Meier graphs
- Cox proportional hazard model
- Predictor variable – presence / absence of locoregional treatment

Outcome Variables

- Drop out rates : patient removed from waiting list due to any cause
- Patient survival: time in years from transplantation until death from any cause.
- Recurrence: defined as recurrence of HCC anytime after transplantation.

Co-variates

- Age
- Gender
- Race (white, black, Hispanic, Asian, unknown/others)
- Tumor size and number
- Time on waiting list (< or > 6 months)
- Tumor marker - alpha-fetoprotein level
- MELD score
- Etiology of liver disease – Hepatitis B, C, Alcohol
- Transplant Region – North East/ West / Midwest / South

Demographics

		Locoregional Treatment	
		Yes	No
		5510	5458
Age	Mean \pm SD	56.7 \pm 7.3	55.4 \pm 7.9
Gender	Male, %	77.9	76.6
	Female, %	22.1	23.4
Race	White, %	62.7	67.8
	Black, %	9.0	7.9
	Hispanic, %	14.7	14.3
	Asian, %	12.1	9.0
	Other, %	1.5	1.0
Region ^{\$}	Northeast, %	28.8	28.9
	Midwest, %	18.9	21.7
	South, %	27.1	27.5
	West, %	25.2	21.9

Tumor characteristics

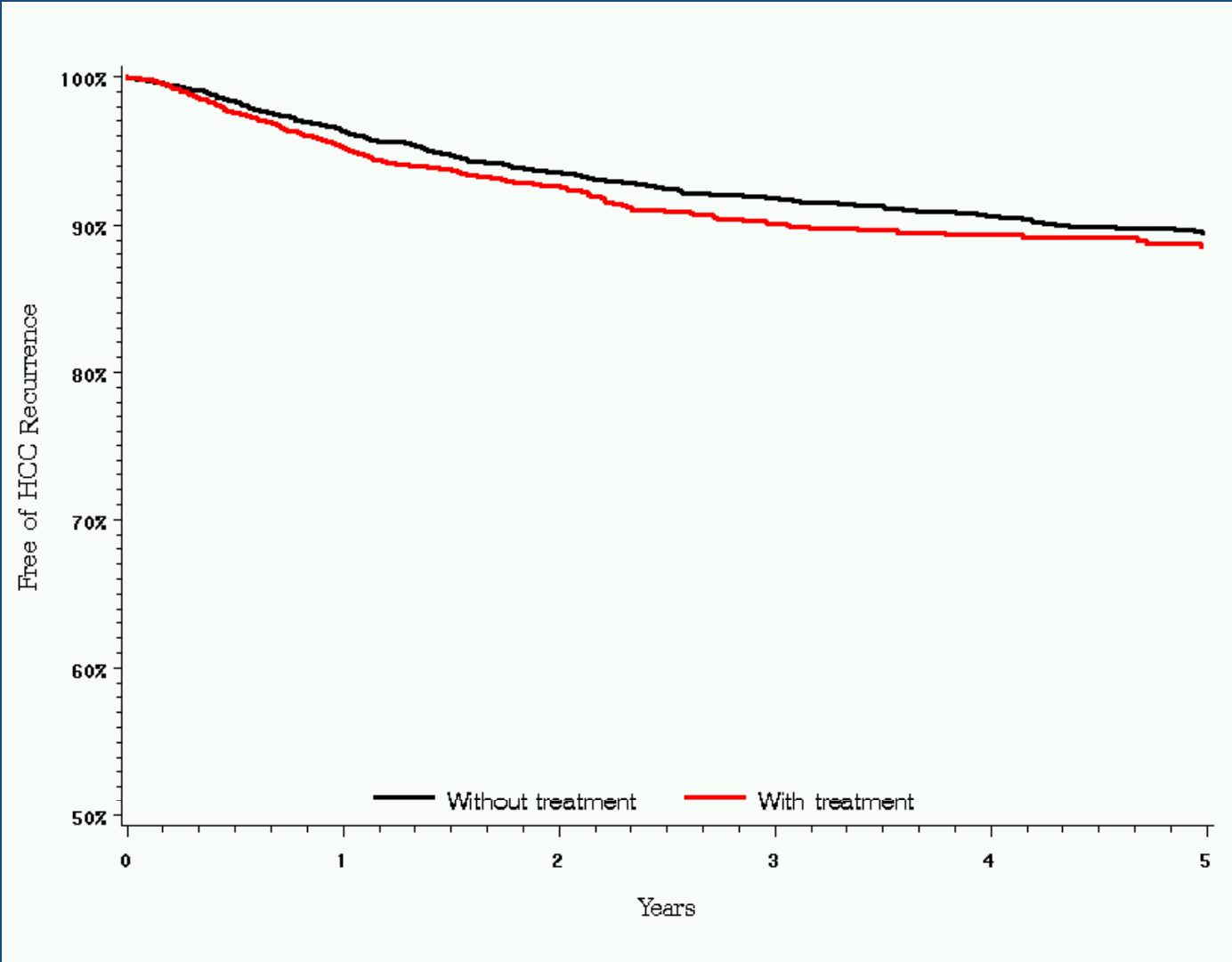
		Locoregional Treatment	
		Yes (N=5510)	No (N=5458)
Tumor number	Mean ± SD	1.4 ± 0.6	1.4 ± 0.7
Tumor size	Mean ± SD	2.8 ± 0.9	2.7 ± 0.9
Meld score	Mean ± SD	11.2 ± 3.9	12.3 ± 4.5
AFP	Mean ± SD	266.5 ± 1745	328 ± 2262
Alcohol	Yes, %	17.5	20
	No, %	82.5	80
Hepatitis B	Yes, %	7.4	4.3
	No, %	92.6	95.7
Hepatitis C	Yes, %	55.5	55.3
	No, %	44.5	44.7
Type of Treatment	TACE, %	76.7	
	RFA, %	32.3	
	Cryo, %	0.7	

Tumor Within Milan criteria

		Drop out	Overall Mortality	HCC Recurrence
		n=9279	n=6428	n=6543
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Treatment (Unadjusted HR)	No	1.0	1.00	1.00
	Yes	0.93 (0.8-1.1)	0.9 (0.8-1.04)	1.2 (1.001-1.5)
Treatment (adjusted HR*)	No	1.00	1.00	1.00
	Yes	0.91 (0.8-1.01)	0.93 (0.8-1.1)	1.1 (0.9-1.4)

* Adjusted for age, gender, race, waiting time, etiology, AFP, MELD , tumor size, number, transplant region

Kaplan Meier Post- Transplant Survival



		Drop out N=9279	Overall Mortality N=6248	HCC Recurrence N=6543
Age	(every 10 years old)	1.03 (1.0-1.04)	1.02 (1.0-1.04)	1.0 (1.0-1.03)
Recipient Gender	Male	1.00	1.00	1.00
	Female	0.82 (0.7-0.9)	0.96 (0.8-1.1)	0.7 (0.6-1.0)
Race	White	1.00	1.00	1.00
	Black	1.04 (0.9-1.3)	1.2 (1.0-1.5)	0.7 (0.4-1.0)
	Hispanic	0.87 (0.8-1.0)	0.83 (0.7-0.9)	0.6 (0.5-0.9)
	Other/Unknown	0.98 (0.8-1.2)	0.71 (0.6-0.9)	0.7 (0.5-1.1)
waiting time	< 6 months	-	1.00	1.00
	>= 6 months	-	1.1 (0.9-1.2)	1.0 (0.8-1.2)
Alcohol	No	1.00	1.00	1.00
	Yes	0.91 (0.8-1.1)	1.1 (0.9-1.2)	1.0 (0.7-1.3)
Hepatitis B	No	1.00	1.00	1.00
	Yes	0.72 (0.6-0.9)	0.91 (0.7-1.2)	1.1 (0.7-1.7)
Hepatitis C	No	1.00	1.00	1.00
	Yes	0.88 (0.8-1.0)	1.3 (1.2-1.5)	1.0 (0.8-1.2)

		Drop out N=9279	Overall Mortality N=6248	HCC Recurrence N=6543
Tumor	2-3 cm, 1 lesion	1.00	1.00	1.00
	<2cm, 2-3 lesions	0.90 (0.7-1.1)	0.9 (0.7-1.1)	0.4 (0.2-0.7)
	2-3 cm, 2-3 lesion	1.20 (1.1-1.4)	0.9 (0.8-1.1)	0.8 (0.6-1.1)
	3-4 cm, 1 lesion	1.40 (1.2-1.6)	0.9 (0.8-1.1)	1.0 (0.7-1.3)
	4-5 cm, 1 lesion	1.96 (1.6-2.3)	1.1 (0.9-1.4)	1.3 (0.9-1.8)
AFP	1st Q	1.0	1.00	1.00
	2nd Q	1.3 (1.1-1.5)	1.0 (0.9-1.2)	1.5 (1.0-2.1)
	3rd Q	1.3 (1.1-1.6)	1.3 (1.1-1.6)	2.3 (1.7-3.3)
	4th Q	2.4 (2.1-2.7)	1.7 (1.5-2.0)	4.2 (3.1-5.7)
MELD	score 6-9	1.00	1.00	1.00
	score 10-12	1.02 (0.9-1.2)	1.1 (0.9-1.3)	0.9 (0.7-1.1)
	score 13-15	1.40 (1.2-1.6)	1.0 (0.8-1.2)	0.6 (0.5-0.9)
	score 16-19	2.29 (1.9-2.7)	0.9 (0.8-1.2)	0.9 (0.6-1.2)
	score >=20	3.60 (2.9-4.4)	1.4 (1.1-1.7)	0.9 (0.6-1.3)
Region	North east	1.0	1.00	1.00
	Midwest	0.93 (0.8-1.1)	0.8 (0.7-0.9)	1.2 (0.9-1.6)
	South	0.94 (0.8-1.1)	0.9 (0.8-1.1)	1.1 (0.8-1.4)
	West	1.10 (0.9-1.2)	0.8 (0.6-0.9)	1.4 (1.0-1.9)

Specific Aim #2

- For tumor Beyond Criteria
- Effect of locoregional treatment
 - Drop out rate
 - Post transplant survival
 - Post-transplant tumor recurrence

Demographics

		Locoregional Treatment	
		Yes	No
		418	164
Age	Mean \pm SD	57.0 \pm 7.4	56.6 \pm 7.7
Gender	Male, %	84.7	79.3
	Female, %	15.3	20.7
Race	White, %	63.2	68.9
	Black, %	10	7.9
	Hispanic, %	14.4	17.1
	Asian, %	11	4.3
	Other, %	1.4	1.8
Region ^{\$}	Northeast, %	24.6	28.1
	Midwest, %	20.8	24.4
	South, %	39.7	38.4
	West, %	14.8	9.2

Tumor characteristics

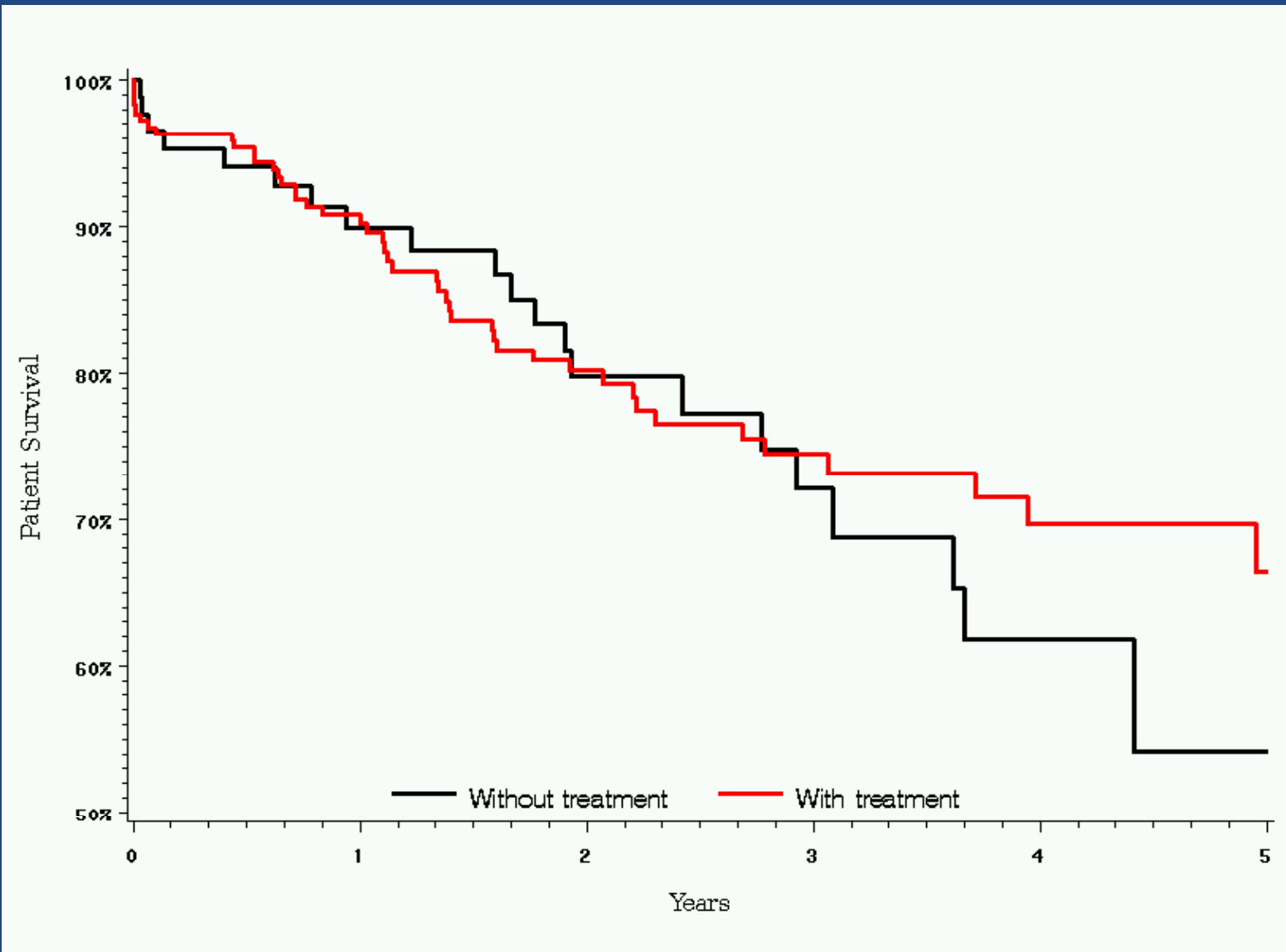
		Locoregional Treatment	
		Yes (N=418)	No (N=164)
Tumor number	Mean ± SD	2.1 ± 0.9	2.1 ± 0.9
Tumor size	Mean ± SD	4.4 ± 1.6	4.2 ± 1.7
Meld score	Mean ± SD	10.7 ± 3.6	11.5 ± 4.2
AFP	Mean ± SD	306.2 ± 1211	329 ± 1270
Alcohol	Yes,%	13.6	17.7
	No,%	86.4	82.3
Hepatitis B	Yes,%	7.6	6.8
	No,%	92.4	93.2
Hepatitis C	Yes,%	52.6	43.9
	No,%	47.4	56.1
Type of Treatment	TACE,%	82.1	
	RFA,%	32.1	
	Cryo,%	0.7	

Results -Tumor Beyond Milan

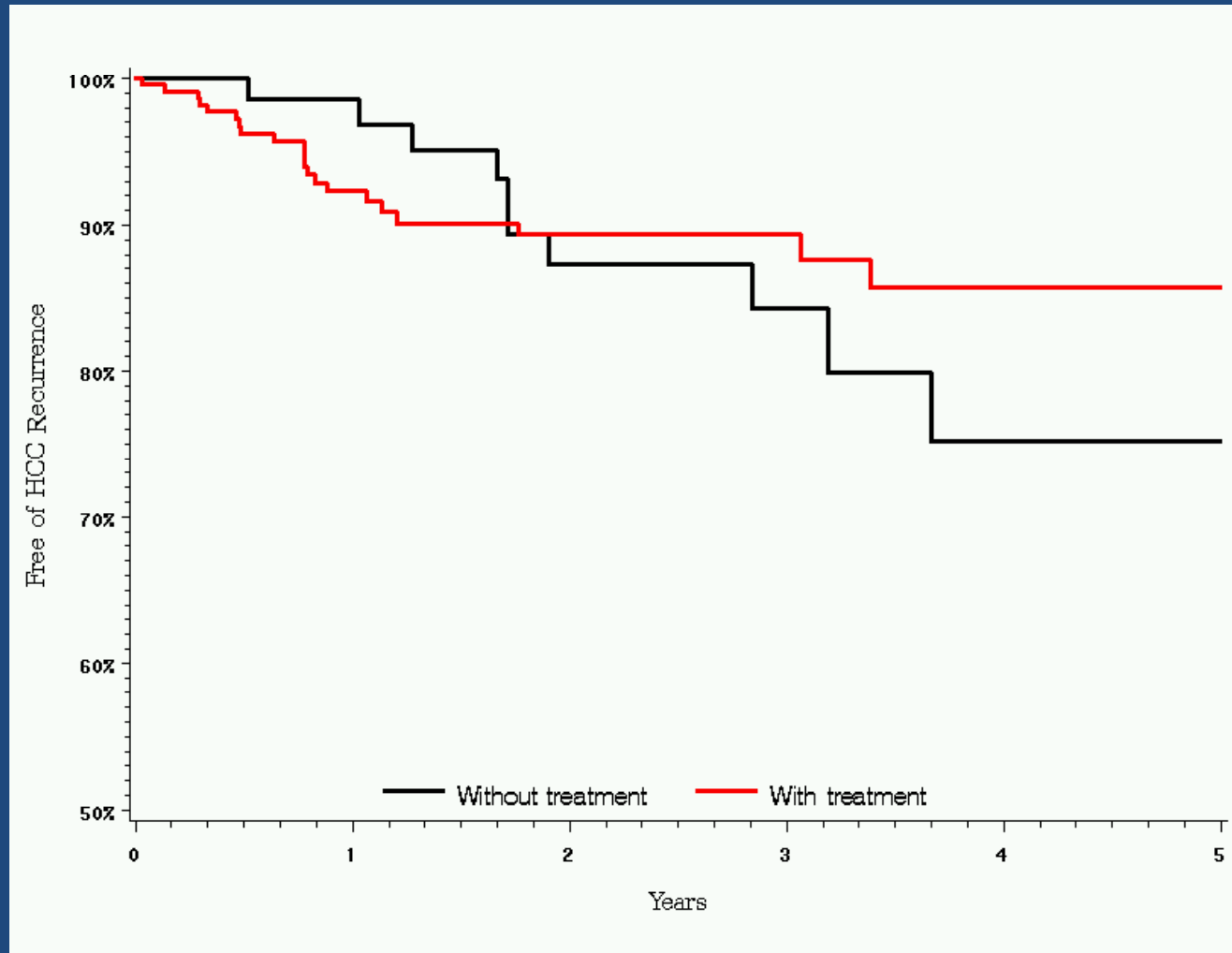
Treatment	Drop out rate N=567		Overall Mortality N=345		HCC Recurrence N=345	
	HR(95% CI)	*HR	HR	*HR	HR	*HR
No	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.8 (0.5-1.1)	0.8 (0.5-1.1)	0.9 (0.5-1.4)	0.9 (0.5-1.6)	0.8 (0.4-1.8)	0.9 (0.4-2.2)

* Adjusted for age, gender, race, waiting time, etiology, AFP, MELD , tumor size, number, transplant region

Kaplan Meier – Post Transplant Survival



Kaplan Meier Post Transplant Recurrence



Conclusion

- Locoregional therapy did not decrease drop out rate or improve post-transplant survival
- For tumor within criteria locoregional treatment was associated with increased post-transplant recurrence
- Results to be interpreted with caution for tumor beyond criteria

Limitations

- Retrospective analysis
- Reporting error
- Selection bias

Thanks

- Dr Goodwin
- Dr Kuo
- Dr Singh
- Ann Harper at UNOS

Thank you