

Sensitivity of Screening Ultrasound for Hepatocellular Carcinoma in a Liver Transplant Center

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Disclosure

The authors have no conflicts of
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Goals and Objectives

- Purpose of the study
- Background: Brief review of current Hepatocellular Carcinoma(HCC) cancer burden worldwide and within the US and US Cirrhosis burden
- Current Recommendations by The American Association for the Study of Liver Disease (AASLD) for screening high risk patients for HCC
- Current therapy recommendations for HCC
- Sensitivity of US and MRI for surveillance
- Retrospective study at a Liver Transplant Center

Purpose of the Study

Measure the sensitivity of non-enhanced ultrasound (NEUS) in screening for HCC lesions less than 2cm and lesions 2-5cm with pathological correlation in explant liver or partially resected liver at our institution.

Current screening guidelines at our Institution (major liver transplant center) include alternating NEUS and dynamic contrast enhanced MRI at 6 month intervals, for high risk patients with chronic liver disease.

The study aims to determine if the use of NEUS may be an inadequate means of screening, due to the false negative detection rate, for small lesions (< 2cm).

Target Audience

- General Radiologist
- Abdominal Radiologist
- Radiology Resident
- Hepatologist
- Hepatobiliary Surgeon

Background: Worldwide Liver Cancer Burden

- Primary liver cancer includes hepatocellular carcinoma (75% to 85% of cases) and intrahepatic cholangiocarcinoma (10% to 15% of cases).
- Liver cancer is the 4th leading cause of cancer death and the 6th most diagnosed cancer worldwide for male and females of all ages.
- The major risk factors vary from region to region at a global level with HCC incidence related to the major risk factors and the length of time the factors has been present in the population.
- The main risk factors include chronic infection from Hepatitis C (HCV) or Hepatitis B (HBV), aflatoxin-contaminated foods, heavy alcohol intake, smoking, type 2 diabetes and obesity.

Background: US Liver Cancer Burden

- Primary liver cancer is among the most common cause of death (5th, men) and (7th, women), in 2019.
- Death rates for liver cancer increased between 2010-2014 for both men and women.
- The increase in liver cancer death rate has been associated with the high prevalence of hepatitis C infection among baby boomers (born between 1945 and 1965) and the obesity epidemic.
- Incident rates for liver cancer is rising faster than that for any other cancer in both men (2.8%) and women (3.8%) between 2010-2014.
- The overall death rate has more than doubled from 1980 to 2016.

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- Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics **Cancer, Volume: 124, Issue: 13, Pages: 2785-2800, First published: 22 May 2018, DOI: (10.1002/cncr.31551)**

Background: US Cirrhosis Burden

- The prevalence of cirrhosis in the US population is 0.27% as of 2010 (633,323 of US adults above the age 18 years).
- Factors strongly associated with cirrhosis include older age, being male, excess alcohol consumption, Hepatitis B, and Hepatitis C. The highest population attributable fraction to cirrhosis is viral hepatitis (47%), alcohol consumption (18%) and diabetes (15%).
- Incidence of cirrhosis ranges from 300 to 1000 per 100,000 persons in North America.

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Current Recommendations by The American Association for the Study of Liver Disease (AASLD)

- AASLD recommends surveillance with US (with or without Alpha-fetoprotein) in adults with cirrhosis with or without HCV every 6 months.
- AASLD Recommendation (2018): For Child Pugh class A and resectable T1 stage (Single lesion 1-5 cm without vascular invasion) or T2 stage (Single lesion > 2cm with vascular invasion or multiple tumors none >5cm), resection is preferred over radiofrequency ablation.

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- Mehta N, Sarkar M, Dodge JL, Fidelman N, Roberts JP, Yao FY. Intention to treat outcome of T1 hepatocellular carcinoma with the “wait and not ablate” approach until meeting T2 criteria for liver transplant listing. *Liver Transplant*. 2016;22(2):178-187. doi:10.1002/lt.24360

Current therapies that exist for HCC

- Locoregional therapies (LRT) are currently implemented as a bridge to transplantation or downstaging to within Milan criteria with no one LRT preferred over the other by the AASLD recommendations:
 - Transarterial chemoembolization (TACE)
 - Transarterial Radioembolization with Yttrium-90 (TARE)
 - Ablative therapy including Radiofrequency ablation (RFA)
 - A combination of LRT
- Liver transplantation
 - Patient who are transplanted within Milan Criteria have a 4-year overall survival rate of 85% and recurrence-free survival rates of 95%.

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Sensitivity of US and MRI in Surveillance Studies

- A 13-year metanalysis study done in 2015 that included 242 (15,713 patients) studies comparing the sensitivity of Non-Enhanced Ultrasound (NEUS), Contrast Enhanced Ultrasound (CEUS), CT and MRI in detecting HCC lesions studies from Asia (149 studies), Europe (60 studies), North America (31 studies) and other (2 studies).
- The overall sensitivity of NEUS was 59.3% (29 studies), 37.3% for lesions ≤ 2 cm (14 studies), and 48.9% for explanted only reference standard (14 studies).

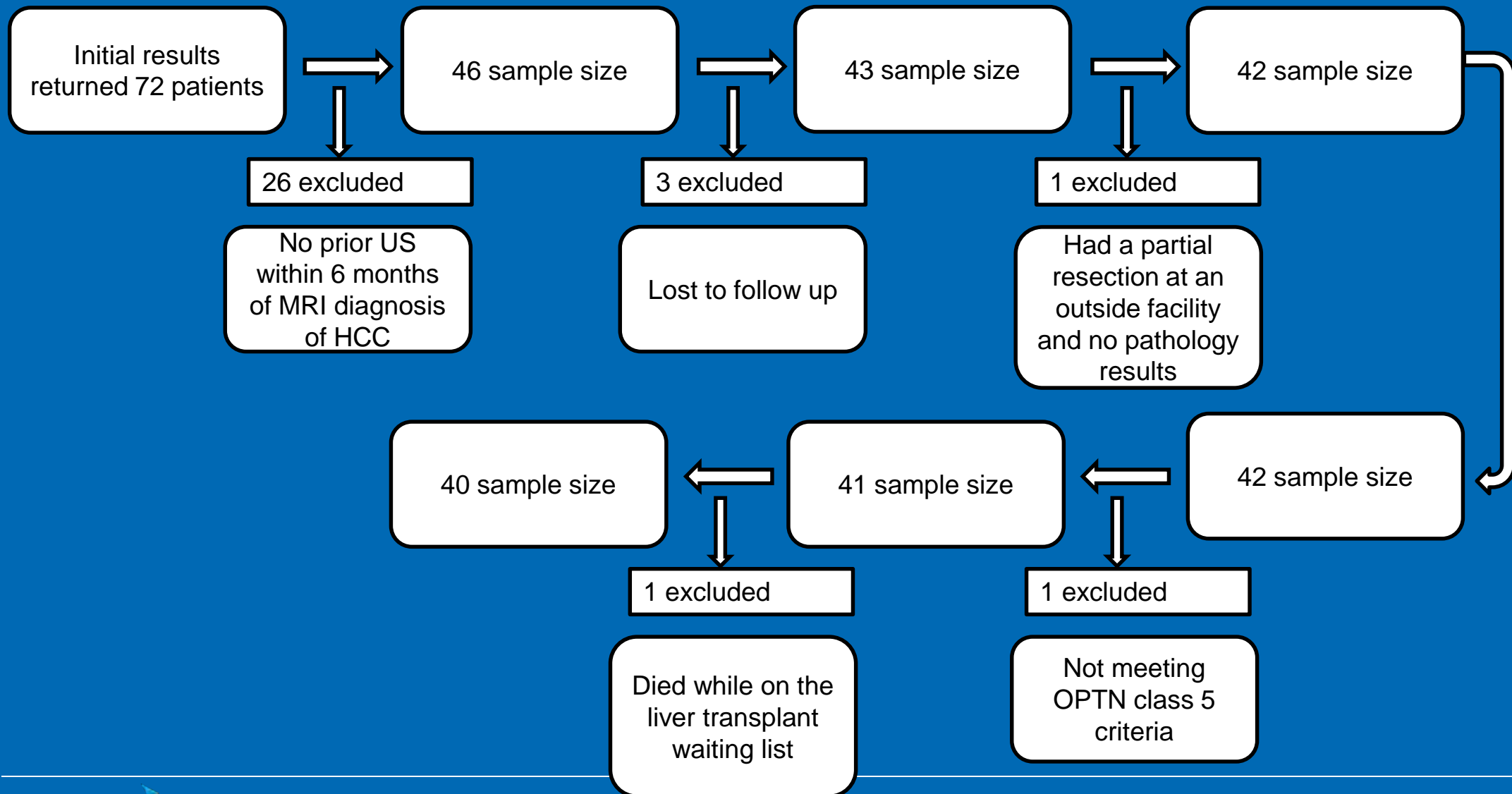
References

- Hanna RF, Miloushev VZ, Tang A, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdom Radiol*. 2016;41(1):71-90. doi:10.1007/s00261-015-0592-8

Materials and Methods

- This study is IRB approved and HIPAA complaint.
- A retrospective study, using the electronic record (April 2014 to February 2018).
- The search criteria was “MRI with and without contrast”, “OPTN class 5”, “Hepatocellular Carcinoma Surgical Pathology Results”, “Age above 18”. Initial results returned 72 patients.
- Inclusion Criteria
 - Age more than 18 years
 - US within 6 months of MRI diagnosis of HCC without prior MRI diagnosis of HCC
 - No prior diagnosis of HCC from an outside facility
 - Strict OPTN class 5 imaging criteria
 - Pathologic results
- Exclusion Criteria
 - No prior US within 6 months of MRI diagnosis of HCC
 - No corresponding pathological diagnosis of HCC
 - Age less than 18 years

Results: Sample size

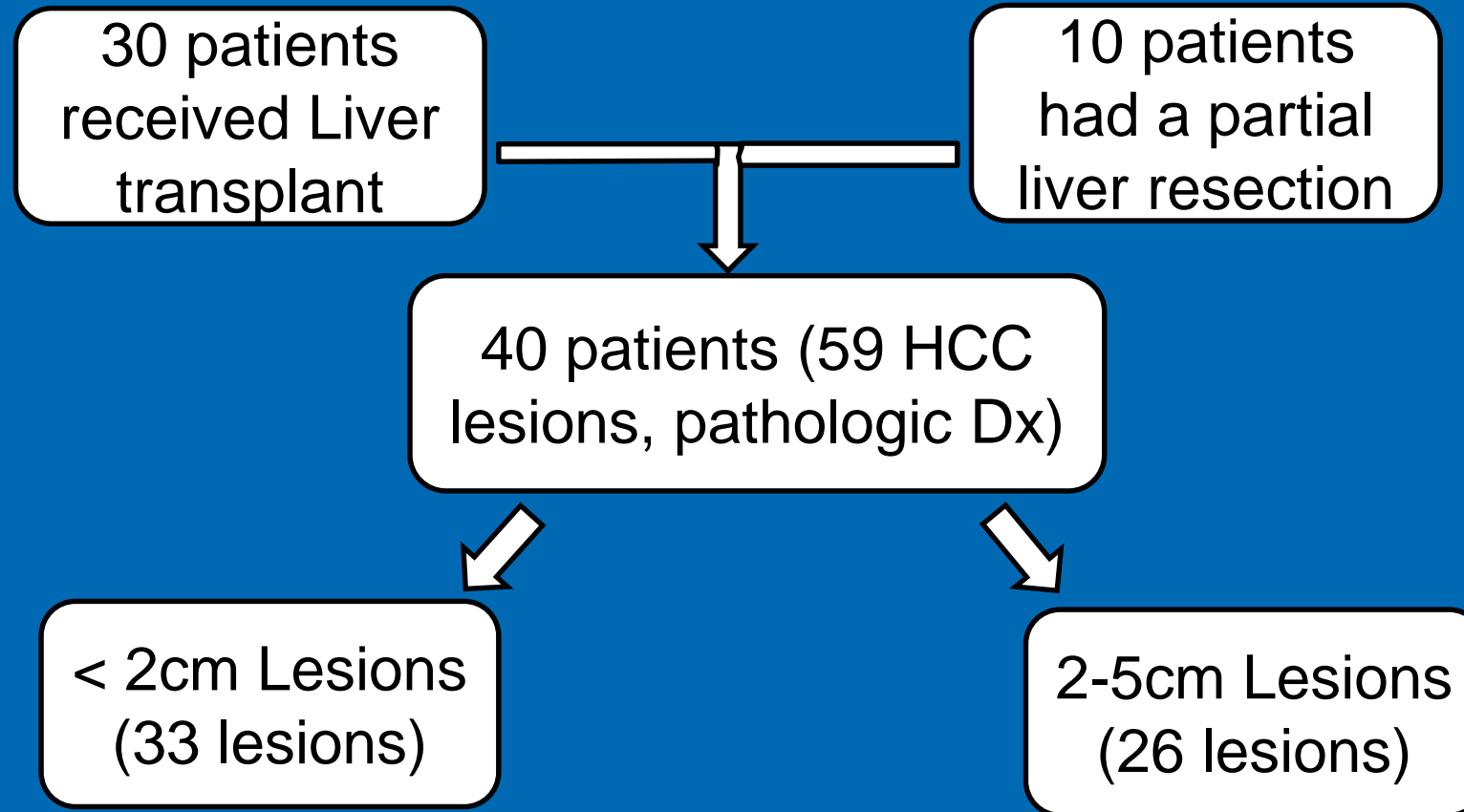


Results: Characteristics of Patients with Hepatocellular Carcinoma

Characteristics	n=40
Median age (Years)	66
Male. No.(%)	28 (70%)
Female. No.(%)	12 (30%)
Total No. of tumors	59
No. of tumors <2cm(%)	33 (56%)
No. of tumors 2-5cm(%)	26 (44%)
Causes of Cirrhosis, No.(%)	
Hepatitis B virus	2 (4%)
Hepatitis C virus	22 (46%)
Alcohol	14 (29%)
NAFLD	9 (19%)
Family history of HCC	1 (2%)

Treatment Received	n=40
Total liver transplant. No. (%)	31 (75%)
Median time from HCC MRI Dx to liver transplant (Months)	10 months
Deceased Donor Liver Transplant. No.	24
Living donor Liver Transplant. No.	7
Partial liver resection. No.(%)	9 (25%)
TACE treatment received. No	38

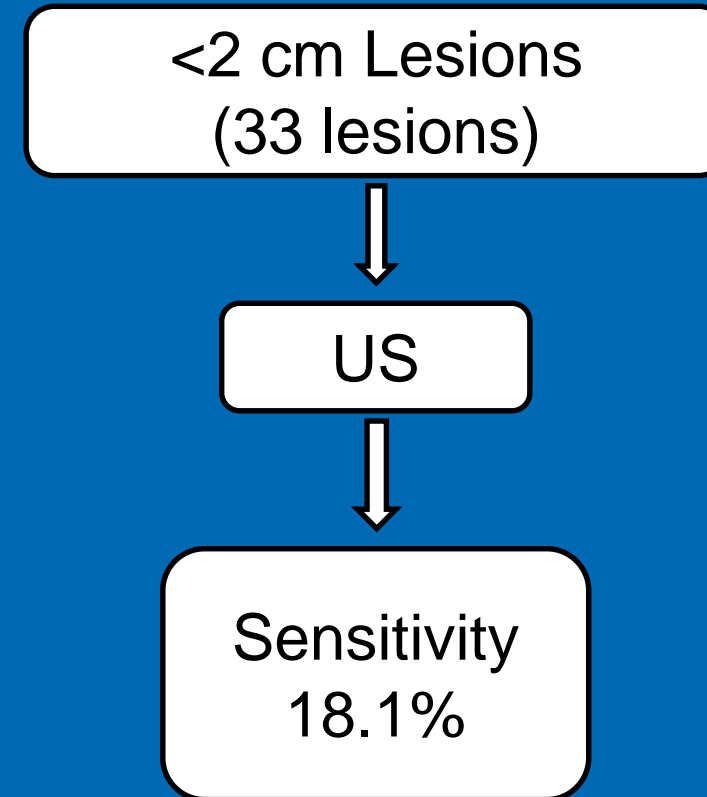
Results



Of 40 patients, 30 received a liver transplant and 10 treated with partial liver resection. A total of 59 HCC lesions was diagnosed by pathology, 33 lesions were < 2cm and 26 lesions were 2-5 cm.

Results: US estimated sensitivity for lesions < 2 cm

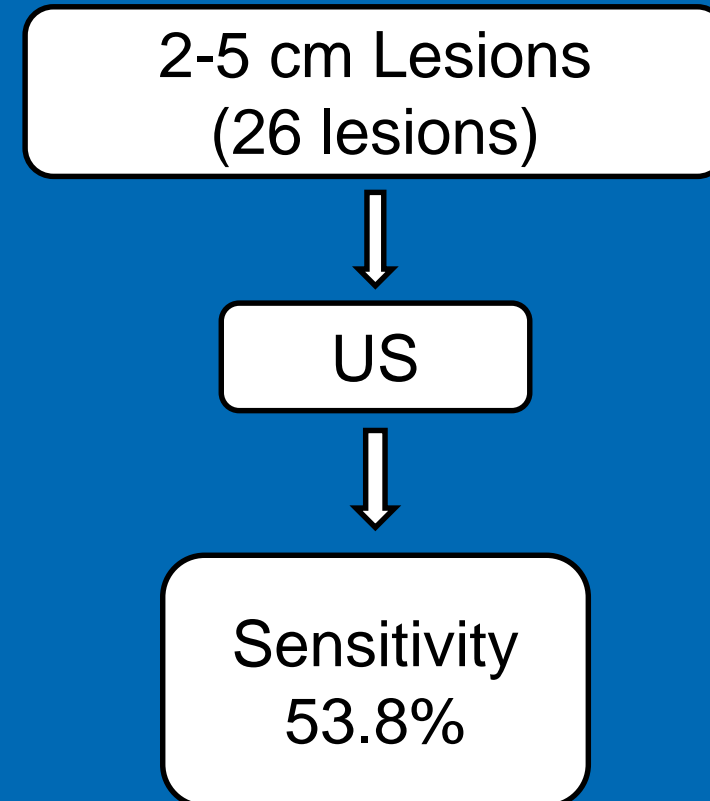
< 2cm	# Lesions=33
TP (True Positives)	6
FN (False negative)	27
US Sensitivity	18.1%



HCC lesions<2cm showed a sensitivity of 18.1% for US.

Results: US estimated sensitivity for lesions 2-5 cm

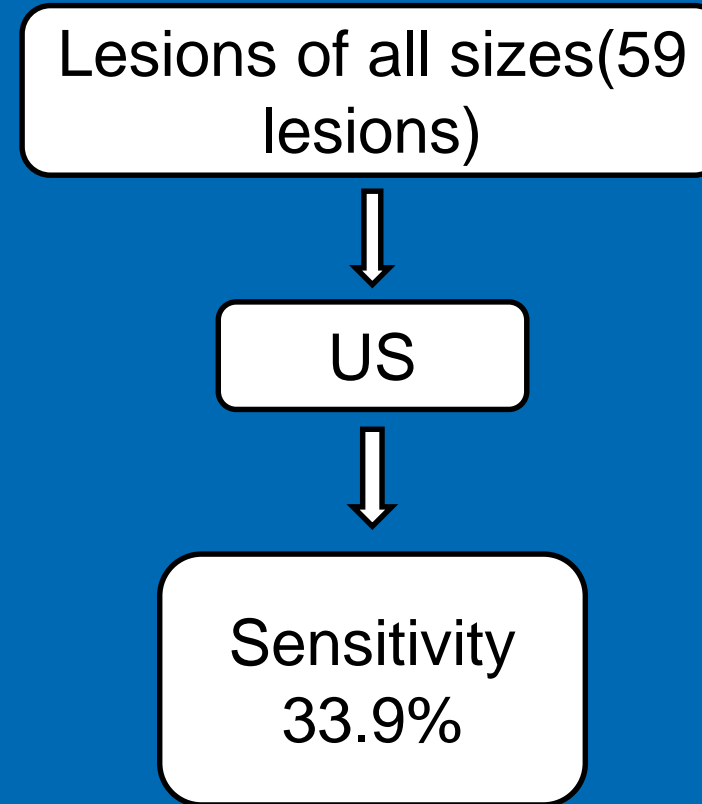
2-5 cm	# Lesions=26
TP (True Positives)	14
FN (False negative)	12
US Sensitivity	53.8%



HCC lesions 2-5cm showed a sensitivity of 53.8% for US.

Results: Overall US estimated sensitivity for lesions of any size

All Lesion sizes	# Lesions=59
TP (True Positives)	20
FN (False negative)	39
US Sensitivity	33.9%



Overall US sensitivity for HCC detection was 33.9%.

Conclusion

- At our institution (a liver transplant center), ultrasound was suboptimal in detecting lesions < 2 cm (18.1%) and lesions 2-5 cm (53.8%), similar to results reported in meta-analyses.
- As a result, in high-risk patients, MRI screening may be advantageous to permit early detection within Milan criteria, and establish treatment with curative intent.
- Additional studies will need to be undertaken to further evaluate efficiency and cost effectiveness of screening MRI in HCC surveillance programs.

Limitations of the study

- This was a single center study, with a small cohort of patients.
- US is operator dependent therefore some variability may be observed, reflecting operator, departmental or Institutional experience with high risk liver transplant candidates.
- The specificity of US as a screening modality can not be evaluated as the dataset relied upon explant gold standard.

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