NON OB ULTRASOUND MORPHOMETRICS AS BIOMARKERS

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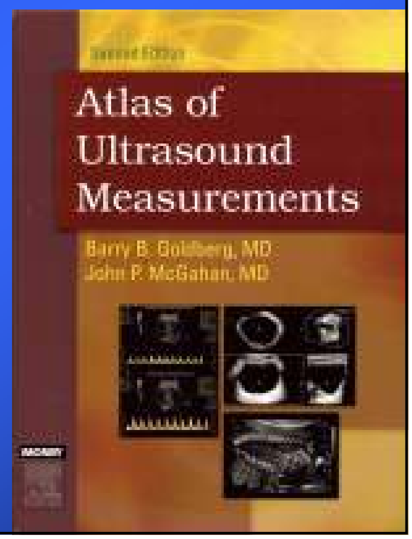
GOALS

- Review Major Types of Clinical Ultrasonic Measurements
- Discuss Sources of Measurement Error
- Review Recent Literature on Key Organ and Tumor Measurements
- Conclusions

ULTRASOUND

THE MOST MEASUREMENT ORIENTED MODALITY

- More US Measurements Reported Than for Any Other Modality
- Measurements Are Generally At A Mature Stage – Well Documented in the Literature



ULTRASOUND MEASUREMENTS

- Have Their Roots in The Strong Influence of OB in US
- Hundreds of Papers on Measurements to Estimate Fetal Growth and Anomalies
- Major Types of Spatial Measures Supported
  - Linear Distance or Diameter
  - Circumference
  - Area
  - Volume

MEASUREMENT METHODS
DISTANCE/DIAMETER

- Manual Measurement Using Digital Calipers
- Errors Due To:
  - Misplaced Caliper
  - Indistinct Organ Margin
  - Wrong Image
  - Wrong (non-standard) Location

MEASUREMENT METHODS
CIRCUMFERENCE

- Methods
  - Manual Freehand Tracing of Boundary
  - Manual Set of Boundary Points With Auto Interpolation
  - Manual Fit of Ellipse to Structure
  - Automatic Boundary Detection
- Errors Due To
  - Irregular non-ellipsoidal Lesion
  - Indistinct Boundaries
  - Incorrect Ellipse Fitting to Boundary

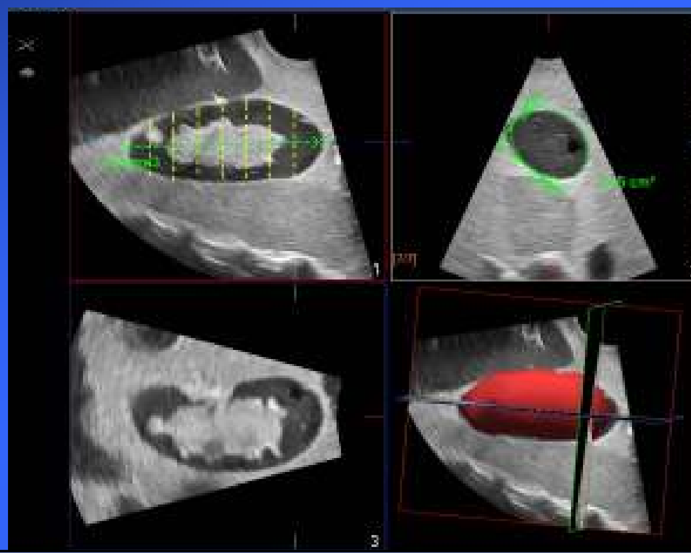
MEASUREMENT METHODS
AREA

- Methods
  - Boundary Methods Similar to Circumference
  - Area Determined By Formula or By Pixel Counting
- Errors
  - Similar to Circumference Errors
  - Larger in Magnitude

MEASUREMENT METHODS
VOLUME

Methods
- Prolate Ellipsoid Model: L x W x H x .523
- Prolate Spheroid: W x W x H x .523
  - Advantage—only one plane required
- Other Model: L x W x H x K K derived experimentally
- Summing Volumes of Multiple Parallel Slices (Simpson's Rule)
- Voxel Counting in 3D Rendering

MODERN AUTOMATED VOLUME ESTIMATION USING 2D ARRAY



MEASUREMENT METHODS

VOLUME

Errors

- Indistinct Boundaries
- Organ Shape Different From Model
- Poor Automatic Boundary Detection
- Non – Parallel Slices
- Inaccurate Slice Spacing

EXAMPLE: POLYCYSTIC KIDNEY SIZE EVALUATION

- Interest : Potential Drug Therapy to Halt Disease Progression and Enlargement
- Kidneys May be Very Large (Larger Than FOV – a problem!!)
- Poorly Delineated Borders
- Poor Visualization of Deep Border
- Irregular Border
- May Obtain Highest Accuracy Before Kidney is too Large

POLYCYSTIC KIDNEY

ORGANS MEASURED CLINICALLY

- Ophthalmic
- Neck/Thyroid
- Carotid Diameter
- Intimal-Medial Thickness
- Liver, Spleen
- Kidney
- Common Hepatic Duct
- Portal Vein
- Bladder
- Prostate Gland
- And others……

RECENT LITERATURE EXAMPLES

THYROID VOLUME

- 2D Method
  - Mean error: 3.2 ± 15.3% (others up to 27.5%)
  - Variation: 14.4 % S.D.
- 3D Method
  - Mean error: 1.8 ± 5.2% (others up to 12%)
  - Variation: 3.4% S.D.
- For Most 3D Methods Give Higher Accuracy and Lower Variability

Ref: Lyshchik et. al. Thyroid 2004:113

RECENT LITERATURE EXAMPLES
PROSTATE VOLUME

- 2D Methods
  - Prolate Ellipsoid: Mean error: -5.7(9.9%)± 6.9 ml
  - Prolate Spheroid: Mean error: -1.4(2.4%) ± 8.9 ml
  - Spheroid: Mean error: 27.1(47%) ± 19.5 ml
- 3D Method
  - One Planimetry: Mean error: -1.1 ± 7.0 ml
  - Second Planimetry: Mean error: 1.1 ± 6.8 ml
- 2D & 3D Methods Performed Nearly the Same
- Avg of Two Planimetries Slightly Better Than Using Just One

Ref: Eri et. al. Prostate Cancer & Prostate Dis 2002:273

RECENT LITERATURE EXAMPLES
KIDNEY

US vs. MRI Volume Via Voxel Counting
  - US Oblate Ellipsoid: Mean Error: -25%
  - MR Oblate Ellipsoid: Mean Error: -19%
  - US Variation (%SD of Two Meas Diff): 15-22%
  - US Inter-observer Variation (%SD of Diff): 31%
  - MR Inter & Intra obs Variation (%SD of Diff): 5%
- Oblate Ellipsoid Model Not Accurate for Kidneys
- Renal Length Correlation With Volume: r = .36
- Another Study in Piglets Showed US Underestimated Length by 3.8 (3.6%) ± 3.2mm

Refs: Bakker et. al. Radiology 1999:211 and Ferrer et. al. Urol 1997:2278

RECENT LITERATURE EXAMPLES

LIVER

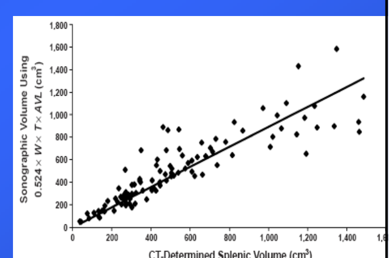
- Direct Volume Measurement of Liver by US Not Feasible Due to Obscuration by Ribs
- Correlation of 2D US With Volume by MRI
  - Only Moderate Correlation With Liver Length at MCL or Max Length (r = .44 & .51)
  - Better Correlation With Liver Length x AP Length (r = .78)
- Further Work Modeling the Liver May be Needed

Ref: Verma et. al. TJU Dept. of Radiology Faculty Papers 4-2010

RECENT LITERATURE EXAMPLES

SPLEEN

- US Oblate Ellipsoid vs. CT Volume
  - Mean error: 0.2%
  - Correlation Coefficient (R^2): 0.75
- CT Linear Indices
  - CC Length x Width x Max Thickness: Corr Coeff: 0.95

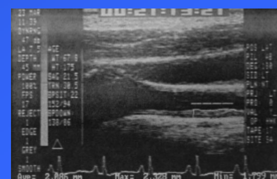


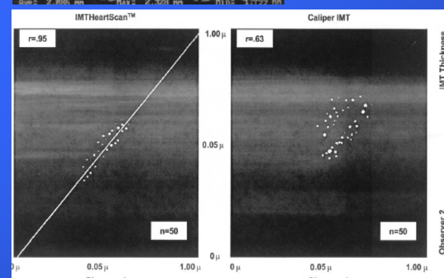
Refs: Yetter et. al. AJR 2003:1615 and Bezerra et. al. AJR 2005:1510

RECENT LITERATURE EXAMPLES

INTIMAL-MEDIAL THICKNESS

- **A Linear Distance Measurement as A Biomarker for Cardiovascular Disease**
- **Automated Detection More Accurate and Reproducible Than Manual Measurements**





Automated Manual

Ref: Barth Am J Cardiol 2002:32B

CONCLUSIONS

- **Linear, Area and Volume Measurements Using Ultrasound are Strong Candidates for Imaging Biomarkers**
- **Accuracy and Variability of Each Measurement Varies by Organ So Utility Must Be Established on an Organ by Organ Basis**
- **Some Still Require a Little More Fine Tuning**
- **Usefulness Will Be For Diseases and Treatments That Result in Size, Thickness or Diameter Changes**

IMPORTANT WORK TO DO

- Development of Standard Methods for Assessing Potential Biomarkers For Investigators to Use as Guidance When Designing Studies
- I Suggest Adapting Some Measurement Systems Analysis Tools From Industry
- Promoting the "Fine Tuning" and Further Assessment of Promising Biomarkers Using Standardized Methodology