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EVOLUTION OF PORTAL VEIN THROMBOSIS

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VALDIG Portal Vein Thrombosis Meeting

Hôtel de Ville de Paris
November 29th and 30th 2022

Summary

- The fluid dynamics of portal vein obstruction
- The practicalities of evaluating portal obstruction on imaging
- Modern clot volumetrics and imaging
- Clinical trial endpoints – clinical outcomes

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How much obstruction of the lumen is physiologically important?

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Fluid dynamics in the portal vein

The Hagen-Poiseuille Equation

$$\Delta p = \frac{8\mu LQ}{\pi R^4}$$

Δp = pressure difference between the two ends

μ = dynamic viscosity

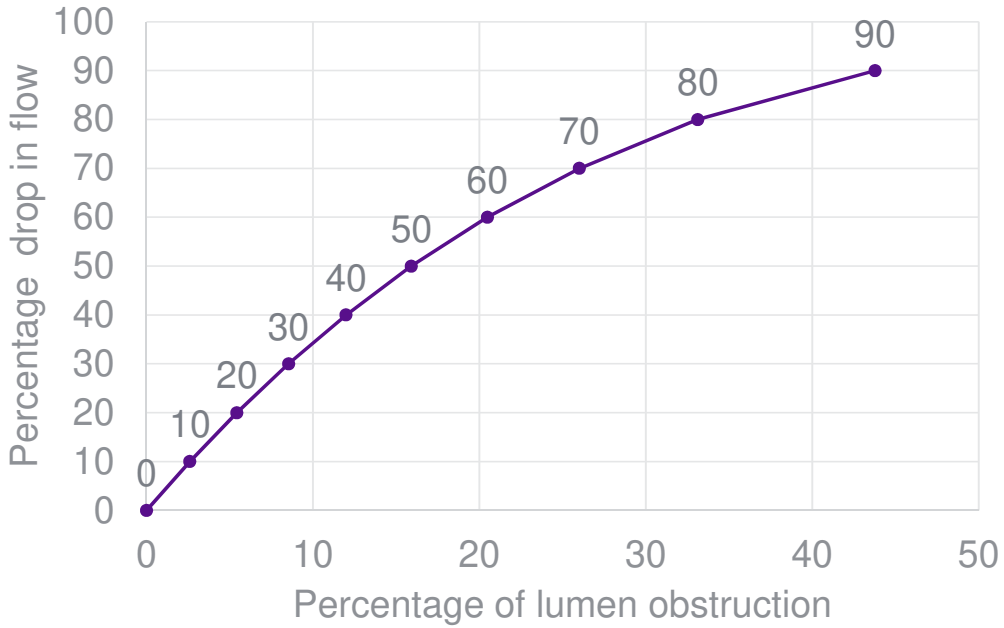
L = length of pipe

Q = volumetric flow rate

π = pi

R = pipe radius

There is approximately a 50% decrease in flow with a 16% luminal narrowing of the vessel



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Acute portal vein ligation in rats

- After acute ligation of the largest PV branch this is an elevation in portal pressure
- After about two weeks the portal pressures return towards controls due to changes in cardiac output and splanchnic vasculature
- In cirrhosis with established portal hypertension, the increase in portal pressures is blunted significantly

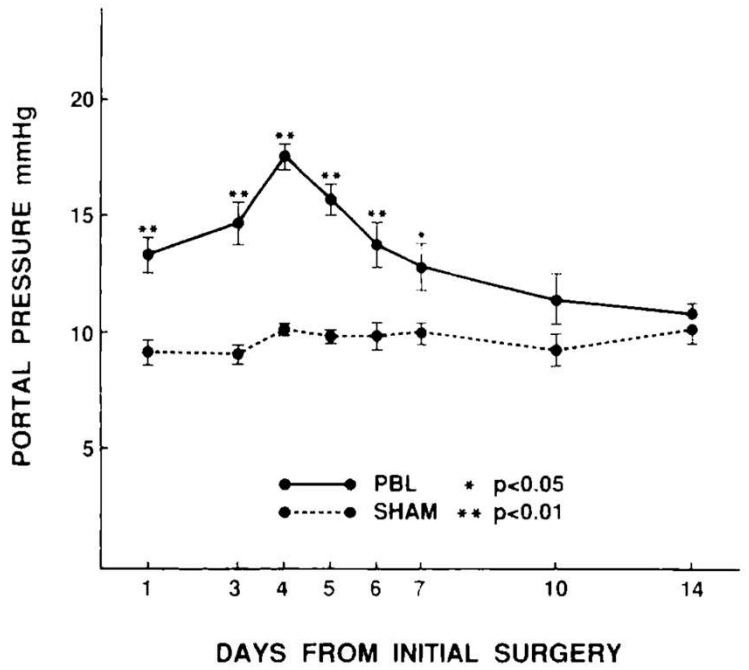

FIG. 2. Portal pressure after ligation of a major portal branch or sham operation. Portal pressure in the PBL rats was significantly higher than in the sham group for 7 days after the operation.

Um, et al., *Hepatology* 1994

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The practicalities of assessing portal vein obstruction

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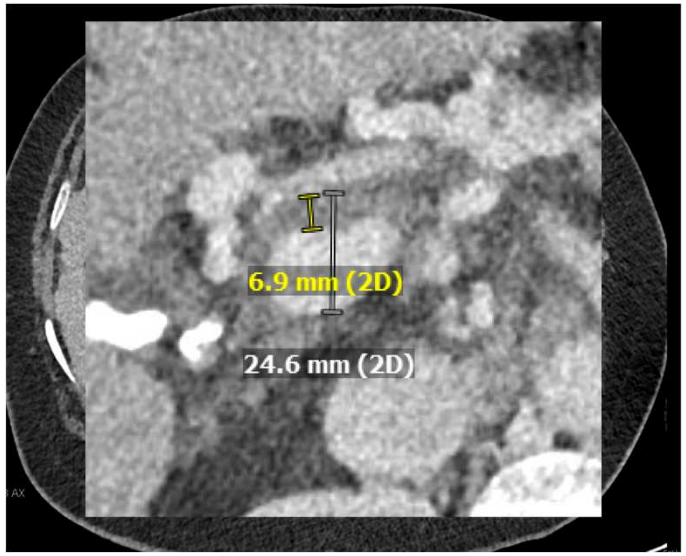
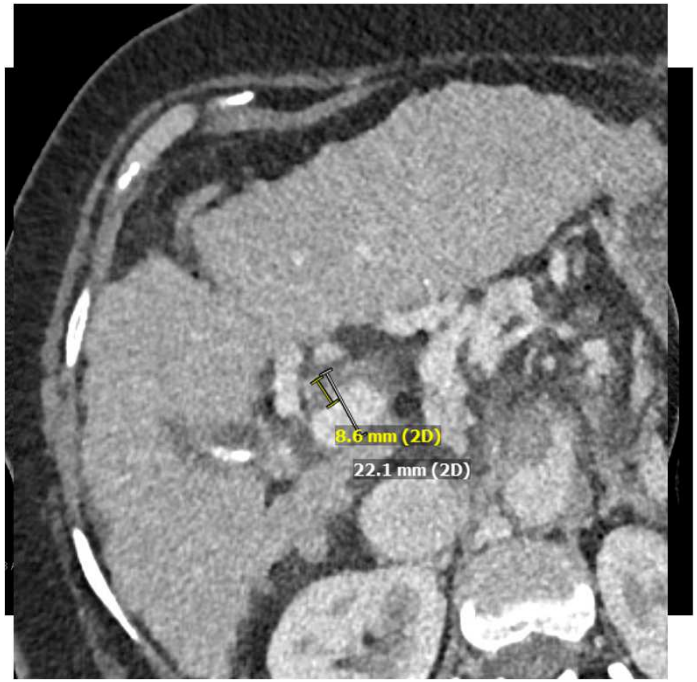
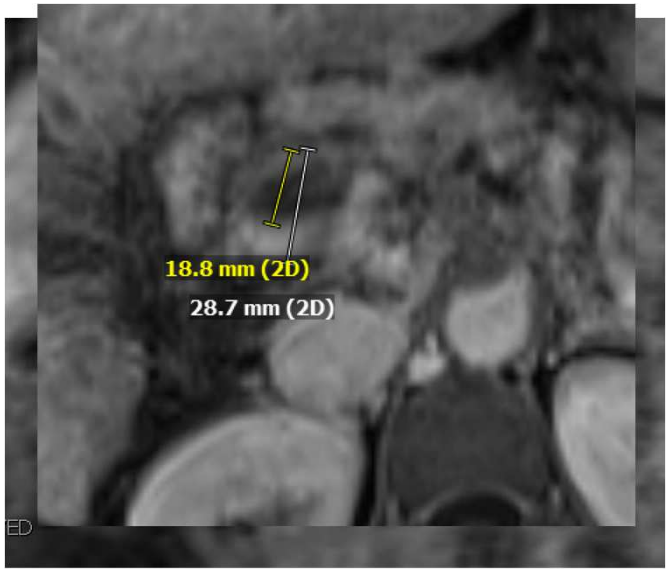
How much luminal occlusion is present?



28% occlusion



39% occlusion



65% occlusion

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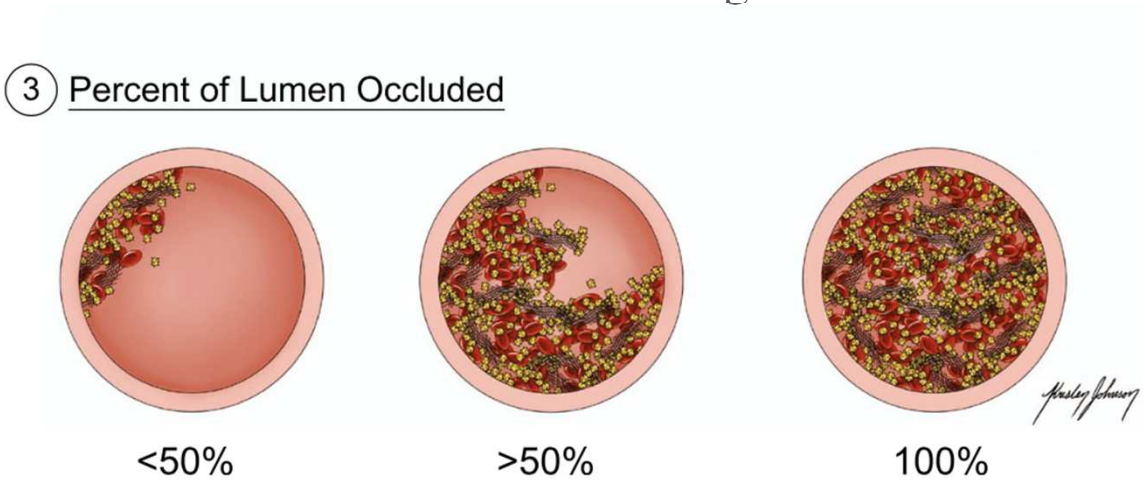
AASLD Guidance Document

- "In patients with cirrhosis who have recent thrombosis of small intrahepatic sub-branches of the PV or minimally occlusive (<50% obstruction of the lumen) thrombosis of the main PV, observation with serial imaging every 3 months without therapy is reasonable. Treatment for progressive clot should then be considered in this setting."



Northup, et al., *Hepatology* 2021

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PVT Imaging: CT vs. MRI?

- There are no comparative trials between CT and MRI in the evaluation of PVT
- Renal function is an issue with CT contrast but images are acquired quickly
- MRI requires significant breath holding by the patient

Requirement	Grey-scale and Doppler US	Contrast-enhanced US	CT	MRI
Minimum equipment requirement	Real-time US equipment; pulsed and colour/power Doppler modules Convex transducers (3.5 and 5 MHz) Linear high-frequency transducers (7.5–10 MHz to examine liver surface)	Real-time US equipment Contrast-specific software mode Convex transducers (3.5 and 5 MHz) Intravenous contrast agent for liver examination	Multislice CT	1.5 Tesla MRI unit using a phased-array coil
Contrast injection	Contrast not needed	Multiple contrast media available (have country-specific licenses)*	120–150 ml non-ionic intravenous contrast (300–350 mg iodine per ml) administered at 3–4 ml/s with a power injector Bolus tracking technique recommended	Gadolinium-based contrast agent (0.5 mmol/l) at a dose of 0.2 ml/kg administered at 2–3 ml/s with a power injector Bolus tracking technique recommended
Protocol of examination	Minimum 6 h fasting Try to visualize the entire portal venous system Use the minimum pulse repetition frequency to differentiate vessels with slow flow vs absence of flow (suggesting thrombosis) For each vessel, the possibility of visualizing direction of blood flow and patency or degree of thrombosis should be clearly stated (international recommendations[22,69])	Use low mechanical indexes (≤0.3, ideally 0.05) to minimize microbubble destruction on continuous real-time imaging) Whole portal venous system can be assessed with a single dose of contrast medium[24]	Anatomical coverage for image acquisition covers diaphragmatic dome to pubic symphisis During image acquisition: Optional: unenhanced and hepatic arterial phase (routinely not recommended due to radiation protection issues) Mandatory: portal venous phase (recommend 80 s after contrast injection for complete venous filling) Detector collimation 0.6 mm Reconstruction 3–5 mm slice thickness images in axial and coronal planes (1 mm thickness optional)	Axial T2-weighted and in and out of phase T1-weighted sequences of the liver Contrast-enhanced MRI: multiphasic dynamic 3D axial and/or coronal images of the liver using fast-spoiled gradient-echo sequences in the arterial, portal and delayed phases. MRC:[60] Heavily T2-weighted images using breath-hold single-shot-fast-spin-echo sequences; multiple thin slabs (4 mm) orientated in axial and coronal plane and multiple oblique thick slabs (30 and 60 mm) orientated radially around common bile duct

Berzigotti, et al., *Nat Rev Gastroenterol and Hepatol* 2014

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Clot volumetrics and clinical outcomes

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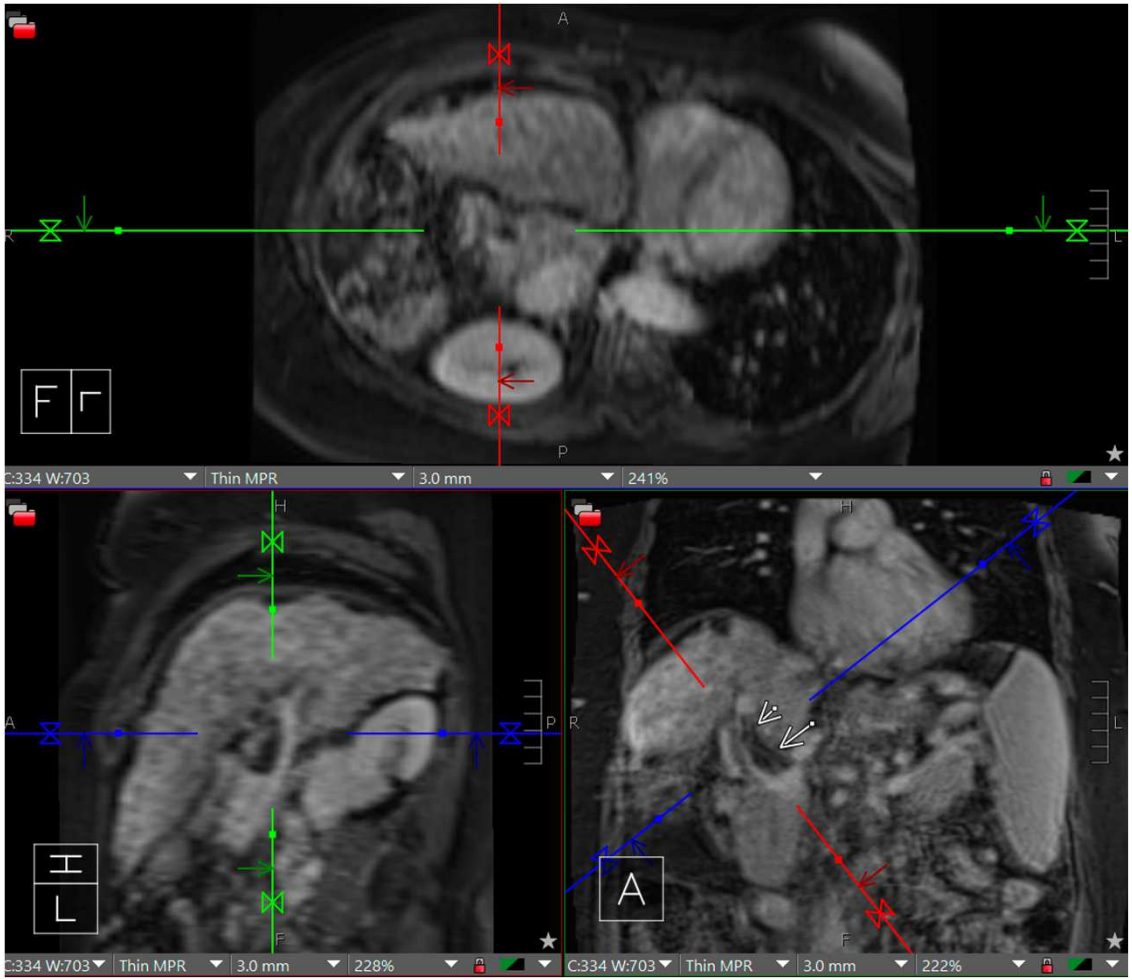
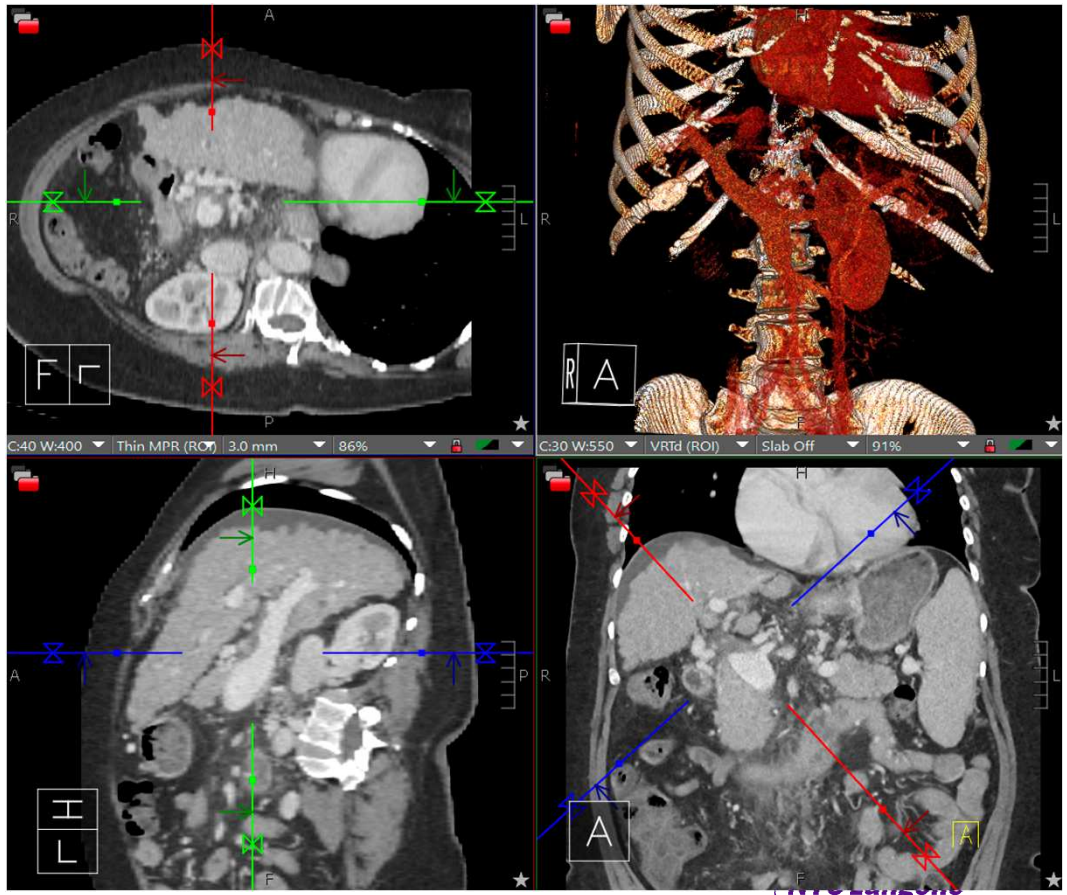
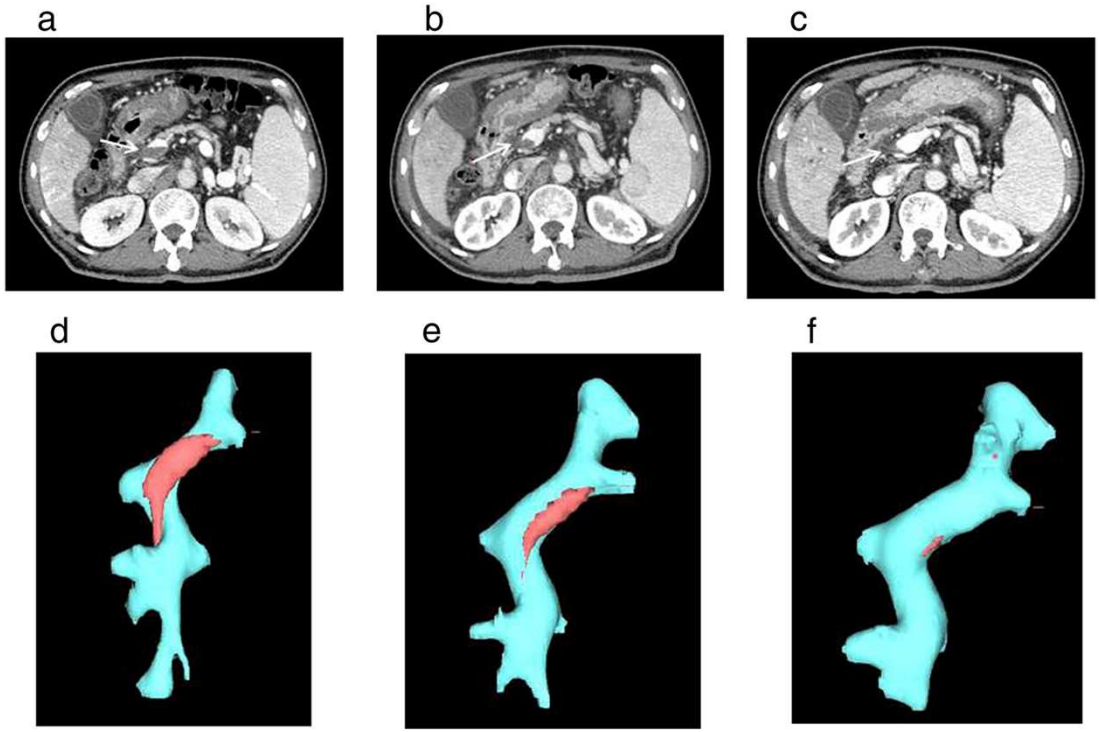
There are difficulties in assessing clot burden





Portal vein and thrombosis 3D reconstruction



- CT imaging (and MRI to a lesser extent) can be used to reconstruct the portal system in 3D with various software packages
- Technique first described for use in the portal system by Luca, et al., *Radiology* 2012.
- Clot volume can be estimated
- Very user dependent, time intensive, and requires expertise

Hidaka, et al., *Hepatol Res* 2017

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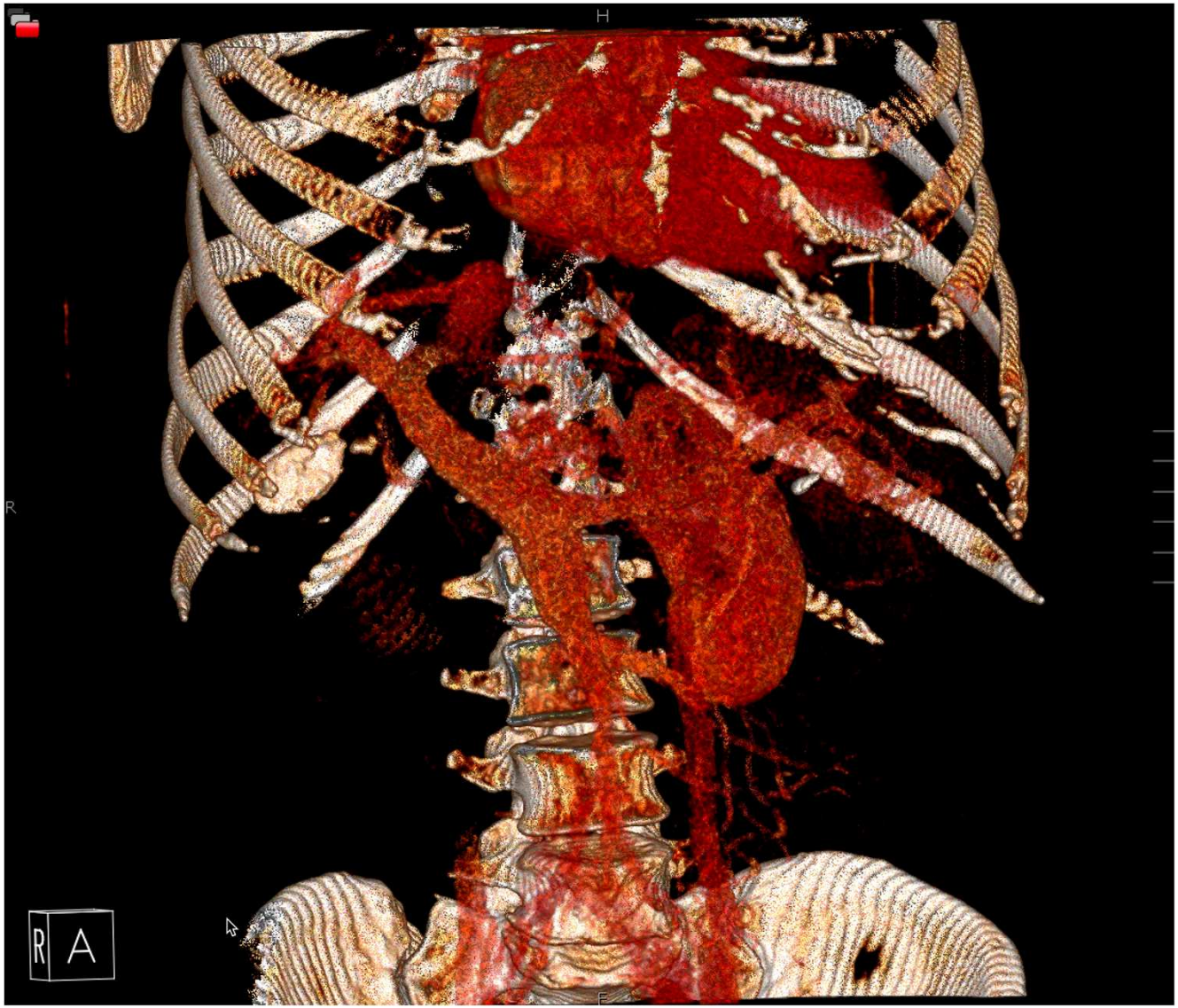

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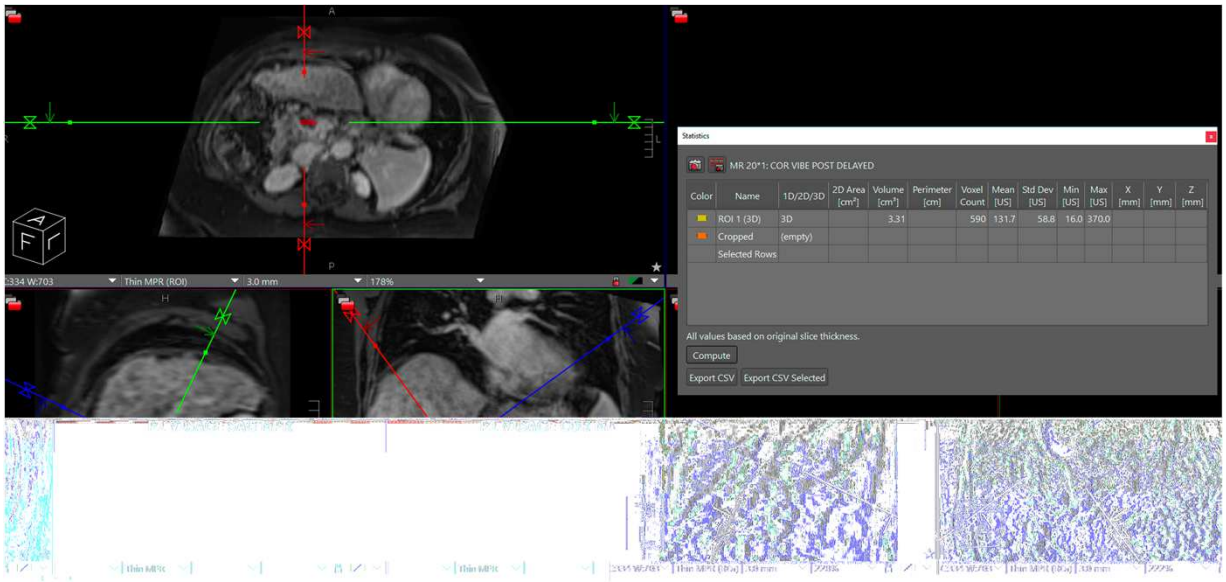
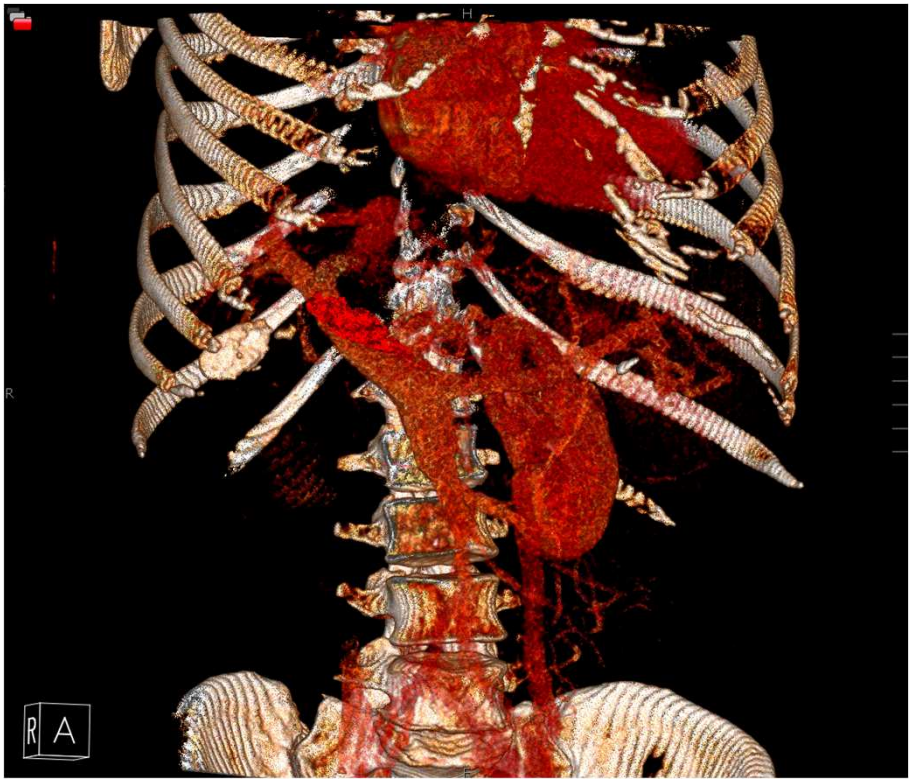
Clot in the vascular system can be quantified





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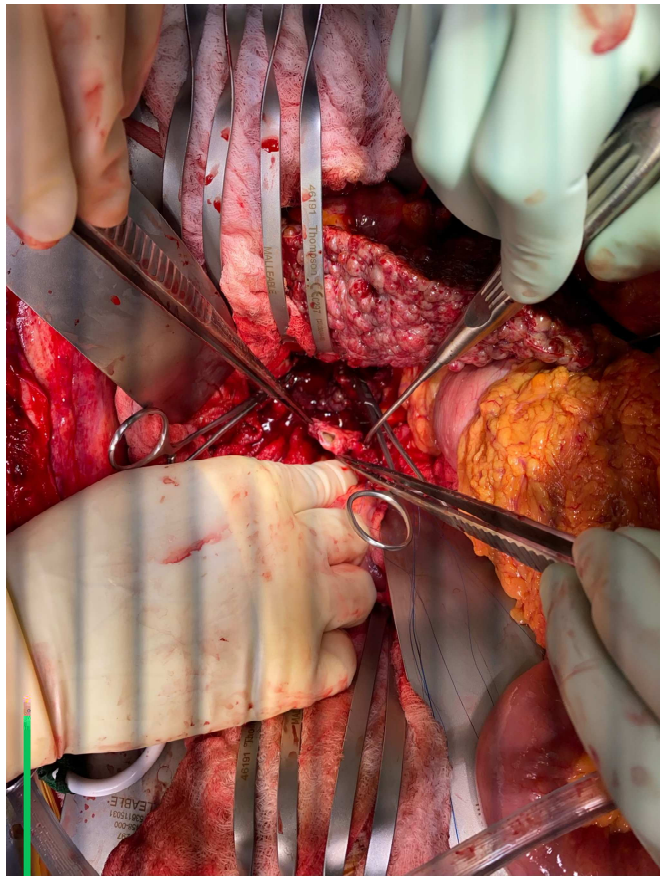
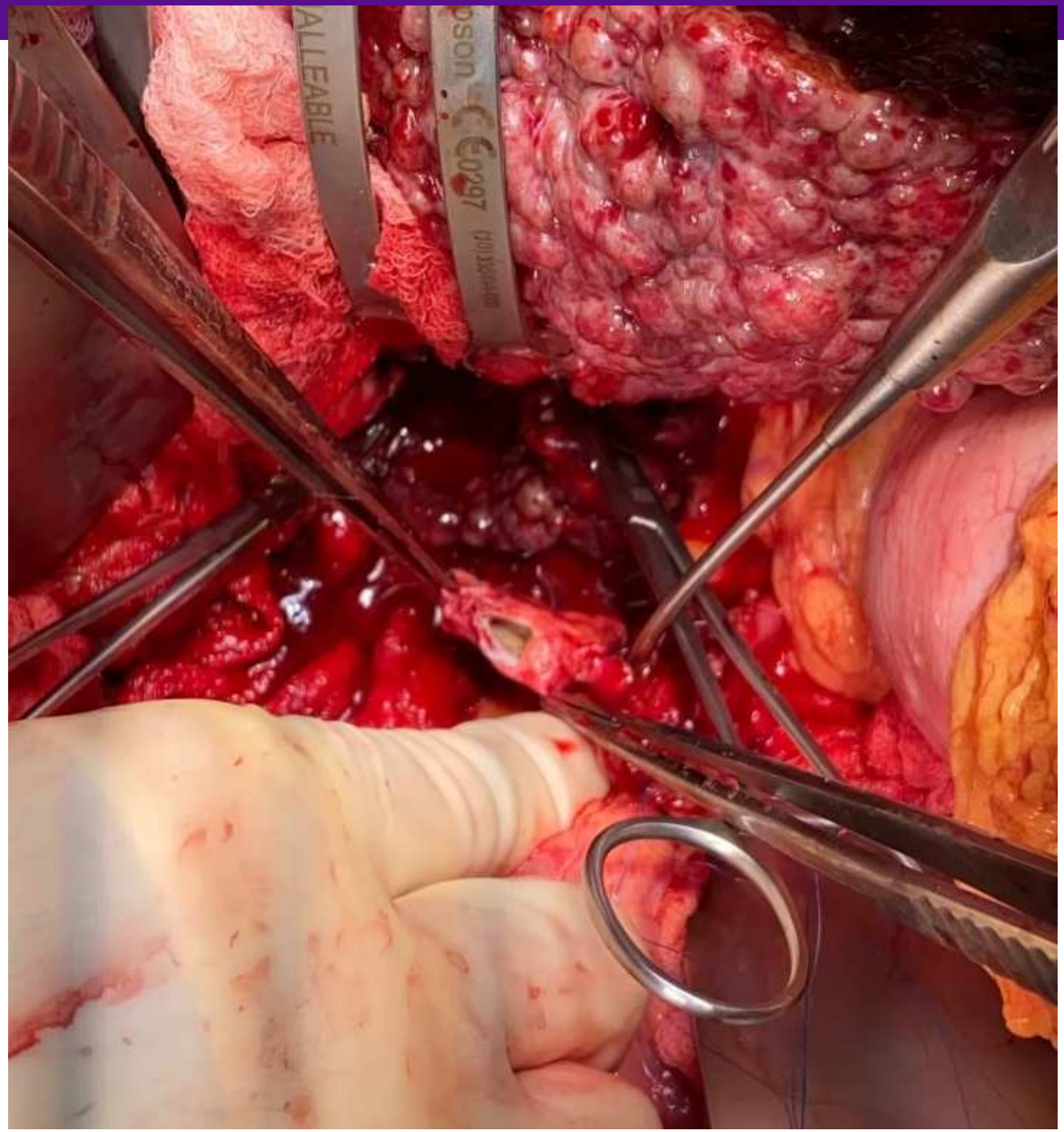
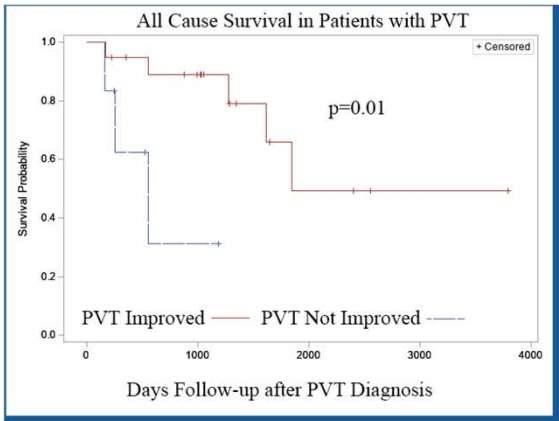
PVT *in vivo*

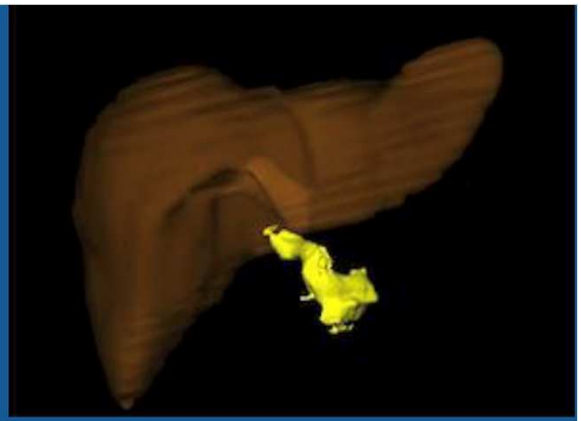




Clot volumetrics as an outcome measure



All-cause survival in patients with PVT who had improvement in clot burden (red line) on surveillance imaging, compared to those with no clot burden improvement (blue line). Patients with improvement in clot burden had significantly higher all-cause survival (p=0.01).



An image from Syngo.via (Siemens) software demonstrating 3-D relationship between liver and PVT. This software was utilized to calculate clot and liver parenchymal volumes, as well as percent of portal vein occlusion and patent portal vein area

- Retrospective 25 patient series
- The average interval between clot formation and follow-up imaging was 156 days (+/-96), and 19 (76%) patients had improvement of clot volume over this period (mean change of -1.75 ml +/- 2.74)
- Patients with a decrease in clot volume showed improved all-cause survival which was independent of baseline MELD score (MELD HR 1.23, p = 0.01 and clot improvement HR 0.16, p = 0.05).

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Carlini L, Northup, et al. EASL Vascular Liver Disorders Conference, Geneva, Switzerland 2021

Clinical trial endpoints – clinical outcomes

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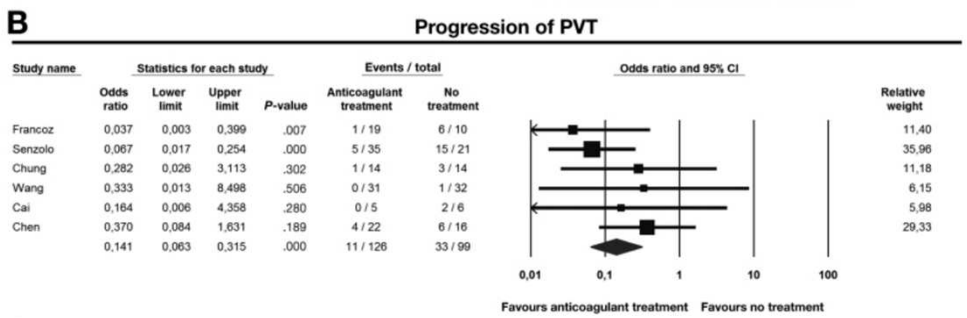
Is PVT progression a given?



Progression rates:
Anticoagulated 9%
Not Anticoagulated 33%

- Progression rates and the definition of progression are highly variable in the literature
- All of these studies reported only “progression” but did not specify amount or type of progression
- None reported directly that the progression of thrombus caused an adverse medical event, including disqualification from transplantation.

Loffredo, et al., *Gastroenterology* 2017

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Endpoints for PVT studies?

- Practical: Any change in maximum luminal obstruction of main PV?
- Practical: Complete resolution of all PV clot? Or complete obstruction of the main PV?
- Less practical: Improvement or worsening in clot volume by 50%?

None of the above endpoints are necessarily related in any way to the important clinical endpoints

- Pure clinical: Clinical progression of portal hypertension?
- Pure clinical: Ability to have liver transplant with physiologic PV anastomosis?

These endpoints would tell us more about whether PVT is a real factor influencing the natural history of liver disease

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Summary

- Percentage obstruction of the PV lumen is probably not the best measure of importance of PVT but it is easy enough to measure and interpret
- More study is needed on comparative imaging modalities of PVT, especially in clinical trials
- Clot volumetrics and PV imaging reconstruction offer more precise information on clot changes with therapies
- The best trial endpoints are yet to be determined but clinical endpoints would be most informative

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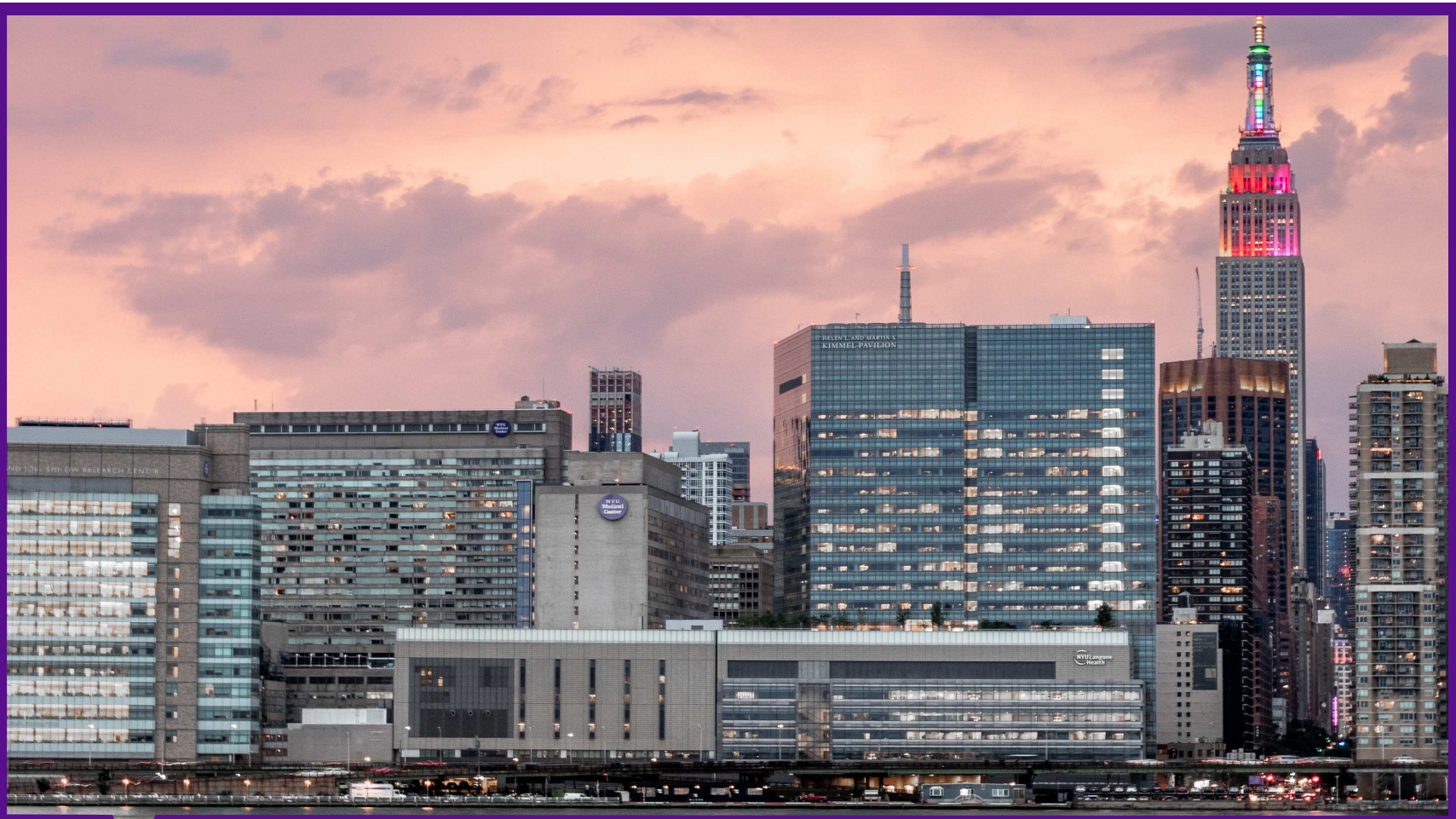

THANK YOU

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