Adrenal Tumors: An Update on Diagnosis & Treatment

Julie Hallanger Johnson, MD, FACP
Associate Member
Endocrine Program Leader
Disclosure

Consultant for HRA Pharma
Objectives

• Explain the differential diagnosis of adrenal nodule or adrenal mass
• Determine the appropriate radiologic and laboratory evaluation of an adrenal lesion
• Outline the surgical approach to adrenal lesions.
• Discover treatment of specific adrenal neoplasms
  • Adrenocortical Carcinoma
  • Pheochromocytoma
  • Functioning adrenal adenoma
Adrenal lesions often discovered incidentally

- 5-7% on CT performed for another reason\(^1\)
- 0.2-3.2% (increased with age) on CT screening study\(^2\)
  - Increase in incidence with increase in imaging
  - Almost equal by gender (45% men, 55% women)
  - Median age 62

- Etiologies
  - Adenoma or nodular hyperplasia
  - Other Benign lesions (myelolipomas, cysts, hamartomas, ganglioneuromas)
  - Adrenocortical carcinoma
  - Other malignancies (metastases, lymphoma, sarcoma)
  - Pheochromocytoma

1. Reimondo et al. JCEM 2020; 105(4):e973-e981
Screening CT Study

- 25,356 participants offered screening CT at time of annual doctor visit
  - Excluded patients on steroids, meds impacting cortisol secretion, and those with adrenal diseases known
- 351 were found to have adrenal tumor
  - 0.2% prevalence ages 18-25
  - 3.2% older than 65
  - 337 diagnosed with adenoma
    - Only 212 of these had endocrine testing
      - 147 (69.3%) non-functioning (similar percentage despite age group)
      - 40 (18.9%) cortisol autonomy
      - 25 (11.8%) with primary aldosteronism
      - 0% with pheo
      - 14 other benign nodule (myelolipoma, TB, ganglioneuroma)
    - No malignancies

Adrenal Lesions—What are they?

- **Benign Lesions**
  - Functional (40%--only 30% adrenal nodule patients see endocrinology)
    - Pheochromocytoma
    - Cortisol-producing (MACS/Cushing’s)
    - Aldosterone-producing adenoma
  - Nonfunctional (50-60%)
    - Adenoma, myelolipoma, ganglioneuroma
- **Malignant (8.6 % of incidental nodules)**
  - Adrenocortical carcinoma (0.3% of all adrenal tumors, 60% are functional)
  - Metastases (7.5 % of all adrenal tumors)
  - Lymphoma
  - Sarcoma
Radiologic Evaluation

- Size-higher risk for malignancy with larger tumors
  - 34% of adrenal tumors larger than 4cm are malignant
  - 6% if under 2cm
- Borders
- Heterogeneity
- CT
  - Unenhanced
    - HU < 10 indicates lipid rich lesion, benign (100% sensitive)
    - Lowest HU in other lesions was 14-18
  - CT Washout is less sensitive
    - Beware the lipid poor adenoma!
    - 16% sensitivity, specificity of 86% for malignancy
- MRI Chemical shift analysis sensitivity 86%, specificity 85 for malignancy

Bancos & Prete JCEM (2021) 106:11;3331-3353
Radiologic Evaluation—FDG PET

- FDG PET: adrenal-to-liver ratio > 3.4 = 83% sensitivity, 90% specificity
  - False positive in functional adenomas, false negative in necrosis\(^1\)

- 109 patients with adrenal lesions studied with FDG-PET\(^2\)
  - 100 had nonfunctional adrenal nodules by testing
  - 9 functional—4 pheo, 4 cortisol, 1 aldosterone
    - Highest SUV in the cortisol-producing adenomas (\(\text{SUV}_{\text{max}} = 10.1\))
    - Pheo (\(\text{SUV}_{\text{max}} = 8.7\))
    - Aldosterone (\(\text{SUV}_{\text{max}} = 3.30\))
    - Nonfunctioning adenomas had \(\text{SUV}_{\text{max}} = 3.20\)

Benign Adenoma
Benign Adenoma—MRI

T2

T1
Pheochromocytoma
Pheochromocytoma--MRI

T2

T1
Pheochromocytoma
Metastatic Paraganglioma—DOTATATE PET
Ectopic Cushing’s
Adrenal Cancer
Adrenal Cancer
pre and post neoadjuvant chemotherapy
Biochemical Evaluation

Adrenal Nodule
Contributors Version 2021.1 (January 12, 2021)

1) H&P
2) Review available imaging
3) Review adrenal pathology if completed, otherwise adrenal biopsy should **NOT** be performed

**Fasting labs (8-9 am):**
1) Plasma metanephrines
2) ACTH and serum cortisol
3) Serum testosterone and estradiol
4) DHEA-S, if elevated consider androstenedione and 17 hydroxyprogesterone
5) CMP
6) Renin and Aldosterone Level
7) dexamethasone Suppression Test

**Day 1 (11-12 pm):**
*dexamethasone 1 mg*

**Day 2 (8-9 am):**
* Cortisol level fasting
* dexamethasone level

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Biochemical Evaluation

• 1mg dexamethasone suppression testing
• Morning aldosterone + renin
• Plasma metanephrines
• If abnormal DST, then ACTH, cortisol, DHEA-S
• If suspected ACC by imaging, then DHEA-S, 17OH prog, 17OH preg, 11-deoxycortisol, androstenedione, testosterone (women), estradiol (men) & also consider urine multi-steroid profiling

• If bilateral indeterminate masses, test ACTH & cortisol in early AM due to risk of AI (10-12%) in patients with metastatic disease.

Bancos & Prete JCEM (2021) 106:11;3331-3353
Non-functioning adenomas or metastatic disease
33 Patients with history of cancer treated with adrenalectomy

- 122 adrenalectomies, 33 in patients with hx of CA
- 10/33 functional (8 pheo, 1 cortisol, 1 aldosterone)
- Consider possibility of collision tumors

### TABLE 2. Previous cancer*

<table>
<thead>
<tr>
<th>Previous cancer</th>
<th>Metastasis</th>
<th>Pheochromocytoma</th>
<th>Adenoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
<td>7 (35)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Non-small cell lung carcinoma</td>
<td>5 (25)</td>
<td>1 (13)</td>
<td>0 (0)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Breast adenocarcinoma</td>
<td>1 (5)</td>
<td>3 (38)</td>
<td>0 (0)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>1 (5)</td>
<td>1 (13)</td>
<td>2 (40)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>0 (0)</td>
<td>1 (13)</td>
<td>1 (20)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
<td>1 (5)</td>
<td>1 (13)</td>
<td>0 (0)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>0 (0)</td>
<td>1 (13)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (61)</td>
<td>8 (24)</td>
<td>5 (15)</td>
<td>33 (100)</td>
</tr>
</tbody>
</table>

*Values reported as n (%).
Adrenal surgery in patients with malignancy

- 81 patients with adrenal mass, malignancy
- Adrenalectomy
  - 42 patients (52%) metastasis
  - 29% (48%) the adrenal mass was an additional primary adrenal tumor process
    - 19 pheochromocytomas
    - 13 adenomas
    - 3 ACC
    - 2 ganglioneuromas
    - 2 nodular hyperplasia

Metastatic disease

- Most commonly from GU, GI, Lung primaries
- 43% bilateral
  - Adrenal insufficiency present in 12.4% of those with bilateral metastases

Adrenal biopsy is rarely needed for adrenal incidentaloma diagnosis

- Plasma metanephrines still required before any adrenal biopsy (unless HU <10)
- If concern for ACC and disease is resectable, do not biopsy
  - Review of 1410 patients with ACC NCDB
  - Biopsy upstages disease
  - Biopsy limits OS: 103.89 ± 15.65 vs. 54.93 ± 8.22 months; p= 0.001

Adrenal Biopsy in 418 patients

Table 1. Histologic diagnosis in 419 adrenal biopsies

<table>
<thead>
<tr>
<th>Diagnosis based on adrenal biopsy histology</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign adrenal cortical tissue/adrenal adenoma</td>
<td>137 (33)</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Metastasis (n = 231)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>122 (29)</td>
</tr>
<tr>
<td>Kidney</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Breast</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Other lesions (n = 23)</td>
<td></td>
</tr>
<tr>
<td>Infectious process</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Haematomata</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Neuroendocrine tumour</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Non diagnostic</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>419</td>
</tr>
</tbody>
</table>

Table 2. Concordance between findings on adrenal biopsy and final surgical pathology following adrenalectomy

<table>
<thead>
<tr>
<th>Concordant (n = 42) (adrenal biopsy = adrenalectomy)</th>
<th>Discordant (n = 8) (adrenal biopsy ≠ adrenalectomy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>ACC</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>Haematomata</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>ACC, adrenocortical carcinoma</td>
<td>Adrenal biopsy</td>
</tr>
<tr>
<td>*11 renal cell carcinoma, 5 non-small-lung carcinoma, 1 uterine carcinoma, 1 thyroid, 1 liposarcoma, 1 leiomyosarcoma, 1 unknown primary carcinoma.</td>
<td></td>
</tr>
</tbody>
</table>

Peri-operative preparation

• If surgery (or biopsy) planned, please assure not an incidental finding of pheochromocytoma
• Work-up as if no history of malignancy
• If bilateral, look for adrenal insufficiency
• Watch for post-operative changes to BP and AM cortisol
Nonfunctioning adenoma

• Watch for adrenal insufficiency in case MACS was missed pre-operatively
Pheochromocytoma
Pheochromocytoma

• Beware the adrenal mass that is present and not evaluated before any surgical procedure....
• Risk of hypertension on surgical induction, abdominal insufflation, open operation, biopsy is not minor.
• 4-6% of incidental adrenal tumors are a pheochromocytoma
• Most are benign
• Metastatic disease not diagnosed upon resection pathology, but upon metastatic findings
Pheochromocytoma

- Classic symptoms:
  - Hypertension, tachycardia, pallor, warmth, headache, chest pain
- Labs: plasma metanephrines
  - 24-hour urine metanephrines, 24-hour urine catecholamines
  - Many medications cause false positives with plasma metanephrines (TCA, ADHD meds, etc)
- Imaging: vascular, bright on T2 weighted MRI imaging
- 30-40% have genetic basis (SDH mutations) so all see genetics
Pre-operative evaluation

- Cardiac evaluation
  - Echocardiogram & EKG
  - Evaluate for hypertensive cardiomyopathy
    - May include acute—Takotsubo cardiomyopathy
  - Evaluate for arrhythmias
    - Prolonged QT, etc.
Surgical Preparation

• Ideally, need 2 weeks to medically prep to be safe
  • Can be done more quickly if urgent
• BP testing at home with orthostatic vitals twice daily
• Report to physician (phone, patient portal, etc) every 2-3 days
• Goal is low normal BP with orthostasis, no spikes in BP
• Add salt load several days pre-op
• Add beta-blocker if not already done about 3 days pre-op
Alpha Blockade

- Start alpha blockade, hold beta-blockade until well-alpha blocked (risk for hypertensive crisis)
- Phenoxybenzamine
- Other alpha blockers which are selective alpha-1 receptor blockers
  - Doxazosin—longest duration of action
  - Terazosin
  - Prazosin
Phenoxybenzamine

- Phenoxybenzamine long-lasting, non-selective, inhibitor of alpha-1 and alpha 2 receptors
- Downside: cost & side effects
- 60 caps of 10mg dose
  - Retail US $7600, lowest price $1162
- Side effects: nasal congestion, orthostasis, diarrhea, dizziness, tachycardia
- Start 5mg daily at bedtime and up titrate
- Risk for post-operative hypotension
How to choose?

- No benefit to any alpha blocker over another in
    - In this same study, patients with Phenoxybenzamine had less intraoperative hypertension and required more pressure support.
- There is data to support NOT using alpha blockade
Alternatives

- Calcium channel blockers
  - Can be add on to alpha blockade
  - Rarely sole medication if mild hypertension or intolerance to alpha-blockade
- Metyrosine (alpha-methyl-paratyrosine)
  - Consider for severe or metastatic disease
  - Use in combination with calcium-channel blocker
  - Side effects: sedation, depression, galactorrhea, and extrapyramidal symptoms
  - Cost: US$ 11,167-$39,000 30 tablets of the 250mg dose
When to add Beta-blockade?

• Assure fully alpha blocked, or could induce hypertensive crisis (unopposed alpha adrenergic action)

• Can add once orthostatic and develop rise in heart rate from the alpha blocker/orthostasis.

• Usually I add 3 days pre-operatively otherwise.
Avoid the use of....

- Dopamine antagonists
- Opioid analgesics
- Norepinephrine reuptake inhibitors
- SSRI
- MOA inhibitors
- Steroids
- Neuromuscular blockade
- Beta-blockers without prior alpha blockade
Intra-operatively

• Treat pre-op anxiety
• Use arterial line/CVP for BP monitoring
• Anesthesia avoids use of desflurane, ketamine, ephedrine, meperidine, morphine, droperidol, pancuronium.
• Intraoperative hypertension can be treated with nitroprusside, esmolol, nicardipine, magnesium
• Endocrine Society recommends open surgery for masses greater than 6cm, but others argue laparoscopic is okay up to 12cm.
• Open surgery recommended for invasive tumors.
• Avoid tumor rupture—peritoneal implants, persistent disease or recurrence
Post-operatively

- Watch for hypoglycemia
- BP monitoring & treatment
- Some patients require pressors until alpha blockade medications are out of the system
- Follow-up of lab work
- Genetics to determine pattern of follow-up
  - SDHx mutations, VHL, etc have full body requirements for follow-up
Mild Autonomous Cortisol Secretion
What is MACS?

• **Definition of mild autonomous cortisol secretion (MACS)**
  • Cortisol following the 1 mg Dexamethasone suppression test is >**1.8 mcg/dL**
  • No overt features of Cushing syndrome
  • Adrenal adenoma/macronodular hyperplasia (very rarely –micronodular hyperplasia)
  • ACTH independence
  • “Subclinical Cushing syndrome” –no longer to be used.
  • May develop over time (4-12% develop functionality in previously nonfunctional adenomas)
Work-up comments

- Consider adding ACTH, cortisol, DHEA-S baseline to your work-up.
- If baseline ACTH is suppressed and DHEA-S is low, likely cortisol autonomy.
- Then, the dexamethasone suppression test is completed on day #2.
- Some experts (Drs. Young & Bancos, Mayo Clinic) say that if the DHEA-S is over 100 and ACTH >15, can avoid DST.
MACS & adrenal Cushing’s syndrome

• Most adrenal cortisol production is subclinical also called mild autonomous cortisol secretion (MACS)
• Cardiovascular and glycemic outcomes are improved for both clinical and subclinical Cushing’s patients
• Preoperatively: goals are to improve glucose control, improve BP control, improve electrolyte abnormalities, vaccinations
• Pneumocystis jiroveci prophylaxis
• Thromboembolism prophylaxis is critical
• Post-op PT to counteract muscle weakness
• Replace cortisol/ adrenal insufficiency treatment post-operatively
Medical management of Cushing’s with adrenal focus

Steroidogenesis in adrenal cortex affected by specific enzyme inhibitors*

Steroidogenesis in the adrenal cortex denoting the specific pathways inhibited by ketoconazole (KTZ), metyrapone (MTR), mitotane, etomidate, and newer steroidogenesis inhibitors.

* Refer to UpToDate table for nomenclature used for steroidogenic enzymes.
† Aldosterone synthase.

From: Daniel E, Newell-Price JD. Therapy of endocrine disease: Steroidogenesis enzyme inhibitors in Cushing’s syndrome. Eur J Endocrinol 2015; 172:R263. Copyright © 2015 BioScientifica Ltd. All rights reserved.
MACS

- For non-suppressed ACTH, consider post-op day #1 AM cortisol. Less than 10 is cause for replacement.
- Post operative adrenal insufficiency replacement:
  - 0.5mg of dexamethasone every 6 hours will allow post-op day 1 endogenous cortisol to be measured.
  - Most use usual care with hydrocortisone IV for stress doses if critically ill is reasonable, vs. oral at double usual doses with hospital stay once eating.
  - Taper can be done as outpatient with endocrinologist.
Adrenal Insufficiency post-operatively

- Patients MUST have education about AI
- Medic Alert bracelet/jewelry/tattoo/wallet card
- Emergency steroid administration kit and teaching how and when to use
- Hydrocortisone is typically used
  - 15mg in AM, 10mg mid-day
- In patients with history of Cushing’s physiologic replacement can lead to steroid withdrawal so at times we have to use supraphysiologic doses and gradually reduce.
Aldosterone-secreting Adenoma
Hyperaldosteronism

- Very common cause for hypertension
- Best test is early AM plasma renin activity and aldosterone for aldosterone to renin ratio
  - Abnormal is aldosterone > 10, and suppressed renin
  - Confirmatory testing is not necessary in patients with hypertension and spontaneous hypokalemia
- Once confirmed, use of adrenal venous sampling is necessary almost always to assure not bilateral.
- Co-secretion with cortisol may be present in up to 22%

Bancos & Prete JCEM (2021) 106:11;3331-3353
Aldosterone-secreting adenoma

- Blood pressure management with spironolactone/eplerenone is reasonable after diagnosis, but pre-operatively to assist in LVH reduction
- Consider stopping 1 week prior to surgery to avoid hypoaldosteronism with hyperkalemia post-op
- Watch BP, as most patients will have improved BP post-operatively, but not come off all meds
- Improvement in BP can take 1-6 months
- Watch for post-op AI
Surgical Approach
Adrenalectomy

• Open
  • Done if concern for ACC as doing laparoscopic approach can lead to seeding, recurrence\(^1\)
  • Large pheochromocytoma

• Laparoscopic

• Robotic

• Posterior retroperitoneal approach

What is Posterior Retroperitoneoscopic Adrenalectomy (PRA)?

- A minimally invasive approach to adrenalectomy performed though the **back** (retroperitoneum) with laparoscopic incisions
Benefits Over Abdominal Approach

• Do not need to enter the abdomen
• Great for patients with extensive prior abdominal operations (don’t have to deal with adhesions)
• Ideal for patients who need bilateral adrenalectomies
  • Don’t have to reposition!
• Less hernia risk
• Some studies say less pain
• More surgical options for patients
Drawbacks

• Need to reposition and flip the patient supine if conversion to open is required

• Different view for the surgeon than with transabdominal surgery

• Time for initial positioning in the OR (next slide)
Positioning

Knee rest

Cloward mattress
Incisions

- Head
- Foot
- Iliac crest
- Paraspinal muscle edge
- Line of 12th rib
View During Right Adrenalectomy

- Retroperitoneal tissue
- IVC
- Adrenal vein
- Adrenal mass
View During Left Adrenalectomy

- Left kidney
- Adrenal mass
- Adrenal vein
- Retroperitoneal tissue
Routine Postoperative Care

• All patients admitted overnight

• Pain is generally minimal

• Clear liquids the day of surgery, regular diet on POD1

• Majority go home POD1
Adrenocortical Carcinoma
Adrenal Biopsy=BAD in ACC

• 1410 patients with ACC (NCDB)
• 830 patients had T1/T2, 365 T3, 162 T4
• 89.4% received clinical diagnosis and 11.6% had biopsy diagnosis
• Overall survival: clinical dx 103.89 months vs. biopsy dx 54.93 months
• Patients with T1/T2 and biopsy had comparable median OS to T3 ACC clinical diagnosis

Resection of Adrenocortical Carcinoma

• Indicated for Stage I-III if technically feasible
• Open
  • Achieve R0 resection
  • Avoid tumor rupture/seeding
• IVC tumor thrombus embolectomy if indicated
  • May need cardiopulmonary bypass
Borderline Resectable

- Need for multi-organ or vascular resection
- High risk for margin-positive resection
  - Liver invasion
  - Major tumor thrombus in vein lumen
  - Involvement of wall of IVC or renal vein
- Abutment or involvement of unresectable vascular structures
- Questionable presence of metastases
- Poor performance status due to comorbidities or symptoms of hormone excess

Diagnostic scan and after neoadjuvant chemo
Initial imaging

Post 6 cycles of EDP+M

Post Nivolumab +Mitotane 4 of 5 cycles
Treatment continued

Preoperative percutaneous portal vein embolization of the right portal vein and segment 4 branches, followed by a first-stage operation:

4/3/19 Open left adrenalectomy with en bloc resection of left hemidiaphragm + Primary repair of left hemidiaphragm defect + Mobilization of the splenic flexure + Left to right visceral rotation + Intraoperative ultrasound of the liver + Partial liver parenchymal transection

4/3/19 Intraoperative liver ultrasound + First stage modified ALPPS procedure: Linear hepatotomy along extended right hepatectomy plane + Placement of antiadhesive barrier.

4/17/2019 Second stage ALPPS: right trisegmentectomy (extended right hepatectomy), cholecystectomy, en bloc partial right peritonectomy, RFA ablation of surgical resection margin (Tissuelink device)