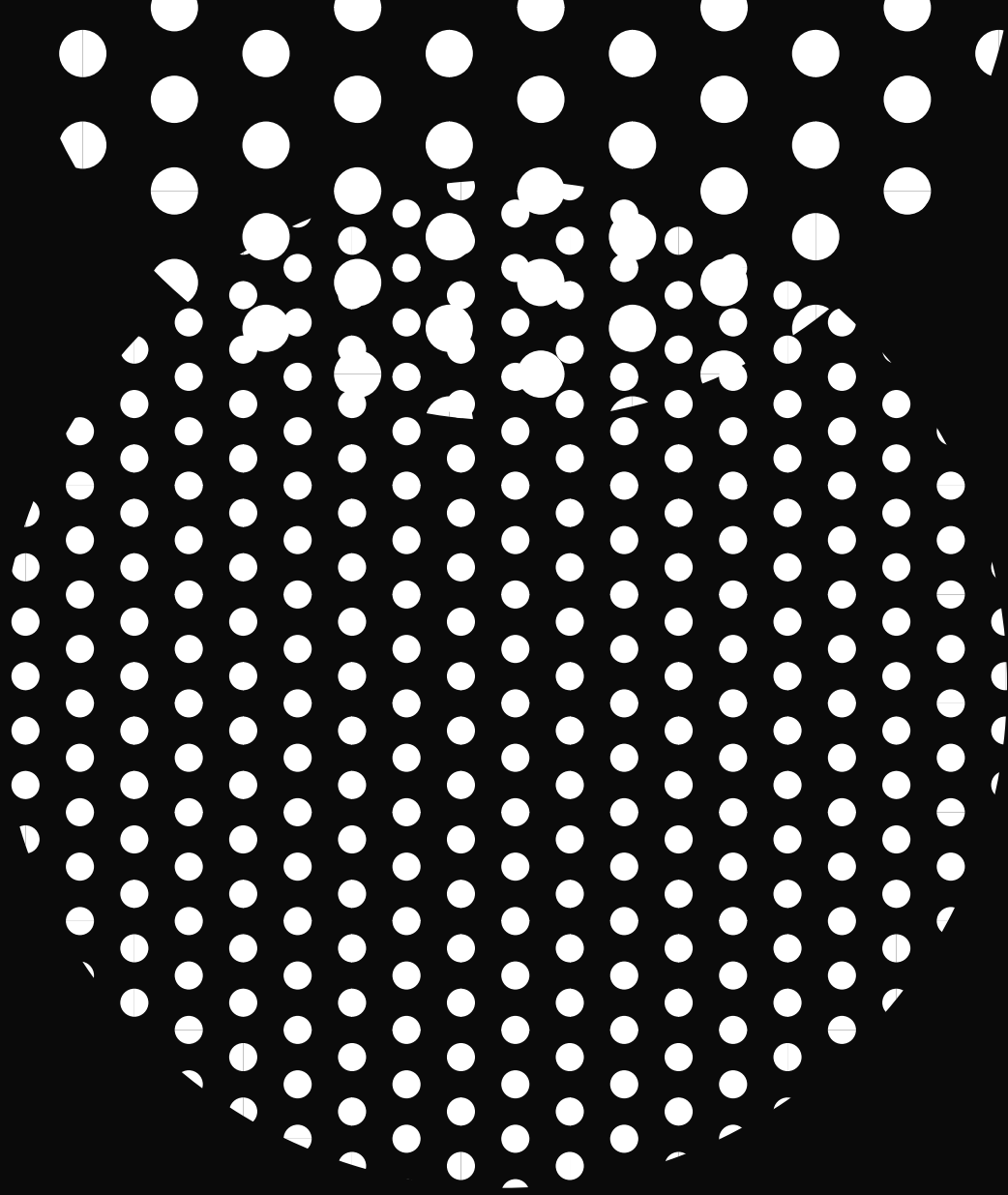




Small cell lung cancers

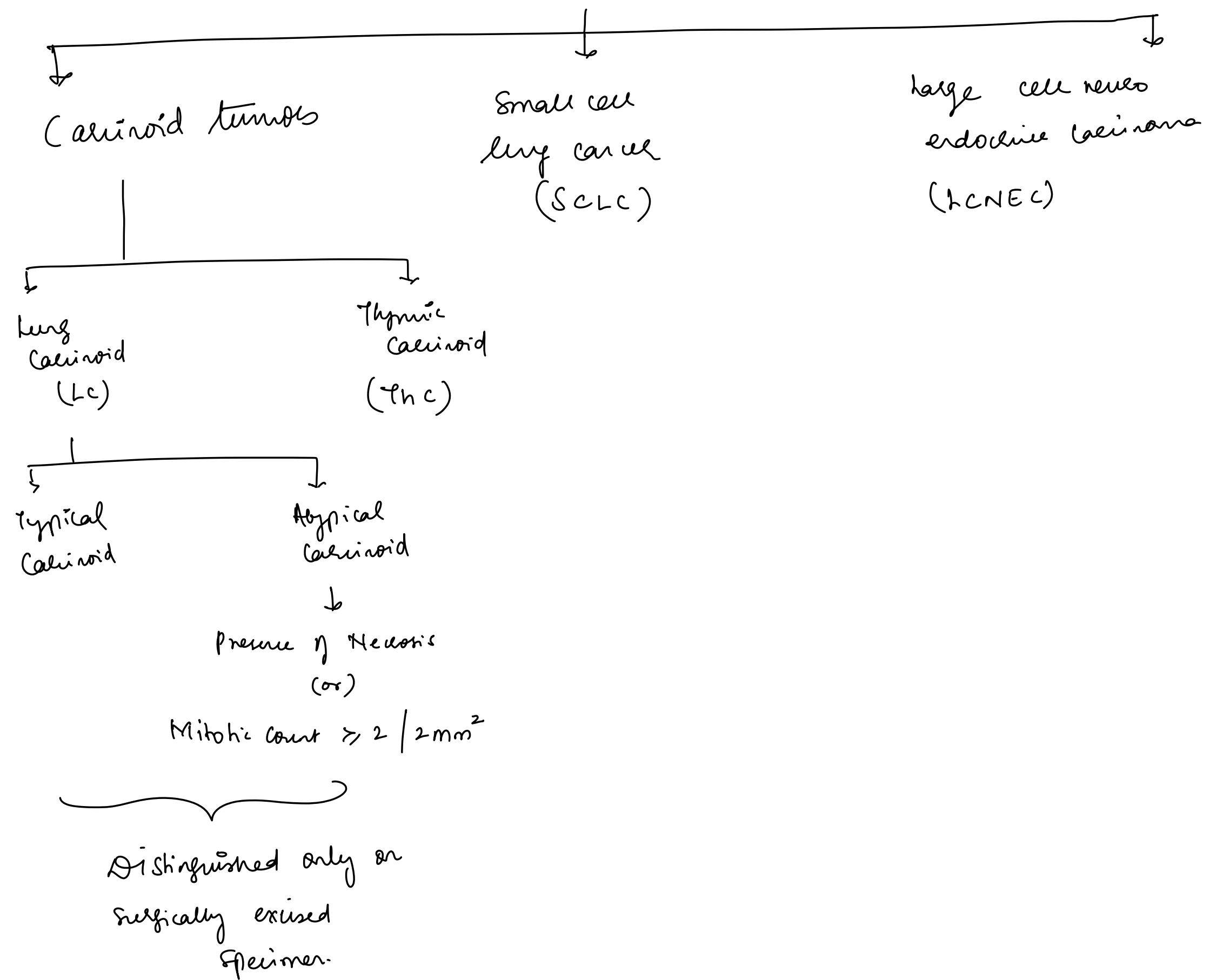
&

Bronchial carcinoid tumours



Neuroendocrine tumors of thorax

WHO classification



→ Etiopathology

- most aggressive lung cancer
- elderly, smokers.
- 5yr OS < 10%. d/t early treatment resistance.
- male = female.
- screening LOCT does not improve survival → "Inkernal cancer"
(diagnosed between 2 screening CTs)

→ Diagnostic & staging work up:

Table 1. Diagnostic and staging work-up of SCLC

History and clinical examination
Medical history (including smoking history and comorbidities)
PS
Physical examination
Assessment of paraneoplastic syndromes (especially when initiating immunotherapy)
Laboratory analysis
CBC, liver enzymes, sodium, potassium, calcium, glucose, LDH and renal functions tests should be carried out
Imaging
CT of the thorax and abdomen should be carried out in all patients; an FDG-PET-CT is optional
In case of a suspicion of bone metastasis and no other metastasis, a bone scintigraphy should be carried out unless FDG-PET is available
Imaging of the brain (preferably MRI) is mandated in patients with stage I-III disease
MRI of the brain is recommended for patients with stage IV disease who are eligible for PCI but who choose not to undergo PCI
Tumour biopsy
A diagnosis of SCLC is preferably assessed based on histological examination of a biopsy
In case of planned surgery, invasive mediastinal staging is required
Functional assessment
Pulmonary function testing (FEV1, VC, DLCO) is required for patients with stage I-III SCLC who are candidates for surgery or RT
VO2 max assessment by cycle ergometry should be carried out if surgery is planned when pulmonary function tests are limited

CBC: complete blood count; CT: computed tomography; DLCO: diffusing capacity of

→ Biopsy features:

- Small round cell tumour differentials
- ↑ Ki67 index.
- IHC neuroendocrine markers
 - × Synaptophysin
 - × Chromogranin
 - × CD56 (NCAM) → more sensitive less specific.
- 10% tumours may be negative for all 3.

↓

Recent markers

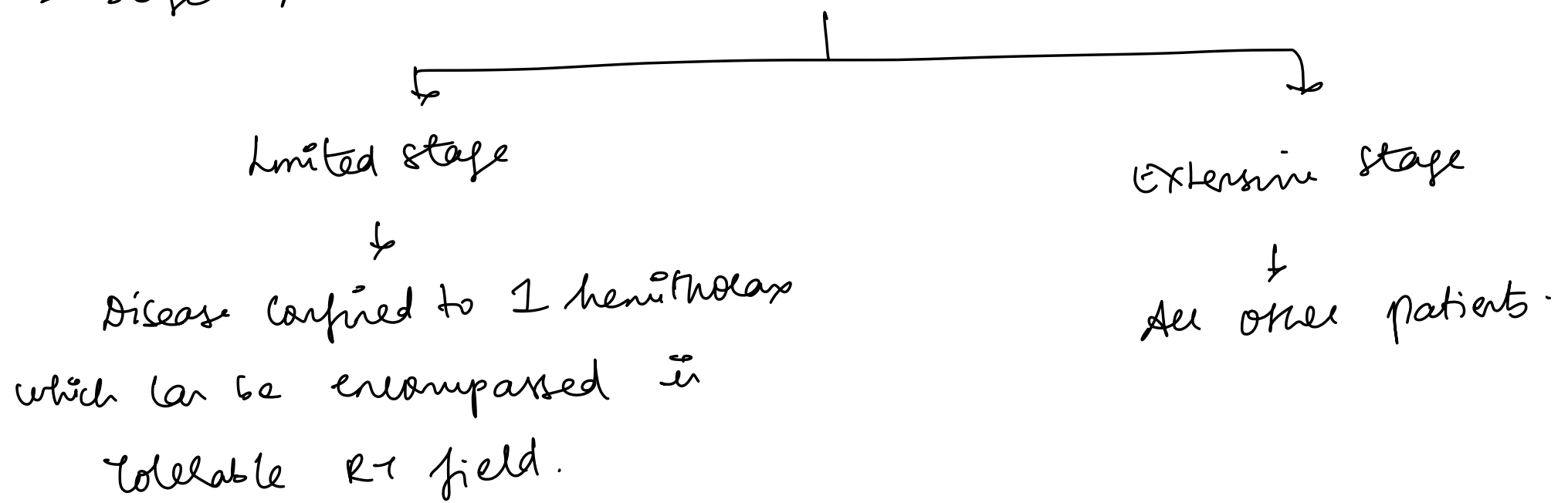
- INSM1 → Insulinoma associated 1.
- TTF1 → Thymid Transcription factor 1
- Pou2f3 → Tuft cell marker

* Poor prognostic factors

- ↓ Performance status
- ↑ age
- male sex
- ↑ LDH
- SIAOH
- ↑ gross tumour volume.

→ Staging of SCLC:

- 2 stage system - Veterans Administration lung study group (VALSG)



- AJCC system stages SCLC same as NSCLC → used in surgical candidates.

→ management:

→ management of limited disease:

→ Role of surgery in SCLC:

- Controversial.
- Current recommendation based on NCCN analysis of retrospective data
- Surgery considered **ONLY** as part of multimodality treatment **AFTER** extensive pathological mediastinal staging.

for $T_1 - T_2 N_0$ → always followed by chemo.

for R_1/R_2 or N_2 on pathology → Adjuvant concurrent CRT.

→ Role of chemotherapy in limited SCLC:

- cisplatin / Carboplatin if cis not tolerated + Etoposide × ④ cycles.

Standard dose → cisplatin 60 mg/m^2 on day 1
+ Etoposide 100 mg/m^2 on days 1, 2, 3 } every 21 days.

* Role of Consolidation immunotherapy after chemo:

- STIMULI trial → nivolumab + ipilimumab consolidation therapy showed No improvement in OS/PFS.

→ Role of lung RT in limited disease SCLC:

Earlier
RCT

→ 45 Gy in 30 #
BD dose to finish
in (3) weeks

VS

45 Gy in 25 #
OD dose to finish
in (5) weeks.



- Superior survival outcomes
- But higher grade 3 toxicity — pneumonitis & esophagitis.



CONVERT
trial

(to minimise
toxicity)

* used IMRT/
3D CRT.
only.

→ 45 Gy in 30 #
BD dose in
3 weeks

VS

66 Gy in 33 #
OD dose in
6.5 weeks.

No significant difference in OS
No significant difference in toxicity.

BUT → CONVERT trial was a Superiority powered trial and not an equivalence trial. Hence the equivalent results were rejected and still the standard of care is 45 Gy in 30 # in BD dose in 3 weeks.

* Timing of RT

- Based on performance score
- Concurrent in PS 0-2
- Sequential in PS ≥ 2

↓
when used Sequential, RT volume should include prechemo volume of primary and nodal status → SWOG trial.

→ Role of Prophylactic Cranial Irradiation (PCI)

- ↑ OS in pts w complete remission - 5.4% improvement
- Dose 25 Gy in 10 # (once daily)
- Given only after CT/RT for primary.

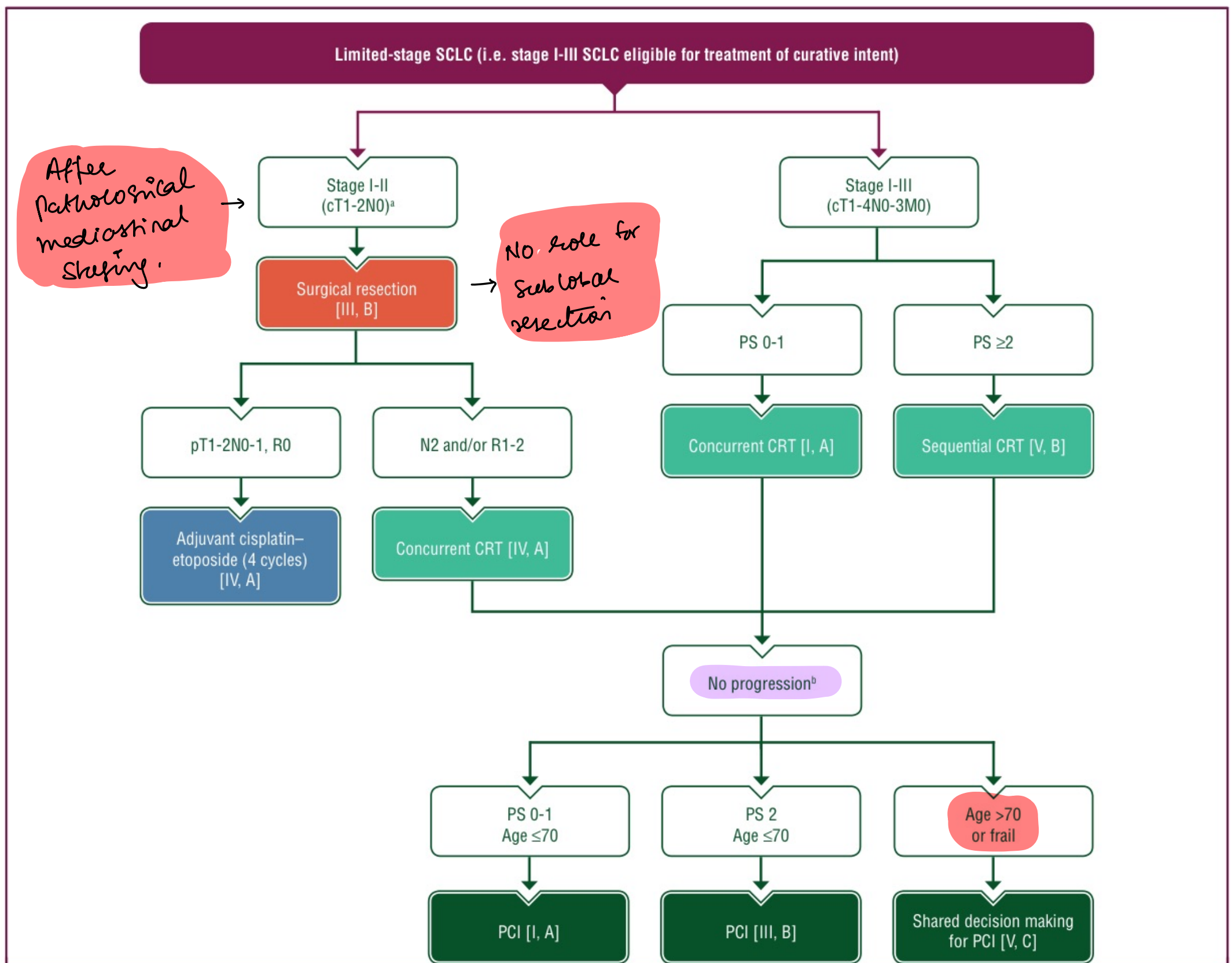


Figure 1. Treatment algorithm for SCLC in patients with limited-stage disease (i.e. stage I-III SCLC eligible for curative treatment).

→ management of extensive SCLC:

- poor prognosis in terms of survival.
- But show rapid response to systemic therapy.

* First line therapy:

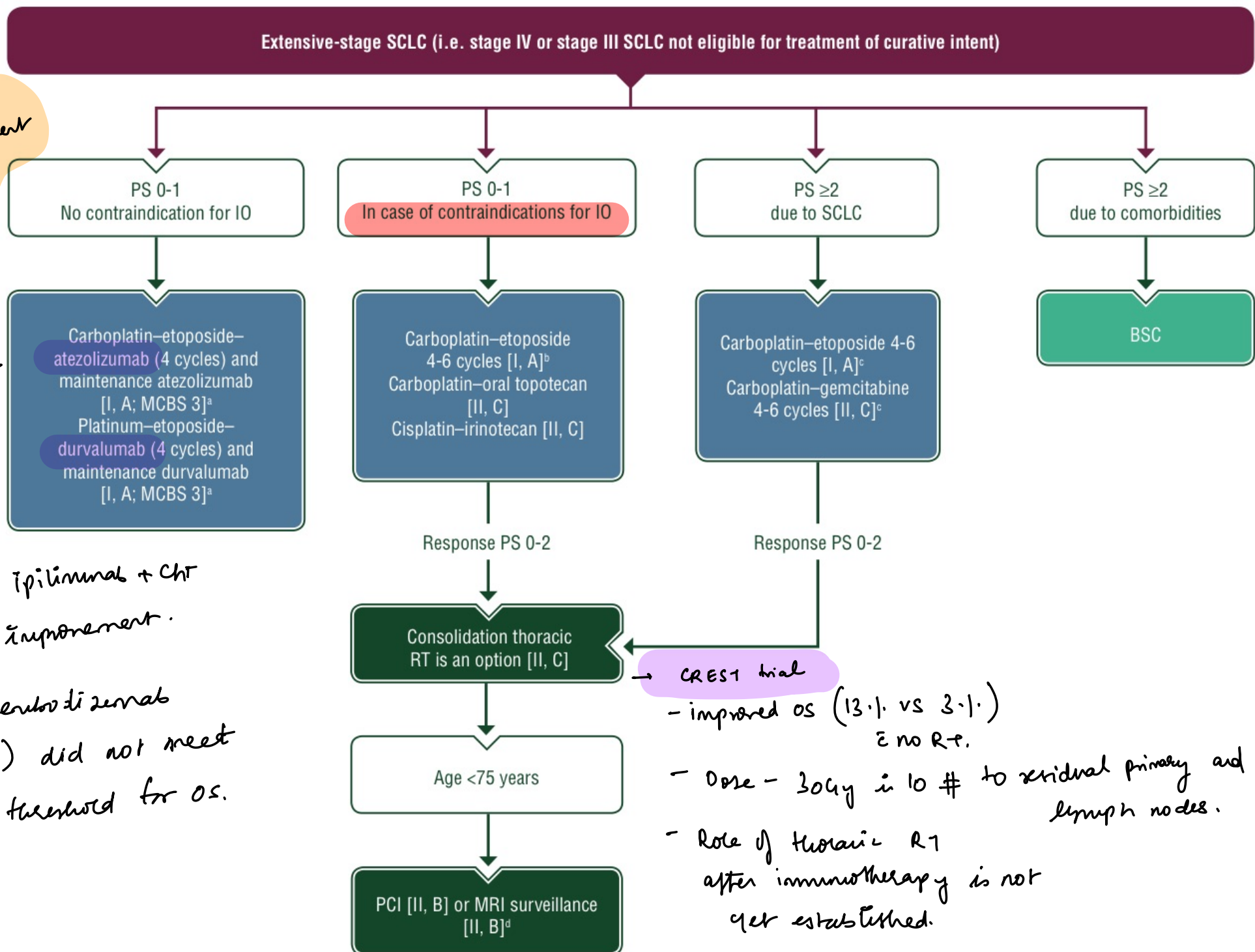
Both showed modest improvement in OS and PS - an improvement of 1-2 months only.

↑
ImPower 133 RCT.

→
CASPIAN RCT.

* Trials with ipilimumab + ChT showed no improvement.

* Trials with pembrolizumab (Keynote 604) did not meet prespecified threshold for OS.



→ Treatment of Relapse.

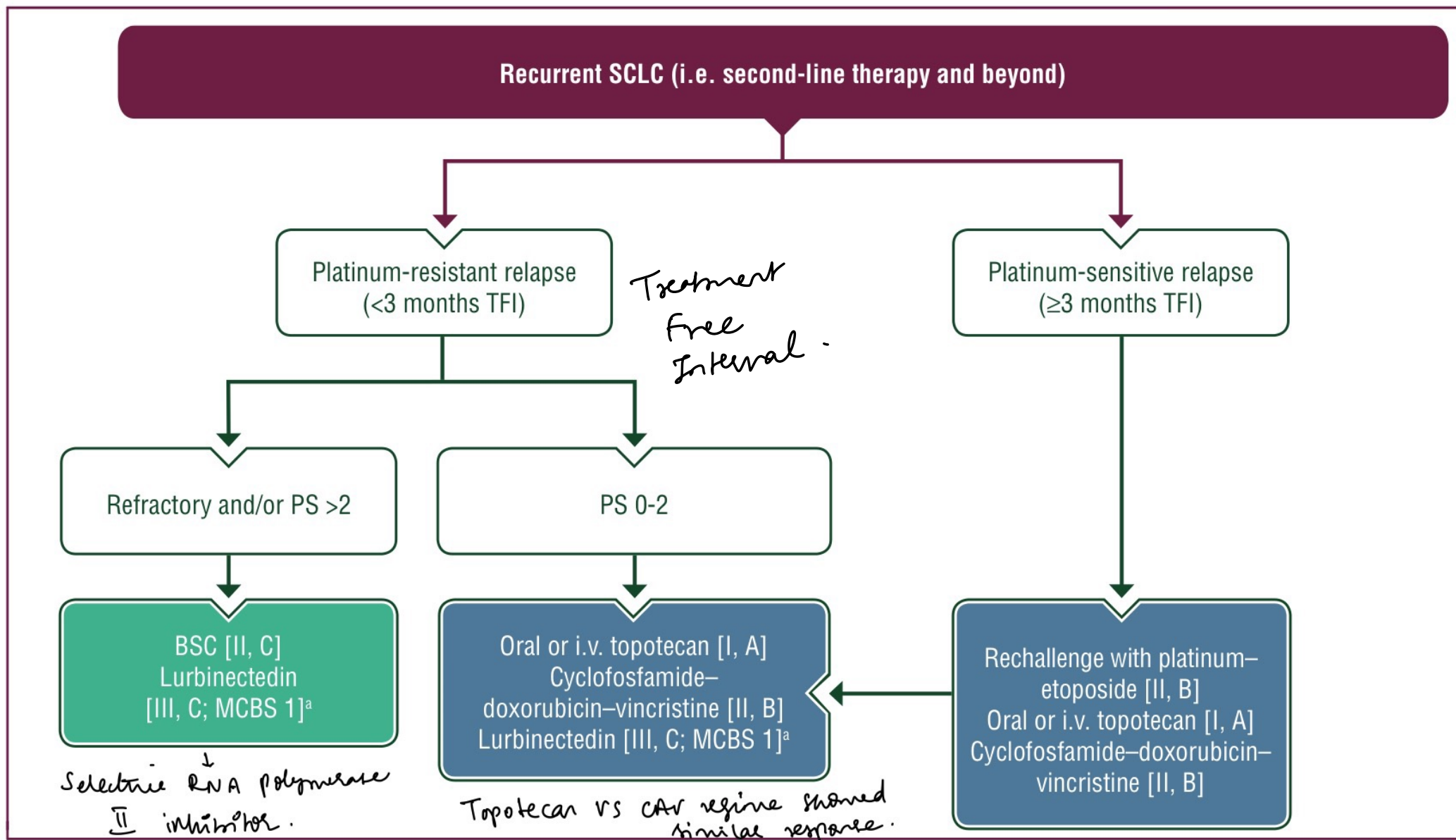


Figure 2 Treatment algorithm for SCLC in patients with recurrent SCLC (i.e. second-line therapy and beyond)

Lung Carcinoid

→ Etiopathogenesis

- Younger, Non smokers
- Female > male
- Better prognosis
- may be associated = MEN-1 Syndrome or (DIPNECH)
diffuse Pulmonary Neuroendocrine cell hyperplasia.
- Symptoms
 - centrally located → Bronchial obstruction
 - peripherally located → Incidental, usually asymptomatic, diagnosed on resection of solitary pulm. nodule.
 - secretory / functional tumors
 - Carcinoid Syndrome → Serotonin release.
 - Cushing Syndrome → ACTH release
 - Acromegaly → GHRH release

Table 1. Diagnostic work-up of lung and thymic carcinoids

Clinical history
• Presence of functioning syndrome • Presence of obstructive syndrome • Family or personal history of MEN-1 syndrome
Pathology
• WHO 2015 classification • Multiple synchronous primaries; DIPNECH features • Specification of node dissection (e.g. number, station) • Resection status
Biochemistry
• Biochemical: K, Ca, glucose • Chromogranin A^a • In syndromic patients: 24 h-urine-5-HIAA, serum cortisol, ACTH, 24 h-urine-free cortisol, serum GHRH, IGF-1^a
Imaging
• TNM staging according to the 8th UICC edition: chest/abdomen CT with i.v. contrast (liver MRI) • ⁶⁸Ga-DOTA SSA PET-CT or ¹¹¹In-DTPA scintigraphy if not available • Consider FDG-PET-CT in AC or high-grade histopathology or negative SRI • Whole spine, brain MRI if symptoms • Bronchoscopy • Transthoracic echocardiography if CS • Tumour growth rate (radiological) over 2-3 months in non-resectable asymptomatic TC or low-grade AC
If considering surgery, carry out:
• Transthoracic echocardiography^b • Respiratory function tests • Bronchoscopy • Mediastinoscopy (or EBUS)^c
Genetic screening
• MEN-1 germline testing when suspected

- IHC neuroendocrine markers.

→ CECT A+P = late arterial phase for detecting liver mets.

→ staging same as TNM for NSCLC

→ Management of Non metastatic lung Carcinoid :

- Surgery is main stay, even in bulky nodal disease.
- Open vs MIS → depending upon tumor location and surgeon expertise.

- Anatomical resection vs Non anatomical resection

↓

- Segmentectomy
- Lobectomy / Bilobectomy
- Pneumonectomy - avoided. Refer to
- Bronchoplasty / Sleeve resections

↓

Anatomic resection
Preferred in all.

↓

wedge resection
indications

- DIPNECH, if they progress on watchful waiting.
- MEN-1 patients.
- pt with comorbid conditions not fit for major resections.

→ Role of LN dissection :

Recommended in all patients → at least 6 stations = 2 hilar + 3 mediastinal including subcarinal LN.

→ Frozen section to confirm R0 resection.

→ No role for adjuvant therapy in R0 resection.

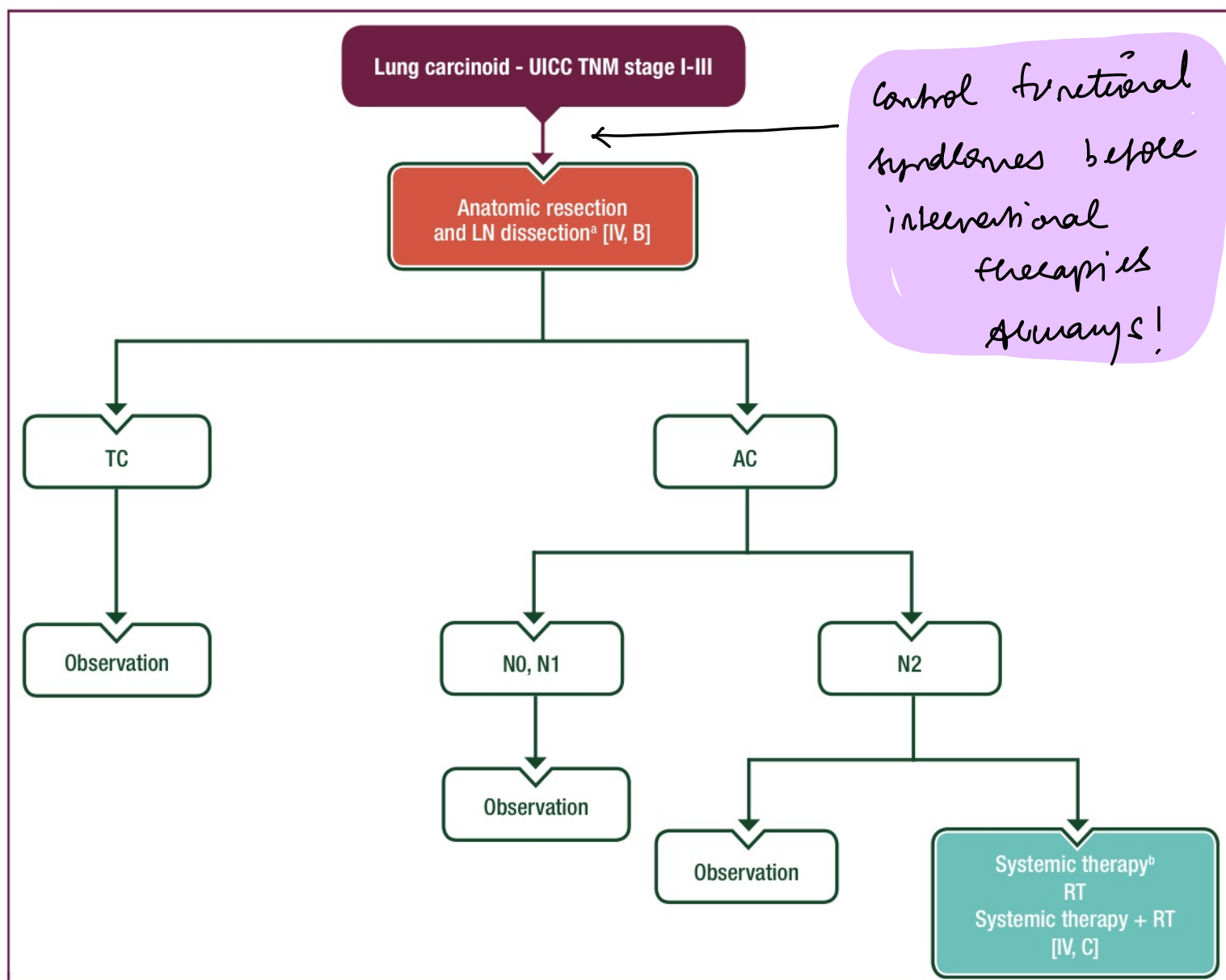


Figure 1. Lung carcinoid adjuvant therapy in UICC TNM stage I-III R0 patients.

→ Management of metastatic lung Carcinoid:

1. Hormone related Symptom management.

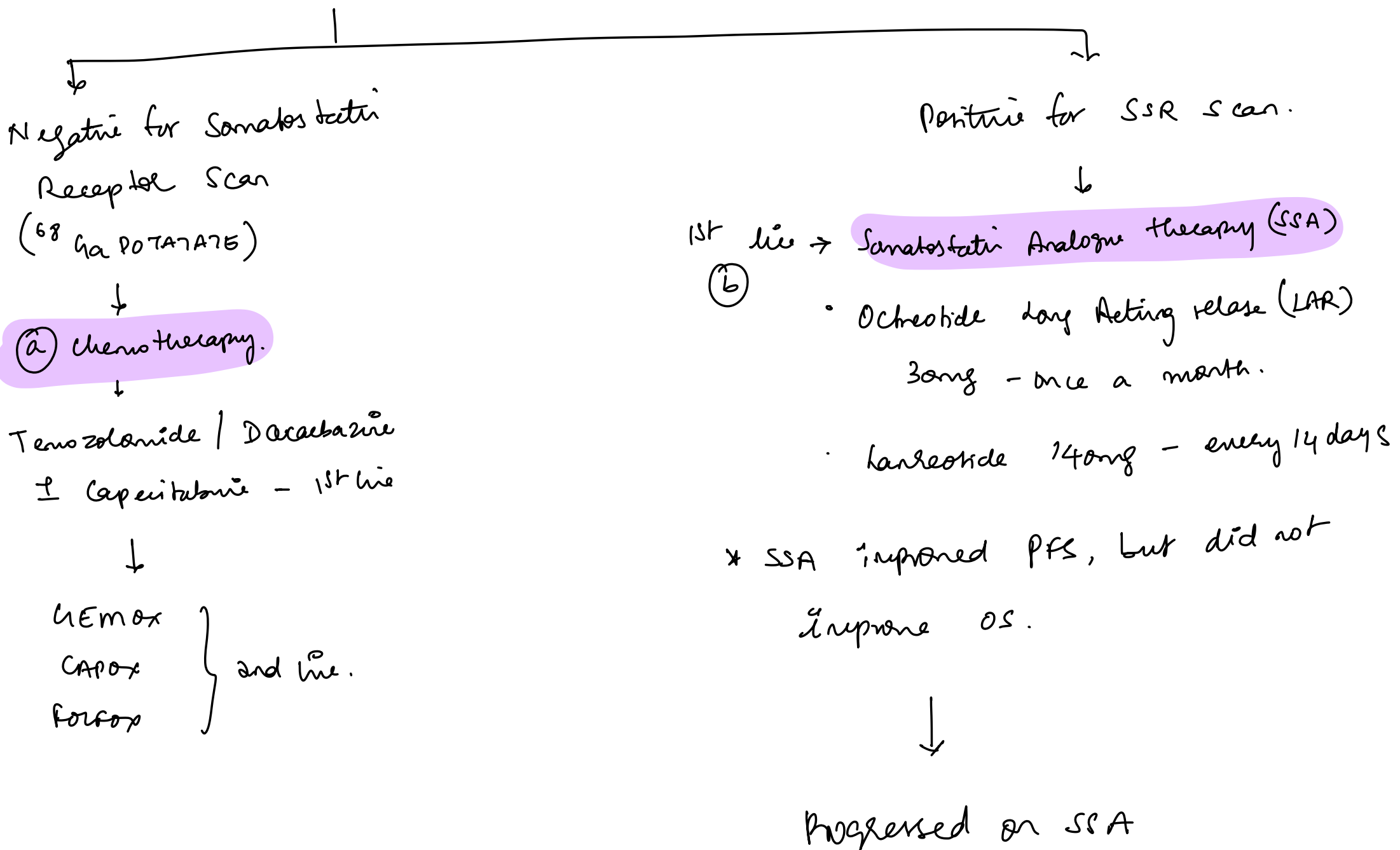
2. Locoregional therapy for primary if symptomatic

- Endobronchial resection
- RFA / Cryoablation
- palliative Sx.

3. Locoregional therapy in liver predominant mets

- Resection
- TACE / TARE
- RFA.

4. Systemic therapy



Progressed on SSA

slow progression



- Increase SSA dose
- Pasireotide
- IFN α .

Significant progression

(c) m-TOR inhibitor.

Everolimus → RADIAN7-4 study.
Improved PFS.

(d) PRRT - peptide Receptor Radionuclide therapy.

* NETTER-1 study in GI Carcinoids.

→ Eligibility for PRRT:

- well differentiated NET.
- SS4 Receptor expression on SST-R-PET/CT.
- Adequate renal, hepatic, marrow function.

→ Pre-therapy Preparation.

- Stop long acting Octreotide LAR 4 weeks prior.
- Switch over to short acting Octreotide for symptoms.
- Counsel regarding radiation exposure / toxicity.
- Amino acid infusion for nephroprotection.

→ Dose → Lutetium 177 dotatate 200mCi IV over 30-40 mins
every 8 weeks x 4 cycles.