UCCH Pathway

UCCH Guideline
Neuroendocrine Neoplasms (NEN)

Version 05, Apr/2020

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Guideline Neuroendocrine Neoplasms

Version 05, Apr/2020

according to TNM classification 8th edition and WHO 2019 classification

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Revised	Aug/2014, Aug/2016, May/2018, Apr 2020
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= Therapeutic procedure

= Clinical or diagnostical condition

= Diagnostic procedure

= Clinical trial

= Supportive measure

= Referral

TB

= Tumorboard (including post tumorboard interaction with patient that follows the principles of shared decision-making)

Pathway: Neuroendocrine Neoplasms

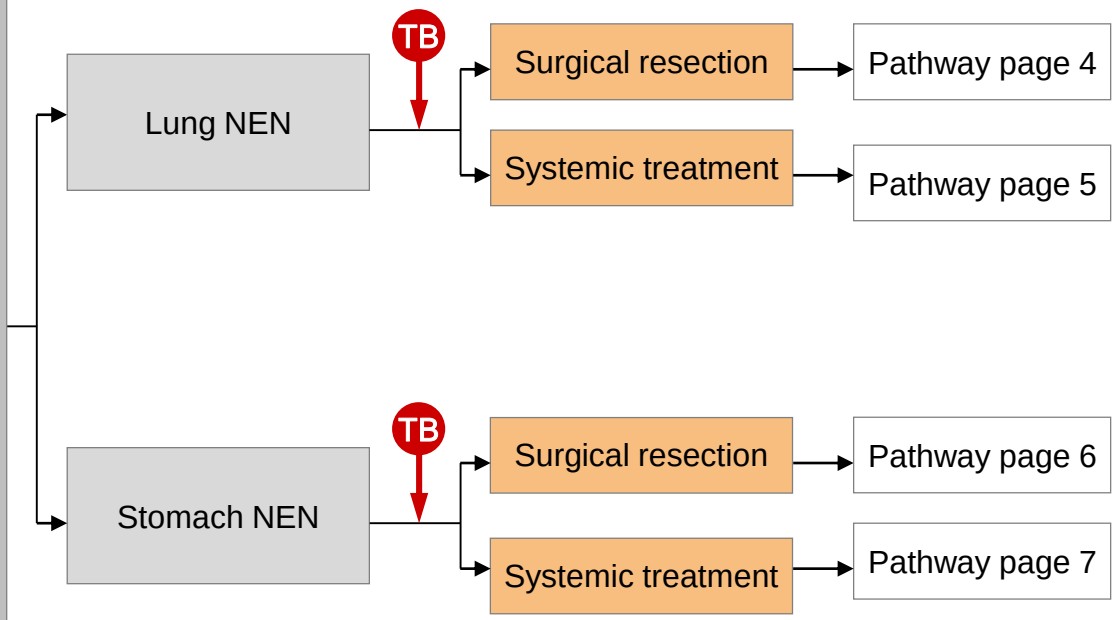
Work up

Baseline
- History
- Physical examination
- Lab exam (incl. chromogranine A and NSE if G3)
- CT/MRI abdomen, additional CT chest if G3 tumor
- DOTATATE PET-CT (if no DOTATE PET-CT before resection, then 3-6 months after resection)
- Biopsy (primary or metastasis) for histological examination:
  - -Proliferation: Ki-67 for grading (G1, G2, G3)
  - -Morphology: well vs. poorly differentiated (LC/SC)
  - -SSTR2A status (if no DOTATE PET-CT before resection)
- Offer supportive measures[1]

Variable

Lung
- History: Exclusion of functional syndrome (eg. carcinoid syndrom: diarrhea, flush, asthma)
- Lab exam incl. urine 5-HIES, pro-BNP
- Consider Bronchoscopy/EBUS
- Consider MRI brain* and/or FDG PET-CT
- Histology (morphology): -Typical / atypical carcinoid?
  -Large / small cell carcinoma?

Stomach
- History: Exclusion of functional syndrome (eg. histamine syndrom: diarrhea, flush, asthma)
- Lab exam incl. gastrin and anti parietal cell antibodies
- Gastroscopy: Random gastric mapping biopsies (Chronic atrophic gastritis?)
- EUS if tumor > 1cm
- Classification: -Type I (associated with CAG)
  -Type II (associated with ZES (MEN-1, sporadic)
  -Type III (sporadic)



* Baseline in case of planned curative resection, otherwise in case of clinical suspicion

[1] See page 22

Pathway: Neuroendocrine Neoplasms

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- History
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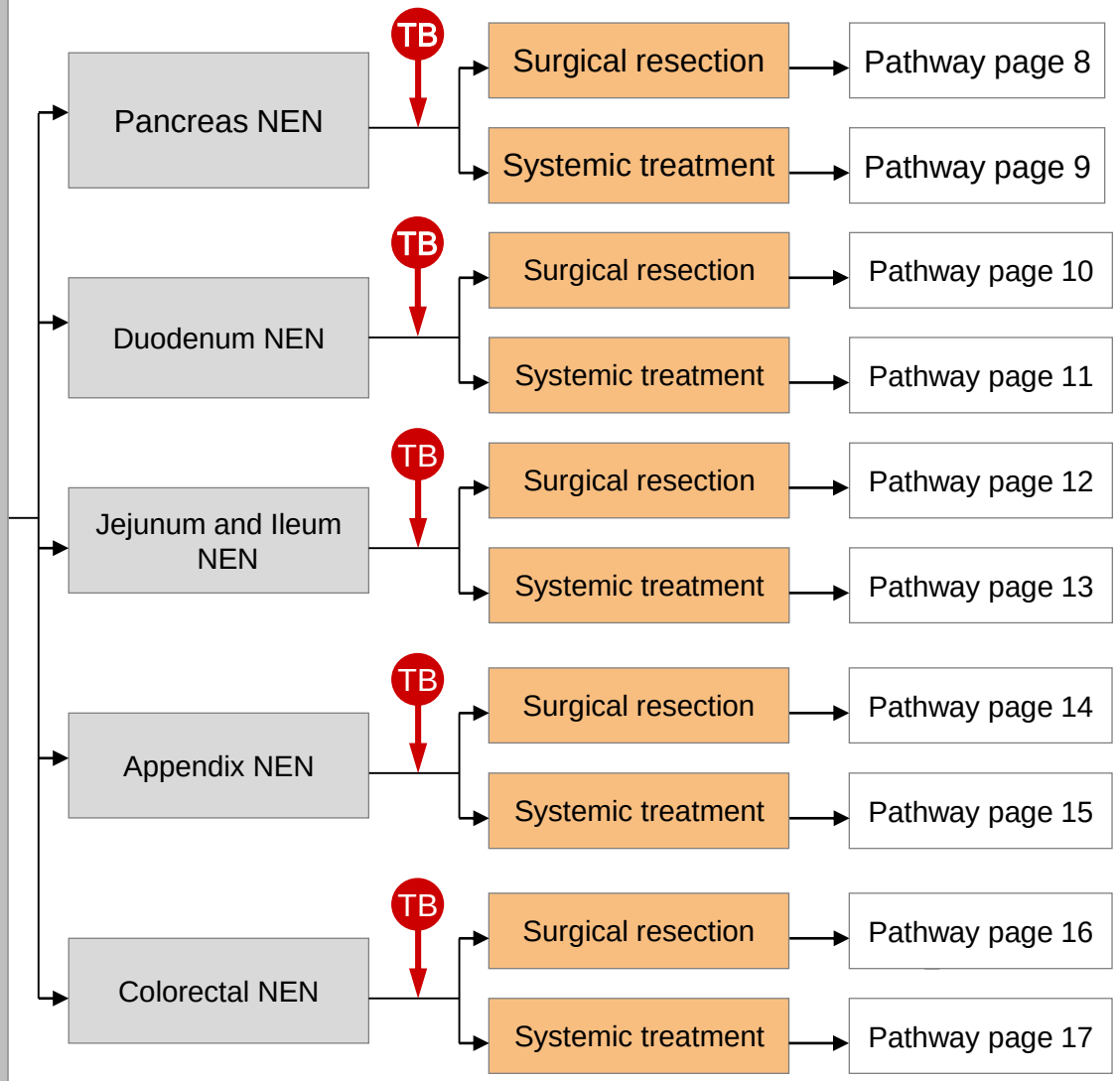
  - -Morphology: well vs. poorly differentiated (LC/SC)
  - -SSTR2A status (if no DOTATE PET-CT before resection)
- Offer supportive measures[1]

Variable

Pancreas
- History: Exclusion of functional syndrome (e.g. insulinoma, glucagonoma, gastrinoma, VIPoma). Family history or pituary disease / hyperparathyroidism?
- Lab exam incl. hormones
- EUS if CT/MRI negative or unclear

Duodenum
- History: Exclusion of functional syndrome eg. carcinoid syndrome (diarrhea, flush, asthma), gastrinoma (ulcera , reflux, diarrhoea), somatistatinoma (diabetes, abdominal pain, malabsorption)
- Lab exam incl. urine 5-HIES, gastrin, pro-BNP
- Echocardiography (exclude Hedinger syndrome if functional active carcinoid syndrome)
- EUS

Jejunum, ileum, appendix, colorectal
- History: Exclusion of functional syndrome (eg. carcinoid syndrom: diarrhea, flush, asthma)
- Lab exam incl. urine 5-HIES, pro-BNP
- Echocardiography (exclude Hedinger syndrome if functional active carcinoid syndrome)
- EUS or MRI pelvis (only rectal)



[1] See page 22

Pathway: Neuroendocrine Neoplasms

Work up

Baseline

- History
- Physical examination
- Lab exam (incl. chromogranine A and NSE if G3)
- CT/MRI abdomen, additional CT chest if G3 tumor
- DOTATATE PET-CT (if no DOTATE PET-CT before resection, then 3-6 months after resection)
- Biopsy (primary or metastasis) for histological examination:
  - -Proliferation: Ki-67 for grading (G1, G2, G3)
  - -Morphology: well vs. poorly differentiated (LC/SC)
  - -SSTR2A status (if no DOTATE PET-CT before resection)
- Offer supportive measures[1]

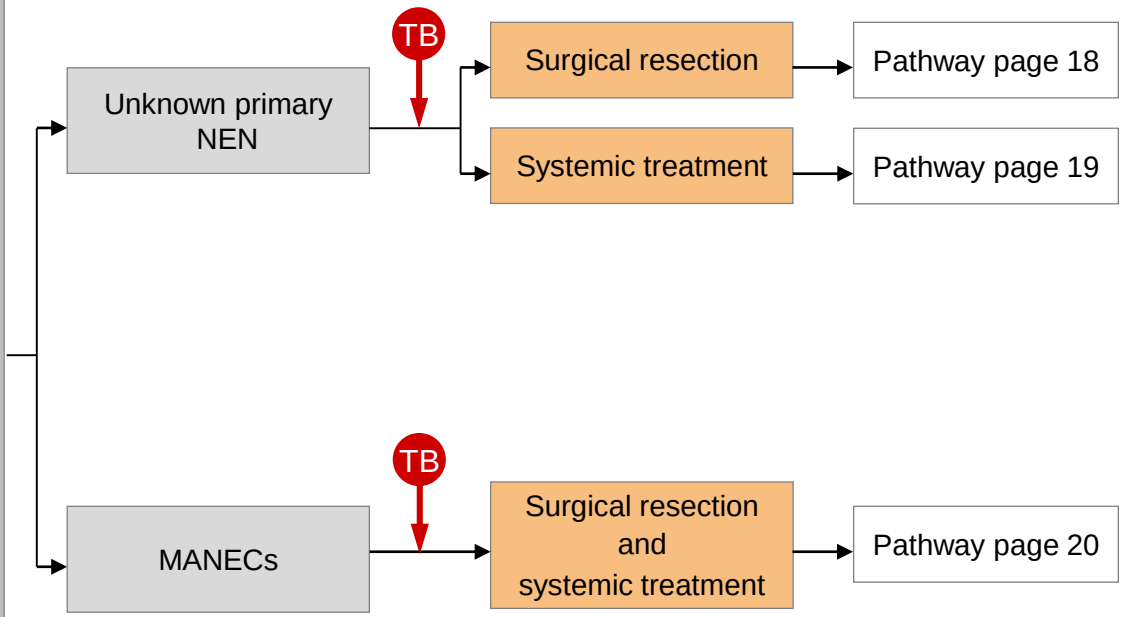
Variable

Unknown primary

- History: Functional syndrome? Appendectomy?
- Lab exam incl. urine 5-HIES, calcitonin, gastrin
- Consider MIBG scintigraphy if standard DOTATE PET-CT shows no primary
- Histology: TTF-1 (lung), Isl-1 (pancreas), CDX-2 (GI tract)
- If
  - TTF-1 positive: Bronchoscopy, CT-Thorax
  - Isl-1 positive: EUS
  - CDX-2 positive: Gastroscopy, colonoscopy, capsule endoscopy

MANECs

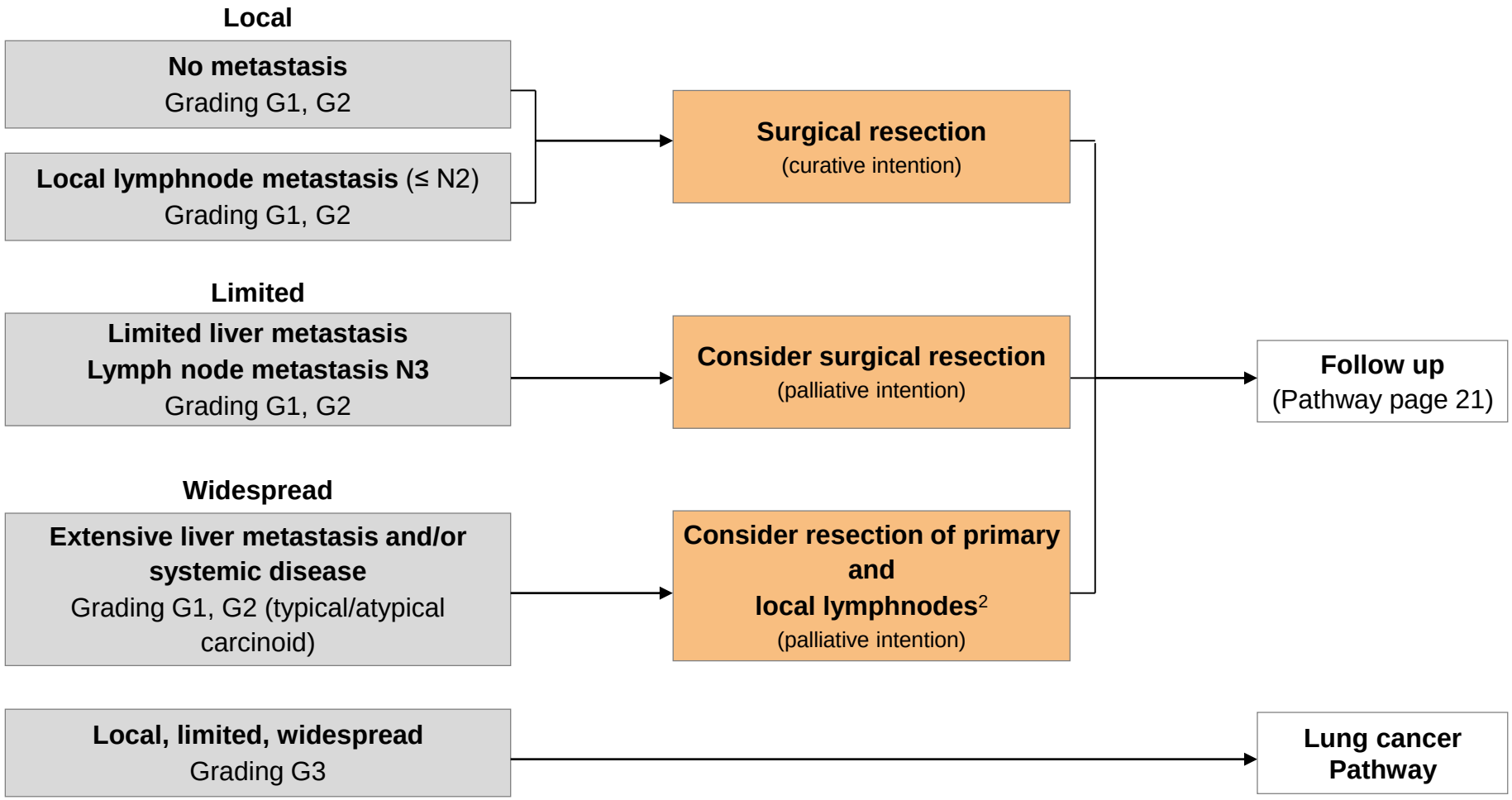
- Lab exam incl. chromogranine A, NSE and CEA (CA 19-9 if pancreas/cholangio)
- CT/MRI, DOTATATE-PET- CT (If NE proliferation <50%) and/ or PET-CT
- Early re-biopsy if recurrence (to define AC or NET/NEC predominance)
- Histology:
  - Percentage of tumor belonging to NET/NEC and AC in primary + metastasis
  - Separate status of differentiation (AC + NET/NEC) and proliferation (NET/NEC)
  - SSTR2A, p53 expression; predictive adenocarcinoma marker
  - Depending on the site of primary tumor in AC predominant tumors, determination of predictive markers according to the respective site (e.g. RAS/BRAF/MSI/HER2 for colorectal, HER-2 for gastric, gallbladder or extrahepatic cholangiocarcinoma, PD-L1 for gastric)



MANECs Mixed adenoneuroendocrine carcinomas

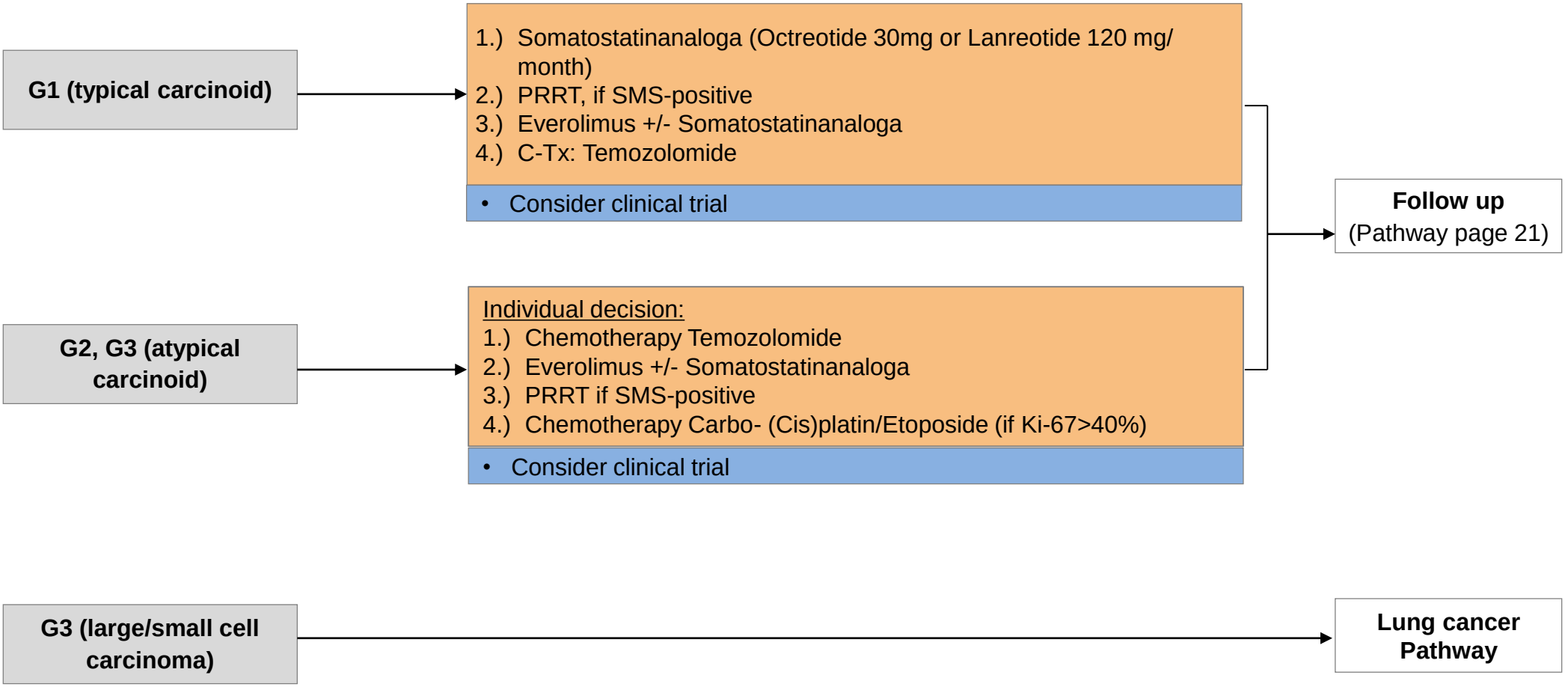
[1] See page 22

Pathway page 4: Lung NEN surgical resection[1]



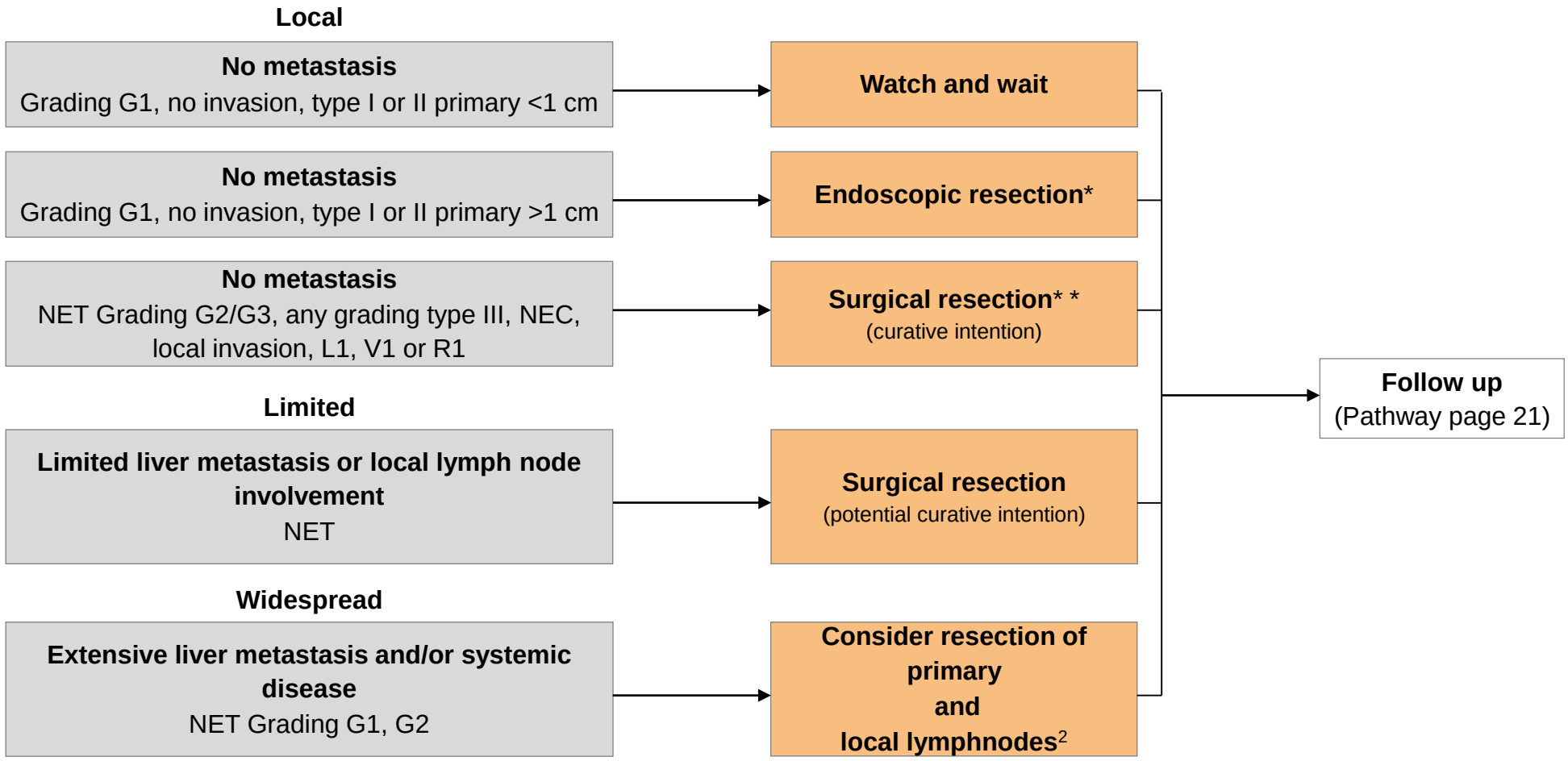
1 See indications for adjuvant therapy page 22
2 Consider surgical resection or debulking to prevent local complications or to increase progression free survival

Pathway page 5: Lung NEN systemic treatment[3,4]



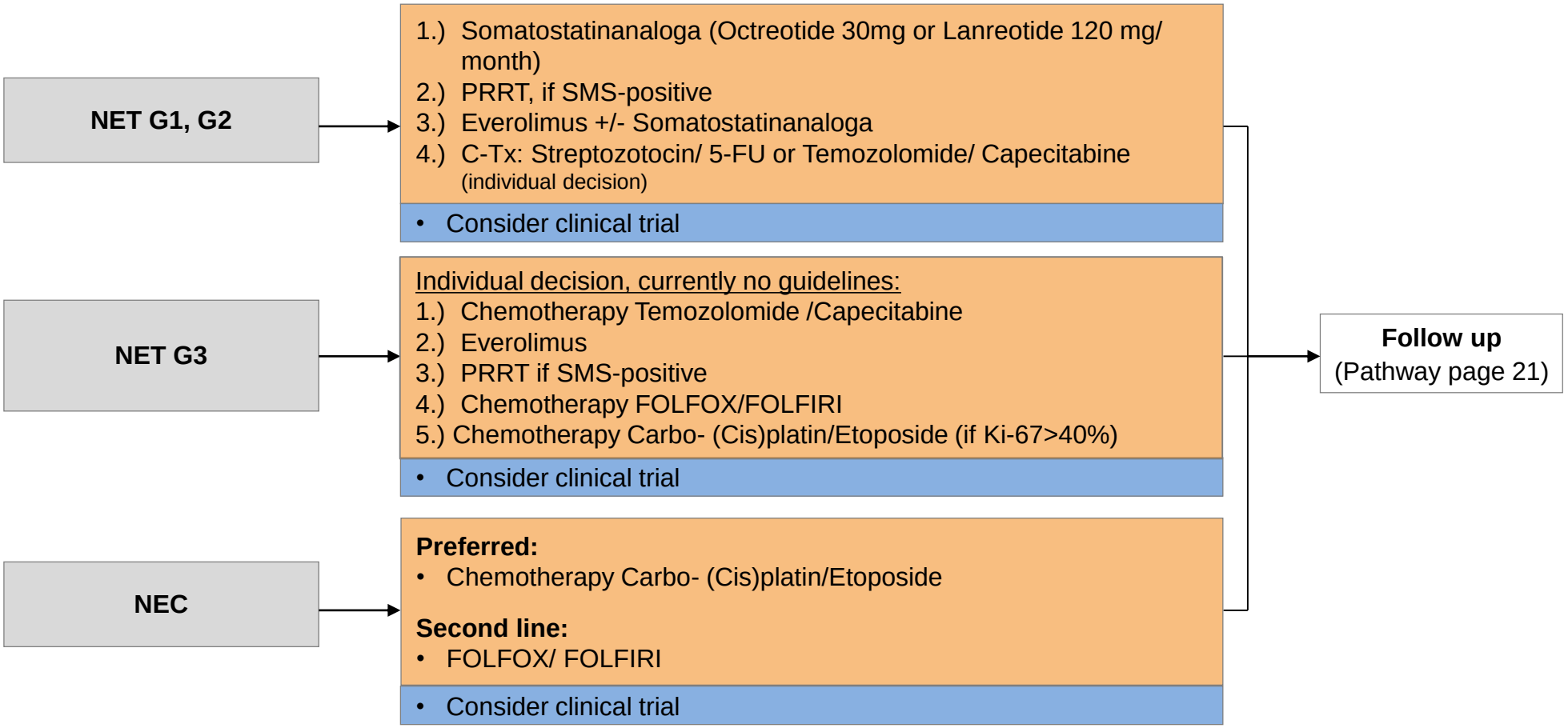
[3] See Indications for systemic therapy page 22
[4] See special circumstances page 24

Pathway page 6: Stomach NEN surgical resection[1]



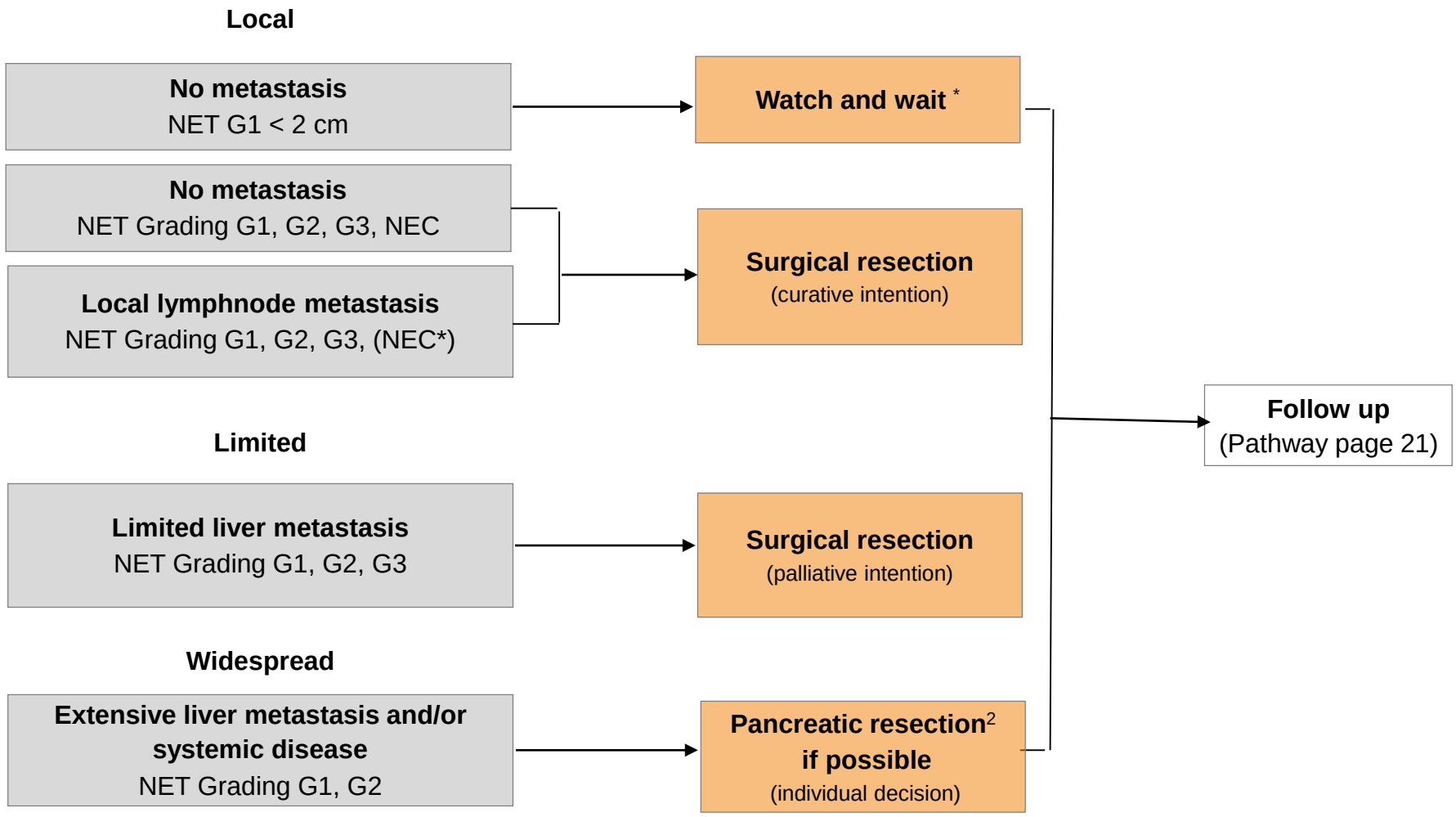
* Proceed to surgical resection if G2/G3, L1, V1, R1 or invasion into muscularis;
** Partial gastrectomy or total gastrectomy
1 See indications for adjuvant therapy page 22
2 Consider surgical resection or debulking to prevent local complications or to increase progression free survival

Pathway page 7: Stomach NEN systemic treatment[3,4]



[3] See Indications for systemic therapy page 22
[4] See special circumstances page 23

Pathway page 8: Pancreas NEN surgical resection[1]



* Offering surgical resection

1 See indications for adjuvant therapy page 22

2 Consider surgical resection or debulking to prevent local complications or to increase progression free survival

Pathway page 9: Pancreas NEN systemic treatment[3,4]

NET G1

1.) Somatostatinanaloga (Lanreotide 120 mg/ month)
2.) Clinical trial (RAMUNET trial – Dacarbazine + Ramucirumab)
3.) Chemotherapy Streptozotocin/5-FU
4.) Everolimus or Sunitinib (depending on co-morbidity)
5.) PRRT if SMS-positive
6.) Chemotherapy Temozolomide/Capecitabine (individual decision)
7.) Clinical trial COMPETE (in progress – PRRT vs. Everolimus)

- Consider clinical trial

NET G2

1.) Somatostatinanaloga, individual decision if Ki-67 <10%
2.) Clinical trial (RAMUNET trial – Dacarbazine + Ramucirumab)
3.) Chemotherapy Streptozotocin/5-FU
4.) Everolimus or Sunitinib (depending on co-morbidity)
5.) PRRT if SMS-positive
6.) Chemotherapy Temozolomide/Capecitabine
7.) Clinical trial COMPETE (in progress – PRRT vs. Everolimus)

- Consider clinical trial

NET G3

<u>Individual decision, currently no guidelines:</u>
1.) Chemotherapy Streptozotocin/5-FU
2.) Everolimus or Sunitinib
3.) Chemotherapy Temozolomide/ Capecitabine
4.) PRRT if SMS-positive
5.) Chemotherapy FOLFOX/ FOLFIRI

- Consider clinical trial

NEC

Preferred:
- Chemotherapy Carbo- (Cis)platin/Etoposide

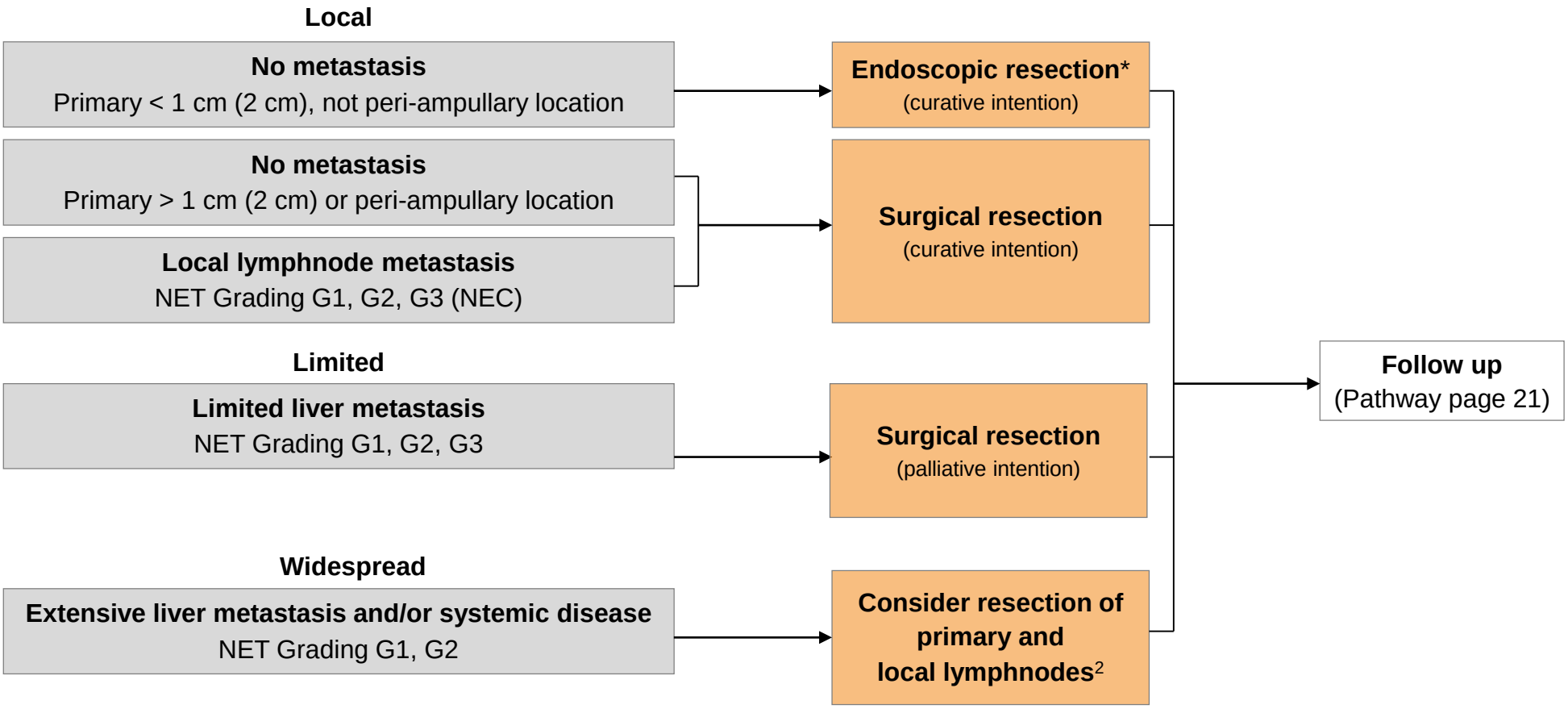
Second line:
- Chemotherapy FOLFOX/FOLFIRI

- Consider clinical trial

Follow up
(Pathway page 21)

3 See Indications for systemic therapy page 22
4 See special circumstances page 23

Pathway page 10: Duodenum NEN surgical resection[1]

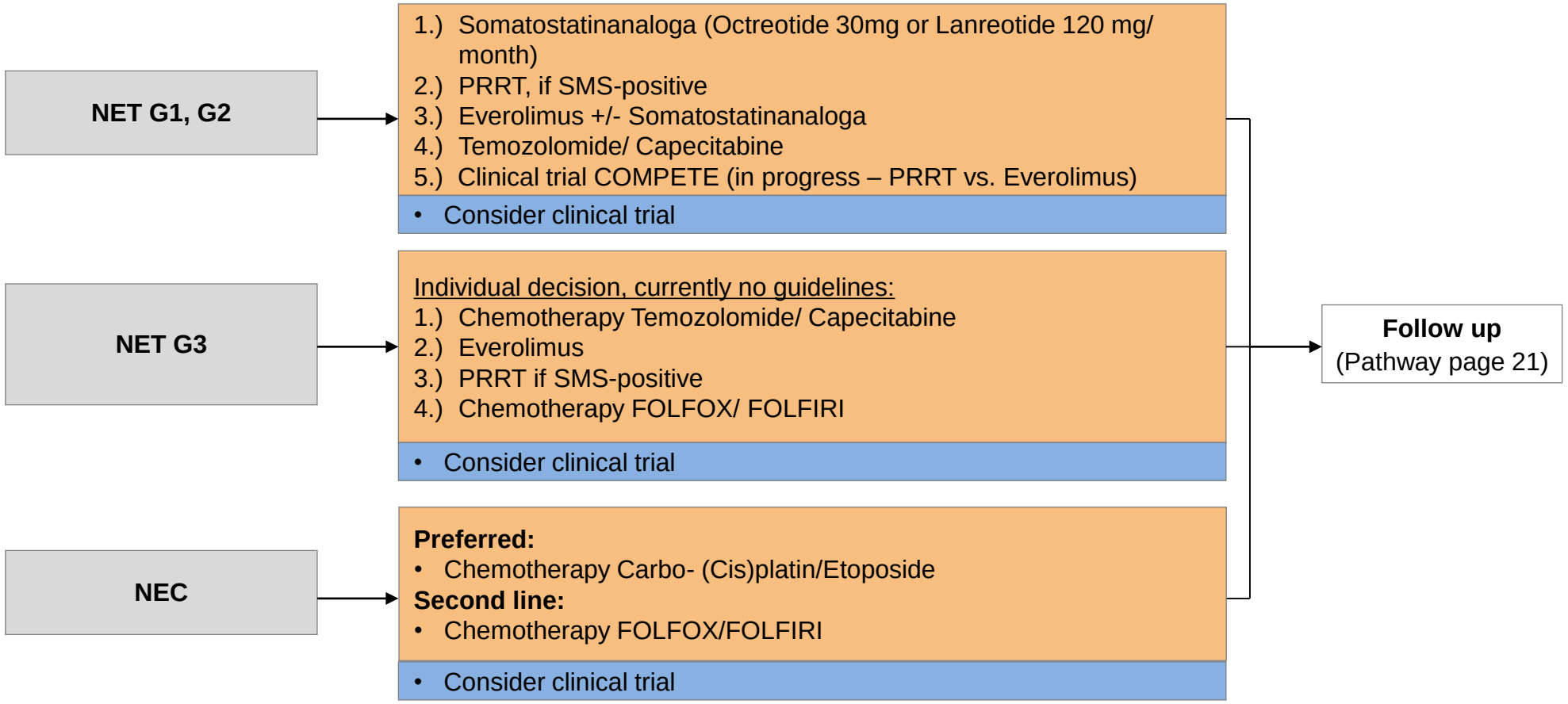


* Proceed to surgical resection if R1, V1, L1, G2/3 or invasion of muscularis

1 See indications for adjuvant therapy page 22

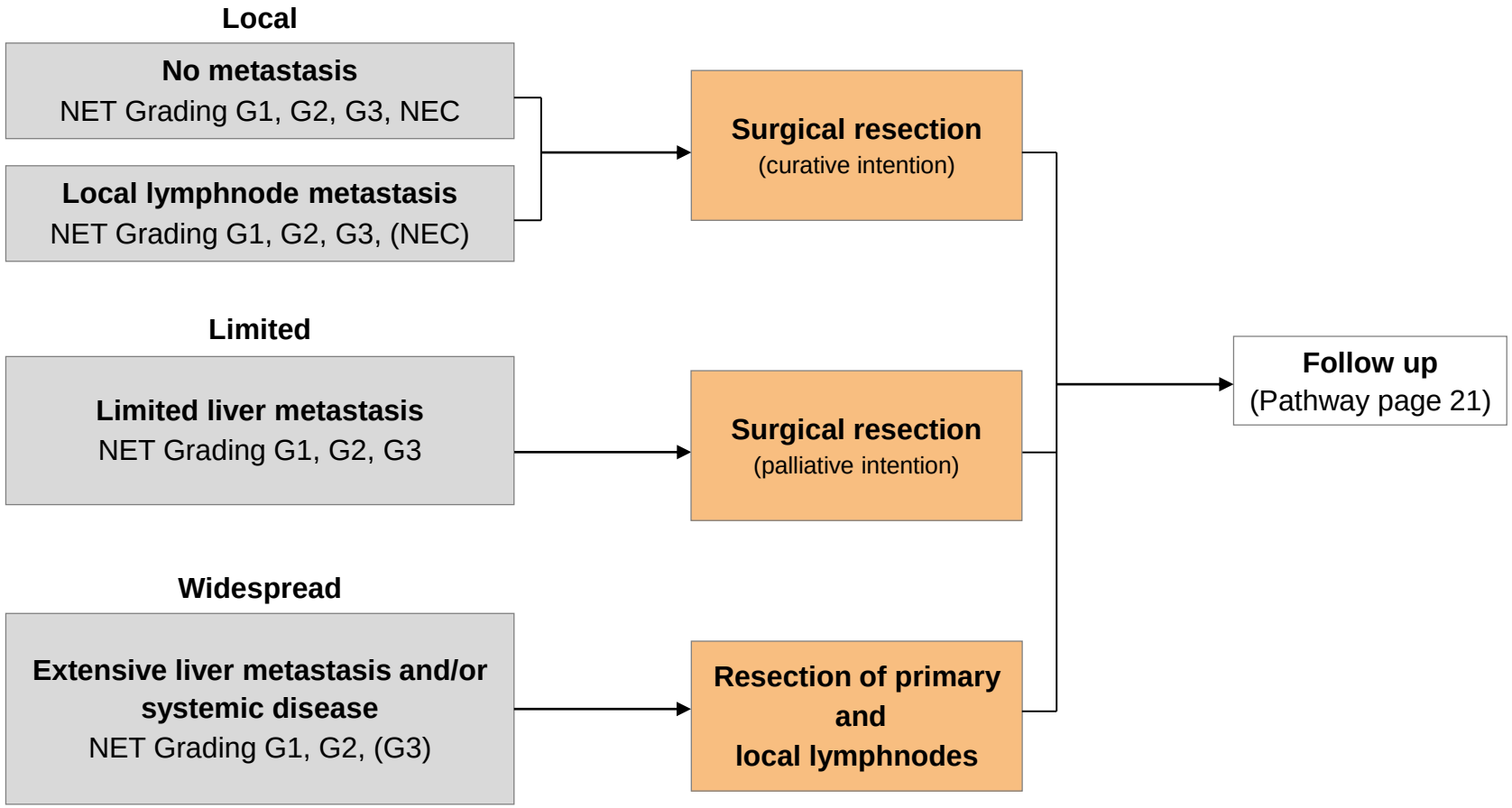
2 Consider surgical resection or debulking to prevent local complications or to increase progression free survival

Pathway page 11: Duodenum NEN systemic treatment[3,4]



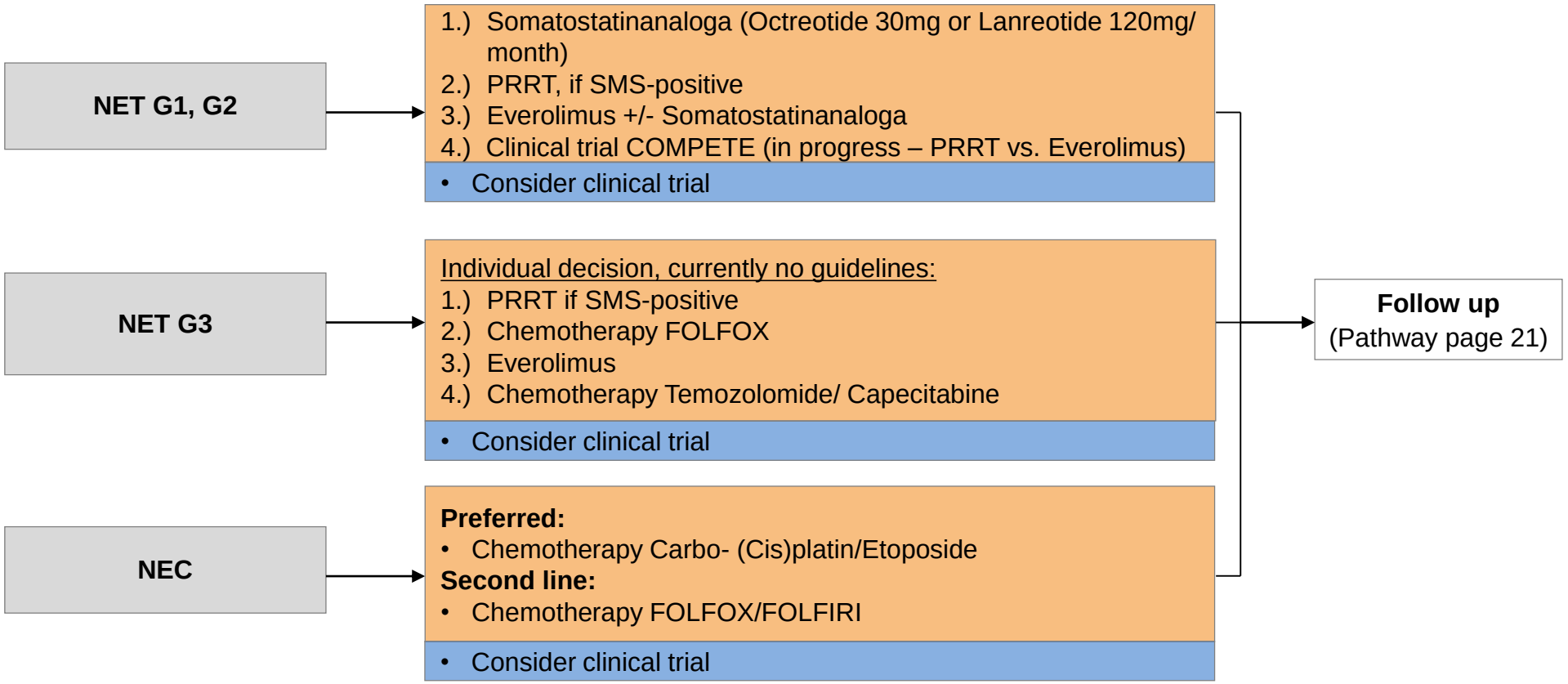
[3] See Indications for systemic therapy page 22
[4] See special circumstances page 23

Pathway page 12: Jejunum and ileum NEN surgical resection[1]



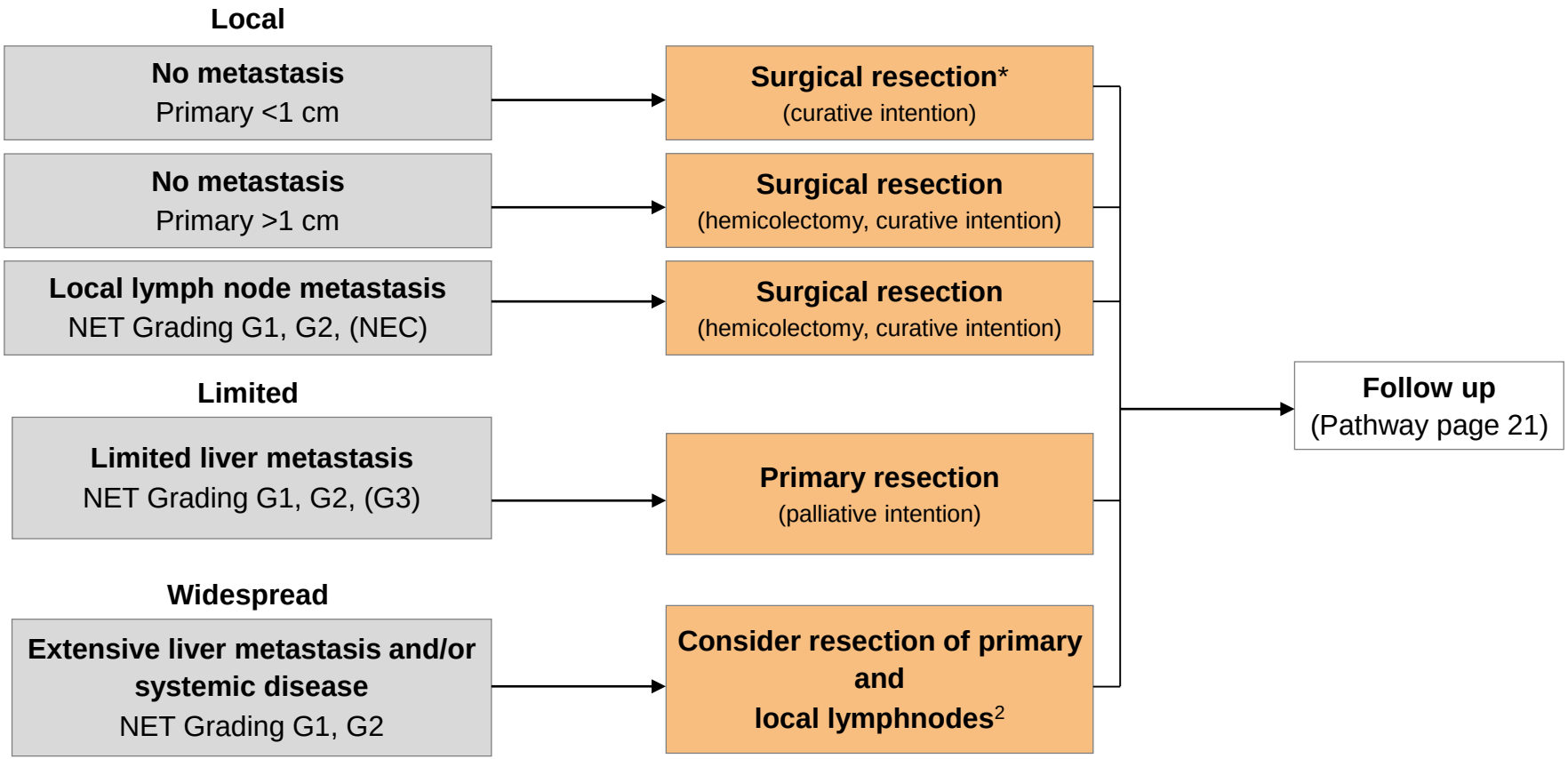
[1] See indications for adjuvant therapy page 22

Pathway page 13: Jejunum and ileum NEN systemic treatment [3,4]



[3] See Indications for systemic therapy page 22
[4] See special circumstances page 23

Pathway page 14: Appendix NEN surgical resection[1]

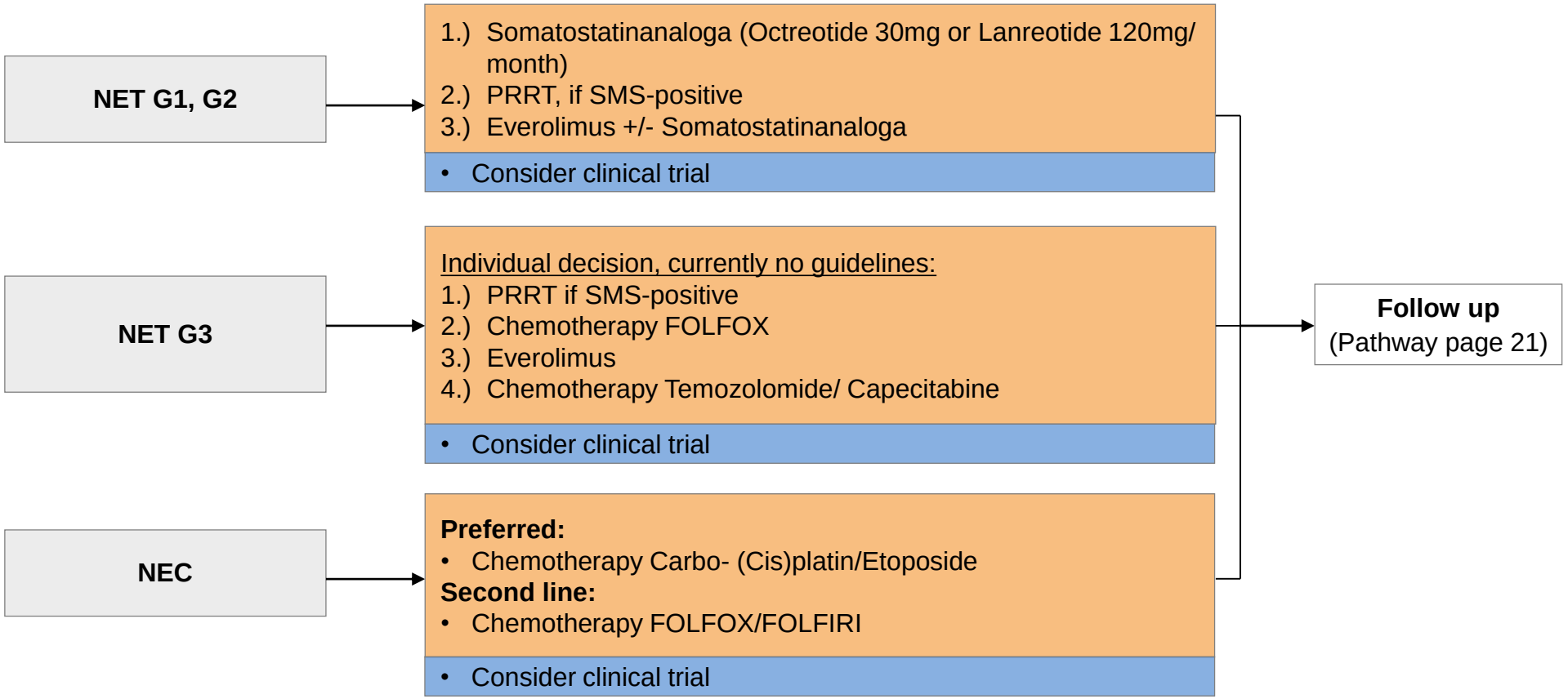


* Appendectomy only if T1a, V0, L0, R0, G1, location at the tip. If initial resection shows V1,L1, R1, G2/3, location at the base or infiltration of the mesoappendix >3mm warrants completion of surgery with right hemicolectomy

1 See indications for adjuvant therapy page 22

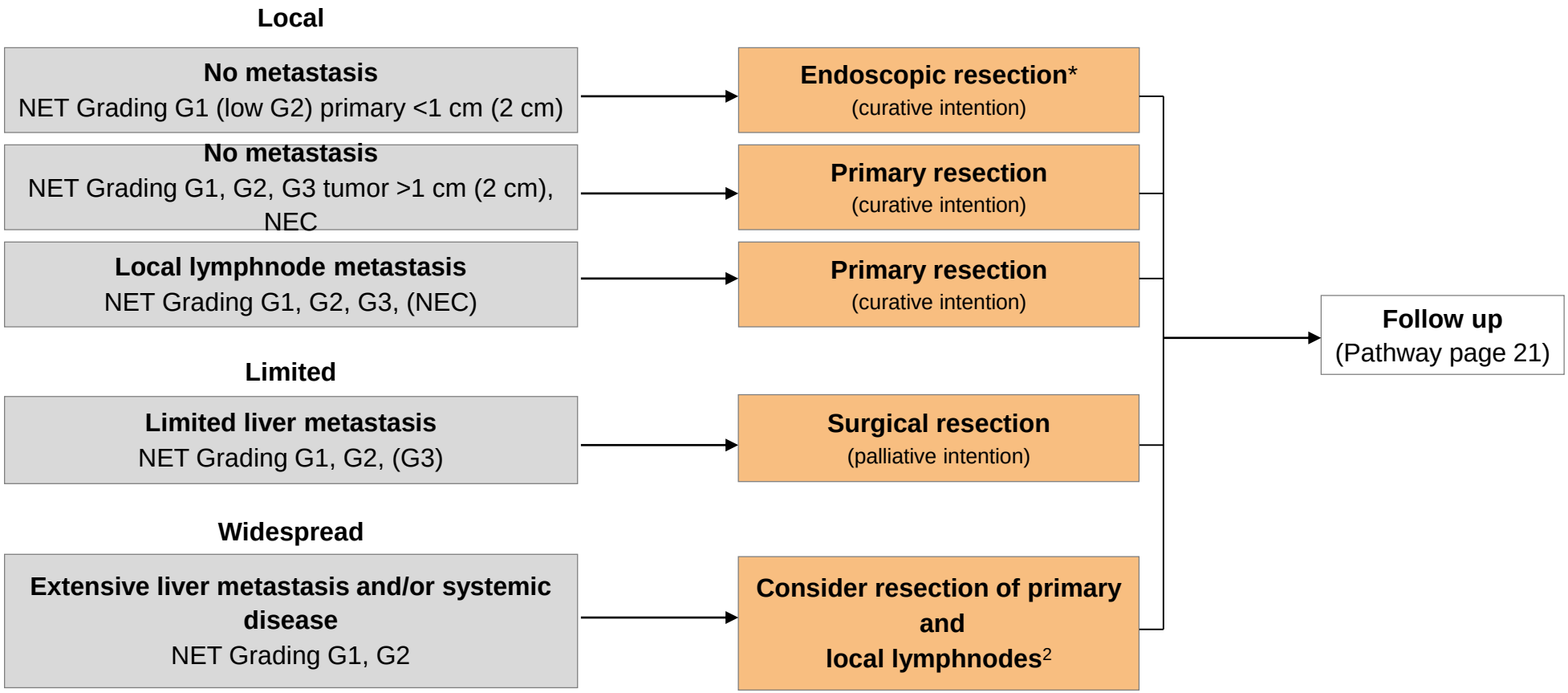
2 Consider surgical resection or debulking to prevent local complications or to increase progression free survival

Pathway page 15: Appendix NEN systemic treatment [3,4]



[3] See Indications for systemic therapy page 22
[4] See special circumstances page 23

Pathway page 16: Colorectal NEN surgical resection[1]

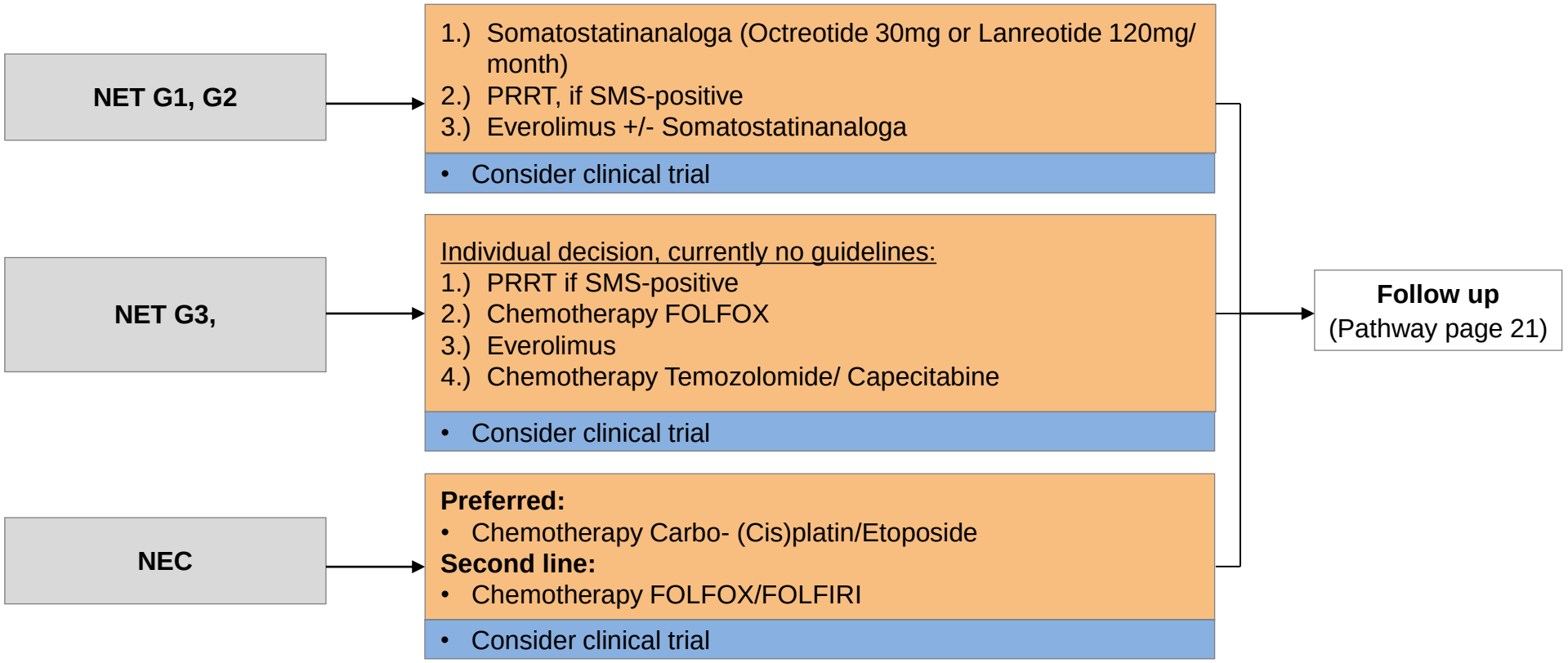


* Proceed to secondary resection if L1, V1 or R1 or invasion of muscularis

1 See indications for adjuvant therapy page 22

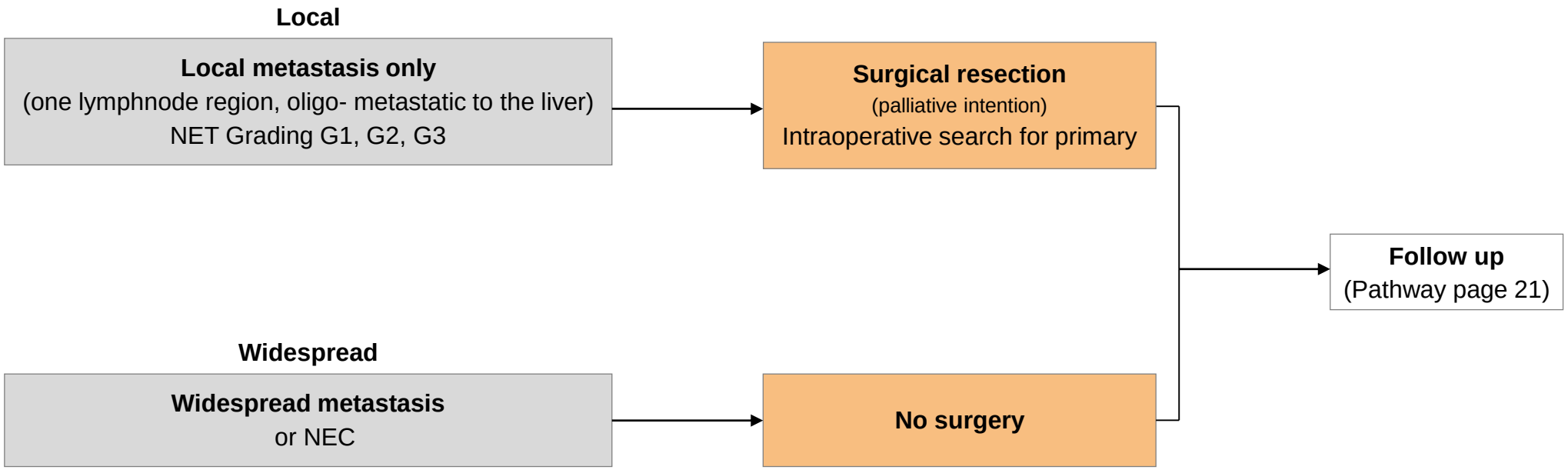
2 Consider surgical resection or debulking to prevent local complications or to increase progression free survival

Pathway page 17: Colorectal NEN systemic treatment [3,4]



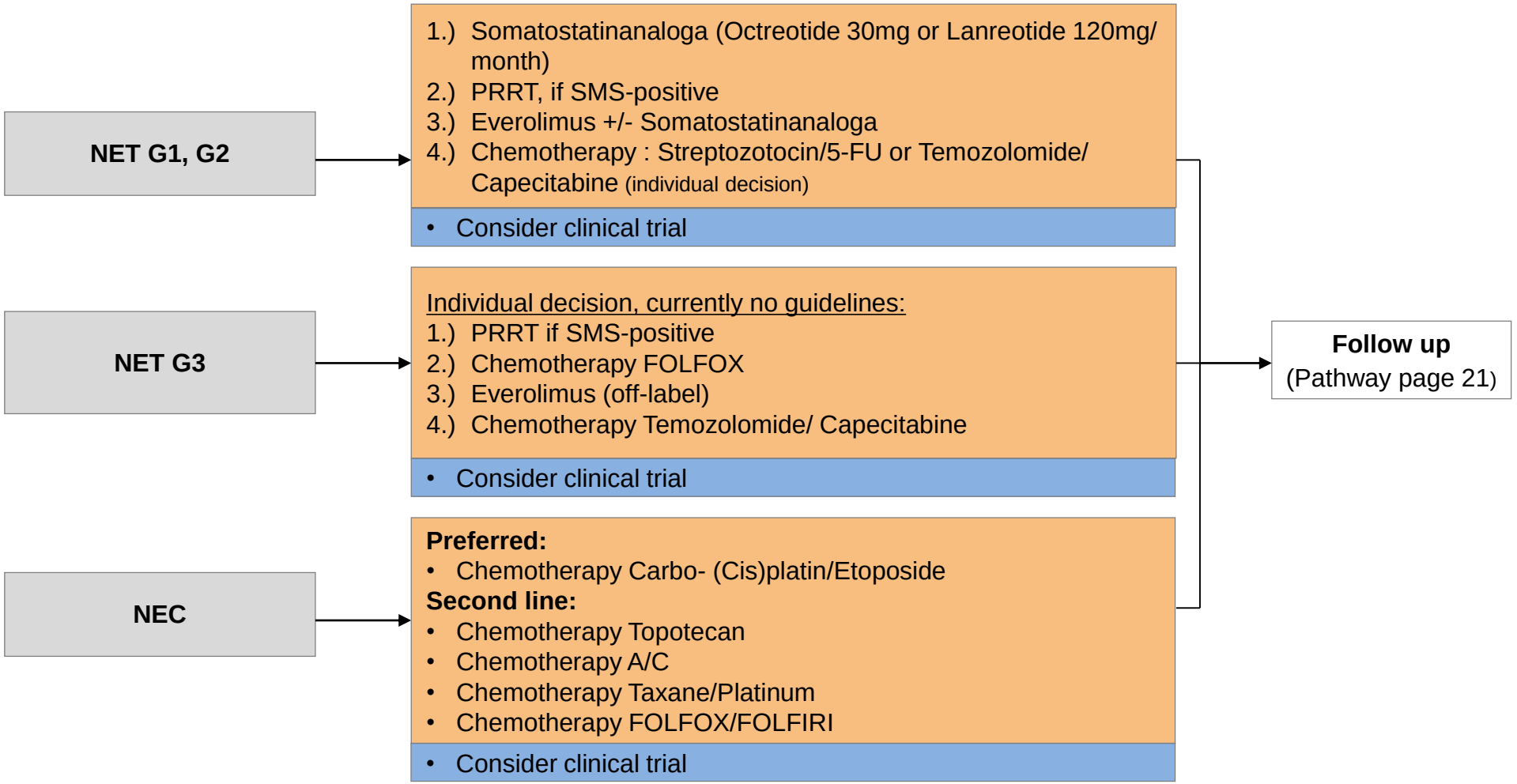
[3] See Indications for systemic therapy page 22
[4] See special circumstances page 23

Pathway page 18: Unknown primary NEN surgical resection[1]



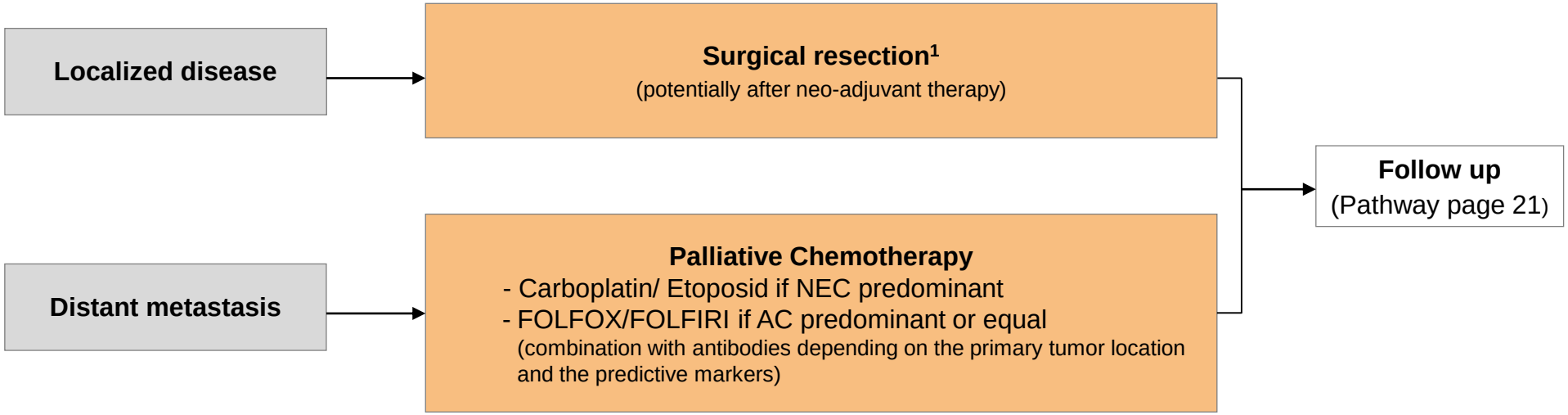
[1] See indications for adjuvant therapy page 22

Pathway page 19: Unknown primary NEN systemic treatment [3,4]



3 See Indications for systemic therapy page 22
4 See special circumstances page 23

Pathway page 20: MANECs surgical resection and systemic treatment



[1] See indications for adjuvant therapy page 22

Page 21: Follow up

General for all Follow up visits:
- Chromogranin A (+NSE if G3)
- Urine 5-HIES (Lung, Duodenum, Jejunum, Ileum, Appendix)
- DOTATATE PET-CT only if initially SMS-positive/SSTR2A-positive

Potentially curative resection

Complete (RO) palliative resection →

Stomach NET G1, R0, L0, V0, type I or II
- Yearly endoscopy

Pancreas T1, R0, L0, V0, Pn0, G1
- Possible no Follow up

Duodenum NET G1, T1a, L0, V0, R0, endoscopic resection:
- Gastroscopy after 3 month, than every 12 month
- CT/MRI abdomen every 12 month
- DOTATATE PET-CT after 3 years
- Follow-up for 3 years only

Appendix NET G1, T1a, L0, V0, R0
- No follow up

Colorectal NET G1, L0, V0, R0
- Endoscopic control after 3 and 12 months, no further follow up

All other:

NET G1 - CT/MRI abdomen (+CT thorax in case of lung NEN) every 6 months for 3 years, than every 12 months
- DOTATATE PET-CT after 3 and 6 years

NET G2 - CT/MRI abdomen (+CT thorax in case of lung NEN) after 3 and 6 months, than every 6 months for 3 years, than every 12 months
- DOTATATE PET-CT after 3 and 6 years

NET G3, NEC
- CT/MRI abdomen + thorax every 3 months for 2 years, than every 6 months for 2 years, than every 12 months
- DOTATATE PET-CT after 1 year, 3 years and 6 years (only NET G3)

Palliative treatment →

NET G1 - CT/MRI abdomen (+CT thorax in case of lung NEN) every 6 months, consider 12 months if stable for >3 years
- DOTATATE PET-CT every 3 years

NET G2 - CT/MRI abdomen (+CT thorax in case of lung NEN) after 3 and 6 months, than every 6 months
- DOTATATE PET-CT every two years

NET G3, NEC
- CT/MRI abdomen + thorax every 3 months
- DOTATATE PET-CT after 1 year, afterwards every 2 years (only NET G3)

MANECs →
- CT/MRI scan every 3 months for three years, continue every 6 months for five years if NET pathology

Page 22: Supportive measures, adjuvant treatment, indications for systemic therapy

Supportive measures

At each stage of the process or whenever indicated:

- Offer contact to self help group
- Offer psychooncological support
- Offer nutritional counselling
- Offer social service
- Consider palliative care and/ or intervention

[1]Adjuvant treatment

- R1-resection: Consider adjuvant postoperative adjuvant chemotherapy, irradiation or combined RCT (lung, pancreas)
- R2-resection: Consider adjuvant postoperative chemotherapy or RCT (lung, pancreas)
- R0-resection: Consider adjuvant chemotherapy for any G3 grading
- MANECs: Adjuvant chemotherapy depending on the primary tumour location (e.g. FOLFOX)

[3]Indications for systemic therapy

- Recurrence after resection, consider re-excision first (endoscopic or surgery)
- Local advanced disease with existent or expected local complications or functional syndrome
- Progress on follow-up (contraindication for surgery, initially widespread disease)
- Grading G3 any manifestation

Page 23: Special circumstances

[4]Special circumstances

- Bone metastasis: Bisphosphonate therapy, local radiation therapy for pain or local destructive disease
- Brain metastasis: Cranial irradiation
- Functional syndrome: single agent or combinational therapy, consider debulking surgery +/- TACE if liver dominated disease

Carcinoid Syndrome:	-Somatostatinanaloga (up to twice regular dose possible); Add-on IFN-α; Add-on Tinctura opii; add-on Telostriat ethyl, (Everolimus)
Hedinger Syndrome:	-Close cardiology follow-up, consider valve repair -Pro-active treatment of tumour manifestation, aim for 5-HIES<40mg/24h
Insulinoma:	-Everolimus, -Diazoxide, -Somatostatinanaloga (only if SMS-positive)
Glucagonoma:	-Somatostatinanaloga if SMS positive, -Interferon-α
VIPoma:	-Somatostatinanaloga if SMS positive, -Interferon-α, Loperamide/Tinctura opii
Gastrinoma:	-Proton pump inhibitors, up to 6 times standard dose, Somatostatinanaloga, consider (partial) gastric resection

- Liver metastasis**:**
  - Consider LTX in case of isolated liver metastasis (see addendum page 24)
  - Consider if systemic medical treatment failure
    or contraindications for medical treatment
    or if liver only disease
    or for symptomatic liver-dominated disease in well differentiated tumours (independent of grading):
      -TACE / TAE
      -SIRT
      -RFA
      -Local ablative irradiation

Page 24: Liver transplantation in isolated liver metastasis of GEP-NEN[6]

Baseline criteria

- Unresectable[7] liver only metastasis[8] of well or moderately differentiated G1/G2 NEN[9] with portal venous drainage[10]
- Stable disease > 6 months after resection of primary and possible extrahepatic findings
- Obligatory presentation and consensus decision making in a tumorboard

Recertification

- Exclusion of extrahepatic manifestations every three months by a –tumorboard determined- appropriate imaging
- The appearance of extrahepatic progression (e.g. lymphnode positivity) leads to delisting. A relisting is possible after a six months interval of absence of extrahepatic metastasis
- The appearance of extrahepatic metastasis in solid organs (e.g. lung, bones) leads to permanent disqualification for liver transplant

6 According to recommendations of “Ständige Kommission Organtransplantation”: Richtlinie zur Wartelistenführung und Organvermittlung zur Lebertransplantation gemäß TPG §16 Abs. 1 S 1 Nr. 2-5.

7 Evaluation of liver metastasis by triphasic contrast CT and or liver specific contrast MRI. Diagnostics have to be performed according to the current state of knowledge and are determined by the tumorboard

8 Exclusion of extrahepatic metastasis by PET or SMS-scintigraphy or DOTA/DOTATOC scintigraphy. Diagnostics have to be performed according to the current state of knowledge and are determined by the tumorboard

9 G1 and G2 with low mitotic rates with Ki-67/ MIB ≤ 10%. Ki-67/ MIB status is necessary.

10 Patients with NEN metastasis of an origin in deep rectal, oesophageal, lung, suprarenal or thyroideal are excluded.