SPECIAL ARTICLE

Neuroendocrine neoplasms of head and neck, genitourinary and gynaecological systems, unknown primaries, parathyroid carcinomas and intrathyroid thymic neoplasms: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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NEUROENDOCRINE NEOPLASMS

Incidence and epidemiology

Neuroendocrine neoplasms (NENs) encompass well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). The primary tumour site for NENs remains unidentified in 13%-20% of cases.[1] NENs account for ∼8% of unknown primary (UKP) malignancies and UKP-NENs represent the fourth most common NEN with an increasing incidence of 8.4 per million, representing 10%-15% of NETs and NECs.[1,2]

Genitourinary and gynaecological (GUGy)-NENs account for 1%-2% of GUGy malignancies, 12% of NECs and 4% of NETs.[3] Their estimated incidence in Europe is 0.5-1 per million.[4] GUGy-NENs arise from the bladder, kidney, ureter, ovary, cervix, endometrium, prostate, testis or presacral space[5-7] (see Section 1 of the Supplementary Material,

available at https://doi.org/10.1016/j.esmoop.2024.103664).

NENs arising from the head and neck (HN) account for <1% of HN malignancies, 2% of NECs and 0.6% of NETs.[4] Their estimated incidence in Europe is 0.1-0.15 per million.[4] HN-NENs arise most frequently from the larynx[8] followed by the middle ear[9] and sinonasal tract[10] (see Section 1 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664).

Diagnosis and pathological classification

Pathological classification. Classification of NENs relies on differentiation (well or poorly differentiated), presence or absence of necrosis and grade (G) assessed by Ki-67 index and/or mitotic count (see Table 1 and Section 2 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664).[11] Immunohistochemistry (IHC) biomarkers may help to identify primary sites[12,13] (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103664). For accurate diagnosis, a comprehensive pathology report should include unequivocal grading with morphological differentiation, mitotic count and Ki-67 index. The International Agency for Research on Cancer (IARC)—World Health Organization (WHO) 2018 consensus terminology is used when referring

Table 1. Current pathological classification of UKP-, GUGy- and HN-NENs and corresponding IARC—WHO 2018 consensus classification[14,68,106-108]

Common classification for UKP-, HN- and GUGy-NENs used in these guidelines[14]	HN-NEN classification[108]	GU-NEN classification[106]	Gy-NEN classification[107]
NET			
G1 NET	G1 NET or middle-ear NET	Well-differentiated NET (no grading)	G1 NET (Ovary: carcinoid tumour, no grading)
G2 NET	G2 NET or middle-ear NET		G2 NET
G3 NET	No G3 NET in the classification		No G3 NET in the classification
NEC			
Small-cell NEC	Small-cell NEC	Small-cell NEC	Small-cell NEC
Large-cell NEC	Large-cell NEC	Large-cell NEC	Large-cell NEC
MiNEN		Mixed NENs	Carcinoma admixed with NEC

G, grade; GU, genitourinary; GUGy, genitourinary or gynaecological; Gy, gynaecological; HN, head and neck; IARC, International Agency for Research on Cancer; MiNEN, mixed neuroendocrine—non-neuroendocrine neoplasm; NA, not applicable; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; UKP, unknown primary; WHO, World Health Organization.

to NENs (irrespective of their primary site), together with the organ-specific WHO classification (see Table 1).[14] In addition, a general template for reporting biopsies has been developed.[15]

Clinical diagnosis. The objective of the initial diagnostic work-up of UKP-NENs is to identify the occult primary tumour. Metastatic patterns can be indicative of primary tumour location. The most common site for the occult primary is the ileum followed by the pancreas.[16] Ileal NETs often present as a mesenteric mass on computed tomography (CT).[16] Somatostatin receptor (SSTR) imaging (SRI) with gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-labelled somatostatin analogue ([68Ga]Ga-DOTA-SSA)—positron emission tomography (PET)—CT is the most sensitive technique for NETs, detecting an occult primary in 61% of cases.[17] If SRI is uninformative, [18F] F-dihydroxyphenylalanine (DOPA)—PET—CT and endoscopy techniques can be useful (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103664, and Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664). For NECs, [18F]2-fluoro-2-deoxy-D-glucose (FDG)—PET—CT may be used. The presence of secretory syndromes and elevated hormone levels may also facilitate identification of the primary NET. A minimum panel of peptide hormones should be measured in patients with UKP-NETs [calcitonin, metanephrines and 5-hydroxyindoleacetic acid (5-HIAA)]. Other hormones may be measured depending on symptoms (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103664, and Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664). Chromogranin A has demonstrated a sensitivity of 71% and specificity of 84%-85% for the detection of gastroenteropancreatic (GEP) NETs.[18]

It is important to distinguish between primary GUGy-NETs and metastasis in the GUGy system from primary tumours in another site. Indeed, ovarian, testicular and renal metastases occur in patients with GEP or lung NETs. Symptoms result from local infiltration in patients with more aggressive GUGy-NENs and performance status (PS) deterioration. Less than 15% of GUGy-NETs present with hormone-related symptoms (mostly carcinoid syndrome).[1]

HN-NENs induce non-specific symptoms such as hoarseness, dysphagia, dyspnoea, nasal obstruction, epistaxis and conductive hearing loss.[19,20] Laryngeal NENs arise from the supraglottic region in 85% of cases.[8] Middle-ear NENs appear as a retrotympanic mass extending into the ossicles, mastoid, auditory canal and Eustachian tube.[9,19] Sinonasal NENs occur in the ethmoid (64% of cases), nasal cavity (32%) and maxillary sinus (14%). The most common metastatic sites are the lymph nodes, lungs, liver and bones.[21] Skin metastases can be extremely painful and suggestive of laryngeal NETs.[22] Functional syndromes are rare and include carcinoid syndrome, syndrome of inappropriate secretion of antidiuretic hormone, ectopic adrenocorticotropic hormone syndrome and Lambert—Eaton myasthenic syndrome.[23]

Recommendations

- Diagnostic and therapeutic recommendations for patients with UKP-, GUGy- or HN-NENs should be discussed in a NEN multidisciplinary tumour board (MTB) [V, A].
- UKP-, GUGy- and HN-NENs should be classified and graded according to the common IARC—WHO 2018 consensus classification together with the organ-specific WHO classification [V, A].
- For UKP-NETs, IHC should be carried out to exclude paragangliomas (cytokeratin) and to identify the primary [as a minimum: thyroid transcription factor-1 (TTF-1) and caudal-type homeobox 2 (CDX-2)]. Calcitonin, serotonin and other IHC markers may be used [IV, B].
- In patients with UKP-, GUGy- or HN-NETs, secretory syndromes should be diagnosed based on hormone-related symptoms. As a minimum, metanephrines, 5-HIAA and calcitonin should be measured in those with UKP-NETs [V, A].
- For UKP-NETs, cross-sectional imaging may identify metastatic patterns suggestive of a primary site (e.g. a mesenteric mass indicative of an ileal NET) [IV, A]. Endoscopy

and endoscopic ultrasound (US) are recommended to identify pancreatic primaries [V, A].

- SRI—PET is recommended for G1-2 UKP-NETs to visualise the primary tumour [IV, A]. FDG—PET—CT may be helpful in NENs with a higher proliferation index (G3 NETs and NECs) [V, B]. [^{18}F]F-DOPA—PET—CT may also detect an ileum primary, pheochromocytoma or paraganglioma in patients with UKP-NETs [V, B].
- In patients with UKP-NECs, searches for the primary should not delay treatment intervention, apart from cutaneous examination for Merkel-cell carcinoma and IHC for cytokeratin 20 and Merkel-cell polyomavirus, if available [V, A].

Staging and risk assessment

Adequate staging of UKP-, GUGy- and HN-NENs relies on cross-sectional imaging and nuclear medicine techniques. CT scans are effective for the detection of lung metastases whereas magnetic resonance imaging (MRI) is better for liver and bone metastases. MRI is also preferred in young patients as radiation exposure is lower. SRI has a high sensitivity for NETs and should be part of the initial work-up. SSTR scintigraphy is less sensitive and should only be carried out when SRI—PET—CT is not available. Whole body CT, or FDG—PET—CT in case of limited tumour burden, are recommended for the staging of G2-3 NETs and NECs.[24]

Staging of middle-ear HN-NENs is based on the system proposed by Marinelli et al.[19] while staging of GUGy- and HN-NENs is based on the eighth edition of the Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) classification[25] (see Supplementary Tables S2-S10, available at https://doi.org/10.1016/j.esmoop.2024.103664). There is no staging classification for UKP-NENs unless an occult primary is identified by the initial diagnostic work-up.

Prognosis for all NENs relies on pathological grading and staging. In patients with metastases, differentiation, WHO grade, age, PS, tumour burden, SRI and/or FDG uptake, the presence of a functional syndrome at baseline and tumour growth rate should be considered for optimal risk assessment.

Recommendations

- CT and/or MRI are recommended for staging. MRI should be mainly considered in young patients to reduce irradiation and—using late arterial phase imaging—improve detection of hepatic, pancreatic, brain and bone NETs [III, A].
- SRI—PET is recommended for initial and preoperative staging, and when indicated for restaging [V, A].
- FDG—PET—CT can be used for staging G2-3 NETs and NECs [IV, B].
- Major independent prognostic factors are disease stage (TNM) and pathological features including differentiation and WHO grade [IV, A]. Age, PS, tumour burden, the presence of functional syndromes and tumour growth rate are additional prognostic factors [IV, B].

Management of local and locoregional disease

Patients with UKP-NENs may present with lymph node metastases without the detection of a primary tumour or distant metastases. For G1-3 UKP-NETs, radical resection of locoregional disease is the preferred treatment (see Figure 1). While searching for an occult primary, the site of lymph node metastasis may guide surgical exploration (e.g. an involved mesenteric node is suggestive of an ileal primary). There is no evidence to support adjuvant therapy following curative resection of NETs. For UKP-NECs, downstaging of locoregional disease with chemotherapy (ChT) and/or radiotherapy (RT) may be considered before surgery. Some patients with NECs, particularly with isolated inguinal or neck nodes, may have prolonged disease control and survival following multimodal treatment including surgery.[26] In this setting, Merkel-cell carcinoma should be ruled out. It is unclear whether post-operative treatment of NECs improves outcomes, but four cycles of carboplatin—etoposide may be considered, particularly if neoadjuvant ChT has not been used.[27]

There are no prospective data on the management of local and locoregional disease in patients with GUGy-NENs. Recommendations are therefore extrapolated from site-specific ESMO Clinical Practice Guidelines (CPGs).[28] For GUGy-NETs, upfront radical surgery without adjuvant treatment is recommended when feasible (see Figure 2); however, a conservative surgical approach should be discussed whenever possible, particularly for low-grade localised NETs. The role of adjuvant therapy for G3 GUGy-NETs is also unknown. For GUGy-NECs, multimodal therapy should always be discussed for localised disease. Further details regarding the management of local and locoregional GUGy-NENs are available in Section 4 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664.

For HN-NENs, locoregional treatment depends on the primary site (see Figure 3). In the larynx, NETs are mainly supraglottic and their sensitivity to ChT and RT may be low. Based on retrospective data, radical resection after completion of whole body imaging (including PET—CT) is recommended whenever possible with homolateral neck dissection, as it may lower the risk of regional lymph node recurrence.[8] Post-operative RT should be discussed in a multidisciplinary meeting, particularly for G2 NETs.[8] For laryngeal NECs, treatment relies mainly on ChT and RT[8]; surgery may be discussed in selected cases.[29] For sinonasal NETs, surgery was associated with longer survival in retrospective series.[30,31] The role of prophylactic neck dissection is unknown. Post-operative RT should be discussed but there is no evidence that it prevents locoregional relapse. For sinonasal NECs, treatment should be multimodal. Retrospective data suggest that induction ChT is beneficial,[10] in combination with RT in most cases and surgery in selected cases.[21,31] Most middle-ear tumours are NETs. Surgery is the mainstay of treatment,[19,32] but complete resection with no tumour at the margin (R0) is challenging and there is a risk of locoregional relapse when ossicles are
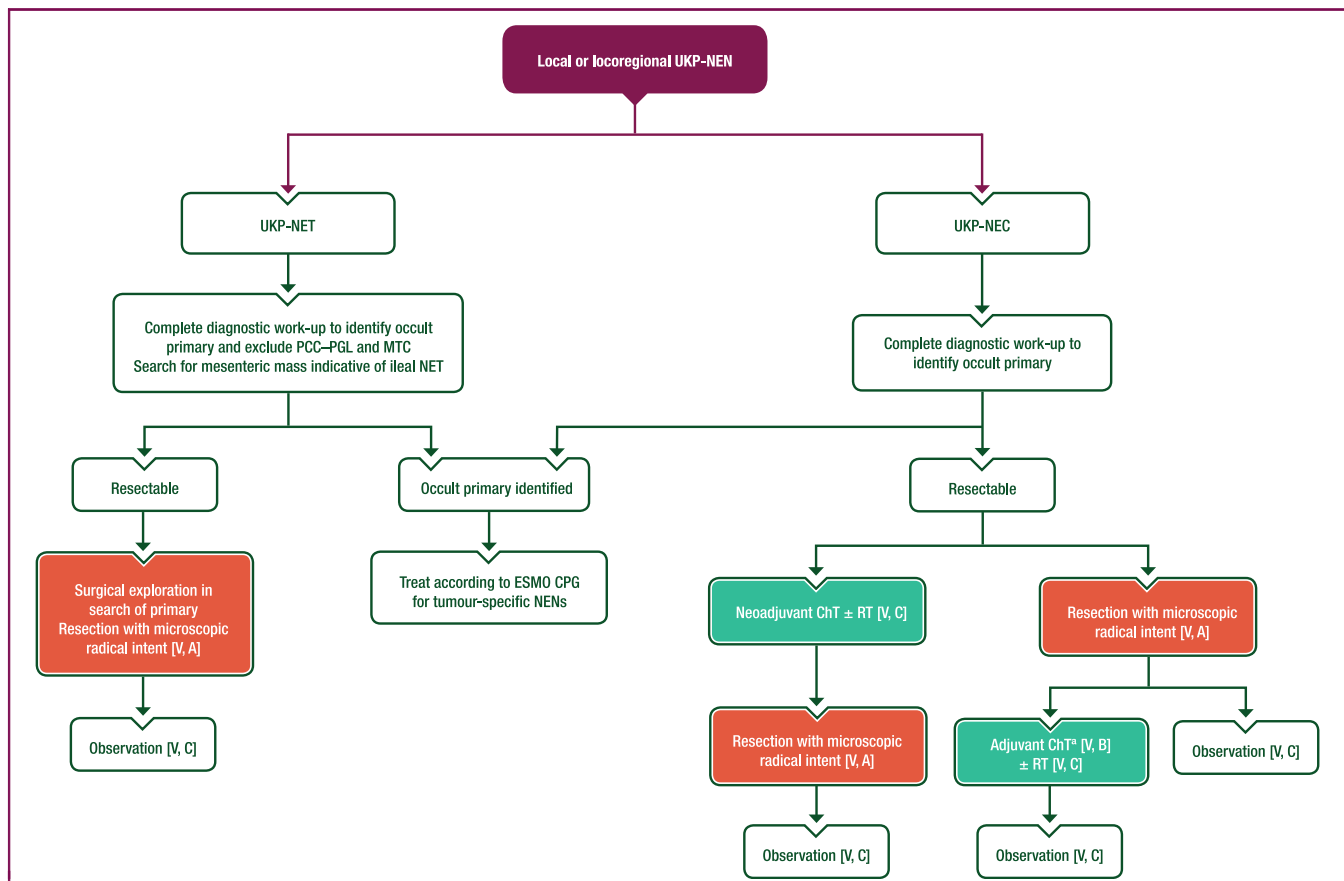
Figure 1. Management of local or locoregional UKP-NENs.
Purple: algorithm title; orange: surgery; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ChT, chemotherapy; CPG, Clinical Practice Guideline; MTC, medullary thyroid cancer; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; PCC—PGL, pheochromocytoma—paraganglioma; RT, radiotherapy; UKP, unknown primary.
[a]Four cycles of platinum—etoposide.

involved. There are no data on post-operative RT; however, RT may be discussed for patients with a higher risk of relapse due to adherence to important neurovascular structures. RT might prevent extension to the skull base and subsequent debilitating complications. This must be balanced against the risk of long-term RT-induced toxicity.

Recommendations

- For patients with UKP-NETs with locoregional disease, the aim of surgical resection with exploration is to identify and treat the primary tumour with microscopic radical intent [V, A].
- For GUGy-NETs, surgery of the primary tumour and nodes with microscopic radical intent (according to site-specific ESMO CPGs) is the treatment of choice for local and locoregional disease, irrespective of grade [V, A]. A conservative surgical approach should be discussed whenever feasible, particularly in low-grade, early-stage NETs [V, B].
- For laryngeal and sinonasal NETs, surgery of the primary tumour with microscopic radical intent and homolateral therapeutic neck dissection is recommended whenever possible [IV, A].

- Adjuvant treatment cannot be recommended for UKP-NETs [V, D] but adjuvant RT may be discussed for GUGy-NETs in patients with microscopic (R1) or macroscopic (R2) tumour at the margin and/or G3 disease [V, C].
- For HN-NETs, adjuvant RT may be discussed after radical resection, particularly in case of locoregional spread, non-R0 resection and G2 disease; however, the benefit in terms of local control is unknown [V, C].
- For locoregional sinonasal NECs, neoadjuvant ChT with platinum—etoposide may be considered before surgical resection [IV, C].
- For NECs treated with radical surgery, adjuvant therapy with four cycles of platinum—etoposide may be considered [V, B].
- Neoadjuvant ChT may be an option for UKP- and GUGy-NECs [V, C].
- Combining RT with ChT is recommended for HN-NECs [IV, A] and could be discussed for UKP- and GUGy-NECs as definitive or (neo)adjuvant treatment [V, C].

Management of advanced and metastatic disease

For UKP-NETs there are few clinical trials with low patient numbers and for UKP-NECs there are only retrospective
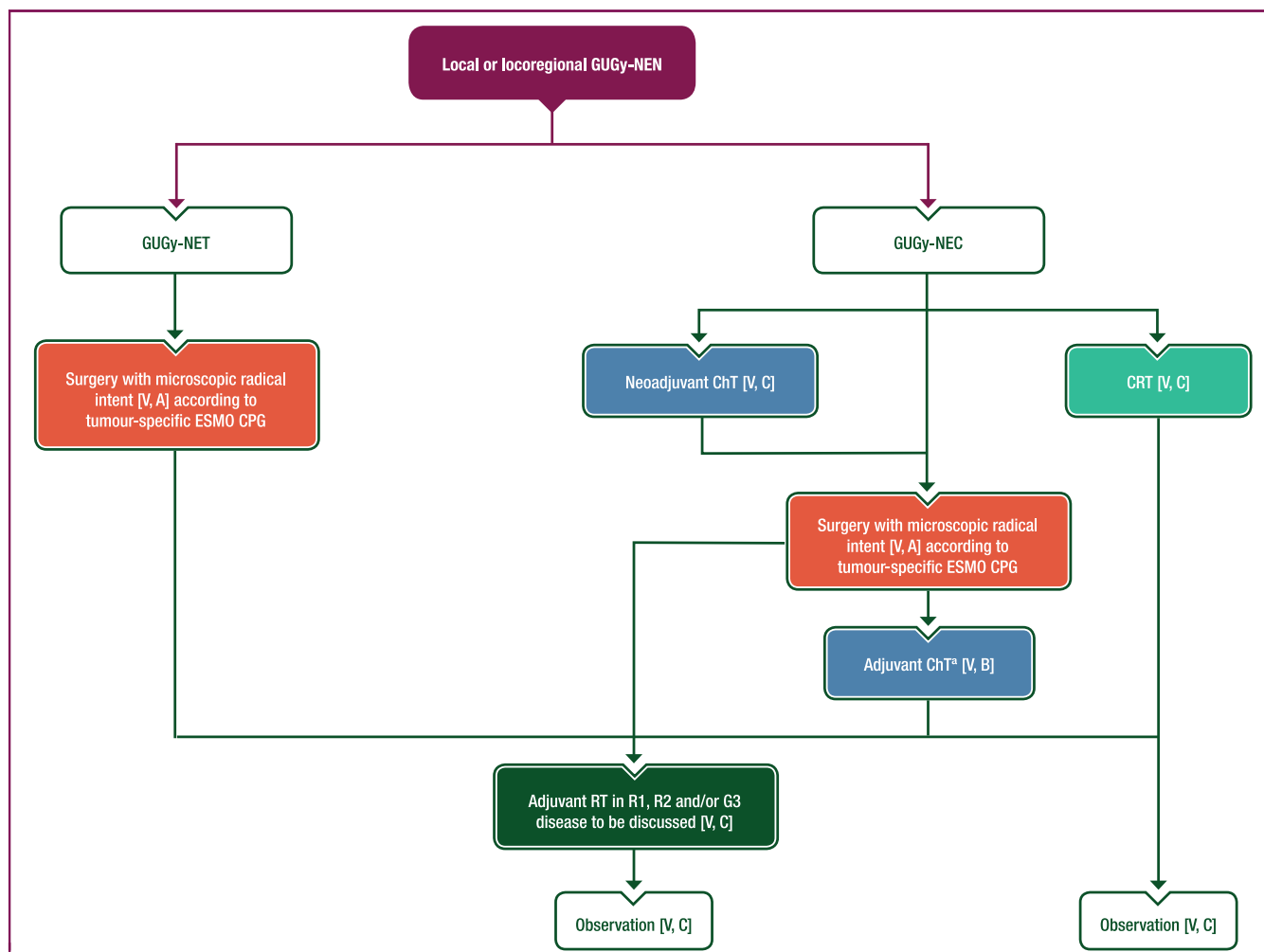
Figure 2. Management of local or locoregional GUGy-NENs.
Purple: algorithm title; orange, surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ChT, chemotherapy; CPG, Clinical Practice Guideline; CRT, chemoradiotherapy; G, grade; GUGy, genitourinary or gynaecological; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; R1, resection with microscopic tumour at the margin; R2, resection with macroscopic tumour at the margin; RT, radiotherapy.
[a]Four cycles of platinum—etoposide.

studies; available data are summarised in Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664. For advanced or metastatic GUGy- and HN-NENs, neither retrospective nor prospective studies are available. Thus, recommendations for the management of UKP-, GUGy- and HN-NENs are based on the management of NENs of GEP or lung origin and so systemic treatments approved for GEP-NETs are used off-label in this setting.[28] When an occult primary is identified or suspected (such as a mesenteric mass from an ileal NET), its management should follow the dedicated guideline.

Treatment decisions (see Figure 4) should be based on comprehensive multidisciplinary characterisation of the tumour (see 'Staging and risk assessment'). In particular, WHO grade, differentiation (well versus poor),[33] SSTR status based on SRI—PET—CT[24] and presence of a functional syndrome should be considered.

Surgery and locoregional therapies. Surgery should be discussed for slowly proliferating (oligo)metastatic tumours in patients with G1-2 UKP-, GUGy- or HN-NETs; this includes surgical exploration for occult primary identification in case of UKP-NETs.[34] Metastatic spread in HN-NETs frequently involves the skin, particularly in those arising from the larynx.[20,22] Skin metastases are usually multiple and small in size, causing hard-to-treat pain and discomfort, which affects patients' quality of life. In most cases, they are resistant to systemic treatment. Repeated locoregional therapies may be used, including surgical resection, electrochemotherapy[35] and RT for the largest tumours.[22]

Somatostatin analogues. Two phase III trials [CLARINET (lanreotide) and PROMID (octreotide)] have reported longer progression-free survival (PFS) or time to progression with somatostatin analogue (SSA) treatment compared with placebo in patients with metastatic GEP-NETs. Both studies included some patients with UKP-NETs but none with GUGy- or HN-NETs.[36,37] Extrapolating the results from CLARINET and PROMID, SSAs may be recommended for tumour
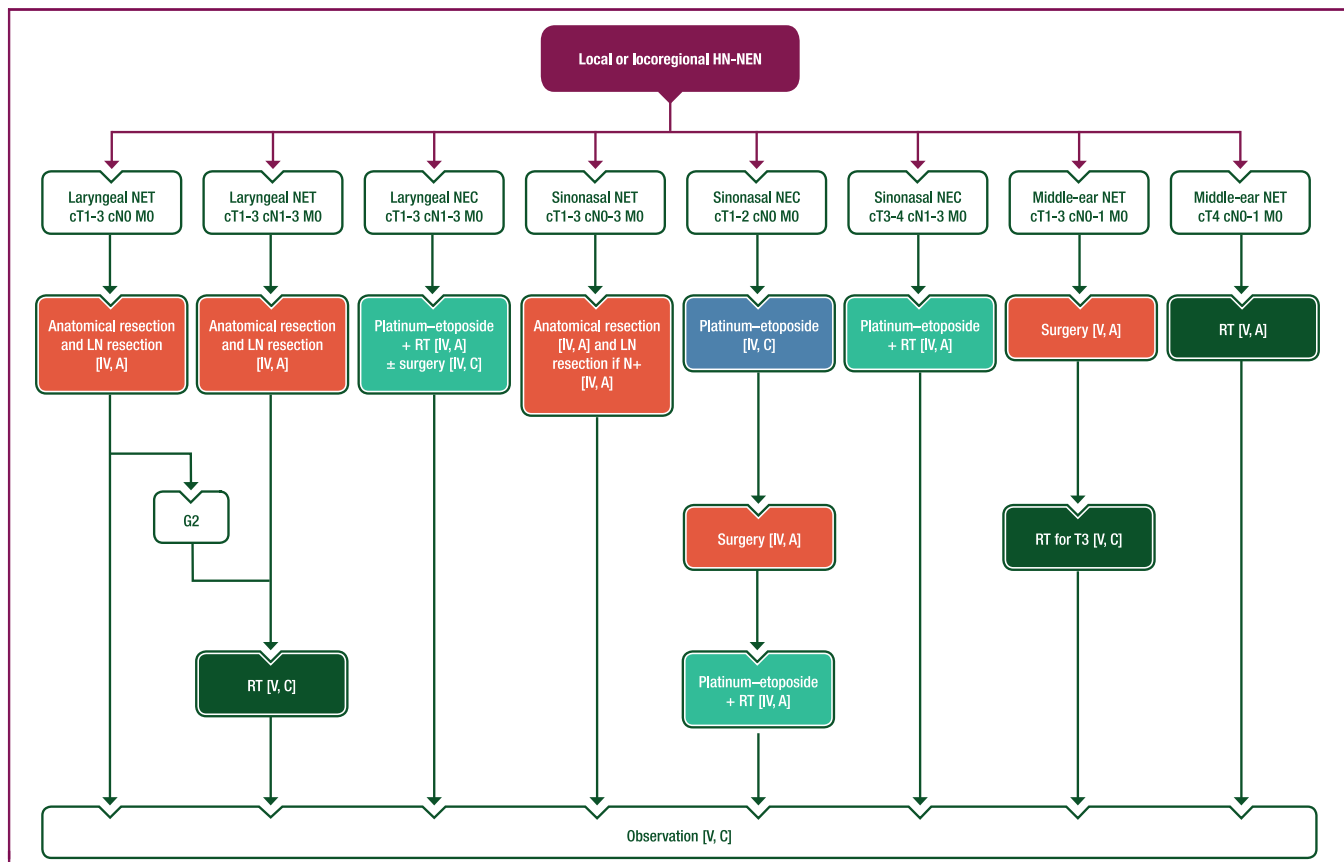
Figure 3. Management of local or locoregional HN-NENs.
Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
c, clinical; G, grade; HN, head and neck; LN, lymph node; M, metastasis; N, node; N+, lymph node metastasis; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; RT, radiotherapy; T, tumour.

control in advanced SSTR-positive, G1-2 NETs (Ki-67 <10%) or slowly progressive NETs.[38]

Management of functional syndromes. SSAs are recommended as first-line therapy for carcinoid syndrome and other functional syndromes (Figure 5). Beyond SSAs, studies exploring the role of telotristat ethyl[39] or interferon-α (IFN-α)[40] for carcinoid syndrome control included patients with any primary tumour site so their use is also applicable to UKP-NETs. No data are available on the treatment of carcinoid syndrome associated with GUGy- or HN-NETs. Management of carcinoid syndrome should follow the European Neuroendocrine Tumor Society 2022 guidance paper on carcinoid syndrome and carcinoid heart disease[41]; management of Cushing syndrome should follow the ESMO CPG on lung and thymic carcinoids.[28]

Targeted therapy. Based on data from the RADIANT-2,[42] RADIANT-3[43] and RADIANT-4[44] trials (NETs of various primaries), everolimus monotherapy may be considered as first-line treatment for SSTR-negative G1-2 UKP-, GUGy- and HN-NETs, or as second-line treatment after SSAs in patients with progressive disease. The RADIANT studies, however, included only 36 patients with UKP-NETs and no patients with GUGy- or HN-NETs. Based on the randomised CABI-NET,[45] AXINET[46] and SANET-ep[47] trials, antiangiogenic

multikinase inhibitors (MKIs) may be considered as alternatives to everolimus for first-line treatment of SSTR-negative G1-2 UKP-, GUGy- and HN-NETs, or for second-line treatment after SSAs in patients with progressive disease. These studies included 34-49 patients with UKP-NETs or NETs of other origin not otherwise specified (see Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664).

ChT. In patients with progressive G2 (Ki-67 >10%) and G3 NETs, alkylating agent-based and oxaliplatin-based ChT regimens may be considered. Most data for management of G3 NETs with these regimens are from patients with pancreatic NETs, with response rates of up to 30% and median PFS of 8-16 months.[48] Loss of O-6-methylguanine-DNA methyltransferase (MGMT) expression or promoter hypermethylation may prompt use of alkylating agent-based ChT (see Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664).[49,50] For the management of NECs, first-line carboplatin—etoposide or cisplatin—etoposide is recommended based on retrospective series showing response rates of 40%-60%, median PFS of 4-6 months and median overall survival (OS) of 12 months.[2,10,21,29,51] Carboplatin—etoposide or cisplatin—etoposide should not be used for well-differentiated NETs, regardless of grade.[33,51]
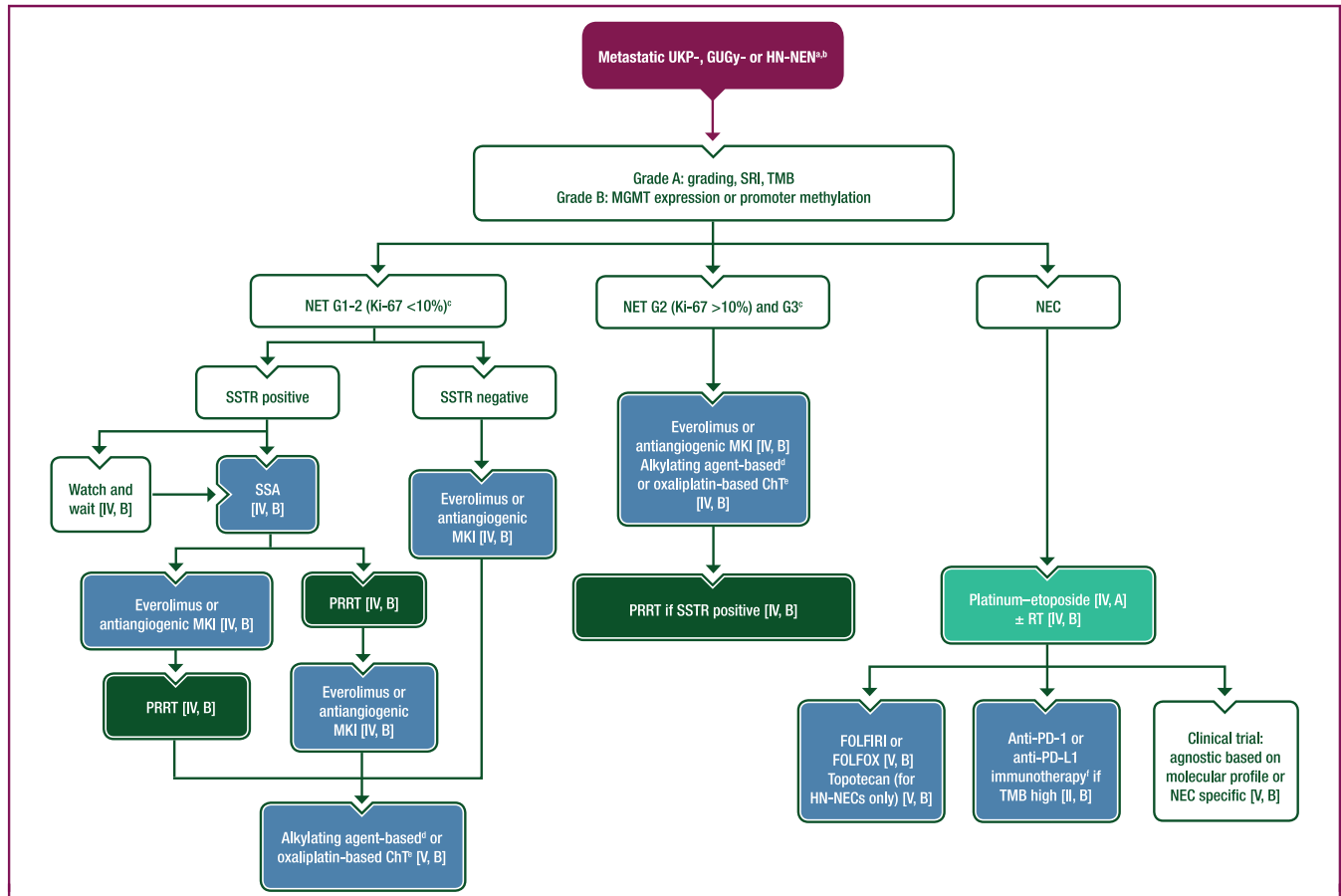
Figure 4. Management of metastatic UKP-, GUGy- and HN-NENs.

Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

5-FU, 5-fluorouracil; ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; G, grade; GUGy, genitourinary or gynaecological; HN, head and neck; MGMT, O-6-methylguanine-DNA methyl-transferase; MKI, multikinase inhibitor; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PRRT, peptide receptor radionuclide therapy; R0, resection with no tumour at the margin; RT, radiotherapy; SRI, somatostatin receptor imaging; SSA, somatostatin analogue; SSTR, somatostatin receptor; TMB, tumour mutational burden; UKP, unknown primary.

[a]Always consider enrolment in a clinical trial [V, A].

[b]Recommendations for the management of metastatic UKP-, GUGy- and HN-NENs are based on the management of NENs of GEP or lung origin and therefore systemic treatments approved for GEP-NETs are used off-label in these settings.

[c]Surgery is recommended if disease is amenable to R0 resection [V, A].

[d]Dacarbazine, temozolomide or streptozocin plus 5-FU or capecitabine.

[e]Oxaliplatin plus 5-FU or capecitabine.

[f]Pembrolizumab is FDA approved (but not EMA approved) for the treatment of patients with unresectable or metastatic TMB high solid tumours that have progressed following prior treatment and have no alternative treatment options. No other anti-PD-1 or anti-PD-L1 agents are approved for use in patients with TMB high solid tumours.

Peptide receptor radionuclide therapy. Patients with UKP-, GUGy- and HN-NETs were excluded from the randomised phase III NETTER-1 study, which evaluated peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lutetium-DOTA-Tyr3-octreotate in patients with mid-gut NETs.[52] Retrospective studies have reported equivalent efficacy with PRRT in patients with UKP-NETs versus other primaries (~30% response rate and PFS of 20-25 months), thereby supporting its use.[53] There are no retrospective studies on the use of PRRT in GUGy- or HN-NETs. PRRT may be an option for patients with SSTR-positive UKP-, GUGy- or HN-NETs who have progressed under SSA treatment.

Precision medicine. The ESMO Precision Medicine Working Group recommends determination of tumour mutational burden (TMB) in NENs,[54] following results from the TMB-high cohort of the KEYNOTE-158 basket trial of pembrolizumab.[55]

In this study, two of five patients with TMB-high NENs had a response (40% response rate compared with 1% in those with non-TMB-high NENs); however, no immunotherapy is approved in Europe for TMB-high tumours and the availability of next-generation sequencing for patients with NENs is limited. No recurrent molecular alterations have yet been reported in UKP-, GUGy- or HN-NENs. Molecular profiling, when available, should be offered and may provide information to guide agnostic clinical trials and/or compassionate treatment requests.

Recommendations

- Comprehensive characterisation, including WHO grade, differentiation (well versus poor), SSTR status and the presence of a functional syndrome, is recommended before making treatment decisions [V, A].
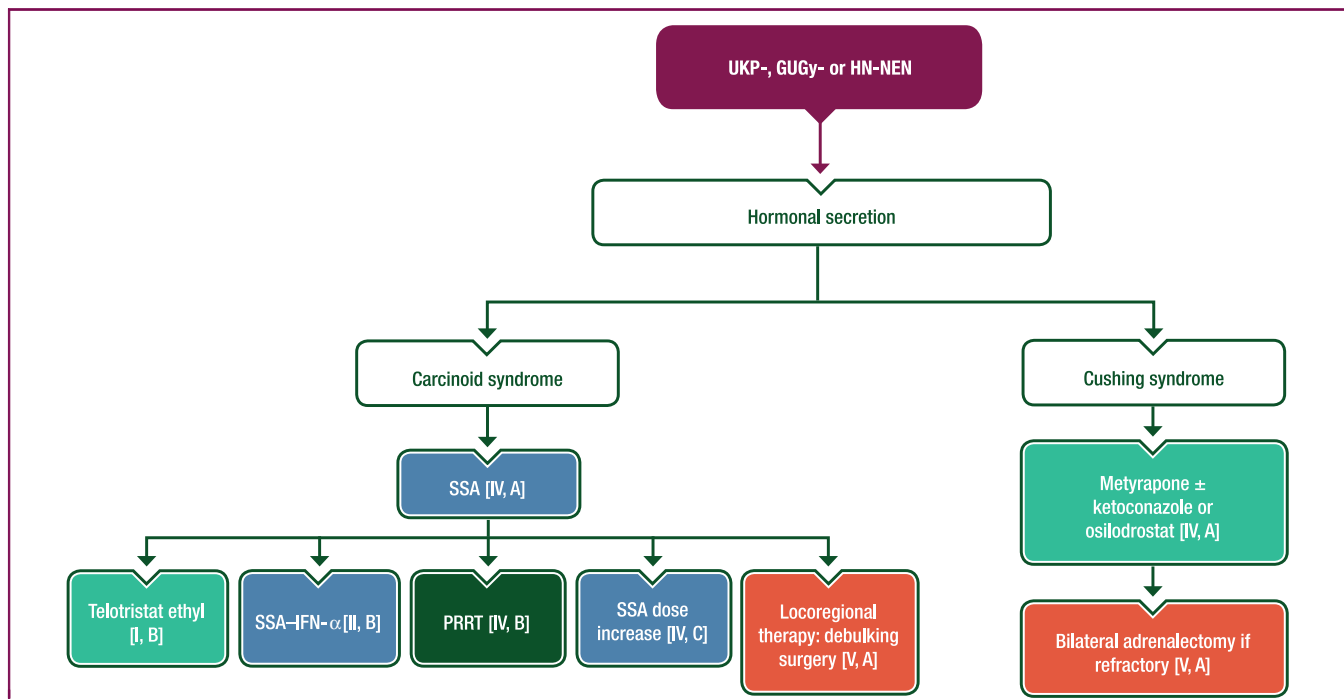
Figure 5. **Management of carcinoid syndrome and Cushing syndrome induced by UKP-, GUGy- or HN-NENs.**
Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
GUGy, genitourinary or gynaecological; HN, head and neck; IFN-α, interferon-α; NEN, neuroendocrine neoplasm; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; UKP, unknown primary.

- For metastatic UKP-, GUGy- and HN-NETs, surgery is recommended if the disease is amenable to R0 resection and/or for debulking to control hormonal syndromes in functional NETs [V, A].
- SSAs are the first-line treatment for patients with carcinoid syndrome [IV, A]. In case of uncontrolled carcinoid syndrome, telotristat ethyl (for syndrome control) [I, B], the combination of an SSA with IFN-α [II, B], PRRT [IV, B], SSA dose increase [IV, C] or locoregional treatment (debulking) of metastatic disease [V, A] can be used.
- For patients with Cushing syndrome, metyrapone ± ketoconazole or osilodrostat are recommended [IV, A]. Bilateral adrenalectomy is recommended in refractory cases [V, A].
- Given the rarity of UKP-, GUGy- and HN-NETs, enrolment of patients in clinical trials is recommended whenever possible [V, A].
- SSAs are recommended as first-line therapy for tumour growth control in advanced, SSTR-positive UKP-, GUGy- and HN-NETs with Ki-67 <10% [IV, B].
- A watch-and-wait strategy may be followed in patients with low Ki-67, low tumour burden and stable disease [IV, B].
- Everolimus is recommended first line in SSTR-negative G1-2 NETs and second line (after SSA treatment) in patients with SSTR-positive progressive disease [IV, B; European Medicines Agency (EMA) and Food and Drug Administration (FDA) approval is for NETs of pancreatic, gastrointestinal or lung origin only]. Antiangiogenic MKIs may be an alternative in these settings [IV, B].

- PRRT may be an option for patients with SSTR-positive (on all evaluable targets) G1-2 UKP-, GUGy- and HN-NETs progressing on SSAs [IV, B].
- For progressive G1-2 UKP-, GUGy- and HN-NETs, alkylating agent-based ChT [dacarbazine, temozolomide or streptozocin combined with 5-fluorouracil (5-FU) or capecitabine] or oxaliplatin-based ChT (oxaliplatin combined with 5-FU or capecitabine) may be used despite limited data [V, B]; MGMT status may guide ChT regimen choice.
- Everolimus [IV, B] or antiangiogenic MKIs [IV, B] can be recommended for first-line treatment of G2 (Ki-67 >10%) and G3 UKP-, GUGy- and HN-NETs. Alkylating agent- or oxaliplatin-based ChT can also be recommended in this setting [IV, B]. PPRT may be recommended for patients with SSTR-positive progressive disease [IV, B].
- Platinum—etoposide is recommended as first-line treatment for UKP-, GUGy- and HN-NECs [IV, A]. For HN-NECs with isolated lymph node metastases and no other metastatic sites, RT may be discussed after ChT [IV, B]. The second-line ChT regimens leucovorin—5-FU—irinotecan (FOLFIRI) and leucovorin—5-FU—oxaliplatin (FOLFOX) can be used [V, B] and topotecan is also an option for HN-NECs [V, B].
- Molecular profiling with TMB determination should be offered when available to guide agnostic clinical trial inclusion [V, B] and/or compassionate programmed cell death protein 1 or programmed death-ligand 1 immunotherapy requests, particularly in high-grade NEC [II, B].

Follow-up, long-term implications and survivorship

Follow-up of patients with metastatic UKP-, GUGy- and HN-NENs should be personalised [based on morphology (well versus poorly differentiated), WHO grade, staging, presence of residual disease or metastases, and SRI or FDG—PET positivity] and include imaging and monitoring of clinical symptoms and biochemical parameters. With the exception of UKP-NENs (see Section 6 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664), there are no data on long-term follow-up. Follow-up carries the risk of excessive radiation exposure, so low-dose CT (for lung metastases) or MRI should be used whenever possible, especially in patients for whom prolonged follow-up is anticipated. There is a consensus for the use of molecular imaging for SSTR-positive NETs, especially SRI with [68Ga]Ga-DOTA-SSA—PET—CT, at initial staging and for post-surgical restaging, but not for routine follow-up.[24] Molecular imaging may play a role, however, in the follow-up of secondary lesions that are hard to evaluate with conventional imaging, such as peritoneal carcinomatosis and bone metastases.

Recommendations

- For patients with completely resected G1 and low G2 (Ki-67 <10%) UKP-, GUGy- or HN-NETs, follow-up using low-dose CT or MRI is recommended every 6 months for 2 years, annually for years 3-5 and every second year thereafter [V, C].
- For patients with completely resected G2 (Ki-67 ≥10%) and G3 UKP-, GUGy- or HN-NETs, follow-up using low-dose CT or MRI is recommended every 3 months for 2 years, every 6 months in year 3, annually for years 4-5 and every second year thereafter [V, C].
- For patients with completely resected UKP-, GUGy- or HN-NECs, follow-up should be carried out every 2-3 months for 2 years, every 6 months in year 3 and then discussed on a case-by-case basis thereafter [V, C].
- For patients with completely resected UKP-, GUGy- or HN-NENs, the best molecular imaging technique (according to SRI—PET and/or FDG—PET—CT positivity at initial staging) is recommended 6 months after resection and then in case of unclear or abnormal imaging results [V, C].
- For patients with UKP-, GUGy- or HN-NENs and residual or metastatic disease, restaging is recommended every 4-6 months [G1 and low G2 (Ki-67 <10%) NETs] or every 3-4 months [G2 (Ki-67 ≥10%) and G3 NETs]; the interval can be increased in case of stable disease [V, C].
- For patients with UKP-, GUGy- or HN-NENs and residual or metastatic disease, systematic follow-up using PET imaging is not recommended but may be considered in case of doubtful or abnormal imaging results, increasing biomarkers, clinical suspicion of new metastasis (particularly in the bone) and/or depending on the metastatic sites and their measurability using conventional imaging, especially when locoregional therapies are discussed [V, C].
- Patients with disseminated disease may benefit from referral to specialised palliative care units for appropriate pain treatment, psychosocial support and rehabilitation [II, B].

PARATHYROID CARCINOMA

Incidence and epidemiology

Parathyroid carcinoma (PC) is a rare neoplasm, accounting for <1% of primary hyperparathyroidism cases.[56] PC affects male and female patients with a mean age at diagnosis of 50 years. PC occurs as a sporadic form, or less frequently as familial forms such as hyperparathyroidism-jaw tumour syndrome (HPT-JT; ~15% of cases) linked to a germline mutation in the *CDC73/HRPT2* gene.[57] Rarely, it can occur as multiple endocrine neoplasia (MEN) type 1 (MEN1) or type 2A (MEN2A).[58] Even in the absence of a family history, 20%-40% of patients with apparently sporadic PC have a germline *CDC73* mutation.[58,59]

Diagnosis, pathology and molecular biology
Diagnosis.

Clinical presentation. PC can be suspected in patients who present with severe primary hyperparathyroidism characterised by severe hypercalcaemia-related symptoms and markedly elevated parathyroid hormone (PTH) levels. Less than 10% of patients have normal serum calcium and PTH levels and present with a non-functional PC with only local symptoms, such as a palpable cervical mass, hoarseness, dysphagia or dyspnoea.[60]

Laboratory studies. Most patients with PC have markedly high levels of calcium (>14 mg/dl or 3.5 mmol/l) and non-suppressed intact PTH 1-84 molecule (3-10 times above the upper limit of normal). The combined presence of high serum calcium (>3 mmol/l) and a parathyroid lesion >3 cm (the so-called '>3, >3 rule'), should raise suspicion of PC. Some patients with PC may overproduce N-terminal PTH fragment and have elevated serum and urinary levels of human chorionic gonadotropin; their determination could be useful for differential diagnosis with benign adenoma, although this has only been tested in a small series.[61]

Imaging. Neck US is the first-line imaging technique for the diagnosis of parathyroid lesions. Its sensitivity varies from 67% to 96% with a positive predictive value of 89.7%-97%[62]; however, there are no specific patterns of malignancy (see Section 7 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664). Fine-needle aspiration (FNA) with cytology and washout PTH measurement can help to differentiate from lesions of other origins (e.g. thyroid, distant metastases from other tumours).[63] Complications associated with the FNA procedure (including occasional seeding) are rare.[64]

Contrast-enhanced CT and MRI can be used in highly suspicious cases to evaluate infiltration of surrounding tissue but are not routinely carried out for differential diagnosis.[65]

Parathyroid scintigraphy with [99mTc]Tc-sesta-methoxyisobutylisonitrile (MIBI) single-photon emission CT (SPECT) or SPECT—CT, in combination with neck US, is the procedure of choice for preoperative identification of hyperfunctioning parathyroids. During initial PC evaluation, the sensitivity and diagnostic accuracy of [99mTc]Tc-sesta-MIBI scintigraphy are

≥80% when used with neck US or CT. Nevertheless, there are no clear scintigraphic parameters that allow a real preoperative differential diagnosis between PC and adenoma. PET procedures such as [^{11}C]-methionine—PET—CT and [^{18}F]-choline—PET—CT are effective for the diagnosis of primary hyperparathyroidism but their added value in the differential diagnosis between PC and adenoma is unknown.[66]

Pathology. Histological diagnosis of PC is based on the 2022 WHO classification criteria: (i) vascular invasion; (ii) lymphatic invasion; (iii) perineural (intraneural) invasion; (iv) local malignant invasion into adjacent anatomical structures; or (v) histologically or cytologically documented metastatic disease. The morphology of PC is usually reminiscent of parathyroid adenoma or hyperplasia.[67,68] Features suggestive of malignancy and warranting a diagnosis of atypical adenoma [also called parathyroid neoplasm of uncertain malignant potential or atypical parathyroid tumour (APT)] are macroscopically evident necrosis, size >3 cm, weight >500 mg, mitotic index >5 mitoses/2 mm^2 and the presence of atypical mitosis[67,69] (see Section 7 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664). Some rare variants have been described, including oncocytic carcinomas and carcinosarcomas with more aggressive behaviour.[70,71] Although PC generally shows a higher proliferation index (Ki-67 6%-9% compared with <4% in adenoma), there is no predefined Ki-67 cut-off to support or exclude a PC diagnosis. The International Collaboration on Cancer Reporting (ICCR) has issued a dataset on PC and APT that covers PC grading, considering it high grade in the presence of sheets of pleomorphic enlarged nuclei, coagulative necrosis, abnormal mitosis and/or increased proliferation rate.[69]

Molecular biology. The most frequent molecular alteration in PC is on the *CDC73* gene (40%-50% of cases). Phosphatidylinositol-3-kinase (PI3K)—protein kinase b (AKT)—mammalian target of rapamycin (mTOR) is the most frequently altered pathway (40%-80% of cases).[65,72,73] IHC evaluation of parafibromin loss of expression to identify a double-hit inactivation of the *CDC73* gene is a recognised ancillary diagnostic method for malignancy, as is evaluation of loss of *p27*, other types of cyclins or cell cycle regulators, galectin-3 and protein gene product 9.5.[69,74]

Recommendations

- Genetic testing for germline *CDC73* mutation should be carried out to rule out HPT-JT in all patients with PC, including those without a family history [IV, A].
- The combined presence of markedly elevated serum calcium [>12 mg/dl (>3 mmol/l)] and parathyroid lesions >3 cm should raise suspicion of PC [IV, B].
- US of the neck should be carried out to assess lesions suspicious for PC [IV, A].
- Contrast-enhanced CT and MRI are used to evaluate locoregional invasion before planning surgery [V, A].
- FNA cytology and washout PTH measurements can be used to differentiate PC from other neck or thyroid nodules but cannot differentiate it from adenoma [V, C].

- [^{99m}Tc]Tc-sesta-MIBI—SPECT may be useful for the diagnosis of PC but cannot differentiate it from adenoma [IV, C].
- PC pathology reporting should follow the 2022 WHO classification (fifth edition) and ICCR template [IV, A].

Staging and risk assessment

The prognosis for patients with PC is variable, with 5- and 10-year OS rates after surgery of ∼80% and 40%-80%, respectively. Good prognosis is associated with early diagnosis and radicality of initial surgery, whereas poor prognosis is mainly related to older age and the presence of lymph node metastases.[75-79]

Staging is based on the eighth edition of the American Joint Committee on Cancer (AJCC) TNM system (see Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2024.103664).[80] Only 15%-30% of patients have level VI lymph node metastases and one-third have distant metastases, most commonly in the lung, liver or bone. The detection of locoregional or distant metastases is based on neck US, thoracic and abdominal CT, or MRI.

Among nuclear medicine techniques, total body acquisition with [^{99m}Tc]Tc-sesta-MIBI can identify possible extracervical uptake and unexpected lesions. FDG—PET—CT can also be applied as PC generally shows high FDG uptake. It can be used to complement conventional imaging in the initial staging and for residual or relapsing disease, albeit based on limited data.[81] Other PET tracers such as [^{11}C]-methionine—PET—CT and [^{18}F]-choline—PET—CT have not been validated for routine staging of PC.[66,81,82]

Recommendations

- PC staging should follow the eighth edition of the AJCC TNM system [IV, A].
- Cross-sectional imaging is the reference method [V, A] but additional FDG—PET—CT may improve staging accuracy [IV, C].

Management of local and locoregional disease

Management of hypercalcaemia. Medical management of hypercalcaemia is the main treatment for patients awaiting surgery and those with inoperable PC. Cinacalcet, a potent second-generation calcium mimetic, is effective for controlling hypercalcaemia in patients with inoperable or persistent disease.[83,84] The greatest reductions in calcium were reported in patients with the highest serum calcium levels before therapy. The cornerstones of treatment for severe or symptomatic hypercalcaemia are intravenous saline hydration and bisphosphonate administration (see Section 7 of the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103664).

Surgery. Surgery is the recommended first-line treatment for PC (Figure 6).[85] Inadequate and non-radical surgery represent the strongest prognostic factors for recurrence and mortality. In case of high suspicion of PC, *en bloc* removal of the parathyroid lesion avoiding capsule rupture and local seeding, homolateral thyroid lobo-isthmectomy and central node dissection are recommended.[86]
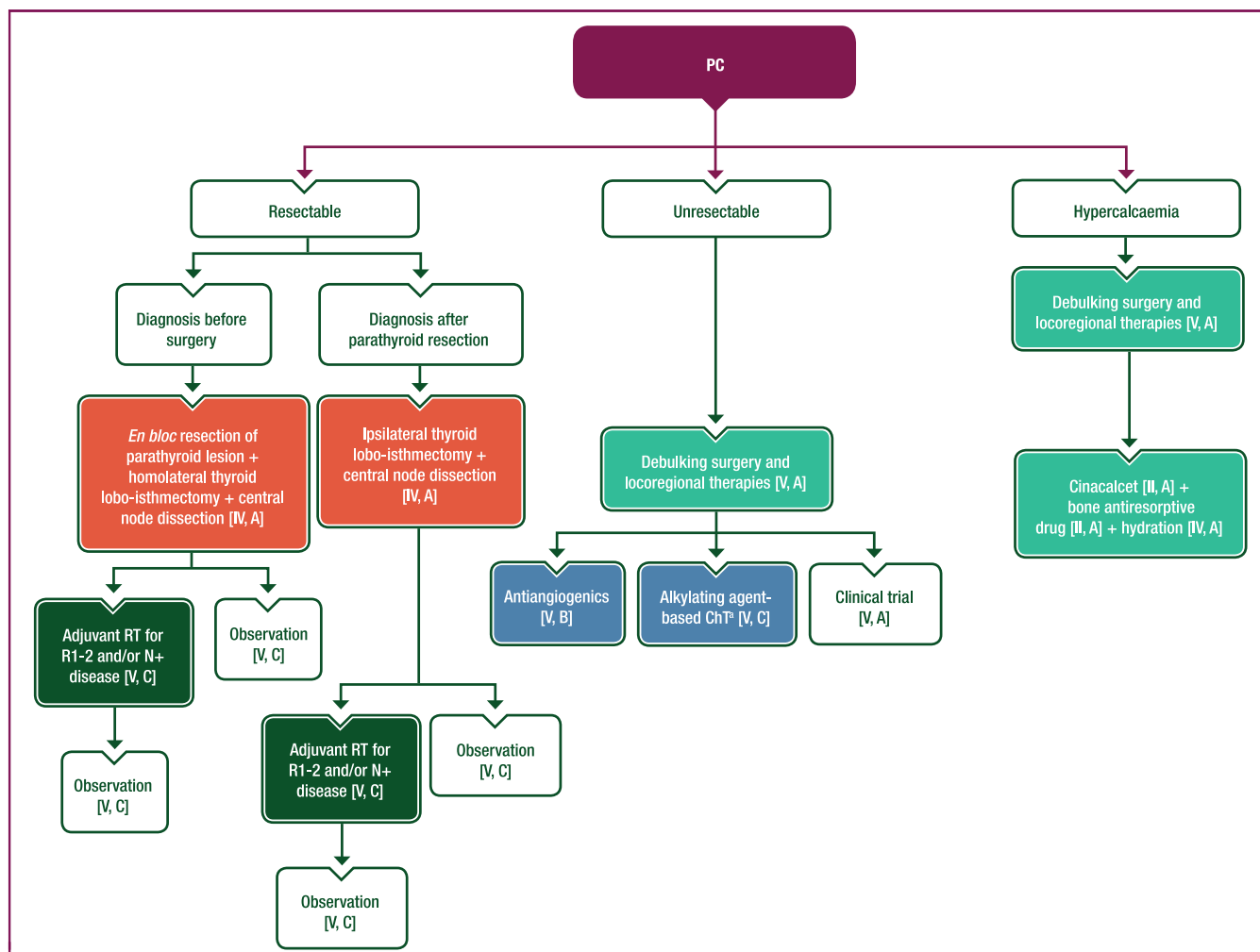
Figure 6. Management of PC.
Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
5-FU, 5-fluorouracil; ChT, chemotherapy; N+, lymph node metastasis; PC, parathyroid carcinoma; R1, resection with microscopic tumour at the margin; R2, resection with macroscopic tumour at the margin; RT, radiotherapy.
aDacarbazine, temozolomide or streptozocin plus 5-FU or capecitabine.

RT. Analysis of data from the National Cancer Database identified 885 patients with PC who underwent surgery between 2004 and 2016, including 126 (14.2%) who also received external beam RT. The latter group had a higher frequency of extensive regional disease, nodal metastases and residual microscopic disease. The 5-year OS rate was 85.3% with a median follow-up of 60.8 months. RT was not associated with a difference in OS based on multivariate analysis[87]; however, small series from highly specialised tertiary centres have reported lower locoregional relapse rates in patients undergoing adjuvant RT,[88-90] particularly in patients with R1 or R2 resection.[90] Although not recommended for all patients, adjuvant RT should be discussed in the case of R1 or R2 resection and/or lymph node metastasis (N+) and/or persistent hypercalcaemia.

Recommendations

- Medical treatment of hypercalcaemia is required before surgery [V, A].

- Cinacalcet is recommended to control hypercalcaemia [II, A].
- Hydration with saline infusion, at a starting dose of 200-500 ml/h, is the first step in the treatment of severe or symptomatic hypercalcaemia [IV, A].
- The bone antiresorptive drug zoledronic acid is recommended as first-line treatment and should be preferred over pamidronate for severe or symptomatic hypercalcaemia [II, A].
- Denosumab is recommended in patients with resistant hypercalcaemia [III, A; FDA approved, not EMA approved].
- When a preoperative diagnosis of PC is made, upfront surgery with en bloc removal of the parathyroid lesion (avoiding capsule rupture and local seeding), homolateral thyroid lobo-isthmectomy and central node dissection is recommended [IV, A].
- In case of pathological diagnosis of PC after parathyroidectomy, reoperation with ipsilateral thyroid lobo-isthectomy and central node dissection should be discussed within 1 month of initial surgery [IV, A].

- RT may be discussed in an MTB, particularly for patients with R1 or R2 resection and/or N+ and/or persistent hypercalcaemia [V, C].

Management of advanced and metastatic disease

PC is often locally advanced and distant metastases can occur in the lung (40%), bone (30%) and liver (10%). Brown tumours (osteolytic lesions of the bone caused by hyperparathyroidism) should be differentiated from bone metastases, but this may be difficult as they can show FDG uptake; MRI can be useful to better characterise bone lesions.[91] In case of known distant metastases, the probability of achieving a complete response is low and frequently only locoregional treatments can control the disease.[92] Cinacalcet should be continued in case of persistent severe hypercalcaemia.

Data on the efficacy of systemic treatments in PC are scarce with only 79 patients reported in the literature between 1898 and 2018.[93] A recent pooled analysis of all metastatic PC cases reported that the most frequent treatments were dacarbazine or anthracycline-containing ChT and antiangiogenic drugs.[93] The most frequent ChT protocols included dacarbazine monotherapy, dacarbazine—5-FU, cyclophosphamide monotherapy or methotrexate—doxorubicin—cyclophosphamide—lomustine, but response rates were low.[93] Most cases in which antiangiogenics were used involved sorafenib.[94,95] PC is usually radioresistant; despite limited data showing that RT can be applied as adjuvant therapy to reduce local recurrence, its role is mainly palliative.[85]

Recommendations

- The efficacy of systemic treatment in advanced and metastatic disease is limited; thus, whenever possible, debulking surgery and/or locoregional treatments should be discussed to control tumour burden and hormonal secretion [V, A].
- First-line systemic treatment may involve antiangiogenic drugs [V, B] or alkylating agent-based ChT (dacarbazine, temozolomide or streptozocin combined with 5-FU or capecitabine) [V, C].
- Inclusion in clinical trials should be prioritised whenever possible [V, A].

Follow-up, long-term implications and survivorship

The reported risk of recurrence is ~50% at 2-5 years (based mainly on cases in which non-radical surgery was used).[56,75-77,79] Laboratory follow-up includes lifelong measurement of calcium and PTH every 3 months, although longer intervals (up to 4-6 months) are an option.[79] Progressive and repeated increases in PTH and calcium levels are suggestive of PC recurrence and cross-sectional imaging (neck US, CT and/or MRI) should be carried out to identify the site of recurrence. There is no validated role for scintigraphy with [99mTc]Tc-sesta-MIBI in the follow-up of PC.

Recurrences and distant metastases can be small or below the resolution of imaging (<1 cm), and occasionally

PC can evolve towards aggressive and rapidly progressive forms and lose the ability for significant uptake of [99mTc]Tc-sesta-MIBI. In these cases, FDG—PET can complement conventional imaging.

The identification of a germline *CDC73* mutation should prompt periodic screening for tumours associated with HPT-JT (ossifying fibromas of the mandible or maxilla, benign and malignant uterine involvement, renal cysts).[58] Genetic testing should be carried out in all family members of affected individuals. In first-degree relatives, measurement of serum calcium levels and US monitoring are recommended.

Recommendations

- Lifelong laboratory follow-up, including measurement of calcium and PTH, is recommended every 3-4 months during the first 2 years, every 6 months during the subsequent 3 years and annually thereafter [V, C].
- In case of calcium and/or PTH elevation, neck US and CT scan of the neck, chest and abdomen together with a neck MRI are recommended [V, A]. FDG—PET can be proposed to complete work-up, especially in rapidly progressing cases [V, C].

INTRATHYROID THYMIC CARCINOMA

Incidence and epidemiology

Previously known as carcinoma showing thymus-like differentiation (CASTLE), intrathyroid thymic carcinoma (ITC) is rare and believed to arise from the thymic remnants or branchial pouch[96] and, more rarely, from major salivary glands.[97] ITC accounts for <0.15% of thyroid neoplasms.[98] Females are affected slightly more frequently than males and the median age at diagnosis is 50 years.[99]

Diagnosis, pathology and molecular biology

ITC presents as a slow-growing neck mass with hard consistency and poor mobility, located at the lower poles of the thyroid gland. It appears as a cold nodule on thyroid scintigraphy and as a solid, heterogenous and hypoechoic mass on US. Most patients have locally advanced disease with invasion of surrounding structures, including the recurrent laryngeal nerve, strap muscle, trachea, oesophagus, soft tissues and skin. Cervical lymph nodes are frequently involved but few patients have distant metastases.[99] At diagnosis, ~20% of patients have dyspnoea, dysphagia, right laryngeal nerve paralysis and pain. FNA does not provide a definitive diagnosis; histological confirmation is warranted.

ITC exhibits histological and immunophenotypic resemblances to eutopic thymic carcinoma. The tumour cells generally grow in a solid or nested pattern, identical to squamous-cell carcinoma arising in the thymus. Positive IHC results for cluster of differentiation (CD)5, CD117 and p63 suggest a diagnosis of ITC (see Section 8 of the Supplementary Material, available at https://doi.org/10.

1016/j.esmoop.2024.103664). Similar to thymomas and thymic carcinoma, on comparative genomic hybridisation ITC is characterised by chromosomal imbalances such as gains on chromosomal arm 1q and losses on 6p, 6q and 16q.[100] The most frequently altered gene is the telomerase reverse transcriptase promoter mutation *C228T*, identified in 22% of cases.[101] *EGFR* mutations have been documented[102] but their prevalence cannot be estimated due to the limited number of cases analysed.

Recommendations

- ITC should be suspected in the presence of a cold nodule in the lower lobes of the thyroid gland with a cytological diagnosis of poorly differentiated carcinoma [V, A].
- Positive IHC for CD5, CD117 and p63 may allow for a pre-operative diagnosis [V, B].
- Histological features that allow for a post-operative diagnosis of ITC are lymphoid stroma, squamous-cell differentiation, infrequent mitoses and rare necrosis, positive IHC for CD5, CD117 and p63, negative IHC for thyroglobulin, TTF-1 and calcitonin, and Ki-67 <20% [IV, A].

Staging and risk assessment

Disease stage is the main prognostic factor. Application of the eighth edition of the UICC staging classification[25] for thyroid tumours is recommended, even if not specific for ITC (see Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2024.103664). Neck US, CT of the neck, thorax and abdomen, and neck MRI can be used for staging. On CT, ITC appears as a well-defined soft tissue density without calcification, whereas on MRI, it appears as an isointense and hyperintense mass on T1/T2-weighted images.[103] Similar to thymoma, ITC can show intense uptake on FDG—PET—CT; however, data on the use of FDG—PET—CT in patients with ITC are very limited.[104]

Recommendations

- Accurate assessment of local extension with US or MRI is crucial for planning appropriate surgical intervention [IV, A].
- CT of the chest and abdomen should be carried out to rule out the rare possibility of distant synchronous metastasis [V, A]. Complementary FDG—PET—CT may be useful in some cases [V, C].

Management of local and locoregional disease

Surgery is the treatment of choice (Figure 7). A pooled analysis of published cases[99] showed that thyroidectomy (total, subtotal or near total) was the most frequent surgical procedure. Due to frequent nodal involvement at diagnosis, neck lymph node dissection [i.e. modified radical neck dissection (levels I-V), selective neck dissection of central compartment (level VI) or lateral selective neck dissection (levels II-IV)] was carried out in >55% of cases. Among patients with a small ITC, 40% underwent thyroid lobectomy without lymph node dissection. RT was used in only two cases of locally advanced ITC not amenable to surgery with radical intent.

The prognosis for patients with local or locoregional disease is very good. In the pooled analysis,[99] estimated median disease-free survival was 144 months (range 91-197 months), median OS was not reached and ~85% of
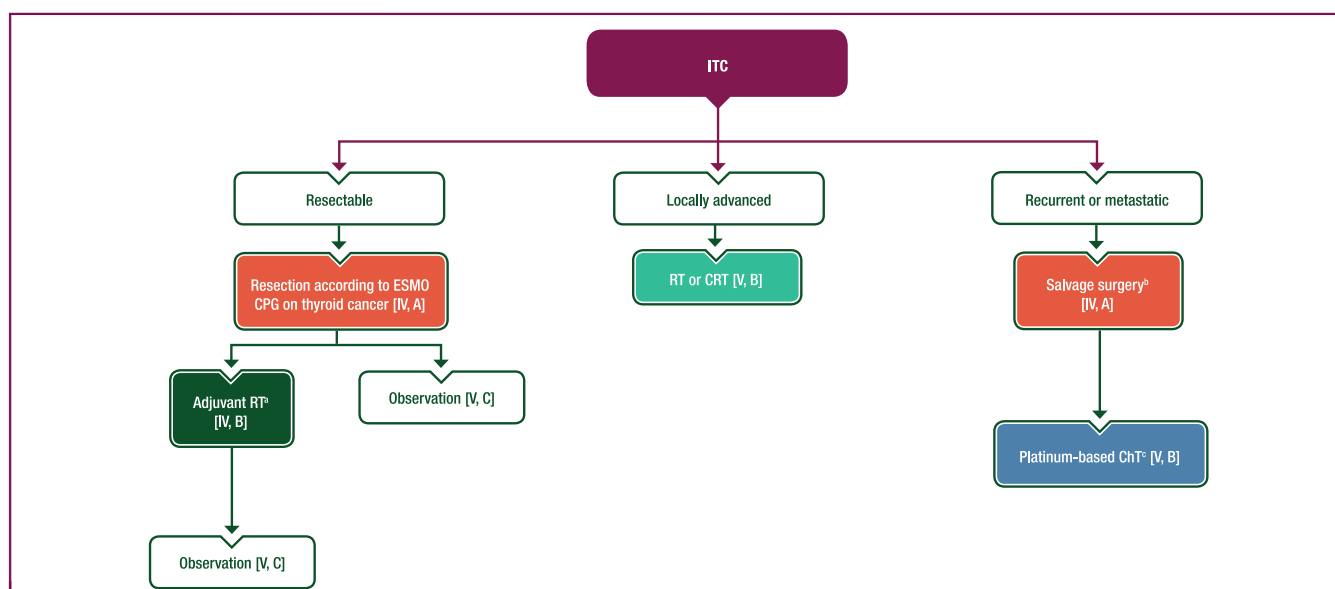
Figure 7. Management of ITC.
Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ChT, chemotherapy; CPG, clinical practice guideline; CRT, chemoradiotherapy; ITC, intrathyroid thymic carcinoma; MTB, multidisciplinary tumour board; RT, radiotherapy.
[a]In selected cases after careful MTB discussion.
[b]Adjuvant RT may be discussed for patients who have not received prior RT [V, B].
[c]Cisplatin-based regimens with either doxorubicin and cyclophosphamide or etoposide.

patients were alive after 5 years. Based on these data, surgery is recommended as the first-line therapeutic option in patients with ITC with locoregional disease. The type of surgery (i.e. lobectomy or thyroidectomy) should be planned according to the available guideline for thyroid cancers,[28] using conservative surgical treatment whenever possible. Adjuvant RT does not improve prognosis and can be avoided in most patients, although it may be discussed for more advanced or aggressive cases. There is no role for adjuvant ChT. Patients with locoregional disease not amenable to surgery with radical intent could be offered RT or chemoradiotherapy (CRT).

Recommendations

- Surgery is the mainstay of therapy. The type of surgery (i.e. lobectomy or thyroidectomy) should be planned according to the available guidelines for thyroid cancers [IV, A].
- Due to the indolent course of the disease and its good prognosis, conservative surgical treatment is preferred whenever possible [V, B].
- Neck dissection should be carried out according to guidelines for thyroid cancers [V, A].
- RT or CRT are reasonable options in case of locally advanced disease not suitable for radical surgery [V, B].
- If possible, adjuvant RT should be avoided due to the indolent disease course of ITC [IV, D]. It is an option in selected cases after careful multidisciplinary discussion [IV, B].

Management of advanced and metastatic disease

Among 120 patients with ITC who underwent primary tumour resection, 29 (24%) experienced recurrence at a median of 19 months (range 13-25 months).[99] The recurrence was locoregional in 21 patients (72%), and was treated surgically in 90% and using RT in 42% of cases, with excellent prognosis. A minority ($\sim$10%) of patients developed distant metastases; five patients (4%) had metastases at diagnosis and eight (6%) developed metachronous distant metastases. The most common metastatic site was the lung. Data on the efficacy of systemic treatments in patients with metastatic ITC are limited. Similar to the recommendations for locally advanced or metastatic thymoma or thymic carcinoma,[28] cisplatin-containing regimens have been used in most ITC cases, with a reported objective remission rate of 58%.[99] Immunotherapy with the immune checkpoint inhibitor pembrolizumab was used in one case, resulting in long-lasting disease control. Based on this single experience, it is not possible to recommend immunotherapy for the treatment of metastatic ITC.

Recommendations

- In case of local recurrence, salvage surgery is recommended [IV, A] and adjuvant RT may be discussed by an MTB for patients who have not received prior RT [V, B].
- In case of metastatic disease, cisplatin-based combination ChT regimens with either doxorubicin and cyclophosphamide or etoposide are the recommended options [V, B].

Follow-up, long-term implications and survivorship

Follow-up is aimed at identifying locoregional recurrences and, more rarely, distant recurrences, usually within the first 5 years after initial treatment.

Recommendations

- In localised disease, neck US and CT scan of the neck and thorax are recommended 6-12 months after initial treatment and then annually up to 5 years [V, C].
- In metastatic disease, follow-up by CT and/or MRI (in case of liver, bone or brain metastases) every 3-6 months is recommended, depending on the tumour growth rate [V, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2024.103664.[105] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/endocrine-and-neuroendocrine-cancers.

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