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

SUPPLEMENTARY MATERIAL

SECTION 1. INCIDENCE AND EPIDEMIOLOGY OF GENITOURINARY, GYNAECOLOGICAL AND HEAD AND NECK NEUROENDOCRINE NEOPLASMS

Genitourinary and gynaecological (GUGy) neuroendocrine neoplasms (NENs) can arise from any location in the genitourinary[1] or gynaecological systems.[2] Neuroendocrine carcinoma (NEC) is the most common histology in the bladder, cervix, endometrium and prostate. NECs account for up to 5% of all malignancies in the prostate gland and therefore represent a significant entity.[1,3,4] Although very rare, low-grade neuroendocrine tumours (NETs) are most common in the kidney,[5-12] ovary,[3] presacral space, testis[13-16] and penis.[17]

Grade (G) 1 or G2 NETs with a primary origin in the bladder are extremely infrequent and are diagnosed incidentally.[18] Mean age at diagnosis is ~56 years and prevalence is higher in men than in women. There is no association with carcinoid syndrome. The most frequent presentation is small nodules or polyps located at the trigone and at the neck of the bladder.[19] In the few cases where long-term outcomes have been documented, no recurrence or disease progression have been reported.[19] Bladder NEC is more frequent, accounting for ~3% of bladder neoplasms. It is more common in men (80% of cases) and smokers.[4,20]

Primary G1 or G2 NETs of the kidney are frequently associated with congenital abnormalities (e.g. horseshoe kidneys) or arise from mature renal teratomas.[21] Between 25% and 30% of tumours are detected incidentally in asymptomatic patients. Tumours >4 cm in patients aged >40 years are more likely to metastasise.[22] Distant metastases are present in ~50% of primary renal NETs, with hilar and para-aortic lymph node involvement in ~47% of patients.[23]

The largest reported series of NETs with a primary origin in the testis shows a benign clinical course even if associated with epidermoid or dermoid cysts or histologically mature teratoma. Lesions with the morphology of atypical carcinoids can, however, occasionally exhibit metastatic spread.[16]

In the genitourinary system, tumours of the prostate gland have the highest prevalence of neuroendocrine features. Almost all prostate carcinomas have focal neuroendocrine differentiation that needs to be distinguished from properly defined, well-differentiated NETs.[18] Compared with small-cell NECs of the prostate, which account for up to 5% of all prostate tumours, G1 and G2 NETs of the prostate are extremely rare.[24-26] These tumours are characterised by the expression of neuroendocrine markers and negativity for prostate-specific antigen and prostatic acid phosphatase. Most of the cases reported are in individuals aged >60 years.

In the ovary, NETs are the most common form of NENs and represent 0.1% of all ovarian primaries. In the cervix, NENs develop from neuroendocrine cells within the glandular and squamous epithelium. Compared with the ovary, cervical NETs are rare. Of the few cases that have been reported in the literature, most were diagnosed post-operatively at a median age of 50 years. Carcinoid syndrome seems to be very rare.[27] NECs, particularly small-cell NECs, are more frequent and represent 1.5% of all cervical carcinomas. Compared with squamous-cell carcinoma, cervical NECs are more often diagnosed at a younger age and with metastatic disease.[28] In the endometrium, NECs, although very rare, also represent the most common NEN.

Head and neck (HN)-NENs occur more frequently in males (50%-70% of cases) irrespective of the HN primary. The median age at diagnosis is ~60 years for laryngeal NENs and ~50 years for middle-ear and sinonasal NENs.[29-33] NETs are less common than NECs at most HN sites[32,34] except for the middle ear.[35-37] Smoking is a recognised risk factor for laryngeal NENs whereas no risk factors have been identified for tumours of other origins.[38,39]

SECTION 2. PATHOLOGICAL DIAGNOSIS AND CLASSIFICATION OF UNKNOWN PRIMARY SITE-, GUGy- AND HN-NENS

NENs are defined by the expression of the neuroendocrine markers chromogranin A (CgA), insulinoma-associated protein 1 (INSM1) and synaptophysin, as well as cytokeratin expression. Expression of these markers may vary according to anatomical site and degree of differentiation.[40]

Typically, well-differentiated tumours exhibit an organoid structure (solid, trabecular, glandular, mixed) consisting of medium-sized round- or oval-shaped monomorph cells with abundant eosinophilic cytoplasm, low nuclear-to-cytoplasm ratio, rare or few mitotic figures and salt-and-pepper chromatin. The stroma is delicate and highly vascular and the tumour cells express CgA, INSM1, synaptophysin and cytokeratins.

In contrast, poorly-differentiated carcinomas exhibit a solid, organoid structure made up of round, irregularly shaped polymorph cells with either scant cytoplasm (in small-cell NEC) or abundant cytoplasm (in large-cell NEC), frequent and atypical mitoses and abundant necrosis. The stroma is abundant and fibrous. The cells express synaptophysin and INSM1, whereas CgA and cytokeratin expression are inconsistent. Retinoblastoma protein expression is often lost and there is global loss or diffuse positive expression of p53 (reflective of mutation); these are useful for distinguishing G3 NETs from NECs.

NETs are graded using the Ki-67 index, a proliferative marker calculated as the number of positive tumour cells in hotspots of 500-2000 cells, or the number of mitoses in 2 mm^2. Accordingly, NETs are graded as G1 (Ki-67 <3% and <2 mitoses/2 mm^2), G2 (Ki-67 3%-20% and 2-20 mitoses/2 mm^2) or G3 (Ki-67 >20% and >20 mitoses/2 mm^2). NECs are classified as small cell or large cell (see **Table 1**). As with G3 NETs, the proliferative index of NECs is high (Ki-67 >20% and >20 mitoses/2 mm^2).[41] Differentiating G3 NETs from NECs can be difficult, especially in locations where they are not yet formally recognised by the World Health Organization (WHO) classification (e.g. GUGy, HN). In these challenging cases, expert pathologist groups and networks have a very important role.

For NENs of unknown primary site (UKP), classification follows the 2022 WHO classification and the 2018 International Agency for Research on Cancer (IARC)–WHO common classification framework for NENs[41,42] (see **Table 1**). Molecular

markers, including genetic alterations, transcriptional profiling and methylation arrays,[43,44] remain investigational.

GUGy-NENs are classified according to the 2022 WHO Classification of Urinary and Male Genital Tumours[45] and the 2020 WHO Classification of Female Genital Tumours[46] as NETs or NECs (see **Table 1**). There are few data regarding the molecular biology of GUGy-NENs. Ovarian NETs can occur either as a pure form of carcinoid tumour or as part of an ovarian teratoma.[47] Clinicians and pathologists must also be aware that ovarian metastasis from other NET primaries may be at least as frequent as true ovarian primaries. Paraganglioma is also a differential diagnosis for GUGy-NETs, particularly in the bladder where, although rare, this tumour is more common than NETs.[48] Ovarian NECs are rare and are mostly large-cell NECs. Small-cell carcinomas of the ovary hypercalcaemic type are, despite the name, unrelated to small-cell carcinoma and are not neuroendocrine. NENs from other parts of the female genital tract are extremely rare. Merkel-cell carcinoma is a differential diagnosis that must be ruled out in suspected cases of vulvar NENs.

HN-NEN classification is evolving. The 2017 WHO classification retained the grading criteria for lung NENs used in the 2005 WHO classification, based on mitotic index (<2, 2-10 or >10 mitoses in 2 mm^2) rather than the Ki-67 index. It also, however, introduced the the term ‘well-differentiated neuroendocrine carcinoma’, which is inconsistent with classifications used for other sites, where the term NET is used.[49,50] The nomenclature in the new WHO 2022 classification is more consistent with the commonly used nomenclature for NENs (see **Table 1**).[51] In the middle ear, the term adenoma was used previously but has now changed to middle-ear NET because the Ki-67 index is 1%-6% in most cases.[52]

Differential pathological diagnoses for NETs are medullary thyroid cancer (MTC) and paraganglioma. In terms of differentiating from paraganglioma, the clinical presentation or tumour localisation may be useful, as well as staining for cytokeratin, S100 and angiotensin-converting enzyme using immunohistochemistry (IHC). For differential diagnosis with MTC, it must be noted that genuine HN-NETs may secrete calcitonin while germline or somatic *RET* mutations would help orientate the final diagnosis towards MTC. Differential diagnoses for HN-NECs[53] can be difficult and often require expert opinion; they include neuroblastoma and embryonal

rhabdomyosarcoma (which are cytokeratin negative), sinonasal undifferentiated and nuclear protein in testis midline carcinoma (which do not express neuroendocrine markers), mucosal melanoma and primitive neuroectodermal tumours [which are positive for cluster of differentiation (CD)99 and *FLI-1*]. In the case of metastatic neck lymph nodes with occult or unknown primary, cytokeratin 20 staining may be useful to distinguish NEC from Merkel-cell carcinoma.[41,54]

SECTION 3. CLINICAL DIAGNOSIS OF UKP-, GUGy- AND HN-NENS

For UKP-NETs, minimal hormonal investigation can lead to primary identification. First, the presence of metanephrins can help to identify paraganglioma or pheochromocytoma, with further confirmation by the lack of cytokeratin expression on IHC. Second, measurement of 5-hydoxyindoleacetic acid can lead to the identification of ileal NETs, the most common occult primary when investigating UKP-NETs. In addition, carcinoid syndrome can be indicative of a lung, ovarian or HN primary. Third, calcitonin may help to identify an MTC, although it is not a specific marker as 12% of patients with NETs can have blood calcitonin levels >100 ng/l, especially when the tumour originates in the pancreas or lung.[55]

During the clinical work-up of UKP-NENs, in addition to pathological and biological markers, the use of radiological, nuclear medicine and other imaging techniques may help to identify the occult primary in up to 87% of cases.[44,56] Bhosale et al. studied radiological findings in 250 patients with histopathologically confirmed NETs.[57] Lung and liver metastases were not associated with any specific primary site,[57] but the pattern of lymph node metastases was a predictive factor for oesophageal, gastric, duodenal, small intestinal and appendiceal primaries. In addition, bone and peritoneal metastases were significant predictors of lung and small bowel or appendiceal primaries, respectively. Among patients for whom no primary site was identified, the most frequent site of metastases was the liver, followed by the lymph nodes and peritoneum, whereas bone and lung metastases were rare.[57,58] The enhancement of liver metastases on multiphasic computed tomography (CT) may also allow indirect identification of the primary tumour. Indeed, lesions with a pancreatic origin are more frequently atypical, appearing as isointense lesions on

portal venous phase images, while small intestinal tumours are more frequently typical, hypoattenuating on portal venous phase images.[59] Although it may not be apparent on cross-sectional imaging, a small-sized (occult) small bowel primary tumour should be suspected in the presence of mesenteric lymphadenopathy.[57,60] In a series of 28 patients with UKP-NENs, 64% had lymphadenopathy on imaging and the primary was located in the small bowel in 89% of cases.[61] In addition to their use for staging, nuclear imaging tracers have a role in the diagnosis of UKP-NENs and can guide the clinician towards primary identification because of a high tracer sensitivity and/or specificity for selected primaries (see **Supplementary Table S1**). Somatostatin receptor imaging is recommended for the detection of well-differentiated UKP-NENs with negative morphological imaging.[62-66] Gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-labelled somatostatin analogue ([^{68}Ga]Ga-DOTA-SSA)-based positron emission tomography (PET) with CT is the most sensitive and specific technique, but in case of uninformative results, [^{18}F]F-dihydroxyphenylalanine (DOPA)–PET–CT is the most sensitive technique for detecting small bowel primaries, the most frequent tumour site when investigating UKP-NETs.[67] For poorly-differentiated NENs and G3 NETs with a high Ki-67 index, imaging with [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)–PET–CT is indicated.[68] The detection rate of primary tumour site in UKP-NENs using these nuclear medicine imaging techniques ranges from 59% to 75%.[69-72] A recent meta-analysis of 12 studies using [^{68}Ga]Ga-DOTA-SSA–PET–CT in patients with UKP-NETs reported a primary tumour detection rate of 55% [95% confidence interval (CI) 48% to 63%], resulting in a change in management for 20% of patients. The most common primary tumour sites were the bowel and pancreas.[73] The use of other tracers such as [^{11}C]5-hyroxytryptophan,[67] as well as dual imaging using [^{68}Ga]Ga-DOTA-SSA–PET–CT and FDG–PET–CT, is supported by some researchers.[74] A CT enterography (preferably using negative oral contrast) with arterial and portal phase is the recommended imaging method for identification of primary small bowel NETs.[75] Capsule endoscopy may also be useful.[76] In addition, endoscopic ultrasound (US) can be used to detect small pancreatic lesions, peripancreatic enlarged lymph nodes and gastric NENs.[77] Endoscopic examination of the HN and GUGy systems is also used in the diagnostic work-up of GUGy- and HN-NENs.

SECTION 4. MANAGEMENT OF LOCAL AND LOCOREGIONAL GUGY-NENS

The gold standard treatment for renal NETs is partial nephrectomy for T1 tumours or cryoablation for tumours of <3 cm to spare nephrons, depending on the location and size of these tumours. Radical nephrectomy is recommended for T2, T3 and T4 tumours, with regional node excision if the tumour is too large. No studies have been carried out to determine the efficacy of nephrectomy versus cryoablation. Nephron-sparing surgery has the benefit of preserving renal function when the renal mass is small or when the mass is near the ureter or another adjacent structure.[23] Due to the indolent behaviour of primary NETs of the bladder, transurethral resection is the most frequently used approach with only a few patients requiring radical cystectomy. Orchidectomy is the most commonly recommended approach for patients with NETs of the testis as these tumours are usually associated with teratomas. There is no standard approach for localised NENs of the prostate and radical prostatectomy remains the most frequently used option.[78,79] The recommended surgical approach in early-stage ovarian cancer is based on removal of both ovaries with a staging procedure.[80] For stage IA low-grade ovarian NETs, unilateral salpingo-oophorectomy with surgical staging may be sufficient, particularly in young patients who wish to preserve their fertility.[47] The recommended surgical procedure for endometrial, cervical and vaginal cancer should follow the ESMO guideline for each primary site as there are no data on which to base less or more aggressive approaches. For presacral NETs, the surgical procedure will depend on the staging work-up: location of the tumour above S3 level will necessitate an anterior approach while a posterior approach is possible for lesions below S3 level. Involvement of contiguous organs and the sacrum or coccyx may be frequent,[81] so the surgical procedure could also necessitate involved-organ resection and/or a coccygectomy.[81,82]

There are no data to support the use of adjuvant treatment in GUGy-NETs. In GUGy-NECs, multimodal therapy including chemotherapy (ChT) ± radiotherapy (RT) ± surgery should always be discussed by the multidisciplinary team (MDT). The use of multimodal therapy with ChT, RT and surgery has been shown to provide long-term control, particularly in patients with NECs of the cervix[83-85] or bladder,[4,86] although no prospective data are available. Neoadjuvant or adjuvant therapy with four cycles of either cisplatin–etoposide or carboplatin–etoposide should be considered whenever surgery is feasible. Local RT can be considered in an MDT discussion if there is

suspicion of margin invasion in patients with NECs or G3 NETs (see **Figure 2**). No data are available on the management of G3 NETs of a GUGy primary. Although rare (1%-2% of GUGy pathological subtypes), the most common GUGy-NECs are found in the bladder, prostate and cervix. In the bladder, retrospective data suggest that neoadjuvant ChT followed by surgery may be the best option for a localised NEC; the decision to add adjuvant ChT and/or adjuvant RT can be made on a case-by-case basis depending on prognostic factors. In the prostate, NECs are more likely to occur following resistance under androgen-deprivation therapy (12%-17% of cases) rather than *de novo* (2% of cases).[87,88] Consequently, there are no data to guide the best treatment combination for localised prostate NECs. In women, NECs are also rare but are more commonly found in the cervix, in which case the therapeutic strategy may vary according to staging, as outlined in the ESMO Clinical Practice Guideline on cervical cancer.[89] Treatment guidelines are based on retrospective data only. Multimodal treatment is used for limited-stage [International Federation of Gynecology and Obstetrics (FIGO) I-II] disease and combines surgery,[90] adjuvant ChT (which reduces the risk of both local and metastatic recurrences with increased survival)[91] and RT [which limits pelvic recurrence but with no proven effect on overall survival (OS)];[84] again, this is based on retrospective data. For locally advanced, non-metastatic disease, definitive chemoradiotherapy is usually recommended, with some retrospective data suggesting prolonged OS with more intensive multimodal treatments.[83]

SECTION 5. MANAGEMENT OF ADVANCED AND METASTATIC UKP-NETS

Everolimus

RADIANT-2 was a placebo-controlled, phase III study in patients with advanced NETs with carcinoid syndrome.[92] A total of 429 patients (including an unknown number with UKP-NETs) were randomised to receive everolimus or placebo, both in conjunction with octreotide long-acting release (LAR) every 28 days. The addition of everolimus resulted in a 5.1-month delay in disease progression [hazard ratio (HR) 0.77, 95% CI 0.59-1.00, $P = 0.026$], although the difference marginally missed the prespecified threshold for statistical significance ($P = 0.024$).

The RADIANT-4 study, in which patients with advanced, progressive, non-functional NETs were randomised to receive everolimus or placebo, reported a progression-free survival (PFS) benefit with everolimus (HR 0.48, 95% CI 0.35-0.67, $P < 0.00001$).[93] A cohort of 36 patients with UKP-NETs were included in RADIANT-4, of which 23 received everolimus and 13 received placebo.[94] Those treated with everolimus showed a meaningful improvement in PFS compared with placebo; median (95% CI) PFS was 13.6 months (4.1 months-not evaluable) versus 7.5 (1.9-18.5) months, respectively (HR 0.60, 95% CI 0.24-1.51). Thus, everolimus is recommended for non-functional UKP-NETs, whereas its role in functional UKP-NETs remains debatable.

Antiangiogenic agents

Patients with UKP-NETs were excluded from clinical trials exploring the role of sunitinib[95] and lenvatinib[96] as treatments for gastroenteropancreatic NETs; however, phase III studies of surufatinib,[97] axitinib[98] and cabozantinib[99] did include patients with UKP-NETs.

In the phase III SANET-ep study, Chinese patients with extrapancreatic NETs were randomised (2:1) to receive surufatinib ($n = 129$) or placebo ($n = 69$).[97] Among these patients, 29 (23%) and 17 (25%), respectively, had a NET of either unknown primary or 'other' not otherwise specified primary. The study met its primary endpoint, showing a benefit in favour of surufatinib in terms of investigator-assessed PFS [9.2 months (95% CI 7.1-11.1) versus 3.8 months (95% CI 3.7-5.7); HR 0.33, 95% CI 0.22-0.50, $P < 0.0001$].

In the phase II/III AXINET study, patients with extrapancreatic G1-2 NETs were randomised (1:1) to receive axitinib–octreotide LAR or placebo–octreotide LAR. Of the 126 and 130 patients in the axitinib and placebo arms, respectively, 14 (9.5%) and 22 (16.9%) patients had a NET of either unknown primary or 'other' not otherwise specified primary.[98] The study failed to meet its primary endpoint of investigator-assessed PFS [median 17.2 months (axitinib) versus 12.3 months (placebo); HR 0.816, $P = 0.169$]. PFS per blinded independent central review (BICR) did, however, reach statistical significance (median 16.6 months versus 9.9 months, respectively; HR 0.687, $P = 0.01$).

In the phase III CABINET study, patients with extrapancreatic G1-3 NETs were randomised (2:1) to receive cabozantinib or placebo.[99] Of the 129 and 68 patients in the cabozantinib and placebo arms, respectively, 38 (30%) and 11 (16%) patients had a NET of either unknown primary or 'other' not otherwise specified primary. Seven of 129 patients in the cabozantinib arm had G3 NETs. The study met its primary endpoint of BICR PFS (median PFS 8.3 months with cabozantinib versus 3.2 months with placebo; HR 0.45, $P < 0.0001$).

Currently, axitinib and cabozantinib are not approved for the management of NETs or UKP-NETs. Surufatinib is approved in China for extrapancreatic NETs but is not approved by the European Medicines Agency or the Food and Drug Administration.

ChT

The most robust evidence supporting the use of temozolomide and capecitabine in NETs is from a prospective phase II randomised study comparing temozolomide–capecitabine with temozolomide alone in patients with pancreatic NETs.[100] Retrospective studies in UKP-NETs have reported clinical activity.[101]

O-6-methylguanine-DNA methyltransferase (MGMT) status is assessed by either IHC (MGMT-deficient NETs are defined by an H score ≤50) or by pyrosequencing evaluation (MGMT-deficient NETs are defined by >7-8% methylated promoter).[102-104] The clinical value of MGMT status as a predictive biomarker of higher response rate and/or PFS with alkylating agent-based ChT in UKP-NETs remains unclear;[102] however, two prospective trials have suggested a role as a putative predictive biomarker. In the randomised phase II ECOG-ACRIN E2211 study in which 144 patients with pancreatic NETs received either temozolomide ($n = 72$) or temozolomide–capecitabine ($n = 72$), lower MGMT expression by IHC was associated with a higher response rate (52% versus 15% in patients with higher expression; odds ratio 6.38, 95% CI 2.19-18.60, $P = 0.0004$).[103] The authors of this trial noted that the absence of a control arm without temozolomide therapy precluded a definitive conclusion regarding the predictive role of MGMT deficiency. In the randomised phase II MGMT-NET study, 105 patients with pancreatic ($n = 55$), thoracic ($n = 38$) or unknown primary ($n = 12$) NETs received either alkylating agent-based ChT ($n = 62$) or oxaliplatin-based ChT ($n = 43$).[104] The primary endpoint of a

higher 3-month response rate under alkylating agent-based ChT for patients with MGMT-deficient NETs (defined as >9% promoter methylation by pyrosequencing) was not met; however, a higher best overall response rate (secondary endpoint) of 38.9% versus 11.5% and a higher median PFS (secondary endpoint) of 14.6 months versus 11.2 months were observed in patients with deficient MGMT versus those with proficient MGMT, respectively, under alkylating agent-based ChT, while the efficacy of oxaliplatin-based ChT did not differ according to this biomarker.

SECTION 6. LONG-TERM FOLLOW-UP DATA ON UKP-NENS

According to the latest Surveillance, Epidemiology, and End Results registry data, OS in patients with UKP-NENs depends on both stage and grade.[105] The estimated median OS for patients diagnosed with UKP-NETs and local, regional and distant metastases is ~20 years, 4 years and 2 years, respectively.[105] Data from other registries indicate that the median OS in patients with metastatic UKP-NENs is ~4 years (5-year OS rate 45.3%), with lower OS in G3 compared with G1-2 UKP-NETs.[106] Compared with outcomes for other NENs, such as those of the small intestine or pancreas, UKP-NENs have a poor prognosis, especially for regional and metastatic disease stages; this likely reflects the challenge of selecting appropriate evidence-based treatment strategies.[44]

SECTION 7. PARATHYROID CARCINOMA

Diagnosis using US

Parathyroid carcinoma (PC) is mainly represented by a solid nodular formation (in some cases with liquid areas or cystic aspect), 3-4 cm in diameter and globus-shaped, with a hypoechoic and non-homogeneous structure and irregular margins. A thick pseudocapsule or signs of infiltration of the thyroid parenchyma can be observed. On colour Doppler US, PC is generally characterised by an evident intranodal and irregular vascularisation. At the time of diagnosis, evaluation of possible metastatic locoregional lymph nodes in the central compartment and at lateral levels should be carried out. Elastography can highlight some suspicious

findings such as increased rigidity but its role in differential diagnosis remains limited.[107]

Atypical parathyroid tumours

Atypical parathyroid tumours (APTs) are lesions of the parathyroid gland which exhibit some histological features found in PC but without evidence of invasive growth. These features are adherence to contiguous structures in the absence of clear invasion, presence of neoplastic cells within the fibrous capsule, a solid and/or trabecular growth pattern, banding fibrosis, mitotic activity without a clear Ki-67 cut-off and coagulative necrosis.[108,109] Based on retrospective series, the clinicobiological presentation and prognosis of APT are more severe than in benign adenoma but less severe than in PC.[108] According to the literature, the estimated risk of relapse of APT is 3% with a median delay from initial diagnosis of 120 months (range 12-204 months).[108] It may be slightly longer, however, as the median follow-up of the retrospective series was only 47 months.[108] The risk of relapse may be higher in case of *CDC73* mutation and/or parafibromin loss identified by IHC[109-111] and in familial cases.[108] Thus, although the outcome for patients with APT is benign in most cases, management should be discussed in a multidisciplinary tumour board, taking into account the pathological parameters, *CDC73* mutational status and/or fibromin loss, hereditary context and the firm or adherent nature of the lesion during the initial surgical procedure. The presence of several of these risk factors may prompt a discussion about using a similar management approach to that of PC. Clinical presentation of water clear cell parathyroid adenoma can overlap with that of PC, but there are usually no atypical features at pathological evaluation.[112,113]

Management of local and locoregional disease

Management of hypercalcaemia. The cornerstones of treatment for severe or symptomatic hypercalcaemia are intravenous saline hydration and bisphosphonate administration. Saline hydration is administered at a rate of 200-500 ml/hour, depending on the baseline level of dehydration and renal function, the patient's cardiovascular status, the degree of mental impairment and the severity of hypercalcaemia.[114] The bisphosphonate of choice is zoledronic acid, with a dose adapted to glomerular filtration rate.[115] In the absence of response, denosumab (120

mg on days 1, 8, 15 and 29 and then every 4 weeks) can decrease calcium levels within 10 days in 64% of patients with calcium levels >3.1 mmol/l despite the use of bisphosphonate, as demonstrated in a prospective clinical trial.[116] Corticosteroids and calcitonin may be used but have a transient effect at best. Diuretics are not recommended.[117] If these treatments are not effective, dialysis may be used to control hypercalcaemia but it has a large impact on quality of life. Although these therapeutics are useful and effective for initial management, there is a high risk of resistance during the clinical course of PC progression and uncontrolled hypercalcaemia may lead to death.

SECTION 8. INTRATHYROID THYMIC CARCINOMA

Pathological diagnosis

Intrathyroid thymic carcinoma (ITC) may be suspected in case of a cold nodule on thyroid scintigraphy located at the lower thyroid pole with a cytological diagnosis of poorly-differentiated thyroid tumour. Specific characteristics of ITC that are useful for the differential diagnosis, are[118]:

(i) Expansive growth pattern (sharp tumour border and pushing margin)

(ii) Lymphoid stroma

(iii) Squamous-cell differentiation with keratinisation and basaloid-cell appearance

(iv) Positive IHC for CD5, CD117 and p63

(v) Negative IHC for thyroglobulin, thyroid transcription factor 1 and calcitonin

(vi) Low-grade histology (infrequent mitoses and rare necrosis)

(vii) Low Ki-67 index (usually <20%).

In partial analogy to primary thymic carcinoma, three histological subtypes of ITC are recognised:

(i) Squamous-cell carcinoma type

(ii) Lymphoepithelioma or basaloid type

(iii) NEC type.

SUPPLEMENTARY TABLES

Supplementary Table S1. Diagnostic work-up of UKP-NENs for identification of occult primary

Exploration	Suspected primary tumour
Clinical history	
Presence of functioning syndrome	Carcinoid syndrome: ileum, lung, HN, ovary NET Cushing syndrome: pancreas, lung, thymus, HN, MTC NET or NEC WDHA syndrome, hypoglycaemia, necrolytic erythema, diarrhoea, gallstones, diabetes: pancreas NET Zollinger–Ellison syndrome: pancreas, duodenum NET Hypercalcaemia with PTH increase: PC Hypercalcaemia with PTH suppression and elevated PTHrp: pancreas Acromegaly: pancreas, lung NET Hypertension, tachycardia, headaches, constipation: PCC–PGL
Family or personal history of endocrine tumours	History of multiple PCC–PGL, bilateral PCC or metastatic PGL: SDHx, von Hippel–Lindau, MEN2, etc. History of MTC and/or PCC (unilateral or bilateral): MEN2 Hyperparathyroidism and pancreas or pituitary NET, more rarely lung, thymus NET: MEN1 Jaw tumour, uterine tumours, renal cyst, PC: HPT-JT
Pathological examination and diagnosis	

According to the IARC–WHO 2018 classification consensus:
• G1 NET (Ki-67 <3%, mitotic index <2/2 mm^2)
• G2 NET (Ki-67 3%-20%, mitotic index 2-20/2 mm^2)
• G3 NET (Ki-67 >20%, mitotic index >20/2 mm^2)
• NEC:
  ○ Large-cell NEC
  ○ Small-cell NEC
• MiNEN	

IHC markers[44,119,120 a]	
Cytokeratins	Negative result: PCC–PGL
CDX-2	Intestinal (small intestine, colon)
TTF-1	Lung, thymus, thyroid
Serotonin	Small intestine, appendix
Calcitonin	Intense positivity: MTC but also HN, pancreas and lung NETs
PDX-1	Pancreas
Islet-1	Pancreas, rectum, duodenum Poorly differentiated NEC
CK20, MCPyV (IHC or PCR)	Merkel-cell carcinoma
Loss of ATRX and DAXX	Pancreas
CK7	Lung, thymus, breast, thyroid, endometrium, cervix, ovary, salivary gland, upper gastrointestinal tract, urothelium
SATB-2	Rectum, colon
Gastrin	Duodenum, pancreas
NESP-55	Pancreas
PAX-6, PAX-8	Pancreas, duodenum (rectum, small intestine)

Progesterone receptor	Pancreas, rectum, breast, lung
OTP	Bronchus
Biochemistry	
All cases	Calcitonin: MTC but also pancreas, lung, HN primaries Blood or urine metanephrines: PCC–PGL Plasma or 24-hour urine 5-HIAA: larynx UKP-NET, low-grade ovary NET
According to functional syndromes	Plasma or 24-hour urine 5-HIAA for carcinoid syndrome Serum or 24-hour urine cortisol, ACTH for Cushing syndrome (including appropriate tests) PTH and/or PTHrp in case of hypercalcaemia VIP, somatostatin, glucagon, insulin, proinsulin and C-peptide (including appropriate tests), and gastrin in case of VIPoma, somatostatinoma, glucagonoma, insulinoma and Zollinger–Ellison syndrome, respectively
Imaging	
Evocative pattern	Mesenteric mass: ileum Mediastinal or cervical lymph nodes: HN, lung NET or MTC Isolated para-aortic lymph mass: PGL Isolated superficial NEC lymph node: Merkel-cell carcinoma, UKP-NEC Cutaneous metastasis: HN or lung Isolated bone metastasis: non-digestive primary

Endoscopy or echo-endoscopy	Digestive and pancreatic NET
Postivity for evocative PET–CT tracers	[^{68}Ga]Ga-DOTA-SSA–PET–CT: occult primary identification, PGL FDG–PET–CT: G2-3 NET and NEC or non-mid-gut NET [^{18}F]F-DOPA–PET–CT: ileum, PCC–PGL, MTC MIBG: PCC

5-HIAA, 5-hydroxyindoleacetic acid; ACTH, adrenocorticotrophic hormone; ATRX, alpha thalassaemia X; CDX-2, caudal type homeobox 2; CK, cytokeratin; CT, computed tomography; DAXX, death domain-associated protein; DOPA, fluorodihydroxyphenylalanine; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; G, grade; HN, head and neck; HPT-JT, hyperparathyroidism-jaw tumour syndrome; IARC, International Agency for Research on Cancer; IHC, immunohistochemistry; MCPyV, Merkel-cell polyomavirus; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; MIBG, metaiodobenzylguanidine; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; MTC, medullary thyroid carcinoma; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NESP-55, neuroendocrine secretory protein 55; NET, neuroendocrine tumour; OTP, orthopedia homeobox; PAX, paired box protein; PC, parathyroid carcinoma; PCC, pheochromocytoma; PDX-1, pancreatic and duodenal homeobox 1; PET, positron emission tomography; PGL, paraganglioma; PTH, parathyroid hormone; PTHrp, parathyroid hormone-related peptide; SATB-2, special AT-rich binding protein 2; SDHx, succinate dehydrogenase A, B, C, D or AF2; SSA, somatostatin analogue; TTF-1, thyroid transcription factor 1; UKP, unknown primary; VIP, vasointestinal peptide; WDHA, watery diarrhoea, hypokalaemia, achlorhydria; WHO, World Health Organization.

[a]Not specific for NEC; can be present regardless of primary site.

Supplementary Table S2. Staging of middle-ear NETs based on the proposal by Marinelli et al.[29]

T1	Tumour confined to the middle-ear cavity that does not envelope or strongly adhere to the ossicular chain
T2a	Tumour fills the middle-ear cleft and encases the ossicles with or without ossicular bone erosion
T2b	A T2a tumour that also extends into the mastoid
T2c	A T2a or T2b tumour that also extends through the tympanic membrane into the external auditory canal
T3	Tumour adheres to important neurovascular structures such as the petrous ICA, facial nerve, sigmoid sinus or dura
T4	Intradural tumour extension
N0	No regional lymph node metastases
N1	Lymph node metastases present (commonly to the parotid and cervical lymph nodes)
M0	No distant metastasis
M1	Distant metastatic disease present (commonly to the bone, liver and lung)

ICA, internal carotid artery; NET, neuroendocrine tumour.

Supplementary Table S3. Clinical classification of RCC according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤4 cm
T1b	Tumour >4 cm but ≤7 cm
T2	Tumour >7 cm in greatest dimension, limited to the kidney
T2a	Tumour >7 cm but ≤10 cm
T2b	Tumour >10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades the perirenal and/or renal sinus fat (peripelvic) fat but not beyond the Gerota fascia
T3b	Tumour extends into the vena cava below the diaphragm
T3c	Tumour extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed

N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis

RCC, renal-cell carcinoma; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

Reprinted with permission.[121]

Supplementary Table S4. Staging and stage grouping of RCC according to the UICC TNM eighth edition[121]

Stage	T	N	M
I	1	0	0
II	2	0	0
III	3	0	0
III	1, 2, 3	1	0
IV	4	Any	0
IV	Any	Any	1

RCC, renal-cell carcinoma; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

Reprinted with permission.[121]

Supplementary Table S5. Clinical classification of prostate adenocarcinomas according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour incidental histological finding in ≤5% of tissue resected
T1b	Tumour incidental histological finding in >5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour that is palpable and confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule[a]
T3a	Extraprostatic extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles and/or pelvic wall
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed

N0	No regional lymph node metastasis[b]
N1	Regional lymph node metastasis[b]
M (distant metastasis)[c]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

PSA, prostate-specific antigen; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

[a]Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

[b]Metastasis ≤0.2 cm can be designated pNmi.

[c]When more than one site of metastasis is present, the most advanced category [(p)M1c] is used.

Reprinted with permission.[121]

Supplementary Table S6. Clinical classification of bladder carcinomas according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	Regional lymph node metastasis
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
N3	Metastasis in a common iliac lymph node(s)
M (distant metastasis)	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

Reprinted with permission.[121]

Supplementary Table S7. Clinical classification of uterus cancer (endometrial carcinomas and carcinosarcomas) according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1 FIGO stage I[a]	Tumour confined to the corpus uteri[a]
T1a FIGO stage IA[a]	Tumour limited to endometrium or invading less than half of myometrium
T1b FIGO stage IB	Tumour invades one half or more of myometrium
T2 FIGO stage II	Tumour invades cervical stroma, but does not extend beyond the uterus
T3 FIGO stage III	Local and/or regional spread as specified here:
T3a FIGO stage IIIA	Tumour invades the serosa of the corpus uteri or adnexae (direct extension or metastasis)
T3b FIGO stage IIIB	Vaginal or parametrial involvement (direct extension or metastasis)
N1, N2 FIGO stage IIIC	Metastasis to pelvic or para-aortic lymph nodes[b]
N1 FIGO stage IIIC1	Metastasis to pelvic lymph nodes
N2 FIGO stage IIIC1	Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes

T4[c] FIGO stage IV	Tumour invades bladder mucosa or bowel mucosa
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis to pelvic lymph nodes
N2	Regional lymph node metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis (excluding metastasis to vagina, pelvic serosa or adnexa; including metastasis to inguinal lymph nodes, intra-abdominal lymph nodes other than para-aortic or pelvic nodes)

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

[a]Endocervical glandular involvement only should be considered as stage I.

[b]Positive cytology has to be reported separately without changing the stage.

[c]The presence of bullous oedema is not sufficient evidence to classify as T4.

Reprinted with permission.[121]

Supplementary Table S8. Clinical classification of ovarian, fallopian tube and primary peritoneal carcinoma according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1 FIGO stage I	Tumour limited to the ovaries (one or both) or fallopian tube(s)
T1a FIGO stage IA	Tumour limited to one ovary or fallopian tube; capsule intact, no tumour on ovarian surface or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b FIGO stage IB	Tumour limited to both ovaries or fallopian tubes; capsule intact, no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c FIGO stage IC	Tumour limited to one or both ovaries or fallopian tubes with any of the following:
T1c1	Surgical spill
T1c2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
T1c3	Malignant cells in ascites or peritoneal washings
T2 FIGO stage II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer
T2a FIGO stage IIA	Extension and/or implants on uterus and/or fallopian tube(s) and/or one or both ovaries

T2b FIGO stage IIB	Extension to other pelvic tissues, including bowel within the pelvis
T3 and/or N1 FIGO stage III[a]	Tumour involves one or both ovaries or fallopian tubes or primary peritoneal carcinoma with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
N1	Retroperitoneal lymph node metastasis only
N1a FIGO stage IIIA1i	Lymph node metastasis ≤10 mm in greatest dimension
N1b FIGO stage IIIA1ii	Lymph node metastasis >10 mm in greatest dimension
T3a any N FIGO stage IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without retroperitoneal lymph node, including bowel involvement
T3b any N FIGO stage IIIB	Macroscopic peritoneal metastasis beyond the pelvic brim ≤2 cm in greatest dimension, including bowel involvement outside the pelvis with or without retroperitoneal nodes
T3c any N FIGO stage IIIC	Peritoneal metastasis beyond the pelvic brim >2 cm in greatest dimension and/or retroperitoneal lymph node metastasis (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
M1 FIGO stage IV	Distant metastasis (excludes peritoneal metastasis)
M1a FIGO stage IVA	Pleural effusion with positive cytology

M1b[b] FIGO stage IVB	Parenchymal metastasis and metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1 IIIA1	Retroperitoneal lymph node metastasis only
N1a IIIA1i	Lymph node metastasis ≤10 mm in greatest dimension
N1b IIIA1ii	Lymph node metastasis >10 mm in greatest dimension
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

[a]Liver capsule metastasis is T3/stage III.

[b]Liver parenchymal metastasis M1/stage IV.

Reprinted with permission.[121]

Supplementary Table S9. Clinical classification of cervix uteri carcinomas according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (pre-invasive carcinoma)
T1 FIGO stage I	Tumour confined to the cervix[a]
T1a[b,c] FIGO stage IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of ≤7.0 mm[d]
T1a1 FIGO stage IA1	Measured stromal invasion ≤3.0 mm in depth and ≤7.0 mm in horizontal spread
T1a2 FIGO stage IA2	Measured stromal invasion >3.0 mm and ≤5.0 mm with a horizontal spread ≤7.0 mm
T1b FIGO stage IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1 FIGO stage IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
T1b2 FIGO stage IB2	Clinically visible lesion >4.0 cm in greatest dimension
T2 FIGO stage II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a FIGO stage IIA	Tumour without parametrial invasion

T2a1 FIGO stage IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
T2a2 FIGO stage IIA2	Clinically visible lesion >4.0 cm in greatest dimension
T2b FIGO stage IIB	Tumour with parametrial invasion
T3 FIGO stage III	Tumour involves lower third of vagina or extends to pelvic wall or causes hydronephrosis or non-functioning kidney
T3a FIGO stage IIIA	Tumour involves lower third of vagina
T3b FIGO stage IIIB	Tumour extends to pelvic wall or causes hydronephrosis or non-functioning kidney
T4[e] FIGO stage IVA	Tumour invades mucosa of the bladder or rectum or extends beyond true pelvis
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). Excludes metastasis to the vagina, pelvic serosa and adnexa

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

[a]Extension to corpus uteri should be disregarded.

[b]The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.

[c]All macroscopically visible lesions, even with superficial invasion, are T1b/IB.

[d]Vascular space involvement, venous or lymphatic, does not affect classification.

[e]Bullous oedema is not sufficient to classify a tumour as T4.

Reprinted with permission.[121]

Supplementary Table S10. Staging and stage grouping of cervix uteri carcinoma according to the UICC TNM eighth edition[121]

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IA	T1a	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB	T1b	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
II	T2	N0	M0
IIA	T2a	N0	M0
IIA1	T2a1	N0	M0
IIA2	T2a2	N0	M0
IIB	T2b	N0	M0
III	T3	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	Any N	M0
IIIB	T1, T2, T3	N1	M0
IVA	T4	Any N	M0

IVB	Any T	Any N	M1

TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

Reprinted with permission.[121]

Supplementary Table S11. Staging of PC according to the AJCC TNM eighth edition[122]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Atypical parathyroid neoplasm (neoplasm of uncertain malignant potential)[a]
T1	Localised to the parathyroid gland with extension limited to soft tissue
T2	Direct invasion into the thyroid gland
T3	Direct invasion into recurrent laryngeal nerve, oesophagus, trachea, skeletal muscle, adjacent lymph nodes or thymus
T4	Direct invasion into major blood vessel or spine
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) or superior mediastinal lymph nodes (level VII)
N1b	Metastasis to unilateral, bilateral or contralateral cervical (level I, II, III, IV or V) retropharyngeal nodes
M (distant metastasis)	
M0	No distant metastasis

M1	Distant metastasis

AJCC, American Joint Committee on Cancer; PC, parathyroid carcinoma; TNM, tumour–node–metastasis.

[a]Defined as tumours that are histologically or clinically worrisome but do not fulfil the more robust criteria (i.e. invasion, metastasis) for carcinoma. They generally include tumours that have two or more concerning features such as fibrous bands, mitotic features, necrosis, trabecular growth or adherence to surrounding tissues intraoperatively. Atypical parathyroid neoplasms usually have a smaller dimension, weight and volume than carcinomas and are less likely to have coagulative tumour necrosis.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2023).[122]

Supplementary Table S12. Staging of thyroid gland carcinomas according to the UICC TNM eighth edition[121]

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤2 cm in greatest dimension, limited to the thyroid
T1a	Tumour ≤1 cm in greatest dimension, limited to the thyroid
T1b	Tumour >1 cm but ≤2 cm in greatest dimension, limited to the thyroid
T2	Tumour >2 cm but ≤4 cm in greatest dimension, limited to the thyroid
T3	Tumour >4 cm in greatest dimension, limited to the thyroid or with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid or omohyoid muscles)
T3a	Tumour >4 cm in greatest dimension, limited to the thyroid
T3b	Tumour of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid or omohyoid muscles)
T4a	Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
T4b	Tumour invades prevertebral fascia or mediastinal vessels, or encases carotid artery
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	Regional lymph node metastasis
N1a	Metastasis in level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum
N1b	Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II III, IV or V) or retropharyngeal nodes
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis

TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

Reprinted with permission.[121]

Supplementary Table S13. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of Oxford University Press on behalf of the Infectious Diseases Society of America.[123]

REFERENCES

1. Fine SW. Neuroendocrine lesions of the genitourinary tract. *Adv Anat Pathol*. 2007;14(4):286-296.
2. Winer I, Kim C, Gehrig P. Neuroendocrine tumors of the gynecologic tract update. *Gynecol Oncol*. 2021;162(1):210-219.
3. Georgescu TA, Bohiltea RE, Munteanu O, et al. Emerging Therapeutic Concepts and Latest Diagnostic Advancements Regarding Neuroendocrine Tumors of the Gynecologic Tract. *Medicina (Kaunas)*. 2021;57(12):1338.
4. Sroussi M, Elaidi R, Fléchon A, et al. Neuroendocrine Carcinoma of the Urinary Bladder: A Large, Retrospective Study From the French Genito-Urinary Tumor Group. *Clin Genitourin Cancer*. 2020;18(4):295-303.
5. González-Lois C, Madero S, Redondo P, Alonso I, Salas A, Angeles Montalbán M. Small cell carcinoma of the kidney: a case report and review of the literature. *Arch Pathol Lab Med*. 2001;125(6):796-798.
6. Kilicarsalan Akkaya B, Mustafa U, Esin O, Turker K, Gulten K. Primary small cell carcinoma of the kidney. *Urol Oncol*. 2003;21(1):11-13.
7. Mardi K, Negi L, Srivastava S. Well differentiated neuroendocrine tumor of the kidney: Report of a rare case with review of literature. *Indian J Pathol Microbiol*. 2017;60(1):105-107.
8. Omiyale AO, Venyo AK. Primary carcinoid tumour of the kidney: a review of the literature. *Adv Urol*. 2013;2013:579396.
9. Palumbo C, Talso M, Dell'Orto PG, et al. Primary large cell neuroendocrine carcinoma of the renal pelvis: a case report. *Urologia*. 2014;81(1):57-59.
10. Shimbori M, Osaka K, Kawahara T, et al. Large cell neuroendocrine carcinoma of the kidney with cardiac metastasis: a case report. *J Med Case Rep*. 2017;11(1):297.
11. Si Q, Dancer J, Stanton ML, et al. Small cell carcinoma of the kidney: a clinicopathologic study of 14 cases. *Hum Pathol*. 2011;42(11):1792-1798.
12. Wann C, John NT, Kumar RM. Primary renal large cell neuroendocrine carcinoma in a young man. *J Clin Diagn Res*. 2014;8(11):ND08-09.
13. Abou Zahr R, Chalhoub K, Mansour E, Chouairy C, Ghazal G, Nohra J. Primary Carcinoid Tumor of the Testis: A Case Report and Review of the Literature. *Case Rep Urol*. 2018;2018:3614387.

14. Darre T, Doukoure B, Kouyate M, Djiwa T, Kwame D, Napo-Koura G. A rare testicular tumor: primary carcinoid tumor. *Tumori*. 2019;105(6):NP20-NP23.
15. Lu C, Zhang Z, Jiang Y, et al. Primary pure carcinoid tumors of the testis: Clinicopathological and immunophenotypical characteristics of 11 cases. *Oncol Lett*. 2015;9(5):2017-2022.
16. Wang WP, Guo C, Berney DM, et al. Primary carcinoid tumors of the testis: a clinicopathologic study of 29 cases. *Am J Surg Pathol*. 2010;34(4):519-524.
17. Landeyro J, Garcia-Fontgivell JF, Condom E, Sirvent JJ. Primary large-cell neuroendocrine carcinoma of the penis: association with human papilloma virus infection. *Histopathology*. 2012;61(2):319-320.
18. Pósfai B, Kuthi L, Varga L, et al. The Colorful Palette of Neuroendocrine Neoplasms in the Genitourinary Tract. *Anticancer Res*. 2018;38(6):3243-3254.
19. Chen YB, Epstein JI. Primary carcinoid tumors of the urinary bladder and prostatic urethra: a clinicopathologic study of 6 cases. *Am J Surg Pathol*. 2011;35(3):442-446.
20. Bhatt VR, Loberiza FR, Jr., Tandra P, Krishnamurthy J, Shrestha R, Wang J. Risk factors, therapy and survival outcomes of small cell and large cell neuroendocrine carcinoma of urinary bladder. *Rare Tumors*. 2014;6(1):5043.
21. Shehabeldin AN, Ro JY. Neuroendocrine tumors of genitourinary tract: Recent advances. *Ann Diagn Pathol*. 2019;42:48-58.
22. Guadagno E, De Rosa G, Del Basso De Caro M. Neuroendocrine tumours in rare sites: differences in nomenclature and diagnostics-a rare and ubiquitous histotype. *J Clin Pathol*. 2016;69(7):563-574.
23. Rosenberg JE, Albersheim JA, Sathianathen NJ, Murugan P, Weight CJ. Five New Cases of Primary Renal Carcinoid Tumor: Case Reports and Literature Review. *Pathol Oncol Res*. 2020;26(1):341-346.
24. Evans AJ, Humphrey PA, Belani J, van der Kwast TH, Srigley JR. Large cell neuroendocrine carcinoma of prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. *Am J Surg Pathol*. 2006;30(6):684-693.
25. Ghannoum JE, DeLellis RA, Shin SJ. Primary carcinoid tumor of the prostate with concurrent adenocarcinoma: a case report. *Int J Surg Pathol*. 2004;12(2):167-170.

26. Tash JA, Reuter V, Russo P. Metastatic carcinoid tumor of the prostate. *J Urol*. 2002;167(6):2526-2527.
27. Papatsimpas G, Samaras I, Theodosiou P, et al. A Case of Cervical Carcinoid and Review of the Literature. *Case Rep Oncol*. 2017;10(2):737-742.
28. Margolis B, Tergas AI, Chen L, et al. Natural history and outcome of neuroendocrine carcinoma of the cervix. *Gynecol Oncol*. 2016;141(2):247-254.
29. Marinelli JP, Cass SP, Mann SE, et al. Adenomatous Neuroendocrine Tumors of the Middle Ear: A Multi-institutional Investigation of 32 Cases and Development of a Staging System. *Otol Neurotol*. 2018;39(8):e712-e721.
30. Strosberg C, Ferlito A, Triantafyllou A, et al. Update on Neuroendocrine Carcinomas of the Larynx. *Am J Clin Pathol*. 2019;152(6):686-700.
31. van der Laan TP, Iepsma R, Witjes MJ, van der Laan BF, Plaat BE, Halmos GB. Meta-analysis of 701 published cases of sinonasal neuroendocrine carcinoma: The importance of differentiation grade in determining treatment strategy. *Oral Oncol*. 2016;63:1-9.
32. van der Laan TP, Plaat BE, van der Laan BF, Halmos GB. Clinical recommendations on the treatment of neuroendocrine carcinoma of the larynx: A meta-analysis of 436 reported cases. *Head Neck*. 2015;37(5):707-715.
33. Nahavandipour A, Jakobsen KK, Grønhøj C, et al. Incidence and survival of laryngeal cancer in Denmark: a nation-wide study from 1980 to 2014. *Acta Oncol*. 2019;58(7):977-982.
34. Turri-Zanoni M, Maragliano R, Battaglia P, et al. The clinicopathological spectrum of olfactory neuroblastoma and sinonasal neuroendocrine neoplasms: Refinements in diagnostic criteria and impact of multimodal treatments on survival. *Oral Oncol*. 2017;74:21-29.
35. Engel MSD, van der Lans RJL, Jansen JC, et al. Management and outcome of middle ear adenomatous neuroendocrine tumours: A systematic review. *Oral Oncol*. 2021;121:105465.
36. Ramsey MJ, Nadol JB, Jr., Pilch BZ, McKenna MJ. Carcinoid tumor of the middle ear: clinical features, recurrences, and metastases. *Laryngoscope*. 2005;115(9):1660-1666.
37. van der Lans RJL, Engel MSD, Rijken JA, et al. Neuroendocrine neoplasms of the middle ear: Unpredictable tumor behavior and tendency for recurrence. *Head Neck*. 2021;43(6):1848-1853.

38. Bell D, Hanna EY, Weber RS, et al. Neuroendocrine neoplasms of the sinonasal region. *Head Neck*. 2016;38(Suppl 1):E2259-E2266.
39. Wenig BM, Gnepp DR. The spectrum of neuroendocrine carcinomas of the larynx. *Semin Diagn Pathol*. 1989;6(4):329-350.
40. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. *Endocr Pathol*. 2022;33(1):115-154.
41. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31(12):1770-1786.
42. International Agency for Research on Cancer. WHO Classification of Tumours. Endocrine tumours. Accessed May 12, 2023. https://tumourclassification.iarc.who.int/welcome/#
43. Berner AM, Pipinikas C, Karpathakis A, et al. PUnNETS (Prediction of Unknown Neuroendocrine Tumour Site) – a DNA methylation-based classifier. *Endocr Abstracts*. 2018;60:OC3.
44. Berner AM, Pipinikas C, Ryan A, et al. Diagnostic Approaches to Neuroendocrine Neoplasms of Unknown Primary Site. *Neuroendocrinology*. 2020;110(7-8):563-573.
45. International Agency for Research on Cancer. WHO Classification of Urinary and Male Genital Tumours. Accessed May 12, 2023. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Urinary-And-Male-Genital-Tumours-2022
46. International Agency for Research on Cancer. WHO Classification of Female Genital Tumours. Accessed May 12, 2023. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020
47. Turla A, Zamparini M, Milione M, et al. Ovarian Stromal Carcinoid: Case Report, Systematic Literature Review and Pooled Analysis. *Front Endocrinol (Lausanne)*. 2022;13:871210.
48. Yu K, Ebbehøj AL, Obeid H, et al. Presentation, Management, and Outcomes of Urinary Bladder Paraganglioma: Results From a Multicenter Study. *J Clin Endocrinol Metab*. 2022;107(10):2811-2821.

49. International Agency for Research on Cancer. *World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. 3rd ed. vol 9. IARC Press; 2005.
50. International Agency for Research on Cancer. *WHO Classification of Head and Neck Tumours*. 4th ed. vol 9. IARC Press; 2017.
51. Mete O, Wenig BM. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Overview of the 2022 WHO Classification of Head and Neck Neuroendocrine Neoplasms. *Head Neck Pathol*. 2022;16(1):123-142.
52. Bell D, El-Naggar AK, Gidley PW. Middle ear adenomatous neuroendocrine tumors: a 25-year experience at MD Anderson Cancer Center. *Virchows Arch*. 2017;471(5):667-672.
53. Choi KY, Amit M, Tam S, et al. Clinical Implication of Diagnostic and Histopathologic Discrepancies in Sinonasal Malignancies. *Laryngoscope*. 2021;131(5):E1468-E1475.
54. La Rosa S, Uccella S. Classification of neuroendocrine neoplasms: lights and shadows. *Rev Endocr Metab Disord*. 2021;22(3):527-538.
55. Nozières C, Chardon L, Goichot B, et al. Neuroendocrine tumors producing calcitonin: characteristics, prognosis and potential interest of calcitonin monitoring during follow-up. *Eur J Endocrinol*. 2016;174(3):335-341.
56. Wang SC, Parekh JR, Zuraek MB, et al. Identification of unknown primary tumors in patients with neuroendocrine liver metastases. *Arch Surg*. 2010;145(3):276-280.
57. Bhosale P, Shah A, Wei W, et al. Carcinoid tumours: predicting the location of the primary neoplasm based on the sites of metastases. *Eur Radiol*. 2013;23(2):400-407.
58. Naswa N, Sharma P, Kumar A, et al. ^{68}Ga-DOTANOC PET/CT in patients with carcinoma of unknown primary of neuroendocrine origin. *Clin Nucl Med*. 2012;37(3):245-251.
59. Ronot M, Cuccioli F, Dioguardi Burgio M, et al. Neuroendocrine liver metastases: Vascular patterns on triple-phase MDCT are indicative of primary tumour location. *Eur J Radiol*. 2017;89:156-162.

60. Chambers AJ, Pasieka JL, Dixon E, Rorstad O. Role of imaging in the preoperative staging of small bowel neuroendocrine tumors. *J Am Coll Surg*. 2010;211(5):620-627.
61. Bartlett EK, Roses RE, Gupta M, et al. Surgery for metastatic neuroendocrine tumors with occult primaries. *J Surg Res*. 2013;184(1):221-227.
62. Ambrosini V, Kunikowska J, Baudin E, et al. Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. *Eur J Cancer*. 2021;146:56-73.
63. Kazmierczak PM, Rominger A, Wenter V, et al. The added value of (68)Ga-DOTA-TATE-PET to contrast-enhanced CT for primary site detection in CUP of neuroendocrine origin. *Eur Radiol*. 2017;27(4):1676-1684.
64. Ma H, Kan Y, Yang JG. Clinical value of (68)Ga-DOTA-SSTR PET/CT in the diagnosis and detection of neuroendocrine tumors of unknown primary origin: a systematic review and meta-analysis. *Acta Radiol*. 2021;62(9):1217-1228.
65. Sadowski SM, Neychev V, Millo C, et al. Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. *J Clin Oncol*. 2016;34(6):588-596.
66. Schreiter NF, Bartels AM, Froeling V, et al. Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET: Evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA octreotide SPECT/CT. *Radiol Oncol*. 2014;48(4):339-347.
67. Imperiale A, Rust E, Gabriel S, et al. 18F-fluorodihydroxyphenylalanine PET/CT in patients with neuroendocrine tumors of unknown origin: relation to tumor origin and differentiation. *J Nucl Med*. 2014;55(3):367-372.
68. Santhanam P, Chandramahanti S, Kroiss A, et al. Nuclear imaging of neuroendocrine tumors with unknown primary: why, when and how? *Eur J Nucl Med Mol Imaging*. 2015;42(7):1144-1155.
69. Alonso O, Rodríguez-Taroco M, Savio E, Bentancourt C, Gambini JP, Engler H. (68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin. *Ann Nucl Med*. 2014;28(7):638-645.
70. Ambrosini V, Campana D, Bodei L, et al. 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. *J Nucl Med*. 2010;51(5):669-673.

71. Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S, Baum RP. Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. *Eur J Nucl Med Mol Imaging*. 2010;37(1):67-77.
72. Pruthi A, Pankaj P, Verma R, Jain A, Belho ES, Mahajan H. Ga-68 DOTANOC PET/CT imaging in detection of primary site in patients with metastatic neuroendocrine tumours of unknown origin and its impact on clinical decision making: experience from a tertiary care centre in India. *J Gastrointest Oncol*. 2016;7(3):449-461.
73. De Dosso S, Treglia G, Pascale M, et al. Detection rate of unknown primary tumour by using somatostatin receptor PET/CT in patients with metastatic neuroendocrine tumours: a meta-analysis. *Endocrine*. 2019;64(3):456-468.
74. Sampathirao N, Basu S. MIB-1 Index-Stratified Assessment of Dual-Tracer PET/CT with (68)Ga-DOTATATE and (18)F-FDG and Multimodality Anatomic Imaging in Metastatic Neuroendocrine Tumors of Unknown Primary in a PRRT Workup Setting. *J Nucl Med Technol*. 2017;45(1):34-41.
75. Kamaoui I, De-Luca V, Ficarelli S, Mennesson N, Lombard-Bohas C, Pilleul F. Value of CT enteroclysis in suspected small-bowel carcinoid tumors. *AJR Am J Roentgenol*. 2010;194(3):629-633.
76. Frilling A, Smith G, Clift AK, Martin J. Capsule endoscopy to detect primary tumour site in metastatic neuroendocrine tumours. *Dig Liver Dis*. 2014;46(11):1038-1042.
77. James PD, Tsolakis AV, Zhang M, et al. Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. *Gastrointest Endosc*. 2015;81(4):848-856.
78. Ketata S, Ketata H, Fakhfakh H, et al. Pure primary neuroendocrine tumor of the prostate: a rare entity. *Clin Genitourin Cancer*. 2006;5(1):82-84.
79. Zaffuto E, Pompe R, Zanaty M, et al. Contemporary Incidence and Cancer Control Outcomes of Primary Neuroendocrine Prostate Cancer: A SEER Database Analysis. *Clin Genitourin Cancer*. 2017;15(5):e793-e800.
80. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. 2019;30(5):672-705.

81. Matrood S, Apostolidis L, Schrader J, et al. Multicenter Analysis of Presacral Neuroendocrine Neoplasms-Clinicopathological Characterization and Treatment Outcomes of a Rare Disease. *Front Endocrinol (Lausanne)*. 2021;12:709256.
82. Reiter MJ, Schwope RB, Bui-Mansfield LT, Lisanti CJ, Glasgow SC. Surgical management of retrorectal lesions: what the radiologist needs to know. *AJR Am J Roentgenol*. 2015;204(2):386-395.
83. Castelnau-Marchand P, Pautier P, Genestie C, et al. Multimodal Management of Locally Advanced Neuroendocrine Cervical Carcinoma: A Single Institution Experience. *Int J Gynecol Cancer*. 2018;28(5):1013-1019.
84. Kim C, Salvo G, Ishikawa M, et al. The role of postoperative radiation after radical hysterectomy for women with early-stage neuroendocrine carcinoma of the cervix: A meta-analysis. *Gynecol Oncol*. 2023;170:328-332.
85. Salvo G, Jhingran A, Ramalingam P, et al. Definitive pelvic radiation therapy improves survival in stage IVB neuroendocrine cervical carcinoma: A NeCTuR study. *Gynecol Oncol*. 2022;165(3):530-537.
86. Teo MY, Guercio BJ, Arora A, et al. Long-term Outcomes of Local and Metastatic Small Cell Carcinoma of the Urinary Bladder and Genomic Analysis of Patients Treated With Neoadjuvant Chemotherapy. *Clin Genitourin Cancer*. 2022;20(5):431-441.
87. Abida W, Cyrta J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci U S A*. 2019;116(23):11428-11436.
88. Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and Genomic Characterization of Treatment-Emergent Small-Cell Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study. *J Clin Oncol*. 2018;36(24):2492-2503.
89. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv72-iv83.
90. Salvo G, Ramalingam P, Flores Legarreta A, et al. Role of radical hysterectomy in patients with early-stage high-grade neuroendocrine cervical carcinoma: a NeCTuR study. *Int J Gynecol Cancer*. 2021;31(4):495-501.
91. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol*. 2010;203(4):E1-E6.

92. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012.
93. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
94. Singh S, Carnaghi C, Buzzoni R, et al. Everolimus in Neuroendocrine Tumors of the Gastrointestinal Tract and Unknown Primary. *Neuroendocrinology*. 2018;106(3):211-220.
95. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
96. Capdevila J, Fazio N, Lopez C, et al. Lenvatinib in Patients With Advanced Grade 1/2 Pancreatic and Gastrointestinal Neuroendocrine Tumors: Results of the Phase II TALENT Trial (GETNE1509). *J Clin Oncol*. 2021;39(20):2304-2312.
97. Xu J, Shen L, Zhou Z, et al. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(11):1500-1512.
98. Garcia-Carbonero R, Benavent M, Jimenez Fonseca P, et al. 1097O The AXINET trial (GETNE1107): Axitinib plus octreotide LAR improves PFS by blinded central radiological assessment vs placebo plus octreotide LAR in G1-2 extrapancreatic NETs. *Ann Oncol*. 2021;32(suppl 5):S907-S908.
99. Chan J, Geyer S, Ou FS, et al. LBA53 Alliance A021602: Phase III, double-blinded study of cabozantinib versus placebo for advanced neuroendocrine tumors (NET) after progression on prior therapy (CABINET). *Ann Oncol*. 2023;34(suppl 2):S1292.
100. Kunz PL, Balise RR, Fehrenbacher L, et al. Oxaliplatin-Fluoropyrimidine Chemotherapy Plus Bevacizumab in Advanced Neuroendocrine Tumors: An Analysis of 2 Phase II Trials. *Pancreas*. 2016;45(10):1394-1400.
101. Chauhan A, Farooqui Z, Murray LA, et al. Capecitabine and Temozolomide in Neuroendocrine Tumor of Unknown Primary. *J Oncol*. 2018;2018:3519247.

102. de Mestier L, Couvelard A, Blazevic A, et al. Critical appraisal of MGMT in digestive NET treated with alkylating agents. *Endocr Relat Cancer*. 2020;27(10):R391-R405.
103. Kunz PL, Graham NT, Catalano PJ, et al. Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients With Advanced Pancreatic Neuroendocrine Tumors (ECOG-ACRIN E2211). *J Clin Oncol*. 2023;41(7):1359-1369.
104. Walter T, Lecomte T, Hadoux J, et al. LBA54 Alkylating agent-based vs oxaliplatin-based chemotherapy in neuroendocrine tumours according to the O6-methylguanine-DNA methyltransferase (MGMT) status: A randomized phase II study (MGMT-NET) on behalf of the French Group of Endocrine Tumors (GTE) and ENDOCAN-RENATEN network. *Ann Oncol*. 2023;34(suppl 2):S1292-S1293.
105. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol*. 2017;3(10):1335-1342.
106. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol*. 2010;21(9):1794-1803.
107. Ünlütürk U, Erdoğan MF, Demir O, Culha C, Güllü S, Başkal N. The role of ultrasound elastography in preoperative localization of parathyroid lesions: a new assisting method to preoperative parathyroid ultrasonography. *Clin Endocrinol (Oxf)*. 2012;76(4):492-498.
108. Cetani F, Marcocci C, Torregrossa L, Pardi E. Atypical parathyroid adenomas: challenging lesions in the differential diagnosis of endocrine tumors. *Endocr Relat Cancer*. 2019;26(7):R441-R464.
109. Erickson LA, Mete O. Immunohistochemistry in Diagnostic Parathyroid Pathology. *Endocr Pathol*. 2018;29(2):113-129.
110. Gill AJ, Lim G, Cheung VKY, et al. Parafibromin-deficient (HPT-JT Type, CDC73 Mutated) Parathyroid Tumors Demonstrate Distinctive Morphologic Features. *Am J Surg Pathol*. 2019;43(1):35-46.
111. Kruijff S, Sidhu SB, Sywak MS, Gill AJ, Delbridge LW. Negative parafibromin staining predicts malignant behavior in atypical parathyroid adenomas. *Ann Surg Oncol*. 2014;21(2):426-433.

112. Parpounas C, Lyssiotis T, Constantinides V. Triple water clear cell parathyroid adenomas: a rare cause of primary hyperparathyroidism. *BMJ Case Rep*. 2022;15(4):e246873.
113. Yang CA, Lin JL, Dai SH, Cheng SP. Double water-clear cell parathyroid adenoma: a case report and literature review. *Endocr J*. 2022;69(6):717-724.
114. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;352(4):373-379.
115. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;19(2):558-567.
116. Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab*. 2014;99(9):3144-3152.
117. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med*. 2008;149(4):259-263.
118. Kakudo K, Bai Y, Ozaki T, Homma K, Ito Y, Miyauchi A. Intrathyroid epithelial thymoma (ITET) and carcinoma showing thymus-like differentiation (CASTLE): CD5-positive neoplasms mimicking squamous cell carcinoma of the thyroid. *Histol Histopathol*. 2013;28(5):543-556.
119. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? *Hum Pathol*. 2020;96:8-33.
120. Zhao LH, Chen C, Mao CY, et al. Value of SATB2, ISL1, and TTF1 to differentiate rectal from other gastrointestinal and lung well-differentiated neuroendocrine tumors. *Pathol Res Pract*. 2019;215(7):152448.
121. Union for International Cancer Control. *TNM Classification of Malignant Tumours*. 8th ed. John Wiley & Sons, Inc.; 2017.
122. Landry CS, Wang TS, Asare EA, et al. Parathyroid. In: Amin MB, Edge S, Greene F, et al, eds. *AJCC Cancer Staging Manual 8th ed*. Springer International Publishing; 2017:911-918.
123. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis*. 2001;33(2):139-144. [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis.* 1994;18(3):421].