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SPECIAL ARTICLE

Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

The latest World Health Organization (WHO) classification from 2015 has grouped lung and thymic neuroendocrine tumours (NETs) (named neoplasm in the digestive WHO classification) within one unique group but confirmed their subdivision into four main categories: typical carcinoid (TC), atypical carcinoid (AC), small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC).[1] These guidelines are restricted to lung carcinoid (LC) and thymic carcinoid (ThC). Patients with carcinoids are generally younger, have a better prognosis and do not have a strong association with smoking, as compared with SCLC and LCNEC.[1] The incidence of LC is very low, ranging from 0.2-2/100 000 persons/year in both the United States and Europe.[2,3] Numbers are increasing, likely due to increased awareness and improved diagnostic techniques, although it may also be a genuine overall increase in incidence.[2,3] LCs account for 20%-25% of all NETs and 1%-2% of all lung cancers. LCs prevail slightly more often in women than in men. LCs occur during the fifth or sixth decade of life for TC and a decade later for AC.[4-10]

ThC is an extremely rare tumour accounting for an age-adjusted rate of 0.02/100 000-0.18/100 000/year in the European or USA populations, respectively.[3,11] In the Netherlands cancer registry or the Surveillance, Epidemiology and End Results (SEER) programme database, <0.5% of all neuroendocrine neoplasms were ThC, representing 5% of thymic tumours.[3,11] The incidence of ThC is increasing in the USA population.[11] ThC prevails in men and the mean age at diagnosis is 55 years.[1,11-13]

LC and ThC may also be present in multiple endocrine neoplasia type 1 (MEN-1) syndrome or when there is a family history of carcinoid tumours or diffuse pulmonary neuroendocrine cell hyperplasia (DIPNECH) (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[1,14-17]

Recommendation

- The scarcity of LCs and ThCs justifies the therapeutic management of these patients by expert multidisciplinary teams in centres grouped within networks (national or European networks) for care and research optimisation [V, A].

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

LC is revealed by non-specific tumour-related respiratory symptoms (mainly, central forms) or incidentally (mainly,

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peripheral forms). A minority of cases present with symptoms related to hormonal hypersecretion, including carcinoid syndrome (CS), due to serotonin and other compound secretions, Cushing's syndrome (CuS), due to adrenocorticotropic hormone (ACTH) secretion and acromegaly, due to growth hormone-releasing hormone (GHRH) secretion.[5,7,18,19] In a recent large population-based study series of 3002 LC patients, CS was present in 229 patients (7.6%) at diagnosis.[20]

Diagnosis is carried out with bronchoscopic technique, transthoracic biopsy or, less frequently, by mediastinoscopy or endobronchial endoscopic ultrasonography (EBUS) (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).

Surgery may be carried out upfront after adequate medical preparation in localised resectable tumours resembling LCs or in tumours considered at high risk of bleeding or hormonal crisis or when previous biopsy has failed. Once the diagnosis is suspected, standardised characterisation of LC comprises several specific steps for evaluation that are described in Table 1 [III, B].[4-9,18,20-34]

ThC is revealed by tumour-related symptoms, or due to functionally active tumours or by chance.[11-13] Diagnostic procedures, including core biopsy under ultrasonography guidance, or preferably through a thoracic computed tomography (CT) scan, or upfront surgery following the guidelines for thymic tumour diagnosis, should be carried out.[35] The authors recommend standardised characterisation of ThC in multidisciplinary expert centres as described in Table 1 [III, B].[11,12,32-37]

The histopathological diagnosis of LC or ThC relies on characteristic morphological features and on the demonstration of the neuroendocrine nature of the tumour through the immunodetection of a panel of markers including at least chromogranin A (CgA) and synaptophysin, which are usually expressed in all carcinoids. This might be expanded to other markers such as CD56.[1] Thyroid transcription factor 1 (TTF1) may be useful in well-differentiated tumours only, when positive, to suggest the lung origin of metastatic tumours.[1] TCs and ACs are distinguished (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.003), on the basis of mitotic count and presence or absence of necrosis.[1] While Ki-67 index is not included in the WHO criteria, the WHO acknowledges that Ki-67 index might be useful for the differential diagnosis between well- or poorly-differentiated NETs (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.003).[1] Carcinoids are characterised by mutations involving either MEN-1 or other genes encoding chromatin-remodelling proteins.[38,39] *TP53* and particularly *RB1* gene alterations, which are rare molecular events in carcinoids, might be potential tools to discriminate between well or poorly differentiated categories in difficult cases like the recently identified LC with high proliferative features. This new subgroup is defined by a mitotic count >10 and/or a Ki-67 index >20%, and a well-differentiated morphology (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.01.003).[39-43] The ratio between TC and AC is about 6 : 10 in surgical series but may be closer to 1 : 1 in advanced cases.[1,4,6,7,20]

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

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

^{111}In, indium-111; 5-HIAA, 5-hydroxyindoleacetic acid; ^{68}Ga, gallium-68; AC, atypical carcinoid; ACTH, adrenocorticotropic hormone; Ca, calcium; CS, carcinoid syndrome; CT, computed tomography; CuS, Cushing's syndrome; DIPNECH, diffuse pulmonary neuroendocrine cell hyperplasia; DTPA, diethylene-triamine-pentaacetate; EBUS, endobronchial endoscopic ultrasonography; FDG, fluorodeoxyglucose; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor 1; i.v., intravenous; K, potassium; MEN-1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PET, positron emission tomography; SRI, somatostatin receptor imaging; SSA, somatostatin analogue; TC, typical carcinoid; TNM, tumour—node—metastasis; UICC, Union for International Cancer Control; WHO, World Health Organization.

[a] In case of clinical symptoms suggestive of CS or CuS or acromegaly. Absence of hypergastrinemia is a prerequisite for chromogranin A interpretation.

[b] If clinically indicated.

[c] To rule out bulky pN2 or pN3 disease.

The ThC WHO classification is identical to that of lung NETs with four categories including TC or AC defined using the same criteria (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.003). The pattern of genetic alterations is different from LC.[1,38] As for LCs, a subgroup of ThC with high proliferative features has recently been recognised.[44] The ratio between atypical and typical ThC is about 2 : 1.[1,33,34,36]

Recommendations

- Management of LC and ThC requires a multidisciplinary standardised approach in specialised centres [IV, A]
- Ki-67 (MIB 1) [IV, A], TTF1 [IV, B], p53/RB1 [IV, B] biomarker analyses are recommended in selected cases for differential diagnosis or site of origin orientation.

STAGING AND RISK ASSESSMENT

Risk assessments depend on pathology and TNM (tumour—node—metastasis) staging based on the combination of

intravenous (i.v.) contrast-enhanced cross-sectional conventional (radiological) imaging, including liver late arterial phase and positron emission tomography (PET)-CT with gallium-68 (^{68}Ga)-labelled somatostatin analogues (SSAs) functional imaging as described in Table 1 and Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003 [II, B].[23-30,37,45]

Serum CgA is measured in all patients, whereas specific biomarkers [5-hydroxyindoleacetic acid (5-HIAA), ACTH, urinary-free cortisol (UFC), GHRH, insulin-like growth factor 1 (IGF-1)] are assessed depending on the presence of functioning syndromes. Insufficient accuracy of CgA (30%-60% at the metastatic stage) makes research on new biomarkers critical. Among these, a multianalyte molecular assay [51 transcripts; neuroendocrine tumor test (NETest)] is currently under development with potentially better sensitivity, but uncertainties remain regarding its positive predictive value and role as a prognostic marker for LC.[22]

The application of the 8th Edition of the Union for International Cancer Control (UICC) TNM staging (Supplementary Tables S3 and S4, available at https://doi.org/10.1016/j.annonc.2021.01.003) is recommended even if not specific to LCs.[31,46,47] More than 80% of LCs are diagnosed at TNM stage I or II.[4,5-7,46] The most common sites of metastasis include liver, bone and lung. The diversity of metastatic sites and the potential overestimation of lung metastasis and underestimation of brain metastasis must be taken into account.[46,47] The WHO classification and pathological TNM (pTNM) staging are intricate.[5,21,48] In a recent study in which patients underwent $\geq$10 lymph node resection, frequency of positive lymph nodes was 17% (including 6% N2-N3) or 46% (including 23% N2-N3) in case of TC or AC, respectively.[48]

Most ThCs are diagnosed at advanced-stage Masaoka–Koga (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.01.003) or TNM stage III or IV.[11,12,32] The most common sites for metastases include the pleura, pericardium, bone, lung and liver.

In LCs, overall survival (OS) is mainly influenced by WHO pathology and the pTNM classifications.[1,5,21,45-49] In stage I, II, III or IV LC patients, 10-year disease-specific survival is 96%, 85%, 81%, 59% and 88%, 75%, 47%, 18%, in TC or AC, respectively, showing the major prognostic influence of the WHO classification.[46]

After resection, WHO classification and pathological lymph node staging (pN) status constitute the two main prognostic parameters (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[4,5,9,21,45,48-51] Although Ki-67 index is considered a promising prognostic marker by the whole author panel, its technique of evaluation and the most accurate thresholds remain a matter of debate; moreover, no definitive validation of its added value to WHO and pTNM classifications has been provided so far in large series of LCs.[18,28,45,52,53] At the metastatic stage, WHO classification, performance status, CgA levels, tumour burden and somatostatin receptor imaging (SRI) uptake, as well as tumour growth slope and the functioning syndrome, should be taken into account for adequate risk assessment [IV, B].[47] Prolonged survival of the majority of patients with LCs (including a 60% 5-year OS for metastatic LC) makes adjusted toxicity profile of therapeutic interventions critical [V, A].[47]

The prognosis of patients with thymic NETs remains poor: in retrospective series, 5- or 10-year OS was 28%-72% or 26%-60%, respectively.[11-14,33] Based on a few large, retrospective thymic NETs series, OS is influenced by stage, mainly tumour size and completeness of resection (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[11-13,32,33,36] No specific staging system has yet been validated for ThC. The authors therefore recommend the use of both staging systems (TNM, Masaoka–Koga) together with the WHO classification and resection status for adequate prognostic stratification.[1]

Recommendations

- WHO and pTNM classifications constitute the basis of the prognostic classification [II, B]
- i.v. contrast-enhanced cross-sectional conventional imaging including liver late arterial phase and PET-CT with ^{68}Ga-labelled SSAs constitute the basis of TNM evaluation [II, B]
- Specific prognostic factors including tumour growth rate or presence of functioning syndromes are taken into account in advanced-stage LCs and ThCs [IV, B]
- Prolonged survival of most patients with LCs makes adjusted toxicity profile of therapeutic interventions critical [V, A].

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE, LOCAL RECURRENCE AND ADJUVANT THERAPY

Local/locoregional disease treatment

Control of a functioning syndrome must be considered before any invasive therapeutic intervention [V, A]. Surgery represents the treatment of choice for LCs (both TCs and ACs), even in the case of N2 lymph nodal metastases [IV, A].[54] The surgical approach depends on tumour size, location and preoperative biopsy specimen assessment. The choice of open surgery or minimally invasive approaches will depend on the experience of the surgeon. Patients with small peripheral nodules may be candidates for minimally invasive access including lung resection and lymph node dissection (usually a video-assisted lobectomy/segmentectomy). The surgical access for centrally located tumours, those with suspected/proven metastatic lymph nodes, usually requires thoracotomy, depending on the surgeon's expertise.

Anatomic pulmonary resection (e.g. segmentectomy, lobectomy, bilobectomy, pneumonectomy) and lymph node resection (with a minimum of six nodal stations: three hilar and three mediastinal—also including subcarinal station—as recommended by the European Society of Thoracic Surgery for non-small-cell lung cancer) is the preferred extent of resection [IV, B]. Indeed, wedge resection may increase the risk of tumour recurrences, especially in N-positive TC or intermediate-grade ACs.[4,5,55,56] In ACs,

but also in N-positive TCs, lobectomy is reported as superior to segmentectomy in terms of OS in some, but not all.[5,7,8,18,51,54,55,57,58] Bronchoplastic procedures (e.g. sleeve resections) are preferred for suitable centrally located tumours, with the aim of avoiding pneumonectomy [IV B]. Transfer of patients to specialist centres for sleeve resection should be discussed [IV, B]. Frozen sections of bronchial and vascular margins are recommended to rule out tumour involvement of resection margins, a condition that consequently imposes a greater pulmonary resection. Systematic lymph node dissection is recommended as lymph node metastases may be observed in up to 27% of TCs and in up to 47% of ACs, and lymph node resection influences the prognosis and the modality of follow-up[5,45,48,49,56] [IV, B]. R0 resection is achieved in >85% of cases.[7,10]

In case of distal lung parenchyma destruction, there is an option for endobronchial resection to relieve the obstruction, followed by reassessment and definitive surgery a few weeks later.

Watchful radiological follow-up, as an alternative to surgery, may be considered in case of cT1N0 carcinoid within the setting of DIPNECH, but also in MEN-1 patients and patients with comorbid conditions, due to the indolent course of most tumours [IV, C]. Rarely, carcinoids within the setting of DIPNECH may progress and be considered for sublobar resection (including wedge resection), especially in case of large tumour size and/or presence of lymph nodes and/or uncontrolled functioning syndrome, as a potential alternative to anatomical surgery in these patients to preserve lung function; medical options (SSAs) or nonsurgical locoregional therapeutic procedures may also constitute potential alternatives to be discussed case by case [V, C].[14,17,24] Patients with non-DIPNECH or non-MEN-1 multifocal LC primaries may constitute a distinct entity which may benefit from a similar management [V, C].[59]

Upfront surgery can be offered for all ThCs deemed radically resectable [IV, B]. Resectability judgement is mostly based on the surgeon's expertise in thymic surgery. Prospective registration of these cases is recommended. Median sternotomy is the standard surgical approach and less invasive forms of access (video-assisted, robotic-assisted) are currently being investigated; in selected cases (tumours invasive to the lung, great vessels or with pleural/pericardial implants), a combined approach (sternotomy plus anterior thoracotomy) or a thoracotomy are required to achieve a complete tumour resection. Palliative surgery is not recommended. Lymphadenectomy has historically rarely been carried out at the time of resection of thymic tumours; however, the latest UICC TNM staging system recommends that locoregional lymph nodal dissection should be carried out also during ThC resection.[60] Due to the poor prognosis of ThC, prophylactic thymectomy could be discussed in young male adult patients with MEN-1 at the time of initial or recurrent parathyroidectomy, especially in families with aggressive thymic tumours [V, C];[14,15,61] the best surgical approach may include cervicotomy and upper sternal split or other surgical procedures to avoid incomplete thymic resection.

Local recurrence therapy

After a median follow-up of 54-121 months, recurrences occur in up to 7% of TCs and up to 35% of ACs.[4,7,18,53,54] One-third are local recurrences.

In case of local recurrence, surgical resection with radical intent is recommended when technically feasible. In patients with significant comorbidity or high operative risk, palliative locoregional procedures or watchful follow-up may constitute an alternative (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[54,62]

Adjuvant therapy

Large retrospective studies have reported no benefit of adjuvant therapy in both TCs and ACs.[5,8-10,18] Therefore, the authors do not recommend routine adjuvant therapy in LCs, [IV, D] for TC; [IV, C] for AC (Figure 1). However, it may be considered in selected fit patients with particularly high risk of relapse (i.e. AC N2) after multidisciplinary discussion [IV, C]. We recommend prospective registration of these cases. Medical options, mainly cytotoxic chemotherapy (ChT) [plus or minus radiotherapy (RT)], cited in these guidelines, should be considered first.

Available literature suggests no benefit from adjuvant therapy in ThCs [V, C].[11-13,32] The majority of the author panel suggests individually discussing postoperative therapies, including RT and/or systemic therapies (with options discussed in these guidelines), with patients with advanced-stage R0 or R1-2 resection [V, C] (Figure 2).

Recommendations

- Control of a functioning syndrome must be considered before any invasive therapeutic intervention [V, A]
- An anatomic pulmonary resection (e.g. segmentectomy, lobectomy, bilobectomy) or bronchoplastic procedures (e.g. sleeve resections) together with lymph node dissection are recommended in localised LCs [IV, B]
- Patients with cT1N0 LC within the setting of DIPNECH or MEN-1 syndromes, or with comorbid conditions, may benefit from an initial radiological follow-up without treatment to determine the growth rate. In these subgroups of patients, watchful follow-up or, in case of clinical (functioning syndrome) and or morphological progression, sublobar surgical resections including wedge resection, but also nonsurgical locoregional therapeutic procedures or medical treatments (SSAs) to preserve lung function constitute alternatives to anatomic pulmonary resection [V, C]
- Patients with non-DIPNECH or non-MEN-1 multifocal LC primaries may constitute a distinct entity which may benefit from a similar management [V, C]
- Pneumonectomy should be avoided where possible and this could include the referral of patients to specialist centres for sleeve resection [IV, B]

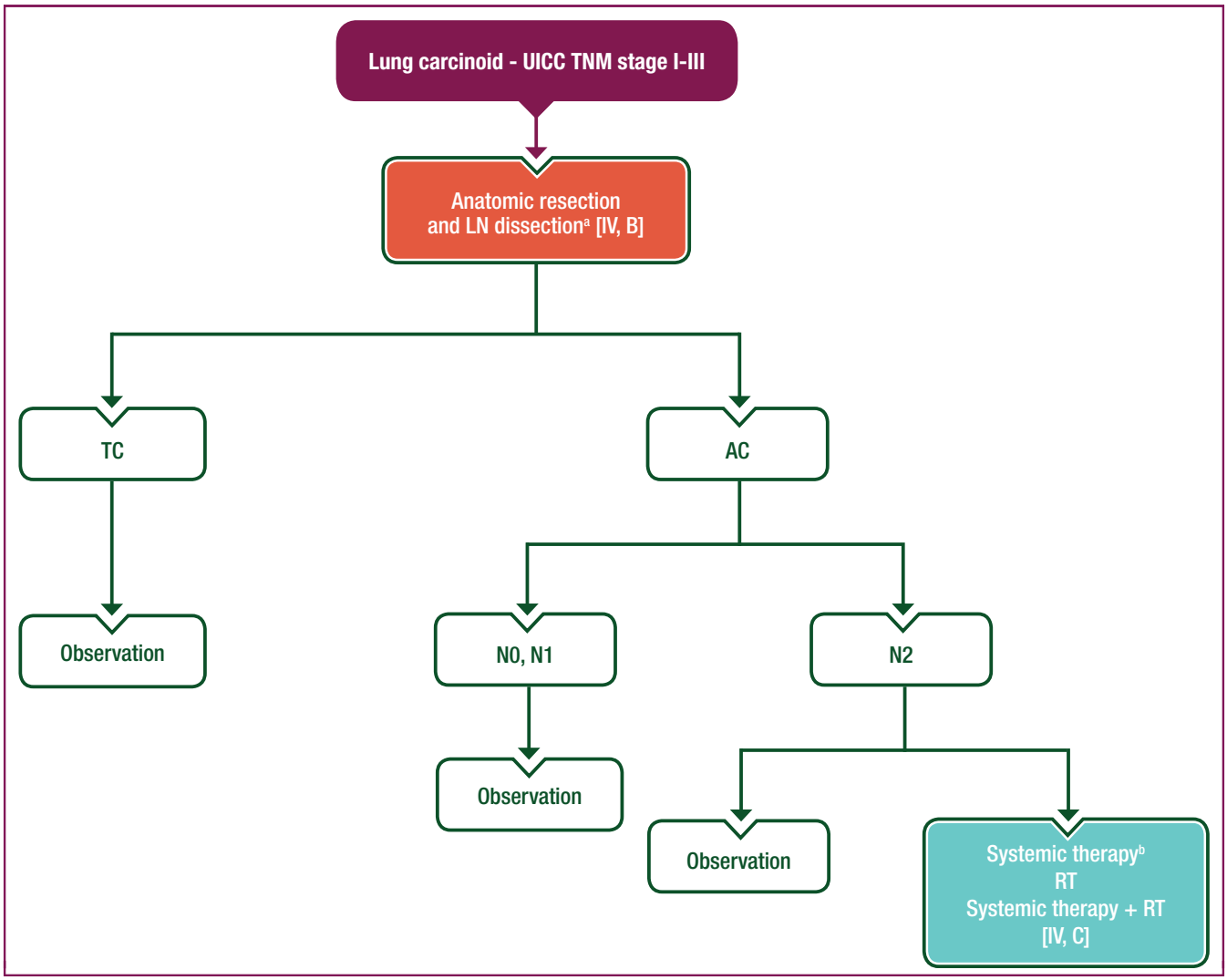

Figure 1. Lung carcinoid adjuvant therapy in UICC TNM stage I-III R0 patients.
AC, atypical carcinoid; ChT, chemotherapy; DIPNECH, diffuse pulmonary neuroendocrine cell hyperplasia; LN, lymph node; MEN-1, multiple endocrine neoplasia type 1; RT, radiotherapy; TC, typical carcinoid; TNM, tumour—node—metastasis; UICC, Union for International Cancer Control.
[a] Watchful follow-up or sublobar resection (in case of progression, large tumours, presence of LNs) may be considered in case of DIPNECH, MEN-1, multiple isolated primaries and patients with comorbid conditions; control of hormonal secretion is advised before any therapeutic intervention.
[b] Alkylating- or platinum-based ChT.

- No routine adjuvant therapy is recommended in LCs [IV, C for AC; IV, D for TC]. However, cytotoxic ChT (dacarbazine/temozolomide- or oxaliplatin-based ChT) ± RT may be considered in selected fit patients with a particularly high risk of relapse (i.e. AC N2) after multidisciplinary discussion [IV, C]
- Thymectomy by median sternotomy and/or thoracotomy and lymph node dissection for ThCs is recommended [IV, B]
- Prophylactic thymectomy could be discussed in young male adult patients with MEN-1 in families with aggressive thymic tumours [V, C]
- Case-by-case discussion is recommended for additional local and or systemic options in ThCs with R0 (if stage 3 or 4) or R1 or R2 resection [V, C].

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Control of tumour growth and functioning syndromes are the goals of the therapeutic management, with the aims of improving both the quality of life (QoL) and survival. The best strategy including sequencing is unknown due to the low number of dedicated trials and absence of predictors of response in NETs. Such information should be shared with the patient. Prognosis, but not predictive factors, guides the decision-making therapeutic management in non-functioning patients [V, A]. Watchful follow-up may be considered in asymptomatic patients with TC and/or slowly radiologically progressing LCs [V, C]. Dedicated LC and ThC trials are urgently needed and should be prioritised.

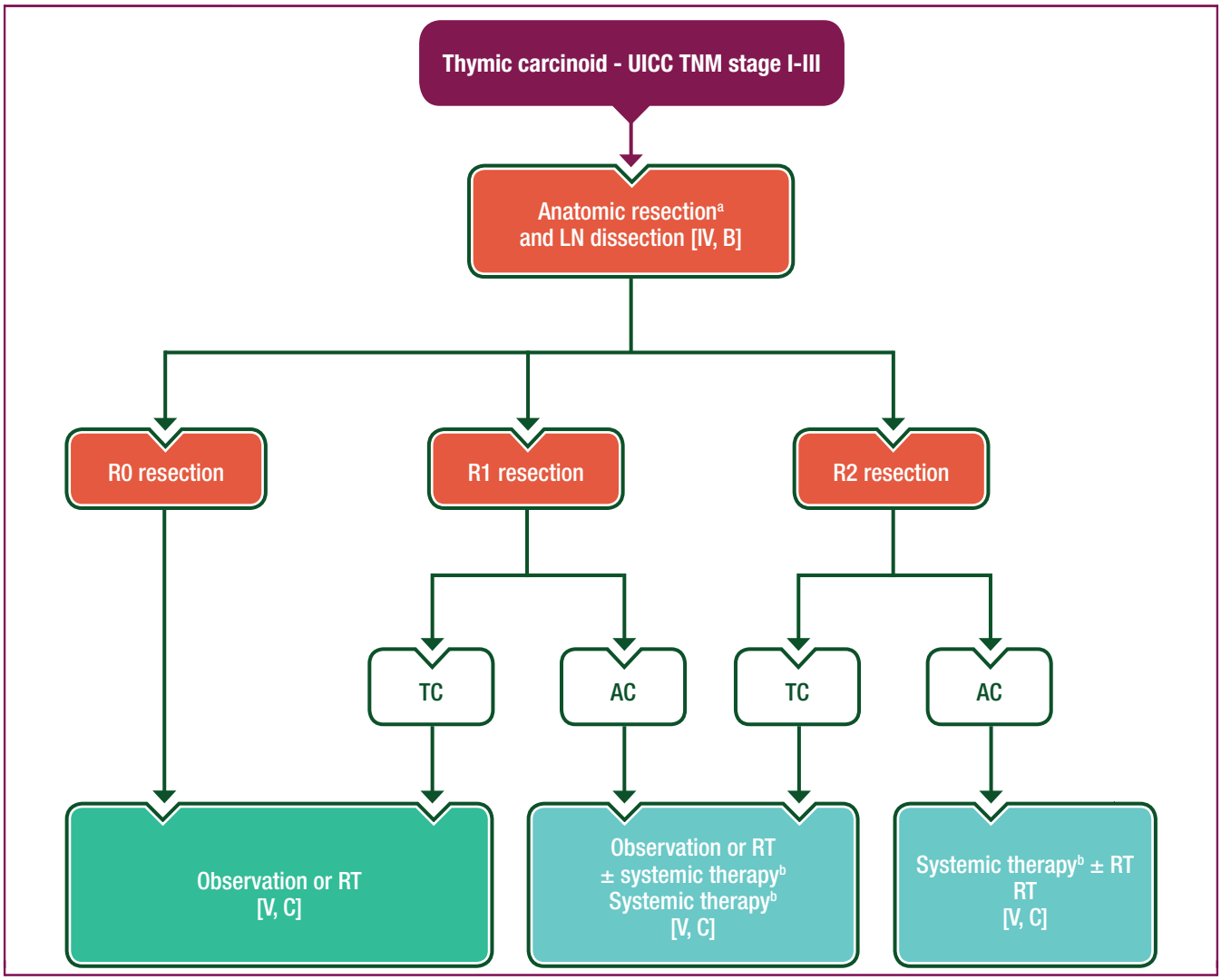

Figure 2. Thymic carcinoid adjuvant therapy in UICC TNM stage I-III patients.
AC, atypical carcinoid; ChT, chemotherapy; LN, lymph node; R0, microscopically margin-negative resection; R1, microscopic tumour at the surgical margin; R2, macroscopic tumour at the surgical margin; RT, radiotherapy; TC, typical carcinoid; TNM, tumour—node—metastasis; UICC, Union for International Cancer Control.
[a] Debulking surgery is not recommended in thymic carcinoids.
[b] Alkylating- or platinum-based ChT.

Recommendations

- Prognosis guides the decision-making therapeutic management [V, A]
- Watchful follow-up may be considered in asymptomatic patients with slowly radiologically progressing LCs [V, C]
- Dedicated LC and ThC trials are urgently needed and should be prioritised.

Hormone-related symptom management

Hormone-related symptoms are caused by autonomous secretion of biogenic amines or peptide hormones and are responsible for both QoL and survival alterations. The most frequent functioning syndrome is CS in LC, which requires annual echocardiography screening for carcinoid heart disease, when present or in case of increased 5-HIAA levels [V, C].[60] In addition, prospective studies are expected to determine the added value of N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) in the detection of carcinoid heart disease. In contrast, CS is rare in ThC. Based on approval and recommendations in gastroenteropancreatic (GEP) NET patients with CS, we recommend long-acting SSAs as first-line symptomatic treatment of CS [V, B].[61,63-65] SSAs are also an option in DIPNECH patients presenting with respiratory symptoms.[65] Among second-line options described in Figure 3 and Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003,[64-71] only telotristat ethyl has been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for the treatment of the diarrhoea of refractory CS. CuS caused by ectopic ACTH secretion is the most frequent functional syndrome in ThC. The treatment of choice for CuS by ectopic secretion of ACTH includes steroid synthesis inhibitors such as metyrapone and/or ketoconazole [IV, B]. Options in case of refractory CuS are discussed in Figure 3 and Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003.[72] Other functional syndromes, such as acromegaly or hypercalcaemia, related to

parathyroid hormone (PTH)-related peptide secretion, are rare and should be treated with SSAs [V, B].[64]

Recommendations

- Annual echocardiography screening in case of CS or increased 5-HIAA levels is recommended [V, C]
- SSAs are recommended as first-line therapy for CS [V, B]
- Short-acting SSAs given intravenously are recommended in perioperative treatment [IV, A]
- In patients with refractory CS, a variety of options exist but there is no consensus on the best strategy, due to the lack of specific LC studies
- Metyrapone and/or ketoconazole are recommended as first-line therapy for CuS [IV, B]
- In patients with refractory CuS, early bilateral adrenalectomy should be considered [IV, B]
- SSAs are recommended for other functional syndromes such as acromegaly or hypercalcaemia [V, B].

Anti-tumour management

Locoregional therapy including surgery. Palliative surgery or radiofrequency ablation (RFA) or cryoablation or endobronchial treatment (EBT) of the primary tumour are occasionally considered in cases of advanced disease at risk of local events or refractory CS [V, B]. More frequently, liver, bone and lung metastases represent potential targets for such strategies with the triple objectives of reducing the locoregional risks, the primary tumour and the secretory burden (Figures 3 and 4). Such multiple locoregional management may represent the only anti-tumour strategy in patients with slowly progressive tumours (Figure 4 and Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003) [V, B].[67,68,73-75]

Recommendations

- Palliative surgery or locoregional procedures (RFA, cryoablation, EBT) of the primary tumour are occasionally considered in cases of advanced disease at risk of local events or refractory CS [V, B]
- Multiple locoregional therapies including surgery, combined or not with SSAs, are recommended to decrease the tumour burden, to control hormonal secretions and to prevent local complications, as a first-line therapeutic approach in patients with advanced slowly progressing LC [V, B].

Systemic anti-tumour therapy

Systemic anti-tumour therapies of patients with advanced LC are various, including SSAs, ChT, everolimus, peptide receptor radionuclide therapy (PRRT) and interferon-α (IFN-α) (Figure 4). These systemic therapies should be discussed within expert multidisciplinary teams for patients with morphologically progressive tumours, high tumour burden or refractory functioning syndromes. No specific phase III trial for LC exclusively has been published so far, therefore evidence comes mostly from retrospective analyses, less from phase II, single-arm trials, and sporadically from randomised phase II or subgroups of phase III trials that enrolled a majority of GEP-NET patients. Everolimus is the only treatment approved by the FDA and the EMA for LC. Based on the very limited data available in advanced ThC, we recommend applying the same strategy as for LC.

SSAs

Octreotide [long-acting release (LAR) 30 mg] and lanreotide (120 mg) are the two SSAs most commonly used in clinical practice. Both showed antiproliferative activity and gains in time to progression or progression-free survival (PFS) in placebo-controlled, phase III trials enrolling good prognostic or slowly progressive GEP-NETs,[64] where they were approved by the FDA and EMA for antiproliferative purposes. The placebo-controlled, randomised phase III trial, which evaluated lanreotide 120 mg in advanced LC, was stopped for insufficient enrolment (SPINET trial NCT02683941). Therefore, the feasibility of phase III trials in LC remains an issue. Two dedicated retrospective case series reported potential positive impact of SSAs, with a PFS of 17 and 11 months, respectively.[76,77] In the single, published, randomised phase II LUNA trial, pasireotide 60 mg every 4 weeks, in first or second line after standard SSA therapy, achieved a 39% progression-free rate (PFR) at 9 months, in a series of 41 LCs or ThCs with Response Evaluation Criteria in Solid Tumours (RECIST) progression before enrolment (LUNA study). The PFR was not significantly different from that achieved with everolimus alone.[20] On this basis, the authors recommend SSA, for its better tolerability, as first-line therapy in TC or slowly progressing somatostatin receptor (SSTR)-positive LC [IV, C].

Targeted therapies

Everolimus has been investigated in several clinical trials which included metastatic LCs and is currently the most studied agent in LC. The RADIANT-4 study represents the largest series of LCs ever included in a phase III trial (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[78,79] Based on these results, the FDA and EMA approved everolimus in advanced, progressing, non-functional pulmonary and digestive NETs in 2016. Furthermore, in the RADIANT-4 trial, everolimus delayed tumour progression while preserving overall health-related QoL.[80] Everolimus has been reported to be potentially effective also in a *post hoc* analysis of the RADIANT-2 trial regarding a subgroup of LC associated with a history of CS (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[71,81] Everolimus is considered as first-line therapy in the majority of ACs or following progression to SSA for both TC and AC patients [II, B] (see Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003 for detailed LUNA trial data).

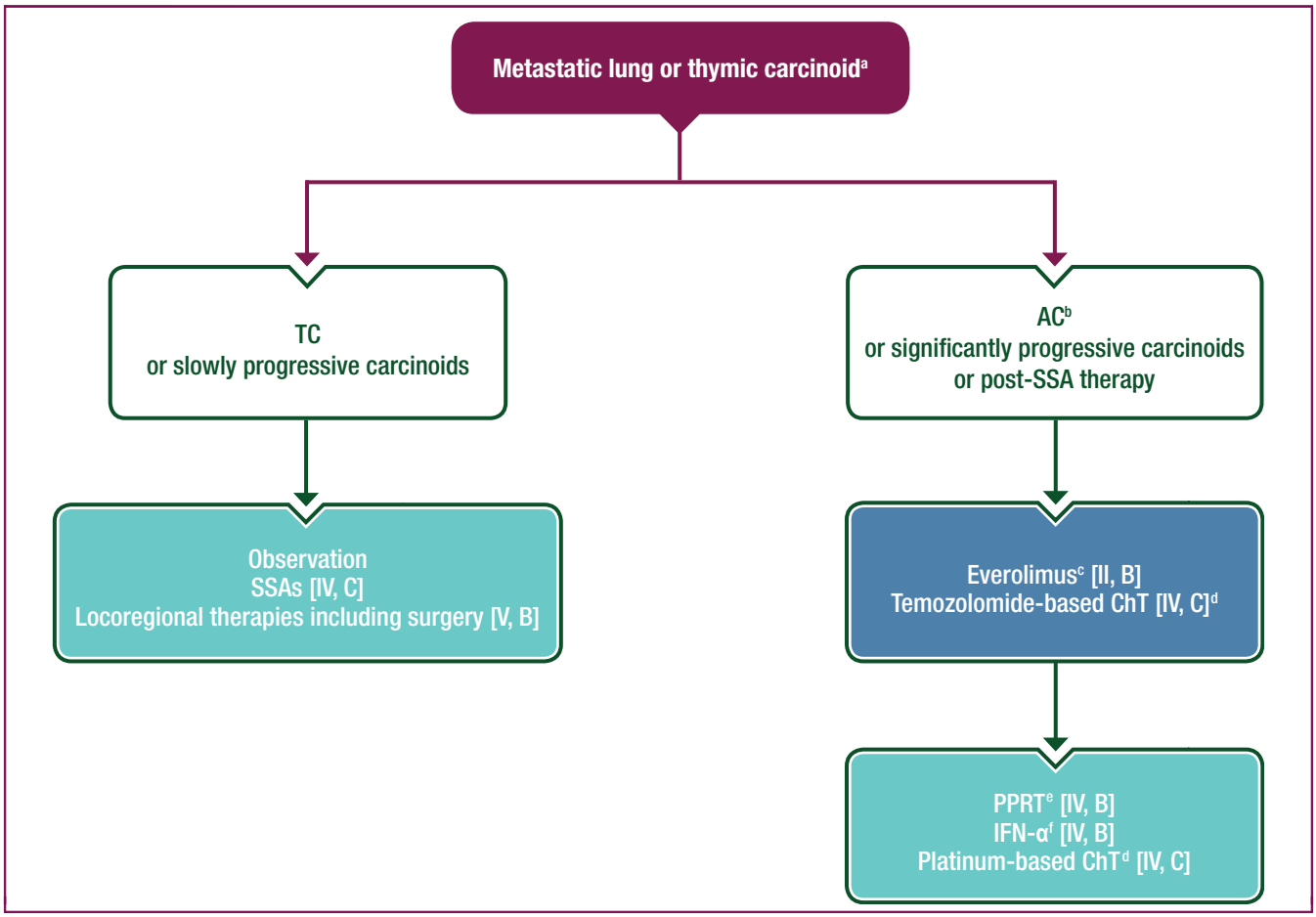

Figure 3. Treatment of functioning syndromes.
In patients with refractory CS, a variety of options exist but there is no consensus on the best strategy, due to the lack of specific LC studies.
ChT, chemotherapy; CS, carcinoid syndrome; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; IFN-α, interferon-α; LC, lung carcinoid; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.
[a] Telotristat ethyl is the only second-line EMA- and FDA-approved agent in patients with refractory diarrhoea due to the carcinoid syndrome. When second-line treatment is given for controlling CS, distinct from increased SSA dose or pasireotide, SSA therapy should be maintained until a significant improvement of CS is observed.

LC patients were enrolled in several antiangiogenic phase II trials,[82,83] dedicated to carcinoids, with partial responses documented in 10%-18% of cases. No sign of increased toxicity was reported as compared with digestive tumours. Recently, a phase III, placebo-controlled trial (SANET) was presented at ESMO 2019 showing a gain in PFS of 5.4 months [hazard ratio (HR) 0.334, 95% confidence interval (CI) 0.223-0.499, $P < 0.001$] of surufatinib compared with placebo in 198 Chinese patients including 11% LC.[84] No recommendation can be made at the present time regarding the use of antiangiogenic agents in LC (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[82-84]

Among targetable molecular alterations described in non-small-cell bronchial carcinoma, only echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangement has been described in a few LC (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[85]

ChT

Several ChT regimens have been used in metastatic LC. Cisplatin or carboplatin combined with etoposide, the standard ChT for SCLC, has also been used in LC and ThC showing an 8%-23% response rate (RR) and 7-8-month PFS.[47,66] More recently, oxaliplatin-based ChT has been reported to be active in retrospective analyses of patients with metastatic LC alone or mixed with other primary sites. Oxaliplatin combined with gemcitabine (GEMOX) or capecitabine (CAPOX) or 5-fluorouracil (FOLFOX) regimens[47,86] led to RRs up to 20% and 8-15-month PFS. Streptozocin combined with 5-fluorouracil in three randomised trials, enrolling 8%-12% LCs, resulted in 16%-22% RRs and 5-7-month PFS.[87-89] Dacarbazine- or temozolomide-based ChT has shown activity in LC and ThC: an objective RR of 10%-30% patients and a median PFS of 5-13 months has been reported (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003).[37,47,90-92] Based on the above, there is currently no shared standard ChT for

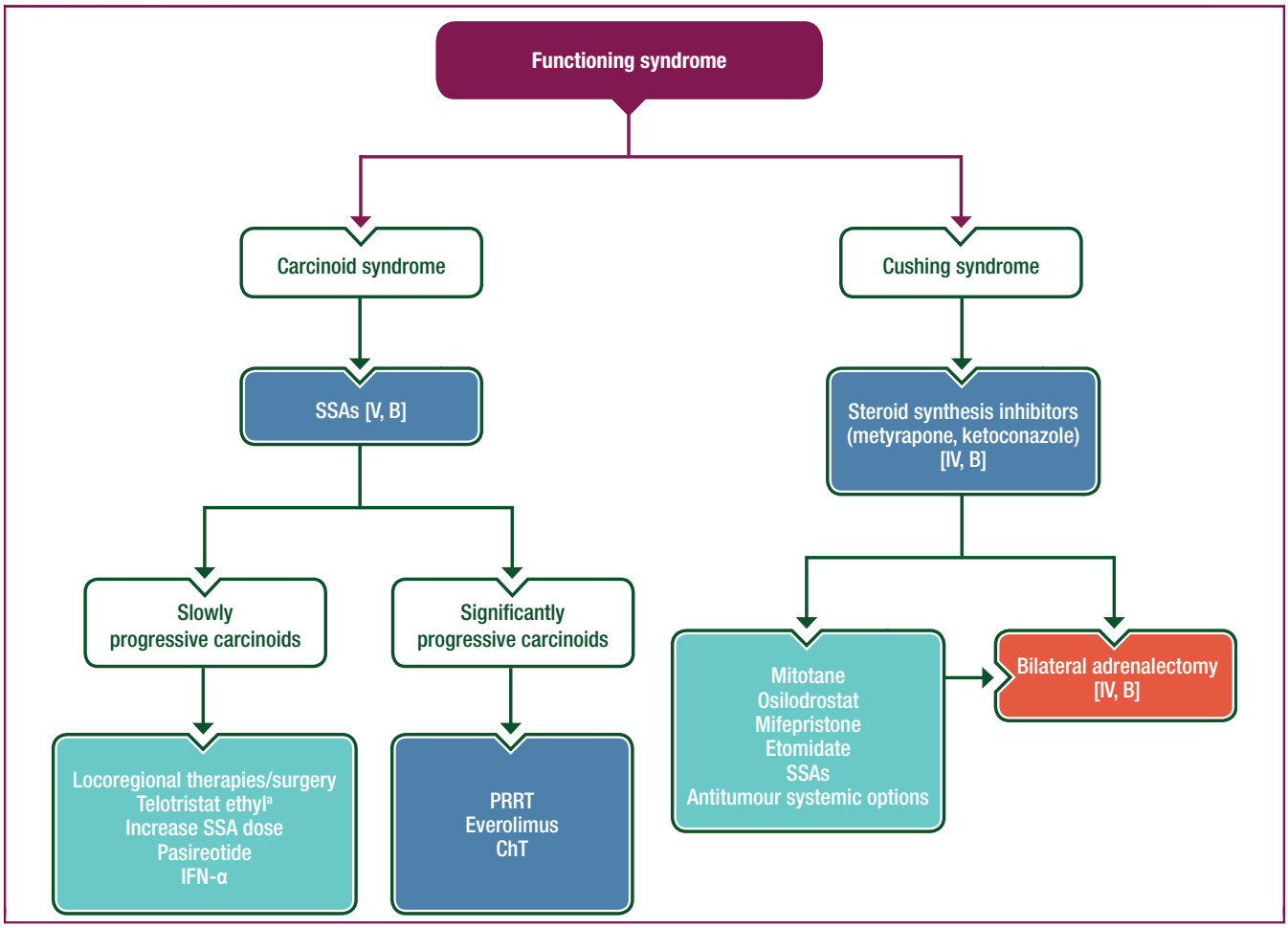

Figure 4. Treatment of unresectable/metastatic lung or thymic carcinoids.
Options are stratified according to prognosis. Best sequence remains unknown.
AC, atypical carcinoid; ChT, chemotherapy; IFN-α, interferon-α; LC, lung carcinoid; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumours; SRI, somatostatin receptor imaging; SSA, somatostatin analogue; TC, typical carcinoid; ThC, thymic carcinoid.
[a] Similar strategies are discussed in unresectable localised lung or thymic carcinoids.
[b] Including high-grade atypical carcinoids.
[c] Everolimus has the most solid evidence of efficacy available and is the only approved treatment.
[d] We recommend alkylating-based ChT as first-line ChT and platinum-based ChT (oxaliplatin-based ChT is favoured by the panel) as second-line ChT in advanced LC patients refractory or intolerant to everolimus therapy [IV, C]. In few cases, with high proliferative ACs (Ki-67 >20%) or rapid growth, platinum-based ChT might be considered upfront (alternatives or second lines include everolimus or PRRT, based on SRI results).
[e] PRRT should be considered as an alternative to ChT in selected patients (refractory carcinoid syndrome, SRI homogenous positive tumour uptake on all RECIST-evaluable targets). PRRT may be considered first line in a few SRI-positive patients with refractory carcinoid syndrome and progressing or bulky tumours.
[f] IFN-α should be considered as alternative to ChT especially if refractory carcinoid syndrome. The development of LC- and ThC-dedicated protocols is strongly encouraged.

advanced thoracic NETs. Due to better tolerance and convenience, we recommend temozolomide (± capecitabine) as first-line and platinum-based ChT as second-line options in patients with progressive advanced LC [IV, C]. Among platinum-based agents, oxaliplatin-based ChT is recommended by the majority of the panel [IV, C]. Prospective validation of predictors of response is expected to rationalise the prescription of ChT. We recommend the same strategy in patients with advanced ThC.

PRRT

In NETs, lutetium (^{177}Luoxodotreotide) (^{177}Lu-DOTATATE, Lutathera®) has been approved in Europe and the United States for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSTR-positive GEP-NETs in adults.[64,93] Several studies showed that PRRT is also effective in LC and deserves urgent prospective trials.[70,94-97] See Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003, for more details about PRRT. Only in the absence of ongoing trials to which patients could be recruited, PRRT is discussed as a potential alternative third-line or fourth-line therapy in patients with all RECIST-evaluable tumour deposits showing a positive uptake on SRI after SSA and everolimus, if available [IV, B].

IFN-α and immunotherapy

In one dedicated study, IFN-α treatment resulted in stabilisation of tumour growth in 14% of patients.[66] Two

randomised trials in carcinoids resulted in partial response (PR) of 4%-9% and median PFS of 14-15 months in the IFN-α arm, whether or not combined with SSAs.[64,98] Based on these results, IFN-α is still considered an option in progressive metastatic LC, especially in case of uncontrolled CS [IV, B]. Although the preclinical rationale is weak, immunotherapy is currently being evaluated in NETs with several active trials (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003)[99] and no conclusion can be drawn yet.

High proliferative LC

Based on available data in digestive NETs (GEP-NET G3 subgroup) but also preliminary data in high proliferative LC, the authors recommend treating these patients like they have aggressive AC and not poorly differentiated carcinomas.[42,100] Everolimus, ChT and, in selected patients, PRRT, constitute the recommended options in this rare subgroup of patients [V C].

Recommendations

- Systemic options should be discussed in an interdisciplinary setting in patients with advanced carcinoids with bulky tumour or progressing tumours at morphological imaging
- SSAs are recommended first-line treatment in patients with TC and/or slowly progressing advanced SRI-positive LC and ThC [IV, C]
- Everolimus is recommended either as first line in case of AC or, second-line post-SSA, in patients with TC and or progressive advanced LCs and ThCs [II, B]
- Dacarbazine/temozolomide-based ChT as first line, and platinum-based ChT as second line, are recommended in advanced LC patients refractory or intolerant to everolimus therapy [IV, C]
- PRRT (based on positive uptake at SRI on all RECIST-evaluable targets) as alternative second-line (in case of uncontrolled CS) or mainly third-line therapy (beyond SSAs and or everolimus) in morphologically progressive or high tumour burden advanced LC and ThCs is recommended [IV, B]
- IFN-α as a potential second-line (in case of uncontrolled CS) or mainly third-line alternative (beyond SSAs and or everolimus) is recommended in morphologically progressive or high tumour burden advanced LC and ThCs [IV, B]
- Upfront everolimus or dacarbazine/temozolomide-based or oxaliplatin-based ChT is recommended, or in selected subgroup PRRT (based on positive uptake at SRI on all RECIST-evaluable targets) in high proliferative ACs [V, C]
- Since there is limited evidence of efficacy for all treatment options, clinical trials should be prioritised.

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Follow-up for LCs should be life-long, since recurrences remain very common over time [IV, C].[4,7,18,50,51,101-103] Recommendations for follow-up are given in Supplementary Material and Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2021.01.003.

Thymic NET recurrences may be local (if located in the anterior mediastinum), regional (intrathoracic especially pleural) or distant (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.003). Radically resected disease and not radically resected, or disseminated disease, should be followed as AC of the lung [V, B]. Patients with disseminated disease may benefit from affiliation to specialised palliative care units concerning pain treatment, psychosocial impact and rehabilitation [II, B].

Recommendations

- Follow-up for LC should be life-long, since recurrences remain very common over time [IV, C]
- After radical resection of LC, life-long follow-up with low-radiation imaging procedures and increasing interval of time, adjusted to prognostic factors, is recommended [V, C]
- Follow-up of LC and ThC patients focuses on tumour and functioning syndrome evaluations as well as evaluations of long-term toxicity and specific conditions including DIPNECH or MEN-1 [V, B]
- In patients with advanced tumours, morphological follow-up is recommended every 2-12 months depending on WHO histology, tumour growth rate and control of functioning syndrome [V, C]
- Follow-up of ThC is recommended in all patients in a similar manner to ACs [V, B]
- Patients with disseminated disease may benefit from affiliation to specialised palliative care units concerning pain treatment, psychosocial impact and rehabilitation [II, B].

METHODOLOGY

This Clinical Practice Guideline was developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development, https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. An ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) table with ESMO-MCBS scores is included in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2021.01.003. ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2021.01.003.[105] Statements without grading were considered justified standard clinical practice by the authors.

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EB has received honoraria from Novartis, Ipsen and Pfizer, research grants from Novartis and he is a member of Ipsen and Novartis speaker's bureau; MC has received research funding and speaker/advisory board honoraria from Ipsen, Novartis, Lexicon and AAA-Pharma; RGC has reported being an advisory board member for Novartis, Ipsen, AAA-Pharma and Pfizer and has received research grants from Pfizer; NF has received honoraria from Novartis, Ipsen, Pfizer, AAA-Pharma, Merck Sharp & Dohme and Merck Serono and research grants from Novartis and Merck Serono; PF has reported advisory board for Novartis, Ipsen, Merck Serono, Pfizer, Lexicon and Italfarmaco and has participated at steering committee for Novartis, Ipsen and Merck Serono; AF is a member of speaker's bureau and has received honoraria from Ipsen, Novartis and Sirtex and has received research grants from Novartis; WWdH has received research grants from Ipsen; DH has received honoraria from Novartis, Ipsen, Pfizer and ROTOP Pharmaka GmbH and research grants from Ipsen and he is a member of Ipsen and Novartis speaker's bureau; UK has received research funding and speaker advisory board honoraria from Ipsen and Novartis; CLB has reported being an advisory board member for Novartis, Pfizer, Ipsen and AAA-Pharma; MP has reported being an advisory board member for and received honoraria from Novartis, Ipsen, Pfizer and Lexicon and has received research grants from Ipsen and Novartis; AB is a member of Novartis speaker's bureau; all other authors have declared no conflicts of interest.

REFERENCES

1. Travis WD, Brambilla E, Burke AP, et al., eds. *Classification of Tumours of the Lung, Pleura, Thymus and Heart*. 4th ed. IARC Press; 2015.
2. 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;3:1335-1342.
3. Korse CM, Taal BG, van Velthuysen MLF, et al. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. *Eur J Cancer*. 2013;49:1975-1983.
4. García-Yuste M, Matilla JM, Cañizares MA, et al. Surgical treatment of low and intermediate grade lung net. *J Thorac Dis*. 2017;9:S1435-S1441.
5. García-Yuste M, Matilla JM, Cueto A, et al. Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multicentric Study of Neuroendocrine Tumours of the Lung. *Eur J Cardiothorac Surg*. 2017;31:192-197.
6. Filosso PL, Guerrera F, Evangelista A, et al. Prognostic model of survival for typical bronchial carcinoid tumours: analysis of 1109 patients on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours Working Group. *Eur J Cardiothorac Surg*. 2015;48:441-447.
7. Filosso PL, Rena O, Guerrera F, et al. Clinical management of atypical carcinoid and large-cell neuroendocrine carcinoma: a multicentre study on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours of the Lung Working Group. *Eur J Cardiothorac Surg*. 2015;48:55-64.
8. Steuer CE, Behera M, Kim S, et al. Atypical carcinoid tumor of the lung: a surveillance, epidemiology, and end results database analysis. *J Thorac Oncol*. 2015;10:479-485.
9. Nussbaum DP, Speicher PJ, Gulack BC, et al. Defining the role of adjuvant chemotherapy after lobectomy for typical bronchopulmonary carcinoid tumors. *Ann Thorac Surg*. 2015;99:428-434.
10. Anderson KL, Mulvihill MS, Speicher PJ, et al. Adjuvant chemotherapy does not confer superior survival in patients with atypical carcinoid tumors. *Ann Thorac Surg*. 2017;104:1221-1230.
11. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. *Ann Surg*. 2010;251:1117-1121.
12. Filosso PL, Yao X, Ahmad U, et al. Outcome of primary neuroendocrine tumors of the thymus: a joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases. *J Thorac Cardiovasc Surg*. 2015;149:103-109.
13. Sullivan JL, Weksler B. Neuroendocrine tumors of the thymus: analysis of factors affecting survival in 254 patients. *Ann Thorac Surg*. 2017;103:935-939.
14. de Laat JM, Pieterman CR, van den Broek MF, et al. Natural course and survival of neuroendocrine tumors of thymus and lung in MEN1 patients. *J Clin Endocrinol Metab*. 2014;99:3325-3333.
15. Ye L, Wang W, Ospina NS, et al. Clinical features and prognosis of thymic neuroendocrine tumours associated with multiple endocrine neoplasia type 1: a single-centre study, systematic review and meta-analysis. *Clin Endocrinol*. 2017;87:706-716.
16. Bartsch DK, Albers MB, Lopez CL, et al. Bronchopulmonary neuroendocrine neoplasms and their precursor lesions in multiple endocrine neoplasia type 1. *Neuroendocrinology*. 2016;103:240-247.
17. Lecomte P, Binquet C, Le Bras M, et al. Histologically proven bronchial neuroendocrine tumors in MEN1: a GTE 51-case cohort study. *World J Surg*. 2018;42:143-152.
18. Daddi N, Schiavon M, Filosso PL, et al. Prognostic factors in a multicentre study of 247 atypical pulmonary carcinoids. *Eur J Cardiothorac Surg*. 2014;45:677-686.
19. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18:525-534.
20. Ferolla P, Brizzi MP, Meyer T, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2017;18:1652-1664.
21. Lim E, Yap YK, De Stavola BL, et al. The impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors. *J Thorac Cardiovasc Surg*. 2005;130:969-972.
22. Filosso PL, Öbergrather K, Malczewska AV, et al. Molecular identification of bronchopulmonary neuroendocrine tumours and neuroendocrine genotype in lung neoplasia using the NETest liquid biopsy. *Eur J Cardiothorac Surg*. 2020;57:1195-1202.
23. Ferolla P, Daddi N, Urbani M, et al. Tumorlets, multicentric carcinoids, lymph-nodal metastases, and long-term behavior in bronchial carcinoids. *J Thorac Oncol*. 2009;4:383-387.
24. Mengoli MC, Rossi G, Cavazza A, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) syndrome and carcinoid tumors with/without NECH: a clinicopathologic, radiologic, and immunomolecular comparison study. *Am J Surg Pathol*. 2018;42:646-655.
25. Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F-DOPA. *Eur J Nucl Med Mol Imaging*. 2017;44:1588-1601.
26. Prasad V, Steffen IG, Pavel M, et al. Somatostatin receptor PET/CT in restaging of typical and atypical lung carcinoids. *EJNMMI Res*. 2015;5:53.
27. Lamarca A, Pritchard DM, Westwood T, et al. 68Gallium DOTANOC-PET imaging in lung carcinoids: impact on patients' management. *Neuroendocrinology*. 2018;106:128-138.
28. Gasparri R, Rezende GC, Fazio N, et al. Fluorodeoxyglucose positron emission tomography in pulmonary carcinoid tumors. *Q J Nucl Med Mol Imaging*. 2015;59:446-454.
29. Cattoni M, Vallières E, Brown LM, et al. Is there a role for traditional nuclear medicine imaging in the management of pulmonary carcinoid tumours? *Eur J Cardiothorac Surg*. 2017;51:874-879.

30. Pattenden HA, Leung M, Beddow E, et al. Test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumours. *Thorax*. 2015;70:379-381.
31. Brierley J, O'Sullivan B, Asamura H, et al. Global Consultation on Cancer Staging: promoting consistent understanding and use. *Nat Rev Clin Oncol*. 2019;6:763-771.
32. Zhao Y, Gu H, Fan L, et al. Comparison of clinical features and survival between thymic carcinoma and thymic carcinoid patients. *Eur J Cardiothorac Surg*. 2017;52:33-38.
33. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. *Am J Clin Pathol*. 2000;114:100-110.
34. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012;97:2990-3011.
35. Girard N, Ruffini E, Marx A, et al. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v40-v55.
36. Ströbel P, Zettl A, Shilo K, et al. Tumor genetics and survival of thymic neuroendocrine neoplasms: a multi-institutional clinicopathologic study. *Genes Chromosomes Cancer*. 2014;53:738-749.
37. Crona J, Björklund P, Welin S, et al. Treatment, prognostic markers and survival in thymic neuroendocrine tumours. A study from a single tertiary referral centre. *Lung Cancer*. 2013;79:289-293.
38. Fernandez-Cuesta L, Peifer M, Lu X, et al. Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. *Nat Commun*. 2014;5:3518.
39. Simbolo M, Mafficini A, Sikora KO, et al. Lung neuroendocrine tumours: deep sequencing of the four World Health Organization histotypes reveals chromatin-remodelling genes as major players and a prognostic role for TERT, RB1, MEN1 and KMT2D. *J Pathol*. 2017;241:488-500.
40. Simbolo M, Barbi S, Fassan M, et al. Gene expression profiling of lung atypical carcinoids and large cell neuroendocrine carcinomas identifies three transcriptomic subtypes with specific genomic alterations. *J Thorac Oncol*. 2019;14:1651-1661.
41. Oka N, Kasajima A, Konukiewitz B, et al. Classification and prognostic stratification of bronchopulmonary neuroendocrine neoplasms. *Neuroendocrinology*. 2020;110:393-403.
42. Vélayoudom-Céphise F-L, Duvillard P, Foucan L, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer*. 2013;20:649-657.
43. Rekhtman N, Desmeules P, Litvak AM, et al. Stage IV lung carcinoids: spectrum and evolution of proliferation rate, focusing on variants with elevated proliferation indices. *Mod Pathol*. 2019;32:1106-1122.
44. Dinter H, Bohnenberger H, Beck J, et al. Molecular classification of neuroendocrine tumors of the thymus. *J Thorac Oncol*. 2019;14:1472-1483.
45. Grøndahl V, Binderup T, Langer SW, et al. Characteristics of 252 patients with bronchopulmonary neuroendocrine tumours treated at the Copenhagen NET Centre of Excellence. *Lung Cancer*. 2019;132:141-149.
46. Yoon JY, Sigel K, Martin J, et al. Evaluation of the prognostic significance of TNM staging guidelines in lung carcinoid tumors. *J Thorac Oncol*. 2019;14:184-192.
47. Robelin P, Hadoux J, Forestier J, et al. Characterization, prognosis, and treatment of patients with metastatic lung carcinoid tumors. *J Thorac Oncol*. 2019;14:993-1002.
48. Kneuertz PJ, Kamel MK, Stiles BM, et al. Incidence and prognostic significance of carcinoid lymph node metastases. *Ann Thorac Surg*. 2018;106:981-988.
49. Travis WD, Rush W, Flieder DB, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. *Am J Surg Pathol*. 1998;22:934-944.
50. Cattoni M, Vallières E, Brown LM, et al. Improvement in TNM staging of pulmonary neuroendocrine tumors requires histology and regrouping of tumor size. *J Thorac Cardiovasc Surg*. 2018;155:405-413.
51. Marciello F, Mercier O, Ferolla P, et al. Natural history of localized and locally advanced atypical lung carcinoids after complete resection: a joined French-Italian retrospective multicenter study. *Neuroendocrinology*. 2018;106:264-273.
52. Rindi G, Klersy C, Inzani F, et al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. *Endocr Relat Cancer*. 2014;21:1-16.
53. Marchiò C, Gatti G, Massa F, et al. Distinctive pathological and clinical features of lung carcinoids with high proliferation index. *Virchows Arch*. 2017;471:713-720.
54. Raz DJ, Nelson RA, Grannis FW, et al. Natural history of typical pulmonary carcinoid tumors: a comparison of nonsurgical and surgical treatment. *Chest*. 2015;147:1111-1117.
55. Huang Y, Yang X, Lu T, et al. Assessment of the prognostic factors in patients with pulmonary carcinoid tumor: a population-based study. *Cancer Med*. 2018;7:2434-2441.
56. Brown LM, Cooke DT, Jett JR, et al. Extent of resection and lymph node assessment for clinical stage T1aN0M0 typical carcinoid tumors. *Ann Thorac Surg*. 2018;105:207-213.
57. Filosso PL, Guerrera F, Falco NR, et al. Anatomical resections are superior to wedge resections for overall survival in patients with Stage 1 typical carcinoids. *Eur J Cardiothorac Surg*. 2019;55:273-279.
58. Chen X, Pang Z, Wang Y, et al. The role of surgery for atypical bronchopulmonary carcinoid tumor: development and validation of a model based on Surveillance, Epidemiology, and End Results (SEER) database. *Lung Cancer*. 2020;139:94-102.
59. Brandolini J, Bertolaccini L, Pardolesi A, et al. Surgical treatment of synchronous multiple neuroendocrine lung tumours (case series): is more always better? *Ann Transl Med*. 2017;5:423.
60. Brierley J, Gospodarowicz MK, Wittekind C. eds., Union for International Cancer Control. *TNM Classification of Malignant Tumours*. 8th ed. Wiley-Blackwell; 2017:1-241.
61. Zandee WT, Kamp K, van Adrichem RC, et al. Effect of hormone secretory syndromes on neuroendocrine tumor prognosis. *Endocr Relat Cancer*. 2017;24:R261-R274.
62. Reuling EMBP, Dickhoff C, Plaisier PW, et al. Endobronchial treatment for bronchial carcinoid: patient selection and predictors of outcome. *Respiration*. 2018;95:220-227.
63. Kaltsas G, Caplin M, Davies P, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pre- and perioperative therapy in patients with neuroendocrine tumors. *Neuroendocrinology*. 2017;105:245-254.
64. Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31:844-860.
65. Al-Toubah T, Strosberg J, Halfdanarson T, et al. Somatostatin analogs improve respiratory symptoms in patients with diffuse idiopathic neuroendocrine cell hyperplasia. *Chest*. 2020;158:401-405.
66. Granberg D, Eriksson B, Wilander E, et al. Experience in treatment of metastatic pulmonary carcinoid tumors. *Ann Oncol*. 2001;12:1383-1391.
67. Frilling A, Modlin IM, Kidd M, et al. Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol*. 2014;15:e8-e21.
68. de Baere T, Deschamps F, Tselikas L, et al. GEP-NETS update. Interventional radiology: role in the treatment of liver metastases from GEP-NETs. *Eur J Endocrinol*. 2015;172:R151-R166.
69. Bushnell DL, O'Dorisio TM, O'Dorisio MS, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. *J Clin Oncol*. 2010;28:1652-1659.
70. Hicks RJ, Kwekkeboom DJ, Krenning E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. *Neuroendocrinology*. 2017;105:295-309.
71. Pavel ME, Hainsworth JD, Baudin E, et al, RADIANT-2 Study Group. 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;378:2005-2012.
72. Young J, Haissaguerre M, Viera-Pinto O, et al. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. *Eur J Endocrinol*. 2020;182:R29-R58.
73. Fairweather M, Swanson R, Wang J, et al. Management of neuroendocrine tumor liver metastases: long-term outcomes and prognostic factors from a large prospective database. *Ann Surg Oncol*. 2017;24:2319-2325.
74. Deschamps F, Farouil G, Ternes N, et al. Thermal ablation techniques: a curative treatment of bone metastases in selected patients? *Eur Radiol*. 2014;24:1971-1980.
75. Frilling A, Clift AK, Braat AJAT, et al. Radioembolisation with 90Y microspheres for neuroendocrine liver metastases: an institutional case series, systematic review and meta-analysis. *HPB*. 2019;21:773-783.
76. Sullivan I, Le Teuff G, Guigay J, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids. *Eur J Cancer*. 2017;75:259-267.
77. Bongiovanni A, Recine F, Riva N, et al. Outcome analysis of first-line somatostatin analog treatment in metastatic pulmonary neuroendocrine tumors and prognostic significance of 18FDG-PET/CT. *Clin Lung Cancer*. 2017;18:415-420.
78. Yao JC, Fazio N, Singh S, et al, RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. 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;387:968-977.
79. Fazio N, Buzzoni R, Delle Fave G, et al. Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis. *Cancer Sci*. 2018;109:174-181.
80. Pavel ME, Singh S, Strosberg JR, et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1411-1422.
81. Fazio N, Granberg D, Grossman A, et al. Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study. *Chest*. 2013;143:955-962.
82. Castellano D, Capdevila J, Sastre J, et al. Sorafenib and bevacizumab combination targeted therapy in advanced neuroendocrine tumour: a phase II study of Spanish Neuroendocrine Tumour Group (GETNE0801). *Eur J Cancer*. 2013;49:3780-3787.
83. Berruti A, Fazio N, Ferrero A, et al. Bevacizumab plus octreotide and metronomic capecitabine in patients with metastatic well-to-moderately differentiated neuroendocrine tumors: the XELBEVOCT study. *BMC Cancer*. 2014;14:184.
84. Xu J, Shen I, Shou Z, et al. Efficacy and safety of surufatinib in patients with well differentiated advanced extra-pancreatic neuoendocrine tumors (NETs): results from the randomized phase III study (SANET-ep). *Ann Oncol*. 2019;30:v851-v934.
85. Nakamura H, Tsuta K, Yoshida A, et al. Aberrant anaplastic lymphoma kinase expression in high-grade pulmonary neuroendocrine carcinoma. *J Clin Pathol*. 2013;66:705-707.
86. Spada F, Antonuzzo L, Marconcini R, et al. Oxaliplatin-based chemotherapy in advanced neuroendocrine tumors: clinical outcomes and preliminary correlation with biological factors. *Neuroendocrinology*. 2016;103:806-814.
87. Engstrom PF, Lavin PT, Moertel CG, et al. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. *J Clin Oncol*. 1984;2:1255-1259.
88. Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. *Cancer Clin Trials*. 1979;2:327-334.
89. Sun W, Lipsitz S, Catalano P, et al. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol*. 2005;23:4897-4904.
90. Ferolla P, Berruti A, Spada F, et al. 1161MO Lanreotide autogel (LAN) and temozolomide (TMZ) combination therapy in progressive thoracic neuroendocrine tumours (TNETs): ATLANT study results. *Ann Oncol*. 2020;31(suppl 4):S773.
91. Saranga-Perry V, Morse B, Centeno B, et al. Treatment of metastatic neuroendocrine tumors of the thymus with capecitabine and temozolomide: a case series. *Neuroendocrinology*. 2013;97:318-321.
92. Al-Toubah T, Morse B, Strosberg J. Capecitabine and temozolomide in advanced lung neuroendocrine neoplasms. *Oncologist*. 2020;25(1):e48-e52.
93. Strosberg J, El-Haddad G, Wolin E, et al. NETTER-1 trial investigators: phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125-135.
94. Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. *Eur J Nucl Med Mol Imaging*. 2016;43:1040-1046.
95. Sabet A, Haug AR, Eiden C, et al. Efficacy of peptide receptor radionuclide therapy with 177Lu-octreotate in metastatic pulmonary neuroendocrine tumors: a dual-centre analysis. *Am J Nucl Med Mol Imaging*. 2017;7:74-83.
96. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol*. 2011;29:2416-2423.
97. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [177Lu-DOTA0,Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res*. 2017;23:4617-4624.
98. Yao JC, Guthrie KA, Moran C, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. *J Clin Oncol*. 2017;35:1695-1703.
99. Naing A, Gainor JF, Gelderblom H, et al. A first-in-human phase 1 dose escalation study of spartalizumab (PDR001), an anti-PD-1 antibody, in patients with advanced solid tumors. *J Immunother Cancer*. 2020;8:e000530.
100. Rubino M, Scoazec JY, Pisa E, et al. Lung carcinoids with high proliferative activity: further support for the identification of a new tumor category in the classification of lung neuroendocrine neoplasms. *Lung Cancer*. 2020;148:149-158.
101. Lou F, Sarkaria I, Pietanza C, et al. Recurrence of pulmonary carcinoid tumors after resection: implications for postoperative surveillance. *Ann Thorac Surg*. 2013;96:1156-1162.
102. Ferolla P, Daddi N, Puma F, et al. Postsurgical follow-up is always necessary in bronchial carcinoid. *Ann Thorac Surg*. 2014;98:1143-1144.
103. Rea F, Rizzardi G, Zuin A, et al. Outcome and surgical strategy in bronchial carcinoid tumors: single institution experience with 252 patients. *Eur J Cardiothorac Surg*. 2007;31:186-191.
104. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol*. 2017;28:2340-2366.
105. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33:139-144.