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ENETS Consensus Guidelines for the Management of Bone and Lung Metastases from Neuroendocrine Tumors

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Introduction

Gastroenteropancreatic (GEP) neuroendocrine tumors (NET) are rare tumors with a low incidence of at least 3–5/100,000 but a considerably higher prevalence of 35/100,000 [1]. The majority of patients at the time of diagnosis are found to have an advanced stage of the disease. Bone metastasis is not an infrequent complication in most neoplasms and has been found in 70–85% of cancer patients at autopsy [2]. GEP-NET bone metastases frequently remain undetected. They are often accompanied by widespread extraosseous metastases and are found to occur predominantly in patients with liver metastases [3, 4]. It is thought that lung metastases occur with a similar frequency to bone metastases [5].

[1] See list at the end of the paper.

Epidemiology

Bone Metastases

In a recent study of 668 NET patients in France, bone metastases were found in 6.4% [6]. A review of 26-year records from the M.D. Anderson Cancer Center database identified 1,633 patients with carcinoid tumors where 18% of patients had metastases to bone and soft tissues [5]. Meijer et al. [4] recently reported a retrospective study where bone metastases were found in 12% of carcinoid patients. Generally, metastases to bone are relatively uncommon in carcinoid disease (7–15% of all metastases) and are often reported as multiple [3, 4, 7]. The incidence of bone metastases remains underestimated as they are frequently undetected or simply not focused on. In a small postmortem study, 42% of patients had bone metastases compared to only 4% detected in live patients with advanced disease [8, 9]. Introduction of new diagnostic modalities (e.g. sensi-

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tive scintigraphic/PET modalities) may reveal asymptomatic bone metastases, thus increasing the overall rate of detection of bone metastases in living patients. Bone metastases may occur at any time, from long before the diagnosis to even 20 years after the initial presentation. No clear time pattern has been noted to facilitate prediction of their occurrence [10]. NET bone metastasis distribution is comparable to that found in non-NET tumors [3]. Opinions regarding the influence of the primary tumor site on the development of bone metastases vary. According to some authors, bone metastases arise more often from foregut or hindgut rather than from midgut tumors. Other studies suggest no preferential primary site [3, 4]. NETs originating from the lungs metastasized (15%) mainly to liver, bone, adrenal glands, and brain [11]. Diagnosis of metastases occurred synchronously with the diagnosis of the primary bronchial carcinoid in all cases [12].

Lung Metastases

GEP-NET lung metastases are relatively uncommon, occurring in 13.6% based on the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) vast database [13]. In a recent French study [6] lung metastases were found in 5.1% while a review of the M.D. Anderson Cancer Center database identified 6% metastases to the lung [5].

Minimal Consensus Statements on Epidemiology

According to the literature, 4–15% of NET metastases develop in bone; similarly lung metastases represent around 5–14%. In the majority of cases, they are found in the advanced stage of the disease (usually stage IV).

The incidence of bone and lung metastases is almost certainly underestimated as these metastases are often asymptomatic and omitted in routine diagnostics.

Clinical Presentation

Bone Metastases

Bone metastases are clinically detected in a low percentage of patients with advanced NET tumors [8].

Characteristic symptoms for bone metastases are: (1) pain, principal symptom, which can be accompanied by (2) pathological fractures and/or (3) symptoms from hypercalcemia [3, 4].

Pain is the main symptom of bone metastases, but only occurs in a minority and can affect work, locomotion, mood, sleep, relations with others, and enjoyment of life [2]. Bone metastases are more often asymptomatic and frequently detected incidentally during staging of GEP-NET disease [3, 4].

Lung Metastases

Symptoms associated with lung metastases are rare. Patients may present with cough, hemoptysis and pneumonia (classical triad) representing the sequel of luminal obstruction and tumor ulceration [14]. The clinical manifestations of endocrine tumors are determined by the functional status of the tumor [15]. In patients with nonfunctional tumors, symptoms depend on tumor load and the location of the metastases. In bone and lung metastases originating from functional NETs, symptoms can be accompanied by characteristic syndromes which depend on the hypersecretion of the specific hormones from primary tumor such as carcinoid syndrome, hypoglycemic syndrome in insulinoma, Zollinger-Ellison syndrome in gastrinoma, necrolytic migratory erythema in glucagonoma or watery diarrhea, hypokalemia and achlorhydria syndrome characteristic for VIPoma (see ENETS Guidelines) [14, 16–27]. Ectopic hormone production from lung metastases (i.e. ACTH, cortisol, IGF-1) can also be the cause of some symptoms.

Prognosis

The stage of disease significantly influences the overall prognosis of well-differentiated GEP-NET. The best 5-year survival rate is for localized disease at 93% and 5-year survival rates in distant metastatic disease are between 20 and 30%. Distant metastases are found in 22% of cases, half of which have unknown primaries [2, 4, 7]. Recent data from the US SEER and the Norwegian Registry of Cancer (NRC) database reported 5-year survival of approximately 55% [1]. Among over 4,000 cases of malignant GEP-NET registered in the UK, relative survival for all NET was 46% at 5 years and 38% at 10 years. Five-year survival was 57% for well-differentiated tumors but a worse prognosis was reported for poorly differentiated tumors (only 5.2% survive for 5 years) [28].

Bone Metastases

Bone metastases are usually accompanied by metastases at other distant sites; however, literature regarding the direct influence of bone metastases on overall survival is unavailable. Less than 50% of patients with metastatic GEP tumors survive 5 years with hepatic and bone metastases being the major causes of death [29].

Lung Metastases

The type of tumor influences survival, as well as its histology and differentiation, disease-free interval, number of metastases, and the presence of mediastinal nodal disease [12]. The lowest 5-year survival rate is found among patients with poorly differentiated tumors with distant metastatic disease at diagnosis.

The overall median survival may be as little as 6 months in patients with pulmonary metastases. According to Khan et al. [12], the computed overall 5-year survival is 61% in NET patients with surgically resectable pulmonary metastatic disease.

Minimal Consensus Statements on Clinical Presentation and Prognosis

Most bone metastases are asymptomatic. When symptoms occur, this may be accompanied by pathological fractures and symptoms associated with hypercalcemia. Most lung metastases are asymptomatic; however, a minority of patients may develop cough, hemoptysis or pneumonia.

Bone and lung metastases appear in advanced disease often associated with other distant metastases.

Based on available literature, the direct influence of individual metastases on NET patients' prognosis is difficult to evaluate. In patients with resectable lung metastases, surgery may increase the overall 5-year survival to over 60%. Among factors influencing survival are the type of primary tumor, its histology and differentiation, disease-free interval, number of metastases, and the presence of other distant metastases.

Diagnostic Procedures

Imaging

For localization of metastatic disease the combined use of cross-sectional (anatomic) and functional imaging methods is always recommended. Single individual methods are not sensitive and specific enough for NET. High-resolution contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are excellent for the detection of metastatic disease. Somatostatin receptor scintigraphy (SRS) most commonly with ^{111}In-pentetreotide (^{111}In-Octreoscan) is widely used because most NETs express somatostatin receptors predominantly subtype 2 [30]. The protocol for ^{111}In- Octreoscan needs to include single photon emission tomography which increases sensitivity. Scintigraphy with technetium (^{99m}Tc-HYNIC-TOC, ^{99m}Tc-HYNIC-TATE or ^{99m}Tc-depreotide) is also used as a sensitive and cost-effective method [30, 31]. SRS is a sensitive method for localizing radiologically occult NET, with a reported sensitivity of 80–100% [32]. This whole-body imaging technique may provide important information about unsuspected metastatic disease. No functional imaging test is perfect; therefore, a combination of different imaging modalities may be required to facilitate the diagnosis. Computer-aided fusion of anatomic and functional image data has been shown to increase the precision of metastatic disease location. Hybrid PET/CT has recently proved to be highly accurate for detection of NET metastases [33]. PET as a single modality does not currently play a major role in the imaging of well-differentiated tumor metastases, because of their slow growth and low metabolic rate. FDG PET may be helpful in staging high-grade, often poorly differentiated NETs. Other PET radiotracers, such as fluorodopa ^{18}F, and ^{68}Ga-labeled radiopharmaceuticals may significantly improve future diagnostics of NET metastases. However, these radiotracers are not commonly available [34, 35].

Bone Metastases

The following imaging methods are useful in the detection of bone metastases:

(1) Localized techniques: (a) plain skeletal radiography and (b) MRI.

(2) Whole body imaging: (a) bone scintigraphy (with ^{99m}Tc-labeled radiopharmaceuticals, e.g. diphosphonates) and (b) SRS [or rarely ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy].

Radiographic signs of bone metastases may be easily missed [3]. MRI is considered the most sensitive technique for demonstrating bone metastases in patients with NETs and it is recommended for precise monitoring of response to therapy [36]. MRI is the most sensitive method of detecting metastases in bone marrow, with a sensitivity of nearly 100% [4] (fig. 1a, b). If marrow deposits are sclerotic, they generally show low signal intensity on T_2-weighted images. Bone scintigraphy is the next sensitive and reliable method to detect NET bone metastases. It identifies those metastases with osteoblastic reaction. Scintigraphy performed with ^{111}In-pentetreotide or less frequently ^{123}I-MIBG may also be a useful method to detect bone metastases; however, its sensitivity is relatively low, being positive in only 50 and 20% of bone metastases, respectively [3]. Intense uptake in spleen, liver and kidneys may lead to an underestimation of uptake in the area of the vertebral column, especially the last thoracic and the first lumbar vertebra. Intense uptake in liver metastases may also lead to nonvisualization of rib metastases [37]. Bone scintigraphy has a high sensitivity of 90–100% for detection of these metastases and therefore it can be

used in patients with suspicion of bone metastases. It is superior to ^{111}In-pentetreotide and ^{131}I-MIBG scintigraphy [3, 4]. The introduction of computer workstations for image reading has facilitated viewing of CT examinations. Different window settings may easily be applied to diagnose lesions in soft tissues, lungs and bone, respectively. Also, current routine use of multiple planar reformatted CT images in the sagittal and coronal view makes it easier to evaluate bone for metastases. The sensitivity for CT when applying current interactive image interpretation routines is, therefore, in this respect, probably higher than has been reported in the literature for the previously used hard-copy reading.

MRI has a slightly higher sensitivity and specificity for bone metastases than bone scintigraphy. Both bone scintigraphy and SRS have the advantage of imaging the whole body. SRS is the first-line investigation in NET patients suspected to have metastatic disease [4].

Lung Metastases

Typical imaging procedures in lung metastases are: chest X-ray, CT/MRI with or without contrast medium, SRS, PET, combined SRS or PET with CT/MRI, endobronchial endoscopy, and transthoracic aspiration biopsy.

Lung metastases can be detected incidentally on chest radiographs. Plain X-rays are nonspecific; therefore, suspicious lesions should be confirmed by a CT of the chest to determine the extent of metastases and involvement of mediastinal lymph nodes (fig. 1c). MRI is not a routine diagnostic modality for lung imaging but may be useful if there is concern about concomitant neural foramen or brachial plexus involvement [14]. SRS can be used to detect all distant NET metastases, including those in lung (once it has been proven positive at the primary site). Combined techniques of SRS or PET with CT or MRI are especially effective (sensitivity 96–100%) for NET detection [30]. The use of ^{68}Ga-labeled octreotide or octreotate (^{68}Ga-DOTA-TOC or TATE) PET to identify NET has a sensitivity of 97%, a specificity of 92% for whole body staging, and an accuracy of 96% [14, 38]. Invasive modalities can be applied when a suspected lesion in the lung has been identified by noninvasive imaging. The visual appearance evaluation (a firm tumor mass growing into, and possibly obstructing, the lumen of a bronchus) with the use of flexible endobronchial endoscopy remains an important tool in the diagnosis of pulmonary lesions. Other alternatives are: CT-guided, percutaneous transthoracic needle biopsy (preferred for peripheral lesions), EUS and biopsy, mediastinoscopy, video-assisted thoracic surgery, and thoracotomy [14, 39].

Minimal Consensus Statement on Imaging

MRI is the most sensitive technique for demonstrating bone metastases in patients with NETs. It has slightly higher sensitivity and specificity than bone scintigraphy; the latter is the most sensitive nuclear imaging technique to detect bone metastases, superior to ^{111}In-pentetreotide and ^{131}I-MIBG scintigraphy.

Suspicious lesions found on chest X-ray should be confirmed by CT. SRS can be generally recommended to stage all NET patients with metastases with a positive primary uptake.

Combined techniques including SRS or PET with CT or MRI are being applied more frequently, which improves sensitivity in detecting all NET metastases including lung and bone. Invasive modalities such as endobronchial endoscopy or CT-guided percutaneous transthoracic needle biopsy may be useful in determining the nature of a pulmonary lesion before considering surgery.

Laboratory Tests

In patients with suspected bone and lung metastases of NET origin, the following peptide/endocrine markers can be determined: (1) chromogranin A (CgA) as a nonspecific general NET marker, (2) hormones and substances specific for a given functional tumor, depending on characteristic clinical symptoms, e.g. 5-hydroxyindoleacetic acid (5-HIAA), serotonin, gastrin, insulin, pancreatic peptide, etc., (3) parathormone, calcium, pituitary hormones (in the case of suspected multiple endocrine neoplasia) [40], and (4) parathyroid hormone-releasing peptide should be considered in patients with hypercalcemia of malignancy and in patients with low parathormone [32].

Bone Metastases

The following markers are often used for evaluation of bone metabolism although they are not specific for an NET origin: (1) serum bone-specific alkaline phosphatase (BSAP), (2) serum amino-terminal propeptide of type I procollagen determined as markers of osteoblastic activity or bone formation, and (3) serum concentration of the cross-linked amino-terminal telopeptide of type I collagen (NTx) determined as a marker of osteoclastic activity or bone resorption.

NETs usually grow slowly (i.e. well-differentiated tumors) and their influence on metabolism of surrounding normal bone is insignificant. Furthermore, when patients are treated with somatostatin analogues, growth hormone and growth factors are inhibited, which therefore may affect bone metabolism and its markers. Excess

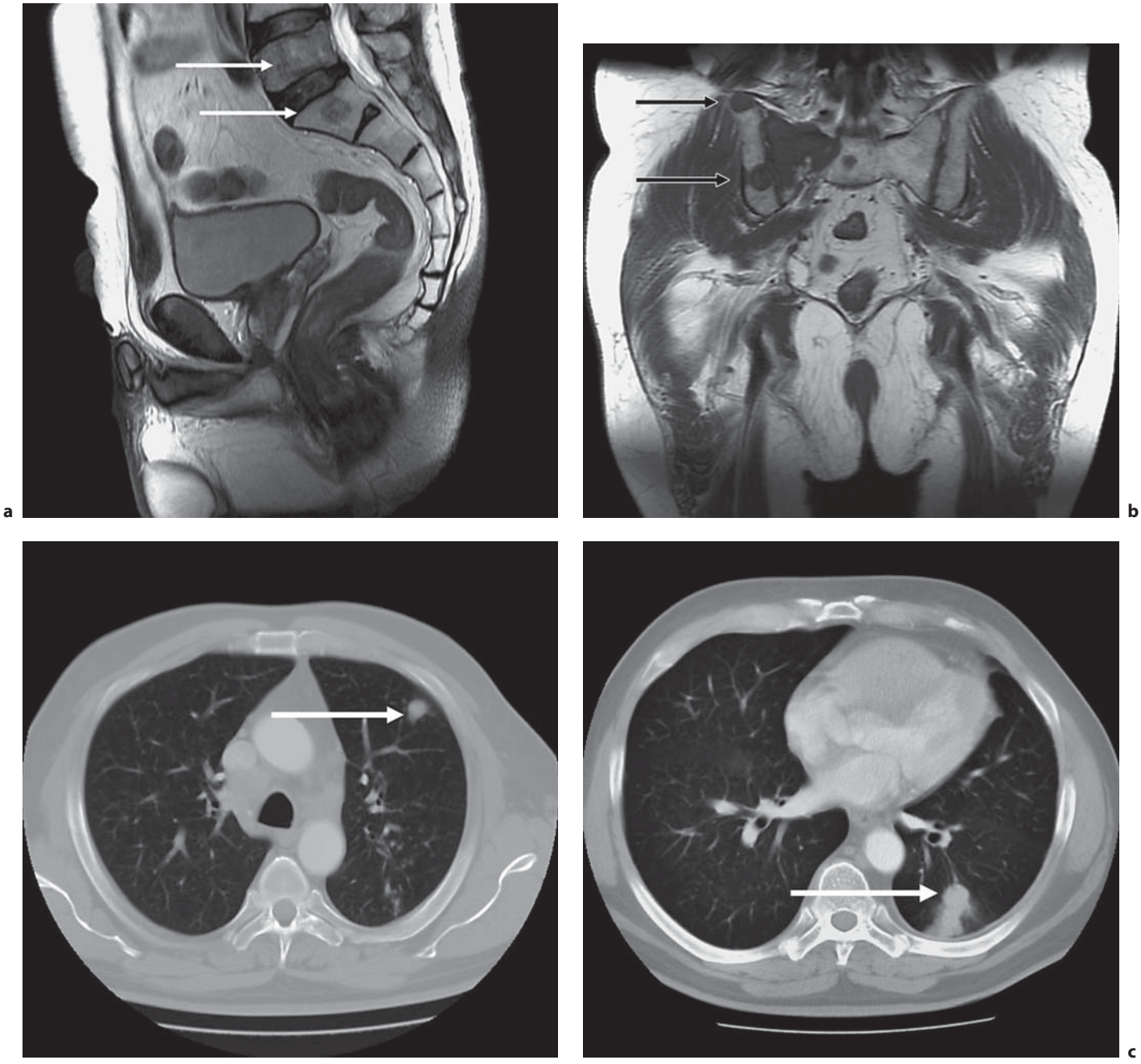

Fig. 1. Male patient aged 52 years with a well-differentiated neuroendocrine carcinoma of unknown primary origin and metastases to liver, lung and bones. **a** MRI: demonstrating metastases to L_1 and L_5 vertebrae. **b** MRI: metastases to the right sacral bone, the iliac and pubic bone on the left iliac ala. **c** Thoracic CT scan: metastatic foci in the left lung (the largest measures 13 mm in diameter) and numerous enlarged mediastinal lymph nodes.

of serotonin secretion stimulates formation of collagen and may cause ambiguous small changes in bone collagen metabolism. Possibly due to these interfering mechanisms, BSAP appeared to be the only marker useful in clinical applications [4].

Lung Metastases

Among the NET markers specified above, the following may be most often detected in hormonally active tumors: serotonin, urinary 5-HIAA and rarely ACTH, cortisol, and IGF-1. Plasma CgA may also be useful as a

marker of the response to treatment and in monitoring patients for recurrent disease [14]. These markers may also prove useful for differential diagnosis of bronchopulmonary lesions.

Minimal Consensus Statements on Laboratory Tests for Diagnosis and Follow-Up

Biochemistry utilizing CgA and specific markers depending on the functional status of primary tumor should be assessed if it had not been done earlier. Furthermore, in lung metastases, assessment of ectopic hormone levels is recommended. For bone metastases, serum BSAP is useful in clinical practice. The follow-up should involve CgA and specific NET markers (if they were previously elevated).

Pathology and Genetics

Histopathology

Bone Metastases

They are often not histologically proven. Obtaining histological proof for the presence of bone metastases is generally impractical, although CT-guided fine-needle aspiration or tru-cut biopsy is occasionally performed where the diagnosis is unclear.

Lung Metastases

Histological confirmation of the origin of lung metastases is usually not required and depends on the clinical context. Histology should be done only if it affects management. Usually detection of somatostatin receptor expression in SRS is sufficient in daily practice.

Histopathologic assessment may be required for indeterminate lesions especially if surgery is being considered. Fine-needle aspiration specimens or thoracocentesis for patients with pleural effusions can be used to confirm diagnosis, but cytologic specimens often provide limited information due to the limited ability to perform immunocytochemistry [14, 39]. Immunocytochemistry is necessary for establishing the diagnosis in core biopsies. It should include CgA and synaptophysin. In all cases, mitotic count and proliferative index need to be assessed. The following features of the tumors should also be taken into consideration before the therapeutic decision is made: (1) morphologic organ-specific criteria, (2) clinicopathologic classification (pTNM), (3) histological grading system (G), and (4) clinical staging (see relevant chapters of ENETS Guidelines) [16–27, 40].

Genetics

Hereditary predisposition to the development of bone and lung metastases has not been proven. Some inherited disorders are associated with GEP and pulmonary NET, e.g. multiple endocrine neoplasia type I, von Hippel-Lindau disease and neurofibromatosis 1.

Minimal Consensus Statement on Histopathology and Genetics

Bone metastases are often not histologically proven and histopathology of pulmonary metastases is only considered if it may affect further treatment. When histology is indicated, immunohistochemistry should include CgA, synaptophysin and Ki-67 proliferation index. The TNM classification should be employed to stage tumors, including tumor grading where possible. There are no specific recommendations for applying genetic tests in routine diagnostics of bone and lung NET metastases.

Treatment

The presence of bone and lung metastases has prognostic and therapeutic implications. Differentiation between patients with and without distant metastases is important for therapy.

Effective treatment of disseminated NETs requires a multimodal approach because maintaining of the quality of life is a priority and may prolong survival [41]. Options for the treatment of patients with advanced disease (biotherapy, chemotherapy and novel-targeted therapeutic approaches) have been dealt with elsewhere [16–27].

Patients with bone metastases should be considered for treatment with bisphosphonates which can be administered either orally or intravenously [42]; in cases of hypercalcemia, adequate hydration is also useful. Painful bony metastases should be treated with adequate analgesics while considering radiotherapy. Patients with lung metastases may need symptomatic inhalers.

Surgery

The influence of surgery on survival in patients with bone and lung metastases has not been formally studied. In this setting, surgery is applied as a palliative method.

Bone Metastases

Surgical therapy for NET bone metastases is rarely recommended and only for individual lesions; surgery may be indicated for mechanical reasons.

Lung Metastases

Surgical resection of pulmonary metastases might be considered in patients with solitary lung metastasis or a small number of lung metastases; such a consideration would depend on whether or not there were other metastatic sites and the overall management plan.

Among surgical methods thoracoscopic resection for unilateral and bilateral lesions may be considered or posterolateral thoracotomy for unilateral lesions and median sternotomy for bilateral lesions [12].

Wedge resection is performed both in cases of single as well as multiple lesions in the same lobe, provided reasonable residual lung function can be preserved. Otherwise, lobectomy is required [12, 43]. Rarely pneumonectomy is considered; however, its effect on quality of life and overall outcome needs to be carefully reviewed before proceeding.

Whether patients with lymph node involvement benefit from resection requires further study, but in this scenario one would be cautious about proceeding to surgery. Occasionally surgery for lung metastases may be effective in treating the metabolic problems associated with NET malignancy such as hypercalcemia and hypertension. It was recently determined that for a limited number and small lung metastases, ablation techniques such as radiofrequency ablation may be considered.

The role of adjuvant chemotherapy is unknown but should be considered, depending on the histology and biology of the individual's NET disease [12].

Minimal Consensus Statement on Surgery

Surgical therapy for NET bone metastases is rarely recommended. Surgical resection of lung metastases is usually palliative but may be considered for patients with no evidence of extrathoracic disease, good control of the primary tumor, no medical contraindication, and with all lesions resectable, provided satisfactory residual pulmonary function is maintained.

Medical Therapy

Biotherapy in Bone and Lung Metastases

Although somatostatin analogues and interferon have a role in the treatment of patients with functionally active GEP-NETs in the presence or absence of metastases, their use in a similar situation in nonfunctional tumors has not been adequately studied. Somatostatin analogues may be considered in some cases where SRS is positive [41, 44, 45].

Chemotherapy

The use and type of chemotherapy depends on tumor grade and origin and the presence of bone or lung metastases does not influence the choice of therapy per se. The presence of such metastases usually indicates advanced disease and a systemic form of therapy is usually warranted. The active and appropriate regimens in relation to the specific metastatic sites in question are dependent on the origin of the primary tumor [16–27].

Minimal Consensus Statement on Biotherapy and Chemotherapy

Somatostatin analogues and interferon have a role in the treatment of patients with functionally active GEP-NETs in the presence of metastases, although their use in nonfunctional tumors has not been adequately studied. Chemotherapy regimens in relation to specific metastatic sites are dependent on the origin of the primary tumor.

Peptide Receptor Radionuclide Therapy and Radiotherapy

Bone and Lung Metastases

Peptide receptor radionuclide therapy (PRRT) with either ^{177}Lu and ^{90}Y has been shown to be effective in a limited number of patients with both bone and lung metastases [30, 45], demonstrating a positive SRS prior to treatment. Treatment with ^{131}I-MIBG may be considered in cases with negative SRS and avid accumulation of MIBG in metastases. It may be effective in alleviating pain and other NET symptoms in these situations. Patients eligible for treatment with radiolabeled SST analogues should have an appropriate expression of SST receptors in metastases with SRS and uptake at least equivalent or greater than that of the liver on planar imaging. Patients with an intensive radiotracer accumulation in all the neoplastic foci, including metastases whose dimensions are small and which are characterized by a uniform radiotracer uptake, are good candidates for intensive treatment aimed at objectively reducing the tumor mass. The likelihood of complete remission is, however, estimated at 5%, although partial remission, according to the RECIST (Response

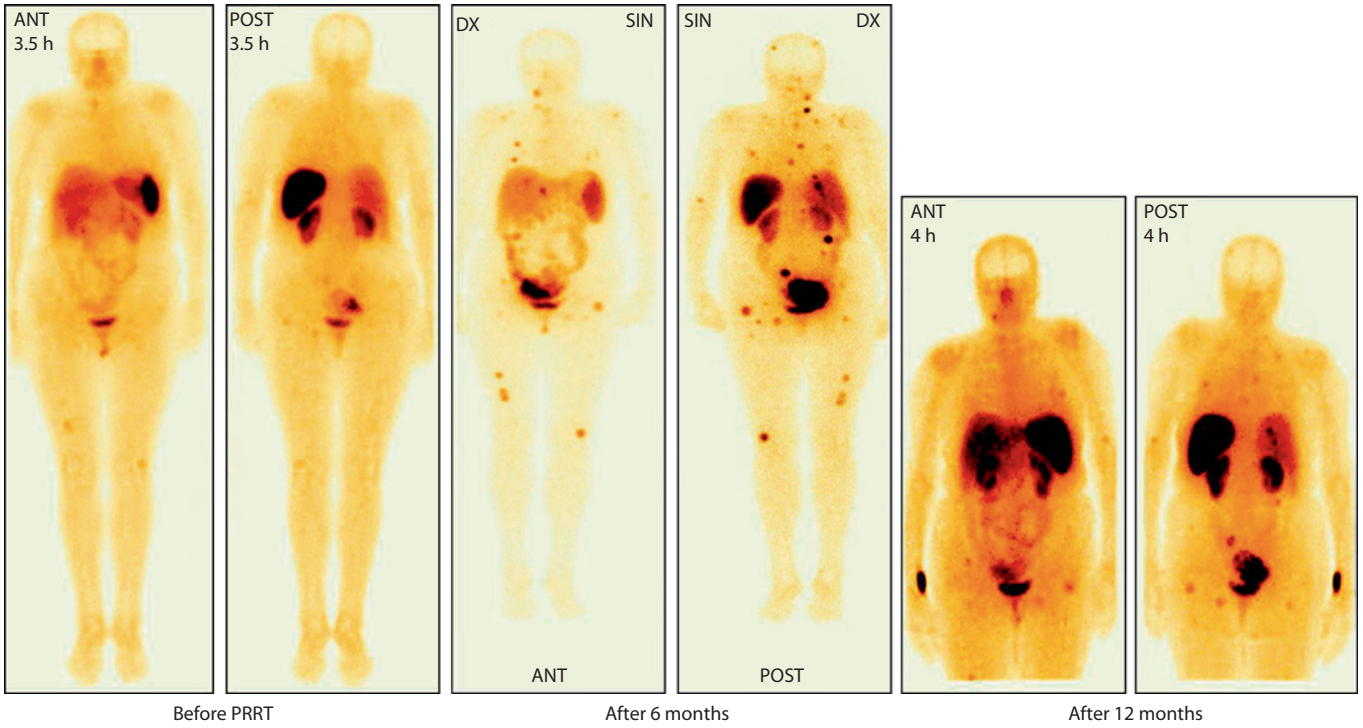

Fig. 2. SRS before, during and after 380 mCi of $^{90}Y/^{177}Lu$ DOTA-TATE combination in a 63-year-old female patient with a well-differentiated NET and numerous distant metastases (including bone). SRS taken before, 6 months into the treatment and 12 months following PRRT; the majority of lesions had disappeared [reproduced with permission of L. Królicki, Department of Nuclear Medicine, Medical University, Warsaw].

Evaluation Criteria In Solid Tumors) criteria, may be expected in almost 50% of cases. Overall treatment is palliative and aims to prolong progression-free survival and to reduce NET symptoms and pain [30, 45].

Treatment with somatostatin analogues labeled with the combination of ^{90}Y and ^{177}Lu is planned to be subject to broader clinical trials in the near future. Available data suggest that ^{177}Lu may be more effective for smaller tumors whereas ^{90}Y may be more effective for larger tumors because of the different mean range of the respective beta decay [44, 46, 47] (fig. 2).

With regard to PRRT for bone and lung metastases, details such as the number of cycles, doses, maximum total activity, and the best time to begin PRRT administration have not yet been established through evidence-based medicine. In patients with large-volume bone metastases, there is a significant risk of bone marrow toxicity.

^{153}Sm has recently been considered in SRS-negative bone metastases for symptom control [48]. External radiotherapy for bone metastases is applied mainly to relieve pain and often provides good palliation [49].

Minimal Consensus Statements on PRRT

PRRT is a promising therapeutic option for patients with a strong uptake of SRS in cases of inoperable or metastatic NETs; a limited number of patients with bone or lung metastases can benefit, although this is still being studied. Currently, the radiotracers which can be employed are ^{177}Lu, ^{90}Y and in some cases ^{131}I-MIBG. Radiotherapy should be considered for patients with bone metastases, especially if they are painful, and it may also be used in a prophylactic setting to avoid fractures.

Follow-Up

Bone and Lung Metastases

The follow-up is usually every 3–6 months and includes laboratory tests (CgA, 5-HIAA or other relevant peptides/hormones). Imaging studies include CT, MRI, bone scintigraphy and/or SRS, depending on the clinical situation.

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