

# ENETS Consensus Guidelines for the Management of Brain, Cardiac and Ovarian Metastases from Neuroendocrine Tumors

Marianne Pavel<sup>a</sup> Ashley Grossman<sup>e</sup> Rudolf Arnold<sup>c</sup> Aurel Perren<sup>d</sup> Gregory Kaltsas<sup>g</sup>  
Thomas Steinmüller<sup>b</sup> Wouter de Herder<sup>h</sup> George Nikou<sup>i</sup> Ursula Plöckinger<sup>a</sup>  
Jose Manuel Lopes<sup>j</sup> Hironobu Sasano<sup>k</sup> John Buscombe<sup>f</sup> Peter Lind<sup>l</sup> Dermot O'Toole<sup>m</sup>  
Kjell Öberg<sup>n</sup> and all other Palma de Mallorca Consensus Conference Participants<sup>1</sup>

<sup>a</sup>Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, and <sup>b</sup>Department of Surgery, DRK Kliniken Berlin – Westend, Berlin, <sup>c</sup>Department of Internal Medicine, Philipps University, Marburg, and <sup>d</sup>Institute for General Pathology and Pathological Anatomy, Technische Universität München, Munich, Germany; <sup>e</sup>St. Bartholomew's Hospital, and <sup>f</sup>Royal Free Hospital, London, UK; <sup>g</sup>G. Genimatas Hospital, Athens, Greece; <sup>h</sup>Erasmus University Medical Center, Rotterdam, The Netherlands; <sup>i</sup>Athens, Greece; <sup>j</sup>Department of Pathology, University of Porto, Porto, Portugal; <sup>k</sup>School of Medicine, Tohoku University, Sendai, Japan; <sup>l</sup>Landeskrankenhaus Klagenfurt, Villach, Austria; <sup>m</sup>Department of Gastroenterology and Clinical Medicine, St. James's Hospital and Trinity College, Dublin, Ireland; <sup>n</sup>Uppsala University Hospital, Uppsala, Sweden

## Introduction

### *Epidemiology and Clinicopathological Features*

Metastatic disease is a critical issue in the management of neuroendocrine tumors (NETs) and forms a key component in the management of such patients. In general, the majority of metastases occur in the liver, lungs and bone; other sites are much rarer. Nevertheless, when present, they pose substantial management issues and therefore require serious consideration. Rare metastatic sites include the brain, heart, ovaries, breast, thyroid, pancreas, skin, adrenal glands, kidney, spleen, orbit, retroperitoneum, testis and pituitary gland. This overview will focus primarily on metastatic lesions of the brain, heart and ovary.

### *Brain Metastases*

Neuroendocrine tumors are considered to be the cause of brain metastases in 1.3–1.4% of all patients with brain metastases [1, 2]. In patients with NETs, the incidence of brain metastases is estimated to be 1.5–5% [3, 4]. This figure, however, is probably an underestimate since many patients do not undergo routine brain imaging as a component of metastatic assessment. Brain metastases occur at different ages ranging from 11 to >80 years [3, 5]. According to the largest report on 24 patients with brain metastases, the median age at diagnosis of brain metastasis was 60 years (range 18–85). Median time from diagnosis of the primary tumor to detection of brain metastases was 1.5 years (range 0–16), with both genders being similarly affected [3]. Time intervals from removal of a bronchial carcinoid to occurrence of brain metastases of up to 25 years are reported [6]. The spread of NET to the cerebrum has been reported in association with all primary tumor locations of the gastroenteropancreatic, bronchopulmonary and genitourinary system [1, 7–16].

<sup>1</sup> See list at the end of the paper.

Nevertheless, bronchopulmonary NETs appear to be the dominant source of cerebral metastases [11, 17]. Thus, in the largest series of brain metastases the primary tumor was located in the bronchi or lungs in 45 and 71% of the patients, respectively [3, 4]. This observation is consistent with the experience documented in the 57 individual case reports published between 1962 and 2007 which identified the bronchopulmonary system as the primary tumor location in >50% of the patients. Since the histological type was not clearly defined in the published series, it is not clear if there is a specific propensity for metastasis based upon tumor grade or type. Based on the available information, it appears that both well-differentiated and poorly differentiated lesions may give rise to brain metastases and are each responsible for 50% of the metastases. With respect to pulmonary NETs, it is reported that typical carcinoids [18], atypical carcinoids [10] and large cell variants [19] may produce brain metastases. In addition to the cerebral metastasis, advanced disease is evident at the time of diagnosis with 75% of the patients having lymph node metastases and 50% exhibiting liver metastases [3]. Other uncommon synchronous or metachronous metastatic sites include the spine, adrenals, skin or breast. It is noteworthy that a minority of patients present with brain metastases as the initial symptom of their disease or as the only metastatic site [1, 10, 20].

#### *Cardiac Metastases*

The incidence of cardiac metastases in patients with NETs is estimated to be <1%, but is probably higher since the majority of patients do not undergo specific cardiac imaging procedures as part of the metastatic work-up and small myocardial lesions are only identified at autopsy. Cardiac metastases generally occur late in the course of the disease and are evident irrespective of carcinoid valvular disease. However, they are almost always associated with other metastases and liver involvement. In living and autopsy studies on patients with metastatic carcinoid neoplasia and concomitant carcinoid syndrome, approximately 4.0–4.5% exhibit myocardial metastases [21, 22]. In a series of 11 patients, cardiac metastases were diagnosed at autopsy in 45% of the patients. The mean size of the lesions was small (0.35 cm) in contrast to those detected by echocardiography, which exhibited a mean size of 2.4 cm (range 1.2–4). The average age at diagnosis of myocardial metastases is 58.2 years (range 39–68 years) and the elapsed time between diagnosis of carcinoid syndrome and identification of cardiac metastases is  $5.6 \pm 3.9$  years [21]. Based on the current experience of 36 published case reports in the literature, it is apparent that the

majority of cardiac metastases originate from NET of the gastrointestinal tract [21]. Other sites of the primary tumor include the pancreas [23] and bronchopulmonary system [24, 25], but in individual patients the location of the primary tumor is unknown [26]. The occurrence of myocardial metastases has been described more often in patients with functioning tumors than in those with non-functioning tumors, although the significance of this observation is unclear. Of note, the histological grade of the lesions associated with cardiac metastasis is predominantly well-differentiated neuroendocrine carcinoma.

#### *Ovarian Metastases*

This is a rare event with more than 60 cases cited in the literature. The estimated incidence is approximately 2%, but the number is probably underestimated. The source of ovarian NET metastases is usually ileal carcinoid tumors; however, other primary tumor sites reported include the jejunum, cecum, pancreas and appendix. It has been proposed that ~2% of intestinal carcinoids >1 cm in size are associated with ovarian metastases [27, 28]. Of note is the fact that they are usually bilateral in contrast to primary ovarian lesions, which are usually unilateral, and this constitutes a significant point in terms of differential diagnosis. Primary carcinoids of the ovary are unilateral and localized in ~90% of the cases [29] and are often associated with teratomatous elements within the tumor. In two reports of 17 and 35 cases, the median age at the time of detection of ovarian metastases was 57 years (range 44–77 and 21–82, respectively) [27, 30]. The size of the ovarian lesions varies and may range from microscopic foci to lesions >9 cm in size [30]. Approximately 30% are identified at autopsy [27]. Clinically, most patients have well-differentiated NETs with synchronous hepatic metastatic disease and present with carcinoid syndrome. Multiple metachronous metastases occur in nearly all individuals with ovarian lesions and the entity is usually consistent with advanced disease. In addition, a substantial number (28–35%) exhibit extensive peritoneal seeding. Apart from the small bowel as a primary tumor site, it is noteworthy that goblet-cell mucinous carcinoids of the appendix may also be associated with ovarian metastases [31, 32]. The mucinous subtype appears to be more aggressive and is consistent with the observation that appendiceal NETs classified as the goblet variety have a significantly worse prognosis than the usual nonmucinous variety [33].

### Minimal Consensus Statements on Epidemiology and Clinicopathological Features

The incidence of brain metastases is 1.5–5%, cardiac metastases 1–4% and ovarian metastases ~2%. There is no gender preference for the occurrence of brain metastases. However, cardiac metastases appear to be more common in males. Broncho-pulmonary NETs are more likely to develop brain metastases, whereas midgut tumors are the usual source of cardiac and ovarian metastases. Both well-differentiated and poorly differentiated (50% each) bronchopulmonary tumors are associated with brain metastases. On the contrary, tumors that produce cardiac or ovarian metastases are usually well-differentiated. The majority of individuals with brain, ovarian and cardiac metastases have an advanced disease stage. Cardiac and ovarian metastases are more commonly associated with carcinoid syndrome.

### Clinical Presentation

Brain metastases are associated with headaches in >95% of the patients. Personality changes and unstable gait are reported in up to 25%, cranial nerve deficits in more than 10% and seizures or nausea and emesis in less than 10% of the patients [3]. Cardiac and ovarian metastases are usually identified incidentally on imaging, but may contribute to the symptoms of carcinoid syndrome. Cardiac metastases rarely display clinical symptoms (<30%) but when present include dyspnea, arrhythmias or accentuation of the carcinoid syndrome [22, 24, 34–38].

### Prognosis

In the largest series described, comprising 11 and 24 patients, respectively, the median survival time from diagnosis of brain metastases was 7–10 months, although occasionally long-term survivors have been reported. Survival times of up to 11 years have been reported and between 33 and 42% of the patients survived >1 year [3, 4]. Overall survival rates are <20% at 2 years and <5% at 5 years. Survival rates in patients with cardiac metastases, although of rather short duration, are overall better than for brain metastases. In 35 patients with ovarian metastases, a 5-year survival rate of 25% was reported in 1974, while a recent report indicates a projected 5-year survival of 94% [27, 30]. Although no clear explanation for this is apparent, it is likely that advances in diagnosis and treatment have led to earlier detection and better therapy, thus providing an optimization of the outcome of the condition. Current assessment suggests that patients with

ovarian metastases exhibit survival rates that are probably comparable to individuals with liver metastases.

### Minimal Consensus Statements on Clinical Presentation and Prognosis

The leading symptom of brain metastases is headache. The median survival is less than 10 months with a 1-year survival rate of <40%. Ovarian and cardiac metastases do not have specific symptoms and are usually identified incidentally. In general, survival rates are comparable to liver metastases but the outcome is worse with cardiac metastases.

### Hereditary Tumor Syndromes

No hereditary predisposition has been described for brain, cardiac or ovarian metastases.

### Diagnostic Procedures

#### Imaging

Brain metastases are usually identified on MRI or CT scanning. Octreoscan and <sup>68</sup>Ga-DOTATOC-PET/CT may be helpful in the early detection of brain metastases, provided that the histological tumor type is well-differentiated. The data are currently inadequate to determine the relative efficacy of the individual methods. Since poorly differentiated bronchopulmonary tumors are considered at greater risk of developing brain metastases, brain MRI is the recommended imaging modality, analogous to the strategy for small cell lung cancer. Most metastatic myocardial lesions are found by 2D echocardiographic screening during evaluation of valvular carcinoid heart disease. Smaller cardiac lesions are often missed, since the spatial resolution of this technique is ~1 cm [21]. Some cardiac metastases only present as wall thickening and may be difficult to identify with echocardiography. As a single method, MRI is superior to echocardiography in the detection and quantification of cardiac metastases [25, 39–41]. Octreoscan or SPECT/CT may be helpful in somatostatin-receptor-positive lesions [23, 42], but when used alone lacks fine discrimination and cannot provide definitive anatomical localization. There is one report of a patient with two cardiac lesions detected by <sup>18</sup>F-DOPA-PET/CT, neither of which was visualized by echocardiography or octreoscan [43]. It is likely that the more frequent use of <sup>68</sup>Ga-DOTATOC-

and  $^{18}\text{F}$  DOPA-PET/CT will probably increase the prevalence of myocardial metastases. Ovarian metastases are either diagnosed by ultrasound if large in size, or by routine imaging such as MRI or CT scanning. In general, they are usually discovered incidentally and more frequently by octreoscan or  $^{68}\text{Ga}$ -DOTATOC-PET/CT.

#### Minimal Consensus Statement on Imaging

MRI is the most sensitive method for detecting single and multiple brain metastases. It is recommended as part of the metastatic workup in patients with neuroendocrine carcinoma of the lung. Echocardiography is the most frequently used method for detecting myocardial metastases, followed by MRI, which should be undertaken in individuals in whom there is suspicion of cardiac metastases. Ovarian metastases are best defined by ultrasound and MRI.

#### Laboratory Tests

There are no specific laboratory tests to detect these metastatic sites.

#### Pathology and Genetics

Pathological diagnosis of metastases is not mandatory if diagnosis is confirmed histologically by resection of the primary tumor or a liver biopsy. Octreoscan or  $^{68}\text{Ga}$ -DOTATOC-PET/CT represent the main imaging methods for staging of the tumors and are helpful in identifying rare metastases such as neuroendocrine tumor lesions. In cases of negative somatostatin-receptor scintigraphy, a second primary tumor as the cause for brain, ovarian or other rare metastases (e.g. breast, adrenal glands) should be considered. Specific biopsy of the rare metastatic lesion may occasionally be necessary to prove its neuroendocrine nature. Determination of the differentiation status and tumor grading are pivotal in determining the therapeutic strategy. Patients should be classified according to the WHO system. The majority of tumors are classified as WHO group 2 grade G1 or G2; up to half of the patients with brain metastases, however, may belong to WHO group 3, grade G3. Overall, metastasis to the heart, brain and ovary indicates that such individuals are stage IV according to TNM classification criteria. There is no known predisposing genetic background for patients who develop rare metastases, and thus there is no need for germline DNA testing or genetic counseling.

#### Minimal Consensus Statement on Pathology and Genetics

In patients with confirmed histology of a primary NET, no additional pathological examination of rare metastatic sites is usually necessary. Indication of the proliferation index, as measured by labeling with Ki-67 and/or mitotic index of at least one tumor localization is mandatory to determine the appropriate therapeutic strategy. There is no indication for genetic testing.

#### Surgery

In patients with rare metastases, surgery plays a palliative role, except in poorly differentiated neuroendocrine carcinomas where chemotherapy is the appropriate treatment. Surgery is the method of choice for single brain metastases. The outcome seems to be superior if combined with external beam irradiation [3]. Local surgical excision is the treatment of choice in patients with symptomatic cardiac metastases. In asymptomatic patients, a 'watch and wait' strategy can be followed. There are no data on the impact of cardiac surgery on the survival rate of patients with myocardial metastases. Resection of ovarian metastases, including debulking surgery, is indicated to alleviate local symptoms due to mass effect or uncontrolled carcinoid syndrome. Cytoreductive surgery of ovarian metastases may be of some benefit in the improvement of 5-year survival rates [30].

#### Minimal Consensus Statement on Surgery

Surgery is indicated in patients with single brain metastases, usually of a well-differentiated nature, and can be considered in individual patients with multiple brain metastases. Surgery is recommended in patients with symptomatic cardiac metastasis and in ovarian metastases if they are locally symptomatic or if carcinoid syndrome is present.

#### Medical Therapy

Steroids are the primary symptomatic therapy for brain metastases and ameliorate brain edema. Cardiac metastases may require the administration of anti-arrhythmic drugs ( $\beta$ -adrenoceptor blockers) and should be assessed by a cardiologist. Somatostatin analogs are the standard treatment for functioning tumors and are indicated prior to other interventions/therapies for rare met-



astatic sites (see ENETS Guidelines on the medical treatment of neuroendocrine tumors). Occasionally they are used in nonfunctioning tumors if they are somatostatin receptor positive, although data are limited to support their use here. Interferon- $\alpha$  can be used alternatively or in combination with somatostatin analogs. Chemotherapy is used according to tumor origin, differentiation status and biology. It is indicated in poorly differentiated (G3) neuroendocrine carcinomas; cisplatin-based regimens represent the standard treatment. Temozolomide can be used as basic therapy in brain metastases originating from foregut tumors, but midgut tumors appear to be much less responsive and there is as yet limited experience (see ENETS Guidelines for foregut and poorly differentiated neuroendocrine tumors).

#### **Minimal Consensus Statements on Medical Therapy**

Steroids are the standard treatment for brain metastases to obviate the consequences of edema or as prophylactic therapy prior to whole-brain irradiation. Medical treatment may be considered in symptomatic but inoperable cardiac metastases. Somatostatin analogs are recommended according to ENETS Guidelines in patients with functioning tumors and occasionally in those with nonfunctioning tumors if they are SRS-positive. Interferon- $\alpha$  is used in individual patients as an alternative to or in combination with somatostatin analogs. Chemotherapy is indicated in poorly differentiated neuroendocrine carcinomas and in foregut tumors, depending on differentiation and growth behavior (see ENETS Guidelines).

#### **External Beam Irradiation/Peptide Receptor Radionuclide Therapy**

In patients with multiple brain metastases, external beam irradiation is the appropriate treatment [1, 3, 4, 44]. It can be combined with surgery in individual cases, with the exception of poorly differentiated tumors. Systemic treatment is usually a better option as opposed to an aggressive local approach, especially when a neurosurgical intervention is not mandatory for neurological deficits. External beam irradiation is reported to be used in some individuals with cardiac metastases; however, it is unlikely to induce major responses in the myocardium [26, 45, 46]. There are no data available on the impact of irradiation or peptide receptor radionuclide therapy (PRRT) on the management of brain, cardiac or ovarian metastases. PRRT either with yttrium-90- or lutetium-177-labeled somatostatin analogs may be used in individual patients, depending on the local availability for progressive disease

and palliation of symptomatic disease. Tumor involvement of the liver, lung and bones is usually the primary determinant for choosing PRRT rather than myocardial, cerebral or ovarian metastases; strong SRS uptake is necessary when selecting patients for PRRT.

#### **Minimal Consensus Statements on External Beam Irradiation/PRRT**

Radiotherapy is indicated for multiple brain metastases. PRRT can be considered in individual patients with brain, cardiac or ovarian metastases, depending on the specific individual situation.

#### **Follow-Up**

The follow-up intervals are highly variable depending on the clinical situation, functionality, differentiation status, growth characteristics and time since diagnosis. Intervals may vary, but generally follow-up should be tailored to individual needs and is usually every 3 months. Involvement of critical organs like the brain and heart may require closer surveillance, especially after the initial diagnosis. In such circumstances, clinical follow-up may be recommended every month and follow-up visits including imaging (MRI of the brain, echocardiography) every 3 months. In patients with ovarian metastases the follow-up is similar to that of patients with liver metastases and is mandated by the specific clinical situation. It may vary from every 3 months in progressive disease to every 6–12 months in stable disease.

#### **Minimal Consensus Statements on Follow-Up**

The time schedule for follow-up examinations depends on the individual clinical situation and ranges from 1 to 3 months for patients with brain or cardiac metastases. The time schedule for follow-up imaging ranges from every 3 months in progressive disease or poorly differentiated neuroendocrine carcinoma to every 6 months. Follow-up visits in patients with ovarian metastases follow the same principles as for patients with hepatic metastasis.

#### **List of Participants**

*Martyn Caplin*, Royal Free Hospital, London, UK; *Yuan-Jia Chen*, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; *Federica Cioppi*, University of Florence, Florence, Italy; *Barbro Eriksson*, University Hospital, Uppsala, Sweden; *Massimo Falconi*, University of Verona, Verona,

Italy; *Nicola Fazio*, European Institute of Oncology, Milan, Italy; *David Gross*, Hadassah University Hospital, Jerusalem, Israel; *Reza Kianmanesh*, Bichat-Beaujon-Louis Mourier University Hospital AP-HP, University of Paris Diderot, Paris, France; *Günter Paul Komminoth*, Institute for Pathology, Kantonsspital, Baden, Switzerland; *Beata Kos-Kudła*, Department of Pathophysiology and Endocrinology, Division of Endocrinology, Medical University of Selesia, Katowice, Poland; *Matthew Kulke*, Dana-Farber Cancer Institute, Boston, Mass., USA; *Dik Kwekkeboom*, Erasmus University Medical Center, Rotterdam, The Netherlands; *Rachida Lebtahi*, Bichat Hospital, Paris, France; *Mickael Lesurtel*, Swiss HPB Centre, University Hospital of Zurich, Zürich, Switzerland; *Mohandas Mallath*, Tata Memorial Hospital, Mumbai, India; *Ola Nilsson*, Sahlgrenska University Hospital, Göteborg, Sweden; *Juan O'Connor*, Instituto Alexander Fleming, Buenos Aires, Ar-

gentina; *Ulrich-Frank Pape*, Charité-Universitätsmedizin, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow Klinikum, Berlin, Germany; *Mauro Papotti*, University of Turin and St. Luigi Hospital, Turin, Italy; *Marianne Pavel*, *John Ramage*, North Hampshire Hospital, Basingstoke, UK; *Guido Rindi*, Department of Pathology and Laboratory Medicine, University of Parma, Parma, Italy; *Philippe Ruszniewski*, Beaujon University Hospital, Clichy, France; *Jean-Yves Scoazec*, Hôpital Edouard Herriot, Lyon, France; *Isabel Sevilla Garcia*, Hospital Clínico Universitario, Malaga, Spain; *Anders Sundin*, Karolinska Institutet, Stockholm, Sweden; *Eric Van Cutsem*, University Hospital Gasthuisberg, Leuven, Belgium; *Bertram Wiedenmann*, Charité-Universitätsmedizin, Campus Virchow Klinikum Berlin, Berlin, Germany.

## References

- Maiuri F, Cappabianca P, Del Basso De Caro M, Esposito F: Single brain metastases of carcinoid tumors. *J Neurooncol* 2004;66:327-332.
- Cho KH, Hall WA, Gerbi BJ, Higgins PD, Bohlen M, Clark HB: Patient selection criteria for the treatment of brain metastases with stereotactic radiosurgery. *J Neurooncol* 1998;40:73-86.
- Hlatky R, Suki D, Sawaya R: Carcinoid metastasis to the brain. *Cancer* 2004;101:2605-2613.
- Patchell RA, Posner JB: Neurologic complications of carcinoid. *Neurology* 1986;36:745-749.
- Broadus RR, Herzog CE, Hicks MJ: Neuroendocrine tumors (carcinoid and neuroendocrine carcinoma) presenting at extra-appendiceal sites in childhood and adolescence. *Arch Pathol Lab Med* 2003;127:1200-1203.
- Gordon DL, Shea JF, Badrinath K, Fine M, Gujrati M: A hyperdense intracranial metastatic carcinoid tumor. *Am J Med* 1990;88:314-316.
- Song DE, Park JK, Hur B, Ro JY: Carcinoid tumor arising in a tailgut cyst of the anorectal junction with distant metastasis: a case report and review of the literature. *Arch Pathol Lab Med* 2004;128:578-580.
- Weed JC, Graff AT, Shoup B, Tawfik O: Small cell undifferentiated (neuroendocrine) carcinoma of the uterine cervix. *J Am Coll Surg* 2003;197:44-51.
- Isaka T, Maruno M, Sato M, Kinoshita M, Nishida T, Kiyohara H, Yoshimine T: Brain metastasis from small-cell neuroendocrine carcinoma of the urinary bladder: a case report. *Brain Tumor Pathol* 2002;19:117-122.
- Nakamura Y, Shimokawa S, Ishibe R, Ikee T, Taira A: Pulmonary carcinoid found in a patient who presented with initial symptoms of brain metastasis: report of a case. *Surg Today* 2001;31:510-512.
- Beasley MB, Thunnissen FB, Brambilla E, Hasleton P, Steele R, Hammar SP, Colby TV, Sheppard M, Shimosato Y, Koss MN, Falk R, Travis WD: Pulmonary atypical carcinoid: predictors of survival in 106 cases. *Hum Pathol* 2000;31:1255-1265.
- Tanaka M, Shibui S, Nomura K, Nakanishi Y: Brain metastases from adenoendocrine carcinoma of the common bile duct: a case report. *Jpn J Clin Oncol* 1999;29:252-255.
- Valli M, Fabris GA, Dewar A, Chikte S, Fisher C, Corrin B, Sheppard MN: Atypical carcinoid tumour of the thymus: a study of eight cases. *Histopathology* 1994;24:371-375.
- Raymond PL, Balaa MA: Diplopia and diarrhea: ileal carcinoid metastatic to the central nervous system. *Am J Gastroenterol* 1992;87:240-243.
- Schiffman FJ, Barnard NJ: Carcinoid tumor of the gastrointestinal tract with metastases to the brain. *Arch Intern Med* 1982;142:1717-1719.
- Bouldin TW, Killebrew K, Boone SC, Gay RM: Metastasis of a rectal carcinoid to the posterior fossa. *Neurosurgery* 1979;5:496-499.
- Lequaglie C, Patriarca C, Cataldo I, Muscolino G, Preda F, Ravasi G: Prognosis of resected well-differentiated neuroendocrine carcinoma of the lung. *Chest* 1991;100:1053-1056.
- Granberg D, Wilander E, Oberg K, Skogseid B: Prognostic markers in patients with typical bronchial carcinoid tumors. *J Clin Endocrinol Metab* 2000;85:3425-3430.
- Doddoli C, Barlesi F, Chetaille B, Garbe L, Thomas P, Giudicelli R, Fuentes P: Large cell neuroendocrine carcinoma of the lung: an aggressive disease potentially treatable with surgery. *Ann Thorac Surg* 2004;77:1168-1172.
- Porter DG, Chakrabarty A, McEvoy A, Bradford R: Intracranial carcinoid without evidence of extracranial disease. *Neuropathol Appl Neurobiol* 2000;26:298-300.
- Pandya UH, Pellikka PA, Enriquez-Sarano M, Edwards WD, Schaff HV, Connolly HM: Metastatic carcinoid tumor to the heart: echocardiographic-pathologic study of 11 patients. *J Am Coll Cardiol* 2002;40:1328-1332.
- Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC, Kvols LK: Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. *Circulation* 1993;87:1188-1196.
- Penz M, Kurtaran A, Vorbeck F, Oberhuber G, Raderer M: Case 2: myocardial metastases from a carcinoid tumor. *J Clin Oncol* 2000;18:1596-1597.
- Goddard MJ, Atkinson C: Cardiac metastasis from a bronchial carcinoid: report of a case presenting with diffuse thickening of the left ventricular wall. *J Clin Pathol* 2004;57:778-779.
- Drake WM, Jenkins PJ, Phillips RR, Lowe DG, Grossman AB, Besser GM, Wass JA: Intracardiac metastases from neuroendocrine tumours. *Clin Endocrinol (Oxf)* 1997;46:517-522.
- Hennington MH, Detterbeck FC, Szwerc MF, Fidler ME: Invasive carcinoid tumor of the heart. *J Surg Oncol* 1997;66:264-266.
- Robboy SJ, Scully RE, Norris HJ: Carcinoid metastatic to the ovary: a clinicopathologic analysis of 35 cases. *Cancer* 1974;33:798-811.
- Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH: Life history of carcinoid tumor of small intestine. *Cancer* 1961;14:901-912.
- Soga J, Osaka M, Yakuwa Y: Carcinoids of the ovary: an analysis of 329 reported cases. *J Exp Clin Cancer Res* 2000;19:271-280.
- Strosberg J, Nasir A, Cragun J, Gardner N, Kvols L: Metastatic carcinoid tumor to the ovary: a clinicopathologic analysis of seventeen cases. *Gynecol Oncol* 2007;106:65-68.

- 31 Hristov AC, Young RH, Vang R, Yemelyanova AV, Seidinan JD, Ronnett BM: Ovarian metastases of appendiceal tumors with goblet cell carcinoid-like and signet ring cell patterns: a report of 30 cases. *Am J Surg Pathol* 2007;31:1502–1511.
- 32 Hirschfield LS, Kahn LB, Winkler B, Bochner RZ, Gibstein AA: Adenocarcinoid of the appendix presenting as bilateral Krukenberg's tumor of the ovaries: immunohistochemical and ultrastructural studies and literature review. *Arch Pathol Lab Med* 1985; 109:930–933.
- 33 Tang LH, Shia J, Soslow RA, Dhall D, Wong WD, O'Reilly E, Qin J, Paty P, Weiser MR, Guillem J, Temple L, Sobin LH, Klimstra DS: Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. *Am J Surg Pathol* 2008;32:1429–1443.
- 34 Wee JO, Sepic JD, Mihaljevic T, Cohn LH: Metastatic carcinoid tumor of the heart. *Ann Thorac Surg* 2003;76:1721–1722.
- 35 Shehata BM, Thomas JE, Doudenko-Rufforny I: Metastatic carcinoid to the conducting system – is it a rare or merely unrecognized manifestation of carcinoid cardiopathy? *Arch Pathol Lab Med* 2002; 126:1538–1540.
- 36 Kasi VS, Ahsanudin AN, Gilbert C, Orr L, Moran J, Sorrell VL: Isolated metastatic myocardial carcinoid tumor in a 48-year-old man. *Mayo Clin Proc* 2002;77:591–594.
- 37 Davis G, Birbeck K, Roberts D, Naqvi N: Nonvalvular myocardial involvement in metastatic carcinoid disease. *Postgrad Med J* 1996;72:751–752.
- 38 Yeung HW, Imbriaco M, Zhang JJ, Macapinlac H, Goldsmith SJ, Larson SM: Visualization of myocardial metastasis of carcinoid tumor by indium-111-pentetreotide. *J Nucl Med* 1996;37:1528–1530.
- 39 Schiavone WA, Baker C, Prasad SK: Imaging myocardial carcinoid with T2-STIR CMR. *J Cardiovasc Magn Reson* 2008;10:14.
- 40 Puvaneswary M, Thomson D, Bellamy GR: Cardiac metastasis from carcinoid tumour: magnetic resonance imaging findings. *Australas Radiol* 2004;48:383–387.
- 41 Lund JT, Ehman RL, Julsrud PR, Sinak LJ, Tajik AJ: Cardiac masses: assessment by MR imaging. *AJR Am J Roentgenol* 1989;152: 469–473.
- 42 Strosberg J, Hoffs S, Hazelton T, Kvols L: External beam irradiation of myocardial carcinoid metastases: a case report. *J Med Case Reports* 2007;1:95.
- 43 Fiebrich HB, Brouwers AH, Links TP, de Vries EG: Images in cardiovascular medicine: myocardial metastases of carcinoid visualized by 18F-dihydroxy-phenyl-alanine positron emission tomography. *Circulation* 2008;118:1602–1604.
- 44 Chakravarthy A, Abrams RA: Radiation therapy in the management of patients with malignant carcinoid tumors. *Cancer* 1995; 75:1386–1390.
- 45 Schlegel PJ, Kralios AC, Terreros DA, Shami PJ: Malignant carcinoid tumor with myocardial metastases. *Am J Med* 1999;107:643–645.
- 46 Fine SN, Gaynor ML, Isom OW, Dannenberg AJ: Carcinoid tumor metastatic to the heart. *Am J Med* 1990;89:690–692.