Imaging and Interventional Radiology management of Neuroendocrine Tumor Liver Metastases

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Learning Objectives:

- To review the role of imaging of Neuroendocrine Tumor Liver Metastases.
- To review the interventional radiology management of Neuroendocrine Tumor Liver Metastases.

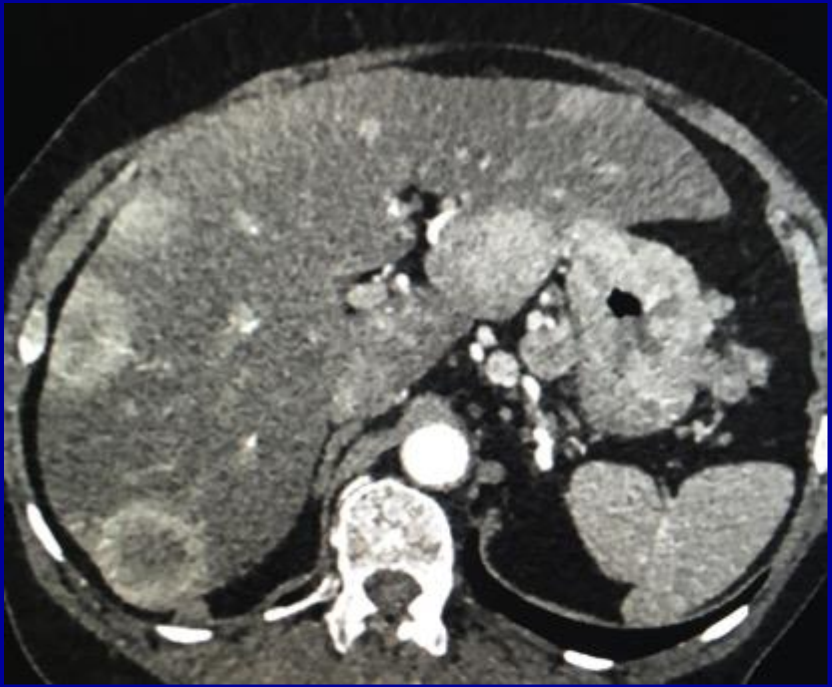
Introduction

- Neuroendocrine (NET) Tumors - diverse range of neoplasms arising from cells of diffuse neuroendocrine system
- 30 per million population per year
  - GI tract (55%) (Small bowel – 45%)
  - Lungs (30%)
  - Pancreas (5%)
  - Reproductive system (1%)
  - Biliary tract (1%)
  - Head and neck (0.4%)[1]

Introduction

- All NETs have a potential risk of metastasizing
- Differ in risk of metastases
  - Poorly differentiated NETs
  - Non-functioning NETs

    - more aggressive
  - Regional & distant metastases are common: 20-40%
- Lymph nodes, Liver - most common sites
- Lungs, bones, peritoneum - rarer sites
- Primary hepatic origin NETs are extremely rare



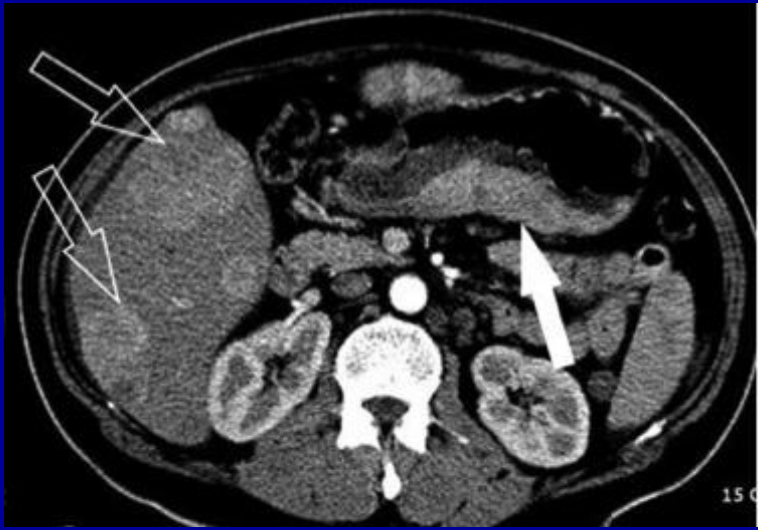
Gastroenteric NETs

Gastric carcinoids (9%) – Types 1, 2 and 3. Metastases most common in Type 3. Occur in 70% of well and 100% of poorly differentiated tumors.

Midgut Gastrointestinal NETs (45%) – distal ileum. The incidence of metastases from midgut carcinoids is dependent on tumor size. Tumors >2 cm over 70% have metastases.

Colonic NETs - Rare large ulcerating poorly differentiated carcinomas. Have already metastasized at the time of diagnosis. Metastases occur to the liver, lungs and bones.

Rectal NETs (27%) - Small (<1 cm) and asymptomatic.[2]



Pancreatic NETs

- Rare - 10 per million.
- Majority – functioning. 15% - 30% - non-functioning.
- Arise from the Islet cells of Langerhans.
- Insulinoma (50%) - 10% malignant. Peripancreatic lymph nodes and liver.
- Gastrinoma - Hepatic metastases >50% at presentation.
- Glucagonoma – 60-70% Malignant. Hepatic metastases >50% at presentation.
- VIPoma - Metastatic in 60% to 80%.
- Somatostatinoma – Metastases in up to 90% of cases, most commonly to liver, also to lymph nodes and bone
- Non-functioning Pancreatic NET- are more commonly metastatic at the time of diagnosis compared with functioning tumors (60%–80% vs 25%). [3]

Bronchial and Thymic NET

Bronchial NET:

•Metastases occur in approximately 15%.

•Low-grade indolent neoplasms to high-grade small cell carcinomas.

•Metastases may be seen in the liver, bones, adrenal glands and brain.

Thymic NET:

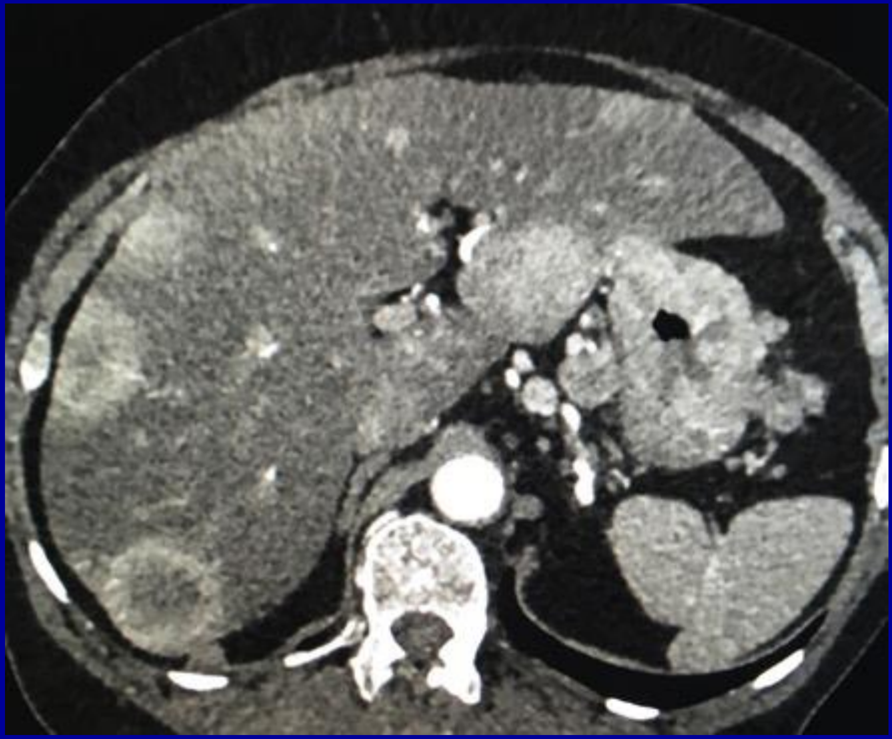
•More aggressive than bronchial carcinoids

•Metastases in up to 30% of patients at the time of diagnosis

•Metastases typically involve the lung, pleura, and brain[4]

Role of Imaging

- Identify primary site
- Stage primary site
- Local structure involvement
- Local lymph node involvement
- Distant Metastasis



Role of Imaging

- Assess response to treatment
- Follow-up of recurrent / metastatic disease
- Nuclear imaging techniques

  - assess uptake on somatostatin-based radionuclide receptor imaging (SRI)

  - may direct treatment with highly targeted radiopharmaceuticals.
- Interventional Radiology

  - Diagnosis - Biopsy

  - Image Guided Therapy (Embolization and Ablation)

Role of Imaging - Liver

- Liver metastases is an important factor that influences both patient survival & prognosis
- 5-year survival of patients with well- to moderately differentiated neoplasms decreased from approximately 82% to 35% with the presence of distant metastases and from 38% to 4% for poorly differentiated neoplasms. [4]
- The goal is to distinguish resectable tumors from unresectable tumors and assess suitability for further management if unresectable.
- Accurate preoperative localisation increases the chances of complete surgical resection and reduces the potential surgical complications.

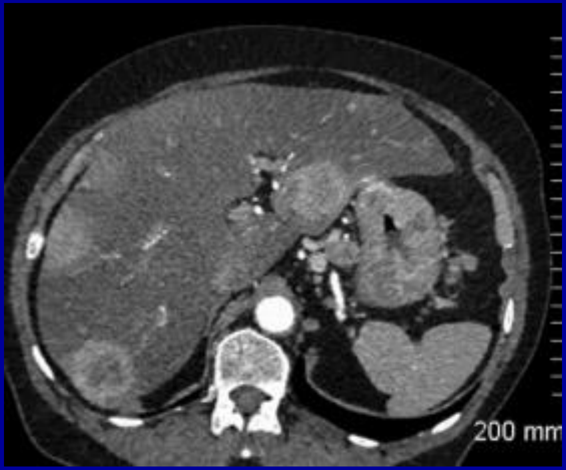
Ultrasound

- Sensitivity of approximately 60%
- Lesions are usually hyperechoic
- Lesion conspicuity is reduced in patients with a fatty, hyperechoic liver
- Used to direct biopsy and ablative therapy

- Endoscopic Ultrasound (EUS) is not reliable in detecting liver metastases, due to its limited depth of penetration

- Intraoperative ultrasound can allow accurate depiction of the relationship between a lesion and hepatic vessels, which may help in determining resectability and help identify additional metastatic lesions.

MDCT

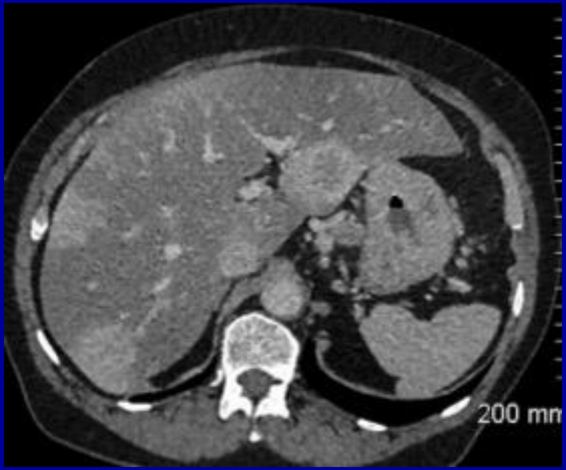


Multiphase imaging in order to increase detection and sensitivity for liver metastases

Mean sensitivity of 82-100% and specificity of 83-100%.

Non- Contrast

•Isodense to the liver on pre-contrast images.



Arterial Phase

•Majority (70%)- hypervascular on arterial phase.

•Small (< 2 cm) are uniformly arterially enhancing

•>2 cm lesions are usually more rim enhancing

•Less frequently show a hypovascular pattern

•Exclusively seen on arterial phase

Response Assessment

- Follow up to assess response to treatment

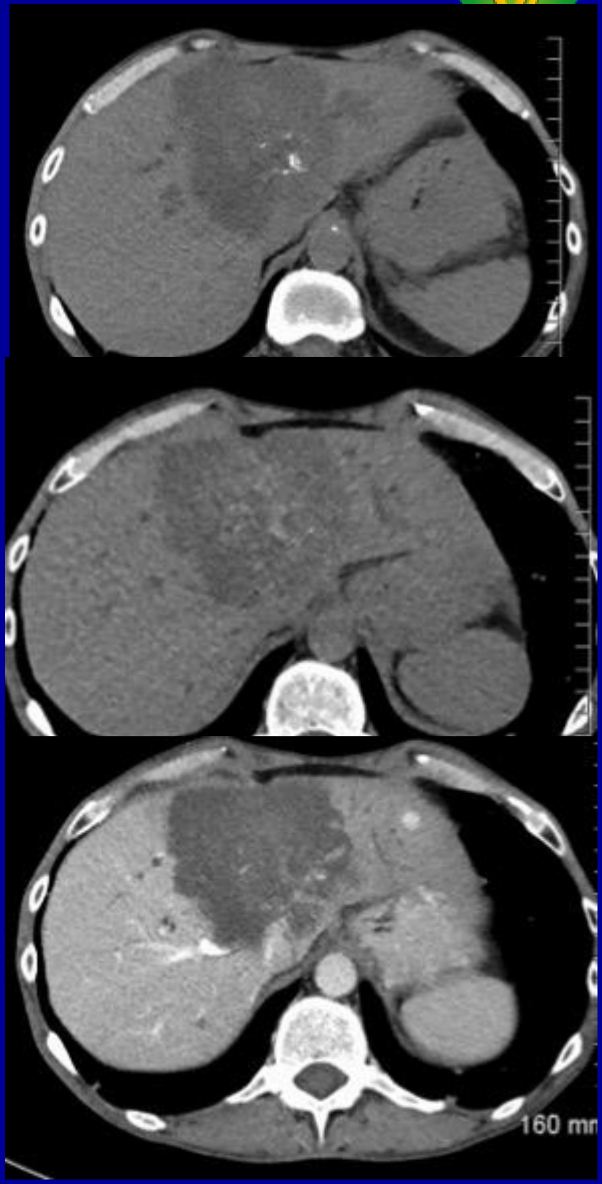
MDCT

Portal Venous Phase

- NETs have been reported to demonstrate washout in the delayed phase in > 2/3 of cases

Atypical appearances

- Not seen on arterial phase only found as hypoenhancing lesion on portal venous phase.
- May rarely demonstrate progressive fill-in like hemangioma (but rim enhancing) or delayed enhancement
- May mimic other primary hepatic lesions or metastases.

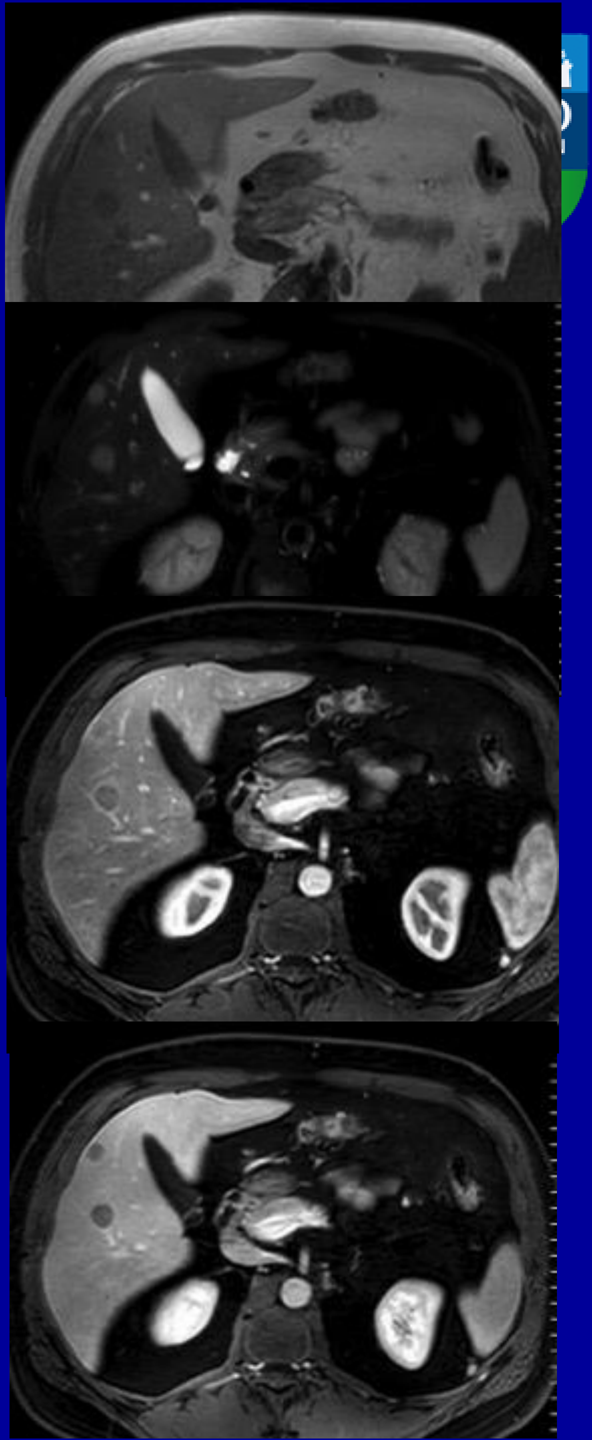


MRI

- Sensitivity of 74%-94% and specificity of 78-100% [5]
- Low signal T1 Fat sat
- Bright, intermediate or even low T2 signal
- Require arterial and portal venous phases post GAD [6]

Arterial phase imaging [7]

- Typical hypervascular enhancement in 73%
- Atypical hypovascular or delayed enhancement in 16%
- Some visualized exclusively on this sequence
- The sequence on which the maximum number of metastases are detected - Hepatic arterial phase revealed 90% of metastases



MRI

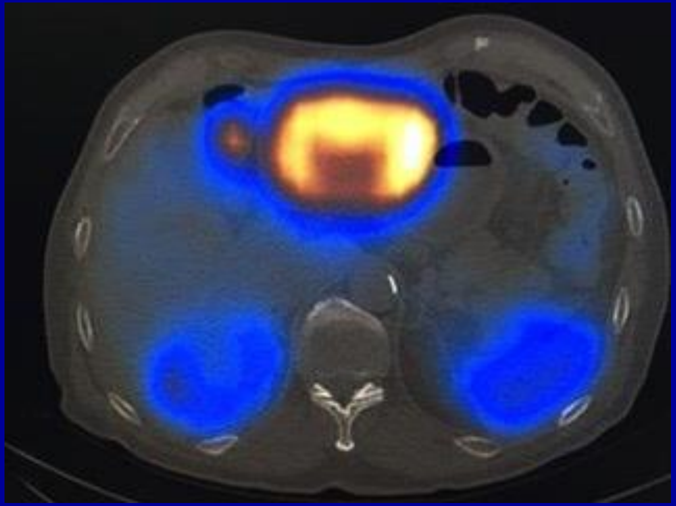
- The portal venous phase images were the least informative, depicting 63% of metastases [7]

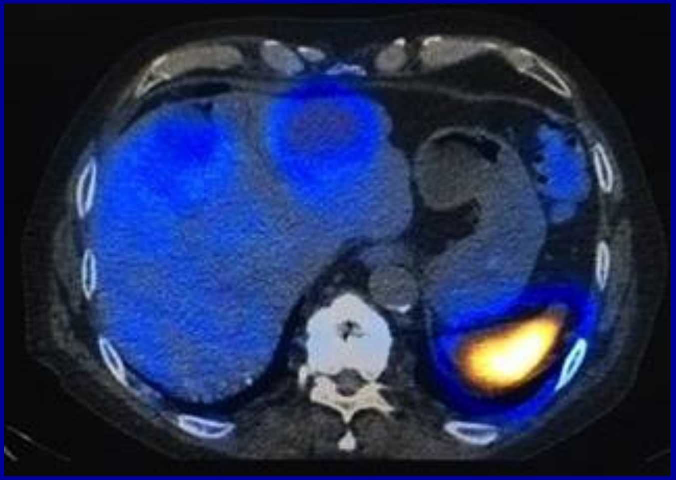
- Low signal with hepatobiliary agents on delayed phase.
- Many more metastasis are identified on the hepatobiliary phase of the post contrast MR

- MRI - May be better for small neuroendocrine metastases

Functional Imaging

- 111In-DTPA octreotide (Octreoscan) most common agent for somatostatin-based radionuclide receptor imaging (SRI)
- SPECT/CT results in higher sensitivity with for detecting PNETs, particularly, gastrinomas, nonfunc and func PNETs

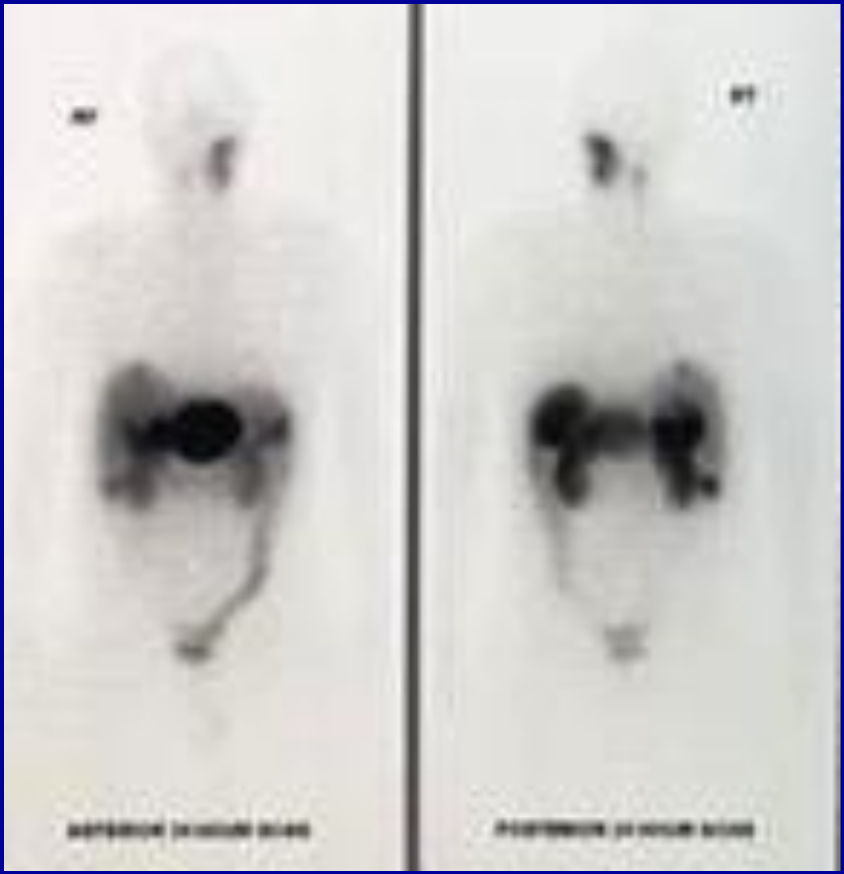




Post Everolimus and Sandostatin

Roles of Imaging

- Follow-up of recurrent and or metastatic disease

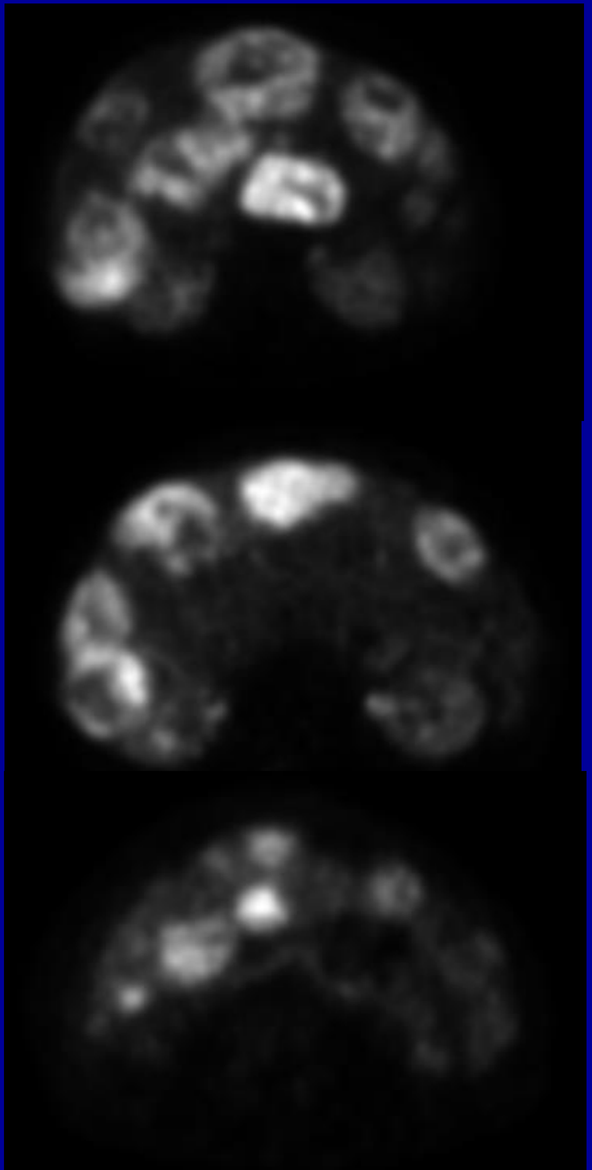


Functional Imaging

- PET/CT Ga-DOTA-Tyr3-octreotide (Ga DOTA NOC) new radiotracer aimed at detecting somatostatin receptors
- Offers higher resolution, three-dimensional and more rapid imaging
- More accurate than Octreotide

  - primary tumor = 83.4%

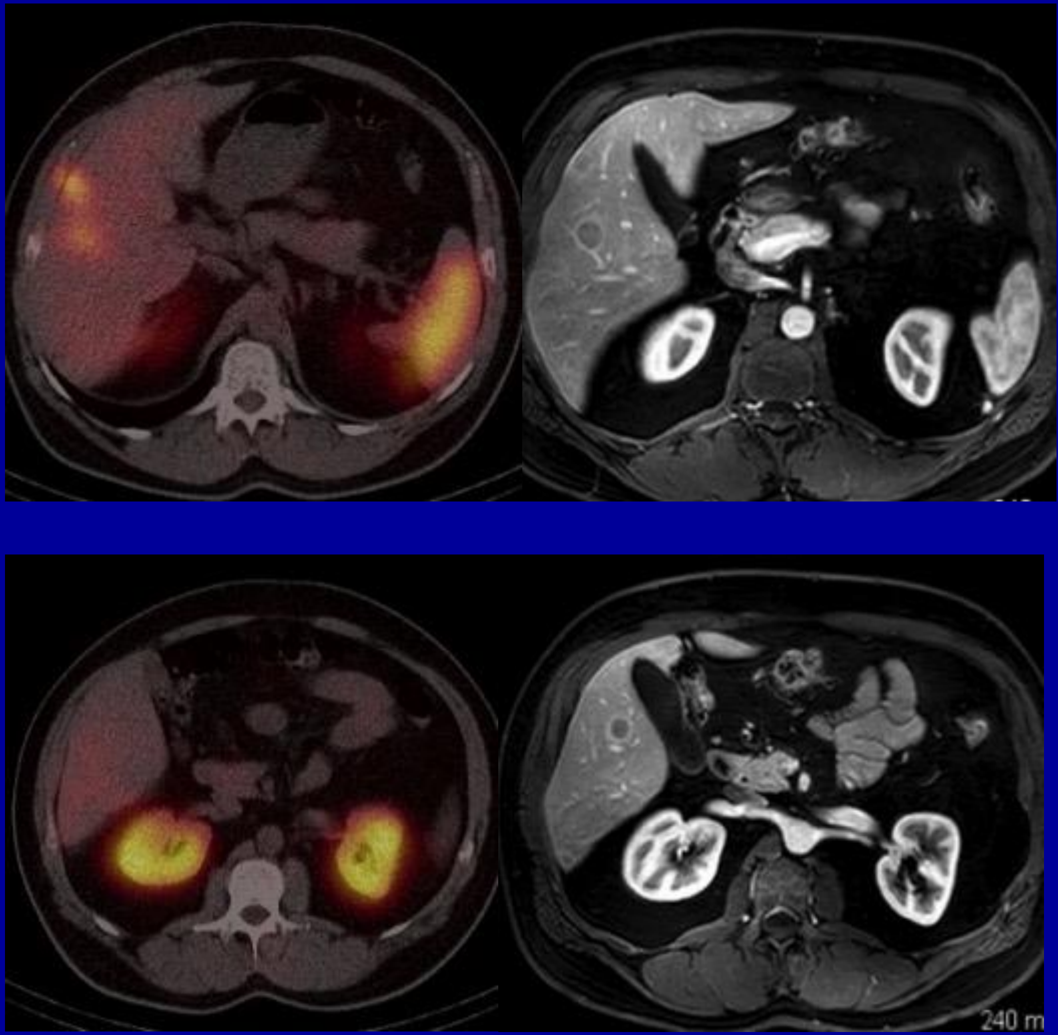
  - metastatic disease = 98.2% [8,9]
- Despite its lower spatial resolution, SRS has a reported high sensitivity (81-96%) & specificity (up to 88%) for hepatic metastases detection
- However detection rates reported in literature are variable



Direct treatment with Targeted Radiopharmaceuticals

- Nuclear imaging techniques – assess uptake on somatostatin-based radionuclide receptor imaging (SRI)

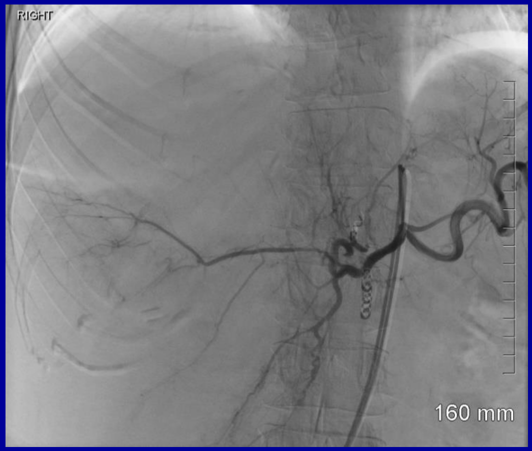
- May direct treatment with highly targeted radiopharmaceuticals.

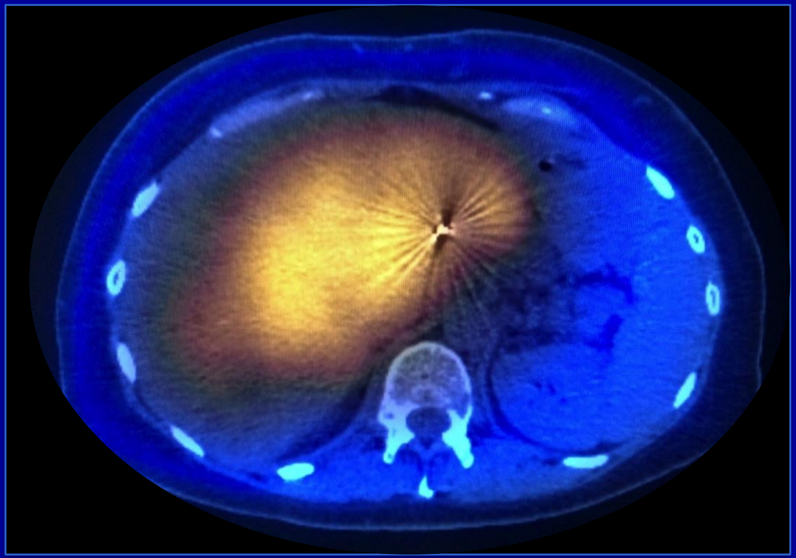


FDG PET

- FDG uptake is usually low in well differentiated, slow growing PNETs.
- FDG useful is usually increased in poorly differentiated aggressive metastasizing PNETs which may express somatostatin receptors
- Serves as a useful prognostic marker, identifying NETs with an increased risk of aggressive features and metastasis [8,10,11]

Management and Interventional Radiology





Multidisciplinary Approach

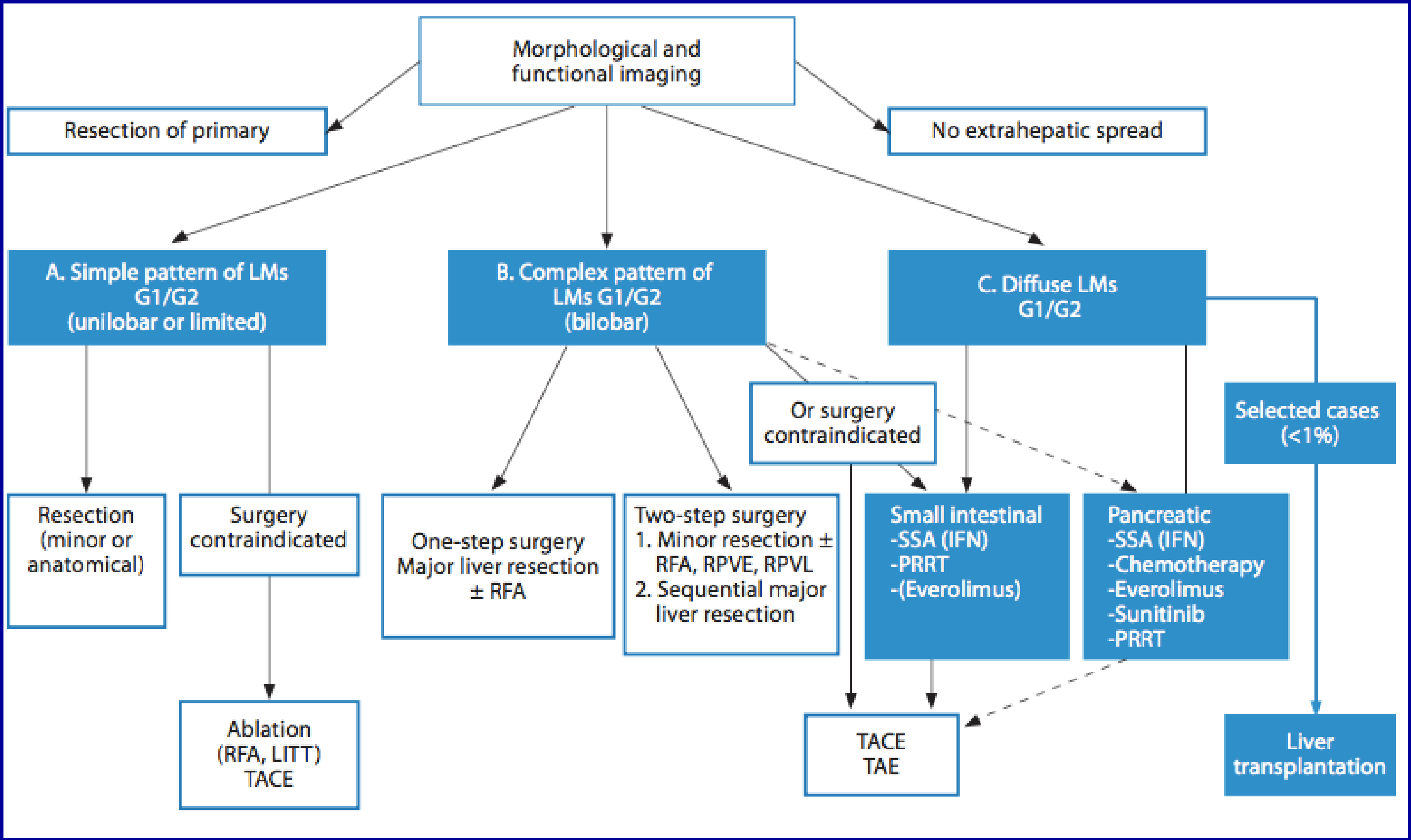
- A multidiciplinary approach is advocated in the management of hepatic neurendocrine metastasis.
- Key input includes:
  - Surgical Oncology
  - Medical Oncology
  - Interventional Oncology
  - Radiation Oncology
  - Gastroenterology
  - Cardiology/Cardiothoracic Surgery

Interventional Radiology

- There has been rapid advances in the treatment options, with numerous options in the IR armamentarium to manage neuroendocrine liver metastasis. IR has several options available to increase the possibility of resection, to offer curative intent where surgery is not an option or in conjunction with surgery, and additional modalities to extend survival and provide palliation when the patient is not a resection candidate.

- The main options for treatment of hepatic metastasis include
  - Embolization
  - Ablation

ENETS Consensus Guidelines



Interventional Radiology Management Options

- Trans-arterial therapy:
  - Bland embolization
  - Chemoembolization
  - Radioembolization

- Percutaneous ablation:
  - Chemical
  - Thermal
    - Cryoablation
    - Radiofrequency ablation (RFA)
    - Microwave ablation
    - IRE

Embolization

- Transarterial embolisation can be performed using bland embolisation, chemoembolization (TACE), or radioemboliation.
- Bland embolisation involves angiography of the hepatic arterial system and embolisation with bland particles.
- Chemoembolisation can be performed in conventional method using lipiodol in combination with chemotherapy solution, or as drug-eluting beads loaded with irinotecan or doxirubicin.
- Radioembolisation is performed with microspheres labeled with the β emitter yttrium-90 (^{90}Y). There are two commercially available microspheres, one composed of a biocompatible resin (SIR-Spheres; SIRTex Medical, Ltd., Sydney, Australia) and the other composed of glass (TheraSphere; MDS Nordion, Inc., Ontario, Canada).

Bland vs. Chemoembolisation

In a comparison of toxicity and efficacy of chemoembolisation versus bland emblolisation, there is evidence of a trend towards improved progression free survival, and overall survival rates in chemoembolisation compared to bland embolisation. [13]

Current US trial recruiting- primary aim of this trial is to estimate the duration of hepatic progression-free survival (HPFS) in participants treated with bland embolization (BE), transcatheter arterial Lipiodol chemoembolization (TACE), and embolization by drug-eluting beads (DEB).

TACE Neuroendocrine

Summary of larger published series of bland / chemoembolisation use in NET hepatic metastasis

1467 pts – Mean RR 52%, Symptom Response >80%, Tumor Marker Response >70%

Author / Year	Pts	Rx	Response CR+PR	↓ Symptom	Median Survival	Hepatic Toxicity
Dong 2005	125	TACE	-	-	3 yr	-
Ho 2007	46	TAE TACE	-	-	33m	-
Gupta 2005	123	TAE TACE	66.7% WHO	nr	33.8m	@8%
Bloomston 2007	122	TACE	nr	92%	33.3m	@3%
Ruutiainen 2007	67	TAE TACE	TTP 6m 12m	93% 92%	3yr 5yr	4%

13,14,15,16,17, 18

Imaging post TACE

Infarction and necrosis of Hepatic NET metastasis post TACE

Radioembolization

- In a retrospective review of 148 patients with liver metastases from neuroendocrine tumors treated with 185 separate radioembolization procedures using resin 90Y micro- spheres, Kennedy et al observed a complete response in 3%, partial response in 66.7%, stable disease in 25%, and progressive disease in 5.3% of patients. The median survival was 70 months.
- These results suggest that 90Y radioembolization represents an alternative therapy for patients with hepatic metastasis from NETs, Although early response rates lag relative to chemoembolization, short-term responses are encouraging. Further mid- to long-term data is awaited.[19]

Radioembolisation Clinical Trials

Summary of larger published series of radioembolisation use in NET hepatic metastasis

Author / Year	Pts	CR	PR	SD	Rad Response	↓ Symptom	Survival %/@
King 2008 Ph IV	34	18%	15%	15%	65%	55%	59% @35.2m
Rhee 2008	42	0	52%	41%	93%	nr	57% @36m
Kennedy 2008	148	2.7%	60.5%	23%	63.2%	nr	70m (mean f/up 42 months)

20,21,18

Percutaneous Ablation of Liver Metastases

- Thermal ablation delivers extreme temperatures to the lesion and adjacent parenchyma causing immediate cell death. The advantages of ablation therapies include the ability to perform percutaneously, under sedation if necessary, the potential to reach difficult or surgically unresectable lesions and the small volume of parenchymal loss.
- Ablation can be used in conjunction with or in advance of other therapeutic options.
- The goal of ablative therapy is the reduction or complete destruction of viable tumor and to preserve liver function and possibly improve survival.

Tumor Ablation

- Ablative therapy indicated for patients with unresectable disease less than 3 cm in size. In a comparison of local recurrence rates post RFA compared with resection per lesion the recurrance rate was 6% for RFA, comparable to 5.5% for surgery [22]
  - If the lesion was smaller than 3cm the recurrance rate for RFA was 2.9%
- In certain circumstances local recurrence can be overcome by repeat applications.

- Combined therapy with chemoembolization may extend local control up to 7 cm. [23,24]

Conclusion

- Morphologic imaging (CT and MR) widely used to exclude metastatic disease – arterial enhancement is most distinctive pattern
- Molecular imaging (SRS, PET- DOTA NOC) role relates to cell membrane increased expression of somatostatin receptors
- FDG - PET useful for poorly differentiated NETs
- Morphologic and functional imaging techniques play a complementary role in assessment of metastases

Conclusion

- Interventional Oncology provides durable therapies to control metastases to the liver
- Integration with surgery and systemic therapies key to long-term success.
- Combination of liver-directed and systemic therapies (multikinase inhibitors; PRRT) is yet to be studied

References

1. Reznek R. CT/MRI of neuroendocrine tumours. Cancer Imaging (2006) 6, S163–S177 DOI: 10.1102/1470-7330.2006.9037
2. Rindi G, D'Adda T, Froio E, Fellegara G, Bordi C. Prognostic factors in gastrointestinal endocrine tumors. Endocr Pathol. 2007;18:145–149
3. Metz DC. Diagnosis and treatment of pancreatic neuroendocrine tumors. Semin Gastrointest Dis 1995; 6: 67–78.
4. Yao JC, Hassan M, Phan A, et al. One hundred years after ‘‘carcinoid’’: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063Y3072.
5. Alsohaibani F, Bigam D, Kneteman N, Shapiro AMJ, and Sandha G. The impact of preoperative endoscopic ultrasound on the surgical management of pancreatic neuroendocrine tumours.Can J Gastroenterol. 2008 Oct; 22(10): 817–820.
6. Herwick S, Miller FH, Keppke AL. MRI of Islet Cell Tumors of the Pancreas. AJR 2006; 187:W472–W480 0361–803X/06/1875–W472
7. Dromain C, de Baere T, Baudin E, Galline J, Ducreux M, Boige V, Duvillard P, Laplanche A, Caillet H, Lasser P, Schlumberger M, Sigal R. MR Imaging of Hepatic Metastases Caused by Neuroendocrine Tumors: Comparing Four Techniques AJR 2003;180:121–128 0361–803X/03/1801–121
8. Naswa N, Sharma P, Kumar A, Nazar AH, Kumar R, Chumber S, Bal C. Gallium-68-DOTA-NOC PET/CT of patients with gastroenteropancreatic neuroendocrine tumors: a prospective single-center study.AJR Am J Roentgenol. 2011 Nov;197(5):1221-8. doi: 10.2214/AJR.11.7298.
9. Krausz Y, Freedman N, Rubinstein R, Lavie E, Orevi M, Tshori S, Salmon A, Glaser B, Chisin R, Mishani E, J Gross D. 68Ga-DOTA-NOC PET/CT imaging of neuroendocrine tumors: comparison with ^{111}In-DTPA-octreotide (OctreoScan®). Mol Imaging Biol. 2011 Jun;13(3):583-593. doi: 10.1007/s11307-010-0374-1.
10. Ichikawa T, Peterson MS, Federle MP, Baron RL, Haradome H, Kawamori Y, Nawano S, Araki T. Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. Radiology. 2000 Jul;216(1):163-71.
11. Nakamoto Y, Higashi T, Sakahara H, Tamaki N, Itoh K, Imamura M, Konishi J. Evaluation of pancreatic islet cell tumors by fluorine-18 fluorodeoxyglucose positron emission tomography: comparison with other modalities. Clin Nucl Med. 2000 Feb;25(2):115-9.
12. Pavela M, Baudinb E, Couvelardc A, Krenningd E, Øberge K, Steinmüllerf T, Anlaufg M, Wiedenmanna B, Salazarh R.ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary. Neuroendocrinology 2012;95:157–176
13. Nazario J, Gupta S. Transarterial Liver-Directed Therapies of Neuroendocrine Hepatic Metastases. Semin Oncol. 2010 Apr;37(2):118-26. doi: 10.1053/j.seminoncol.2010.03.004.

References

14. Ruutiainen AT, Soulen MC, Tuite CM, Clark TW, Mondschein JI, Stavropoulos SW, Trerotola SO. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. J Vasc Interv Radiol. 2007 Jul;18(7):847-55.
15. Dong XD, Yin X, Zwh HJ. Long term outcome in patients with liver metastasis from neuroendocrine tumours treated with chemoembolization. Proc ASCO 2005 23;349S (abstract 4167)
16. Long-Term Outcome After Chemoembolization and Embolization of Hepatic Metastatic Lesions from Neuroendocrine Tumors. Ho AS, Picus J, Darcy MD, Tan B, Gould JE, Pilgram TK, Brown DB. American Journal of Roentgenology 2007 188:5, 1201-1207
17. Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC, McRae SE, Hicks ME, Rao S, Vauthey JN, Ajani JA, Yao JC Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer. 2005 Oct 15;104(8):1590-602.
18. Bloomston M, Al-Saif O, Klemanski D, Pinzone JJ, Martin EW, Palmer B, et al. Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. J Gastrointest Surg. 2007;11:264–271. [5] JVIR July 2007 (18) 7, 847-855
19. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembo- lization for unresectable neuroendocrine hepatic metas- tases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol. 2008;31:271–9.
20. King J , Quinn R , Glenn DM , Janssen j, Tong D , Liaw W , Morris DL Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer [01 Sep 2008, 113(5):921-929] DOI: 10.1002/cncr.23685
21. Rhee TK, Lewandowski RJ, Liu DM, Mulcahy MF, Takahashi G, Hansen PD, Benson AB 3rd, Kennedy AS, Omary RA, Salem R. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. Ann Surg. 2008 Jun;247(6):1029-35.
22. Tanis E, Nordlinger B, Mauer M, Sorbye H, van Coevorden F, Gruenberger T, Schlag PM, Punt CJ, Ledermann J, Ruers TJ. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer. 2014 Mar;50(5):912-9. doi: 10.1016/j.ejca.2013.12.008.
23. Morimoto M, Numata K, Kondou M, et al: Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 116:5452-60, 2010
24. Peng ZW, Zhang YJ, Chen MS, et al: Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 31:426-32, 2013