# TRATTAMENTO CHIRURGICO DELLE METASTASI EPATICHE DA NET: LINEE GUIDA


**PIERLUIGI PILATI**

**UNIVERSITA' DEGLI STUDI DI PADOVA**
**DIPARTIMENTO DI SCIENZE ONCOLOGICHE E CHIRURGICHE**
**SEZIONE DI CLINICA CHIRURGICA II**
**DIRETTORE: PROF. DONATO NITTI**


*San Vito al Tagliamento 30 gennaio 2009*

# LIVER METASTASES FROM NET

- 10% of all liver metastases are neuroendocrine in origin
- 75% of NET have metastastic disease at presentation, most commonly in the liver
- 75% of patients with primary NET will develop liver metastases during follow-up
- 90% of liver metastases are multifocal and bilateral

**Suttcliffe, Am J Surg 2004**

# LIVER METASTASES FROM NET

## ORIGIN

*From carcinoid*:

1. small intestinal
2. colon
3. trachea and bronchi
4. appendix
5. rectum
6. stomach

*From pancreatic NET*:

1. gastrinoma
2. islet cell tumor

**Modlin, Cancer 1997**

## LIVER METASTASES FROM NET

# TIMING

Liver mts may be:

1. Found *synchronously* with the primary tumor
2. Occur *metachronously* at follow-up
3. Occur *in the absence of detectable primary tumor*

**Suttcliffe, Am J Surg 2004**

# CLINICAL FINDINGS

- carcinoid syndrome is associated with 4-10% of the primary carcinoid tumors, but the frequency goes up to 60% in the presence of liver metastases

Vasomotor symptoms (90%)
Flushing
Telangiectasias
Chronic facial cyanosis
Rhinitis

Heart failure (40%)

Increased intest.motility (80%)
Diarrhoea
Borborygmia
Abdominal pain

Bronchial constriction (15%)

- liver failure

**K. Oberg Acta Oncol 2004**

# BIOCHEMICAL DIAGNOSIS

- Serum assay:
  Gastrin, VIP, Insulin
  Chromogranin A
  NSE
- Urinary assay:
  5 – Hydroxyindoleacetic acid

**Eriksson, Digestion 2000**

# DIAGNOSIS

## IMAGING

- Selective angiography and portal venous sampling used in the past, but no longer used

- US, CT and MRI have a sensitivities of 46%, 42%, 43% respectively

- Combination of Somatostatin Receptor Scintigraphy (SRS) and CT/MR detects 96% of liver metastases

**Doppman, It J Gastroenter hepatol 1993**
**Gibril, Ann Int Med 1996**

## LIVER METASTASES FROM NET

# DIAGNOSIS

## IMAGING

Comparison of somatostatin receptor scintigraphy plus CT with conventional radiographics imaging procedures (US, CT, MR) for the detection of liver mts in neuroendocrine gastroenteropancreatic tumours

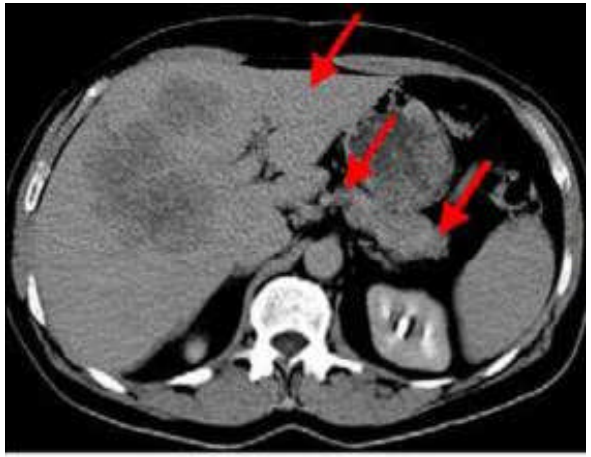
| Liver mts | SRS-CT (%) | US, CT, MR (%) |
|---|---|---|
| Sensitivity | 92 | 79 |
| Specificity | 100 | 44 |
| Pos. predictive value | 100 | 89 |
| Neg. predictive value | 97 | 27 |
| Accuracy | 96 | 74 |

**Plockinger, Best Pr & Res Clin Gastr 2005**

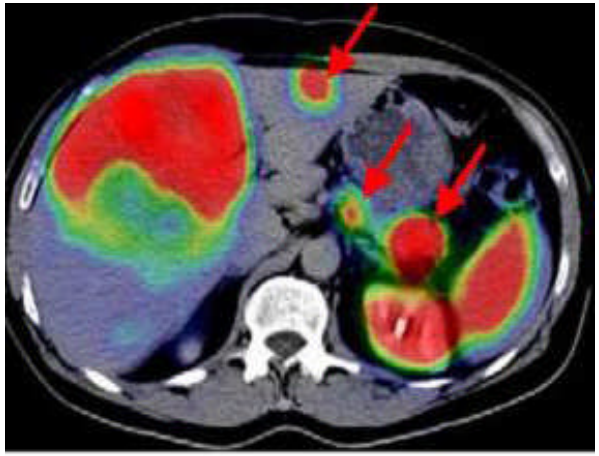
LIVER METASTASES FROM NET

# DIAGNOSIS

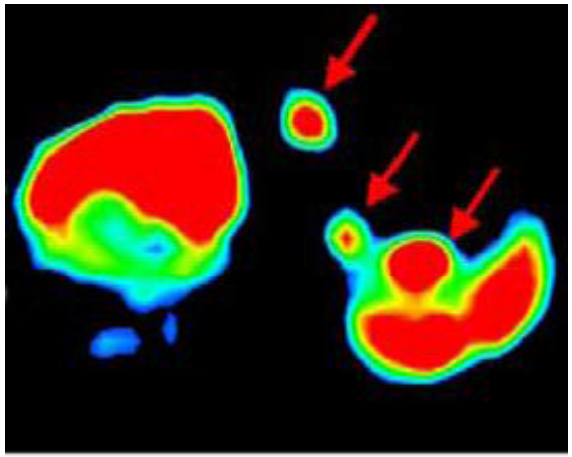
## SRS – CT/RMI



Computertomography



fused image



scintigraphy

96% accuracy

**Plockinger, Best Pr & Res Clin Gastr 2005**

LIVER METASTASES FROM NET

# DIAGNOSIS

## PET

- $^{18}$F-FDG PET shows high spatial resolution, but poor sensitivity to detect tumors with low metabolic activity and slow growth

- Recent studies reported high sensitivities for $^{18}$F-DOPA PET but better sensitivity (97%) for $^{68}$Ga-DOTA-TOC PET

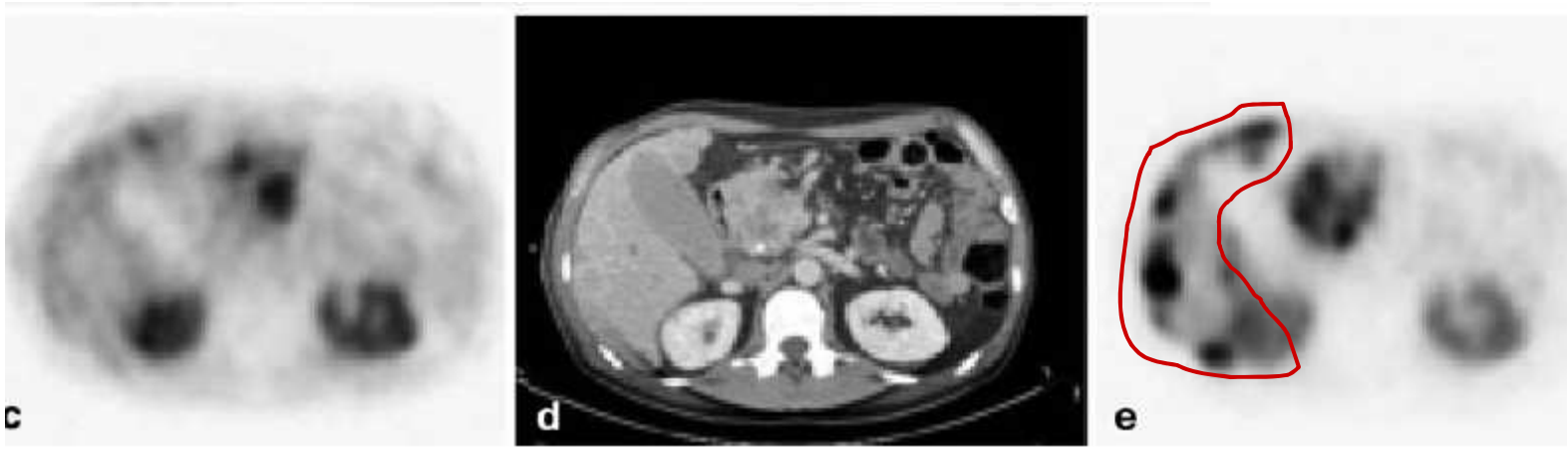
  ($^{68}$Ga-labeled 1,4,7,10-tetra-azacyclododecane-tetraacetic acid-D-Phe$^{1}$-Tyr$^{3}$-octreotide)

**Haug, Eur J Nucl Med Mol Imaging, 2008**
**Gabriel, J Nucl Med, 2007**

LIVER METASTASES FROM NET

# DIAGNOSIS

## 68Ga-DOTA-TOC PET




18F-FDG PET

CT

68Ga-DOTA-TOC PET

**Haug, Eur J Nucl Med Mol Imaging, 2009**
**Gabriel, J Nucl Med, 2007**

# DIAGNOSIS

## FNAC/CORE BIOPSY

- Correct diagnosis in only a third of cases due to similarities between the cytological features of NET and adenocarcinomas

- Indicated only in the selection for liver transplantation: DFS and OS was shorter in dedifferentiated tumors

**Coppa, Transpl Proc 2001**
**Nicholson, Cancer 2001**

# LIVER METASTASES FROM NET

Treat these patients for:

1. Control the liver lesions ⇒ improve the survival
2. Control the symptoms ⇒ improve quality of life

**Touzios, Ann Surg 2005**

## LIVER METASTASES FROM NET

# MANAGEMENT

3 groups of patients:

- ✓ liver mts rectable with no extra-hepatic disease
- ✓ liver mts unresectable with no extra-hepatic disease
- ✓ liver mts unresectable with extra-hepatic disease

**Suttcliffe, Am J Surg 2004**

# RESECTION CRITERIA

1. **Vascular inflow and outflow must be preserved**
2. **Two adjacent liver segments need to be spared**
3. **Adequate remnant liver**
4. **R0 resection, but also palliative resection if more than 90% of liver disease is removed**

Severe carcinoid heart disease with hepatic venous pressure, may cause intra-operative bleeding → cardiac valve replacement prior to liver resection

## LIVER METASTASES FROM NET

# *RESECTABLE HEPATIC DISEASE*

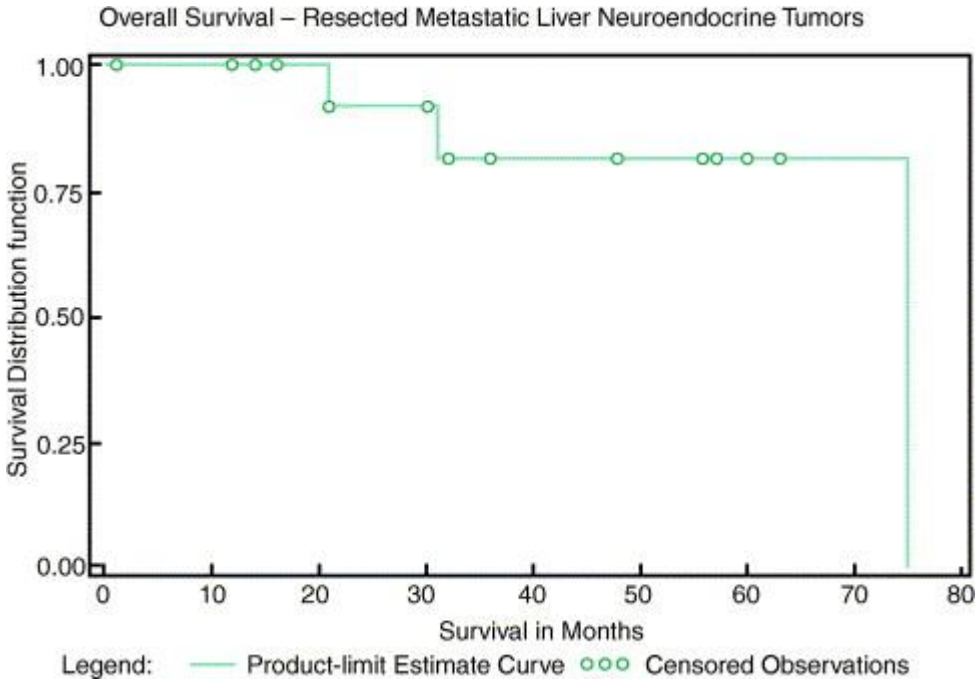
Recent Published Series Evaluating Outcome
After Liver Resection For Hepatic NET

| Source | Median Follow-up | Treatment | No Pts | Surv. Rate% 5-yrs |
|---|---|---|---|---|
| Sarmiento 2003 | not given | surgery | 170 | 61 |
| Norton 2003 | 32 | surgery | 16 | 82 |
| Chamberlain 2000 | 27 | surgery | 34 | 76 |
| Chen 1998 | 27 | surgery | 15 | 73 |

**Musunuru, Arch Surg 2006**

## LIVER METASTASES FROM NET

# *RESECTABLE HEPATIC DISEASE*




**Survival of patients with resected liver metastases from neuroendocrine tumours : 5 yrs surv 82%**

**Norton, Surgery 2003**

LIVER METASTASES FROM NET

# *RESECTABLE HEPATIC DISEASE*

## Prognostic Factors

**Anatom location (5yrs surv)**

Appendix 85.9%
Lung/bronchus 76.6%
Rectum 72.2%
Small intestine 55.4%
Colon 41.6%
Pancreas 34.1%

**Histological subtype**

Carcinoid better than noncarcinoid

**Histological grade**

17% vs 70% 5-year survival for poorly and well-differentiated tumors

**Expression of Ki-67 antigen**

(increase Ki-67 expression poor survival)

**Suttcliffe, Am J Surg 2004**

## LIVER METASTASES FROM NET

# *RESECTABLE HEPATIC DISEASE*

**Surgery** is the only potentially curative treatment for NET

Resection can provide:

- effective symptomatic relief (90%)
- 5-year SV 50-79%
- mortality < 5%
- morbidity 25%

Tumor recurrence 5-year 76%;  median 21-50 months

**Suttcliffe, Am J Surg 2004**
**Norton, Surgery 2003**

LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

## Treatment modality

Chemoembolization

Radiofrequency

Cryotherapy

Intralesional ethanol

Systemic or HAI CT

Pharmacological therapies ($\alpha$-IFN; Octreotide)

**Garrot, Hem Oncol Cl N Am 2007**

LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

## Chemoembolization

***RATIONALE***:

1. LIVER TUMORS DERIVE THEIR BLOOD SUPPLY FROM HEPATIC ARTERY
2. NUTRIENT FLOW FROM HEPATIC ARTERY TO A TUMOR IS TWICE THAT FROM THE PORTAL VEIN
3. PHARMACOKINEITC ADVANTAGE OF LOCOREGIONAL DRUG ADMINISTRATION: 10 TIMES HIGHER INTRATUMORAL CONCENTRATION

**Garrot, Hem Oncol Cl N Am 2007**

LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

## Chemoembolization

***INDICATIONS***:

- RAPID ENLARGEMENT OF TUMOR MASS
- INCREASING SYMPTOMS OF TUMOR BULK
- PATIENT PREFERENCE FOR THE PROCEDURE IN LIEU OF OTHER TREATMENTS (systemic chemotherapy)

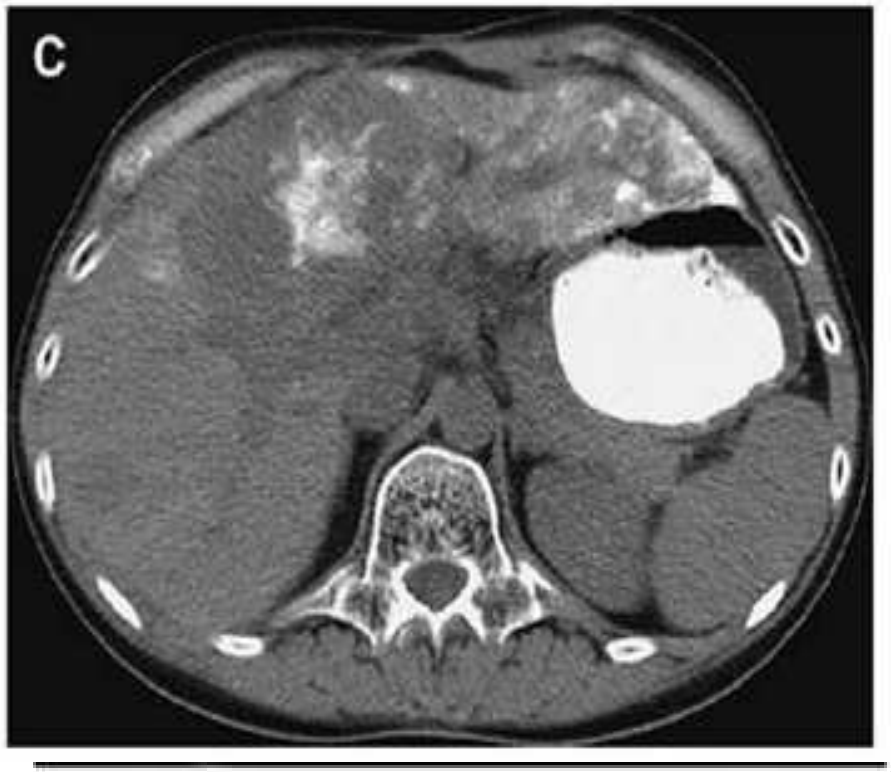
***CRITERIA***:

- RADIOGRAPHICALLY APPROPRIATE TUMOR
- PATENT PORTAL VEIN
- TOTAL BILIRUBIN <3 mg/dL
- ALBUMIN > 2.8 mg/dL
- ADEQUATE HEMATOLOGIC AND RENAL FUNCTION

LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

## Chemoembolization




- Mortality ≅ 0%
- Morbidity 20-30%
- Symptomatic response 53-95%
  for a period of 10-55 months
- Tumor size response 35-74%
  for a period of 6-63 months
- Survival 5-year 43-83%

# *RESECTABLE HEPATIC DISEASE*

## Chemoembolization

Hepatic artery chemoembolization may be used preoperatively:

- effective symptomatic relief (90%)
- reduce tumor bulk and facilitate resection

**Suttcliffe, Am J Surg 2004**
**Norton, Surgery 2003**

LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

## Radiofrequency

- percutaneously US-guided or laparoscopic/tomic
- local tumor control in the vast majority of patients (69-90%)
- endocrine symptoms abolished or reduced in 70-90%
- reduction plasma hormones in 60%
- 5 years SV: 40%
- local recurrence: 6-13%

**Mazzaglia, Curr Treat Opin Oncol 2007**

**Gilliams, Abdom Imag 2005**

# *UNRESECTABLE HEPATIC DISEASE*

## Criotherapy

- procedure similar to RF
- abandoned due to high rate of severe complications (21%), such as bleeding, bile leakage

## Alcohol injection

- alcohol causes coagulative necrosis with fibrosis and thrombosis of smaller vessels
- 3 years SV: 39%

**Bilichik, Surgery 1997**

**Giovannini, Cancer 1994**

## LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

| Treatment modality | Limitations |
|---|---|
| Chemoembolization | Adeguate hepatic function, patent portal vein, local toxicity |
| Radiofrequency | < 3 lesions, each < 5cm |
| Cryotherapy | small lesions, rarely done percutaneously |
| Intralesional ethanol | < 3 lesions, each < 5cm |
| Systemic or HAI CT | toxicity, lack of efficacy |

**Garrot, Hem Oncol Cl N Am 2007**

## LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

PHARMACOLOGICAL THERAPIES:

- $\alpha$-IFN (3-9 milion UI): biochemical response 50%
  CR <1%, PR 8%, SD 66%, PD 25%
- Octreotide (100-300$\mu$g/die): biochemical response 70%
  CR 8%, PR 36%, SD 34%, PD 22%

→ after 8-12 months no more effective because tumor become refractory to the medication

SYSTEMIC CHEMOTHERAPY:

- Streptozocin (alone or in combination): respose rate 36-73%

→ short duration
systemic toxicity

**Oberg, Ann Oncol 2001**
**Moertel, NEJM 1992**

# *UNRESECTABLE HEPATIC DISEASE*

## Liver Transplantation

- Less than 0.1% of patients are candidate for OLT
- Better 3 year survival than patients that underwent OLT for other tumors (64% vs 25% of the HCC)
- Recurrence at 5 years 50-75%, mainly in bone and liver

**Blonski W J Gastroenterol, 2005**
**Lehnert Transplantation, 1998**

# *UNRESECTABLE HEPATIC DISEASE*

## Liver Transplantation

Selection of patients with non-resectable metastatic NET for liver transplantation should be based on the Milan criteria:

- ✓carcinoids confirmed by histology
- ✓less than 50% of the liver replaced by metastases
- ✓primary tumor (originating from the gastrointestinal tract) drained by the portal venous system
- ✓absence extrahepatic disease
- ✓stable disease during the pretransplantation period

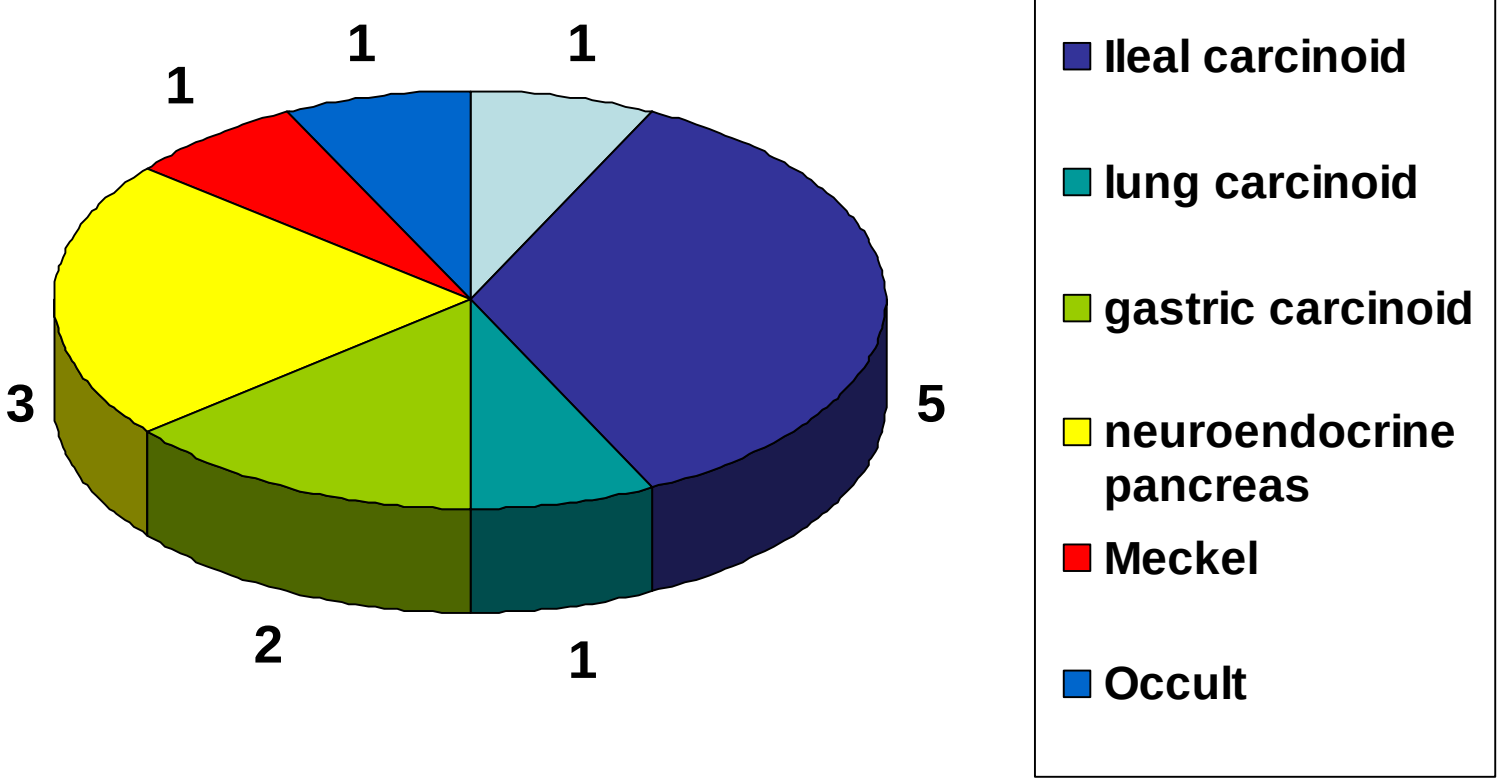
**Blonski W J Gastroenterol, 2005**
**Lehnert Transplantation, 1998**

# LIVER RESECTION FOR NET METASTASES

| | |
|---|---|
| • number of patients | 14 |
| • Age range | 23-71 years (median 44,5) |
| • Sex | 9 male |
| | 5 female |

# LIVER RESECTION FOR NET METASTASES

## PRIMARY TUMOR




CLINICA CHIRURGICA 2 1980-2008

# LIVER RESECTION FOR NET METASTASES

| | |
|---|---|
| • Number of lesions: | 1 - 4 |
| • Mean diameter of lesions | 5 cm |
| • Synchronous | 6 (43%) |
| • Metachronous | 8 (57%) |

Treatments before surgery:

- 1 case neoadiuvant CT
- 4 cases HAI
- 1 case neoadiuvant TACE

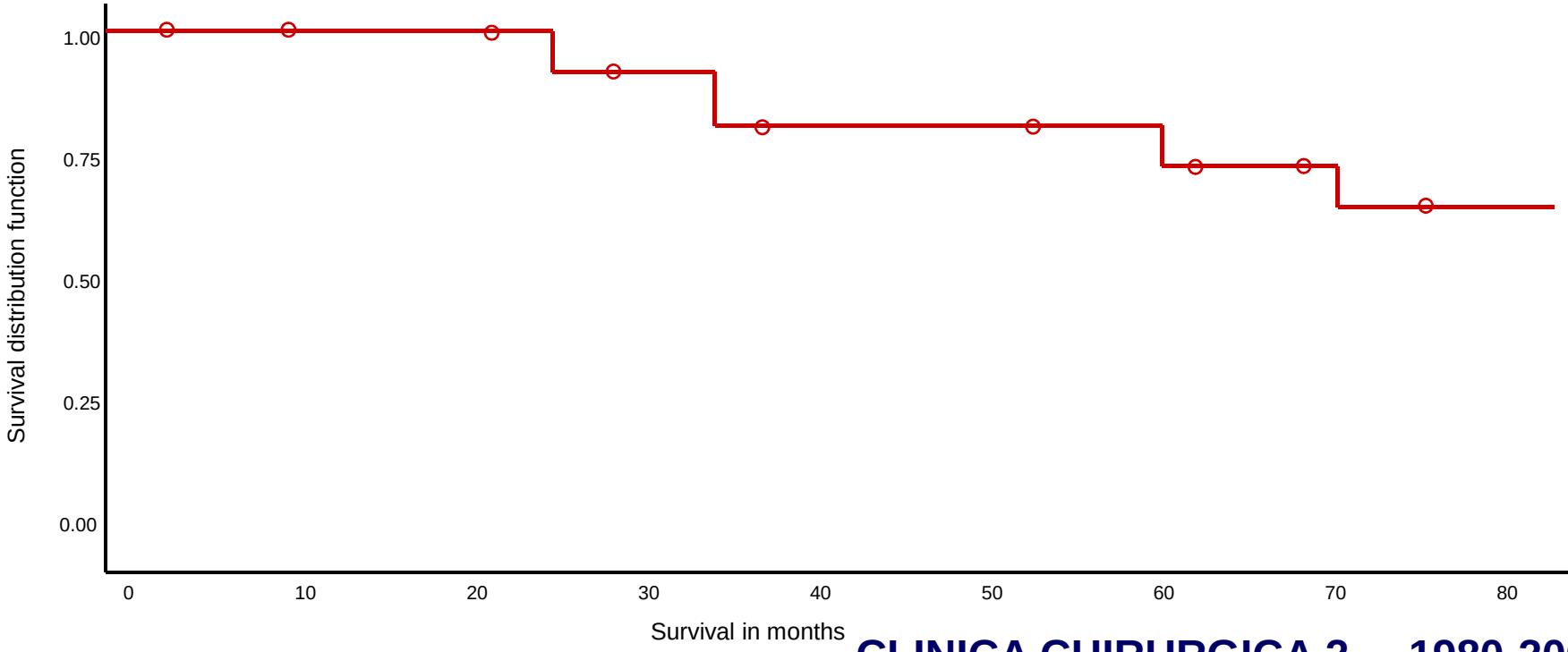
# LIVER RESECTION FOR NET METASTASES

## Type of Surgery

| | |
|---|---|
| Minor hepatectomy (≤ 3 segments) | 3 (22%) cases |
| Major hepatectomy (> 3 segments) | 11(78%) cases |

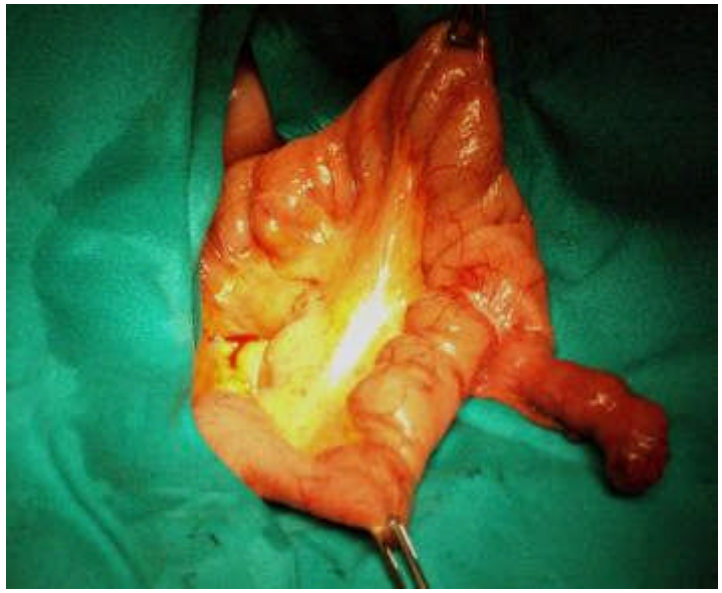
# LIVER RESECTION FOR NET METASTASES

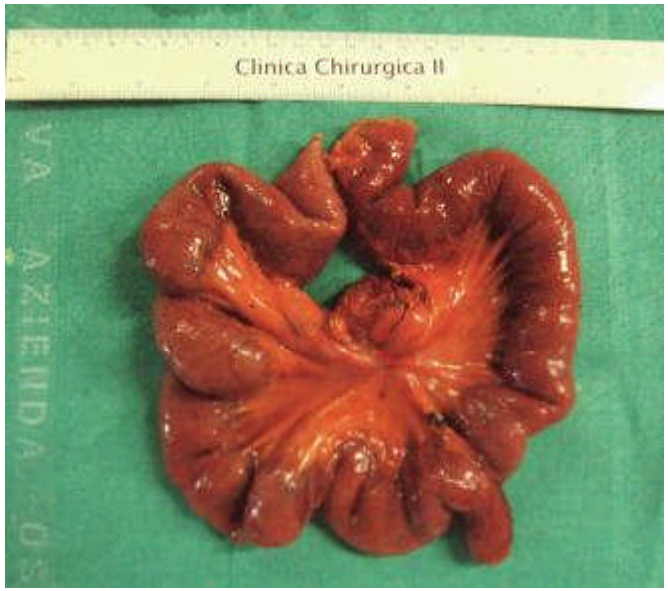
- Recurrence of disease: 3 cases (liver and lung mts) from 5 to 11 months after surgery
- Survival rates from 14 to 260 months (median 103)
- 5 year survival 70%




**CLINICA CHIRURGICA 2 1980-2008**

# LIVER RESECTION FOR NET METASTASES

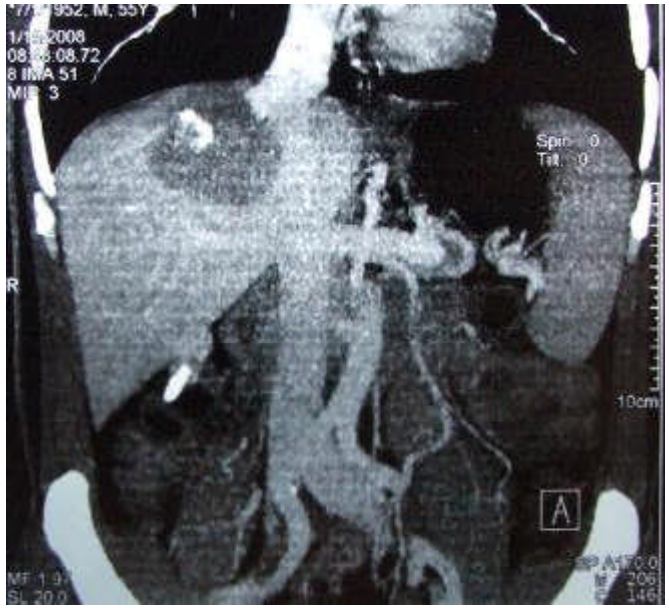


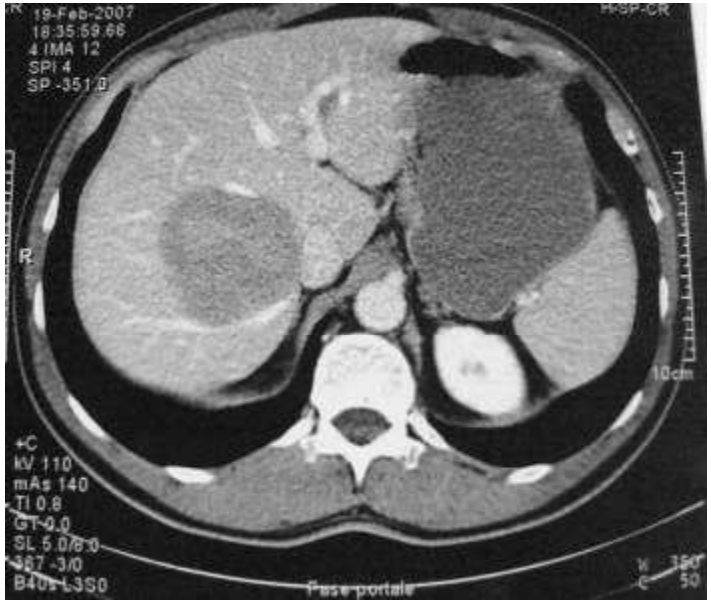



M.R. 55aa. 05/2007 resezione ileale segmentaria e biopsia epatica per carcinoide ileo (T2N1M1)

**CLINICA CHIRURGICA 2 1980-2008**

# LIVER RESECTION FOR NET METASTASES

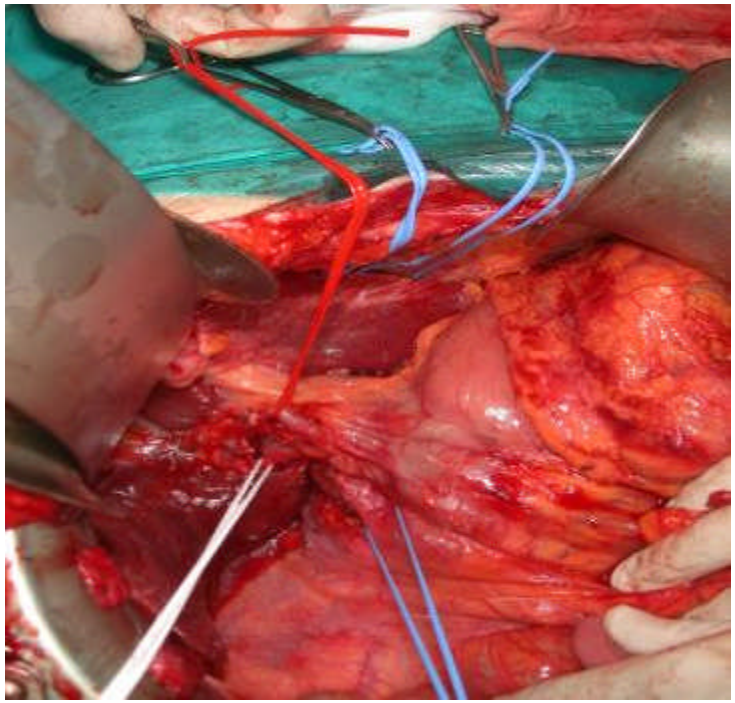


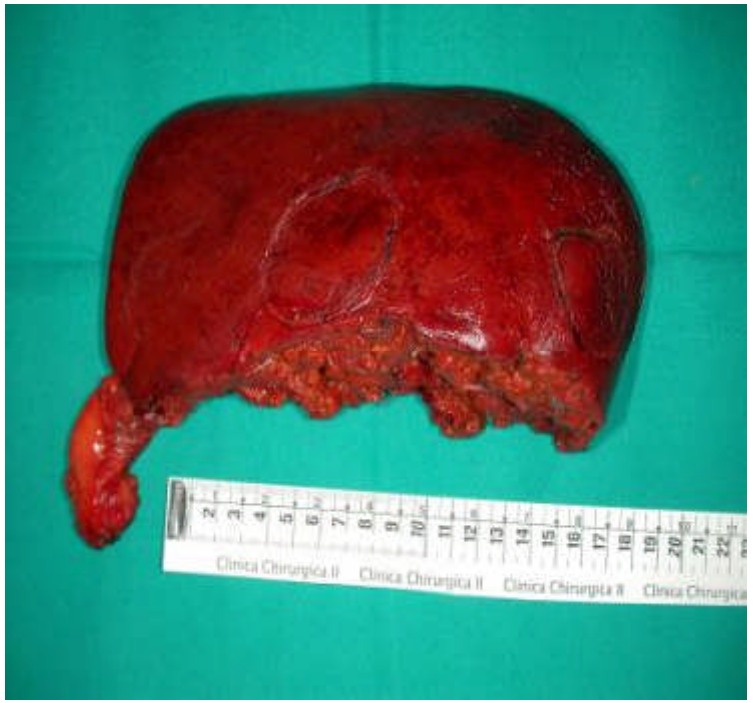



3 sedute di TACE con doxorubicina

**CLINICA CHIRURGICA 2 1980-2008**

# LIVER RESECTION FOR NET METASTASES



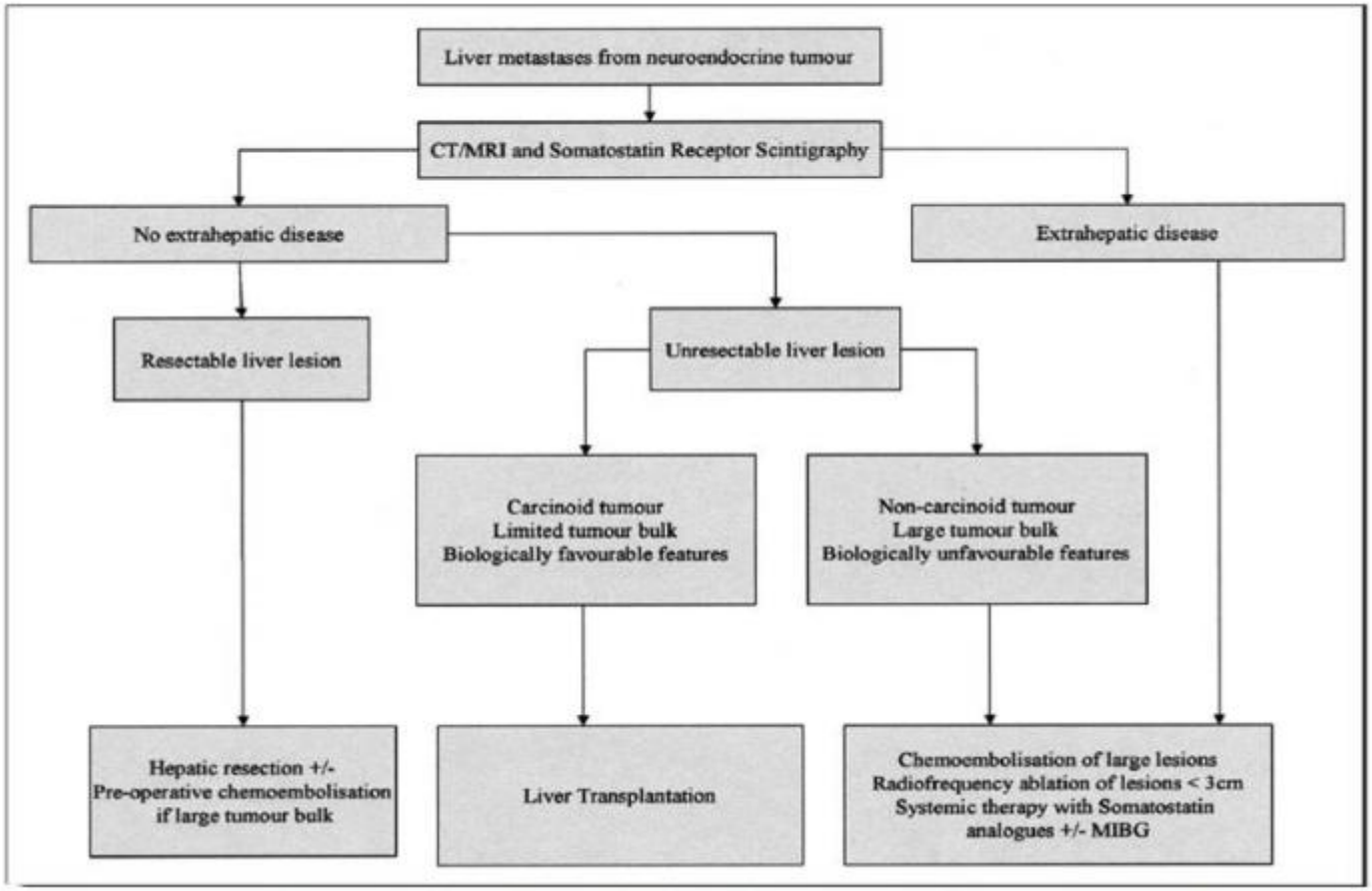


02/2008: EPATECTOMIA DESTRA

**CLINICA CHIRURGICA 2 1980-2008**

## LIVER METASTASES FROM NET

# MANAGEMENT




**Suttcliffe, Am J Surg 2004**

# LIVER RESECTION FOR NET METASTASES

## CONCLUSIONS

- Surgical treatment of NET metastases is the only curative treatment and should always be considered

- Some Authors recommends palliative resection if more than 90% of hepatic metastases are resectable

- However, less than 20-25% of the patients are eligible for either curative or palliative surgery

- Interventional palliative treatments of hepatic metastases, in combination with medical treatments, are relevants to reduce endocrine symptoms, to improve quality of life and to prolong survival

# LIVER METASTASES FROM NET

DISTRIBUTION BY SITE AND STAGE

| Carcinoid | Loco-regional | Distant |
|---|---|---|
| Esophagus | 33.4% | 66.6% |
| Stomach | 79.4% | 20.6% |
| Small Intestine | 68.6% | 31.4% |
| Colon | 62.2% | 37.8% |
| Appendix | 91.5% | 8.5% |
| Trachea/bronchi/lung | 93.0% | 7.0% |
| Cervix uteri | 66.4% | 33.3% |
| Ovary | 72.5% | 27.5% |
| Pancreatic endocrine tumor | | |
| gastrinoma | | |
| insulinoma | | |

Modlin, Cancer 1997

# LIVER METASTASES FROM NET

- Gastrointestinal carcinoid generally become symptomatic when associated with liver metastases

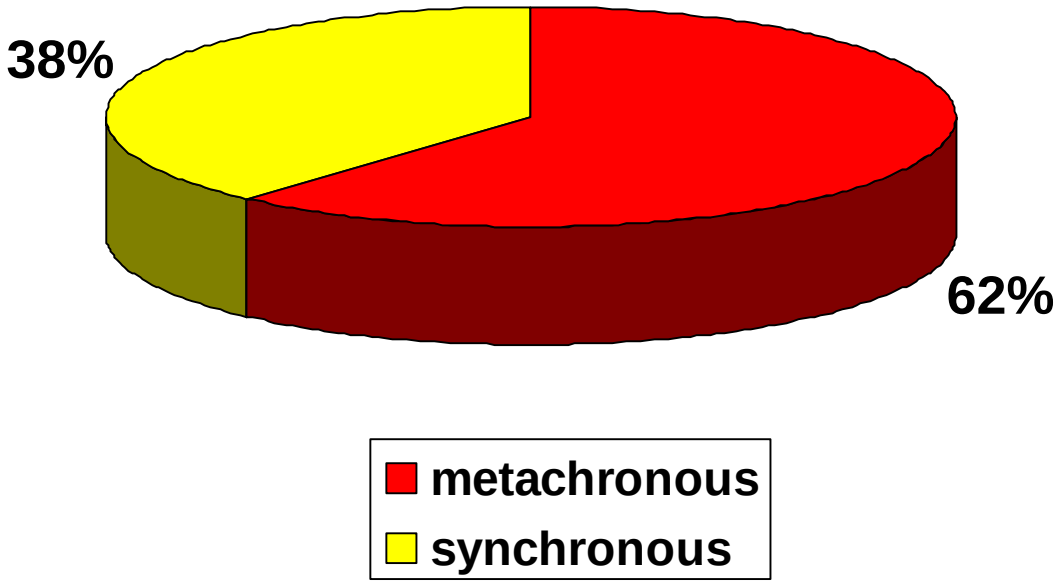
- Carcinoid syndrome is only associated with 4-10% of the primary carcinoid tumors, while the frequency goes up to 60% in the presence of liver metastases

**Suttcliffe, Am J Surg 2004**

CLINICA CHIRURGICA 2 1980-2008

# LIVER RESECTION FOR NET METASTASES

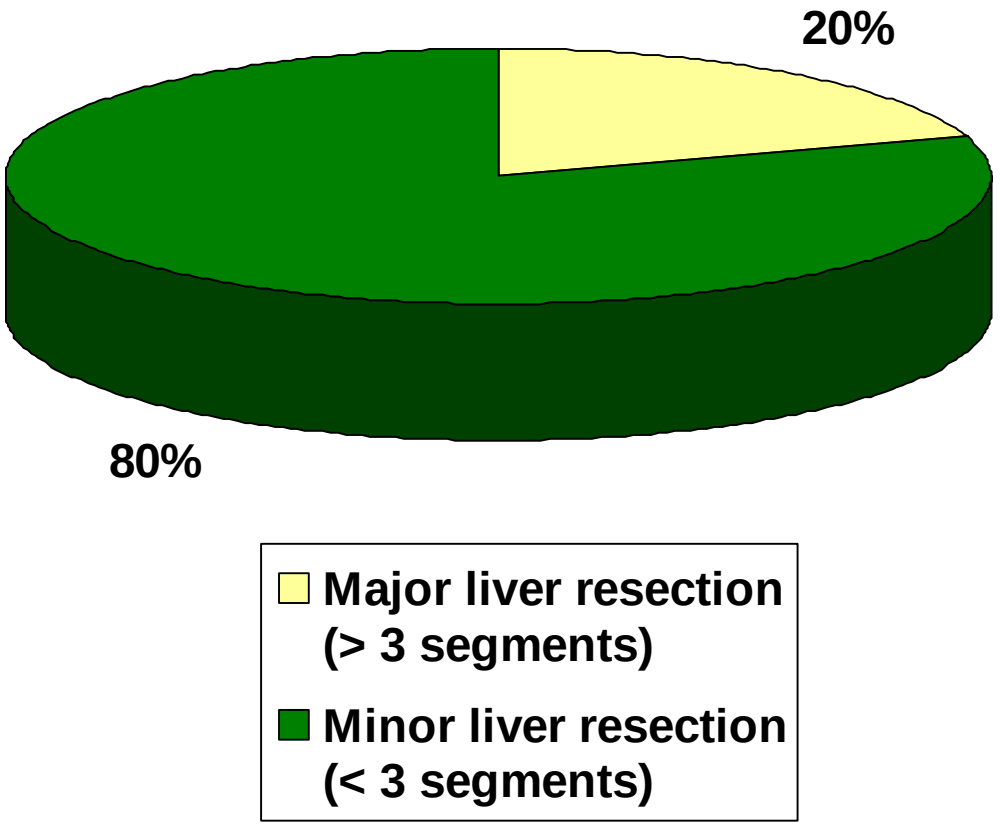
## TIMING OF METASTASES



CLINICA CHIRURGICA 2 1980-2008

# LIVER RESECTION FOR NET METASTASES

## SURGICAL TECHNIQUE



## LIVER METASTASES FROM NET

# *UNRESECTABLE HEPATIC DISEASE*

TACE, pharmacological therapy, systemic chemotherapy aims at a reduction of the tumour mass intending:

- to improve the response to systemic chemotherapy
- after systemic chemotherapy has failed
- to reduce the symptoms of progressive metastatic disease confined to the liver

# *UNRESECTABLE HEPATIC DISEASE*

## Liver Transplantation

OLT is indicated in very small group:

- ✓young patients (less than 50 years)
- ✓carcinoids confirmed by histology
- ✓well differentiated carcinoid tumors
- ✓medically uncontrolled endocrine symptoms
- ✓non extra-hepatic tumor
- ✓failure of all other treatment modalities

**Knigge, The Surgeon 2008**

## LIVER METASTASES FROM NET

# *RESECTABLE HEPATIC DISEASE*

**Pathological features of neurondocrine tumors suggestive of malignancy**

Tumor size
Invasion of nearby tissue or submucosa
Structural atypia with prevalence of broad solid areas
Presence of necrosis
Cellular atypia with reduced nuclear cytoplasmic ratio
Greater than two mitoses per 10 HPF
Increased Ki-67 positive nuclei counts
Evidence of angioinvasion and invasion of perineural spaces
Cellular dedifferentiation (loss of chromogranin A)
Nuclear p53 accumulation

**Suttcliffe, Am J Surg 2004**