

Friday, November 3, 2006

TOPIC: WELL-DIFFERENTIATED HINDGUT ENDOCRINE TUMORS AND METASTATIC LIVER

1:00 - 2:30 p.m. **LUNCH AND SIESTA**

2:30 - 5:35 p.m. Metastatic Liver
Chair: B. Taal, Amsterdam, The Netherlands

2:30 - 2:50 p.m. **Case presentation: liver with metastases from neuroendocrine tumors of midgut, hindgut or unknown origin**
B. Taal, Amsterdam, The Netherlands

2:55 - 4:05 p.m. **Working Group Sessions**
Pathology and Genetics
Group leader: A. Scarpa, Verona, Italy
Medicine and Clinical Pathology
Group leader: G. Delle Fave, Rome, Italy
Surgery
Group leader: R. Kianmanesh, Colombes, France
Imaging
Group leader: S. Pauwels, Brussels, Belgium

4:05 - 4:35 p.m. **COFFEE BREAK**

4:35 - 5:35 p.m. **General assembly**
Presentation of statements by the session chairs & general discussion
B. Taal, Amsterdam, The Netherlands

7:30 p.m. **GALA DINNER**

 Pathology and Genetics  Medicine and Clinical Pathology  Surgery  Imaging

ENETS Guidelines Neuroendocrinology 2004;80:394-424

Liver metastasis

Epidemiology

Clinicopathological staging

Prognosis/Survival

Q1: According to the current literature and to your experience, do you agree that the above headings for liver metastases of endocrine tumors depend almost entirely on the tumor site of origin?

- 5-10% of pts. with liver metastasis have no primary found in spite of intensive work-up (CUP)

- in referral centers mid- and hindgut tumors may present with 60-75% liver mets

- SEER: midgut 26%, hindgut 6% distant mets

Clinicopathological staging:

- depending on the grading

- extent and lobarity of the liver involvement influence clinical decisions

Prognosis is depending on the site of the primary.

Clinical presentation

Q2: According to the current literature and to your experience what are the major symptoms related to liver involvement in endocrine tumor disease metastatic to the liver?

- related to hypersecretion syndrome
- in nonfunctioning depending on tumor load there may be clinical signs (e.g. cholestasis and nonspecific tumor-related symptoms such abd. pain, weight loss, early satiety, lower leg edema)
- in nonfunctioning liver metastasis may be an incidental finding e.g. on ultrasound study
- in nonfunctioning liver metastasis tumor load is frequently higher than in functional tumors (expert opinion)

Q3: According to the current literature and to your experience, are these symptoms more frequently due to endocrine hyperfunction or to the simple tumor burden?

See Q2

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Diagnostic procedures

1. Tumour imaging

Ultrasonography, EUS, contrast-enhanced CT or MRT of the abdomen, MR-angiography for surgical decision-making, SRS.

Q4: Which procedure(s) is/are required for a *minimal (erase)* diagnostic approach?

Ultrasound, liver biopsy (min. size of biopsy cylinder-discuss with pathol), if NET Octreoscan, complete staging incl. CT (thorax, abdomen, pelvis), endoscopy

Q5: Which procedure should be initially performed?

See Q4

Q6: Is EUS required? When is it recommended? What is the role of CT, MRI, PET and SRS?

Histology

Poorly differentiated: Chest/Abdomen/pelvis CT for baseline. Octreoscan.

Well differentiated

In search of a primary if available: CT-SPECT (contrast enhanced, triphasic diagnostic CT of the chest, abdomen and pelvis, SPECT OctreoScan) or CT-PET (contrast enhanced, triphasic diagnostic CT of the chest, abdomen and pelvis, PET: Ga-68 somatostatin analogue).

If no hybrid camera available: whole body CT (1. abdomen+pelvis, if negative chest), as above, plus octreoscan.

If indicated, colonoscopy (including the distal ileum) or if available colon CT (with neutral enema), and depending on the treatment planning.

If partial liver surgery is planned or if CT is inconclusive, (T2 weighted thin slice) dynamic Gd-enhanced MRI, and if available, contrast enhanced US.

Planned liver transplantation: see search primary tumor plus local requirements according to protocol.

F-DOPA PET is investigational and promising.

Q7: Which type of PET is recommended?

See Q6

Q8: Please suggest your imaging/procedure flow-chart for metastatic liver.

See Q6

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2. Biochemistry

Chromogranin A, 5-HIAA in 24-hour urine, insulin, C-peptide, gastrin, PP, VIP, glucagon family peptides, calcitonin, somatostatin,...

Q9: What is the **minimal** biochemical work-up for metastatic liver?

CgA, 5-HIAA

Q10: When should biochemical tests be performed?

At diagnosis and follow-up

Q11: Is germline DNA testing recommended?

N.A.

If so, which genes?

N.A.

Which method?

N.A.

Q12: Is somatic (tumor) DNA testing recommended?

N.A.

If so, which genes?

N.A.

Which method?

N.A.

Q13: When is genetic counseling recommended?

N.A.

Q14: Would you recommend collecting a consensus statement for genetic testing?

N.A.

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3. Histopathology

Hematoxylin-eosin, chromogranin A, synaptophysin, specific hormones (5HT, gastrin etc), silver impregnation tSts, Ki-67,...

Q15: Is histology required?

Yes

Q16: Is cytology recommended and, if so, in which clinical situations?

Yes, if histology not feasible.

Q17: What are the minimal ancillary tests required to support the histological diagnosis?

For **known primary**: CgA and synaptophysin; for MEN patients, primary-specific markers (e.g. gastrin, insulin, PP, etc.).

For **unknown primary**: CgA, synaptophysin and markers characteristic of specific primary sites (to be further specified: TTF1-bronchial, CDX2-gastrointestinal, serotonin-midgut, PP-foregut, etc.; consider cost-effectiveness, hierarchical algorithm).

Q18: Is the mitotic index necessary? If so, which method?

Yes, see VA TNM paper1.

Q19: Is the Ki-67 index necessary? If so, which method?

Yes, see VA TNM paper1.

Q20: Is IHC required for tumor cell subtyping and, if so, when?

See Q17.

Q21: Would you recommend IHC for P53?

No.

Q22: Would you recommend IHC for SSR2A receptor?

On demand.

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Surgical therapy

Surgery for Liver Metastases

Midgut origin. If functional symptoms of the carcinoid syndrome cannot be managed by medical therapy alone, debulking of the hepatic tumour mass may be a life-saving procedure. Symptomatic response to hepatic resection is seen in up to 90% of the patients [11–13, 29], with a median duration of 19.3–45.5 months [11]. Most tumours progress/recur after palliative surgery (probability of progression/recurrence 84–91% at 5 years) [11, 13]. The median time to progression varies between 20 and 16 months [13] depending on the type of surgical intervention (complete or palliative resection). While historical data give a 5-year survival of 30% [17], 5- and 10-year survival after surgical intervention is 39–76 and 35–60%, respectively [10, 11, 13, 14, 19, 20, 26, 27], there is an indication that surgery can delay tumour progression [13, 27]. In addition, the reduction of functionally active tumour volume may increase the efficacy of adjuvant medical therapy [19]. As no difference has been observed in the outcome of functioning and non-functioning midgut tumours with liver metastases [13], resection of liver metastases should be considered for both tumour types.

Comments

Surgery should only be undertaken if at least 90% of the tumour mass can be removed successfully [3, 24, 26, 28]. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection [26, 29]. If the criteria for extensive hepatic surgery are fulfilled, mortality of palliative hepatic surgery should not be higher than 3–5% and morbidity about 30% [3, 19]. For palliation, metastatic disease should be confined to the liver [9, 24, 26]. It is unclear whether hepatic surgery should be performed only after prior surgery of the primary, synchronous with surgery of the primary or even in cases of non-resectable primaries [9]. With multiple liver tumours a two-stage liver resection strategy is an option [29]. Cholecystectomy should be undertaken synchronously during hepatic surgery to prevent the formation of gallstones during somatostatin analogue therapy and ischaemic complications of the gallbladder subsequent to chemo-embolisation [24]. As carcinoid heart disease has a profound effect on survival, it should be excluded or, if significant, treated surgically before tumour debulking is undertaken [10, 20, 24]. Specific anaesthesiological procedures and peri-operative somatostatin analogue infusion are indicated to prevent a peri-operative carcinoid crisis in patients with functional tumours [3, 24].

Hindgut origin. Hindgut tumours rarely have functional symptoms hence resection for a hormonal syndrome is unlikely. There is no evidence for debulking resection for hindgut tumours; however, for bi-lobar liver metastases a two-stage liver resection strategy is an option. As for midgut carcinoid, most tumours recur after palliative surgery; however, there may be a delay of progressive tumour disease. Surgery should only be undertaken if at least 90% of the tumour mass can be removed successfully. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection. If criteria for extensive hepatic surgery are fulfilled, mortality of palliative hepatic surgery should not be higher than 3–5% and morbidity about 30%. Metastatic disease should be confined to the liver. It is unclear whether hepatic surgery should be performed only after prior surgery of the primary, synchronous with surgery of the primary or even in the case of a non-resectable primary. Cholecystectomy should be undertaken synchronously with hepatic surgery to prevent the formation of gallstones in patients requiring somatostatin analogue therapy and ischaemic complications of the gallbladder subsequent to chemo-embolisation.

Q23: What are the minimal criteria required for “curative intended” liver surgery?

Resectable* metastases with low morbidity (patient and surgical procedure).

- No right heart deficiency.
- No extraabdominal metastases.

- No peritoneal carcinomatosis.

*sufficient postoperative liver parenchyma to avoid liver insufficiency

Q24: When is “curative” liver surgery recommended?

As first line option after specialized evaluation, if LMs are resectable with low risk.
After down-staging by other procedures in some patients.

Q25: What surgical procedures are recommended for liver metastases in both curative and palliative settings?

-Complete surgery (R0/R1) for curative surgery.

-Incomplete surgery (R2) only in selected cases, if more than 80-90% (debulking) of the tumor volume can be resected (and or ablated) with low risk.

Rq: valid also for other WDEC.

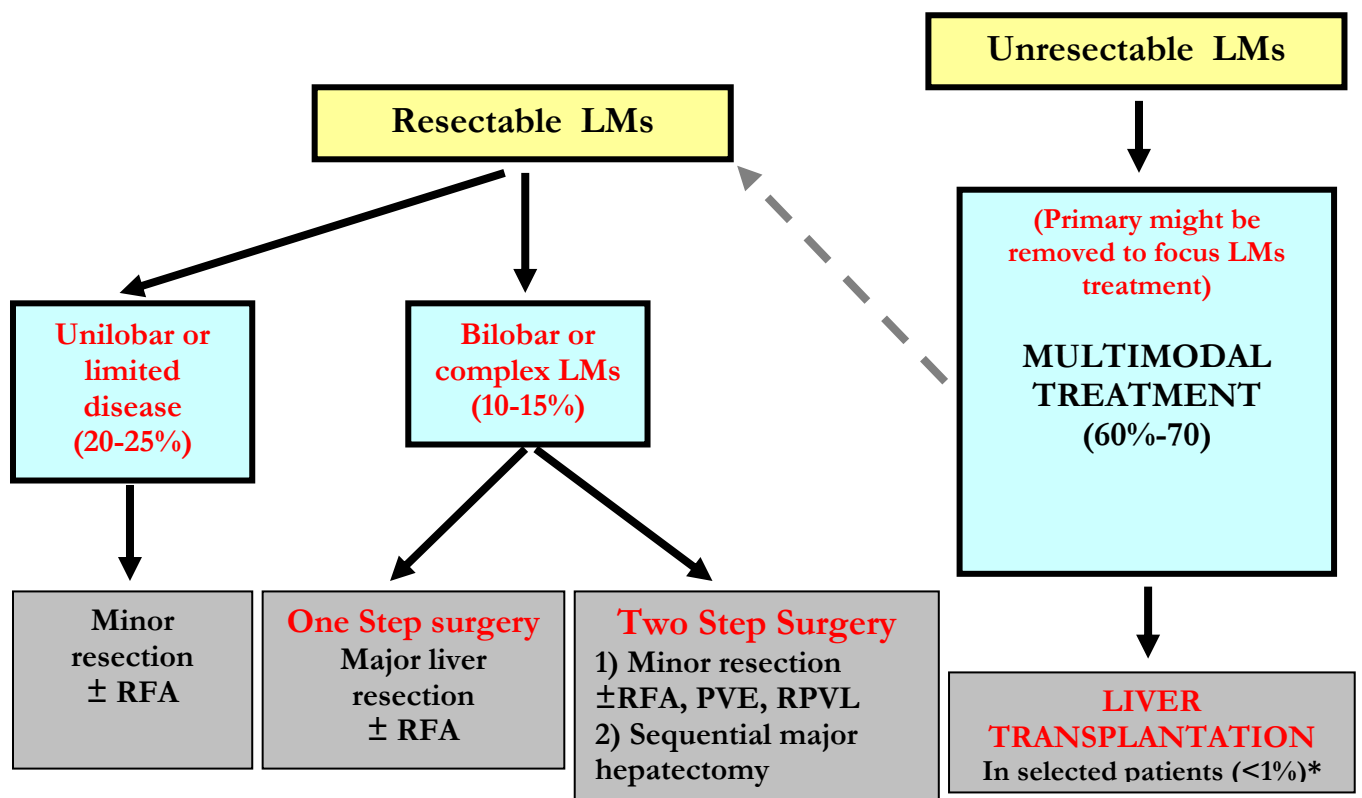
Q26: If heart surgery is required, when should this be done?

Before liver surgery (wait at least 3 months after heart surgery, because of the need of antivitamine K treatment after valvular replacement).

Q27: Please define your recommended flow-chart for liver metastases treatment in both “curative” and palliative settings.

Percentage of respectable liver mets (40%) reflects surgical bias, lower in medical-oncological population

See chart.



Q28-Q29: In any surgical setting, is medical therapy required? If so which type, modality and timing should be adopted?

Carcinoid syndrome needs medical treatment prior to intervention (surgery, ablative therapies).

Synchronous versus Metachronous Surgery of Primary Tumour and Liver Metastases

Midgut origin. There are no studies specifically comparing the effect of synchronous versus metachronous surgery of the primary tumour and liver metastases. Analyses of subgroups thus far indicate a better prognosis for patients with hepatic surgery after resection of the primary. However, the effect may well be due to selection bias, owing to a better prognosis in those diagnosed with localized disease [26].

Q29: On the bases of your experience and the current literature, what would you recommend as for curative synchronous vs metachronous surgery for primary and for liver metastases?

- **Synchronous LMs:** resection of both primary and LMs if low risk patient and intervention (unilobar metastases). If major or complex liver resection required a two stage surgery is preferred to reduce the operative risk (resection first of the primary+LN resection, and second the treatment of LMs).
- **Metachronous LMs:** uni- or bilobar and resectable → resection ±RFA, ±portal vein embolization. Major hepatectomy in one or two stages (after verifying no local recurrence).
- Intraoperatively unresectable LMs: resect the primary+LN (upon operative and occlusive risks).

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Liver Transplantation

Midgut origin. Liver transplantation may be an option in patients with metastases confined to the liver. Possible indications for liver transplantation: tumours not accessible by curative surgical therapy or major cytoreductive therapy; tumours not responding to medical therapy, and tumours that cause life-threatening hormonal symptoms. Aggressive, rapidly proliferating carcinomas should be excluded [12, 18, 30–37].

Comments

Experience with liver transplantation is restricted. Liver transplantation is fraught with a high peri-operative mortality and a high rate of recurrent disease. Improved methods for the detection of extrahepatic metastases are necessary before liver transplantation can be used, more frequently for patients with a large bi-lobar tumour burden. The timing of transplantation is not well-defined (i.e. whether patients with bulky, but stable liver metastases should be operated on or, preferably, when the disease is slowly progressive). Up to now, liver transplantation cannot be considered a routine therapeutic option.

Hindgut origin. Liver transplantation may be an option in patients with metastases confined to the liver. There would need to be robust determination that there is extra-hepatic disease. Consideration would be on an individual patient basis [34, 35].

Q30: When is liver transplantation recommended? Please define the minimal criteria required for liver transplantation.

- Unresectable diffuse LMs in selected patients without extrahepatic disease. (QS: uncontrolled hormonal syndrome from insulin, histamine, catecholamine and life threatening diseases).
- Low anesthetic risk for LT; age < 50-60 (vs 65 for conventional criterion for LT)
 - No extrahepatic disease (unless LNs on recent morphological assessment).
 - Primary resected
 - Low Ki67 (5-10%?)

Q31: What is the recommended surgery for liver transplantation?

Most data in the literature are reported with cadaveric entire transplants. However few cases of partial LT with living donor have been successfully performed.

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Cytoreductive therapy

Loco-Regional Ablative Therapy

Midgut origin. Hepatic artery occlusion is directed at interrupting the arterial supply of highly vascularised neuroendocrine hepatic metastases. Initially ischaemia has been achieved by surgical ligation of the hepatic artery alone or in combination with intra-arterial chemotherapy. Due to the substantial peri-operative risk, mortality and rapid revascularisation with collateral formation and surgical hepatic artery occlusion is no longer recommended. The following options are available.

1. Selective (Chemo)-Embolisation

Selective embolisation of peripheral arteries induces temporary, but complete ischaemia. The procedure can be performed repeatedly. Survival rates in patients treated with arterial embolisation are between 59 and 64 months after the occurrence of the first symptoms of the carcinoid syndrome [38]. For chemo-embolisation the cytotoxic agent most often used is doxorubicin [39–44]. Indication: If surgery is not feasible, (chemo)-embolisation as an anti-proliferative treatment modality is an option. The combination of peripheral hepatic artery embolisation with local cytotoxic chemotherapy effectively reduces symptoms of an otherwise untreatable hypersecretion syndrome as well as symptoms caused by extensive tumour burden.

Comments

Complete or partial responses for symptoms, tumour markers and imaging occurred in 73–100, 57–91 and 33–35% of the patients, respectively [39–42]. The duration of symptomatic response and mean survival time were 14–22 and 24–32 months, respectively [39–42]. Whether survival is prolonged following chemo-embolisation has yet to be demonstrated. All the results given include repeated chemo-embolisation procedures as deemed necessary or possible in an individual patient. Doxorubicin is the cytotoxic drug most often used [39–46]. Due to its hepatic clearance, doxorubicin-specific systemic side effects are decreased. However, toxic effects on the endothelium may reduce the feasibility of repeated chemo-embolisation. Mortality (0–3.3%) of the procedure is low in experienced hands [39–44, 46]. As significant morbidity may result from this procedure, chemo-embolisation should be performed only in experienced centres. Minor side effects such as nausea and vomiting (50–70%), right upper quadrant pain (50–60%), fever (30–60%), and elevation of transaminases (100%) are common [45]. This post-embolisation syndrome is often observed. Major observable side effects include: gallbladder necrosis; hepato-renal syndrome; pancreatitis; liver abscess, and formation of aneurysms. The procedure is contraindicated in patients with complete portal vein thrombosis and hepatic insufficiency [3, 39–44]. The following points remain unclear: whether chemo-embolisation is preferable to embolisation alone; timing of sequential (chemo)-embolisations, and choice of cytotoxic agents (e.g., doxorubicin vs. streptozotocin). The only study which compared the results of hepatic resection with chemo-embolisation demonstrated prolonged survival in the former. However, selection bias may have influenced the outcome towards hepatic surgery [11].

Hindgut origin. Hepatic Artery Occlusion – Embolization treatment is directed at interrupting the arterial supply of highly vascularised neuroendocrine hepatic metastases. Hepatic artery occlusion may be indicated in patients with nonresectable bi-lobar hepatic metastases or in patients with untreatable hormonal hyper-secretion syndrome. Ischaemia can be achieved by hepatic artery ligation, alone or in combination with subsequent systemic chemotherapy or by selective embolisation alone or combined with intra-arterial chemotherapy (chemo-embolisation). There is no evidence to suggest benefit of chemo-embolisation alone vs. particle embolisation.

Q32: Which criteria should be adopted to define the type and select the timing for loco-regional ablative therapy?

No prospective study comparing RFA versus limited hepatectomy.

In the treatment of other LMs, RFA is associated with a rate of local recurrence (10-20% within 2 years).

RFA usually indicated for tumors with less than 4 cm in diameter, far from major liver structures (biliary duct, major vessels) and capsula, for unique or limited number of nodules (<5).

PS: in selected patients, RFA can be associated at pre-, intra- and postoperative period. RFA can repeatedly be performed.

Q33: When and which type of selective chemo-embolization is most recommended?

PS: in patients who might benefit from LDLT, multiple TACE can induce endoarteritis rendering more difficult the partial liver transplantation (arterial thrombosis...).

For comment by medical group refer to Q43

Q34: Which cytotoxic agents are recommended?

See Q43.

Q35: On the basis of the current literature and of your experience, are there differences in response to selective chemo-embolization therapy according to the tumor primary?

See Q43.

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2. Local Ablative Therapy

Radiofrequency ablation is now preferred to cryotherapy in most centres. There are no published data on laser-induced thermal therapy in neuroendocrine tumours.

2.1 Radiofrequency Ablation

Midgut origin. Indication: Radiofrequency ablation is effective in reducing hepatic (or even extrahepatic) tumour mass in functioning and non-functioning midgut carcinoids. Depending on the tumour location radiofrequency ablation can be performed laparoscopically or percutaneously [47–49]. However, intra-operative ultrasonography is essential for staging [50].

Comments

Radiofrequency ablation can be used repeatedly within one metastasis [47]. Depending on the technique, tumour volume and tumour numbers are limiting factors. Symptomatic improvement could be achieved in 95% of the patients, a partial or significant decrease in tumour markers was observed in 65%, and median survival was 1.6 years after radiofrequency ablation in the largest series so far (34 patients with 234 neuroendocrine metastases). During a median follow-up of 1.6 years, 41% of the patients showed no disease progression [51]. In experienced hands mortality and morbidity are low (5%) [51]. The method can be used as an adjunct to surgical therapy [47–52]. No data exist on whether tumour volume reduction by radiofrequency ablation has any effect on survival.

Hindgut origin. Radiofrequency ablation is effective in reducing hepatic tumour mass in functioning intestinal carcinoids. Radiofrequency ablation can be used repeatedly. For tumours >4 cm diameter and more than 6 tumours, radiofrequency ablation is not recommended. The method can be used as an adjunct to surgical therapy. No data exist on whether tumour volume reduction by radiofrequency ablation has any affect on survival [33].

2.2 Cryotherapy

Midgut origin. Cryotherapy has been performed as an adjunct to open surgery but is now replaced by radiofrequency ablation in most centres. Few data on this technique in the treatment of neuroendocrine tumours are available [53–56]. A combination of radiofrequency ablation and cryosurgery may reduce the morbidity (coagulopathy and thrombocytopenia) of cryosurgery. Lesions of >3 cm may be treated more effectively by cryosurgery than by radiofrequency ablation [56].

Hindgut origin. Cryotherapy effectively reduces tumour mass in patients with intractable hypersecretion syndrome. It can be performed repeatedly and does not preclude subsequent surgical debulking. Cryotherapy is mostly performed as an adjunct to open surgery. No data exist showing whether tumour volume reduction by cryoablation has any affect on survival [23].

2.3 Hepatic Radioembolisation

Midgut/hindgut origin. Radioembolisation is an experimental approach for hepatic metastases.

Microspheres labelled with radioactive isotopes are used for hepatic embolisation and simultaneous local irradiation (brachyradio therapy) [58].

2.4 Alcohol Injection

Midgut origin. Alcohol injection into liver metastases has been used for metastases of different tumours. Experience with midgut carcinoids is small [49].

Hindgut origin. Alcohol injection into liver metastases has no evidence base for neuroendocrine tumours but may be useful for tumours >3 cm in size.

Q36: Which type of local-ablative therapy is recommended and when?

RFA and laser induced thermal therapy are preferred to alcohol injection and cryotherapy.
No data for NET are available.

Q37: What are the minimal criteria required for local-ablative therapy?

See Q32.

Q38: What are the recommended criteria for choosing the best local-ablative therapy (radiofrequency ablation vs cryotherapy vs radioembolization vs alcohol injection)?

RFA for limited small nodules. No data are available for NET.

In limited disease first line surgery

The outcome of RFA-Tx is not clear up to now. A recommendation cannot be made and it is open to the treating center.

Q39: On the basis of the current literature and of your experience, are there differences in response to local-ablative therapy according to the tumor primary?

No ?

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Medical therapy (see specific tumor sessions)

1. Biotherapy

1.1. Somatostatin analogues

1.2. Interferon.

2. Systemic chemotherapy

3. Somatostatin Receptor Radionuclide Therapy

Q40: Is somatostatin analog therapy recommended for liver metastases treatment? If so, when and how?

- for syndrome control, prevention of carcinoid crisis (i.v.-drip)
- for antiproliferative treatment see midgut session, surgery needs to be considered first
- when & how: see guidelines (Ann Oncol)

Q41: Is interferon therapy recommended for liver metastases treatment? If so, when and how?

See midgut session

Q42: When is chemotherapy recommended in patients with liver metastases?

Not systemic CTx recommended, but with chemoembolization

Q43: Which cytotoxic agents and what regimens for locoregional are recommended?

No current evidence existing that TACE is superior to TAE.

If TACE: doxorubicin or streptozotocin (in general anaesthesia) in mixture with lipiodol

Difference in efficacy of the procedure depending on the primary

Control of symptoms, tumor growth, biochemical markers

Q44: Can PRRT be recommended? If so, when and which type?

Yes, if inoperable and SRI positive.

See also midgut session

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Follow-up during/ after treatment

Ultrasonography or MR/CT and biochemical markers, including those initially elevated every 3 months. Diagnosis of bone metastases (if clinical signs are present?) by Octreoscan and/or bone scan and MR

Q43: What is the scheduled follow-up?

3 months for the first year or according to the protocol

Q40: What are the minimal examinations required and for how long?

CgA, CT-scan every 3-6 months

Bone metastasis: octreoscan/bone-scan (ask nuclear medicine experts), if positive: MRI, follow-up according to clinical requirements

Symptomatic treatment of bone metastasis: local radiation, bisphosphonates (expert opinion, no data)

Antiproliferative Tx of bone metastasis: PRRT, if octreoscan-positive

Imaging of distant metastasis according to clinical requirements, octreoscan as first-line screening method