Recommendations for management of patients with neuroendocrine liver metastases

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Many management strategies exist for neuroendocrine liver metastases. These strategies range from surgery to ablation with various interventional radiology procedures, and include both regional and systemic therapy with diverse biological, cytotoxic, or targeted agents. A paucity of biological, molecular, and genomic information and an absence of data from rigorous trials limit the validity of many publications detailing management. This Review represents the views from an international conference, for which 15 expert working groups prepared evidence-based assessments addressing specific questions, and from which an independent jury derived final recommendations. The aim of the conference was to review the existing approaches to neuroendocrine liver metastases, assess the evidence on which management decisions were based, develop internationally acceptable recommendations for clinical practice (when evidence was available), and make recommendations for clinical and research endeavours. This report represents the final clinical statements and proposals for future research.

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Introduction

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (GEP NENs), also called GEP neuroendocrine tumours (NETs) or carcinoids, were previously regarded as rare, but in fact are increasing in incidence (3·65 per 100 000 individuals per year[1]) and occur as frequently as testicular tumours, Hodgkin's disease, gliomas, and multiple myeloma.[2] They represent an important clinical issue for two reasons: first, 40–95% are metastatic at diagnosis, and second, evidence-based best practice strategies are scarce. Most present management is based on a synthesis of experience, local practice patterns, or archaic concepts.[2] The central management issue is that at diagnosis about 65–95% of GEP NENs (excluding appendiceal, gastric, and rectal NETs, about 85–90% of which are local) show hepatic metastasis.[3,4] Indeed, liver metastases represent the most crucial prognostic factor, irrespective of the primary NET site. In historical series, 5 year survival is 13–54% compared with 75–99% for patients without hepatic metastases.[5,6] Experience indicates 5 year overall survival of 56–83% for metastatic intestinal NETs and 40–60% for pancreatic NETs,[7] which is indicative of earlier diagnosis, more advanced imaging techniques, amplified surveillance, and the implementation of new treatment approaches.[2] Despite various complex management strategies for neuroendocrine liver metastases, surgery is the only treatment that offers potential for cure.[7] For unresectable lesions, optimum selection of palliative treatment options (timing and method) is crucial to maintain or improve quality of life and prolong survival. A key need is for the development of strategies that identify patient subgroups that would benefit from specific treatment and personalise management of neuroendocrine liver metastases.

To this end, the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) initiated a consensus conference to address optimisation of management of neuroendocrine liver metastases. The aims were to: critically review the existing approaches to neuroendocrine liver metastases, assess the evidence on which management decisions were based, develop internationally acceptable recommendations for clinical practice (when evidence was available), and make recommendations for clinical and research endeavours.

Methods

The conference was organised by the E-AHPBA and seven national and international societies focused on liver diseases or NETs, and was held on Dec 12–13, 2012, in London, UK. The Danish Consensus Conference model[8] was used. 15 key questions about diagnosis and management were defined for assessment by 15 groups selected by the scientific committee on the basis of their expertise in the specific area. The recommendations presented by the working groups were debated in plenary sessions and modified in real time by the session chairpersons on the basis of the conclusions of the open debates. At the end of the conference, the jury met to develop final recommendations based on individually submitted expert reports, material accumulated during the topic discussions, attendee responses, and individual judgment. Final statements were developed on the basis of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[9] The grade strength of the clinical recommendations included assessments of the quality of evidence, the balance of desirable versus undesirable outcomes, the values and preferences of patients and physicians, and resources available—eg, a large randomised trial (potentially grade A) versus studies with heterogeneous populations, techniques, and outcomes (grades C or D). We discuss the 15 key issues. Additional meeting text and references are provided in the appendix.

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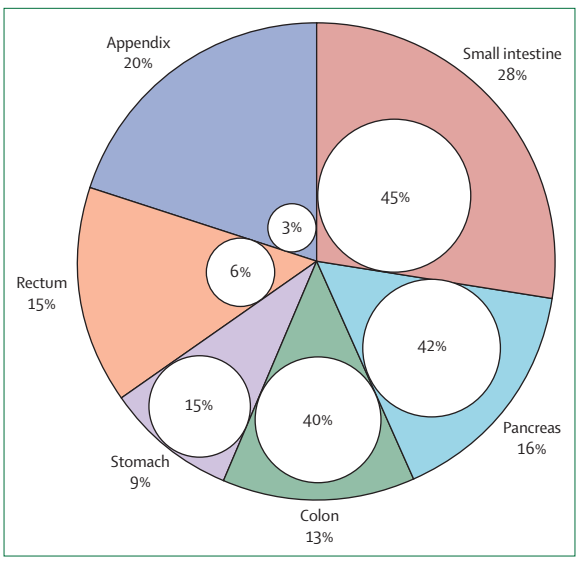

Figure 1: **Sites of primary GEP NETs (segments) and metastases (circles)**
The most common site of primary GEP NETs and metastases is the small intestine. Rectum and appendix rarely metastasise (<10%).[1]

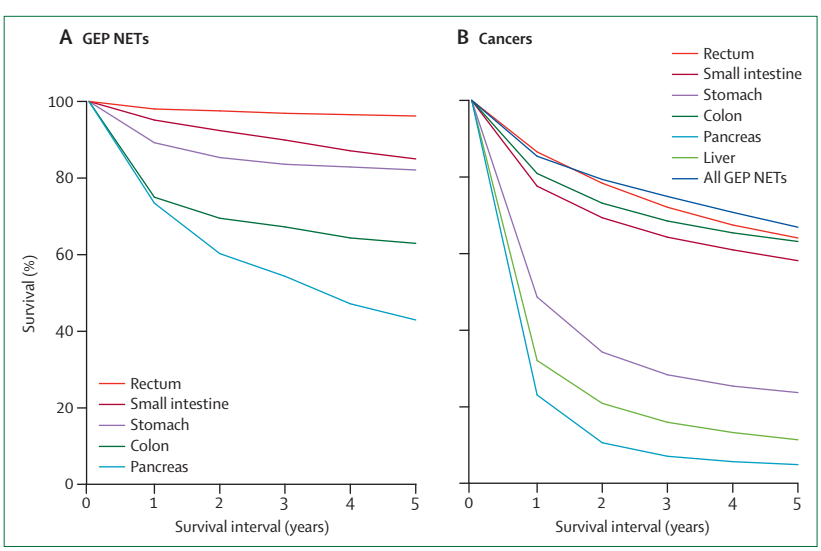

Figure 2: **5 year survival for NETs (A) and gastroenteropancreatic cancers (B)**
Gastroenteropancreatic neuroendocrine tumours (GEP NETs) have a significantly better survival than adenocarcinoma at the same location. The 5 year survival of neuroendocrine liver metastases is less than 50%.[1]

What are the incidence, prevalence, and prognosis of NETs and neuroendocrine liver metastases?

Despite decades of mandatory cancer registration, the precise incidence and prevalence and survival from NETs remain difficult to define. Nevertheless, the incidence of NETs recorded since 2000 is between 1·9 and 5·7 per 100 000 people per year, about 60% of which are GEP NETs.[1] The common GEP NET primary sites are small intestine (about 30%), rectum (about 15%), colon (about 13%), pancreas (about 16%), stomach (9%), and appendix (about 20%).[1] Distant metastases at diagnosis are found in about 40–45% of pancreatic, small intestinal, and colonic NETs, and about 5–15% of appendiceal, gastric, and rectal NETs (figure 1). The Surveillance, Epidemiology, and End Results (SEER) database reported a 29 year limited duration prevalence (all NETs diagnosed during the preceding 29 years and still alive in 2004) as 35 in 100 000 individuals.[10] Data from 19 cancer registries in 12 European countries, including 3715 malignant NETs (in 1985–94), showed an overall 5 year survival of 47·5% (58·1% for differentiated and 8·1% for small-cell tumours; 55·9% for age ≤65 years and 37·5% for age >65 years).[11] 5 year survival was worse with distant metastases (about 30–60%) at diagnosis, although survival from neuroendocrine liver metastases was not specifically defined. NETs originating from the stomach, rectum, or appendix had better survival than did those originating from other locations.[1] The 5 year relative survival in European studies was 60·7–64·1% for stomach, small intestinal, and colorectal NETs compared with 32·0–44·1% for liver, gallbladder, and pancreas NETs. Registries maintained at specialised centres probably overestimate neuroendocrine liver metastases because of a referral bias towards advanced disease.[7] The prevalence of neuroendocrine liver metastases in SEER is 27%[10] (*vs* 40–95% in registries[7]), comprising pancreas (64%[10] *vs* 28·3–77% in registries[7]) and small intestine (30%[10] *vs* 67–91%).[7] Overall incidence, prevalence, and survival with neuroendocrine liver metastases cannot be fully ascertained in current registries (figure 2). We therefore recommend that an international registry for neuroendocrine liver metastases linked to the cancer registries should be developed, with meticulously defined entry criteria to quantify incidence, prevalence, and survival (panel 1).

Should patients with a low Ki-67 index be followed up after resection of the primary tumour for the detection of liver metastases?

No published data specifically address this question. The Ki-67 index is known to strongly correlate with patient survival (particularly for pancreatic NETs) and is prognostic for pancreatic lesions.[13] However, NETs from other sites (eg, ileum) have a high probability of developing liver metastases despite a low (<2%) Ki-67 index.[14–16] Additionally, tumours from specific organs—eg, stomach, appendix, rectum—rarely metastasise.[1] Gastric and rectal NETs are usually diagnosed serendipitously at endoscopy and have an excellent prognosis because they are low grade, smaller than 1 cm (often <0·5 cm), and occur either intramucosally or in the superficial submucosa. Appendiceal NETs have an excellent prognosis even if mural invasion up to the serosa is evident. No data are available to recommend regular follow-up after resection or ablation of grade 1 rectal NETs that are 1 cm or smaller

Panel 1: Clinical practice recommendations

What are the incidence, prevalence, and prognosis of NETs and NELMs?

- The incidence of NETs is about 1·9–5·7 per 100 000 people per year
- The prevalence of NETs is about 35 per 100 000 people
- The 5 year survival of malignant NETs and NELMs is about 37·6–60·3% and 56·0%, respectively
- The prognosis of patients with malignant NET is determined by liver metastases
- Level of evidence=1
- No data for benefit:harm analysis
- Cost=low
- An international registry is mandatory

Should patients with a low Ki-67 index be followed up after resection of the primary tumour for detection of liver metastases?

- Patients with NETs with low Ki-67 index should be followed up for detection of liver metastases (with the exception of well differentiated appendix NETs ≤1 cm or T1) (strong recommendation)
- Level of evidence=1
- Benefit is greater than harm
- Cost=low
- Follow-up should be considered but site is important in decision-making process

Should genetic signature and the presence of circulating tumour cells be used to predict liver metastases and to inform treatment decisions?

- Evidence is insufficient to make a recommendation
- The jury felt it is too early to provide a clinical recommendation
- Level of evidence=1
- Benefit is greater than harm
- No data available for cost

Which biochemical markers should be used for detection and post-treatment follow-up of liver metastases?

- Chromogranin A should be used for detection and post-treatment follow-up (weak recommendation)
- The consensus was based on the group of 400 attendants. The jury themselves could not reach an agreement
- Level of evidence=1
- Benefit is greater than harm
- Cost=low

Which morphological imaging method should be used to assess resectability of liver metastases with a curative intent?

- MRI is the best imaging method for identification of NELMs (weak recommendation)
- Three-dimensional CT is useful for the assessment of intrahepatic anatomy and the future liver remnant in cases of anticipated complex surgical techniques (weak recommendation)
- Combined morphological and functional imaging should be used for identification of extrahepatic disease (weak recommendation)
- Jury concerned by evidence that 50% of metastases will be missed by all imaging
- Level of evidence=1–2
- Benefit is greater than harm
- Cost=moderate

Which functional imaging method should be used to assess resectability of hepatic metastases with a curative intent?

- Gallium-68 (^{68}Ga)-somatostatin receptor PET/CT should be used to assess resectability of hepatic metastases in grade 1/grade 2 NETs with the caveat that this technology could be limited to certain centres and is not broadly available (weak recommendation)
- ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT should be used to assess resectability of hepatic metastases in grade 2 NETs, potentially in combination with ^{68}Ga-somatostatin receptor PET/CT (grade 3 are not candidates for liver resection) (weak recommendation)
- Consensus difficult to obtain; wide difference in opinions
- Level of evidence=1–3
- Benefit is greater than harm
- Cost=moderate

Is a biopsy of both the primary and liver metastases needed for the treatment decision of liver metastases?

- A recommendation was made against multiple biopsies for Ki-67 assessment
- A biopsy of the primary tumour was not necessary if the biopsy of liver metastases provided positive and comprehensive information on tumour disease (weak recommendation)
- In less informative settings, a biopsy of both the primary and liver metastases might be needed for a treatment decision (weak recommendation)
- Level of evidence=1
- Benefit is greater than harm
- Cost=moderate

When should a liver resection be done?

- Liver resection should be considered the first choice for patients with completely resectable grade 1 or grade 2 liver metastases and no resectable extrahepatic disease (weak recommendation)
- Very weak recommendation based on the Cochrane review data (poor quality of data). Requires centre of excellence.
- Level of evidence=1–2
- Benefit and harm are equal
- Cost=high

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Should a primary tumour be resected in the presence of non-resectable liver metastases?

- For pancreatic NETs evidence is inadequate (no recommendation)
- Small intestinal NETs including locoregional lymph-node disease can be considered for resection (weak recommendation)
- No firm consensus. Jury vote for pancreas (head) 100% against. Jury vote for pancreas (tail) 30% for, 50% against, 20% abstain. Jury vote for small intestine 60% for, 40% against
- Level of evidence=1
- Benefit and harm are roughly equal
- Cost=high

When should a liver transplantation be done?

- Liver transplantation should be offered to selected patients with unresectable neuroendocrine liver metastases and no unresectable extrahepatic disease (weak recommendation)
- Jury voted on inclusion as a treatment: 80% for, 20% abstain
- Level of evidence=1
- Benefit is greater than harm
- Cost=high

Should neoadjuvant and adjuvant treatment strategies be used?

- Inadequate evidence for use of neoadjuvant or adjuvant strategies for resectable grade 1 and grade 2 NETs (no recommendation)
- Jury supported a weak recommendation against using these strategies. Could be used in a clinical study protocol
- Level of evidence=1
- No data for benefit:harm analysis
- No data available for cost

When should locally ablative techniques be used?

- Locally ablative techniques (radiofrequency ablation, microwave, laser ablation) should be used in the treatment of unresectable hepatic metastases. To achieve greater evidence of patient selection and treatment efficacy, use within clinical study protocol should be encouraged (weak recommendation)
- Could be included as part of a treatment panel
- Level of evidence=1
- Benefit is greater than harm
- Cost=low

When should angiographic liver-directed techniques be used?

- Transarterial embolisation, transarterial chemoembolisation, and selective internal radiotherapy should be used as part of a treatment panel. To achieve a higher level of evidence regarding patient selection and treatment efficacy, use within clinical study protocol should be encouraged (weak recommendation)
- Level of evidence=1
- Benefit and harm are roughly equal
- Cost=high

When should peptide receptor radionuclide therapy be used?

- Peptide receptor radionuclide therapy should be used as part of a treatment panel. To achieve better evidence about patient selection and treatment efficacy, use within clinical study protocol should be encouraged (weak recommendation)
- Level of evidence=1
- Benefit is greater than harm
- Cost=high

When should chemotherapy, targeted therapy, or biotherapy be used?

- In the palliative setting, chemotherapy, everolimus, and sunitinib should be included in treatment of pancreatic NETs (strong recommendation)
- Somatostatin analogues should be used as part of a treatment panel in midgut NETs (low hepatic tumour burden) (strong recommendation)
- Level of evidence=1–4
- Benefit is greater than harm
- Cost=high

NET=neuroendocrine tumour. NELM=neuroendocrine liver metastases. *Based on Guyatt and colleagues.[12]

in the absence of negative prognostic factors. Because gastric NETs frequently recur (continued hypergastrinaemia targeting the enterochromaffin-like cell population), endoscopic follow-up is recommended. However, data supporting necessity for follow-up for neuroendocrine liver metastases after resection or ablation of grade 1 tumours (70–80% of all gastric NETs) are scarce. Overall, the working group concluded that any metastasis prediction using the Ki-67 index should include the primary site; although a high probability of neuroendocrine liver metastases might be associated with a high Ki-67 index, there might be no low cutoff for this index. Additionally, questions were raised about the relevance of a low Ki-67 index. Although the Ki-67 index has a role in the prediction of neuroendocrine liver metastases (and survival), the working group recommended that follow-up for the detection of neuroendocrine liver metastases after resection or ablation of low-grade NETs should not be based only on the Ki-67 index but also on the primary site of the NET and the TNM classification. We conclude that NETs with low (<2%) Ki-67 index should be followed up longitudinally for the detection of liver metastases. Follow-up is not necessary for well differentiated appendiceal NETs 1 cm or smaller (or T1; panel 1).[17]

Should genetic signature and the presence of circulating tumour cells be used to predict liver metastases and to inform treatment decisions?

Gene signatures derived from transcriptome studies[18] and the detection or quantification of circulating tumour cells, either with capture-based approaches or real-time PCR (so-called liquid biopsies), have been done in NETs. In four studies in small intestinal NETs, different sets of genes were identified to be differentially expressed between primaries and metastases, including *NAP1L1* and *MTA1,*[19] *CXCL14* and *NKX2-3,*[20] *REG3A* and *TGFBR2,*[21] and *CD302.*[22] *MTA1* has been confirmed to be over-expressed whereas loss of *TGFBR2* was identified in neuroendocrine liver metastases. In colorectal NETs, *ATM* (a candidate tumour suppressor,[23] identified to have lower expression in metastatic lesions compared with primary lesions) was inversely correlated with Ki-67 index and was predictive of survival.[24] Loss of miRNA-133a is associated with metastasis.[25] None of these signatures have been rigorously assessed in the prediction of neuroendocrine liver metastases. Measurement of circulating mRNA has been reported to identify metastatic tumours (gastric and small intestinal NETs) (82%).[26] A 51-multimarker gene signature is effective (in >95% of cases) for identification of GEP NENs.[17] Attempts to identify known cancer mutations (eg, RAS-RAF or *TP53*),[27] particularly those useful in therapeutic decision making (eg, *BRAF* V600E), have not proven successful in NETs.[28] Exome analyses of pancreatic NETs[29] identified that the most frequently mutated genes (about 50% of tumours) are associated with epigenetic modifications (*MEN1, DAXX, ATRX*) but only 14% of the tumours show mTOR pathway gene mutations (eg, *PIK3CA*). This information has not been used to develop companion diagnostics to identify responsive lesions. Circulating tumour cells have been detected in GEP NENs, and concentrations seem to correlate with increased tumour burden and grade.[30] None of the methods provide sufficient information to recommend use for prediction of neuroendocrine liver metastases. By contrast, blood-based tests (circulating tumour cells and PCR) were promising as prognostic methods. Therefore, although no clinical practice recommendation could be provided, development and use of molecular diagnostic strategies is still a crucial need (panel 1).

Which biochemical markers should be used for detection and post-treatment follow-up of liver metastases?

Chromogranin A is the most widely used biomarker. Plasma chromogranin A is increased in neuroendocrine liver metastases, and concentrations generally correlate with hepatic NET burden. Chromagranin A concentration correlated with hepatic burden (when assessed as <25%, 25–50%, >50%) and survival.[31] Increases in chromogranin A were associated with tumour progression and shorter survival. Chromogranin A concentrations are reduced after hepatic resection or transplantation.[32] Few studies have specifically assessed the usefulness of chromogranin A measurements in neuroendocrine liver metastases. Investigators of a retrospective study reported that a chromogranin A decrease of 80% or more was predictive of complete symptom resolution and disease stabilisation.[33] By contrast, reduction of urinary 5-hydroxyindoleacetic acid concentrations of 80% or more (or normalisation) was predictive of symptomatic relief but not of disease stabilisation. Although chromogranin A is of value as a biomarker, measurements can be increased by factors including proton-pump-inhibitor drugs, other cancers, and inflammatory bowel disease.[34] Other constraints include weak association with tumour grade, an increase observed in non-metastatic GEP NETs, and absence of standard assay methods. We therefore recommend that chromogranin A can be used as a biomarker in detection and post-treatment follow-up of neuroendocrine liver metastases, although substantial inaccuracies and limitations are evident (panel 1).

Which morphological imaging method should be used to assess resectability of liver metastases with a curative intent?

The morphological imaging methods used for assessment of hepatic metastases include conventional ultrasonography or a contrast-enhanced ultrasonography technique, CT, and MRI. A mixed hyperechoic and hypoechoic pattern with central cystic appearance and hypervascularity on colour Doppler imaging are characteristic ultrasonography features of neuroendocrine liver metastases.[35]

Contrast-enhanced ultrasonography identifies significantly more hepatic metastases with a higher specificity than does conventional ultrasonography.[36] Multiphase helical CT with a multirow detector CT scanner is more efficacious than conventional single portal venous phase CT.[36] Diffusion-weighted MRI is a more sensitive MRI technique than T2-weighted fast spin-echo and dynamic gadolinium-enhanced MR sequences.[37] An assessment of CT and MRI in a per-lesion analysis indicates an increased sensitivity with MRI.[37] However, when compared with thin slice pathological examination, which identifies liver metastases smaller than 5 mm, preoperative morphological imaging detects less than 50% of neuroendocrine liver metastases.[38] Computer-assisted three-dimensional CT provides added information about intrahepatic vascular and biliary extension and enables assessment of the future liver remnant. For the detection of extrahepatic tumour, combined morphological and functional imaging should be done. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET or CT is of value after surgery because morphological imaging has limitations in discrimination of malignancy from

post-surgical tissue alterations.[39,40] Of considerable therapeutic and prognostic significance is the axiomatic observation that more than 50% of all neuroendocrine liver metastases will be understaged by present preoperative imaging.[38] We recommend that MRI be used to identify neuroendocrine liver metastases. Three-dimensional CT is helpful in calculation of future liver remnant. A combination of morphological and functional imaging is recommended to identify extrahepatic disease (panel 1).

Which functional imaging method should be used to assess resectability of hepatic metastases with a curative intent?

NETs variably express somatostatin receptors (60–100% of tumours, about 85% are somatostatin subtype receptor 2) thereby providing a target for functional imaging with labelled somatostatin analogues. Indium-111 (^{111}In)-octreotide scintigraphy has a lower sensitivity (69–86%) and a higher cost for detection of GEP NETs than do PET or CT using gallium-68 (^{68}Ga)-labelled somatostatin analogues (DOTATOC, DOTATATE or DOTANOC).[41]

A novel isotope, copper-64 DOTATE could be more sensitive than indium-111 and ^{68}Ga.[42] ^{18}F-FDG PET is useful in the detection of intermediate and high-grade NETs (sensitivity of 92% with Ki-67 >15% compared with 69% for somatostatin receptor scintigraphy).[43] ^{18}F-DOPA PET and ^{11}C-5-hydroxy-tryptophan (^{11}C-5-HTP) PET are useful in functional NETs and individuals with inconclusive findings.[44] ^{68}Ga-somatostatin receptor PET or CT shows the highest sensitivity and specificity for detection of neuroendocrine liver metastases (82–100% and 67–100%, respectively) and extrahepatic metastases (85–96% and 67–90%, respectively) in low-grade NETs.[39,40] ^{68}Ga-somatostatin receptor PET or CT can detect lesions not identified by CT or MRI in up to 67% of cases, and can identify individuals unsuitable for curative intent hepatic surgery. The clinical (and biological) relevance of subcentimetre bone lesions frequently detected on ^{68}Ga-somatostatin receptor PET or CT is unclear. We therefore conclude that ^{68}Ga-somatostatin receptor PET or CT should be used to assess resectability of metastases in grade 1 or grade 2 NETs. ^{18}F-FDG PET or CT should be used to assess resectability of grade 2 NETs. Imaging results should be correlated with surgical findings and histology (panel 1).

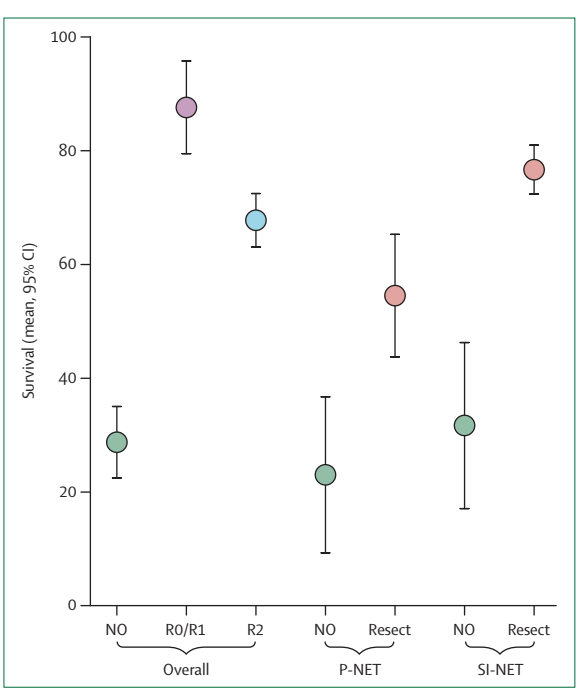

Figure 3: **5 year survival after neuroendocrine liver metastases resection**
Resection of grade 1 or grade 2 gastroenteropancreatic neuroendocrine tumours has about 85% survival compared with 30% with no resection (irrespective of other treatment). Small intestinal NETs survival is greater than pancreatic NETs. NO=no resection. Resect=liver resection. P-NET=pancreatic NET. SI-NET=small intestinal NET. R0=complete removal of tumour, microscopic examination of margins indicate no tumour cells. R1=tumour cells detected by microscopy in margins. R2=visible tumour remains.

Is a biopsy of both the primary and liver metastases needed for the treatment decision on liver metastases?

Therapeutic GEP NET decision making is based predominantly on the grade of the tumour. About 50% of GEP NETs show distant metastasis, including liver metastases, at diagnosis.[45] The *National Comprehensive Cancer Network*[46] and the European Society for Medical Oncology[47] guidelines do not address liver metastases sampling or consider multiple biopsies, and suggest that Ki-67 assessment is optional. No difference in Ki-67 expression between primaries and metastases has been reported.[48] However, molecular analyses indicate gene expression differences (proliferation-associated) between primary tumour and metastasis.[19–21] Prerequisites for a valid Ki-67 measurement are appropriate fixation criteria, antibody specificity (eg, MIB-1), and other technical requirements. However, intratumour variability in Ki-67 staining is substantial; thus single biopsy interpretation is unreliable (about 50% of tumours were differently graded dependent on sampling selection).[49] Ki-67 expression heterogeneity is of relevance in tumours that are ultimately deemed to be of higher grade. Additional issues include needle size (smaller needles provide less tissue, larger bore devices increase haemorrhage), carcinoid crisis induction, and needle-track seeding. One study concluded that a Ki-67 index lower than 2% at either the primary site (ileal NET) or within metastases was the only significant predictor of progression-free survival.[50] When dealing with a functionally (and histogenetically) less informative metastasis, biopsy of the primary tumour might be necessary to inform a sound treatment recommendation. We conclude that a biopsy of the primary tumour is not always necessary if the biopsy of the liver metastases provides positive and

comprehensive information. In less informative settings, a biopsy of both the primary tumour and liver metastases might be needed. Multiple individual tumour biopsies for Ki-67 assessment are not recommended (panel 1).

When should a liver resection be done?

Resection of neuroendocrine liver metastases, primary tumour, and locoregional lymph node metastases is thought to positively benefit long-term survival and quality of life (figure 3). The overall survival after hepatic resection is 46–86% at 5 years and 35–79% at 10 years.[51–53] These results should be viewed with caution (complete resection in only 20–57% and local recurrence evident in up to 94% at 5 years).[54] Candidates for resection include: grade 1 or 2 tumours; when no evidence of non-resectable extrahepatic disease exists; type I or II metastatic growth assessable for R0 or R1 resection with an anticipated liver remnant of at least 30%; when no evidence of advanced carcinoid heart disease exists; and when access to a hepatic surgery centre is possible.[55] Although counter-intuitive, resections with microscopically positive margins (R1) had no apparent negative effect on overall survival,[53] but contrary results have been published.[52] Liver metastases of grade 3 NETs are usually not amenable for resection (with multifocal or bilobar growth, or both, and anticipated high recurrence rates). Several non-randomised series document the benefits of surgical resection, either complete or cytoreductive, compared with non-resectional treatment—eg, 74% 5 year survival for resection versus 30% for angiographical techniques. These results probably represent selection bias. The Cochrane systematic reviews (see appendix references 36 and 37) did not identify benefit of liver resection, either in terms of complete resection (R0 or R1) or cytoreduction (R2). Despite poor data, surgery is the main treatment of choice because it is the only approach with intent to cure. Whether cytoreductive surgery (90% resection) should be done when alternative non-surgical treatment options are available is unknown. We therefore conclude that liver resection should be considered the first choice for completely resectable grade 1 or 2 liver metastases with or without resectable extrahepatic disease (panel 1).

Should the primary tumour be resected in the presence of non-resectable liver metastases?

Resection of an asymptomatic primary NET in the presence of unresectable hepatic metastases is controversial. No randomised controlled trials exist. Unresectable liver metastases are present in about 15–80% of GEP NETs.[45] Positive aspects of resection are the prevention of local symptoms induced by tumour mass (pain, bleeding, perforation, obstruction), amelioration of hormonal symptoms, and a positive effect on survival.[56] In a single retrospective series of small intestinal NETs,[15] survival after primary resection was significantly better than after no surgery (median survival 7·4 for the surgery group *vs* 4·0 years for the no surgery group).[14] Capurso and colleagues[57] reported in a systematic review a beneficial effect of primary resection with an overall survival of 75–139 months versus 50–88 months with conservative management. In small intestinal NETs, resection of an asymptomatic primary plus locoregional lymph-node disease might be necessary to obviate associated mesenteric desmoplasia and pre-empt mesenteric vascular ischaemia. Patients with unresectable pancreatic neuroendocrine liver metastases might benefit from primary tumour resection if low surgical morbidity is assured. The absence of study homogeneity, the bias to operate on less advanced tumours, and better overall performance status of patients selected for resection precludes a recommendation. In the debate about surgical timing, neuroendocrine liver metastases should be initially addressed and, if the response is satisfactory, then primary resection should be undertaken. We felt that there is weak evidence that small intestinal NET locoregional disease should be resected. We could make no recommendation for pancreatic NETs (panel 1).

When should a liver transplantation be done?

Neuroendocrine liver metastases are an accepted indication for liver transplantation, because most show low biological aggressiveness and grow slowly. Experience is scarce because liver transplantation for NET disease represents 0·3% and 0·2% of transplants (European Liver Transplant Registry and United Network for Organ Sharing database, respectively).[58] Assessment is hampered because disease-free survival is not routinely reported, follow-up is not uniform, and no studies directly examine quality of life. Nevertheless, 5 year survival

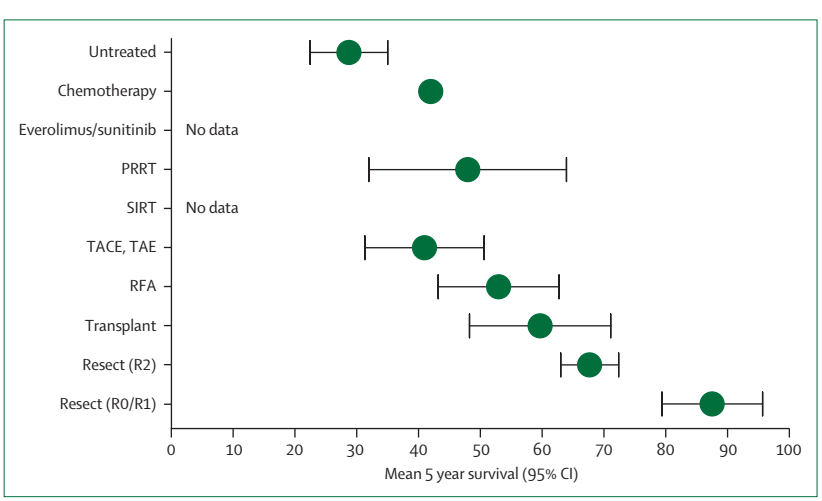

Figure 4: **Rates of 5 year survival by treatment method**
Complete liver resection for grade 1 and grade 2 neuroendocrine tumours shows about 85% 5 year survival. Mean 5-year survival for all treatments and combinations is about 50% except for transplantation (about 60%). PRRT=peptide receptor radionuclide therapy. SIRT=selective internal radiotherapy. TACE=transarterial chemoembolisation. TAE=transarterial embolisation. RFA=radiofrequency ablation. Resect (R2)=cytoreduction. Resect (R0/R1)=complete resection.

results from long-term series are comparable and, in some, better than those achieved for primary hepatic cancer.[58] Since 2000, 5 year overall survival is 36–90% and disease-free survival is 30–77% in single centres (figure 4). In multicentre series 5 year overall survival is notably lower at 49% and 47%, emphasising the effect of strict selection criteria (see appendix references 46 and 47). Contraindications for transplantation include poorly differentiated tumours, non-portal system tumour drainage, extrahepatic metastases (apart from perihilar lymph nodes), and severe carcinoid heart disease. However, a variety of criteria—age, functional status, tumour histology, tumour localisation, primary resection before transplantation, hepatic tumour burden, the dynamic of hepatic tumour growth, Ki-67 index, the wait-time for disease stabilisation, and transplantation timing—need to be objectively considered. Selection criteria (adverse risk factors) have not been validated in prospective studies and have not been derived from multivariate analyses. Assessment of real benefit is difficult because randomised studies comparing outcome of non-surgical treatments and transplantation are not feasible. Propensity analyses and survival-benefit analyses probably provide the best evidence available. A down-staging strategy has not been assessed in patients with NET. Because of variable organ allocation regulations in different countries, individuals with neuroendocrine liver metastases might not have optimum access; thus, living donor transplantation could become a viable option. We conclude that liver transplant should be offered, with rigorous selection criteria. Contraindications for transplantation are grade 3 tumours, non-portal systemic tumour drainage, extrahepatic metastases, and severe carcinoid heart disease (panel 1).

Should neoadjuvant and adjuvant treatment strategies be used?

Neoadjuvant and adjuvant treatment is not considered for hepatic resection. In a retrospective cohort study (59% pancreatic NETs), no difference in survival was noted between the treatment (streptozotocin and fluorouracil) and non-treatment groups after resection of liver metastases (or transplantation).[59] Findings from smaller series and case reports indicate that downstaging of neuroendocrine liver metastases with immuno-chemotherapy or peptide receptor radionuclide therapy (PRRT), or both, might result in enhanced tumour resectability.[60–62] We thus concluded that evidence is insufficient for neoadjuvant or adjuvant treatment of resectable grade 1 and grade 2 NETs (panel 1).

When should locally ablative techniques be used?

Locally ablative methods have been used extensively in treatment of secondary hepatic malignancies alone or as an adjunct to surgical resection. The methods include radiofrequency ablation, microwave ablation, laser ablation, and cryotherapy, and can be done with percutaneous, open, or laparoscopic approaches. Microwave ablation is thought to be more efficacious than radiofrequency ablation because a shorter time is needed for each ablation and higher intratumour temperatures can be reached.[63] Laser ablation is done under MRI guidance, enabling continuous monitoring of the treatment.[62] Experience with microwave ablation and laser ablation is scarce. Cryotherapy has a higher complication rate than do radiofrequency, microwave, and laser ablation, and is less frequently used.[63]

A small number (three to four) of lesions smaller than 5 cm is deemed a suitable case for ablation, although more than ten lesions of up to 10 cm have been treated.[63–65] Radiofrequency ablation series document a 5 year overall survival of 53% (figure 4). Local liver recurrence rate was 22%, 63% of patients developed new liver metastases, and 59% of patients developed extrahepatic disease at a median of 30 months (IQR ±3). Histological proof of the complete ablation or tumour cell dissemination is unavailable. Although a relatively inexpensive treatment method with low morbidity, tumour tissue is not completely removed. We therefore recommend that locally ablative techniques be used; this is a safe strategy for limited unresectable liver metastases. In view of the poor evidence about selection and efficacy, we encourage clinical study protocols (panel 1).

When should angiographic liver-directed techniques be used?

Liver-directed intra-arterial therapies for the treatment of unresectable neuroendocrine liver metastases include transarterial embolisation, transarterial chemo-embolisation, and selective internal radiotherapy with yttrium-90 (^{90}Y)-microspheres. Transarterial embolisation or chemoembolisation produces symptomatic responses in 53–100% of patients (10–55 months) and morphological responses in 35–74% (6–63 months), with progression-free survival of about 18 months and 5 year survival of 40–83%.[63,66,67] Mortality varies from 0–5·6 and morbidity (ie, post-embolisation syndrome) varies from 28–90%;[63] transarterial embolisation is better than transarterial chemoembolisation for small intestinal NETs. Hepatic intra-arterial injection of ^{90}Y-DOTA-lanreotide (with or without embolisation) is effective in large-volume somatostatin receptor-positive liver metastases.[68] In a multicentre selective internal radiotherapy study, stable disease by imaging was reported in 22·7% of patients, partial response in 60·5%, and complete response in 27%. In 4·9%, a 70-month median survival with progressive liver disease was recorded. Clinical toxicities included fatigue and nausea (in <10% of cases).[69] Long-term outcome analysis after selective internal radiotherapy indicated treatment response in 62·7% and disease stabilisation in 32·5%, and with survival of 72·5% at 1 year, 62·5% at 2 years, and 45·0% at 3 years (figure 4).[70] Findings from an international

multicentre prospective treatment registry showed that safety and response rates for selective internal radiotherapy and transarterial chemoembolisation were similar at 6 months.[71] At 12 months the group receiving selective internal radiotherapy had a significantly lower response rate than did the group receiving transarterial chemoembolisation (46% *vs* 66%).[71]

Adverse events associated with selective internal radiotherapy include lung shunting of beads, radiation gastritis, duodenal ulceration, and hepatic fibrosis; the procedure is also expensive.[72,73] Radiation lobectomy after selective internal radiotherapy of right lobe tumours can induce contralateral lobe hypertrophy and can be used for downstaging.[74] Additional long-term outcome data are needed to assess SIRT efficacy. We conclude that transarterial embolisation or transarterial chemoembolisation and selective internal radiotherapy should be used as a treatment panel in predominant liver disease and low hepatic tumour burden. We encourage use within a clinical study protocol (panel 1).

When should peptide-receptor radionuclide therapy be used?

Most GEP NETs express somatostatin receptors, and treatment with ^{90}Y or lutetium-177 (^{177}Lu) somatostatin analogues is therefore feasible. PRRT has been extensively used since 1999.[44] It is effective with about 75% stable disease and outcomes including progression-free survival (17–40 months) and overall survival (22–46 months) better than those with other methods. In a clinical phase 2 single-centre trial of 1109 patients, morphological response was evident in 34·1%, biochemical response in 15·5%, and clinical response in 29·7% of cases.[75] In a comparative cohort study of single versus combination isotopes in metastasised NETs (liver metastases in 75–88%), the combination of isotopes led to a survival benefit.[76] Adverse events—eg, myelosuppression—might occur (<1%), particularly with previous chemotherapy. No prospective trials or studies comparing efficacy of PRRT with other treatment options have been done. A phase 3 trial comparing PRRT and octreotide has started (NETTER-1, NCT01578239). The most important positive predictive factor for response is the ratio of radiolabel uptake on diagnostic scans (normal to tumour). Extensive hepatic metastatic involvement is a significant negative predictive factor for progression-free survival or overall survival.[77] Controversially, experts recommended that in the absence of randomised trials of alternative treatments, non-resectable low and intermediate grade somatostatin receptor-positive NETs should be treated with PRRT as a first option. A caveat is the limited access to this therapy in Europe and its very poor availability in the USA or Japan. The use of registries for prospective clinical studies was recommended.[78] We recommend that PRRT be used for treatment of hepatic and extrahepatic metastases, and that use within clinical study protocol is encouraged (panel 1).

When should chemotherapy, targeted therapy, or biotherapy be used?

The type of therapy used is dependent on the grade and proliferation of the tumour. High-grade lesions, especially from the pancreas (neuroendocrine carcinoma [grade 3]), are amenable to chemotherapy (fluorouracil, doxorubicin, and streptozotocin). Targeted therapies—eg, everolimus or sunitinib—and biotherapy—somatostatin analogues or interferon—are used in slow-growing lesions (NET grade 1 or grade 2). Objective response rates (35–40%) in pancreatic neuroendocrine tumours[79,80] are higher with chemotherapy than with everolimus or sunitinib. The molecular markers that identify benefit from therapies, apart from somatostatin-receptor expression, are unknown. For chemotherapy, the volume of liver metastases is the most significant predictor of outcome and directly correlates with progression-free survival.[79] Potential problems include cumulative risks of nephrotoxicity or myelosuppression and systemic adverse events. For targeted therapies, evidence suggests a specific use in neuroendocrine liver metastases. The everolimus study of pancreatic NETs (92% with liver metastases) yielded an improved progression-free survival (6·4 months longer than placebo), an effect that was long-lasting (35% of patients stable at 18 months). Tumour remissions were very rare (5%).[81] The sunitinib study (95% of pancreatic NETs had distant metastases including liver metastases) showed a significant prolongation of progression-free survival with 11·4 months versus 5·5 months with placebo, and tumour remissions of less than 10%.[82] No evidence exists for the use of everolimus or sunitinib in liver metastases of intestinal origin. For biotherapies, few data exist for interferon; however, for somatostatin analogues, results of a single low-powered study of mostly midgut NETs suggested that benefit was connected to volume of liver involvement (<10%).[83] Three randomised trials therefore provide marginal evidence for efficacy in neuroendocrine liver metastases. The expert group could identify no evidence that outcome was better after any of these therapies compared with liver resection. Because different patient populations would be candidates, comparative studies are unlikely to be undertaken, which emphasises the need for pre-screening molecular protocols to identify patients most likely to respond. No randomised studies have been undertaken to assess the efficacy of any of these therapies as combination methods. The experts and jury concurred that additional randomised studies are necessary to guide decision making, with the caveat that molecular-based analyses be developed to assess individual therapies. We recommend that, in the palliative setting, chemotherapy, everolimus, and sunitinib be included in pancreatic NET treatment. Somatostatin analogues could be considered for midgut NETs with less than 10% hepatic tumour volume (panel 1).

Panel 2: Clinical and basic science research proposals

What are the incidence, prevalence, and prognosis of NETs and NELMs?

- Establish an international registry with defined entry criteria to quantify incidence, prevalence, and survival

Should patients with a low Ki-67 index be followed up for the detection of liver metastases?

- The Ki-67 index should be refined by including molecular genomic information to amplify tissue-specific grading
- Groups with different clinical behaviour within each grade (eg, a subgroup with shorter survival within the grade 1 group and subgroups with less aggressive behaviour within the grade 2 and the grade 3 group) need to be identified

Should genetic signature and the presence of circulating tumour cells be used to predict liver metastases and to inform treatment decisions?

- A consortium-based study along Cancer Genome Atlas guidelines[84] should be established to elucidate molecular signatures that predict metastasis and/or responsiveness to a therapy—eg, mTOR mutations
- Controlled trials should be undertaken to assess the usefulness of blood-based molecular PCR signatures and circulating tumour cells in clinical trials
- Site-specific molecular fingerprint generated from transcriptome data should be developed for refinement of tissue-specific grade

Which biochemical markers should be used for detection and post-treatment follow-up of liver metastases?

- Standardisation of chromogranin A measurement is needed
- Prospective studies to assess chromogranin A versus other potential biomarkers—eg, circulating tumour cells and blood-based molecular PCR signatures are needed to establish the best markers for detection and to quantitate treatment responses

Which morphological imaging method should be used to assess resectability of liver metastases with a curative intent?

- Hepatobiliary MRI contrast agents should be assessed in a large comparative series
- Novel criteria for disease progression or response to treatment should be identified

Which functional imaging method should be used to assess resectability of hepatic metastases with a curative intent?

- Large prospective studies to evaluate the added value of combined morphological and functional imaging method to assess resectability of hepatic metastases should be undertaken

Is a biopsy of both the primary and liver metastases for the treatment decision of liver metastases needed?

- Repeat liver biopsies should be undertaken to reassess prognosis if the disease pattern changes with time
- Proliferation should be redefined at a molecular level
- Cryopreserved tissue should be acquired to define molecular markers that correlate with prognosis and therapeutic responses of an individual patient

When should a liver resection be done?

- A registry for neuroendocrine liver metastases linked to cancer registries should be established
- Novel genomic or metabolic biomarkers need to be identified from tumour biobanks to identify patients who will benefit from resection
- Neoadjuvant and adjuvant trials (targeted drugs or peptide receptor radionucleotide therapy) are needed

Should the primary tumour be resected in the presence of non-resectable liver metastases?

- Prospective randomised study of asymptomatic patients with small intestinal NETs comparing primary tumour resection versus observation is needed

When should a liver transplantation be done?

- Requirement for identification of genomic/metabolic biomarkers to identify individuals who will benefit from transplantation

Should neoadjuvant and adjuvant treatment strategies be used?

- Neoadjuvant and adjuvant treatment strategies should be assessed in randomised trials (eg, adjuvant therapy versus placebo) to ascertain 5 year disease-free survival
- Tissue analysis should be undertaken to direct the type of adjuvant treatment (targeted drugs, PRRT) and biomarkers—eg, circulating tumour cells or liquid biopsies—included as links to clinical outcome

When should locally ablative techniques be used?

- Data showing histological proof of completeness of ablation or dissemination of tumour cells are needed
- A trial comparing resection (R0/R1) with radiofrequency ablation would be desirable, but such a trial is less likely to be realistic

When should angiographic liver-directed techniques be used?

- More data are needed for long-term outcome after SIRT
- A randomised controlled trial on SIRT compared with bland embolisation or palliative hepatic resection should be encouraged
- Quality-of-life metrics should be incorporated in future comparative studies
- Evaluation of whether SIRT could convert patients to resectability after radiation-lobectomy techniques

When should peptide receptor radionuclide therapy be used?

- Randomised controlled trials comparing peptide receptor radionuclide therapy to a variety of treatments are needed

When should chemotherapy, targeted therapy, or biotherapy be used?

- Identification of the master regulators of tumour proliferation should be encouraged
- Drug addiction targets of NET cell interactome should be established
- Patient-specific and tumour-specific molecular data should be identified to ascertain the choice of drugs

NET=neuroendocrine tumour. NELM=neuroendocrine liver metastases. SIRT=selective internal radiotherapy. PRRT=peptide receptor radionuclide therapy.

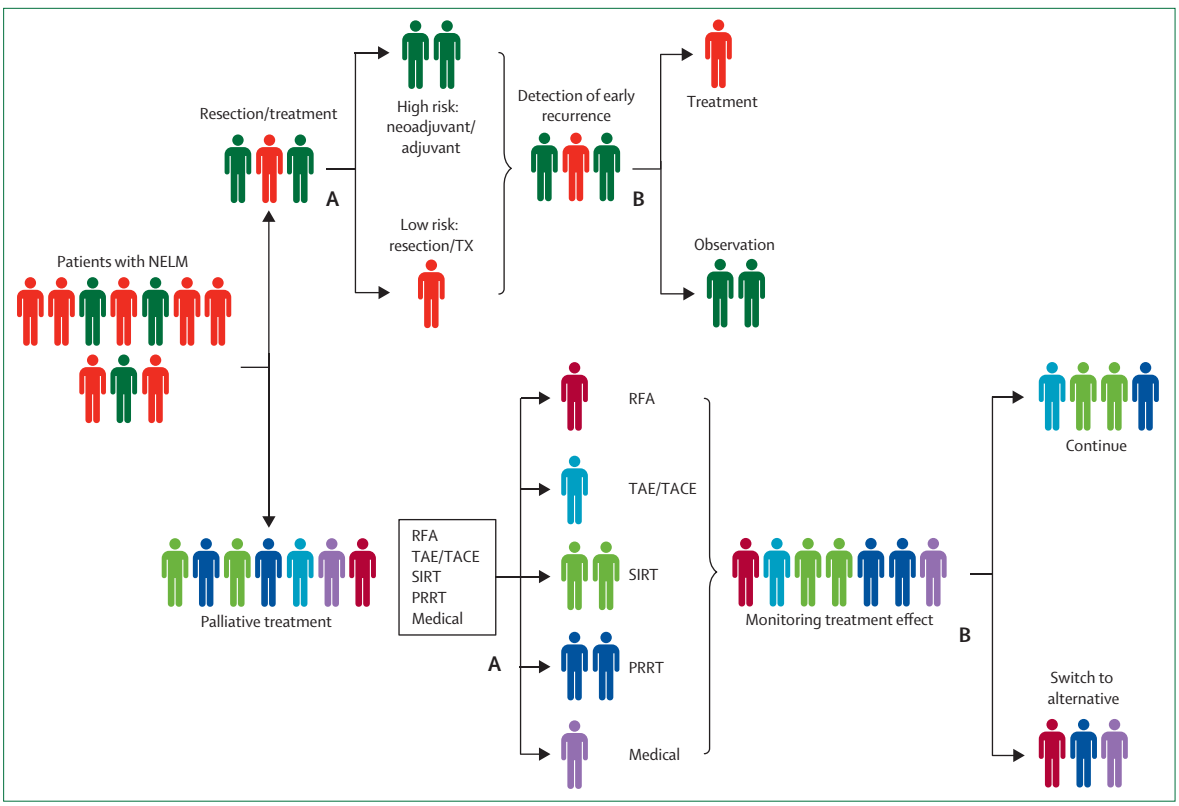

Figure 5: **Potential strategies for neuroendocrine liver metastases management in the era of personalised medicine**
Figure adapted from Maitland and Schilsky.[85] A=genetic/metabolic signatures. B=circulating tumour cells/mRNA. NELM=neuroendocrine liver metastases. RFA=radiofrequency ablation. TAE=transarterial embolisation. TACE=transarterial chemoembolisation. SIRT=selective internal radiotherapy. PRRT=peptide receptor radionuclide therapy. Tx=treatment.

Conclusions

The recommendations (panel 1) and research proposals (panel 2) from this consensus meeting represent current knowledge of the management of neuroendocrine liver metastases. They present a rationale for therapeutic strategy and serve as a basis for the development of clinical and research programmes necessary to advance the specialty. A crucial need identified was delineation of cellular and molecular indicators of metastatic growth and blood, urinary, and tissue biomarkers of neuroendocrine liver metastases disease. With regard to clinical practice, little evidence-based information is available to guide therapy, and most recommendations are based on low-quality evidence. Large-scale, randomised controlled trials with preplanned subgroup analyses are crucial to appropriately establish therapeutic benefit. The usefulness of such studies will be dependent on correlative studies using cryopreserved tissues for molecular, genomic, and metabolic tissue analysis of tissue biomarkers that can be used as prognostics and selectants of therapy. Similarly, the development of molecular, cellular (circulating tumour cell or PCR signatures), and metabolic indices of NET disease in blood, tissue, or urine is necessary to amplify assessment of therapeutic efficacy. The paucity of molecular, genomic, and metabolic information is combined to provide an adequate scientific basis to define and guide rational therapy (figure 5). Management of neuroendocrine liver metastases is based on little more than balanced clinical opinion and judgment interfaced with diverse therapies that are only marginally effective and are unpredictable in outcome. Establishment of a core clinicoscientific-based programmatic reassessment of this disease is necessary to advance knowledge and improve outcomes.

Search strategy and selection criteria

Before the plenary presentation, a team of methodologists, clinical epidemiologists, and clinicians systematically reviewed the literature. A search of Medline, Embase, and the Cochrane Library was done. The search strategy included the term "neuroendocrine tumours" AND/OR search strings connected to the topics of interest—eg, incidence. Results were restricted to human trials and those published between January, 1940, and October, 2012. 293–3050 records were identified at each session. Randomised controlled trials, prospective and retrospective comparative cohort studies, and case-control studies were identified for the qualitative and quantitative synthesis of the systematic review by expert reviewers. Case series were included for descriptive purposes only. Single-case reports were not included. High-quality systematic reviews were not identifiable for most topics because of the poor quality of data. Between eight and 108 records for each session were available for review and presentation.

Contributors
All authors contributed equally.

Conflicts of interest
AF has received research funding and speaker's honoraria from Ipsen and Novartis. IMM has received honoraria from Clifton Life Sciences, and Ipsen. MK has consulted for Clifton Life Sciences. RS has served on the advisory boards of BTG International, Nordion, Sirtex, NCCN (National Comprehensive Cancer Network), Merit, Boston Scientific, Bayer/Onyx, and Abbott. DK owns stock in Applied Accelerator Applications (AAA). MC has received research funding, and advisory board and speaker's honoraria from Novartis, Ipsen, and Lexicon. All other authors declare that they have no conflicts of interest. All authors received travelling expenses to and from the NET consensus meeting.

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