# Net-Liver-Mets Consensus Conference

## Scientific Questions v21

### Part I — Natural history and epidemiology of NET

***Session 1*** — ***What is the incidence, prevalence and prognosis of NET and NET liver metastases?***

- What is the incidence of NET?
- What is the incidence of NET liver metastases at presentation?
- What is the prevalence of NET?
- What is the prevalence of NET liver metastases at presentation?
- What are the incidence rates of NET according to the site of the primary tumour?
- What are the incidence rates of liver metastases according to the site of the primary tumour?
- What are the primary NET features that are associated with liver metastases at presentation?
- What is the prognosis of prinary NET and of NET liver metastases?

### Part II — Histopathological classification

***Session 2*** — ***Should patients with low Ki-67 index be followed up for the detection of liver metastases?***

- In patients with a primary NET, what is the predictive value of Ki-67 index, mitotic count, or tumour grading, obtained from the primary tumour, in predicting the development of liver metastases?
- What other tissue markers have value in predicting liver metastases?

### Part III — Role of molecular biology

***Session 3*** — ***Should genetic signatures and the presence of circulating tumour cells be used in the prediction of liver metastases and to inform treatment decisions?***

- In patients with a primary NET, what is the predictive value of genetic signatures obtained from the primary tumour, in predicting the development of liver metastases?
- In patients with a primary NET, what is the predictive value of circulating tumour cells obtained from the primary tumour, in predicting the development of liver metastases?
- In patients with a primary NET, should genetic signatures be used on the treatment decision (surgery, locally ablative techniques, liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- In patients with a primary NET, should the presence of circulating tumour cells be used on the treatment decision (surgery, locally ablative techniques, liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?

### Part IV — Diagnosis of liver metastases

***Session 4*** — ***Which biochemical markers should be used for detection and post treatment follow-up of liver metastases?***

- In patients with a primary NET, what is the diagnostic accuracy of the available biochemical markers (e.g. chromogranin A and B, Serotonin, NSE, tumour specific hormones) in detecting liver metastases?
- In patients receiving a liver resection, what is the diagnostic accuracy of the available biochemical markers (e.g chromogranin A and B, serotonin, NSE, tumour specific hormones) obtained during follow up, in detecting recurrent disease or disease progression?

***Session 5*** — ***Which morphological imaging modality should be used to assess resectability of liver metastases with a curative intent?***

- In patients with NET liver metastases, what is the diagnostic accuracy of different morphological imaging modalities (US, CT, MRI) in identifying liver lesions and extrahepatic disease?
- In patients with NET liver metastases, what is the diagnostic accuracy of different morphological imaging modalities (US, CT, 3D-CT, MRI) in detecting vascular and biliary invasion, in order to assess resectability (R0/R1)?

***Session 6*** — ***Which functional imaging modality should be used to assess resectability of liver metastases with a curative intent?***

- In patients with NET liver metastases, what is the diagnostic accuracy of different functional imaging modalities (octreoscan, DOTA-SSTR-PET/CT, F-18 FDG-PET/CT, DOPA PET, other) in identifying liver lesions?
- In patients with NET liver metastases, what is the diagnostic accuracy of different functional imaging modalities (octreoscan, DOTA-SSTR-PET/CT, F-18 FDG-PET/CT, DOPA PET, other) in detecting extra-hepatic disease?

***Session 7*** — ***Do we need a biopsy of both the primary and liver metastases for the treatment decision of liver metastases?***

- In patients with a primary NET and synchronous liver metastases, what is the agreement of the biopsy of the primary and the liver metastases with regards to tumour grading?
- In patients with metachronous liver metastases, what is the agreement of the biopsy of the primary and the liver metastases with regards to tumour grading?
- In patients with liver metastases, what is the agreement of single *vs.* multiple liver biopsies with regards to tumour grading?
- In patients with NET liver metastases, do we need additional biopsies of the normal parenchyma to detect micrometastases?

## Part V Surgical Treatment of liver metastases

***Session 8*** ***When should a liver resection be performed?***

- o In patients with resectable NET liver metastases, does liver resection with a curative intent (R0/R1) improve outcome (tumor-free survival, overall survival, quality of life) when compared to non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o In patients with NET liver metastases, does R2 liver resection (debulking) improve outcome (progression-free survival, overall survival, quality of life) when compared to non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o In patients with NET liver metastases, do locally ablative techniques as an adjunct to R2 liver resection improve outcome? (progression-free survival, overall survival, quality of life)
- o In patients with synchronous resectable primary NET and resectable NET liver metastases, should the primary and the liver metastases be resected together or separately to improve outcome (progression-free survival, overall survival, quality of life)?
- o In patients with both synchronous resectable primary NET and NET liver metastases, should the primary or the liver metastases be resected first to improve outcome (progression-free survival, overall survival, quality of life)?

***Session 9*** ***Should the loco-regional primary tumour be resected in the presence of non-resectable liver metastases?***

- o In patients with a pancreatic primary NET and non-resectable liver metastases, does resecting the primary tumour improve outcome (progression-free survival, overall survival, quality of life) when compared to non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o In patients with an intestinal primary NET and non-resectable liver metastases, does resecting the loco-regional primary tumour improve outcome (progression-free survival, overall survival, quality of life) when compared to non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o In patients with a lung primary NET and non-resectable liver metastases, does resecting the primary tumour improve outcome (progression-free survival, overall survival, quality of life) when compared to non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?

***Session 10*** ***When should a liver transplantation be performed?***

- o In patients with non-resectable NET liver metastases, does liver transplantation improve outcome (disease-free / progression-free survival, overall survival, quality of life) as opposed to R2 liver resection (debulking) or non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o In patients with NET liver metastases, which selection criteria should be used for liver transplantation in order to improve outcome (disease-free survival, overall survival, quality of life)?
- o In patients with NET liver metastases and consideration for liver transplantation, does a delay (≥6 months) to assess tumour progression before transplanting improve the selection of patients (disease-free survival, overall survival, quality of life) as opposed to early transplantation (<6 months)?
- o In patients with NET liver metastases listed for liver transplantation, does downstaging (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy) improve outcome (tumor-free survival, overall survival, quality of life)?
- o In patients with non-resectable NET liver metastases, does living donor liver transplantation improve outcome (disease-free survival, overall survival, quality of life) as opposed to deceased-donor transplantation or non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o Does the outcome of the recipient justify the risk of the donor in the setting of liver transplantation for NET liver metastases?

***Session 11*** ***Should neoadjuvant and adjuvant treatment strategies be used?***

- o In patients with NET liver metastases, does neoadjuvant treatment improve outcome (increase in R0/R1 resectability, tumour-free survival, overall survival, quality of life) after liver resection compared to no neoadjuvant treatment?
- o In patients with NET liver metastases, does adjuvant treatment improve the outcome (tumour-free survival, overall survival, quality of life) of liver resection as opposed to no adjuvant treatment?
- o In patients with NET liver metastases, do both neoadjuvant and adjuvant treatment strategies improve the outcome (tumour-free survival, overall survival, quality of life) of liver resection compared to no neoadjuvant and adjuvant treatment?

## Part VI Non-Surgical Treatment

***Session 12*** ***When should locally ablative techniques (RFA, microwave, cryotherapy) be used?***

- o In patients with non-R0/R1 resectable NET liver metastases, do locally ablative techniques (RFA, microwave, cryotherapy) improve outcome (progression-free survival, overall survival, quality of life) when compared to non-ablative treatment (R2 liver resection, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy)?
- o In patients with non-resectable NET liver metastases, which locally ablative technique (RFA, microwave, cryotherapy) achieves best outcome (progression-free survival, overall survival, quality of life)?
- o In patients with non-resectable NET liver metastases, do locally ablative techniques (RFA, microwave, cryotherapy) in conjunction to systemic treatment (peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy) improve outcome (progression-free survival, overall survival, quality of life) as opposed to systemic treatment alone?
- o In patient with NET liver metastases, what is the incidence of tumour dissemination during the use of locally ablative techniques, evident on imaging/biopsy during follow up?

***Session 13*** ***When should angiographic liver-directed techniques be used?***

- o In patients with non-resectable NET liver metastases, do percutaneous liver-directed techniques (bland embolisation, chemoembolisation, selective internal radiotherapy) improve outcome (progression-free survival, overall survival, quality of life) as opposed to R2 liver resection?
- o In patients with non-resectable NET liver metastases, which percutaneous liver-directed technique (bland embolisation, chemoembolisation, selective internal radiotherapy) achieves best outcome (progression-free survival, overall survival, quality of life)?
- o In patients with non-resectable NET liver metastases, do percutaneous liver-directed techniques (bland embolisation, chemoembolisation, selective internal radiotherapy) improve outcome (progression-free survival, overall survival, quality of life) in combination with systemic treatment (peptide receptor radionuclide treatment, chemotherapy, targeted therapy, biotherapy) when compared to percutaneous liver-directed technique alone?
- o In patient with NET liver metastases, what is the incidence of tumour dissemination during the use of percutaneous liver-directed techniques, evident on imaging/biopsy during follow up?

***Session 14*** ***When should peptide receptor radionuclide therapy be used?***

- o In patients with non-resectable NET liver metastases, does peptide receptor radionuclide therapy improve outcome (progression-free survival, overall survival, quality of life) when compared to R2 liver resection?
- o In patients with non-resectable NET liver metastases, does outcome (progression-free survival, overall survival, quality of life) of peptide receptor radionuclide therapy depend upon the size of liver metastases (>5 vs. <5cm diameter of the largest tumour) or their uptake on a diagnostic scan?
- o In patients with non-resectable NET liver metastases, does outcome (progression-free survival, overall survival, quality of life) of peptide receptor radionuclide therapy depend upon the percentage of liver volume involvement (e.g. <75% vs.>75%) ?
- o In patients with non-resectable NET liver metastases, does outcome (progression free survival, overall survival, quality of life) of peptide receptor radionuclide therapy depens upon the site of the primary tumour?
- o In patients with non-resectable NET liver metastases, does peptide receptor radionuclide therapy in combination with percutaneous liver-directed techniques (bland embolization, chemoembolization, selective internal radiotherapy) and or locally ablative techniques improve outcome (progression-free survival, overall survival, quality of life) when compared to peptide receptor radionuclide therapy as a single technique?

***Session 15*** ***When should chemotherapy, targeted therapy or biotherapy be used?***

- o In patients with non-resectable NET liver metastases, does chemotherapy, targeted therapy and biotherapy improve outcome (progression-free survival, overall survival, quality of life) as opposed to R2 liver resection?
- o In patients with non-resectable NET liver metastases, does outcome (progression- free survival, overall survival, quality of life) of chemotherapy, targeted therapy and biotherapy depend upon the size of liver metastases (>5 vs. <5cm diameter of the largest tumour)?
- o In patients with non-resectable NET liver metastases, does outcome (progression- free survival, overall survival, quality of life) of chemotherapy, targeted therapy and biotherapy depend upon the percentage of liver volume involvement (e.g. <75% vs. >75%)?
- o In patients with non-resectable NET liver metastases, does outcome (progression free survival, overall survival, quality of life) of chemotherapy, targeted therapy and biotherapy depend upon the site of the primary tumour?
- o In patients with non-resectable NET liver metastases, does chemotherapy, targeted therapy and biotherapy in combination with percutaneous liver-directed techniques (bland embolization, chemoembolization, selective internal radiotherapy) and or locally ablative techniques improve outcome (progression-free survival, overall survival, quality of life) when compared to chemotherapy, targeted therapy and biotherapy as a single technique?