Chapter 6

Liver-directed therapies

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Contents

1. Practice Points

- The decision to choose liver-directed therapy depends on the pattern of hepatic disease, histologic grading of the tumour and the extent of the extra-hepatic disease, if present.
- The choice of which liver-directed therapy to use depends on a number of factors including the size, number of hepatic metastases, experience of the local centre and consensus of the MDM. For example:
    - Ablative techniques, including SABR, may be used for small volume/small number metastases
    - Trans-arterial embolisation techniques and SIRT are used in more extensive disease
- Trans-arterial embolisation includes bland embolisation (TAE) or chemoembolisation (TACE). Radioembolisation or Selective Internal Radiation Therapy (SIRT) use radioactive beads that are injected through the liver arteries.
- TAE, TACE and SIRT are all effective in controlling symptoms and tumour growth, with an objective response rate of approximately 50%.
- All patients need to be assessed at an appropriate multidisciplinary meeting before a decision is made regarding therapy.
- These treatments may result in a post-embolisation syndrome and/or "carcinoid flare" and need to be carefully medically managed.
- Other liver-directed techniques are still in the investigational phase.

2. Liver-directed therapies

2.1 Indications for liver-directed therapies

One of the major prognostic factors that dramatically effects survival in patients with NENs is the presence of liver metastases. Unfortunately, liver metastases are common in patients with NENs.

Key point: up to 75% of patients who present with NENs also have liver metastases.

Furthermore, NEN liver metastases that are either extensive or progressing are associated with poorer prognosis.

Liver-directed therapies may be contraindicated by pre-existing hepatic insufficiency, or if this can be predicted to be likely following therapy. Selection of patients must be based on a combination of morphologic and functional imaging to establish the presence and extent of extra-hepatic disease. Unlike colorectal cancer where presence of unresectable extra-hepatic metastases generally contraindicates surgical resection of liver metastases, palliative hepatic resection in NENs may be considered in the context of multi-modality treatment paradigms.

For these reasons, the optimal management of patients with NEN liver metastases should involve evaluation in a multi-disciplinary environment with access to advanced imaging techniques, interventional radiology, surgical and medical expertise.

The options available can be categorised as follows:

- Surgical
- Medical (e.g. somatostatin analogues, chemotherapy)
- Targeted nuclear medicine (e.g. peptide receptor radionuclide therapy)
- Interventional radiological/liver-directed therapies
- If debulking of liver metastases is under consideration, other liver-directed therapies and/or systemic therapies in addition to surgery may also be considered.

The liver-directed therapies that will be discussed in this chapter include:

- Selective Internal Radiation Therapy (SIRT)
- Trans-catheter arterial embolisation
    - TACE – trans-arterial chemo-embolisation,
    - TAE (bland trans-arterial embolisation)
    - Drug-eluting beads (DEB-TACE)
- Radio-frequency ablation (including microwave ablation, cryo-ablation and chemical ablation)
- Investigational techniques
    - SABR
    - Intra-arterial PRRT
    - Rose Bengal

2.2 Treatment approaches to NEN liver metastases

The treatment approach to patients with NEN liver metastases is dictated by the pattern of disease within the liver. Morphologically, there are three different patterns of liver metastases:

2.2.1 Treatment approach to liver metastases without extra-hepatic spread

A. Simple Pattern (Type I):

The metastases are confined to one liver lobe or limited to two adjacent segments so that they can be resected by a standard anatomical resection. This “simple pattern” occurs in 20‑25% of the cases.

These patients are treated with:

(i) Surgery‑liver resection or
(ii) Liver-directed therapy if not fit for surgery.

B. Complex Pattern (Type II):

There is one major lesion but with smaller satellite lesions contra-laterally. This “complex bi-lobar pattern” occurs in 10‑15% of the cases. These patients are treated with:

(i) Surgery‑major one-stage or two-stage (i.e. sequential) resection. Prior to resection, portal vein embolisation can be performed to increase the size of the functional liver remnant (FLR).

(ii) Liver-directed therapy if not fit for surgery.

C. Diffuse Pattern (Type III):

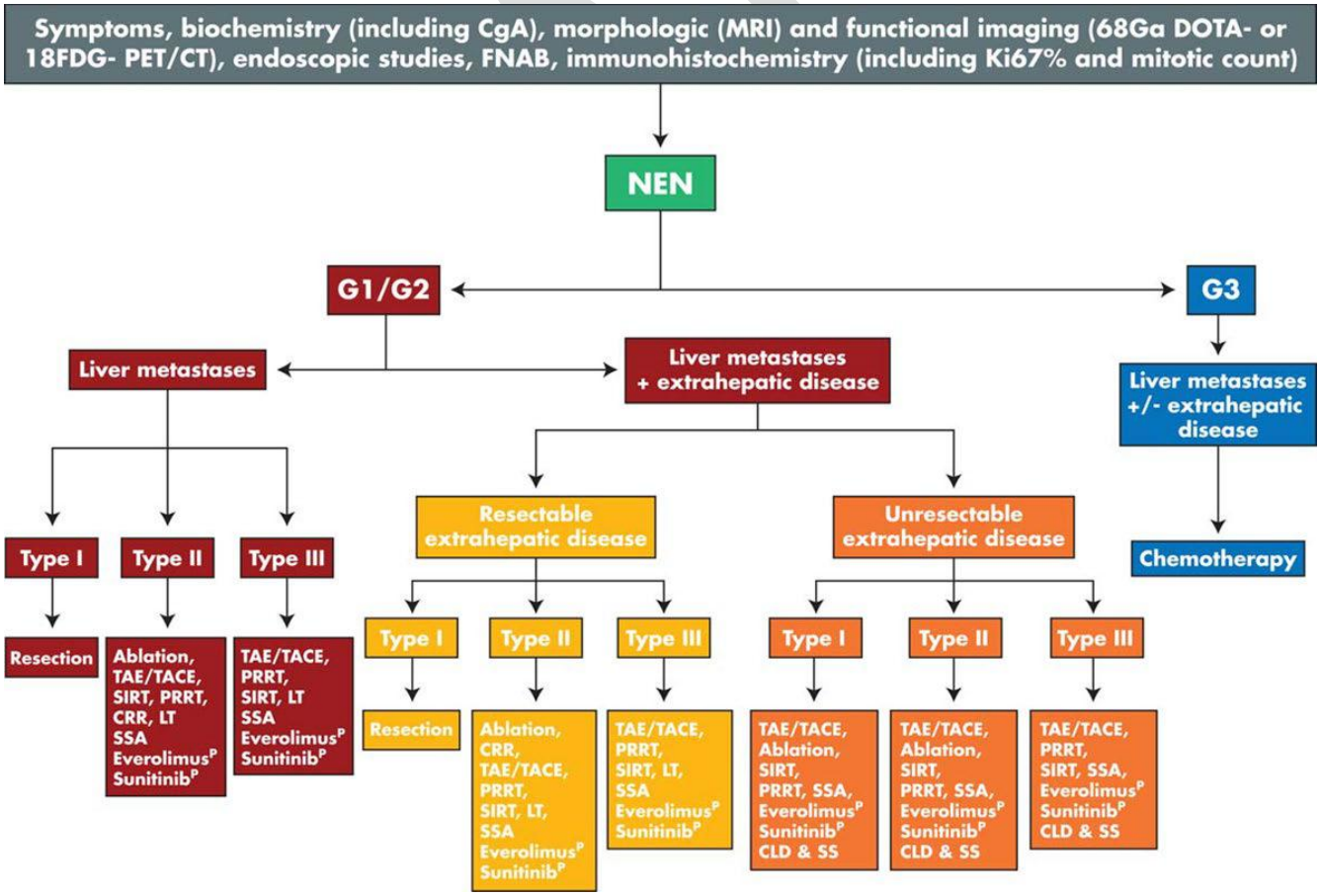
There are diffuse, multifocal liver metastases. This "diffuse pattern" occurs in 60 – 70% of the cases. These patients are unresectable and are thus treated with:

(i) Liver-directed therapy.

2.2.2 Patients with liver metastases with inoperable extra-hepatic spread

- Should initially be treated using non-surgical methods (biotherapy, chemotherapy, etc) regardless of the extent of liver disease.
- If palliative steps are also required, liver-directed therapy may be used in "simple pattern", "complex pattern" and "diffuse pattern" liver metastases.
- Surgery (of a debulking nature) may be undertaken for selected candidates.

The choice of which liver-directed therapy to use also depends on the size and number of liver metastases, with ablative techniques being used for small volume/small number metastases, while the trans-arterial embolisation techniques and SIRT are used in more extensive disease.



Picture from Frilling A, Clift A, "Therapeutic Strategies for Neuroendocrine liver Metastases". Cancer 2015; 121:117296. *Reproduced with permission from authors.*

2.3 Surgery and liver transplantation

These topics are covered in chapter 5.

2.4 Ablative techniques

Ablative techniques such as RFA can be used effectively as anti-tumour treatment and in relieving symptoms in patients with NEN liver metastases, either as a sole therapy or in combination with surgery.[2][3][4][5]

While surgery remains the therapy of choice in limited metastatic disease, RFA may be employed for palliation in order to avoid a major surgical procedure and it can also effectively supplement a surgical resection. In patients with tumours > 5 cm in diameter or near vital structures, RFA or other ablative techniques are not the most suitable single therapy.[6][7][8][9]

Ablation

Ablation techniques can be broadly categorised into the following:

- Thermal
  - Heat: radiofrequency (RF) and microwave (MW)
  - Freeze: cryoablation
- Chemical
- Irreversible electroporation (IRE)
- Others
  - High intensity focused ultrasound (HIFU)
  - Laser interstitial thermal therapy (LITT)

Technology

Both RF and MW are a form of electromagnetic radiation, which results in raising the local temperature to a supraphysiologic temperature, causing structural damage to the tumour and protein coagulation. The physics behind the technologies are briefly described below, but details are beyond the scope of this section.

In RF, an electric current is generated from a generator (source) and delivered through the probe, the patient and to the grounding pads. Electric current is converted to heat by way of rapid ion oscillations, resistive heating and conductive heat transfer to the adjacent tissue {10}. As tissue is heated and becomes charred, impedance of the tissue rapidly increases, reducing the effectiveness of radiofrequency ablation. RF ablation is susceptible to heat sink effect from large vessels. This is a phenomenon where the relative cool temperature of larger vessels washes the heat away and reduces the temperature of the ablation zone. This is a common cause of technical failure, with residual disease and ablation marginal “recurrence”, and must always be considered as part of the planning process.

MW is emitted from the antenna placed within the lesion, causing polar molecules, predominantly water (H2O) in tissue, to oscillate rapidly which is transferred into heat {11}. Because this

technology does not rely on electric current flowing through the body, grounding pads are not required. Microwave ablation has been shown to be less susceptible to heat sink effect {11} and is not affected by charred tissue, as it is not affected by tissue impedance.

Cryoablation relies on freeze-thaw cycles to destroy tissue. Mechanisms of cryoablation have been described {12, 13, 14} including changes in osmotic pressure and cell shrinkage, and formation of ice crystals at the intracellular and extracellular level which damages organelles and cell membranes.

Chemical ablation is performed by injecting absolute ethanol into the tumour, which is highly toxic to tissue and tumour, leading to cell death and necrosis.

Literature

Mohan et al {15} in a systematic review on radiofrequency ablation alone or in combination with surgery for neuroendocrine hepatic metastases, have demonstrated symptomatic relief in up to 92% patients, but recurrence was common (63-87%), while Norlen et al {16} showed no survival benefits in patients who have undergone RF ablation +/- surgery. In appropriately selected patients with symptomatic, oligometastatic liver disease, ablation can be considered alone or in combination with other options.

Data on cryotherapy for neuroendocrine hepatic metastases are sparse {17,18} with no direct prospective trials exploring overall survival or hepatic progression free survival rates compared with other locoregional therapeutic options.

While chemical ablation has been largely superseded by thermal ablation techniques, small tumours which are close to vessels or central bile ducts may be amenable to ethanol ablation to avoid heat sink effects or central biliary injury {19}. This can be used alone, or as an adjunct with other locoregional therapy (i.e. thermal ablation) to treat smaller lesions. Atwell et al {20} has demonstrated ethanol injection for chemical ablation in a small cohort of neuroendocrine liver metastases, and it is recommended that alcohol injection should be limited to lesions smaller than 50mm {19}.

Technique

Ablation can be performed under image guidance or during surgery. Radiological guidance is most commonly done under ultrasound, although CT can be used for deeper lesions, lesions near the dome or obese patients.

Ablation is a painful procedure and is ideally performed under general anaesthesia (GA). This mitigates a very unpleasant experience for the patient and staff alike. GA also allows a degree of respiratory control to facilitate probe placement in more difficult located lesions.

If GA is difficult to access, ablation can be performed satisfactorily with judicious use of intravenous conscious sedation, with local anaesthetic especially over the peritoneum and liver capsule, and a periportal splanchnic block.

If a pre-ablation biopsy is required, a coaxial needle can be placed next to the lesion to facilitate both procedures while avoiding multiple passes through the liver capsule. The proceduralist should ensure the coaxial needle is large enough to fit the ablation device. A 13G coaxial needle may be required to fit larger microwave antennas. If this technique is utilised, the probe/antenna should be

long enough to expose the active component beyond the coaxial needle. A table test is usually sufficient to make sure the right equipment is ready.

For chemical ablation, needles used are often in the 18-22 G size. Either end hole needles, such as a Chiba needle, or multiple side hole needles, such as the 18 G percutaneous ethanol injection therapy (PEIT) needle {21} can be selected. Volume of ethanol injected should be at a ratio of 1:1 to the lesional volume, obtained either using volumetric software (such as syngo.via, Siemens Healthineers, Erlangen, Germany) or a rough estimation using three orthogonal dimensions assuming elliptical shape of the lesion.

As previously discussed, GA or deep sedation is recommended during ethanol injection as this can be extremely painful for the patient. In the awake patient, this can lead to patient distress, loss of needle position and risk of non-target injection of ethanol.

The proceduralist should be wary of leaks into the peritoneal cavity, which are extremely painful. The proceduralist should also be mindful of inadvertent intravascular injection. At sufficient volume, this can lead rapidly to cardiovascular collapse and disseminated intravascular coagulopathy (DIC) {22}.

Defining the morphology of the tumour is critical in technical success of thermal ablation. Tumours do not grow in spheres and are often irregular or oblong in shape. The long axis of the tumour should be identified so that, whenever feasible, the probe can be inserted through the middle of the lesion along the long axis to maximise tumoural coverage.

Large vessels (hepatic and portal veins > 5 mm, hepatic artery > 3 mm) should be identified to assess the risk of heatsink effect, which is detrimental to the effect of thermal ablation.

Biliary injury, leak, and chronic benign strictures can occur after ablation and care must be taken in centrally located lesions.

RF ablation is susceptible to tissue desiccation and charring resulting in reduced flow of electricity and therefore reduced efficacy of ablation. Some devices have been devised to limit the effect of charring by infusion of saline into the tissue or by cooling the probe tip with chilled saline.

2.5 Trans-arterial embolisation

Selective hepatic trans-catheter arterial embolization (TAE) or chemo-embolization (TACE) may be used to treat liver metastases in patients where surgery is not feasible regardless of the origin of the primary tumour {23,24,25}.

Transarterial embolisation encompasses a wide range of techniques, including but not limited to:

Conventional TACE (c-TACE): c-TACE is performed by injecting an emulsion of a chemotherapeutic agent with lipiodol followed by an embolic agent such as polyvinyl alcohol (PVA) particles or Gelfoam slurry. Variations of this technique exist, such as slow infusion of chemotherapeutic agents followed by embolic agents without lipiodol. The most commonly used chemotherapeutic agent is doxorubicin.

Bland embolisation (TAE): Bland embolisation forgoes administration of chemotherapeutics and only injection of embolic agents until stasis.

Drug eluting bead TACE (deb-TACE): Chemotherapeutic agents are imbued into microscopic beads before embolisation into the target artery. Beads release chemotherapy over a longer period of time, increasing the overall duration of chemotherapy circulating in the body and reducing the peak serum concentration and thereby improving the toxicity profile. However, DEB-TACE is relatively contraindicated in NEN due to increase risk of biliary ischaemia and subsequent complications of biloma and sepsis, compared to C-TACE.

Radioembolisation (RE, Y90 RE, TARE, SIRT): This highly complex, multi-session procedure involves combined efforts from the Diagnostic and Interventional Radiology and the Nuclear Medicine departments and will be covered in the section on Selective Internal Radiation Therapy.

Key point: These modalities are effective in controlling symptoms and tumour growth and result in a significant decrease in biochemical markers with objective tumour responses in about 50% of patients.

Literature

In a series of hepatocellular carcinoma studies, including a systematic review with meta-analysis {26} TACE has failed to demonstrate superiority in response rate or overall survival compared to TAE, and is associated with worse toxicity profile.

A small retrospective study of thirty patients with neuroendocrine liver metastases by Fiore {27} has shown that there was no significant difference in lesion size reduction or median progression free survival in both TAE and TACE populations.

In a NET-Liver-Metastases Consensus Conference, Kennedy et al {28} reviewed eighteen publications and found that TAE, TACE and Y90 are acceptable methods of locoregional therapy but due to rarity of disease and quality of studies, superiority of each modality cannot be determined. There are also suggestions that Y90 shows a lower toxicity profile than TAE or TACE.

More recently, Minh et al {29} in a retrospective study with propensity score analysis in 251 patients, suggested superiority in overall survival with c-TACE over Y90 and DEB-TACE and hepatic progression free survival with c-TACE over Y90.

The current Randomized Embolisation Trial for NeuroEndocrine Tumour Metastases To The Liver (RETNET) https://clinicaltrials.gov/ct2/show/NCT02724540 aims to compare the duration of hepatic progression-free survival between TAE, TACE and DEB-TACE, and the results are eagerly awaited. It is noted that the DEB-TACE arm of the RETNET trial has been closed after the first analyses because of an unacceptably high incidence of severe hepatobiliary complications.

Because of their potential morbidity, TAE or TACE should be performed in experienced centres. A common side effect is post-embolisation syndrome (presenting as pain, low grade fever, nausea and general malaise with little change in blood biochemistry usually lasting 3 days), but major side effects are rare.{30,31}

The procedures are contraindicated in the case of complete portal vein thrombosis and hepatic insufficiency. In patients in whom liver transplantation may subsequently be considered, multiple TAE or TACE can induce endoarteritis rendering the vascular reconstruction at transplantation more difficult due to arterial thrombosis.{32,33}

2.6 Portal vein embolisation

Portal vein embolisation is not a direct locoregional treatment for neuroendocrine hepatic metastases. It is an adjunct endovascular therapy to aid hepatic resection if it is determined that the future liver remnant cannot adequately sustain liver function to prevent acute hepatic insufficiency {34}.

2.7 Selective Internal Radiation Therapy (SIRT)

Selective Internal Radiation Therapy (SIRT), also known as Trans-Arterial Radio-Embolization (TARE), may be used to treat liver metastases in patients where surgery is not feasible regardless of the origin of the primary tumour.{35}

Neuroendocrine liver metastases are generally very vascular and derive nearly all of their blood supply from the hepatic artery. Due to the smaller size of the radio-active microspheres (25‑35 microns), these particles embolise more distally, in the tumour vascular bed and do not destroy the main and segmental hepatic arteries. As they lodge at the margins of the tumour(s), there is a more important direct beta radiation effect on the tumour cells. The procedural endpoint differs from other embolisation techniques. Vascular stasis is not required, and in fact may result in non-target embolisation or premature termination of radio-embolisation to prevent reflux.

The majority of studies in the literature use resin Spheres (SIR-Spheres), although “glass” spheres (TheraSpheres) have also been used outside of Australia.

SIRT requires a diagnostic hepatic angiogram and MAA breakthrough scan to be performed initially to exclude significant lung shunting (> 20%) and also to embolise any feeding vessels to the stomach, small bowel or pancreas that may otherwise preclude treatment. Treatment then requires a second separate hepatic angiogram session, usually one to two weeks later. In patients with extensive bi-lobar disease, sequential whole liver treatment can be performed, with one lobe treated initially and the second 1-2 months later.

This technique is effective in controlling symptoms and tumour growth and results in a significant decrease in biochemical markers in patients with objective tumour responses.

There have been no controlled trials comparing SIRT to TACE or TAE. However, the available evidence suggests that the effectiveness for these 3 therapies is similar. One systematic review {36} of SIRT and TACE found that both were effective and safe, with comparable results regarding tumour response, symptom palliation and patient survival, with some differences in the side effect profile and cost, being slightly more expensive for SIRT.

A meta-analysis on SIRT in NETs by Devcic et al in 2014 {37} identified 12 studies that met the selection criteria. 144 studies were excluded, mainly because they did not provide separate and complete RECIST data. Most were retrospective and non-comparative. A total of 414 patients were included in the 12 studies. There was very high inter-study heterogeneity. The pooled response rate was 50% and the disease control rate was 86% by RECIST criteria.

Pooled survival data could not be assessed as 95% confidence limits were not sufficiently provided. The median overall survival ranged from 14-70 months, with a median of 28.5 months.

Median progression-free survival was poorly reported in most of these studies, and of those that reported it, the range was between 4-14 months. A more recent single centre retrospective study reported a median hepatic progression-free survival of 18 months {45}.

In a second more recent meta-analysis by Frilling et al in 2018 {38}, 27 studies were identified, with 843 patients, including 12 more recent studies that were not included in the original meta-analysis by Devcic et al {37}. Eighteen of the included studies reported survival data. An Objective Response Rate (ORR) of 51% was identified from the 27 studies, with a fixed effects weighted mean Disease Control Rate (DCR) of 88%. The median overall survival was 32 months (range 18-57 months). In their analysis, there was no significant inter-study heterogeneity identified in the assessment of ORR or DCR.

A separate systematic review by Jia & Wang in 2018 {39} also included seven abstracts. There was a total of 870 patients. The median disease control rate was 86%, with a similar median survival.

Fidelman et al {40} reported that the maximum imaging response after SIRT took longer for NET liver metastases (median 11 months) compared with a median of 2.8 months for colorectal liver metastases.

The response rate in individual studies varied, in part due to patient selection. In general, the survival pattern was more favourable in patients with lower grade tumours, no extra-hepatic disease, lower tumour burden, and female gender.

Potential advantages of SIRT

1. SIRT can still be used, albeit with slightly less efficacy, when there is branch or main portal vein thrombus. The latter is an absolute contra-indication for TACE or TAE, while the former is a relative contra-indication for TACE or TAE.
2. Several studies reported a complete response rate in a selection of patients. In those studies with greater than 20 patients, the CR ranged between 0% and 18.2% {37}.
3. Post-embolization syndrome is reported as being less common and less pronounced in patients undergoing SIRT compared to TACE and major side effects are rare in experienced institutions.
4. There have been two small quality of life studies on patients receiving SIRT. One, with 30 patients, showed temporary increases in mental health and social functioning at medium term follow-up at 6-12 months, while the other showed a significant improvement on QoLs in 6/7 evaluable patients at 6 months {41,42}.
5. Looking at the various side-effect profiles of the liver directed therapies, the impression is that the SIRT is associated with a lower acute toxicity profile, shorter hospitalisation and a more rapid return to normal daily activities compared with TAE or TACE {28}
6. SIRT may allow subsequent TACE, but TACE may rule out subsequent SIRT:
    a. Due to smaller size of RE microspheres (25 – 35 microns), these particles embolize more distally, in the tumour vascular bed and do not destroy main and segmental hepatic arteries. This means that if disease progresses after RE, then TACE or TAE may still be used.

b. On the other hand TACE and TAE may target the main and segmental hepatic arteries (if not a selective TACE), and thus may prevent the subsequent use of SIRT in the event of tumour progression. However, it was noted in the systemic review that the prior use of TACE or TAE occurred in up to 20% of patients {39}.

7. SIRT can also be used after PRRT, as long as the liver function is satisfactory and there is a sufficient time interval (months) between treatments to allow recovery of normal liver tissue.

Side effects of SIRT

Acute:

- Not well reported in NEN patients but the most common were abdominal pain, nausea and vomiting and fatigue affecting approximately 30% of patients {39}. A multi-centre study of 244 patients reported adverse events in 56% within the first 3 months (fatigue 28%, abdominal pain 27% and nausea 23%), which only persisted in 6% at 6 months, mainly abdominal pain. {43}
- Serious acute complications such as radiation gastritis, gastric or duodenal ulcer and death due to liver failure were poorly reported but appeared to be very infrequent, particularly in major centres. Braat reported an incidence of gastric ulceration in 2.8% {43}.

Long-term:

- Tomozawa et al looked at long term toxicity after SIRT {44}. 15/52 patients exhibited imaging signs of cirrhosis-like morphology and portal hypertension. While many patients had significant increases in ALP, AST and ALT, only 4/52 had grade 3 serological toxicities. Both sets of findings were more common in patients who had bi-lobar rather than uni-lobar treatment. These findings were generally clinically silent.
- Another single centre retrospective review {45} found that 3/59 patients died of hepatic failure that was possibly therapy related, while Braat reported 2/244 patients with radioembolisation induced liver disease {43}.

2.8 Investigational liver-directed therapies

Stereotactic Ablative Radiation Therapy (SBRT)

To date, no randomized phase III data have been published on SBRT for liver metastases, but there are several retrospective and prospective clinical studies.

Most studies have combined multiple different tumour histologies, with colon cancer, lung cancer, and breast cancer being the most frequently represented. Studies to date have generally limited treatment to patients with five or fewer liver metastases, with reported local control ranging from 68% at 18 months up to 92% at 2 years {46}.

Tumour size appears to be an important factor. Tumours smaller than 3cm or tumour volume less than 75mL demonstrated more favourable response.

Small bowel neuroendocrine malignancies are predicted to be more radiosensitive than pancreatic and large bowel neuroendocrine malignancies.

There are only anecdotal reports or small case studies of NEN liver metastases being treated but these appear to show that a clinically relevant, radiographic, biochemical and symptomatic control can be achieved {47}.

Long-term follow-up after SBRT and prospective randomized trials will be necessary to determine where it fits into nonsurgical approach for NEN liver metastases.

Intra-arterial (hepatic) injection of PRRT

Preliminary data using quantitative comparison of tracer uptake in NET lesions on PET/CT following intravenous versus intra-arterial Ga-68 DOTA-octreotate administration suggest that substantially higher dose can be achieved to lesions compared to other organs, including normal hepatic parenchyma, with direct intra-arterial administration {48}. The LUTIA trial is currently underway to evaluate this and the results are awaited.

An initial retrospective trial of 55 patients receiving intra-arterial PRRT of SSTR-expressing tumours showed that it was effective and prolonged median OS and PFS, particularly in patients with hepatic tumour burden. It was well-tolerated and safe with a low rate of severe haematotoxicity, without severe nephrotoxicity or hepatotoxicity {49}.

Rose Bengal

Rose Bengal is a chemical stain, originally discovered in 1882, and used as a dye in cancer diagnosis.

Rose Bengal, in a 10% solution known as PV-10, has already displayed promise in the treatment of melanoma. A bystander effect was also seen in untreated lesions, suggesting a positive immune response, although it was more effective when all lesions were injected with PV-10. PV-10 causes acute oncolytic destruction of injected tumours, releasing damage associated molecular pattern molecules (DAMPs) and tumour antigens that initiate an immunologic cascade, facilitating systemic anti-tumour immunity by the adaptive immune system.

An initial single-centre Phase 1 study looking at progressive NET with liver lesions not amenable to potentially curative therapies is being conducted in Adelaide, Australia to evaluate the potential safety, tolerability, and preliminary efficacy of PV-10 in metastatic NET patients. Six patients have been enrolled. There were no safety concerns and there was encouraging evidence of both local and systemic control on the early data {50}.

Link to Chapter 7 Functional NEN/ carcinoid syndrome.

2.9 Peri-procedural carcinoid crisis prophylaxis and management

"Carcinoid syndrome" is characterised by episodic flushing, diarrhoea, wheezing and right heart valve disease due to functional NENs secretion of mediators including histamine, 5-hydroxytryptamine (serotonin) and 5-hydroxytryptophan. "Carcinoid crisis" is a potentially very serious life threatening complication of carcinoid syndrome defined as the severe combination of carcinoid syndrome symptoms, including severe hypo- and/or hypertension, and bronchospasm.

Although the commonest causes of carcinoid crisis are anaesthesia and surgery, it can also be induced by liver-directed procedures (including biopsy, intra-arterial treatments and ablation) and PRRT. It is important that this is recognised such that preventative measures are taken to reduce this risk and have a management plan if they occur.

Preventative measures include the use of long acting somatostatin analogues, and peri-procedural use of short acting SSA octreotide via subcutaneous or intravenous injection (300-500mcg) or via IV infusion (50-200mcg/hr) depending on symptoms/risk. Peri-procedural antihistamine, steroids (dexamethasone) and antiemetics (ondansetron), and adequate intraprocedural pain control are also recommended to reduce other stimuli (nausea, pain, inflammation) {51,52,53}.

2.10 Therapy choice

In summary, given the similar effectiveness between the various hepatic intra-arterial embolisation options, the decision as to which to choose will depend on:

- Individual patient characteristics,
    - i.e. the number, size and site of the hepatic metastases
    - uni-lobar or bi-lobar burden of disease
    - prior therapies
    - underlying liver function
    - the presence or absence of main or branch portal vein involvement.
- The local expertise and the availability of each of these options.
- The decision of the multi-disciplinary meeting.

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