An Overview of the Surgical Management of Hepatic Neuroendocrine Metastases

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Abstract Neuroendocrine tumours (NET) frequently metastasise to the liver (NLM) and are associated with significant morbidity and mortality. Numerous treatment options have been implemented both for cure, and to implement disease control. Surgical treatment includes curative resection, palliative cytoreductive resection and transplantation. Complete surgical resection is only possible in a subset of people with NLMs due to excessive metastatic burden and anatomical location. Ablative therapies may be used either as an adjunct to surgery or as a primary treatment. The purpose of the following article is to summarise surgical treatment strategies in the management of patients with hepatic neuroendocrine metastases, based on the available literature.

Keywords Neuroendocrine tumours · Liver metastases

Introduction

Neuroendocrine tumours (NET) arise from neuroendocrine cells and are a group of neoplasms with distinct biological and morphological manifestations [1, 2]. Once considered extremely rare, NET is now increasing in incidence and prevalence and are likely to be underdiagnosed [3–5]. They can be defined as either non-functioning tumours causing

symptoms by mass effect or as a malignant tumour secreting specific hormones (or neuropeptide hormones) to induce specific clinical syndromes. The most common sites of origin for neuroendocrine tumours are the bronchopulmonary system and the gastrointestinal tract [1, 6–8].

NET frequently metastasizes to the liver and cause significant morbidity and mortality. Between 46–93% of patients with NETs have liver involvement (NLM) at the time of diagnosis [1]. The disease course of these tumours is far from universally indolent, and metastatic involvement of the liver typically represents the greatest threat of morbidity and mortality posed by these malignancies [9]. This is due to excess tumour production and replacement of the normal hepatic parenchyma. The 5-year survival of patients with NLMs on supportive care is 0–20% [1, 10], which illustrates that the disease is far from indolent.

Surgical interventions for NLMs have demonstrated superior outcomes to non-operative therapies. Resection alone is supported by favourable long-term outcomes in large retrospective trials [11]. However, complete surgical resection is only possible in a subset of people with NLMs due to excessive metastatic burden and anatomical location [1, 11].

Treatment options for patients that are not surgical candidates have evolved over the last several years. Neuroendocrine carcinomas constitute a substantial fraction of non-colorectal metastases to the liver and some of the techniques applied in the management of metastatic colorectal cancer have been implemented in NLM. Median survival in patients with NLM is longer than in those patients with stage IV colorectal cancer, and so there is a wider time frame for treatment. However, the tumour biology is different, and usually more vascular, which may limit therapeutic options [12].

Numerous treatment options have been implemented both for cure, and to implement disease control. Surgical

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resection with curative intent, palliative tumour de-bulking surgery, liver transplantation, locally applied ablative techniques and systemic medical regimens have all been implemented with success. However, the optimal method of treatment is still a matter of debate

The purpose of the following article is to provide an overview of the surgical management options in the management of patients with neuroendocrine hepatic metastases.

Surgical Management of Hepatic Metastases in Neuro-endocrine Tumours

Surgical resection is still thought to be the mainstay of curative treatment, however there is a lack of prospective studies comparing modalities of treatment [1]. The most recent Cochrane review [13] concluded that there was no good level of evidence comparing surgical resection versus other treatment modalities and hence, surgical resection remains the gold standard treatment where possible.

Patients with liver metastases (LM) secondary to NET may develop weight loss, anorexia and pain due to tumour load in addition to the systemic symptoms caused by circulatory secretion of hormones such as flushing and palpitations [14].

Surgical management of LM includes; resection for curative intent, palliative cytoreductive resection to reduce systemic hormonal symptoms or symptoms due to tumour expansion and liver transplantation for patients with unresectable LM. Most liver centres will only consider curative liver resection in patients whom either total or >90% of the LM are amenable to resection.

The key factor emphasized in the literature is that meticulous patient selection is imperative to ensure optimal post-operative outcomes [1]. These include reasonable performance status with few co-morbidities, primary tumour already resected or potential for synchronous resection with LM and the absence of advanced stages of carcinoid heart disease. Pre-operative imaging is highly important to determine metastatic spread patterns, three of which have been described [3];

Type I; a single metastasis of any size

Type II; isolated metastatic bulk with accompanying smaller deposits, with both lobes involved

Type III; disseminated metastatic spread with both lobes involved and very little normal liver parenchyma left.

The different patterns affect the resections possible, with Type 1 more suitable for a curative resection, Type 2 more suitable for palliative cytoreductive surgery in addition to adjuncts and Type 3 more likely to require liver transplantation.

It is also imperative to ensure the post-resectional liver volume can be calculated; if this is calculated to be less than 30%, then portal vein embolization or portal vein ligation can be performed, thereby inducing hypertrophy of the future remaining section [1]. An alternative strategy to ensure the future liver remnant is (FLR) >30% is to perform a 2 staged resection [15].

Liver resections currently performed are grouped according to the Brisbane 2000 criteria [16, 17]. However it is often found that patients will need at least 3 segments resected [12]. The timing of surgical resections depends on whether the LM are synchronous or metachronous [3], as well as whether the LM are uni or bi-lobar. In synchronous unilobar metastases, a one stage procedure of primary tumour and LM resection with little additional risk, however in metachronous or synchronous bilobar disease, a two stage procedure of primary tumour resection with LM from one lobe followed subsequently by LM resection from the other lobe approximately 9 months later may be done to reduce peri-operative risk [18].

A large multicentre case series has reported a 5 and 10 year survival rate of 74% and 51% respectively following surgery for LM, however this does not correlate with disease free survival, as 5 year tumour recurrence has been quoted to be as high as 94–97% of patients [15]. Sarmiento et al [19] reported a case series of 170 patients of which 44% had a curative resection and 56% had a debulking of >90% of tumour load whose average 5 year survival rate was 61%, yet with a tumour recurrence rate of 84%. Glazer et al [17] reported a 5 year survival rate of 77% and 10 year survival of 50%. Despite the high tumour recurrence rate found in most case series, increase in survival time and the symptom control achieved are why aggressive surgical resection is still the mainstay of treatment. It has been found that even incomplete surgical resections (R1 or R2) can offer a survival benefit to patients, with a 5 year survival of 70% and 60% respectively in a prospective study of 47 patients [9].

Palliative cytoreduction therapy or resection is indicated in patients who pre-operatively are unlikely to achieve an R0 resection, but have less than 70% of their liver involved with tumour, with no unresectable extrahepatic metastases and where potentially staged liver resections will reduce systemic symptoms [3]. The terminology of ‘palliative resection’ is not clear, as historical recommendations have been that palliative surgical resection should only occur if elimination of at least 90% of tumour load is achievable, without comparison of survival and symptom improvement with resection of lesser percentage of tumour load. ‘Palliative resection’ can apply to R1 or R2 resection, incomplete cytoreductive resection as well as partial tumour debulking [1]. The reduction of tumour load to improve palliative relief of systemic and tumour related symptoms is the main rationale to performing incomplete resection of metastatic disease [1],

with one study showing a 95% improvement in symptoms subsequent to surgical resection [18]. The discrepancy in terminology used makes it difficult to draw definitive conclusion from the literature, though it does appear to be effective in reducing morbidity from symptoms.

Liver transplantation is currently not considered an option for curative management, due to the high mortality (between 10–20%) and morbidity often associated with the procedure, and also the lack of tumour free recurrence. In a meta-analysis of 103 patients, the 5 year survival was 47% with 76% of patients showing evidence of disease recurrence [14]. Between 1988 and 2011, 185 liver transplants were performed in the United States for neuroendocrine LM, and the overall 5 year survival was only 57.8%, comparably lower than transplants performed for other reasons (74% for all other patients), as well as lower than the survival rate following resection [9]. It is *potentially* an option for young patients who fit into the following criteria [9];

- 1) LM not amenable to resection
- 2) Resection of primary malignancy at least 1 year prior to evaluation
- 3) No evidence of unresectable extra-hepatic metastases
- 4) Disease stability for at least 1 year
- 5) Failure of non-operative treatments

In conclusion, although surgical resection does not offer increased disease *free* survival, the net benefit of symptom control and overall survival means that patients should be actively considered for surgical treatment of their neuroendocrine LM. Unfortunately this is based solely on case series results, as no prospective randomised trials have been published, with accuracy of evidence further compounded by terminology and local practice differing widely between centres. Despite this, close liaison with medical oncologists, specialist radiologists and specialist surgeons in a tertiary referral centre will allow each patient to be managed on an individual patient specific basis.

Locally Ablative Techniques for Management of Neuroendocrine Liver Metastases

Radiofrequency Ablation (RFA) can be utilised during open or laparoscopic surgery, or as an image-guided percutaneous procedure. Furthermore, it can be used as the primary mode of treatment of the liver metastases, or as an adjunct to surgical resection [20, 21]. Additionally, the application of RFA can be repeated as there is growing recognition that technically unresectable metastatic disease should not inevitably lead to palliative support, as the concept of managing disease burden as a treatment is supported [22, 23]. However, there is evidence that suggest surgical approaches provide

enhanced local tumour control when compared with percutaneous approaches [23, 24].

The largest series looking at neuroendocrine liver metastases assessed 452 lesions treated laparoscopically in 63 patients [25]. The mean number of lesions treated as first RFA session was 6 (range 1–16) and mean tumour size was 2.3 cm (range 0.5–10 cm). There was no 30 day mortality and the procedure associated morbidity was only 5%. Median survival was 3.9 years, calculated from the first RFA session. The size of the dominant liver metastases was predictive of survival, with patients having a tumour diameter of less than 3 cm having a more favourable outlook. The lowest local recurrence was seen in metastases sized less than 3 cm and with a 1 cm post ablation margin.

Hellman et al [26] looked at 21 patients who underwent either percutaneous or intra-operative RFA. In total they looked at 43 metastases and had a mean follow up of 2.1 years. 95% of these patients had complete tumour ablation at follow up. Akyildiz et al [27] looked at 89 patients with neuroendocrine hepatic metastases who underwent 119 laparoscopic RFA episodes. Mean tumour size was 3.6 cm and mean number of lesions was 6. Perioperative morbidity was 6%, and 30-day mortality was 1%. Symptom relief was achieved in 97% of patients after radiofrequency ablation. Twenty-two per cent of patients developed local recurrence, 63% developed new hepatic lesions, and 59% developed extrahepatic disease. Repeat radiofrequency ablation (27%) and chemoembolization (7%) were used to achieve additional local tumour control in follow up, again illustrating the concept of NET metastases as a chronic disease. Median disease-free survival was 1.3 years and the overall survival was 6 years after RFA. RFA appears to be safe and provides symptomatic relief. However, further well designed trials are needed to gauge its efficacy.

Other locally ablative therapies such as laser therapy, cryoablation and percutaneous ablation have been implemented in smaller case series and have achieved local tumour control. However, they have largely been superseded by the superior results and higher safety profile of RFA. In fact, histopathological assessment of lesions produced by cryotherapy has shown that tissue adjacent to larger blood vessels may remain undamaged by the ablation [28]. This reverse heat-sinking effect can result in viable tumour remaining within treated lesions and may explain the relatively high local recurrence seen with this technique. Complication rates are relatively high and the major concern with cryotherapy is the cryoshock phenomenon, whereby patients develop a systematic inflammatory response to ablation [29–32]. The physiological mechanism remains unclear, and the true incidence of cryoshock is difficult to establish because of lack of precise definitions [22].

Microwave coagulation therapy has several theoretical advantages over other ablative techniques. It causes agitation

of water molecules in the tissues which generates friction, causing heat and tissue destruction by coagulative necrosis [33–35]. There is growing evidence that complete hepatic inflow occlusion (Pringle manoeuvre) increases the size of ablated lesions [36], although this is only feasible during laparoscopic or open intervention. In contrast to RFA, the active heating by microwave energy is not affected by charred and desiccated tissue, allowing more controlled tissue ablation. Microwave ablation takes less time than an equivalent RFA [37, 38]. Microwave coagulation offers larger and more uniform ablations than other technologies. A systematic review by Gravante et al [39] considered changes in lesions that were ablated and then resected for histopathological review. They found no viable cells 6 cm away from the centre of the ablation zone in 93% of cases treated with microwave ablation. Future research should be directed towards the role of microwave ablation in patients with neuroendocrine hepatic metastases.

Radioembolisation

Radioembolization is similar in principle to chemoembolization but uses radioactive microspheres of yttrium-90 (^{90}Y) in combination with embolic agents [40]. The hypervascularity of neuroendocrine metastases makes them amenable to this approach, as high-energy beta-particles can be preferentially delivered to well perfused tumours with relative sparing of normal liver parenchyma [41]. Murthy et al looked at 8 patients given SIR-Spheres for NETs. All patients had unresectable disease that had previously been treated. The SIR-Spheres produced a partial response in 1 patient and the disease remained stable in 4 patients, but 3 patients progressed [41]. King et al looked at 34 patients with unresectable NETs. They demonstrated that radioembolization with (^{90}Y) resin microspheres can achieve relatively long-term responses in selected patients. These studies demonstrate the potential for radioembolisation but also highlight the fact that further studies are needed to define the safety profile and efficacy of radioembolisation [42]. In the Murthy et al study, postembolization sequelae were considered more tolerable after radioembolization when compared to the after effects of hepatic artery embolization (HAE) and chemoembolization (HACE). However, 3 patients in this study developed abdominal pain after the first ^{90}Y treatment that then prevented them from proceeding to a planned second treatment [42].

Radioembolization patients should undergo preprocedural evaluation for hepatopulmonary shunts to ensure that minimal blood flow is diverted to the lungs to minimize the extrahepatic delivery of yttrium [40]. Circulatory reflux into the gastroduodenal arteries also increases the risk of irradiation beyond target lesions in the liver. Pretherapeutic technetium-

$^{99\text{mTc}}$ -labelled macroaggregated albumin (MAA) scans can exclude these conditions [43, 44]. Patients who are deemed untreatable on the basis of unacceptably high shunting can actually have their shunts occluded through the temporary inflation of balloons within the hepatic veins, which may then enable radioembolization to occur more safely [50]. A careful risk-balance assessment is needed to ascertain which patients are likely to gain benefit from radioembolisation.

Hepatic Artery Embolisation and Chemoembolisation

Liver metastases derive the majority of their blood supply from the hepatic artery. Local devascularization offers a targeted approach that takes advantage of neoplastic hypervascularity. Selective tumour ischemia by occlusion of the hepatic artery, accomplished either through “bland” embolization using only particles of polyvinyl alcohol or through the augmented infusion of a chemotherapeutic agent (such as doxorubicin/mitomycin) [45], is an attractive strategy with which to reduce the NET metastatic burden for patients who are not surgical candidates.

Response rates vary between 50 and 96% from study to study, depending partly upon which criteria of regression, symptom control, and/or biochemical improvement are used [46–50]. Median duration of response extends up to 18 months [51]. Low and intermediate-grade neuroendocrine carcinomas are more likely to show a durable response to hepatic artery embolization (HAE) and chemoembolization (HACE) [52].

Complications of this procedure include damage to normal liver parenchyma alongside neoplastic areas due to the interruption of vascular supply. Postembolization syndrome—which manifests as deranged liver function tests, right upper quadrant abdominal pain, fever and nausea—may occur and appropriate supportive care placed. It is now more common to perform sequential, lateralized embolization of the left or right hepatic artery rather than the common hepatic artery. This has decreased the incidence of fulminant hepatic failure after HAE and HACE [53, 54].

Conclusion

Surgical resection has been shown to give both improvement in 5 year survival and reduction in symptoms associated with neuroendocrine tumours. Hence, it remains the gold standard of treatment in patients with NETM. However, most patients are not amenable to surgery. Ablative techniques offer a safe alternative and can also be used as an adjunct to surgery to extend the margins of resectability.

Further research is needed to clearly define the role of ablative therapies and other adjunctive treatments in the algorithm of care of patients with NETM.

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