Neuroendocrine Liver Metastases

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KEYWORDS

• Neuroendocrine liver metastases • Resection • Ablation
• Liver transplantation • Hepatic arterial infusion • Chemotherapy

The liver is the most common site of metastatic disease for neuroendocrine tumors and ultimately dictates outcomes in most patients. Liver involvement develops in 46% to 93% of patients with neuroendocrine malignancies.[1] The majority of patients with neuroendocrine liver metastases (NLM) have a multiplicity of lesions, with many residing in difficult locations. While the NLM may behave in a relatively indolent manner from an oncologic perspective, additional morbidity and mortality may be caused by excess hormone production when compared with metastatic liver disease from other primaries.[2] Nonoperative therapies for advanced neuroendocrine malignancies are associated with minimal response rates, short durations of disease stability, and no clear survival benefit. For example, ^{131}I-metaiodobenzylguanidine therapy is associated with a mean duration of tumor response of approximately 15 months whereas ^{111}In-octreotide therapy has a mean duration of tumor response of 20 months in patients with progressive unresectable neuroendocrine neoplasms.[3] Tumor progression is common after treatment with lanreotide and/or interferon-α without complete tumor remission.[4] Similarly, chemotherapy is associated with low response rates (15%–56%), short progression-free survival (median 4–5 months), and relatively short overall survival after start of treatment (median 15–26 months)[5,6] when applied to patients with advanced disease. Surgical therapy, on the contrary, offers the only chance at durable survival prolongation and/or improvement in quality of life. The objectives of this review are to summarize regional strategies for management of NLM, including hepatic resection, ablation, liver transplantation, and hepatic arterial embolization/chemoembolization.

RESECTION

Resection of NLM is supported by the favorable long-term outcomes noted in large retrospective series. Because neuroendocrine tumors are often detected after extensive liver metastases are present, complete surgical extirpation via hepatic resection is

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often not possible.[1,7] Consequently, only 10% to 20% of patients with NLM are eligible for resection. Because of the relative rarity and biologic heterogeneity of NLM, there are no prospective randomized controlled trials, cohort studies, or case-control studies comparing liver resection with other treatments in patients with resectable NLM.[8] Designing such a randomized study would be challenging, because to identify a 10% difference in survival (with an alpha of 0.05 and power of 0.8) between surgical debulking over other palliative treatments, 776 patients would be required. Inability to blind patients or health care providers, cross-over to completely resected patients because of down-sizing of liver metastases, and the need for prolonged follow-up due to the indolent nature of disease are all additional obstacles to the development of a prospective randomized trial.[9] Furthermore, the evolving criteria of resectability and recent improvements in the safety of liver resection have complicated comparisons of recent series to older studies.[2] Even when complete resection of NLM is performed, early recurrence is common relative to other common hepatic lesions such as colorectal metastases (**Table 1**).[2,10] However, due to the overall indolent course of neuroendocrine neoplasms, long-term survival is common after even incomplete resection (see **Table 1**). Moreover, initial symptom improvement, particularly for hormonal symptoms, is observed in most patients. These positive results suggest that most patients with disease that can be grossly resected with a sufficient liver remnant with intact biliary and vascular drainage should undergo resection.[2] When complete resection of gross liver disease is not feasible or in the presence of unresectable extrahepatic disease, resection as a tumor debulking strategy should be considered in patients with extreme hormonal symptoms refractory to other treatments or with tumors in locations that would affect short-term quality of life, such as large lesions abutting the hepatic hilum (resulting in biliary obstruction) or the colon/duodenum (resulting in gastrointestinal obstruction).[2,18] Combinations of resection and ablation may be used to achieve complete tumor response when all liver disease cannot be resected. Given the prolonged survival observed following resection of NLM, liver resection should be used as the standard by which all other treatments should be measured.[8,19,20]

Radiofrequency ablation (RFA) can provide local control and short-term symptomatic relief from NLM when resection is not possible. Mazzaglia and colleagues[21] describe the largest experience of ablation in patients with NLM, encompassing a total of 384 lesions in 63 patients via 80 laparoscopic RFA sessions. Eleven and 3 patients underwent 2 and 3 sessions, respectively, and 49% of all patients were treated (medical or radiation) before the first RFA session. The mean number of treated lesions at first session was 6 $\pm$ 0.5 lesions with mean tumor size of 2.3 $\pm$ 0.1 cm. Thirty-six patients were symptomatic from disease and 94% experienced symptom relief after ablation for a median duration of 11 $\pm$ 2.3 months after RFA. After a mean follow-up of 2.8 years, median survival following the first ablation was 3.9 years with a 2-year survival of 77%. Progressive liver disease developed in 80% of patients. Male gender (hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.1–9.1, $P = .04$) and tumor size greater than 3 cm (HR 3.3, CI 1.1–10.1, $P = .03$) were associated with poor survival after ablation. Similarly, Gilliams and colleagues[22] reported results aftr ablation of 189 lesions in 25 patients with median tumor number of 12 and maximum tumor diameter of 3.5 cm. These patients were heavily treated with liver resection, chemotherapy, and/or hepatic arterial embolization. Ablation of at least 90% of the tumor burden was achieved in 26 treatments, 50% to 89% in 33 treatments, and less than 50% in 7 treatments. Sixty-nine percent of patients experienced symptom improvement. Median survival after tumor ablation was 29 months. Elvin and colleagues[23] reported the application of 109 RFA treatment sessions in the management of 198 lesions in 42 patients.

Table 1
Results after resection of neuroendocrine liver metastases

Authors	n	Survival	Symptom Improvement	Comments
Reddy et al[10]	33	3-y 75%	—	Median disease-free survival 13 mo, 3-y disease-free survival 32% 33% with >5 lesions, 58% synchronous disease
Touzious et al[11]	37	—	> 88%	>60% bilobar disease, 79% synchronous disease, 21% with extrahepatic disease Median survival of 96 months after resection ± ablation is better compared with no treatment (median 20 mo, $P<.05$) <50% of liver involvement associated with better survival ($P<.05$)
Sarmiento et al[12]	170	5-y 61% Median 81 mo	96%	44% R_0 resection, 76% with bilateral lesions 5-y recurrence symptom-free rate 84% and 59% Better recurrence-free survival for complete vs incomplete resection (median 30 vs 16 mo, $P = .0004$)
Chen et al[13]	15	5-y 73%	—	All patients with liver-only disease
Osborne et al[14]	61	Mean 50 mo[a]	93%	62% curative resections, 69% complete symptom relief Longer symptom relief with resection compared with embolization (median 56 vs 32 mo, $P = .08$)
Landry et al[15]	23	Median 52 mo	—	16 patients underwent adjunctive therapy 13/23 patients with bilobar disease Performance status better for resected compared with unresected patients
Yao et al[16]	16	5-y 70%	—	Survival better for resected patients (5-y 70% vs 40%, $P<.05$) Better disease-free survival associated with prior resection of primary tumor and <4 metastases
Chamberlain et al[17]	34	5-y 76%	100%	82% curative resections, 62% bilobar disease Curative treatment associated with improved survival Hepatic tumor burden associated with survival among resected patients

[a] For curative resections.

Ninety-eight lesions were successfully treated (as shown by follow-up computed tomography) after a mean follow-up of 3.2 years.

Whereas hormonal treatment alone does not provide durable symptom-free nor reliable long-term survival, adjuvant octreotide and/or interferon α treatment after extirpation does improve symptom relief. Chung and colleagues[24] examined the outcome of 31 patients (90% with hormonal symptoms) with NLM who underwent hepatic resections and/or ablation. Mean duration of symptom relief after surgical therapy was 11 months with symptom recurrence in all patients. Adjuvant octreotide in 10 patients resulted in a median duration of symptom relief of 60 months compared with 16 months with other adjuvant therapies in 21 patients (P = .001). Similarly, Kolby and colleagues[25] described the outcomes of 68 patients who underwent surgical extirpation of the primary tumor followed by hepatic arterial embolization of NLM followed by treatment with octreotide (n = 35) or octreotide + interferon-α (n = 33). Overall 5-year survival was 46.5% with no difference in survival according to treatment after hepatic artery embolization. However, patients treated with octreotide + interferon-α had significantly lower risk of disease progression.

HEPATIC ARTERIAL THERAPY

Hepatic arterial embolization with or without local instillation of chemotherapy may induce disease response, symptomatic improvement, and prolonged survival in patients with unresectable NLM. Because neuroendocrine tumors are prone to produce highly vascular lesions that predominantly derive blood supply from the hepatic artery (as opposed to the normal hepatic parenchyma that derive the majority of blood supply from the portal vein), opportunities exist for selected ischemia of NLM and/or delivery of directed chemotherapy via hepatic artery therapy. Hepatic arterial embolization with cyanoacrylate, gel foam particles, polyvinyl alcohol, and microspheres have all been used to achieve distal embolization without surgical ligation of the hepatic artery.[1] Chemoembolization provides an intratumoral concentration of chemotherapy that is 10 to 20 times higher than systemic administration.[1] Several single-center series report medium-term survival and symptomatic relief after hepatic artery embolization and/or chemoembolization (**Table 2**). Among these studies, carcinoid histology is associated with better outcomes after initiation of therapy. Although in theory synergistic effects can be achieved with ischemia and local chemotherapy, several institutions interestingly report no difference in outcomes between hepatic artery embolization and hepatic artery chemoembolization (see **Table 2**). Of importance is that complete response and long-term survival are not common after hepatic arterial therapy, as the periphery of the tumor is spared from ischemia or chemotherapy. Thus, embolization of lesions close to the hepatic hilum is generally unsuccessful, as the periphery of the tumor will still cause mass-effect associated symptoms. The morbidity of embolization approaches include liver abscess, transient liver failure, pleural effusion, and postembolization syndrome, the latter consisting of fever, abdominal pain, leukocytosis, and a transient increase in liver enzymes and/or bilirubin.[1] Multiple sessions of therapy are often needed with varying intervals between sessions.[1] While not universal, commonly proposed contraindications to hepatic arterial therapy include hepatic failure, portal vein occlusion, uncorrectable coagulopathy, and renal failure.[26–31]

LIVER TRANSPLANTATION

Early disease recurrence, high postoperative mortality, the absence of extensive experience, and lack of universal indications for organ allocation preclude orthotopic

Table 2
Recent large series of hepatic arterial therapy for neuroendocrine liver metastases

Authors	n	Overall Survival	Comments
Pitt et al[26]	49 HACE 51 HAE	Median 25.5 mo, 2-y 52% Median 25.7 mo, 2-y 54%	No difference in survival between HACE and HAE
Gupta et al[27]	74 HAE 49 HACE	PIS: median 23 mo, 2-y 48.7% Carcinoid: median 33.8 mo, 2-y 68.6%	No difference in survival between HACE and HAE Carcinoid histology associated with longer survival, $P = .012$
Vogl et al[28]	48 HACE	3-y 72% and 80% Median 32.9 and 42.8 mo	No systemic chemotherapy or hormonal treatment 19% partial response after therapy
Sward et al[29]	107 HAE	Median 56 mo	71% symptomatic relief Male gender, degree of decline in urinary 5-HIAA and plasma chromogranin A, and postembolized AST levels associated with survival
Christante et al[30]	77 HAI/HACE	Median 39 mo 5-y 27%	Median progression free survival: 19 mo All treated with octreotide Primary tumor resection associated with improved survival
Strosberg et al[31]	84 HAE	Median 36 mo	75% symptomatic, 80% symptom improvement 48% partial response Survival longer for carcinoid vs pancreatic endocrine vs poorly differential histology
Ho et al[32]	46 HAE/HACE	3-y 41%	54% symptomatic, 78% symptom relief Median progression-free survival 563 d

Abbreviations: AST, aspartate aminotransferase; HACE, hepatic arterial chemoembolization; HAE, hepatic arterial embolization; HAI, hepatic arterial infusion; HIAA, 5-hydroxyindoleacetic acid; OS, overall survival, PFS, progression-free survival; PIS, pancreatic islet cell origin.

Table 3
Survival after liver transplantation for neuroendocrine liver metastases

Authors	n	Survival	Comments
Rosenau et al[33]	19	5-y OS: 80% 5-y RFS: 21%	Median RFS: 10.5 mo Ki-67 positivity and E-cadherin staining associated with survival
Lang et al[34]	10	Median OS: 33 mo	All patients symptom-free after transplant 90% tumor recurrence
Le Treut et al[35]	31	3-y OS: 47% 3-y DFS: 29%	23/31 patients treated with medical therapy before transplant 19% postoperative mortality 35% had uncontrolled hormonal and tumor mass effect symptoms, respectively Patients with carcinoid disease had better OS and DFS compared with other patients
van Vilsteren et al[36]	19	1-y OS: 88% 1-y RFS: 77%	All patients had surgical and/or radiologic intervention before transplantation
Florman et al[37]	11	1-y OS: 73% 5-y OS: 36%	10/11 patients with recurrent disease after transplantation
Routley et al[38]	11	1-y OS: 82% 5-y OS: 57%	All patients with symptom relief after transplantation Recurrence in 6/11 patients after transplantation

Abbreviations: OS, overall survival, RFS, recurrence-free survival.

liver transplantation as an option for most patients with unresectable NLM. While transplantation has the benefits of removing all hepatic disease burden, rapid disease recurrence is near universal (**Table 3**). Moreover, long-term actuarial survival among patients transplanted for NLM is poor compared with overall patient and graft survival rates for all indications. Lenhert[39] reviewed the results of 103 patients who underwent liver transplantation for NLM at 23 institutions. Ten and 40 patients underwent antecedent liver resection and chemotherapy treatment, respectively. Postoperative mortality was 14% at 60 days. Three-year overall and recurrence-free survival after transplantation was 53% and 42%. Synchronous upper abdominal operations (HR 4.8, CI 2.3–10.0, $P<.001$) and age greater than 50 (HR 2.1, CI 1.1–4.0, $P = .027$) were associated with poor overall survival. Given these poor initial experiences, liver transplantation cannot be considered a viable option for unresectable NLM.

SUMMARY

The relatively indolent course of many patients with NLM and the lack of randomized controlled trials comparing the various treatment strategies make it difficult to present definitive statements regarding their appropriate roles. Nonetheless, in the current era the following general guidelines represent reasonable approaches to the management of these patients. As resection offers the most effective and durable option for symptom relief and long-term survival, surgical extirpation should be considered for eligible patients. When a curative resection cannot be envisioned, a debulking strategy that removes 80% to 90% of NLM can be beneficial in prolonging survival and improving symptom control. Ablation may be performed in combination with resection or in cases where resection is not possible. Hepatic artery embolization can be used to treat unresectable liver disease or recurrent disease

after previous resection, or as a "neoadjuvant" strategy to down-size initially unresectable disease before surgical extirpation is considered.[18] In lieu of data on the relative effectiveness, the choice of embolization strategy (transarterial embolization, transarterial chemoembolization, radioembolization) is largely determined by institutional preference as well as tumor size and distribution. Orthotopic liver transplantation is reserved for very selected patients with isolated, unresectable liver disease and with extreme symptoms refractory to hepatic arterial therapy, immunotherapy, or hormonal suppressive treatments, with recognition that early disease recurrence is common. Patients with widespread unresectable disease are not candidates for liver-directed therapy and should be treated with salvage chemotherapy or hormonal suppression.

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