Review Article

# Surgical management of neuroendocrine tumor-associated liver metastases: a review

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**Abstract:** Liver metastasis is common among patients who suffer from neuroendocrine tumors (NETs). Radical surgery is the standard treatment whenever possible but there is still controversies concerning the treatment strategies such as resection of the primary, role of debulking surgery, liver transplantation (LT) and neoadjuvant or adjuvant therapies. This article aims to review the current evidence available, together with some latest updates, focusing on the surgical management.

**Keywords:** Neuroendocrine tumors/therapy; liver neoplasms/secondary; liver neoplasms/surgery; hepatectomy; liver transplantation (LT)

Submitted Nov 06, 2017. Accepted for publication Nov 20, 2017.
doi: 10.21037/gs.2017.11.16
**View this article at:** http://dx.doi.org/10.21037/gs.2017.11.16

## Background

Liver metastases are commonly encountered in intestinal and pancreatic neuroendocrine tumors (NETs). Around 12–34% of patients presented with distant metastases at initial diagnosis (1-5), and another 38% after the initial diagnosis (2). Majority of them presented with liver and/or lymph node metastases. Interestingly, various studies found that the incidence of gastroenteropancreatic NET has been rising in the past decades around the world (3,6), though partly maybe contributed by the changes in the classification and registration of the disease entity. Nonetheless, what was previously considered as a rare disease is now beginning to accumulate more evidence, giving a clearer picture about the optimal treatment strategy.

Known by its indolent clinical course, it was once controversial to offer surgery to patients with asymptomatic NET liver metastases (NELM) (7). A mean overall survival up to 8.1 years from symptom onset has been reported, with a range up to 41 years (8). Over the years, growing evidence showed that the overall survival is improved after resection with curative intent, or other modalities such as ablation and liver transplantation (LT). In 2016, the European Neuroendocrine Tumor Society updated their guidelines on NELM and provided a comprehensive overview of the disease. This article aims to review the current evidence on the management strategies of NELM, mainly focusing on the potential challenges and controversies from a surgeon's point of view.

## Liver resection

As mentioned in the latest update of the ENET guidelines (9), surgery with curative intent should always be considered first in grade 1 (G1) and grade 2 (G2) NET, even in the presence of liver and/or lymph node metastases. Although there is no randomized controlled trial to support such practice (10), various reports already showed prolonged survival following resection of the primary tumors and liver metastases with a 5-year survival rate ranging from 58% to 70% and a 10-year survival rate of 35% (11-14). Liver resection is now used as the benchmark against all other

treatments for resectable NELM.

In a systematic review on the surgical outcomes by Saxena *et al.* (15), 29 clinical studies on liver resection with or without concomitant ablation for NELM were included. It showed that the 5-year median overall survival (OS) was 70.5% (range, 31–100%) and 10-year median OS was 42% (range, 0–100%). The overall perioperative mortality rate was 0–9% (median 0%) and morbidity rate ranged from 3% to 45% (median 23%). These figures were comparable to the liver resections for hepatocellular carcinoma, if not better (16-18). Given the relatively preserved liver function in most of the patients suffering from NELM, liver resection should be safe and feasible in experienced hands.

Despite the prolonged overall survival, many studies showed a high rate of recurrence. From the review by Saxena *et al.* (15), the 5-year median progression-free survival (PFS) was 29% (range, 6–66%). Nearly all patients experienced recurrence by 10 years after resection, with a 10-year median PFS of 1% only (range, 0–11%). In a retrospective study from Zhang *et al.* (19), 46.4% of patients (223 out of 481 patients) were found to have recurrences after 5 years. 70.9% of those recurrences (158 patients) occurred early (defined as recurrence occurring within 3 years after curative-intent resection). It was shown that there is no difference in PFS between early and late recurrence as long as curative treatment was given, although the overall survival was not mentioned in this group of patients.

Resection also offers excellent results in terms of symptomatic relief, especially for hormone-related symptoms, with a response rate up to 90–100% in certain reports (13,20,21). However symptoms are bound to recur with high rate of tumor recurrence, be it hormone-related or symptoms related to tumor bulk. The 5-year symptom-free survival ranges from 15% to 46%, reflecting the high rate of tumor recurrence (15).

In order to guide management, three types of metastases pattern have been described (22):

- Type I: single metastasis;
- Type II: isolated metastatic bulk with smaller deposits;
- Type III: disseminated metastases.

It was suggested that type I would be more suitable for resection, whereas types II and III would be more suitable for ablation and other non-surgical therapies. This can only serve as a rough guide for clinical decision, as sometimes type II tumors may still be amenable to combined surgery with ablation. In case of inadequate liver reserve, surgery may not be feasible in even type I tumors.

A number of prognostic factors were identified to predict the outcomes of resection. Due to the heterogeneity in patient inclusion criteria and treatment strategies, it is difficult to identify the exact risk factors affecting the OS and PFS. From a meta-analysis by Yuan *et al.* (23), factors favoring survival include resection with curative intent and functional tumors. Several clinical studies also reported that the presence of extrahepatic disease, Ki67 expression and the level of differentiation of the tumor affect survival (24-26). Ruzzenente *et al.* (25) has recently developed a simple nomogram with number of liver metastases, maximum tumor size and Ki67 expression to predict the overall survival at 5 and 10 years. This may be useful clinically to aid decision-making, but further validation is still needed.

It was still controversial as to whether the site of primary tumor affects prognosis. In a large population series by Fairweather *et al.* (24) of over 600 patients with NELM, it was found that primary small bowel tumors was one of the significant independent prognosticators for overall survival (hazard ratio 0.5, P<0.001). However in another study by Spolverato *et al.* (26), there was no significant difference in 5-year OS and 5-year PFS between pancreatic NET and non-pancreatic NET after propensity score matching.

### *Resection versus non-surgical therapies*

Cochrane review was previously performed by Gurusamy in 2009, and concluded that there was no good quality evidence to show that surgery is superior to other non-surgical treatment (10). A summary of studies comparing surgery to other non-surgical treatments was listed in *Table 1*. All of the studies showed a significantly better survival for surgery group.

In the more recent meta-analysis by Yuan *et al.* (23), the efficacy of liver resection versus nonsurgical regimens was investigated with the results of seven clinical studies. It was found that liver resection was significantly associated with a higher rate of symptomatic relief, longer median survival time and 5-year survival. However one should note that there was statistically significant heterogeneity in the studies included, and none of the studies is randomized controlled trial.

One of the largest series so far comparing surgery with intra-arterial therapy (IAT) was by Mayo *et al.* Propensity score matching analysis was used. Median survival was significantly longer in surgery group (84 *vs.* 38.9 months; P=0.05). Patients with more than 25% liver tumor burden

 

**Table 1** Summary of studies comparing liver resection +/– ablation and non-surgical treatments

| Citation | Study period | No. of patients | Non-surgical treatment | Study design | 5-year survival resection | Non-surgical treatment | P value |
|---|---|---|---|---|---|---|---|
| Chen *et al.* (27) | 1984–1995 | 38 | IAT, medical therapy, radiotherapy, conservative | Retrospective | 73% (actuarial) | 29% (actuarial) | 0.003 |
| Chamberlain *et al.* (7) | 1992–1998 | 85 | IAT, medical therapy, conservative | Retrospective | 76% | 50% (IAT) | <0.05 |
| Yao *et al.* (12) | 1994–2000 | 36 | IAT | Retrospective | 70% (actuarial) | 40% (actuarial) | Not mentioned |
| Touzios *et al.* (28) | 1990–2004 | 42 | Medical therapy, external beam radiotherapy, conservative | Retrospective | 72% | 25% | <0.05 |
| Musunuru *et al.* (29) | 1996–2004 | 48 | IAT, medical therapy, conservative | Retrospective | 83% (3-year survival) | 31% (3-year survival) | 0.01 |
| Osborne *et al.* (30) | 2000–2004 | 120 | IAT | Retrospective | 43±26.1 months (mean survival) | 24±15.8 months (mean survival) | <0.001 |
| Mayo *et al.* (31) | 1985–2010 | 753 | IAT | Retrospective | 74% | 34% | <0.001 |

IAT, intra-arterial therapy.

and asymptomatic disease did not derive as much benefit from surgery (median survival 16.7 *vs.* 18.5 months; P=0.78).

### *Role of debulking surgery*

Even if curative surgery could not be carried out, debulking surgery could still be performed to alleviate symptoms. When >80–90% of the tumor load could be resected, there may be associated survival benefit as shown in some studies (13,32). Some studies even allow a larger proportion of residual tumour up to 30%, while still able to demonstrate survival benefit (33,34). In a retrospective study by Osborne *et al.* (30), debulking surgery was performed in 23 out of 191 patients (12%). In combination with ablation intra-operatively, there was significant survival benefit when comparing debulking surgery with embolization (P=0.03), although the benefit was not as great when compared with curative surgery.

### *Resection of grade 3 (G3) tumors*

Due to the very different behavior of high-grade NET, the ENETS deliberately published a separated guideline for high-grade tumors and neuroendocrine carcinoma. In the ENETS guidelines (35), surgical resection and ablation of metastases were not recommended. Chemotherapy was suggested as first line therapy. Other non-surgical therapies including peptide receptor radionuclide therapy (PRRT) and radiotherapy could also be considered in individual patients.

However there are new reports showing that there may be potential benefits in surgery in selected patients. Galleberg *et al.* (36) reported 5-year OS of 43% and 5-year PFS of 13% in 32 patients with curative-intent resections for high-grade NELM. Patients with relatively lower Ki67 expression (21–54%) and those who received adjuvant chemotherapy were found to have a better OS but there was no benefit in PFS. In another retrospective study by Du *et al.* (37), resection was performed in seven patients with G3 tumors. Three-year OS was 42.8%, while another nine patients treated with non-surgical therapies all died in 3 years (P=0.049). Further data is needed to determine the best treatment strategy in these patients.

### *Resection of primary tumors*

In patients with unresectable liver metastases, one would assume that resection for the primary tumor would not provide any benefit. Both the ENETS (9) and NCCN guidelines (38) suggested that resection of primary tumors should not be considered if the metastasis is not resectable. However another school of thought was that primary tumor resection can help prevent subsequent complications like obstruction and malnutrition (39).

 

**Table 2** Summaries of studies on liver transplantation (LT) as treatment for neuroendocrine tumor with unresectable liver metastases

| Citation | Study period | No. of patients | Study design | 5-year overall survival (%) | 5-year disease-free survival (%) |
|---|---|---|---|---|---|
| Coppa *et al.* [2001] (11) | 1987–1999 | 9 | Retrospective | 70 | 53 |
| Frilling *et al.* [2006] (49) | 1992–2004 | 15 | Prospective | 67.2 (actuarial) | 48.3 (actuarial) |
| Olausson *et al.* [2007] (50) | 1997–2005 | 15 | Retrospective | 90 | 20 |
| Gedaly *et al.* [2011] (51) | 1988–2008 | 150 | Retrospective | 49 | 32 (out of 83 patients) |
| Nguyen *et al.* [2011] (52) | 1988–2011 | 184 | Retrospective | 49.2 | Not mentioned |
| Le Treut *et al.* [2013] (53) | 1982–2009 | 213 | Retrospective | 52 (59 in later 10 years) | 30 |
| Grat *et al.* [2014] (54) | 1989–2013 | 12 | Retrospective | 78.6 | 51.6 |
| Mazzaferro *et al.* [2016] (48) | 1995–2010 | 88 | Prospective | 97.2 | 13.1 |

In a study by Bettini *et al.* (40), it was shown that the only benefit of resecting the primary tumors was to prevent any symptoms arising from the tumor bulk such as biliary obstruction or symptoms from functional tumors. There was no difference in PFS between two groups. However, Bertani *et al.* has published several studies showing that there is a survival benefit in resecting the primary for metastatic disease (41-43). The author proposed that even in the absence of complication or symptoms, the primary tumor should still be removed as it may enhance the efficacy of systemic therapy. His findings were further supported by Citterio *et al.* in a recent retrospective study (44). However as none of the studies above is randomized, the potential bias arisen from patient selection should not be neglected. Patients who underwent operation were probably having a smaller tumor load and better performance status. In patients requiring pancreaticoduodenectomy, there is another potential complication of sepsis if IAT is to be considered after the operation.

## Local ablative therapies

In patients who have multifocal disease, suboptimal liver function or poorer performance status, ablative therapies such as radiofrequency ablation (RFA) can be considered. It could be used as both a primary treatment or as combined treatment with resection in order to maximize tumor clearance. Mazzaglia *et al.* (45) reported outcomes for 63 patients who underwent RFA for NELM and demonstrated a median survival of 11 years, with only a 6.3% recurrence rate. Most of the other studies included RFA as an adjunct to resection, which showed a clear survival benefit in oppose to non-surgical treatments (*Table 1*). Taner *et al.* (46) reported an overall survival of 80% and 59% at 5 and 10 years respectively when RFA was used as combined treatment. RFA is particularly useful in recurrent disease, when resection becomes limited after multiple operations (19).

The limitation of effectiveness of ablation is mainly by the size of the tumour. It would be difficult to achieve complete ablation once the tumour diameter exceeds 3 cm, whereas lesions over 5 cm should deem unsuitable. If there are large number of bilobar lesions, ablation alone is contraindicated (45,47).

## LT

LT as a treatment for NELM is still highly controversial. Due to the lack of long-term results and prospective trials, the selection criteria are still poorly defined. Some of the guidelines such as Milan-NET criteria (48) or the ENETS guidelines (9) may provide some reference. *Table 2* summarizes the results from various studies. There was no randomized study comparing LT versus other treatment modalities (55,56). According to the review by Fan *et al.* (57), the 5-year OS was similar between transplanted and non-transplanted patients, but the 5-year DFS was improved for post-LT patients (50% *vs.* 34%). When interpreting the results, one must bear in mind that LT is usually only performed when all other treatment modalities have been exhausted. It would be better to measure survival after diagnosis of NELM rather than survival after LT, and any pre-LT treatment should be taken into account.

Some of the more commonly used selection criteria includes younger age (<45–55 years old), low Ki67

 

expression (<10%), primary tumors solely draining into portal system, lower hepatic tumor load (<50%) and absence of extrahepatic disease (11,54,58,59). With these criteria, the 5-year OS was up to 70–90% and the 5-year PFS was as high as 80% (60). Some suggested a delay in LT for over 6 months may help to select a group of patient with better prognosis (58). This was also recommended in Milan-NET criteria, ENETS guidelines and the Organ Procurement and Trans-plantation Network in the United States (61). This may imply these patients simply would have a better survival because of their stable disease. Whether LT should be offered to patients with stable disease, or those with progressive disease despite other treatment, is still a matter of debate.

## Role of neoadjuvant or adjuvant treatment

Neoadjuvant and adjuvant treatment for down-staging or preventing recurrence have been introduced in single case reports and smaller series. Therapies such as PRRT are reported to be useful in down-staging unresectable NELM (62-65). The combination of PRRT with radiosensitizing chemotherapy has also been considered as promising to improve resectability of NELM (66). In another retrospective cohort of 52 patients (67), it was found that the PFS at 5 years were similar in patients who received adjuvant chemotherapy with streptozotocin-5-FU when compared with observation group. Since there was no randomized controlled trial performed, the results may be confounded as those who are with advanced disease are more likely to be selected for neoadjuvant or adjuvant therapy (19). Concrete evidence is still lacking in this topic and these therapeutic strategies should be used with caution (68).

## Conclusions

Surgical resection remains to be the mainstay of treatment for NELM. Radical resection of both the primary and NELM should be contemplated whenever possible. If the tumor load could be reduced by 80–90%, surgical debulking with or without the combination of ablation should still be considered. LT is possible in patients with unresectable NELM, but only applicable in a highly selected group. Otherwise in patients with bilobar involvement or disseminated disease, intra-arterial therapies and medical therapies still play an important role.

Currently there are still a lot of unknowns in the management of NELM, as it is particularly difficult to conduct large scale randomized controlled trial in a relatively rare disease. Since complete resection is still the only hope of cure so far, ways to downstage or downsize tumor should be explored in patients with NELM. Although there are proven efficacy in multiple systemic treatments (somatostatin analogues, PRRT, chemotherapy, targeted therapy), there are few studies which explored the potential in neoadjuvant setting. There is also no clear answer to the management of recurrent disease and the optimal treatment after debulking surgery. In order to come up with the best treatment strategy, collaboration between different specialties such as oncologists, radiologists and surgeons is of paramount importance.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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**Cite this article as:** Chan MY, Ma KW, Chan A. Surgical management of neuroendocrine tumor-associated liver metastases: a review. Gland Surg 2018;7(1):28-35. doi: 10.21037/gs.2017.11.16

 