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TOPIC HIGHLIGHT

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Role of surgery and transplantation in the treatment of hepatic metastases from neuroendocrine tumor

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Core tip: This is an extensive review of the literature focusing on the role of surgery (resection and transplantation) and the recently published literature in the treatment of liver metastases from neuroendocrine tumors.

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Abstract

Neuroendocrine tumors (NET) are a heterogeneous group of cancers, with indolent behavior. The most common primary origin is the gastro-intestinal tract but can also appear in the lungs, kidneys, adrenals, ovaries and other organs. In general, NET is usually discovered in the metastatic phase (40%-80%). The liver is the most common organ involved when metastases occur (40%-93%), followed by bone (12%-20%) and lung (8%-10%). A number of different therapeutic options are available for the treatment of hepatic metastases including surgical resection, transplantation, ablation, trans-arterial chemoembolization, chemotherapy and somatostatin analogues. Recently, molecular targeted therapies have been used, usually in combination with other treatment options, to improve outcomes in patients with metastases. This article emphasizes on the role of surgery in the treatment of liver metastases from NET.

Key words: Neuroendocrine tumors; Liver metastases; Hepatectomy; Liver transplantation

INTRODUCTION

Neuroendocrine tumors are a heterogeneous group of neoplasms, with indolent patterns of growth and bizarre hormonal symptoms. Although sporadic, a small group of patients are affected by Multiple Endocrine Neoplasia type 1. They include carcinoid tumors, pancreatic islet cell tumors, paragangliomas, pheochromocytomas and medullary thyroid carcinoma. These tumors can be broadly classified into two categories as high grade malignant neuroendocrine carcinomas with characteristic small cell, anaplastic or undifferentiated appearance in light microscopy and low grade malignant neuroendocrine carcinomas with characteristic, well differentiated histologic features that arise primarily in the gastro-intestinal tract but also appear in the lungs, kidneys and ovaries. In general, NET is usually discovered in the metastatic phase (40%-80%). The liver is the most common organ involved when metastases occur (40%-93%), followed by bone (12%-20%) and lung (8%-10%). Liver metastases from NET is the main cause of death with 90% of the patients affected having multifocal and bilateral metastases[1-4].

A number of different therapeutic options are avail-

able for the treatment of hepatic metastases including surgical resection, transplantation, transarterial chemoembolization, radiofrequency ablation, chemotherapy and somatostatin analogues. The low proliferative rate of NET makes cytotoxic chemotherapeutic agents ineffective in controlling the growth and spread of the majority of these lesions. The 5-year survival rate in untreated patients is approximately 30%. The use chemo-therapeutic agents prolong survival by only a mean of 12-24 mo. Somatostatin analogues remain the priority of treatment of functioning syndromes with unresectable metastases[5,6]. The standard treatment for neuroendocrine tumors is surgery even in the presence of hepatic metastases. Some experts have suggested that resection should be considered if resection of 90% or more of the tumor volume is feasible. The use of image guided ablative techniques has served as an adjunct to surgery in selected patients to improve patient symptoms and overall survival. Although all these approaches are associated with favorable response rates, metastatic NET is ultimately a fatal disease with high rates of tumor recurrence after treatment. The recurrence rate is high even in patients with unilobar disease with no evidence of extra-hepatic metastases. Surgical resection provides excellent disease control with an overall survival rate of 47%-92%. Resolution of symptoms is possible in more than 90% of patients with very low operative mortality[7,8]. Total hepatectomy and Liver transplantation has been advocated in selected patients with bilateral unresectable symptomatic liver metastases. There has been an increasing interest in determining the role of liver transplantation in treating these patients. Recent evidences suggested that 5 year overall survival after liver transplantation for unresectable Liver metastasis can be as good as 60%-80% with improved patient selection and adjustments in the clinical-pathological definition of stages[9,10].

The aim of this study is to do an extensive review of the existing literature on the use of liver resection and transplantation in patients with liver metastases from NET.

ROLE OF SURGERY

Surgical resection is considered the best treatment option for patients with hepatic metastases from neuro-endocrine tumors. Resection is feasible only when 90%-100% of the tumor metastases are amenable to resection[11-15]. Søreide *et al*[16] compared the overall survival in patients who underwent surgical resection *vs* conservative management and found a median survival of 216 mo in resected patients with 48 mo in the unresected patients. However, relatively long survival rates have been reported in untreated patients commonly due to the indolent nature of these tumors.

The various strategies of surgical resection have been suggested such as resection with curative intent and palliative cyto-reductive surgery to reduce local and systemic effects of the disease. Curative resection of liver metastases is possible only in 10%-25% of the patients. In a significant number of patients, residual tumor is left behind which is associated with disease progression. Recent evidences have suggested that the reason behind high incidence of intra-hepatic recurrence is related to underestimated disease by current imaging techniques in close to 50% of patients. Mayo *et al*[11] reported an R0 resection rate of only 53.7% with an R1 resection rate of around 33%. Saxena *et al*[14] did a systematic review of all the 29 studies conducted between 1990 and 2009 and found a median rate of 63% R0 resection in a total of 1469 patients who underwent liver resection of hepatic metastases from neuro-endocrine tumors. Interestingly, the median overall progression free survival was only 21 mo and disease free survival (DFS) median at 5 and 10 years of 29% and 1% respectively.

Palliative cytoreduction is indicated in patients with the main intent to control the systemic and local tumor related symptoms. A recent study demonstrated an improvement of symptoms in 95% of the patients after cyto-reduction. The rationale behind this approach is that removal of more than 90% of the tumor bulk allows a significant clinical improvement otherwise not achievable by other non-surgical approaches[13].

Liver resection of metastases from NET has an overall survival rate in the range of 47%-92% with resolution of symptoms in more than 90% of the patients with very low operative mortality (Table 1). Que *et al*[4] proposed that surgical resection in metastatic NETs is indicated if the primary tumor is resectable and if 90% of the liver metastases are resectable and/or are amenable for ablation. Their overall survival is 75% with this approach. However, in the same group disease free survival was only 15% indicating again the high incidence of recurrence after hepatectomy. Due to these low rates of DFS and high rates of recurrence, several experts have questioned the role of surgical resection in these patients. A study from the Mayo Clinic reported a 5 year overall survival for patients treated by surgical resection and intra-arterial therapy be 74% and 30% respectively with also an increased median survival in the surgically resected group of 123 mo *vs* only 34 mo for the Intra-arterial therapy. They also reported a 10-year survival rate of 51% post-surgical resection but very high recurrence rates after resection at 5 and 10 years[21]. Glazer *et al*[26] also reported similar results with 5-year survival of 77% in patients undergoing hepatectomy for NET metastases.

Saxena *et al*[24] also reported in a review of the literature a median perioperative mortality of 0%, a surgical morbidity of 23% and a median overall survival of 70.5% at 5 years and 42% at 10 years. These findings support aggressive surgical resection if feasible.

A study by Glazer *et al*[26] from the Mayo Clinic reported 60 among the initial 159 patients underwent repeated surgery for recurrence with an overall survival was higher than 60%[23,26]. Although the data suggests a benefit from the second surgery, the selection of patients should be carefully done based on a number of factors including a thorough assessment of the perioperative risk. Ablation is frequently used with surgical resection as the metastases are frequently multifocal and bilateral. It has been re-

Table 1 Comparison of outcomes

Labels	Publication year	Number of patients LR/other	5 yr OS LR/other	Median survival LR/other (mo)
Liver resection *vs* no Liver resection				
Søreide *et al*[16]	1992	36/39		216/48
Chen *et al*[17]	1998	15/23	73%/29%	[1]/27
Grazi *et al*[7]	2000	9/19	92.6%/18.5%[2]	
Ahmed *et al*[18]	2009	50/310	78%/52%	135/66
Surgery *vs* Ablation				
Yao *et al*[19]	2001	16/20	70%/40%	[3]/32
Osborne *et al*[20]	2006	38 Complete and 23 palliative/53	78% and 64%/35%	50 ± 27.6/32 ± 18.9
Surgery *vs* Intra-arterial therapy				
Mayo *et al*[21]	2011	339/414	74%/30%	123/34
Surgery *vs* Transplantation				
Coppa *et al*[22]	2001	9/20	67%/70%	29%/53%
Surgical resection				
Mayo *et al*[23]	2011	Resection +/- Ablation (66 simultaneous ablation)	339	
Saxena *et al*[24]	2011	Resection +/- Ablation	74	
Karabulut *et al*[25]	2011	Resection	27	
Glazer *et al*[26]	2010	Resection +/- Ablation (18 Patients only RFA)	172	77.40%
Scigliano *et al*[27]	2009	Resection	41	79%
Fischer *et al*[28]	2008	Resection	118	44%
Kianmanesh *et al*[29]	2008	Resection	23	94%
Gomez *et al*[30]	2007	Resection	18	86%
Osborne *et al*[20]	2006	Cytoreduction	70[4]	
Musunuru *et al*[31]	2006	Resection +/- Ablation	13	83%[5]
Touzios *et al*[32]	2005	Resection +/- Ablation	18	72%
Sarmiento *et al*[2]	2003	Complete resection in 70 patients	170	61%
Elias *et al*[33]	2003	Resection and 36 with concurrent extrahepatic resection	47	71%
Coppa *et al*[22]	2001	Resection	20	67%
Grazi *et al*[7]	2000	Resection	19	92%[6]
Chen *et al*[17]	1998	Resection	15	73%

[1]Median survival not reached during the study period; [2]4 year survival; [3]Median survival not reached during the study period; [4]Mean survival; [5]3 year survival; [6]4-year survival.

Table 2 Comparison of outcomes of liver transplantation

Ref.	Publication year	Number of patients	Overall survival (5 yr)	Progression/ disease free survival (5 yr)
Le Treut *et al*[10]	(1982-2009)	213	52%	30%
	(2000-2009)	106	59%	39%
Nguyen *et al*[39]	(1988-2011)	184	49%	
	(2002-2011)	110	58%	
Gedaly *et al*[9]	2011	150	49%	32%
Máthé *et al*[38]	2011	89	44%	
Le Treut *et al*[37]	2008	85	47%	
Lehnert *et al*[36]	1998	103	47%	

ported that ablation is performed in at least one-fifth of the patients undergoing surgery for treatment of NET metastases[34]. The role of ablation *vs* resection was studied by Osborne *et al*[20] reporting a 5 year overall survival of 35% and 78% respectively. A similar study by Yao *et al*[19] reported similar overall survival of 70% and 40% after hepatectomy *vs* ablation respectively. Elias *et al*[33] reported an improved overall survival of 84% at 3 years with disease free survival of 50% when combining surgical resection and ablation. Hence, ablation can be used as an adjunct with hepatic resection as initial treatment and to treat local recurrence[34].

Elias *et al*[33] also reported current imaging techniques underestimated the disease burden in almost 50% of patients resulting in increased recurrence. Although extrahepatic disease has been shown to have a worst prognosis in several series, patients with stable limited extra hepatic involvement can be considered for surgery, especially in symptomatic patients based on the underlying tumor biology and grade.

ROLE OF LIVER TRANSPLANTATION

Until recently, clear evidence was lacking regarding the role of Orthotropic Liver Transplantation in the treatment of unresectable liver metastases from NET (Table 2). The inconsistency in the data available can be attributed to the low incidence of the disease leading to a small sample size and a wide variety of treatments and algorithms offered in the initial stages. Considerable controversy exists due to the absence of adequate available data comparing transplantation for unresectable liver metastases to other treatment modalities. Also, transplantation for any malignancy should generate a sustained response with satisfactory 5 year overall survival rates to be considered an

option[35,36]. Mazzaferro *et al*[40] emphasized the importance of patient selection. He initially proposed a selection criteria for patients undergoing transplantation for hepatocellular carcinoma (HCC) which has been used now for several years in transplant centers around the world. More recently and based in his previous results with hepatocellular carcinoma patients, the group from Milan has suggested selection criteria for potential candidates for LT with diagnosis of liver metastases from NET. They proposed that age less than 55, Ki-67 proliferation index of less than 10%, primary that is limited to tumors with portal venous drainage, no other spread to a secondary organ other than the liver, and metastatic disease involving no more than 50% of the hepatic volume. This criteria was based on limited number of patients and has not been significantly validated by other transplant groups[40].

However, using this approach they reported excellent results with a 5-year survival rate close to 90%. These results are significantly better than those obtained in similar patients undergoing conservative management. They also observed that liver transplantation was associated with a recurrence free survival of about 80% at 5 years, which is significantly higher compared to less than 50% associated with the non-transplant strategy[41].

Other groups have obtained comparable overall survival rates (70%-90%). Olausson *et al*[42] transplanted 10 patients with expanded criteria with higher proliferation rate, large tumor burden and increased age but were still able to show a 90% 5-year survival. Le Treut *et al*[10] did a systematic review of the European Liver Transplant Registry and observed the following; three month postoperative mortality was 10%, after 5 years of LT the overall survival was 52% and disease free survival was 30%. The most significant predictors of poor outcome were other major procedure in addition to LT, poor tumor differentiation and liver size and involvement. The highest risk factor for peri-operative mortality was upper abdominal exenteration at the time of Liver transplantation. They also observed that since 2000, the 5-year survival has increased to 59% in relation to the recent advances in patient selection, surgical techniques, increased wait time for stabilization of the disease and possibly the use of pre-transplant treatments. They also suggest that a multistage approach for the removal of primary prior to LT is associated with an improved overall survival.

It has been reported that overall 5-year survival rates of untreated NET is around 35% at 5 years with a median survival of 39 mo. It is interesting to note that although Liver transplantation is usually performed after all other treatment options have been exhausted, the 5 year overall survival rate from the time of diagnosis was 73% in this large European series. Although it is very difficult to compare studies using different treatment options and without standardizing of patients characteristics it seems to be some evidence that selected patients may benefit from LT.

Our group, in a systematic review analysis of the UNOS database found an overall survival after transplantation for liver metastases of NET not significantly different than Hepatocellular carcinoma which is the second most common indication for liver transplantation in the United States after 2010. It is important to remember that HCC patients are usually transplanted within certain criteria (Milan, UCSF, *etc.*,) while there is not a clear selection criteria for patients with liver metastases from NET. However, tumor recurrence rate was 31% which is higher than the rates in the range of 10%-15% reported in patients undergoing transplantation for HCC. We performed an analysis of survival by quartile of wait-time and found the longer the wait the better the overall survival in these patients. The mean wait time was around 60 d in the UNOS series. Patients who underwent transplantation for liver metastases of NET have significantly better survival if they have to wait more than 60 d. We proposed that patients should wait for disease stability before being considered for LT[9].

Nguyen *et al*[39] also conducted a review of the UNOS database and found a significant increased 5-year survival from 49.2% to 57.8% compared to the pre MELD era after the introduction of the MELD/PELD score in 2002. However the overall survival of patients transplanted for non-malignant indications was 73.7%, still significantly higher than patients transplanted for malignant indications. They also found a deleterious effect with elevated serum creatinine in the donor, elevated serum bilirubin in the recipient and a protective effect with normal serum albumin in the recipient at time of transplant.

The role of transplantation as a salvage or curative procedure in this patient population is still under debate. Available data suggested that transplantation can offer a significant survival benefit when patients are selected properly[43]. LT can therefore be used as a treatment option in patients who have stable disease, well differentiated unresectable symptomatic or asymptomatic liver metastases of NET, confined to the liver and in which the removal of the primary tumor was performed before the liver transplant procedure. Prospective multi-centric studies are still warranted to validate a specific selection criteria for liver transplantation.

IMAGE GUIDED ABLATIVE TECHNIQUES FOR THE TREATMENT OF LIVER METASTASES FROM NET

Ablation therapy has been extensively used to treat liver metastases from NET (Table 3). Some experts believe that aggressive ablative techniques with reduction in tumor volume of more than 90% should provide good results similar to surgical resection. RFA of oligonodular liver metastases of less than 5 cm can result in symptomatic response in 70%-80% of patients with hormonal syndromes. The role of RFA in symptom control, reducing octreotide dependence and in the treatment of metastases that are amenable to surgical resection has been well documented in the literature[34,44-48]. Ablation treatment provides complementary treatment in the operative management of patients with bilobar or extensive liver disease. Only a small number of patients are eligible for complete resection at the time of diagnosis either due to extensive tumor

Table 3 Comparison of outcomes of ablative techniques

Ref.	Publication year	Mode of therapy	Number of patients ablated	Median PFS	Median OS
Taner *et al*[34]	2012	RFA and extra-hepatic resection	94	24 mo	
Karabulut *et al*[25]	2011	RFA	69	10.5 mo	73 mo
Akyildiz *et al*[44]	2010	RFA	30	15.6 mo	72 mo
Martin *et al*[45]	2010	MWA and extra-hepatic resection	11	8 mo	18 mo
Mazzaglia *et al*[46]	2007	RFA and extra-hepatic resection	63		47 mo
Gillams *et al*[47]	2005	RFA	25		29 mo
Seifert *et al*[49]	1998	Cryotherapy	13		103 mo
Shapiro *et al*[50]	1998	Cryotherapy	5	[1]	
Bilchik *et al*[51]	1997	Cryotherapy	19	10 mo	49 mo

[1]Mean follow-up 2.5 years, overall survival 20%. MWA: Microwave ablation.

Table 4 Comparison of outcomes of Intra-arterial therapies

Ref.	Publication year	Mode of therapy	Number of patients ablated	Median PFS	Median OS
Paprottka *et al*[58]	2011	RE	42	[1]	
Dong *et al*[59]	2011	HACE	123		40 mo
Saxena *et al*[60]	2010	RE	48		35 mo
Cao *et al*[61]	2010	RE	58		36 mo
Kennedy *et al*[62]	2008	RE	148		70 mo
King *et al*[63]	2008	RE	37		29 mo
Ho *et al*[64]	2007	HAE/HACE	46	18 mo	42 mo
Ruutiainen *et al*[65]	2007	HACE	57	36 mo	
Strosberg *et al*[66]	2006	HAE	84		36 mo
Gupta *et al*[67]	2005	HAE/HACE	123		
			74 HAE	22 mo	34 mo
			49 HACE	16 mo	23 mo
Touzios *et al*[32]	2008	HAE/HACE	100		
			51 HAE		25.5 mo
			49 HACE		25.7 mo
Ruszniewski *et al*[68]	1993	HACE	24	14 mo	

[1]Mean follow up 16. 2 mo, 95.2% alive. HACE: Hepatic artery chemo-embolization; HAE: Hepatic artery.

burden, critical location of the metastases within the liver and the presence of significant extrahepatic disease. The incorporation of RFA as an adjunct to surgical resection has led to an increase in the number of patients eligible for resection of hepatic metastases from neuroendocrine metastases. Taner *et al*[34] reported a 5-year survival of 80% and 10-year survival of 59% with if more than 90% of the intrahepatic disease can be resected or ablated. Use of cryotherapy along with RFA has also been described in the literature[52].

In completely inoperable patients due to co-existing medical conditions, percutaneous ablation can be safely used to treat hepatic metastases. This reduces the hepatic tumor burden and may improve the patient survival (Table 3). Percutaneous ablation can also be used to treat recurrences in previously resected patients. Microwave ablation is being used in some centers as an alternative to RFA[53]. The use of interstitial laser ablation, microwave ablation, complications encountered in such ablations versus radiofrequency coagulation has been extensively studied both in animal models as well as in multi-center hospital settings[54-56]. Microwave ablation (MWA) can reduce the time required to ablate this lesions and could also be used in metastases closer to major hepatic vasculature where RFA might not be that effective due to the heat sink effect. Martin *et al*[45], reported a success rate of 90% with MWA for hepatic metastases from NET. Gravante *et al*[57] did a systematic review and found no viable cells as far as 6 cm away from the center of ablation in 93% of cases treated with MWA. There is no available data comparing the effectiveness of RFA to MWA for the treatment of hepatic metastases form NET.

INTRA-ARTERIAL THERAPIES

NET liver metastases are highly vascular and amenable to ischemia and necrosis if blood supply is occluded. The blood supply of these metastases is mostly dependent on hepatic artery for their oxygenation[58-71].

The vascular blockade can be accomplished through bland embolization of the hepatic artery (HAE), chemoembolization (HACE), or embolization with drug eluting beads (DEB-HACE) (Table 4). Chemoembolization involves the use of chemo-therapeutic agents such as doxorubicin, cisplatin, mirplatin, gemcitabine, streptozocin, mitomycin C, 5-FU mixed with an embolic agent like ethiodized oil or lipoidol with the slurry then infused. Potential contraindications to embolization include oc-

clusion of the portal vein, severe liver dysfunction and presence of a biliary anastomosis. Vascular occlusion can achieve reduction of hormonal symptoms, reduced tumor burden and improved survival in patients not candidates for surgical resection. Sequential embolization of hepatic artery can offer prolonged palliation for responsive patients even if performed later in their course of the disease. Clinical response rates of over 90% have been reported with a median survival ranging 3 years with a progression free survival of 18 mo[72-80] (Table 4). A small randomized trial by Touzios *et al*[32] comparing TAE *vs* TACE in all NETs has shown no difference in time to progression (25.5 mo *vs* 25.7 mo). DEB-HACE aims for a durable and less toxic impact from chemotherapy by loading larger embolic beads with a drug that is released over a period of time with less systemic exposure and toxicity thereby. Mayo *et al*[13] reported a 90% symptom control in 6 mo using drug eluding beads, however their trial was interrupted by a higher than anticipated rate of bilomas. Ho *et al*[64] reported that even in patients with unresectable extra-hepatic disease, liver directed embolization can be done with a post-embolization survival benefit and 80% symptomatic improvement.

Recently, radio-embolization using Yttrium 90 microspheres in patients with inoperable or even disseminated disease have been utilized to treat NET metastases even in patients with previous TAE/TACE[74,76]. They deliver a form of internal radiation therapy to selected vascular territory. Contra-indications to this therapy are a large tumor burden and severe liver dysfunction with vascular involvement such as portal vein thrombosis. Median survival in this approach varies from 36 to 70 mo with tumor grade, radiographic response to treatment and presence of extra-hepatic disease being the most significant prognostic factors reported. Most causes of death were due to disease progression outside the liver[58,60,61]. Evidence is lacking comparing the effectiveness of radio-embolization to other modes of intra-arterial embolization. The advantage of radio embolization is that the hospital stay is usually shorter and procedures are fewer when compared to HAE/HACE. Also repeated radio-embolization to treat recurrence is possible as the microspheres are smaller and leave the vascular supply patent the so called pruning effect. Complications including radiation pneumonitis, gastritis, etc have also been reported in the literature. Hence pre-procedural scans with 99 mTc labeled macro aggregate albumin is necessary to rule out major pulmonary shunting[58,60].

SYSTEMIC THERAPIES

Somatostatin analogues are used for symptom relief in most patients because over 70% of NETs express somatostatin receptors that can be targeted. Octreotide provides symptomatic benefit in about 85% of patients and biochemical response in 70% of patients within weeks of commencement[81]. Carcinoid syndromes due to the release of serotonin intra-procedurally can be overcome by the pre and post procedural administration of Octreotide. Somatostatin analogues also have an anti-proliferative property as they lengthen the time of tumor progression as compared to placebo injections. This benefit is seen both in functionally active as well as inactive tumors[82]. The PROMID study group conducted a double blind randomized phase Ⅲ placebo controlled trial for Octreotide LAR and found the median survival for patients receiving Octreotide LAR to be 14.3 mo *vs* 6 mo on the placebo arm. Octreotide can be safely and effectively used in patients in whom primary has been resected and have a low hepatic tumor burden[6,83-85].

The role of systemic chemotherapy is highly variable in treating NETs because of the disparities in the underlying tumor biology, differences in the endpoints that are measured and the regimens used. Chemotherapeutic agents usually target the actively dividing cells and tumors with a high proliferation index are more susceptible to chemotherapy. Poorly differentiated tumors with a high proliferation index are more susceptible to chemotherapy than well differentiated tumors with a low proliferation index. The overall response to chemotherapy varies from 25%-78% with progression free periods between 4-22 mo. Hence, patient selection and individualized chemotherapy are required to maximize response and prevent hepatic toxicity. Response can be measured radiologically by decreased or stabilized tumor size, improved biochemical markers and improvement in the overall quality of life[86-98].

Interferon alpha has also been used in place of somatostatin analogues for some symptomatic response but no clear survival benefit or reduction in tumor size and progression has been established. It may be an alternative for patients who have failed therapy with somatostatin analogues[94,95].

No difference has been shown to exist between the new agents as monotherapy such as paclitaxel, gemcitabine[97], temozolomide[92], topotecan[86] and the older ones like streptozocin[88,93,96], dacarbazine[87], 5FU[93,96] and doxorubicin[93]. Traditionally a combination of two agents to treat has been shown to have a higher response rate and improved overall survival when compared to a single agent[5]. Response rates for the combination of streptozocin and doxorubicin vary from 30%-70% emphasizing the importance of patient selection and individualization of treatment[91]. Recently a combination of capecitabine and temozolomide has been shown to have a progression free survival of 70% at 18 mo and a 2-year survival of 92%[90]. A triplet combination of streptozocin, doxorubicin and 5 FU in 84 patients with locally advanced or metastatic pancreatic NETs was shown to have an overall response rate of 39%. The standard chemotherapeutic regimen continues to be streptozocin based due to the absence of randomized trials evaluating the efficacy of other regimes. A combination of cisplatin and etoposide has been used to treat anaplastic NETs. The prognosis remains poor in this group with a 2-year survival at 20%-30%[89].

NETs that express somatostatin receptor subtype 2 showing an uptake in octreotidescintigraphy or soma-

tostatin based PET imaging can be treated with beta emitting 90 Y and 177 Lu labeled somatostatin analogues. This presents a therapeutic option in patients with otherwise systemic inoperable and drug resistant disease having a survival ranging from 40-72 mo. The use of these treatments stabilizes the disease with a time to progression of 40 mo and response rates of up to 30%. With this method there is a delivery of the radio-isotope selectively to all the to both intra-hepatic and extra-hepatic somatostatin avid metastases[99-106]. Adverse effects including radiation induced bone marrow toxicity, nephrotoxicity and gastro intestinal disturbances have been reported. The use of alpha emitting isotopes with higher cytotoxicity than the beta emitting isotopes such as Act 225 and addition of radio-sensitizers like gemcitabine and capecitabine may improve clinical outcomes[99,103].

Patients with a positive MIBG uptake scan can be treated with 131 I-MIBG therapy. This is associated with an improved overall survival with marked improvement in clinical symptoms as well as biochemical markers[104].

The evolution of molecular genetics and targeting the molecular mechanisms involved in the pathogenesis of NETs have resulted in newer drugs that target the intra-mural pathways in these tumors. Liver metastases from NETS show a significantly up regulated VEGF C expression which may be involved in their progression and can be used as a potential target[106,107]. Some of the recent drugs that have been implicated in the treatment of NETs include Sunitinib-a multi targeted tyrosine kinase inhibitor having activity against a wide range of molecular pathways including VEGF derived and platelet derived growth factor receptors[108,109], Bevacizumab-a ligand monoclonal antibody directed against VEGF[110,111] and Everolimus-an oral inhibitor of mammalian target of rapamycin[112]. Adverse effects such as diarrhea, vomiting, fatigue, stomatitis and nausea have been reported in all these therapies. The median progression free survival was 11.4 mo for sunitinib and 11.0 mo for everolimus *vs* 4.6 mo and 5.5 mo on placebo respectively. There are also reports of clinical benefit when these are combined with existing chemotherapy treatments. Targeted therapy is appropriate in patients who have a progressive disease where tumor stability would yield a clinical benefit.

CONCLUSION

The care of patients with hepatic metastases of neuroendocrine tumors should involve a multi-disciplinary team of surgeons, interventional radiologists and nuclear medicine physicians to assess the potential of various therapies including liver directed and systemic therapies. The first step in management would be assessing the tumor biology, grade and considering the patient for hepatic metastasectomy which is associated with the best long term outcome and overall survival. Transplantation should be considered in selected patients with abdominal portal vein drained NET in which primary lesion has been resected, less than 50% of liver involvement, no extrahepatic disease and in those with disease stability for a period of time prior to surgery. The role of transplantation for the treatment of hepatic metastases from NET is still to be defined. The combination of hepatectomy plus ablation could be recommended specially in symptomatic patients and if more than 90% of the tumors can be resected or ablated. Radio or chemoembolization should have a role in those patients not candidates for surgery or ablation alone or combined. Somatostatin analogues should be used for symptom control and also for their anti-proliferative effect. Molecular targeted therapies can be used before, during or after conventional chemotherapy. An individualized treatment approach to patient care is needed given the breadth of symptoms and disease, the lack of a validated treatment pathway, as well as the indolent nature of the disease. Future trials are needed to still validate the role of specific therapies in the management of this difficult neoplasm.

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