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REVIEW

Palliation of hepatic tumors

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Interventions

Summary
Palliation is treatment aimed at alleviating the symptomatic effects of a disease rather than at curing the disease. The four most common types of liver tumors that often require palliative treatment include hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), metastatic colorectal carcinoma (mCRC), and metastatic neuroendocrine tumors (mNET). Modalities employed in the palliative treatment of these tumors most often include resection, stenting, chemotherapy, radiation, ablation, and the general treatment of liver failure symptoms. Many of these modalities can be applied to the palliative care of all hepatic tumor types, regardless of the specific tumor histology—as incurable cancers often converge along a final common pathway. We herein provide a review of the therapeutic approaches to palliate hepatic tumors, as well as how such therapies are designed to alleviate the symptoms of patients with end-stage liver tumors.

Contents

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Introduction: history, definitions, and epidemiology

Although liver operations have been performed since antiquity to treat traumatic battle wounds, the elective operation of the liver for tumors could not begin until the later 19th century, when anesthesia and antisepsis permitted such endeavors. The first resection of a liver tumor was reportedly performed by Cousins in 1874, although documentation of the details of this case are lacking [1,2]. In 1897, Langenbuch performed the first successful, elective, hepatic resection for a liver tumor ever recorded [3]. This earliest resection, much like the modern treatments that are the subject of this chapter, was performed for pain and other symptoms of advanced tumors of the liver requiring palliation.

A survey of the palliative cancer care literature reveals that the term *palliation* is employed in so many different ways as to render it problematic [4–7]. In the Oxford English Dictionary, the verb *to palliate* comes from the Latin, *palliare* (to cloak or cover), and means to alleviate without effecting a cure [8]. The American College of Surgeons Palliative Care Symposium, following the lead of the World Health Organization, has defined *palliative care* as "the active total care of patients whose disease is not responsive to curative treatment" [9,10].

Limited data exist regarding the relevant palliative therapeutic approach for patients with unresectable, uncurable advanced hepatic malignancies. While hepatocellular carcinoma (HCC) and perihilar cholangiocarcinoma (CC) are the predominant *primary* liver malignancies that require palliation, metastatic colorectal cancer (mCRC) and metastatic neuroendocrine tumors (mNET) are the most common *secondary* hepatic malignancies that require palliation. As such, these four tumor types are the focus of the current review. However, for the purpose of clarity, the review has been organized primarily by therapeutic approach (surgery; systemic and local [intraarterial] chemotherapy; radiation; ablation; and other palliation) and secondarily by disease process. This is consistent with the reality that, as incurable cancers advance and dedifferentiate, they often converge upon a final common pathway. Here, therefore, palliation is more relevantly considered in light of the therapeutic approach rather than the underlying tumor type. Furthermore, because palliation, by definition, addresses the symptoms of a disease in preference to the histology of a disease, discussion of palliative treatment of liver tumors should focus on the symptoms that the tumors produce, and that the treatments serve "to cloak."

Symptoms of advanced liver tumors are often similar despite different histologies, with few exceptions. Large nonfunctional intrahepatic tumors in an otherwise normal liver, such as HCC, CC, or very extensive mCRC, are likely to cause a similar constellation of symptoms. For example, large intrahepatic tumors—whether they be HCC, intrahepatic CC, or mCRC—can be associated with nonspecific symptoms such as pain, weight loss, fever, night sweats, malaise, anorexia, and fatigue [11]. In contrast, patients with perihilar CC or HCC in the setting of a poorly compensated liver may present with jaundice. Jaundice may even be a presenting symptom in the occasional patient with mCRC with a hilar tumor or bulky hilar adenopathy that causes biliary obstruction. In the setting of HCC with underlying cirrhosis, symptoms may result from the liver failure (e.g., portal hypertension, ascites, etc.) rather than directly attributable to the tumor itself [12–14]. Liver tumors from mNET origin can release hormones, biogenic amines, or other functioning substances. These can result in a tumor-related syndrome, such as the carcinoid syndrome, which is markedly distinct from nonfunctional liver tumors [15].

It should be remembered that patients—not practitioners—are the final judge of what is or is not a relevant symptom. A patient's symptom, and perhaps more importantly, the physiologic and psychological response to that symptom and to the causative disease process is largely determined by the meaning that the patient attributes to the symptom [16]. Most patients value being alive, and hence survival itself. The perception of a terminal disease and the corresponding knowledge of decreased survival may be perceived as another of the many symptoms that patients with incurable cancer must confront. Therefore, despite the focus on palliation, and not cure, prolongation of survival with a meaningful quality of life (QOL) should be an inherent goal relevant to any discussion on palliation of hepatic tumors.

Epidemiology: assessing the extent of the problem

HCC is the third most common cause of cancer death worldwide [17]. In 2005, 667,000 cases occurred worldwide, with 17,500 in the United States, double the number a few decades ago [18,19]. The overwhelming majority of HCC cases develop in cases of alcoholic or viral hepatitis; an epidemic of hepatitis C may well be responsible for the increasing incidence seen in the United States. Untreated HCC has a dismal median survival of 3–8.3 months [20,21]. Treatment of HCC is complex and marked geographic, racial, and possibly insurance-related variations in the management of HCC, are at least as important as tumor-related features, and may determine the extent and type of HCC therapy. In fact, up to 25% of patients receive no therapy at all, including no attempt at palliative therapies [22].

CC is much less common, with about 5000 cases occurring annually in the United States, the vast majority of which arise in the perihilar ducts and distal common bile duct [11,23]. Risk factors for CC include sclerosing cholangitis (8–20% lifetime risk) and choledochal cysts (3–28% lifetime risk). Asian descent and male gender confer an approximately 1.5–2-fold increased risk [23]. Perihilar CC usually spreads by direct extension to the adjacent blood vessels and organs, including the parenchyma of the liver. Because most patients present with advanced loco-regional disease (e.g., involvement of the bilateral secondary bile ducts or main vessel invasion) curative surgical resection is possible in less than 30% of patients with perihilar CC. In fact, even in those patients believed to have localized disease based on cross-sectional imaging, about 15–30% will have liver or peritoneal metastases on operative exploration. Given the high rate of unresectability, as well as the loco-regional issues with ductal obstruction, palliation is of major therapeutic importance for patients with perihilar CC.

Table 1 Palliative treatment modalities for cholangiocarcinoma.

Palliative modality		Morbidity	Adequate relief of symptoms
Biliary decompression (mandatory)	Surgical bypass [35]	17–51%	Yes (56–100%)
	Endoscopic or Percutaneous stenting [33]	4–58%	Yes (73–100%)
Other therapies (optional)	Chemotherapy [35]	Insufficient data	Insufficient data
	Radiotherapy [124,128]	8–40%	No
	Photodynamic therapy [142,154]	35%	Yes (significantly increase QOL scores)

Table adapted from Singhal et al. Surgical Oncology 2005;14:59.

CRC is the third most common malignant disease and the second most common cause of cancer-related death in the United States. In 2007, there have been an estimated 153,760 new cases of CRC [24], and about half of those patients initially diagnosed with local disease will eventually develop liver metastases. Only about 10,000–15,000 patients per year are candidates for local therapy with a curative intent (e.g., resection or ablation).

NET are uncommon, typically nonfunctional, and generally slow growing [25]. The rate of malignancy (typically defined by the presence of metastasis) varies according to both primary tumor site and histology, ranging from 25% to 50% [26–28]. Frequently, patients with nonfunctional tumors present with extensive disease with multiple hepatic metastases, all of which may not be amenable to a complete resection. As such, there has been considerable interest in assessing whether a debulking procedure is warranted in these patients. Specifically, patients with functional NET (e.g., carcinoid, insulinoma, glucagonoma, etc.) may derive a significant palliative benefit from debulking of the disease if it leads to symptom alleviation.

Surgery, including stenting

The improved morbidity and mortality associated with hepatic resection over the past several decades has widened its application for both primary and secondary tumors of the liver. In specialized centers perioperative mortality associated with liver resection now ranges from 1% to 3% [29,30], likely due to advancements in surgical technique and anesthetic management, as well as a better understanding of hepatic anatomy. The role of resection specifically for palliation of liver tumors includes predominately the relief of biliary obstruction for perihilar CC and the resection of symptomatic mNET.

Although unresectable HCC can occasionally be downstaged with multimodal therapy so that resection is feasible, there is little if any role for palliative cytoreductive surgery for HCC. Although previous investigators [31,32] have reported on the use of cytoreductive surgery for HCC to extend survival and alleviate symptoms, surgery was associated with a median survival of only 10 months and only a marginal improvement in symptoms [31]. More effective, and less morbid, palliative therapeutic modalities are currently available. Specifically, nonresection techniques such as transarterial chemoembolization (TACE), systemic chemotherapy, radiation, and ablation therapy are more reasonable palliative options for patients with incurable HCC.

The mainstay of therapy for unresectable perihilar CC is biliary decompression (Table 1). Although most patients with perihilar CC present with painless jaundice alone, cholangitis can develop in the setting of untreated biliary obstruction with progression to sepsis and hepatic failure. When preoperative assessment confirms that the lesion is unresectable, nonoperative stenting is preferable to operative decompression. Stenting is associated with relatively lower morbidity and mortality rates compared with operative biliary bypass. Biliary drainage can be accomplished either endoscopically or percutaneously. The choice of which approach (endoscopic vs percutaneous) is somewhat controversial and may depend on the expertise of the treating center. Endoscopic retrograde cholangiography (ERC) involves passing a wire up the bile duct, through the stricture, in order to place a stent. In general, plastic stents are preferable because they are technically easy to insert. However, plastic stents frequently become occluded due to their relatively small lumen and the biliary sludge that is present in the biliary tree. Because of problems with occlusion, some investigators have advocated for self-expanding metal (SEM) stents for patients with perihilar CC and an expected life-expectancy of greater than 6 months. When employed, uncovered SEM stents (vs covered stents) should be utilized so that the open mesh design can allow for drainage of secondary biliary branches via the stent. Other investigators, however, advocate for percutaneous biliary drainage. Percutaneous biliary drainage can be done as external or internal drainage, with internalization usually accomplished in later sessions (Figure 1). Advocates point to the simplicity of the procedure, as well as the ability to have ongoing access to the biliary tree. Regardless of the approach, partial or complete relief of jaundice can be achieved in 73–100% of patients using nonsurgical biliary drainage techniques [33].

In those patients who are explored for potentially curable disease, but are found to have unresectable CC, operative

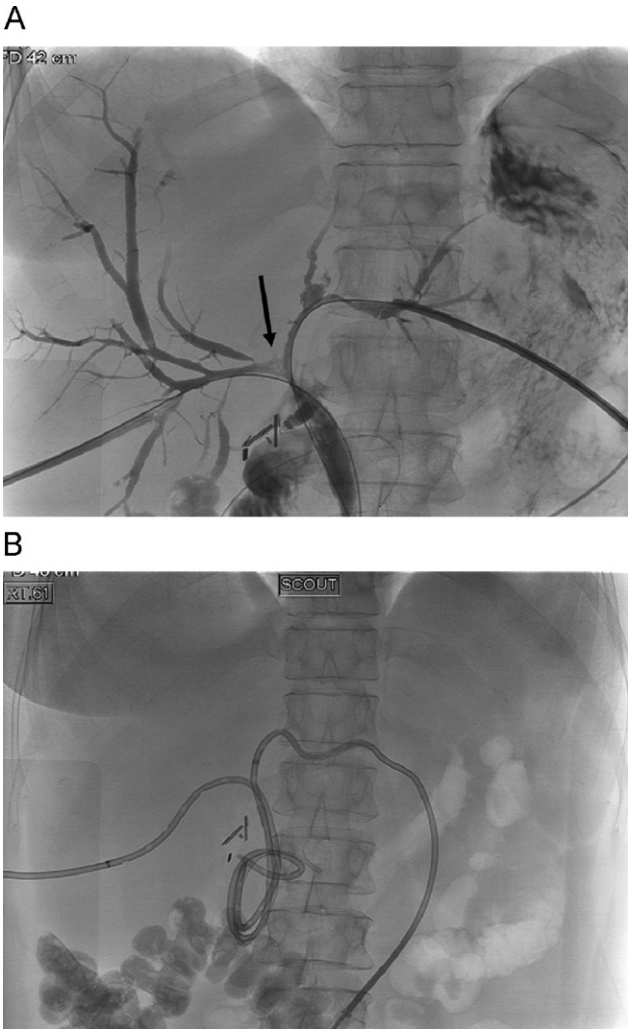

Figure 1 The mainstay of therapy for unresectable perihilar CC is biliary decompression. In general, nonoperative stenting is preferable to operative decompression. Patients with a hilar stricture (A, arrow) can be managed with bilateral percutaneous biliary drainage (B). Percutaneous biliary drainage can be done as external or internal drainage, with internalization usually accomplished in later sessions.

biliary decompression is a reasonable option. Specifically, surgical decompression is indicated when extensive dissection of the hilar plate and transection of a bile duct is required to determine unresectability [34]. Segment III cholangiojejunostomy is the most commonly performed surgical procedure for palliation of perihilar CC [35]. Specifically, a Roux-en-Y enteric anastomosis to the segment III duct, which is located posterior and superior to the segment III branch of the portal vein, is performed. In general, 30% of the liver needs to be drained for cholestasis and pruritis to be relieved. Segment III cholangiojejunostomy is associated with a morbidity ranging from 17% to 50% and mortality from 6% to 20%. The procedure is successful in alleviating symptoms in about 70% of patients [36–38]. Resection of perihilar CC with positive surgical margins has also been referred to as palliative surgery [35]. Figueras and colleagues reported ''much better'' QOL and improved survival in patients who underwent resection with microscopically positive margins (9 of 28 resections). However, mortality and morbidity were high (11% and 65%, respectively) and details of QOL assessment were not provided [39]. In general, resection of perihilar CC should only be done with curative intent (e.g., goal of achieving microscopic negative surgical margins). Intraoperatively if a margin negative resection is not feasible, palliation is best achieved with either a surgical bypass or percutaneous methods as outlined above.

Similarly, surgical resection of mCRC should be curative in intent (negative surgical margins) and surgical debulking of mCRC should rarely be performed. Patients with isolated liver metastases can achieve excellent long-term outcomes with operative treatment. Specifically, 5-year survival from hepatic resection from CRC metastases range from 35% to 58% [40–47] with 10-year survival rates of 22–28% [40,45–47]. In the past, resection was reserved for patients with only limited intrahepatic disease and no extrahepatic disease. Recently, however, there has been a shifting paradigm regarding the criteria of resectability dictating which patients with mCRC may be candidates for surgery [48–52]. Although surgical placement of hepatic arterial infusion catheters has been advocated by some to treat extensive liver-only disease, largely for prolonging life and without curative intent, this procedure has not been shown to specifically afford symptom relief and therefore has not been widely accepted.

In contrast, surgical resection, both with curative intent and for planned debulking, has been broadly utilized in selected patients with mNET. Patients with mNET may present with pain from bulky disease or severe hormonal symptoms. The liver is the most common site of metastases for both pancreatic endocrine and carcinoid neuroendocrine tumors. Although, as discussed later, medical management of mNET with a somatostatin analog successfully controls symptoms early in the course of the disease, tumors tend to become resistant to antisecretory therapy [25]. When resection is employed in selected symptomatically refractory patients, improvement in symptoms can be achieved in greater than 90% of patients—however, over time many patients will have recurrence of their symptoms (Figure 2(a)) [53,54]. Regarding survival and long-term outcome, cytotoxic chemotherapy is associated with only a 10–20% response rate for mNET. Surgical resection of hepatic metastases can, however, improve 5-year survival from 20% to 40% in untreated patients [54,55] to 45–90% in patients with complete or near-complete resection (Figure 2(b)) [54–56]. Frequently, the extent of metastatic disease in patients with mNET prohibits a complete extirpation of all measurable disease. Unlike with most other malignancies, there does appear to be some survival benefit to surgical resection if at least 80–90% of the disease can be removed [54,57–59]. Therefore, surgical debulking does have a role in well-selected patients with mNET. The benefit of debulking is obviously greater in patients with symptomatic NET disease. Yet studies have shown that debulking of mNET can also lead to improvement in survival that are similar for patients with functional vs nonfunctional tumors [54,57–59]. Therefore, while mNET can follow an indolent course punctuated by recurrences, surgical resection can lead to prolongation of survival and alleviation of symptoms in a subset of patients.

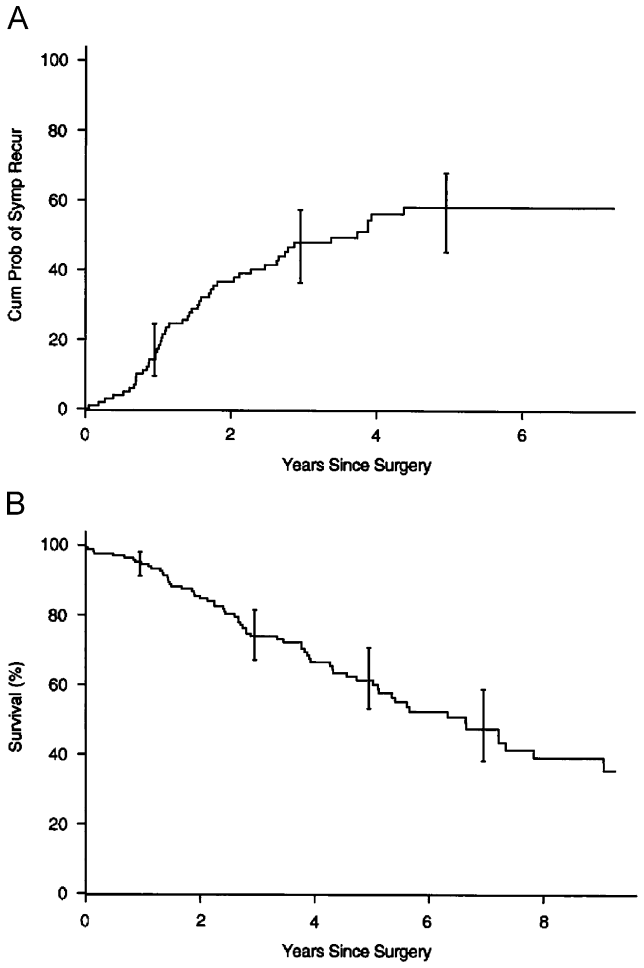

Figure 2 (A) In the series from the Mayo clinic, the overwhelming majority of patients (96%) achieved a partial or complete response for their hormonal symptoms following surgery. However the symptom recurrence rate was 59% at 5 years, with a median time to recurrence of 45.5 months. (B) Overall survival for patients after partial hepatectomy for mNET was 61% and 35% at 5 and 10 years, respectively. (Figures used with permission, Sarmiento JM, et al. Journal of the American College of Surgeons 2003;197:29.)

The complication rate associated with resection for mNET is similar to that associated with resection of other hepatic metastases [53,56]. For patients with symptomatic endocrinopathies, perioperative management is required to avoid potential increased morbidity. For example, hypoglycemia from insulinomas, hypokalemia from VIPomas, and peptic ulcer disease from gastrinomas can all complicate perioperative management [60]. Administration of octreotide in the perioperative period should be used to prevent carcinoid crisis [61]. Patients with right-sided heart failure from carcinoid syndrome constitute a significant surgical risk. Back bleeding of hepatic veins affected by increased right heart pressures can cause uncontrollable hemorrhage if hepatic resection is attempted in this population of patients [57]. In addition, correction of valvular disease secondary to carcinoid syndrome may be necessary prior to surgery [61].

Transplantation has also been studied for the treatment of mNET not amenable to local resection [62–66]. The 5-year survival for metastatic carcinoid tumors treated with transplantation ranges from 36% to 80% with multimodal therapy. However transplant for pancreatic endocrine tumors has a significantly lower 5-year survival rate [62]. As with resection, the symptomatic relief with transplantation exceeds 90%. Given the shortage of cadaveric organs and the morbidity of the procedure for both recipients and potential living donors, transplantation should be pursued only with intent to cure and not as purely palliative therapy.

Systemic chemotherapies

While great strides have been made in the area of systemic chemotherapy for some advanced cancers (e.g. mCRC), other liver malignancies (e.g. HCC, perihilar CC) remain largely recalcitrant to systemic therapies. For the treatment of mCRC, whereas a decade ago 5-fluorouracil (5-FU) was the only available treatment, the introduction of irinotecan and oxaliplatin has increased response rates and extended survival to 14–20 months for patients with unresectable disease. In addition, targeted biologic agents (e.g., bevacizumab, cetuximab, and panitumumab) have been associated with median survival exceeding 20 months when combined with newer cytotoxic chemotherapy drugs [67]. In contrast, both HCC and CC remain relatively chemoresistant. Similarly, while mNET represents a diverse group of cancers, response to systemic chemotherapy has traditionally been poor. Patients with functional tumors seem to benefit the most from symptomatic relief with effective palliative ''chemotherapy'' using somatostatin analogs.

HCC has been particularly unresponsive to chemotherapy, as evidenced by response rates of 10–15% following treatment with doxorubicin-based regimens [68]. Furthermore, because most of the available medications are at least partially metabolized in the liver, patients with hepatic dysfunction have a narrow therapeutic window. As such, chemotherapy has traditionally had a minimal role in treating patients with unresectable liver disease. More recently, however, there have been several emerging agents that have shown some activity in HCC. Such drugs target specific molecular pathways found to be relevant to HCC, including growth-factor-activated mitogenic pathways that include the Wnt/β-catenin, the MAPK, and the PI3 kinase/AKT/mTOR pathways [68]. Similarly, Sorafenib has recently been demonstrated to provide some survival benefit to patients with metastatic HCC. However, the actual tumor response rate was poor. Given that most symptoms of unresectable HCC relate to loco-regional tumor progression (e.g., tumor enlargement, invasion of portal structures, etc.) loco-regional therapies are more commonly employed in HCC palliation [12].

Like HCC, CC also responds poorly to palliative chemotherapy. A recent review of chemotherapy trials revealed rates of disease stabilization or partial response ranging from 20% to 73% [69]. Chemotherapy, however, was associated with no survival benefit compared with biliary decompression followed by observation [69]. Unfortunately, most studies on CC include only a small number of patients

with significant heterogeneity with respect to both stage of disease and choice of therapeutic modality used [35,69].

Unlike primary liver cancer, significant advances have been made over the past decade with systemic chemotherapy for patients with mCRC. Since the 1960s, standard chemotherapy has consisted largely of 5-FU ± leucovorin with response rates of only about 20%, which lead to minimal improvements in survival or symptom relief for patients with incurable mCRC [70,71]. The addition of irinotecan- and oxaliplatin-based regimens (FOLFIRI and FOLFOX, respectively) have improved response rates in the range of 40–50% and have led to a median survival of 14–17 months for patients with unresectable mCRC [72,73]. The addition of biologic agents, such as bevacizumab and cetuximab, have now increased survival to greater than 20 months [74,75]. This increase in survival has had noteworthy implications for patient QOL. Chemotherapy can be associated with an increased risk of severe diarrhea, neurotoxicity, with some studies reporting that nearly three-quarters of patients suffered severe toxicities [76]. While these regimens clearly have a valuable role in treating patients with incurable mCRC, the increase risk of chemotherapy-related toxicities needs to be balanced against the desire to minimize and control adverse symptoms. This balance can be achieved, as evidenced by a recent QOL assessment of irinotecan therapy that showed that adding irinotecan to the standard double therapy did not compromise QOL [73]. This QOL report was criticized, however, for not more specifically evaluating diarrhea [77]. Combinations of oxaliplatin and irinotecan can also be associated with an increase in neurotoxicity and neutropenia [78]. In aggregate, modern era chemotherapy for incurable mCRC can be associated with response rates exceeding 40% with prolongation of survival. The toxicity of these agents, however, needs to be appropriately managed and balanced against the relative benefit provide by the drug being administered.

Compared with epithelial cancers, mNET are typically less responsive to chemotherapy [25]. Notable exceptions to this observation include small-cell carcinomas of the gastrointestinal tract which respond to chemotherapy in up to 100% of cases [27]. Infrequently, metastatic carcinoid tumors have been reported to regress with octreotide therapy [79]. Although there have been no large prospective randomized controlled trials (RCTs) assessing systemic cytotoxic chemotherapy in the treatment of liver mNET, smaller trials have shown measurable regression of poorly (but not well) differentiated NET after systemic treatment. Specifically, etoposide and cisplatin have been associated with a response in some patients with mNET, but drug toxicity is a substantial limitation that makes use of these drugs problematic in a palliative setting [25,80,81]. Combination therapy with lomustine and 5-FU were found in a small retrospective study to be associated with a partial tumor response of 21%, with few serious adverse effects (6%) and no therapy-related death [82]. In general, most chemotherapy approaches (whether single- or multidrug) are associated with response rates of only 15–20%.

While cytotoxic chemotherapy is largely associated with poor survival results, drug therapy for symptom control in patients with functional mNET can be effective. Unfortunately, although functioning tumors are more amenable to palliative systemic medical treatment, they account for only a small percentage of NET. For example, carcinoid syndrome is present in less than 10% of all gastrointestinal carninoids [15], although those patients with liver metastases or liver primaries are widely recognized to have a higher rate of carcinoid syndrome. Nearly 90% of patients suffering from symptoms of malignant carcinoid syndrome may have improvement of symptoms with the administration of the somatostatin analogue octreotide [83]. Other drugs have not been as widely employed. For example, lomustine and 5-FU have been associated with an improvement in symptoms in 44% of patients who presented with symptoms (and in 60% of those who presented with carcinoid tumors) [82]. Interferon has been associated with both symptom relief [84] and tumor regression [85], but has not gained widespread acceptance, likely due to unfavorable adverse reactions [86].

Intraarterial therapies

Intraarterial chemotherapeutic therapies are those in which the drugs are administered directly into the hepatic arterial circulation. When the infusion, which is often selectively directed to the affected area of the liver, is continuous it is known as hepatic artery infusion (HAI) chemotherapy. Alternatively, the selective infusion may be administered as a bolus with concomitant embolization (TACE). Vascular isolation and nonselective perfusion of the entire liver is another loco-regional option, known as isolated hepatic infusion (IHP). While intraarterial radioembolization is another form of intraarterial therapy, this topic is discussed in the section on radiation therapy (RT).

Intraarterial therapy is the most common method used to palliate HCC (Figure 3). HCC tumors receive most of their blood supply from the hepatic artery, while the normal liver parenchyma receives the larger proportion of its blood supply from the portal vein [87,88]. In addition, HCC lesions are often highly vascularized. This observation is one of the theoretical underpinnings of TACE therapy to treat HCC. In addition to delivering higher concentrations of cytotoxic agents directly to the tumor, TACE also interrupts the tumor blood supply. Disruption of the afferent blood supply not only induces ischemic necrosis of the tumor, but also is associated with longer retention times of the chemotherapeutic agents within the tumor. As such, drug concentrations during chemoembolization can reach 10–25 times those obtained with intraarterial infusion alone. In addition, when cytotoxic chemotherapeutic agents are mixed with lipiodol—an iodized poppy-seed oil that destroys the capillary bed—tumor necrosis may be even more pronounced. The role of the chemotherapy component to intraarterial embolization therapy remains controversial. Some centers believe that bland embolization (TAE) performs as well as embolization with chemotherapy.

Good clinical judgment must be exercised in selecting HCC patients for TACE or TAE therapy. In general, patients should have liver-only or liver-predominant disease and adequate hepatic reserve. Although in the past portal vein thrombosis was considered a contraindication to TACE, more recent reports have noted that TACE can be performed safely in patients with portal vein thrombosis using more selective catherization techniques [89,90].

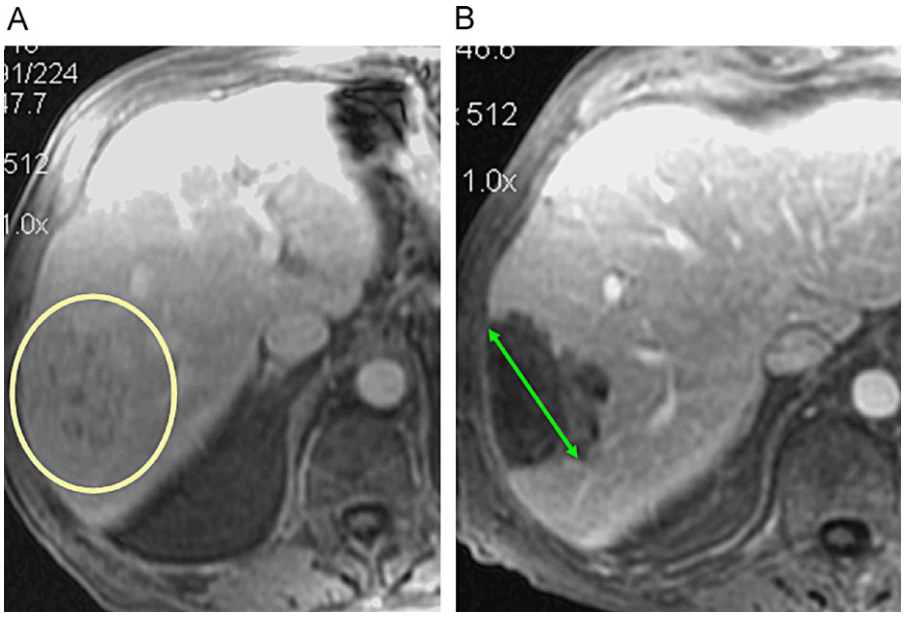

Figure 3 (A) Pretreatment MRI T1 post-gadolinium imaging showing tumor with heterogeneous enhancement before TACE (circle). (B) Following TACE there was complete lack of enhancement, consistent with necrosis and response (double-headed arrows indicate tumor diameter). (Images courtesy of Jean-Francois Geschwind, Department of Radiology, Johns Hopkins Hospital, Baltimore, MD.)

A meta-analysis of retrospective matched and non-matched studies, as well as prospective randomized studies, recently reported a survival benefit in those patients receiving TACE [91]. Interpretation of these data are difficult because many of the studies included in the meta-analysis were characterized by heterogeneous populations of patients whose stage of disease and treatment goals were diverse. In addition, the techniques for administering TACE were varied. Among those studies showing a significant survival benefit are two RCTs comparing TACE with best supportive care in patients with unresectable, incurable HCC. One study used doxorubicin as the chemotherapy agent and found an increase in median survival from 18 to 29 months [92]. The other randomized trial utilized cisplatin and noted a similar incremental improvement in overall survival from 6 to 12 months [93]. Neither study included an adequate QOL assessment. While TACE is generally well tolerated [91,94], it has been reported to be rarely associated with treatment-related deaths (2.5%) and septic shock [92]. TACE or TAE, however, should be considered a reasonable palliative option for patients with incurable HCC who have a large liver burden of disease.

The role of intraarterial chemotherapy for CC depends on the anatomic site of disease. While there is minimal role of intraarterial chemotherapy for perihilar CC, TACE may be a reasonable palliative option for patients with incurable intrahepatic/peripheral CC. Early experience in the 1980s was promising, as partial responses of 55–65% were reported in some very small studies [95,96]. The combination of HAI and systemic chemotherapy in a phase II study of 30 patients with advanced intrahepatic CC provided a response rate of 40%, a median survival of 13 months, and an improved performance status in 30% of patients [97]. More recently, TACE has been proposed as an effective means to palliate intrahepatic CC [98]. In one study, 17 patients who were treated with TACE had a median survival of 23 months. The procedure was well tolerated by 82% of the patients, who experienced no side effects or mild side effects that quickly resolved with conservative therapy alone. The authors concluded that TACE may be an appropriate palliative therapy for patients with unresectable intrahepatic CC.

Intraarterial therapies for hepatic mCRC may be considered for palliation in selected circumstances. HAI was initially studied without added systemic chemotherapy, and found to be associated with significantly increased response rates (41% vs 14%), but no increase in survival when compared to systemic chemotherapy alone. More recently, HAI plus systemic chemotherapy has been studied, and found to have response rates as high as 90%, with rare toxicities [99]. Nevertheless, such treatments are typically administered with curative, and not palliative, intent [100]. In general, systemic therapy is strongly favored over loco-regional therapy for mCRC. However, some investigators have suggested that HAI pump therapy may have a role in palliating a very select group of patients with extensive liver-only disease who fail to respond to systemic chemotherapy. TACE has also been evaluated in mCRC. Unlike HCC, hepatic colorectal metastases are less vascular and therefore less responsive. Yet, in several small series in selected patients with hepatic dominant disease who have progressed on systemic chemotherapy, TACE or TAE have been shown to have some benefit [101]. Salman et al [102]. reported a randomized phase II comparing intraarterial embolization with or without regional chemotherapy in 50 patients with advanced liver dominant mCRC. Overall partial response was seen in 18% of patients with a median survival in liver-only patients of 15 months [102].

Intraarterial therapy for unresectable hepatic NET metastasis has also been investigated (Table 2). In a recent review of 23 studies evaluating TAE or TACE in a total of 312

Table 2 Recent series of intraarterial embolization therapies for mNET.

First author, year[ref]	*N*	Histology	Morbidity	Mortality (%)	Clinical response	
					Palliation of symptoms	5-Year survival
Ho, 2007 [109]	46	31 Carcinoid 15 Islet cell	85% Mild 15% Severe	4	80% (20/25)	29%
Fromigue, 2006 [162]	12	MTC	92% mild 8% Severe	0	40% (2/5)	NR
Strosberg, 2006 [163]	84[a]	59 Carcinoid 20 Islet cell 5 Poorly diff.	85% Mild 15% Severe	0	80% (44/55)	36%
Gupta, 2005 [164]	123[b]	69 Carcinoid 54 Islet cell	12–20%	0	NR	28.6%
Roche, 2003 [165]	14	NR (10/14 had carcinoid syndrome)	86% Mild 14% Severe	0	90% (9/10)	83%
Loewe, 2003 [166]	23[a]	NR	NR	9	NR	65%
Chamberlain, 2000 [55]	85[a]	41 Carcinoid 44 Islet cell	NR	6	92% (24/26)	50%

Abbreviations: NR, Not reported.
[a]69 carcinoid (42 receiving embolization only, 27 chemoembolization); 54 islet cell tumors (32 embolization, 22 chemoembolization).
[b]All patients received bland embolization only.

patients with mNET, the authors reported widely varying response rates, ranging from 0% to 100% (average 48%) [103]. Survival following intraarterial therapy was markedly improved in metastatic carcinoid, but not as much in patients with metastatic pancreatic endocrine tumors [103]. From a palliative care standpoint, perhaps equally as important as the ability of TACE to affect a tumor response or to prolong survival, is its ability to reduce hormone-related symptoms by cytoreduction. Although large RCT are lacking, several retrospective studies have found TACE therapy for symptomatic mNET to be associated with an improvement in symptoms in most patients (Table 2) [104–109].

Radiation

RT is administered in wide array of forms, including external-beam radiotherapy (EBRT), intraluminal brachytherapy (ILBT), intraoperative radiation therapy (IORT), and intraarterial radiation therapy (IART). Although RT has historically played a minor role in the palliation of liver tumors because of radiation-induced liver disease, several recent technical advances have increased the role of RT in palliative liver tumors. Common indications for palliative RT of liver tumors include the reduction of pain and other symptoms caused by the enlarging tumor mass.

Although HCC is generally radiosensitive, as evidenced by the relief of pain in most patients with painful bone and adrenal metastases treated by radiation [110–113], the nonneoplastic liver parenchyma surrounding primary lesions is also sensitive, resulting in risk of liver injury [114,115]. However, recent advances in radiation oncology, such as tumor tracking and respiratory-gating techniques to account for respiratory motion [116], three-dimensional conformal radiation techniques [110,117,118] and daily ultrasound-based, image-guided targeting [119] have allowed far higher doses of radiation to be administered to HCC and other liver tumors with a low risk of complications [120]. IART with yttrium-90 microspheres has also been studied in patients with HCC, and endpoints such as response rate, interval to progression, survival, and toxicity profile have generally been promising [121–123]. Unfortunately, palliative endpoints such as improvements in symptoms and QOL assessments have not been adequately studied. In general, locoregional therapies such as TACE tend to be favored over RT for HCC.

EBRT is the most common type of RT used to treat CC. EBRT has been used to treat both resectable and unresectable CC, either alone or in conjunction with other radiation modalities, such as ILBT and IORT [34]. Because of the

relatively small number, and varied quality of studies of RT for CC, clear conclusions are difficult to make. Furthermore, few studies include QOL assessments. One of the only prospective studies of EBRT as an adjunct to resection of CC did include a QOL assessment but found that EBRT had no significant effect on the length or quality of survival (or on late toxicity) [124]. In a more recent study, using improved, three-dimensional conformal high-dose RT, but now in the setting of unresectable CC treated in addition with intraarterial chemotherapy ($N = 44$), 12 patients responded, 20 had stable disease, 1 progressed, and 13 were not evaluated; median survival (13.3 months) was improved compared with historical controls (9 months). In this study, QOL was not assessed and 30% of patients had severe or life-threatening complications [125]. Several small studies employing both EBRT and ILBT to treat advanced CC have found median survival to be 9–15 months, but therapy was associated with complications such as cholangitis and gastrointestinal hemorrhage [126–129]. These studies are difficult to interpret, however, because of their small size and the diverse patient populations (e.g., inclusion of patients with extrahepatic as well as hepatic or perihilar CC).

As with other hepatic malignancies, RT has not traditionally been considered a good treatment option for patients with hepatic mCRC because of poor tolerance of the normal liver to whole-liver RT. However, with the introduction of more conformal RT approaches, there has been some renewed interest in using RT to palliate liver-dominant mCRC disease. In particular, in those patients who have failed multiple chemotherapy regimens and otherwise are not candidates for resection or ablation, RT of large dominant mCRC lesions may be a reasonable approach to palliate tumor pain. Several groups have reported acceptable toxicities with the use of RT [130–132]. Studies using escalating doses of focal liver radiation for the treatment of mCRC have not only reported an increase in survival, but also an improvement in QOL. Dawson et al. [133] showed a significantly increased survival of patients receiving a high-dose regimen (16.4 months), compared with a low-dose regimen (11.6 months). Mohiuddin et al. [134] found that higher doses of radiation were associated with both improved symptom control and with longer survival. Similarly, Krishnan et al. [130] reported that conformal radiotherapy of mCRC resulted in an actuarial in-field local control rate of 62% at 6 months with acceptable toxicity. Such studies support the concept that, despite poor initial results with whole-liver radiation, tumor and symptom control for patients with large mCRC liver metastases that fail other therapeutic modalities may be amenable to palliation with RT. Predictive models such as the normal tissue complication probability (NTCP) model also allows radiation oncologists to individualize and focus maximal tolerated doses of radiation so that toxicity is minimized [117,135,136].

In addition to EBRT, IART treatment with ytrrium-90 either alone or in combination with systemic chemotherapy (oxaliplatin, fluorouracil, and leucovorin) has been recently evaluated for mCRC. Sharma et al. [137] reported a phase I study using ytrrium-90 therapy with FOLFOX for inoperable mCRC to the liver. Partial responses were observed in 18 of 20 patients with chemotherapy-naïve mCRC and the median progression-free survival was 9.3 months. The dose-limiting toxicity was grade 3 or 4 neutropenia, with one episode of transient grade 3 hepatotoxicity.

Ytrrium-90 IART has also been used to successfully palliate large-volume hepatic metastases from mNET. In a recent prospective study [138], ytrrium-90 high-energy radiation was administered via the hepatic artery to patients with histologically proven metastases from NET. RT with ytrrium-90, chelated to the somatostatin analogue lanreotide, was associated with a partial response or disease stabilization in 79%, a reduction in biologic marker levels in 60%, and symptomatic improvement in 61% of the 23 patients [138].

Ablation

Ablative therapies applied to liver tumors may be grouped into two broad categories, those using chemicals and those using extreme temperatures. The first group includes percutaneous ethanol injection (PEI) and percutaneous acetic acid injection. The second group consists of therapies employing both very low temperatures (cryoablation) and very high temperatures, in which heat is produced either by electromagnetic waves, such as radio waves (radiofrequency ablation [RFA]), microwaves (microwave ablation), light waves (laser ablation), or by sound waves (high-intensity focused ultrasound [HIFU]) [139,140]. Photodynamic therapy (PDT) is another form of ablation in which a photosensitizing drug is allowed to accumulate in the tissue of interest, which is then exposed to nonthermal laser light. A photochemical process then ensues in which oxygen radicals are produced and cause local cell death [141,142]. Whereas PDT is largely utilized only for perihilar CC, the other ablative techniques can by employed to treat all types of hepatic malignancies. While the choice of technique depends largely on physician preference and local expertise, RFA is currently the most common interstitial ablative technique [139].

RFA can be an effective means of destroying focal areas of tissue within the liver. In most cases, the goal of RFA is complete tumor destruction with curative intent. However, in selected cases, much as with resection, RFA can be employed with palliative intent, either to achieve symptom relief or survival prolongation. The use of RFA to ablate otherwise incurable lesions has become increasing common. In general, lesion must be in the 3–5 cm size range [91]. Larger ablation zones can be achieved but adjunctive maneuvers such as temporary occlusion of the hepatic arterial [143,144] or portal venous [145] inflow or overlapping of the zones of ablation using multiple deployments of the RF probe. RFA has been compared with PEI in a prospective randomized studies of patients with HCC. Livraghi et al. [146] found RFA to be more effective (complete necrosis in 90% vs 80%) in fewer treatments, but to be associated with a slightly higher rate of minor complications. Shiina et al. [147] similarly found RFA to be more effective than PEI (4-year survival 64% vs 54%), with a similar rate of adverse effects. In a study comparing RFA and cryoablation in a mixed group of patients with liver tumors (28% HCC and 63% mCRC) [148], RFA was found to be associated with a lower complication rate (41% vs 3%) and a

lower recurrence rate (2% vs 14%). As such, RFA—rather than chemical or cyroablation—is the currently preferred method of ablation for HCC lesions. In a large, recent, Chinese series ($N = 288$) of patients treated by microwave ablation for HCC (70% with lesions >2.5 cm and 27% with lesions >4 cm), the 5-year-survival was a promising 51% [149], suggesting microwave ablation may hold promise.

Although RFA and related thermoablative procedures have been widely utilized for HCC, RFA for CC has only been reported in a limited number of small case series and reports [150–152]. Thermo- or cryoablation is contraindicated around the hilum, since, unlike large blood vessels that act as a heat sink to protect the endothelium, bile ducts do not tolerate heat. As such, ablative techniques can injure the bile duct, leading to biliary fistulae or abscesses [140,153]. Traditional ablative approaches therefore have no role in palliating perihilar CC and should only be considered for small peripheral CC lesions. Given that only 8% of all CCs are intrahepatic (peripheral) while about 50% are perihilar [11], less than 5% of CC tumors are amenable to RFA. In contrast, PDT is a nonthermal ablation therapy that can be used safely to treat CC tumors in the hilum. In two recent RCTs [154,155], patients with unresectable perihilar CC were treated with either stenting alone, or with PDT plus stenting. PDT was associated with a significant increase in both the quality and the quantity of life. Formal QOL testing revealed a decrease in disease-specific symptoms and an increase in overall QOL. Median survival increased 3–5-fold in the PDT cohorts [154,155]. While these results require independent validation in larger series, PDT appears to potentially offer a reasonable palliative approach for patients with unresectable perihilar CC.

The use of ablative approaches has also been reported for patients with incurable mCRC and mNET. In patients with mCRC, however, ablative approaches are largely used either alone or in conjunction with resection for curative intent. In general, patients with incurable mCRC hepatic metastases usually have a tumor burden (e.g., either number of lesions or size of lesions) that does not lend itself to palliative ablative approaches. In contrast, from a palliative perspective, the role of ablation of mNET is a valuable tool, especially for those patients with functional mNET. Patients with mNET can have a long survival; as such, patients with functional tumors may require symptom control over a prolonged period of time. RFA can often be employed to achieve cytoreduction in an effort to alleviate symptoms. In one of the largest series of RFA for mNET, RFA resulted in complete relief of symptoms in 63% of patients and partial relief of symptoms in 95% of patients [156]. Similarly, in another study by Gillams et al. [157] using image-guided percutaneous thermal ablation 69% of mNET patients had symptom relief.

Treatments to palliate symptoms of liver failure

Incurable liver tumors are frequently associated with liver insufficiency/failure during the terminal phases of their clinical course. Ascites is the most common symptom of end-stage liver disease (ESLD) [158]. Although most patients have improvement of symptoms initially with sodium restriction and diuretic therapy, refractory ascites may require more invasive treatments, such as periodic large-volume paracentesis, indwelling drains, or indwelling peritoneovenous shunts [159]. Pruritis from jaundice is also a frequent symptom of ESLD. Pruritis may be treated in most patients with medication, including antihistamines, antidepressants, hepatic enzyme inducers (e.g., rifampin and phenobarbital), and nonabsorbable resins (e.g., cholestyramine). In rare cases of severe refractory pruritis, removal of circulating pruitogens by plasmapheresis or dialysis may be an option [160]. Because depression in cirrhotic patients is associated with worse QOL, poor coping skills, and lower functional status, attention to the patient's psychological state is an essential component of palliative care of these patients [161]. Typically, depression can be managed with antidepressants and psychotherapy, similar to that in noncirrhotic patients [14]. Hepatic encephalopathy, which can be one of the most disabling symptoms of ESLD, is usually managed with cathartics (e.g., lactulose). Intolerant or refractory patients may benefit from nonabsorbable antibiotics (e.g., neomycin or metronidazole) [14].

Conclusion

HCC, CC, mCRC, and mNET are the four most common advanced malignancies of the liver. When curative therapy is not possible, palliative approaches may achieve significant improvement in the quality, and at times the QOL. Such palliative therapies include resection, biliary stenting, chemotherapy (systemic and local), radiation, ablation, and the general treatment of symptoms attributable to ESLD. Some tumor types respond better to a given palliative intervention compared with other types. Palliative therapy of liver malignancies needs to be highly individualized—keeping in mind not only the efficacy of a given therapy, but also the underlying goals of the patient.

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