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Treatment Strategies for Noncolorectal Nonendocrine Liver Metastasis (NCNELM)

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Abstract

The liver is one of the commonest sites for metastatic spread of tumors, particulary for those originating from the gastrointestinal tract. Treatment and outcome of liver metastases from colorectal and neuroendocrine tumors has been extensivily studied during the last decade, this is not the case for metastatic disease originating from others sites. The author discuss the emerging treatments strategies for NCNELM, including liver resection, and the potential benefits of such therapeutic modalities.

Keywords: Noncolorectal; Nonendocrine; Resection; Therapy

Introduction

The liver is one of the commonest sites for metastatic spread of tumors, particulary for those originating from the gastrointestinal tract. Autopsy studies have shown that in patients who die of malignant disease, hepatic metastases are found in up to 36% of cases, with the most frequent primaries being colon and rectum, bronchus, pancreas, breast, stomach and primary of unknow origin [1]. Almost half of patients who die of cancer of the stomach, pancreas or breast are found to have liver metastases [2]. Aproximatelly 40% of patients with endometrial tumours develop liver metastases [2]. Less commonly hepatic metastases can occur from soft tissue sarcomas, particularly visceral leiomyossarcomas [3]. The prognosis of these untreated hepatic metastases is generally poor with the majority of patients sucumbing to their disease within 12 months from the time of diagnosis [4].

While the evolution, treatment and outcome of liver metastases from colorectal and neuroendocrine tumors has been extensivily studied during the last decade, this is not the case for metastatic disease originating from others sites (organs). Now, as more patients are detected at an earlier stage of their disease due to improvements in imaging techniques and screening, eventually agressive oncological and surgical therapies may provide long term survival for selected patients, therefore, liver resections for NCNELM are gaining popularity [5].

Investigation Modalities

The aim of a thorough preoperative work-up and routine follow-up after treatment of a primary tumour is to identify eventual liver metastases as early as possible in order to select patients who might benefit from further surgery or systemic therapy and exclude those for whom such treatment might not be helpful.

Serum Markers

The specificity of each serum marker varies according to the primary tumor (Table 1). Independently to the primary lesion, serum levels of Carcino-Embryonic Antigen (CEA), alkaline phosphatase, Aspartate Aminotransferase (AST), and, occasionally, alpha-fetoprotein may be increased in the presence of NCNELM [6].

Gastric cancer [7]	Ampullary cancer [8]	Breast cancer [9,10]	Ovarian cancer [11,12]	Uveal melanoma [13]
ACE				LDH
Ca 19-9	ACE	ACE	Ca 125	Alkaline phosphatase
Ca 72-4	Ca 19-9	AST	ACE	γ-GT

Table 1: Predictive serum markers for detection of hepatic metastasis according to each primary.

Imaging Work Up and Tumoral Vascularization

Following the detection of metastases an initial Computed Tomography (CT) scann, or Magnetic Resonance Imaging

(MRI), in case of contraindication to CT scann, should be done. Sometimes, the ultrasound alone may be sufficient if it can provide the necessary information, particularly so when the Ultrasound (US) is associated with contrast. If the ultrasound fails to yield the necessary information, the next evaluation modality should be MRI. This is prefered as it has a high sensitivity for these lesions. In case of hypervascular metastases, the CT scann or MRI must have an arterial phase (three phasic). Nodule characterization by MRI and contrast ultrasound is more efficient compared to CT scann. For the evaluation of intrahepatic extension of the NCNELM, CT scann and/or MRI are usefull techniques, depending on the case, a Positron Emission Tomography (PET) scann can be added if a surgical treatment is planned [14].

The correct caracterization of the tumoral vascularization is an essential element in the NCNELM investigation. The contrast ultrasound and the MRI allow the study of the vasculature of a tumor, and whatever the technique is used, there are hypervascular metastases and hypovascular metastases. Hypervascular are classically metastases of neuroendocrine and carcinoid tumors, kidney, breast, thyroid and sometimes lesions originating from sarcomas. On the other hand, metastatic lesions originating from a primary tumor of lung, prostate, bladder and pancreas are hypovascular [14] (Table 2).

Hypervascular metastases	Hypovascular metastases	Hypovascular or hypervascular metastases
Neuroendocrine		
Kidney	Bladder	Pancreas (70% hypovascular)
Thyroid	Lung	Breast (70% hypervascular)
Sarcomas	Prostate	
Melanoma		

Table 2: Vascularization of hepatic metastases from noncolorectal nonendocrine tumors on imaging study [14].

Chemotherapy for Metastatic Liver Disease According to Each Primary

In contrast to the treatment of colorectal liver metastases where chemotherapy acts as an adjuvant treatment to surgery, the reverse situation is currently observed for noncolorectal nonendocrine liver metastases, where systemic chemotherapy plays the key role and surgery acts as an adjuvant therapy, and mainly, with the emergence of effective therapies for most tumors, the prognostic value of chemotherapy response is of major importance in the decision making process [15].

Gastrointestinal Tumors

In general adenocarcinoma of the esophagus is treated by analogy to gastric cancers. For metastatic squamous cell carcinoma, the combination of cisplatin and irinotecan is recommended due to its good tolerability and high response rate (overall response of 57% and complete response of 6%) [16]. The use of oxaliplatin and capecitabine demonstrated in a study an objective response rate of 35% [17]. In patients with poor clinical condition, paclitaxel is suggested with overall response of about 15% [18]. The use of molecular therapies have shown promising results, but is still considered experimental. Like adenocarcinoma of the esophagus, the gastroesophageal junction tumors are treated according to gastric tumor guidelines. Recent advances in the treatment of these tumors include the targeted therapies such as bevacizumab. The last one combined with irinotecan and cisplatin demonstrated response rates of 65% and median survival of 12.3 months [19]. Further studies of chemotherapy in combination with bevacizumab are ongoing.

The spontaneous survival in cases with synchronous bilobar liver metastases from gastric cancer is 4 months and 7 to 8 months in the case of unilobar liver metastatic disease [20]. A recent meta-analysis demonstrated a gain in overall survival in patients undergoing chemotherapy versus best supportive care for metastatic gastric cancer. This study established the superiority of combination regimens with cisplatin on 5-fluoracil (5-FU) monotherapy [21]. On the other hand, hepatic metastases from gastric cancer are modestly sensitive to chemotherapy. The cisplatin and 5-FU regimen remains the most popular regimen in Europe and is still used as a control arm in several studies. A randomized study included oxaliplatin, capecitabine or epirubicin combined to cisplatin and 5-FU, with similar response rates among the regimens [22]. Regimens containing irinotecan or docetaxel were also tested in randomized studies in patients with advanced disease and had variable results [23-26]. The FOLFOX regimen showed objective response of 43% in first-line treatment, consistent with other first-line regimens [27]. Like breast cancer, approximately 20% of gastric tumors show over expression of Human Epidermal Growth Factor Receptor 2 (HER-2). A randomized study assessed the role of trastuzumab in first-line treatment for patients with HER-2 positive gastric cancer, and there was an increase in overall survival (13.8 vs 11.1 months, $p = 0.0046$) in favor of the trastuzumab arm [28].

More than half of patients diagnosed with tumors of the small intestine present with locally advanced or metastatic disease, including the liver. In the past, systemic treatments similar to those described for cancers of the stomach were used in cases of more proximal cancers, and similar treatment of colon cancer in cases of distal. However, the use of platinum combined with 5-FU appears to confer survival advantage to these patients [29]. A recent study evaluated the combination of capecitabine and oxaliplatin with objective response rate of 50%, time to progression of 11.3 months and median survival of 20.4 months [30].

Biliary-pancreatic Tumors

In metastatic biliary tract cancer, the fluoropyrimidine-based regimens achieve response rates of 10% and median survival of

approximately 6 months [31-33]. The addition of platinum agents appears to increase the survival and response rates [34,35]. A recent meta-analysis of 104 clinical trials [36] suggested differences in biological behavior of tumors of the biliary tract, with gallbladder carcinoma being more sensitive to systemic chemotherapy than cholangiocarcinoma (objective response of 36 vs 18%), but with a tendency to shorter median survival (7.2 vs 9.3 months). It was also demonstrated in this meta-analysis the superiority of gemcitabine-based regimens compared to other regimens, particularly in combination with platinum agents. The combination of gemcitabine and capecitabine also proved to be active, with response rates around 30% [37]. Overexpression of the receptor of epidermal growth factor receptor has been observed in advanced tumors of the biliary tract, suggesting that the combination with cetuximab may increase effectiveness of chemotherapy. A study that evaluated the activity of gemcitabine and oxaliplatin in combination with cetuximab showed an objective response rate of 63% [38].

Hepatic metastases from pancreatic cancer are modestly sensitive to chemotherapy. The use of gemcitabine is associated with a low objective response with clinical benefit in only 24% of patients. A recent meta-analysis evaluating the combination of gemcitabine with other drugs has shown a benefit in progression-free survival and objective response with combination chemotherapies [39]. The addition of gemcitabine to biological agents (tipifarnib [40] and marimastate [41]) resulted in no benefit in overall survival compared with gemcitabine alone. One exception was a study which compared gemcitabine combined with erlotinib or placebo [42]. The combination arm demonstrated superiority in terms of overall survival (6.2 vs 5.9 months, p=0.038) and survival free progression (3.8 vs 3.5 months, p=0.004). Based on these data, erlotinib was approved for the treatment of metastatic pancreatic cancer.

Breast Tumors

Patients with predominantly visceral metastases from breast cancer are sensitive to chemotherapy and prolonged remissions are obtained in about 50% of cases, however, isolated hepatic metastases from breast cancer are uncommon, therefore, the evaluation of the results is difficult to achieve. The recent advances include trastuzumab as first line treatment in combination with chemotherapy (paclitaxel or anthracyclines and cyclophosphamide) with increased response rates, progression-free survival and overall survival [43].

Reproductive System Tumors

In metastatic uterine cancer (endometrial), response rates with progestins correlated with tumor grade and to the state of the progesterone receptor (37% vs 8% when no expression) [44]. For patients with aggressive behavior disease, such as hepatic metastases, combined chemotherapy is recommended with agents such as doxorubicin, cisplatin and paclitaxel [45]. The most active cytostatic agents in metastatic ovarian cancer consist of cisplatin, carboplatin and paclitaxel, and the most widely used alkylating agent is cyclophosphamide. The number of cycles depends on the stage of disease and on the antitumor response obtained. Drugs such as docetaxel, gemcitabine, adriamycin and 5-FU are active to a lesser extent [46].

Urologic Tumors

In metastatic bladder cancer, a randomized study showed that the combination of carboplatin and gemcitabine has efficacy similar to M-VAC regimen in terms of overall and survival at five years [47,48], and the regimes containing carboplatin/gemcitabine/paclitaxel are equally active in metastatic disease [49]. The use of interleukin-2 (IL-2) in high doses for metastatic renal cancer showed complete response of 9.3%, partial response of 9.7% and overall response of 19% [50,51]. The combination of IL-2 and interferon (IFN) shows similar response rates [52]. Recently, targeted therapies with sunitinib [53] or temsirolimus [54] can be recommended as the first line treatment. The treatment of metastatic prostate cancer is complex taking into account patient's age, prostate-specific antigen values and tumor aggressiveness (Gleason score). Essentially the prostate cancer is a hormone sensitive tumor, androgen-dependent, and the treatment initially consists of hormone therapy by surgical castration or drugs. When the disease becomes hormone-resistant, the chemotherapy can be indicated [55]. In metastatic disease of testicle tumors the treatment necessarily involves bleomycin, etoposide and cisplatine schemes. Despite the higher myelotoxicity, the scheme with etoposide, ifosfamide and cisplatin has the same efficacy in metastases response [56,57].

Sarcoma and Stromal Tumors

Today, the chemotherapeutic treatment for sarcomas is based on the histological type. Liposarcomas have increased sensitivity to anthracyclines [58,59] and have a high response rate to trabectedin-based treatments [60,61]. Leiomyosarcomas respond well to combinations of gemcitabine with docetaxel [62-65] and to trabectedin [66]. The most active drug in the treatment of synovial sarcoma is ifosfamide [67] and targeted therapies with pazopanib and sunitinib have been tested for metastatic disease [68]. Angiosarcomas are highly responsive to taxanes isolated [69,70] or in combination with other drugs, such as docetaxel and gemcitabine [71]. Dermatofibrosarcoma protuberans appears to be responsive to Imatinib, with an objective response rate of 36% [72]. Metastases from gastrointestinal stromal primary tumors have a high objective response rate (over 50%) to imatinib, up to 70% of responding tumors remain in remission up to 3 years post treatment [73]. The relevance of the initial dose of imatinib in patients with advanced disease was evaluated in several studies [74,75], with an increased progression-free survival with no difference in overall survival with higher doses of imatinib.

Melanoma

Chemotherapy agents with activity in melanoma, with overall response between 10% and 20%, include dacarbazine, temozolomide, carmustine, lomustine, vinblastine, and taxanes, but the response rate of hepatic metastases, particularly in uveal melanoma, is less than 5% [76]. Non-responding patients (to chemotherapy) may respond to IFN or high doses of IL-2 [77]. Studies involving combined biological agents to standard chemotherapy show an overall response of 40-60% and complete response of 10-30% [78,79]. A study showed significant increase in response rate (48 versus 25%, p = 0.001), progression free interval (4.9 versus 2.4 months, p = 0.008) and overall survival (11.9 versus 9.2 months, p = 0.06) in favor of patients treated with biochemotherapy versus chemotherapy alone [80]. Preliminary data from a study with chemotherapy with or without sorafenib, showed increased response rate (overall response of 24 vs 12%) and progression free interval (HR = 0.66) with the addition of sorafenib [81].

Head and Neck Tumors

Randomized studies (conducted before the era of cetuximab) demonstrated that polychemotherapy had no benefit in overall survival compared to monochemotherapy in metastatic head and neck cancer despite higher response rates with combined regimens [82]. The actual recommendation of adding cetuximab to chemotherapy in patients with stage IV is based on a randomized study that demonstrated that adding cetuximab had advantage in overall survival compared to chemotherapy alone (10.1 vs 7.4 months, p = 0.036) [83].

Lung Tumors

Combined or isolated chemotherapy for non-small cell lung carcinoma in the metastatic context achieves an increase in survival [84], but the evaluation of the results in isolated hepatic metastases is difficult to achieve because liver-only dissemination occurs in about 5% of metastatic cases [85]. The use of combined regimens has a lower toxicity, and these combinations include carboplatin/ paclitaxel/ cisplatin/ docetaxel/ gemcitabine and vinorelbine [84]. Targeted therapies have also been evaluated, and the combination of chemotherapy with these agents, such as gefitinib, erlotinib and bevacizumab, have resulted in better response rates compared to chemotherapy alone [86].

Liver Resection

In practice, liver surgery for noncolorectal nonendocrine metastases should be considered only when the metastatic disease is well controlled or responding to systemic therapy, and the efficacy of hepatic resection for patients with NCNELM can be noted by the outcomes observed in patients selected for hepatic resection, being better than those achieved with currently available nonsurgical therapies, suggesting that hepatic resection may provide an independent survival benefit [15]. There are studies on this topic that, have suggested that hepatic resection for NCNELM is safe and approximately as effective as hepatic resection for colorectal liver metastases, with reported 5-year survivals between 30% and 40% [85-93]. A study carried out [15] determined that the overall survival following hepatic resection was 36% at 5 years and 23% at 10 years. The disease-free survivals at the same time points were 21% and 15%, respectively, with a median disease-free survival of 13 months. During posthepatectomy follow-up, recurrent liver metastases were identified in 49% of patients, these metastases were solely intrahepatic in 24% of patients and were associated with extrahepatic metastases in 25% of patients. From the group with only intrahepatic recurrences, 32% underwent a second hepatectomy. Initial extrahepatic metastases were surgically treated in 23%, and subsequent recurrences were surgically treated in 37%. Following first hepatectomy, the 5-year and 10-year recurrence-free survivals were 14% and 10%, respectively, with a median recurrence-free survival of 11 months.

In the same study [15] patients with liver metastases from primary breast tumors following hepatic resection experienced 5 and 10 - year survivals of 41% and 22%, respectively, with a median survival of 45 months, and patients with liver metastases that originated from gastrointestinal primary tumors experienced favorable to intermediate survivals following resection, including an overall 5 - year survival of 31% and a median survival of 26 months. However, within the gastrointestinal category, some groups experienced relatively better survivals (ie, small bowel tumors had a 5 - year survival of 49%), whereas other sites experienced poor outcomes (ie, gastroesophageal junction 5-year survival, 12%). Metastases from urologic primary tumors were associated with a 5-year survival of 48% and a median survival of 51 months. In descending order, adrenal, testicular, and renal metastases were associated with 5-year survivals of 66%, 51%, and 38%, respectively. For melanomas, including choroid melanoma and cutaneous melanoma, the 5-year survivals for each of these melanoma types were 21% and 22%, respectively. Patients with gynecologic primary tumors were associated with a 5-year survival of 48%, however, the 5-year survival for patients with ovarian primary tumor sites (50%) exceeded that of patients with uterine primaries (35%). Patients with primary tumors of pancreatic or biliary origin experienced an intermediate 5-year survival of 27%, with only those patients with ampullary primary tumors had a favorable 5-year survival (46%). Patients with liver metastases from pancreatic primary tumors had a 5-year survival of 25%, and the subset with pancreatic adenocarcinoma had a 5-year survival of 20%. Patients with head, neck, and pulmonary primary tumors with squamous cell histology experienced poor outcomes following hepatic resection with 5-year survivals less than 15%. Tumors of unknown origin were associated with a 5-year survival of 38% (Table 3).

Primary tumor	No	5- year survival %	Median survival (mo)
All patients	**1452**	**36**	**35**
Group 1 : 5-yr survival >30%			
Adrenal	28	66	63
Testicular	78	51	82
Ovarian	65	50	98
Small bowel	28	49	58
Ampullary	15	46	38
Breast	454	41	45
Unknown	28	38	30
Renal	85	38	36
Uterine	43	35	32
Group 2 : 5-yr survival 15-30%			
Gastric adenocarcinoma	64	27	15
Exocrine pancreatic	40	25	20
Cutaneous melanoma	44	22	27
Choroid melanoma	104	21	19
Duodenal	12	21	34
Group 3 : 5-yr survival <15%			
Gastroesophageal junction	25	12	14
Pulmonary	32	8	16
Esophageal	20	32*	16
Head and neck	15	24*	18
*Three-year survival.			

Table 3: Five-year and median survivals for patients with NCNELM from individual primary tumor sites grouped by Favorable (Group 1), Intermediate (Group 2), and Poor outcomes (Group 3) [15].

The operative risk of hepatic resection has diminished even as the indications have expanded, given the progressive increase over time in the number of patients with noncolorectal nonendocrine liver metastases treated with resection. The surgical series and studies of NCNELM resection report rates of 0% to 3.6% of mortality with up to 33% of mobidity [15, 87-93]. Resection may be considered in patients fit enough to tolerate general anaesthesia, with no major comorbidity and normal liver function. Absolute contraindications for resection of noncolorectal nonenndocrine liver metastases have not been clarified, but should not be offered resection to patients with uncontrolled primary disease or such widespread intrahepatic involvement that the residual liver function after resection would be inadequate. Most that authorities would agree that presently it would be safe to resect up to 70% of a healthy (non-cirrhotic) liver. Relative contraindications include situations where resection is not performed easily, such as caudate lobe involvement or tumours invading the inferior vena cava. Tumor involvement of the portal vein confluence would also limit the potential curability of the resection. Bilobar distribution of metastases or size of metastases are relative contraindications and do not necessarily limit resectability.

Liver Transplantation

Unlike liver metastases from endocrine or carcinoid tumors, liver metastases from noncolorectal and nonendocrine cancer are not good indications for Liver Transplantation (LT). A concensus conference about the indications of liver transplantation concludes that the place of the LT in dealing with malignant tumors other than HCC is uncertain because of multiplicity of etiologies, heterogeneity on staging and there is a methodological insuficiency data available [94]. The results of LT for metastases from colorectal cancer, pancreatic endocrine tumors, peripheral cholangiocarcinoma contraindicate such indications. A customary survival at 5 years of 50% allows us to perform the transplantation in rare patients with hepatoblastoma, hemangioendothelioma epithelioid or metastases of carcinoid tumor.

Radiofrequency Ablation

The Radiofrequency Ablation (RFA) is a relatively recent techinque in the treatment of the most common malignant liver tumors such as hepatocellular carcinoma and colorectal metastases. In a serie of treatment by RFA of NCNELM of only breast cancer origin [95], a great concern was the incidence of continuous and adjacent tumor recurrence after the ablation according to the size of the lesions treated, mainly lesions with diameter >4 cm. Another serie described the using of laparoscopic RFA of liver tumors, and according to the results the liver recurrence rate per tumor was highest for colorectal metastasis (34%), followed by noncolorectal nonneuroendocrine metastasis (22%) [96]. The results of intraoperative RFA of liver tumors in addition to resection were published [97], the group of patients with metastases noncolorectal (comprised 20% of endocrine tumors) had a median survival significantly higher than the metastatic colorectal group, respectively 59 months and 37.3 months. The overall survival was negatively influenced by lesions superior of 3 cm in diameter. Factors to be considered in the indication of percutaneous radiofrequency ablation, or combined surgery are the diameter of the lesions, the presence of extrahepatic disease and sensitivity to medical treatment. A less aggressive disease with a tumor progression-free interval exceeding 24 months may be a factor that encourage agressive local treatments [98,99].

Chemoembolisation

The chemoembolization is a therapeutic modality that can be used in association with percutaneous ablation techniques, surgical resection or chemotherapy. Whereas there is no reported serie with improved survival in patients with NCNELM treated by chemoembolization, it is in the majority of cases well tolerated and can induce a durable response, especially in hypervascular metastases. The tumor regression in patients iniatilly considered as non-resectable can allows secondary resection. The main branch portal thrombosis is a classical contraindication to

chemoembolization, although hyperselctive chemoembolization decreases the risk of parenchymal necrosis, and a severe hepatic insufficiency may decompensate after chemoembolization [100].

Final Considerations

The variety of the clinical situations in NCNELM scenario, like primary tumor site and histology, disease-free interval before hepatic progression, metastases response to chemotherapy, and the presence of extrahepatic disease makes the decision process very complex, but agressive treatment strategies, like liver resection in selected patients, may be promising. Therefore, it is critical that treatment decisions for patients with NCNELM should be made by multidisciplinary treatment groups in attempt to achieve better survival outcomes [101].

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