Staging and management process of cholangiocarcinoma.

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Abstract

A holistic approach to prognostication, treatment classification and outcome comparison is best provided by staging systems. However, none of the CCA staging systems that are currently in use meets these requirements.

Intrahepatic CCA: The American Joint Committee on Cancer/Union for International CancerControl (AJCC/UICC), the Liver Cancer Study Group of Japan (LCSGJ) and the National Cancer Center of Japan (NCCN) staging methods are now the three main staging systems for iCCA. The staging mechanism of the AJCC/UICC is the only method that has demonstrated a link between stage and survival, although it is constrained by its need for histology to determine Tis and T4. The seventh edition AJCC/UICC staging method was outperformed by recently created prognostic nomograms and improvements to the existing LCSGJ staging system, however additional validation is needed.

Perihilar CCA: Although it was created to direct surgical therapy, the Bismuth-Corlette classification is not a staging system in the traditional sense. The AJCC/UICC and the Memorial Sloan Kettering Cancer Center (MSKCC) staging systems are the two most often used staging systems for pCCA. Since pCCA and dCCA are now staged independently for the first time in the most recent seventh edition of the AJCC/UICC staging system, further research is needed to confirm its predictive significance. The MSKCC staging system was unable to accurately separate patients with resectable cancer from those who weren't. There have been new staging mechanisms proposed, pending further evaluation. Very recently, a staging approach that was created exclusively from clinical data outperformed the TNM staging system and had outstanding predictive performance both with and without treatment.

Distal extrahepatic: The sole staging system for dCCA at the moment is the seventh edition of the AJCC/UICC. Its utility is constrained by the need for microscopic assessment of tumour infiltration depth and the lack of association between its T-stages and outcomes following resection.

Keywords: Prognostication, Bismuth-Corlette classification, Prognostic nomograms, T-stages

Introduction

Clinical presentation and diagnosis

CCA has a vague clinical presentation. Combining the interpretation of various diagnostic modalities is necessary for its diagnosis.

Intrahepatic CCA: Inadvertent diagnoses account for 19%-43% of iCCA cases. Patients typically start showing symptoms at an advanced stage of the disease and present with vague symptoms such cachexia, malaise and abdominal discomfort. In contrast to 58% of patients who do not have symptoms, just 25% of symptomatic individuals have resectable disease. CCA's most often employed tumour marker is Carbohydrate Antigen 19-9. (CA 19-9). It is 63% to 67% accurate at differentiating between iCCA and HCC [1]. However, CA 19-9 can also be increased in benign cholangiopathies, pancreatic, gynecologic and other gastrointestinal malignancies. Regardless of tumour load, CA 19-9 is not expressed in the 8% of the population who lack the Lewis antigen. In order to characterise intrahepatic masses and plan the preoperative course of action for CCA, dynamic cross sectional imaging is crucial [2]. With up to 52% of diagnoses being incorrect, HCC and iCCA cannot be consistently distinguished by ultrasound, including contrast enhanced ultrasound.

Perihilar and distal CCA: 90% of patients with pCCA have painless jaundice as their first symptom, while 10% have acute cholangitis. At the time of their initial presentation, 56% of pCCA patients exhibit systemic symptoms of malignancy, such as anorexia, weight loss and lethargy. An infrequent sign of a hypertrophyatrophy complex is the palpable protrusion of one hepatic lobe (Unilobar biliary obstruction with ipsilateral vascular encasement resulting in ipsilateral hepatic lobe atrophy with contralateral hepatic lobe hypertrophy).

The difference between benign and malignant biliary duct strictures is a common diagnostic conundrum. Postoperative examinations reveal that up to 15% of suspect biliary strictures are benign. IgG4 cholangiopathy must be ruled out by analysing IgG4 serum level. The Negative Predictive Value

(NPV) of CA 19-9 serum concentrations 100 U/L is 92% in non-PSC patients with benign biliary strictures. Before performing any biliary procedures or undergoing surgery, cross sectional imaging should be done [3]. The surgical strategy can be guided by using multidetector CT to detect anatomical changes and the extent of the tumour. Biliary tree and hepatic parenchyma can be evaluated by MRI and magnetic resonance cholangiopancreatography. It is up to 95% accurate in determining the local extent and resectability, but only 67% to 73% and 75% to 80% accurate in identifying vascular and parenchymal invasion, respectively.

Biliary strictures can be accessed *via* percutaneous transhepatic cholangiography or Endoscopic Retrograde Cholangiopancreatography (ERCP), depending on how accessible the biliary tree is pCCA often manifests as a filling deficiency or dominant structure. The implantation of therapeutic biliary stents and sampling of the strictures are made possible by interventional cholangiography. The sensitivity of biliary brushings' cytology is only 20% to 43%; however, by doing further analysis for chromosomal aneuploidy using fluorescent *in situ* hybridization, the sensitivity can be raised to 46% to 68% FISH.

Description

Management

The only possibly curable therapeutic options for CCA are surgical procedures. Though 10% to 45% of patients with CCA who were thought to be resectable following exploratory laparotomy were discovered to be unresectable, the majority of CCA patients are detected at late stages of the disease [4].

Surgical resection: For CCA, surgical resection is the primary course of action. Bilateral, multifocal disease, distant metastases and comorbidities linked to operative risks outweighing the anticipated benefits of a surgery are all indicators against surgical resection. Due to the field malfunction in PSC and the frequent underlying severe fibrosis, liver transplantation should be the preferred course of treatment for PSC patients with pCCA. Despite the fact that N1 disease is a standalone prognostic factor for worse outcomes, regional lymph node metastases are not considered to be an absolute contraindication to resection.

In recent years, postoperative morbidity and mortality rates have dropped. Bile duct leaks and intraabdominal abscesses are two serious surgical consequences. There is debate concerning preoperative biliary draining in patients with malignant jaundice. Untreated preoperative jaundice has been linked to greater incidence of sepsis, bile leaks, biliary fistulas and postoperative abscesses. Preoperative biliary drainage did not, however, significantly reduce morbidity or mortality in a number of investigations and some even found a rise in overall and postoperative complication rates.

Nonsurgical therapies: The phase III randomised controlled ABC-02 study found that patients with CCA who received gemcitabine/cisplatin combination therapy as opposed to gemcitabine monotherapy experienced a 6 month survival benefit. Locoregional therapies, such as radiofrequency ablation, Transarterial Chemoembolization (TACE), drug eluting bead TACE, selective intra narterial irradiation using 90Y microspheres or external beam radiation therapy are provided by specialised facilities in the palliative situation [5].

Conclusion

Small sample size, simultaneous analysis of CCA, gallbladder cancer and a lack of randomization are all drawbacks of current therapeutic trials. Only a small number of research examined the therapeutic effectiveness of targeted drugs in conjunction with transcriptome data analysis. Targeting EGFR in combination with other molecular targets (such as HER2 and VEGFR) and/or chemotherapy is supported by preclinical and early clinical research, nevertheless.

In order to stratify patients based on their prognostic and oncogenic pathway analyses, transcriptomic analysis identified prognostic classifiers that were independent of anatomical location and next generation gene profiling indicated separate subclasses prediciting survival and recurrence. In the future, these classifiers might be used to expand OLT or resection criteria. Better staging approaches will be required for outcome comparison, but randomised controlled studies are required that prospectively assign patients based on their transcriptome and genetic profiles.

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