Original Article

Utility of CT Scan and CA 19-9 in Predicting Non –Resectability in Malignant Obstructive Jaundice

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Abstract

Background: Most patients with malignant obstructive jaundice (MOJ) present with non-resectable disease. Non curative laparotomy has been associated with adverse outcome. There is need to predict non-resectable disease and prepare patients for planned palliative procedures. **Objective**: To study the utility of Ca 19-9 serum levels and CT scan in predicting the non-resectability of MOJ tumours at Kenyatta National Hospital. **Methods**: Eligible consenting patients were recruited. All had a CT scan of the abdomen and serum CA 19-9 levels determined preoperatively and staging was done using the LRCC criteria. At surgery, intraoperative findings were then compared in terms of non-resectability with the preoperative CT scan prediction and the CA 19-9 levels. **Results**: A total of 49 patients were recruited into the study. During the study, 14 patients were later excluded due to inadequate information of imaging, non-surgical intervention or pre-operative death. At a confidence level of 95%, CA 19-9 level of 466 has 92.3% sensitivity and 100% specificity indicative of non resectability in MOJ lesions. When compared with intra-operative findings on non-resectability, the cut off level of 466 has a positive and negative predictive value of CA19-9 was 100% and 71.4%, respectively. CT scan had 85.2% sensitivity and 100% specificity on predicting non resectability of MOJ lesions, 84% sensitivity in detecting nodal involvement but predicted only 33% of liver metastases. **Conclusion**: Combining CA 19-9 levels and CT scan are useful tools in detecting non resectability of MOJ lesions preoperatively.

Key words: Malignant obstructive jaundice, non-resectability, CA 19-9, CT scan.

Introduction

Primary malignancies of the biliary tree and surrounding organs that cause Malignant Obstructive Jaundice (MOJ) include Cholangiocarcinoma, ampullary carcinoma, carcinoma of the head of pancreas and rarely gall bladder carcinoma. The incidence of MOJ tumours is increasing worldwide (1, 2, 3) . Despite the better diagnostic facilities available, the mortality and morbidity associated with these diseases still remains high. About 10-20% of patients with carcinoma of the pancreas (4) and less than 30% of those with cholangiocarcinoma (1, 5) have potentially resectable disease at presentation. Carcinoma of the ampulla of Vater has been associated with better prognosis with 50% of the patients having resectable disease at presentation, and better five year survival rate than cholangiocarcinoma and pancreatic carcinoma (3, 6).

Complete surgical resection remains the only definitive curative procedure for these tumours. There is no improvement in outcome following incomplete surgical resection (7). Non curative resections have in fact been associated with higher morbidity and increased mortality rates (7, 8) . In patients with non resectable lesions, palliation of the biliary obstruction can be either by surgical bypass or non surgical procedures.

In order to minimise the rate of surgical procedures that are neither curative nor palliative, the utility of several factors in predicting either the resectability or non resectability of MOJ lesions pre-operatively have been studied.

The most frequently alluded to factors are tumour markers CA 19-9, CEA and the use of imaging modalities, more specifically contrast enhanced CT scan of the abdomen. Several authors have studied the utility of CA19-9 in predicting resectability of MOJ lesions with differing cut off values for resectability (9,10,11,) . CA 19-9 serum level is not a routine preoperative test for patients with obstructive jaundice at Kenyatta National Hospital.

Several authors had questioned the sensitivity of CT scan in predicting resectability of MOJ lesions (12, 13). Others accept its utility (14, 15) with criteria for resectability being developed. (16).

Our objective was to study the utility of pre-operative CA 19-9 and CT scan of the abdomen in predicting the non resectability of MOJ lesions.

Materials and Methods

Following institutional approval by the Kenyatta National Hospital (KNH) Ethics and Research Committee, all patients diagnosed with MOJ due to non-metastatic disease presenting at Kenyatta National Hospital during the period June 2009- March 2010 and consenting were enrolled into the study. Using the statistical formula below and an estimated local prevalence of 32.5 in 100000(based on previous local study indicating an incidence of 11.4 in 100000 for

Carcinoma of the pancreas (17) and international studies indicating that carcinoma of the pancreas account for approximately 35% of MOJ (18, 19)), a sample size of 33 would be the minimum required for the study.

$$N = \frac{Z^2 \times p\,(1-p)}{d^2}$$

N = sample size to be determined

p = estimated prevalence of MOJ.

Z = standard errors of the mean corresponding to 95% confidence interval

d = Absolute precision (0.05)

The demographic characteristics for all the patients were noted. CA 19-9 levels were determined preoperatively at the KNH Biochemistry Laboratory and CT scan of the abdomen reported by a consultant radiologist. KNH uses Roche Cobas E411 immunology analyser with the Roche (South Africa) CA19-9 test kit based on the monoclonal 1116-NS-19-9 antibody. The London Regional Cancer Centre (LRCC) CT scan criteria were used for predicting resectability (absence of nodal metastases or other liver metastases, absence of involvement of portal vein/main hepatic artery/superior mesenteric artery involvement, absence of direct invasion of surrounding organs or disseminated disease). The surgeon was not aware of the patient's preoperative CA 19-9 levels.

The decision to intervene and the mode of intervention were exclusively made by the primary surgeon. The intra-operative findings were documented by primary surgeons, who were requested to document the visual presence and number of nodal metastases, vascular involvement/ encasement and peritoneal metastases in the operative notes. Biopsies of nodal and peritoneal metastases where possible were taken. This information was then used by the authors to determine potential tumour resectability as per the LRCC CT scan criteria. The form of surgical intervention was then documented. The post operative details of: hospital stay, other intervention, liver function tests (at 14 days), morbidity and mortality were documented.

The pre-operative CT scan and CA 19.9 were then compared with intra-operative findings for resectability and non-resectability.

Data collected was coded and entered into the SPSS(Version 17.0) software by a statistician. Descriptive statistics were done for all continuous variables, obtaining measures of central tendency and dispersions. Proportions of frequency were used for categorical variables. The chi-square test was used to determine association between the categorical independent variables and outcome (non resectability). Significance was set at 0.05

Results

During the study period a total of 49 patients were admitted to KNH with MOJ. Of these 30(61%) were female. The age range was from 34 to 81 years, with a mean of 62 (63 for females and 61 for males).

Of the 49 patients admitted, 32 had Carcinoma of the head of the pancreas (65%), 10 had Cholangiocarcinoma (21%) and 7 had peri-ampullary tumours (14%). During the study period, 45402 patients were admitted to KNH, of which 2737 patients were admitted to the general surgical units of KNH. As such for the period, the incidence of admission of patients with MOJ at KNH was 49:45402 (107:100,000) and into the surgical units was 41:2737 (14.9: 1000).

Of the 49 patients admitted with MOJ, 16 were excluded from the final analysis for the following reasons: pre-operative death (6), 3 patients had non surgical palliative procedures (percutaneous transhepatic drainage), 7 patients had inadequate imaging information.

Using the TNM-AJCC staging system, the patients were staged as shown in table 1.

Insert Table 1 here

CA 19.9 and non-resectability

The serum CA 19.9 levels at presentation ranged from 152 to 16 000. The spread of CA 19-9 when compared with the intraoperative non resectability was as shown in Table 2.

Receiver operating characteristics (ROC) analysis was done. The Area under the curve (AUC) was 0.809. Confidence interval is between 0.591 – 1.027 with standard error of 11.1% at a confidence level of 95%, our study identified a cut off level of 466, which has 92.3% sensitivity and 100% specificity indicative of non resectability in MOJ lesions. When the preoperative prediction of non- resectability is compared with the actual operation, the positive and negative predictive value of CA19-9 were 100% and 71.4%, respectively.

Insert Table 2 here

CT scan and non-resectability

Non resectability was predicted using the LRCC criteria. Table 3 is a breakdown of the T stage on CT scan and the non resectability of the lesions using LRCC criteria determined intra-operatively. All of the patients with lesions categorised as T4 at preoperative CT scan imaging had non resectable disease at laparotomy.

Insert Table 3 here

An analysis was made of the preoperative nodal prediction as per the CT scan imaging. Table 4 summarises the CT scan nodal prediction. All the lesions predicted to have N1 nodal involvement were found to be non resectable.

Insert Table 4 here

All the 21 patients with predicted N1 nodal involvement were confirmed to have the same intra-operatively. 4 of the 5 patients in whom nodal involvement was not preoperatively assessed on CT scan had N1 nodal involvement and in one patient no nodal involvement was noted. This patient had a resectable lesion. From this study, CT scan imaging has 84% sensitivity in predicting nodal involvement. CT scan though predicted only 2 of 6 liver metastases noted intra-operatively (33%). When CT scan prediction of T, N and M stage are taken together, the CT scan has 85.2% sensitivity and 100% specificity in predicting non-resectability of MOJ lesions.

Discussion

Our study adds to a body of knowledge that suggests that a combination of CT Scan and CA19.9 levels are useful in predicting whether a patient should be subjected to attempted resection of their MOJ tumour. We largely discuss prediction for non-resectability since most of our patients fall in this group. However, this may be used as a proxy for resectability.

As alluded to earlier, several authors have studied the utility of CA19-9 in predicting resectability of MOJ lesions with differing cut off values for resectability (9, 10, 11). Some have dissented such as, John et al who in a prospective study found CA 19-9 serum levels to be a useful diagnostic tool in the diagnosis of CC in patients without Primary Sclerosing Cholangitis (PSC) but concluded that its level did not correlate with the stage of the disease (20).

Forsmark et al concluded that a CA 19-9 level of 300u/l is diagnostic of non resectable pancreatic carcinoma (21) though they did not correlate the levels with those of the patients found to have resectable lesions at surgery.

Schliemann et al conducted a meta-analysis of patients who had undergone laparotomy for pancreatic cancer over a seven year period (1996-2002) in a tertiary care centre and all had pre-operative CA 19-9 levels. Their study found the levels for those with non resectable lesions to have been five times higher than in patients with resectable lesions, but fell short of giving a cut off level for predicting non resectability (11).

Mehta et al concluded that the level of CA 19-9 in patients with non resectable lesions was twice that in patients with resectable ones but also fell short of precluding a cut off level (22). They do though in their conclusion advice that levels of CA 19-9 greater than 1000u/l indicate a dismal survival in patients with non resectable lesions (22). Our study shows a similar trend for non-resectability, with our ROC plot obtaining a figure of 466 iu/l. This, to our knowledge, is the first study in literature involving an African population.

Contrast enhanced CT scan of the abdomen is an accepted tool in the diagnosis of MOJ lesions and staging of these lesions. Previously, several authors had questioned the sensitivity of CT scan in predicting resectability of MOJ lesions (12, 13).Other authors (14, 15) have found it a useful tool, with Phoa's study on the CT criteria for resectability of pancreatic carcinomas finding that CT scan was able to predict absence of vascular ingrowths with 100% sensitivity and also able to predict a high risk of vascular invasion in potentially resectable lesions (23). In addition Kalbhen et al have even proposed that repeat reporting of CT scan done outside tertiary care centres to be invaluable and more cost effective than repeat imaging (15).

Our study also adds to this observed trend, and shows that CT scan has a sensitivity of 85% and 100% specificity in predicting non-resectability of MOJ lesions. In addition it had 84% sensitivity in predicting nodal involvement but has a poor (33%) ability to pick liver metastasis.

Study Limitations

This was a single centre prospective study limited by the small number of patients presenting with MOJ at Kenyatta National Hospital. The study was also limited by the study period. A study with a larger study population and with a longer patient follow up would yield higher power.

Conclusion

Combining CA 19-9 levels and CT scan are useful tools in detecting non resectability of MOJ lesions preoperatively

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Table 1: Preoperative staging of patients using the TNM-AJCC Staging System

Stage		**Ca Head**	**CC**	**Ampullary**	**No of pts**
0	TisN0M0	0	0	0	0
IA	T1N0M0	0	0	2	2
IB	T2N0M0	0	0	0	0
IIA	T3N0M0	1	1	2	4
IIB	T1-3N1M0	3	0	2	5
III	T4, Any N, M0	14	4	1	19
IV	Any T, Any N M1	3	2	0	5
TOTAL		**21**	**7**	**7**	**35**

Table 2. Spread of CA-19-9 levels compared with non-resectability.

Range of CA 19.9 (iu/l)	**Resectable**	**Non-resectable**
0-250	2	0

251-500	4	1
501-750		4
751-1000		8
1001-2000		7
2001-5000		0
>5000		7
TOTAL	**6**	**27**

Table 3: Pre-operative CT scan T predictions(as per TNM) compared with intra-op resectability

LRCC-intra-op vs. CT-T Cross tabulation

		CT-T					
		T1	T2	T3	T4	Tx	Total
LRCC-intra-op	Non Resec	1	4	11	10	1	27
	Resec	2	1	3	0	0	6
Total		3	5	14	10	1	33

Table 4 Cross tabulation of Pre-op CT scan prediction on nodal status vs. intra-op resectability

	Total			
	N0	N1	Nx	

LRCC-intra-op	Non Resec	1	21	5	27
	Resec	5	0	1	6
Total		6	21	6	33