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Original Research Article

Correlation between CT and operative findings in pancreatic cancers and role of pre-operative CA19-9 values in predicting metastatic disease

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ABSTRACT

Background: Pancreatic cancers carry a poor prognosis with 20-30% of cases found resectable on MDCT (Multi-detector CT). 60-91% of these lesions are actually found resectable during surgery. CA 19-9 is an extensively studied tumour marker in pancreatic cancers and its abnormally high value may point towards metastatic disease.
Methods: A study was conducted in a tertiary care centre in which all patients of pancreatic cancers found resectable on imaging were subjected to surgery after staging laparoscopy to find metastatic disease missed on MDCT, the findings were noted and correlated with the radiological findings. Also, pre-operative CA 19-9 levels were analysed to predict metastatic disease in patients with high CA 19-9 values.
Results: The study included 34 patients of pancreatic cancers deemed resectable on imaging. Out of these, four (11.7%) patients were found to be unresectable on staging laparoscopy in the form of subcentimetric liver/peritoneal metastasis. It was also found that preoperative CA 19-9 levels were higher in patients found to be metastatic. By using ROC curve, it was found that pre-operative values of CA 19-9 had 100% sensitivity and 80% specificity at the cut off level >106.75 U/ml.
Conclusions: MDCT fails to identify some unresectable diseases because of presence of distant metastasis in the form of liver and peritoneal metastatic nodules and malignant ascites. Staging laparoscopy prior to laparotomy is a useful procedure which prevents unwanted laparotomy in some cases of metastatic pancreatic cancer not identified on imaging. Abnormally high values of CA 19-9 may point towards metastatic disease.

Keywords: Pancreatic cancer, Resectability pancreatic cancer, CA19-9, Staging laparoscopy

INTRODUCTION

Pancreatic cancers are relatively uncommon and consequent to their location and vague clinical features, their presentation is quite late. The annual incidence of pancreatic cancers worldwide is about eight per 1,00,000 persons.[1] Similar data from our country is scarce and a study by Dhir et al reports the incidence of pancreatic cancers in India as 0.5-2.4 per 1,00,000 males and 0.2-1.8 per 1,00,000 females.[2]

Surgical resection is the only curable treatment for patients with resectable pancreatic cancers. However, 70-80% of patients suffering from pancreatic cancer present with locally advanced or metastatic disease at the time of diagnosis.[3] Since the outcome in most patients of pancreatic cancers is poor, accurate staging allows appropriate treatment selection. Multi detector CT scan (MDCT) is the most commonly used imaging study for staging pancreatic tumours but only 60-91% of lesions

deemed resectable at MDCT are actually so, whereas the remaining manifest local tumour invasion, lymph node metastasis or small hepatic or peritoneal metastasis intra-operatively.[4]

Hence, in patients with likely resectable pancreatic cancers, after imaging studies, staging laparoscopy prior to laparotomy under a single anaesthesia induction is routinely used by many surgeons. It may identify patients with unsuspected metastatic disease and hence, prevent unnecessary laparotomy. For patients who appear resectable on imaging studies alone, laparoscopy identifies additional unresectable disease in up to 30% of cases.[5] John et al reported that liver metastasis and peritoneal metastasis on pre-operative laparoscopy were seen in 25% and 20% of patients thought to be resectable on CT respectively.[6] Also, MDCT is not 100% accurate in assessing vascular invasion. The accuracy of MDCT in predicting vascular invasion by pancreatic tumour is reported between 92-99%.[7-9] CA 19-9 is the tumour marker extensively studied in pancreatic cancers and its abnormally high values may point towards unresectability.[10] In view of this, the present study was conducted in a series of cases of pancreatic cancers, so as to observe correlation of the radiological and operative findings in terms of resectability and usefulness of pre-operative CA19-9 values in predicting metastatic disease.

METHODS

This cross-sectional observational study was conducted over a period of two years, from December 2013 to November 2015, at a tertiary level teaching hospital in the south western part of India after obtaining due clearance from the Institutional Ethics Committee. All cases of operable pancreatic cancers reporting to our centre were included in our study. Patients unwilling/unfit for surgery and patients diagnosed with metastatic disease on presentation were excluded from the study. All patients of suspected pancreatic cancers presenting to this hospital were subjected to history taking, clinical examination, haematological and biochemical investigations, CA 19-9 and imaging in the form of an ultrasonography (USG) of abdomen, initially, followed by 64 slice triple phase multidetector CT scan. If found resectable on imaging, a staging laparoscopy was performed before proceeding ahead with open surgery and the findings were noted and correlated with the radiological findings. Only if deemed resectable on laparoscopy, the surgeon proceeded with open surgical procedure for resection. If distant metastasis was present, frozen section examination of the suspicious nodule was carried out to confirm malignancy and formal resection was abandoned.

Various parameters were considered for comparison between CT findings and intra-operative findings which were size of lesion, location of the tumour, vascular involvement by tumour, liver and peritoneal metastasis, ascites and overall resectability of tumour. Also, pre-operative CA 19-9 levels were analysed in these patients to assess usefulness of its higher values in predicting metastatic disease.

Statistical analysis

Data analysis was done using SPSS (Statistical Package for social sciences) Version 20.0. Chi-square test, ROC curve and student T-test were used to analyse the data. $P<0.05$ was considered as significant.

RESULTS

The study included 34 patients who were identified to have pancreatic neoplasms and were worked up for surgery. Out of them, 67.6% were males and the remaining females. The mean age of the population was 58.4 years. 38.2% of the study population was in the age group of 51-60 years (Table 1).

Table 1: Gender distribution, age distribution and clinical presentation.

	Category	Number of patients (%)
Gender distribution	Male	23 (67.6%)
	Female	11 (32.4%)
Age distribution	≤ 50 years	8 (23.5%)
	51 – 60 years	13 (38.2%)
	61 – 70 years	8 (23.5%)
	> 70 years	5 (14.7%)
Clinical presentation	Obstructive Jaundice	25 (73.53%)
	Abdominal pain	15 (44.12%)
	Constitutional symptoms	8 (23.53%)
	Cholangitis	3 (8.82%)

The most common clinical presentation of the study population was obstructive jaundice which was seen in 25 (73.53%) patients. Other common presentations were pain in abdomen (44.1%) and constitutional symptoms (23%) like weight loss and anorexia. Three (8.8%) of the patients presented with features of cholangitis (Table 1).

CA 19-9 was found to be normal (<37 U/ml) in half the study population (n=17). Amongst those patients who had abnormal CA 19-9 levels, 11 patients had CA 19-9 values of >100 U/ml and 6 patients had CA 19-9 values between 37-100 U/ml. The difference in CA 19.9 levels between

resectable and unresectable disease was found to be statistically significant (p<0.05) (Table 2).

Table 2: CA 19-9 levels in patients having resectable and unresectable disease.

CA19-9 (U/ml)	Resectable disease		Total N (%)	P value
	Yes	No		
Normal (<37)	17	0	17 (50)	
37 - 100	6	0	6 (17.6)	**0.012**
>100	7	4	11 (32.4)	
Total	30	4	34	

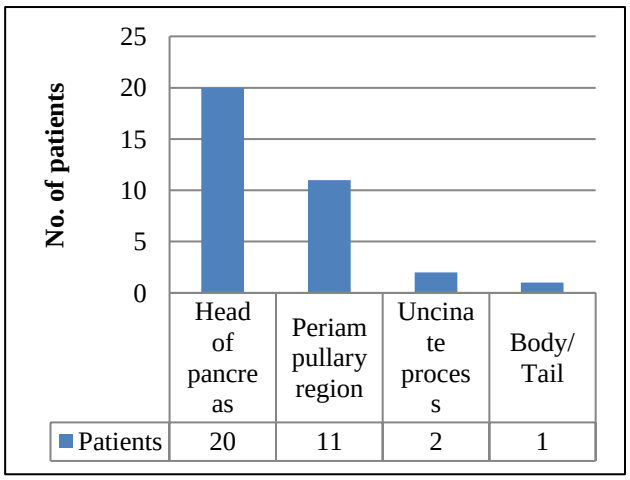
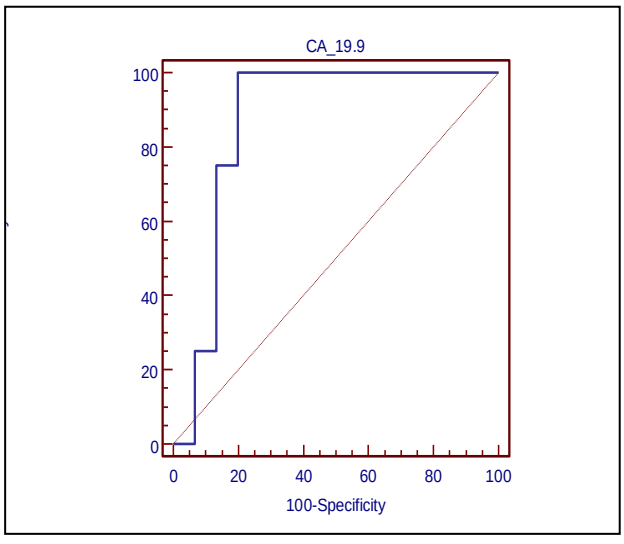


Figure 1: Sites of pancreatic cancer.



Area under the ROC curve = 0.867, Standard error=0.119
95% Confidence interval = 0.706 to 0.958.

Figure 2: ROC curve for CA19-9 for unresectable disease.

Triple phase MDCT was done for all patients who were worked up for surgery. There was no statistically significant difference in the size of tumour identified on CT as compared to intra-operative finding. The most common location of tumour was Head of pancreas (HOP) (58.8%), followed by periampullary (32.4%), uncinate process (5.9%) and body/tail of pancreas (2.9%) (Figure 1). There was no difference in the CT and intra-operative findings as far as identifying site of lesion is concerned (overall sensitivity of CT in identifying site of lesion - 100%).

None of the patients were reported to have vascular involvement, presence of ascites, liver or peritoneal nodules on CT. Out of 34 patients, 33 patients were planned for Whipple's pancreaticoduodenectomy out of which 30 patients underwent whipple's resection on the day of surgery as the others (n=3) were found to be unresectable because of metastasis during staging laparoscopy. One patient was planned for distal pancreatectomy as the lesion was in tail of pancreas. However, he was found to be metastatic on staging laparoscopy and hence resection was not performed.

Total of four (11.7%) patients were found to be unresectable on staging laparoscopy and hence did not undergo laparotomy and resection. One of them was found to have subcentimeteric liver surface nodules on laparoscopy. One patient had ascites and multiple peritoneal nodules. Two patients were identified to have multiple subcentimeteric peritoneal nodules. All patients with metastatic disease were confirmed as having metastatic deposits from adenocarcinoma on histopathological examination. Thus, our study revealed NPV (negative predictive value) of MDCT in predicting liver metastasis, peritoneal metastasis and overall unresectability as 97%, 91% and 88% respectively. None of the patients deemed resectable on laparoscopy was found to have unresectable disease at laparotomy.

It was also found that preoperative CA 19-9 levels were higher in patients found to be metastatic. ROC curve identified the cut off value of CA 19-9 as 106.75 U/ml (Figure 2). By using ROC curve for diagnosis of intra-operatively found unresectable or metastatic disease with pre-operative values of CA19-9, it was found that pre-operative values of CA 19-9 had 100% sensitivity and 80% specificity at the cut off level >106.75 U/ml.

DISCUSSION

Pancreatic cancer carries a very poor prognosis and represents 3% of all new diagnosed cancer cases, 11th most common cancer, and third leading cause of cancer deaths in the United States.[11] Surgical resection is the only potentially curative treatment for resectable pancreatic cancers. However, around half of the patients of pancreatic cancer present with metastatic disease and 35% present as locally advanced disease which is surgically unresectable.

Only 10-20% of patients present with a disease which is resectable.[12]

Pancreatic cancers are found to be commoner in males than females with an incidence ratio of 1.3:1 in United States. Though very little literature is available for pancreatic cancers in Indian subcontinent, our study reported a male predisposition of around 2:1. Most pancreatic cancers occur in the age group of 40-80 years with less than 3% cases seen in patients <44 years of age. Around 54% of patients of pancreatic cancers are in the age group between 65-84 years.[13] The mean age of the population in our study was 58.4 years.

Pancreatic cancers have varied clinical presentations. The clinical picture may range from incidentally detected asymptomatic patients to features of cholangitis – pain abdomen, high grade fever with chills and obstructive jaundice. The two most common clinical presentations of pancreatic cancers are obstructive jaundice and pain in abdomen usually in epigastrium, which may radiate to back in advanced disease.[14] Kalser et al found that 84% of resectable and 44% of metastatic HOP lesions presented with jaundice.[15] Modolell et al have reported pain abdomen followed by jaundice as the commonest presenting complaint in pancreatic cancer patients, jaundice being more prominent and early presentation in periampullary carcinoma.[16] In our study, 25 patients (73.5%) presented with features of obstructive jaundice as the commonest clinical presentation. Upper abdominal pain in 15 (44%) patients was the second most common clinical presentation. Constitutional symptoms like anorexia, weight loss were seen in 23.5% cases. 8.8% cases presented with features suggestive of cholangitis.

CA 19-9 as a tumour marker has high sensitivity for pancreatic cancers which ranges from 80-85% in various studies which is increased to 92% in patients with positive Lewis blood type.[17] Also, abnormally high values of CA 19-9 may help in pointing towards metastatic disease, different levels of which have been identified by various authors in their studies. Schlieman et al in their study found that CA 19-9 level more than 150 U/ml had a 88% PPV (positive predictive value) in identifying unresectable patients who are deemed resectable on pre-operative imaging.[18] In another study, specificity, sensitivity, NPV and PPV of determining unresectability by pre-operative imaging due to metastatic peritoneal/liver nodules were found to be 100%, 42%, 94.7% and 100% respectively. Based on ROC curve analysis, optimal CA 19-9 cutoff in predicting metastatic disease was at 215.37 U/ml with a specificity of 58.3%, sensitivity of 72.7%, a NPV of 95.5% and PPV of 15.1%.[19] In our study, 50% of the patients had normal CA 19-9 levels, 17.6% had CA 19-9 levels between 37-100 U/ml and 32.4% patients had CA 19-9 levels more than 100 U/ml. Out of the patients who had CA 19-9 levels more than 100 U/ml, four patients had metastatic disease identified on staging laparoscopy. This relationship of CA 19-9 levels more than 100 U/ml with unresectable disease was found to be statistically significant (p=0.012). By using ROC curve, it was found that pre-operative CA 19-9 cut off values in predicting metastatic disease was at 106.75 U/ml with 100% sensitivity and 80% specificity.

The two most common locations of pancreatic cancer are HOP and periampullary region, various studies quoting different percentages of patients having lesions in different locations in pancreas. The figures stated in literature also depend upon the locations taken into account while studying pancreatic cancers. HOP has been found to be the primary location of pancreatic cancers in 56-75% patients. Body/tail of pancreas has been identified as the site of lesion in 15% of pancreatic cancers.[20-22] Some studies include uncinate process as a different site from HOP. In our study, we categorised location of tumour into HOP, periampullary region, uncinate process, body/tail of pancreas. Around 59% of patients in our study had lesion in HOP, 32% in periampullary region, 6% in uncinate process and one patient (3%) had lesion in body/tail of pancreas. The only patient who had lesion in the body/tail region was found to be metastatic on staging laparoscopy. It has been found that body/tail lesions present later in course of disease as the symptoms in these patients do not appear till the lesion is large enough. None of the lesions in the periampullary region were metastatic as they tend to present early because of early obstruction of CBD.

Various imaging modalities used in investigation and staging of pancreatic cancer are USG, triple phase MDCT, MRI/MRCP, FDG - PET/CT and invasive modalities like ERCP (Endoscopic Reterograde Cholangio-pancreaticography) and EUS (Endoscopic USG). USG is usually considered as first line of imaging modality in patients of pancreatic cancers. The accuracy for diagnosing pancreatic cancers is 50-70% by conventional USG.[23] Triple phase MDCT done using pancreatic protocol is currently the standard of imaging modality in investigating and staging the patients of pancreatic cancers. However, the staging determined by CT is accurate in only 50-66% of cases, primarily because of underestimation of locoregional tumour extension in the form of peripancreatic microinvasion, lymph node metastasis and inability to detect small hepatic or peritoneal metastatic nodules. Also, the detection of tumours less than 1 cm is almost impossible.[24] In our study, all patients were staged based on triple phase MDCT done as per pancreatic protocol. The mean size of tumour based on CT and intra-operative findings was 2.76 and 3.02 respectively. This is almost comparable to mean tumour size of 3.6 and 3.1 cm reported by two studies. The lesion was identified in all the patients on MDCT, the accuracy in identifying pancreatic cancer being 100%. Vargas et al reported the accuracy of MDCT in diagnosing pancreatic cancer as 84% and Tummala et al reported it as 76-92%.[7,21] There was no statistically significant difference in the size of tumour identified on CT as compared to intra-operative finding. The accuracy of MDCT in detecting absence of vascular invasion was 100%. Lu et al, O'Malley et al and Vargas et al reported

the accuracy of CT in predicting vascular invasion by pancreatic tumour as 94%, 92% and 99%.[7-9]

Overall resectability of pancreatic cancer is influenced by presence of vascular invasion, lymph node metastasis, liver and peritoneal metastasis and presence of malignant ascites. In our study, four (11.7%) patients were found to be unresectable because of presence of distant metastasis on staging laparoscopy and hence did not undergo laparotomy. One of them was found to have subcentimeteric liver surface nodules. One patient had ascites and multiple peritoneal nodules. Two patients were identified to have multiple subcentimeteric peritoneal nodules. All these patients were later confirmed as having metastatic deposits from adenocarcinoma on histopathological examination. None of the patients deemed resectable on laparoscopy was found to have unresectable disease at laparotomy. Thus, our study revealed NPV of MDCT in predicting liver metastasis, peritoneal metastasis and overall unresectability as 97%, 91% and 88% respectively. Karmazanovsky et al have reported correlation of CT resectability with intra-operative findings in 83% patients. The NPV in determining unresectability in their study was found to be 91% whereas Vargas et al found the same to be 87%.[7,25] John et al in their study reported that liver metastasis and peritoneal metastasis on pre-operative laparoscopy were seen in 25% and 20% of patients thought to be resectable on CT respectively.[6] Because of these reasons, pre-operative laparoscopy is practiced at various institutions which can prevent unnecessary laparotomies in 10-30% of HOP lesions and upto half of lesions involving body/tail of pancreas. Laparoscopy with laparoscopic Ultrasonography (LUS) has been found to further increase the accuracy in predicting resectable disease to around 98%.[26] However, in our study, LUS was not performed because of lack of availability at our centre.

Other imaging modalities like MRI/MRCP, FDG-PET, EUS and ERCP are usually used as an adjunct to MDCT in evaluation and staging of pancreatic neoplasms. MRI does not have significant diagnostic advantage over MDCT (sensitivity of 84% on MRI versus 86% on CT).[27] The role of FDG-PET in evaluation of pancreatic neoplasms is uncertain. The data published on this topic has had conflicting results. Few studies have found that FDG-PET is useful in identifying metastatic disease not picked up by CT whereas few other studies suggest that it misses small volume peritoneal/liver metastasis.[21,28,29] EUS has been found to have highest accuracy in assessment of size of tumour and lymph node involvement as compared to MDCT. Legmann et al have reported that accuracy in prediction of unresectability in pancreatic cancers in not significantly different in EUS as compared to CT (86% and 100% respectively).[30,31] Pre-operative tissue diagnosis is not mandatory before performing resectional surgeries in suspected pancreatic neoplasms as the imaging studies can categorize the lesion with good accuracy. The tissue diagnosis is mandatory in patients planned for neo-adjuvant or palliative therapy.[32] The limitation of our study is relatively small sample size due to less incidence of operable pancreatic cancers in study population and the study being single centre study.

CONCLUSION

MDCT is the imaging modality of choice in pancreatic cancers which accurately identifies the size and site of pancreatic cancer and absence of vascular invasion when compared with operative findings. However, it fails to identify some unresectable diseases due to presence of distant metastasis in the form of liver/peritoneal metastatic nodules and malignant ascites. Abnormally high pre-operative CA 19-9 values have a definitive role in predicting metastatic pancreatic cancers. Staging laparoscopy is a useful procedure which prevents unwanted laparotomy in some cases of metastatic pancreatic cancer not identified on imaging.

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