REVIEW ARTICLE

Indications for staging laparoscopy in pancreatic cancer

Antonella De Rosa, Iain C. Cameron & Dhanwant Gomez

Department of Hepatobiliary and Pancreatic Surgery, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Abstract

Background: To identify indications for staging laparoscopy (SL) in patients with resectable pancreatic cancer, and suggest a pre-operative algorithm for staging these patients.

Methods: Relevant articles were reviewed from the published literature using the Medline database. The search was performed using the keywords 'pancreatic cancer', 'resectability', 'staging', 'laparoscopy', and 'Whipple's procedure'.

Results: Twenty four studies were identified which fulfilled the inclusion criteria. Of the published data, the most reliable surrogate markers for selecting patients for SL to predict unresectability in patients with CT defined resectable pancreatic cancer were CA 19.9 and tumour size. Although there are studies suggesting a role for tumour location, CEA levels, and clinical findings such as weight loss and jaundice, there is currently not enough evidence for these variables to predict resectability. Based on the current data, patients with a CT suggestive of resectable disease and (1) CA 19.9 $\geq$150 U/mL; or (2) tumour size >3 cm should be considered for SL.

Conclusion: The role of laparoscopy in the staging of pancreatic cancer patients remains controversial. Potential predictors of unresectability to select patients for SL include CA 19.9 levels and tumour size.

Received 20 May 2015; accepted 26 August 2015

Correspondence

Dhanwant Gomez, Department of Hepatobiliary and Pancreatic Surgery, E Floor, West Block, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, United Kingdom. Tel: +44 0 115 9249924. Fax: +44 0 115 8493398. E-mail: dhanny.gomez@nuh.nhs.uk

Introduction

Pancreatic cancer is associated with a poor prognosis, with 5-year survival rates of only 10% following resection with curative intent.[1–4] Surgery is offered to patients without evidence of locally advanced or metastatic disease, which accounts for only 15–20% of patients at diagnosis. Accurate staging is essential for treatment planning, and high-resolution, contrast-enhanced spiral computed tomography (CT) is the mainstay in determining resectability,[5] being able to predict resectability in >75% of patients.[6] Despite this, a proportion of patients have occult metastatic disease, where hepatic or peritoneal metastases are not identified.[7]

Staging laparoscopy (SL) is a minimally invasive modality for staging pancreatic cancer in patients at high-risk of unresectable disease despite CT evidence of resectable disease,[6] and can identify occult metastases in 15–51% of cases.[8] Some authors argue against using SL routinely, as the proportion of patients found to have metastatic disease at laparoscopy is decreasing due to the increased sensitivity of CT.[6,9,10] Currently, there are no standard criteria for selecting patients who may benefit from SL as part of their pre-operative staging.

The aim of this review is to identify indications for SL in patients with resectable pancreatic cancer, and suggest a pre-operative algorithm for staging these patients.

Methods

An electronic search was performed of the Medline database for the period 2000–2014 using the MeSH headings: "pancreatic cancer" and "staging." The search was limited to English language publications and human subjects. All titles and abstracts were reviewed, and appropriate papers further assessed. The reference sections of all papers deemed appropriate were further reviewed to identify papers missed on the primary search criteria.

Studies were included if: (i) they investigated resectability in patients with pancreatic cancer; (ii) CT was used for pre-operative staging; (iii) studies investigated features suggestive of unresectable disease despite pre-operative staging suggestive of resectable disease; (iv) resectability was ultimately determined operatively (either laparotomy or laparoscopy); (v) a minimum of 20 patients were included; and (vi) data was published after 2000. Only studies published after 2000 were included as this coincides with the introduction of multi-detector CT (See Fig. 1).

Data collated included predictors of resectability, staging modalities used and outcomes at exploration. Case reports, editorials, abstracts and reviews were excluded.

Results

Tumour markers

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are serum tumour markers used in the management of pancreatic cancer. Both tumour markers have limitations with respect to specificity, being elevated in other cancers and benign disease.[11,12] In addition, CA 19-9 is undetectable in 4–15% of the population with a Lewis negative (a^-,b^-) phenotype,[13] and is increased in the presence of hyperbilirubinaemia, which makes interpretation in the presence of obstructive jaundice difficult.[14,15]

Predictor of resectability

Several researchers have demonstrated a correlation between CA 19-9 levels and advanced disease,[16,17] and resectability.[12,18,19]

A study by Mehta *et al.* of 49 patients with resectable pancreatic cancer on CT, demonstrated that CA 19-9 and CEA levels of >3 times above the upper limit of normal had an increased risk of inoperability at laparotomy.[20] More recently, Koenigsrainer and co-workers observed a significantly higher CA 19-9 level in pancreatic cancer patients (n = 29) with peritoneal carcinomatosis, compared to patients matched for clinico-pathological factors that had resectable disease (2,330 U/ml *versus* 387 U/ml; p = 0.041).[21]

Determination of a cut-off value for resectability

Numerous authors have attempted to determine a cut-off value for CA 19.9 and CEA as markers for advanced/metastatic disease in patients with a CT suggestive of resectable disease (Table 1). Such a cut-off value could be used to stratify patients according to risk of unresectable disease, and used as an indication for SL.

In a study by Kilic *et al.* of 51 patients with assumed resectable pancreatic cancer on CT, 33 patients had unresectable disease at laparotomy.[22] The median CA 19-9 levels of these patients was 622 U/mL compared to 68.8 U/mL for patients with resectable disease. When a CA 19-9 level of 256.4 U/mL was used as a cut-off, the specificity and sensitivity was 92.3% and 82.4% respectively. In a similar study of 89 patients by Schlieman *et al.*, the mean adjusted CA 19-9 levels were significantly lower for patients with resectable disease compared to patients with locally advanced (63 U/mL *versus* 592 U/mL; p = 0.003), or metastatic (63 U/mL *versus* 1387 U/mL; p < 0.001) disease. With a threshold adjusted CA 19-9 level of 150 U/mL, the positive predictive value for determining unresectable disease was 88%.[23] Interestingly, the authors found no association between CEA levels and unresectability. Zhang *et al.*, reported the median CA 19-9 levels in patients with unresectable disease was 5× higher when compared to patients with resectable disease (p < 0.01) in a study of 104 patients.[24] When a cutoff value of 353.15 U/mL was used, the sensitivity and specificity were 93.1% and 78.3%, respectively.

Although the combined role of CEA and CA 19-9 levels for diagnosis and recurrence in pancreatic cancer have been previously investigated,[25–28] their combined role in determining resectability in patients with resectable disease on CT is less well defined. In a study by Fujioka *et al.*, of 244 patients who underwent surgery for potentially resectable disease, a combined negative CEA and CA 19.9 predicted resectibility in 85%.[19] They reported cut-off values for resectability of 157 U/ml and 5.5 ng/ml for CA 19-9 and CEA respectively. Similarly, Kim *et al.*, in a study of 72 patients, of whom only 24 (33.3%) had completely resectable disease intra-operatively, calculated optimum cut-off values of CEA and CA 19.9 to predict resectability was 2.47 ng/mL and 92.77 U/mL, respectively.[29]

Table 1 Published studies on CA 19.9 cut-off values to predict resectability. SL: Staging laparoscopy

Study	n	CA 19.9 level	Type of surgery to determine resectability	Positive predictive value	Sensitivity	Specificity
Kilic *et al*. 2006	51	256.4 U/mL	Laparotomy	91.4%	82.4%	92.3%
Schlieman *et al*. 2003	89	150 U/mL	Laparotomy	88%	71%	68%
Zhang *et al*. 2008	104	353.15 U/mL	Laparotomy	84.38%	93.1%	78.3%
Fujioka *et al*. 2007	244	157 U/ml	Laparotomy	–	69.2%	58.7%
Kim *et al*. 2009	72	92.77 U/mL	Laparotomy	–	67.8%	75.0%
Karachristos *et al*. 2005	63	100 U/ml	SL	–	100%	64%
Maithel *et al*. 2008	262	130 U/ml	SL	–	50%	74%
Connor *et al*. 2005	159	150 U/ml	SL	95%	44%	88%
Halloran *et al*. 2008	164	150 U/ml	SL	79%	52%	93%