Dr. Morris-Stiff: the diagnosis and management of pancreatic adenocarcinoma

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Expert introduction

Dr. Morris-Stiff (*Figure 1*) graduated from the University of Wales College of Medicine in 1992 and obtained his FRCS in 1997, chosing the specialty of hepato-pancreatico-biliary surgery as his clinical domain. He trained in HPB and laparoscopic surgery in Cardiff, as well as in Birmingham and Leeds, and also undertook an American HPB Association Clinical Fellowship in HPB Surgery at the Cleveland Clinic. He is currently an Assistant Professor in the department of HPB surgery at the Cleveland Clinic, Cleveland, Ohio.

Figure 1 Dr. Gareth Morris-Stiff.

Interview

HBSN*: *Do you have an algorithm for the radiological investigation of patients suspected of having pancreatic cancer?

Dr. Morris-Stiff: For a patient attending the clinic or emergency department with painless obstructive jaundice, I favour a pancreas protocol CT scan with intravenous and oral contrast that includes portal venous and arterial phases. In addition to excluding metastatic disease, the CT scan allows full assessment of the relationship between the tumour and the porto-venous system as well as the superior mesenteric artery. This is critical as it determines the resectability of the lesion (resectable, borderline resectable, locally-advanced or metastatic) and this in turn allows provision of the appropriate treatment algorithm. Some centres prefer a pancreatic MRI as the primary imaging modality and this is comparable in accuracy to CT. In my institution we reserve the later for patients in whom a mass is not identified on CT or patients with a contrast allergy unable to undergo CT. It is preferable that these scans are performed within a pancreatic centre of excellence and interpreted by radiologists specializing in pancreatic disease as this improves the accuracy of the interpretation. They should also be performed within 1 month of resection, as there is otherwise a risk of disease progression and inaccurate staging.

HBSN: Do you routinely use endoscopic ultrasound?

Dr. Morris-Stiff: Historically, I would have said no. I used to use endoscopic ultrasonography (EUS) primarily in patients with obstructive jaundice in whom cross-sectional imaging had failed to reveal a mass as I feel that with modern CT and MRI, these modalities are usually good enough to identify vascular invasion. However, at our institution, and many others, we try and enroll patients into clinical trials and for these a tissue biopsy is require pre-therapy and so EUS is enjoying increasing usage. This is the case for borderline resectable lesions for some time and trials are now opening for neoadjuvant therapy for resectable tumours.

HBSN*: *What about PET-CT imaging for pancreatic cancer?

Dr. Morris-Stiff: Personally, I do not feel that PET-CT imaging offers a great deal of advantage over cross-sectional imaging in the initial diagnosis of pancreatic adenocarcinoma and the literature available certainly does

not support its routine use. There are strong proponents for its use in all cases, but I think it may have a more targeted role such as: patients whose cross-sectional imaging was non-diagnostic; patients with small lesions that are inconclusive on CT/MRI; and monitoring for recurrence when CA 19-9 is high but no mass is seen. I think that the new modality of PET-MRI may be of more value and this is currently being evaluated at our institution.

***HBSN**: Could you give us a brief overview of how you select patients for surgery?*

Dr. Morris-Stiff: In 2017, the selection process for pancreatic cancer resection can no longer simply be what the surgeon determines appropriate. All patients should be discussed in a multidisciplinary team (MDT) meeting consisting of clinicians with a specialist interest in pancreatic cancer or the broader field of HPB disease. There are several elements to patient selection. Firstly is the resectability of the tumour based on imaging studies. The next is to determine if the patient is suitable for the proposed intervention. In this regard we consider the performance status of the patient (ECOG), their co-morbidities as related to fitness for surgery, and an assessment of patient frailty. A patient may have a resectable tumour but may be 'borderline' in terms of suitability for resection based on the aforementioned factors. These need to be taken into consideration in terms of patient consent and provision of morbidity and mortality estimates. Frailty is important to assess, as this is open to modification before intervention. In patients with pancreatic cancer, frailty may be transient as a result of factors such as jaundice and weight loss. In this regard, the insertion of a stent, and commencement of pancreatic enzyme replacement surgery may allow the patient to become less frail and thus a better candidate for surgical intervention, a process known as prehabilitation.

HBSN: How has the treatment of pancreatic cancer evolved over time, especially in terms of surgical treatment?

Dr. Morris-Stiff: To be honest, unlike hepatic surgery where there have been marked changes in operative technique over the past two decades, there have been few alterations in relation to the surgical management of pancreatic cancer over the past 50 years. The technique of pancreatoduodenectomy (PD) has been and factors such as sparing or resection of the pylorus and pancreatogastrostomy or pancreatojejunostomy have been evaluated in randomized controlled trials (RCTs) and found to be comparable. Other factors such as: the use of stents; use of Octreotide; and surgical techniques (method of pancreatojejunostomy; route of reconstruction of gastric/duodenal-jejunal anastomosis; handsewn versus stapled) have also been assessed and shown to provide no benefit. Two areas that have shown positive results are the use of Pasireotide and the addition of a Braun jejunojejunostomy. Of late, the use of laparoscopic and robotic surgery for PD has been explored and shown in meta-analysis to be safe and oncologically sound, with potential benefits of reduced length of stay and reduced blood loss, but it takes longer and the complication rates are similar. To date these minimally invasive procedures have been performed in tertiary centres and so it waits to be seen if these techniques are adapted uniformly. For pathologies in the tail of the pancreas, laparoscopic distal pancreatectomy has become the standard of care. For pancreatic cancer, many tumours of the body and tail are amenable to laparoscopic surgery but many prefer an open approach for patients with pancreatic cancer. The latest adaptation of care is the incorporation of enhanced recovery after surgery (ERAS) pathways. With pre-operative patient education and optimisation together with early ambulation and opiate avoiding regimens, the length of stay following PD can be cut to 4 or 5 days, something that would have been unheard of when I commenced training in the 1990's.

***HBSN**: How do you approach borderline pancreatic cancer?*

Dr. Morris-Stiff: In our institution as in many, patients with borderline cancer are offered recruitment into a trial of neoadjuvant chemo-radiation. The patients undergo a diagnostic laparoscopy and if negative are commenced on radiotherapy with chemosensitization using capecitabine. After completion of radiotherapy they undergo a CT scan and if no contraindication they continue on to chemotherapy using a Folfirinox regimen. After this they are re-staged, and in the absence of disease progression are offered exploration with a view to resection. In some cases it is difficult on imaging to discern between tumour and fibrosis and so unless there is clear disease progression these patients are explored and multiple biopsies performed of suspicious tissue prior to commitment to resection. In cases in which there was evidence of mesenteroportal venous involvement pre-therapy, there is a likelihood that a venous resection may be required to achieve tumour clearance and

so it is important that this is incorporated into the operative planning rather than as an afterthought. Some patients however do not want to consider neoadjuvant therapy and in which case an upfront resection may be performed, but again there is likelihood that a venous resection may be required in order to obtain a negative margin.

HBSN*: *Are there any controversial aspects to the pancreatic cancer surgery?

Dr. Morris-Stiff: One new technique that has shown promise as a potential means of improving outcome is the use of an arterial first approach, targeting dissection of the superior mesenteric artery prior to dissection of the gland. It has been proposed that this technique leads to reduced manipulation of the tumour and provides an improved dissection of the tumour from the mesenteric vessels thus potentially achieving better tumour clearance.

A second area previously regarded as being controversial is the pathological assessment of pancreatic head lesions. Caroline Verbeke and colleagues redefined the assessment of PD specimens such that a margin <1 mm should be regarded as a positive margin and not a negative one as previously. The group also stressed the importance of assessment of tissue margins in particular the retroperitoneal margins and showed that this margin is frequently positive in pancreatic cancer as a result of the disease biology and careful assessment rather than a failing of surgery.

Another controversial area relates to pancreatic fistulae. The ISGPS recently changed the classification such that grade A fistulae are now regarded as biochemical leaks. Also in relation to fistula development is the use of drains. There is accumulating data that drains she be removed early on day 3 based on day 1 drain amylase levels. The use of the validated Fistula Risk Score allows prediction of risk for the development of a pancreatic fistula and it is being proposed that those with a low risk of fistula may not need a drain at all.

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HBSN: In your opinion, what are the challenges facing the management of pancreatic cancer?

Dr. Morris-Stiff: The main challenge in the management of pancreatic cancer is the identification of improved neoadjuvant and adjuvant therapies. For a long time the available agents had low response rates, however the early results of studies including Folfirinox and Gemcitabine-Abraxane regimens would suggest that these combinations lead to improve survival. In addition to these agents, newer therapies such as immunotherapy are being evaluated and may be of value. As well as the ESPAC 5 study comparing upfront resection and neoadjuvant therapy (chemotherapy or chemoradiotherapy), there are several studies looking at neoadjuvant therapy in resectable pancreatic cancer including the SWOG sponsored study comparing Folfirinox with Gemcitabine-Abraxane currently recruiting in the US. There are also several randomized controlled trials in this field ongoing in Europe. In addition, there are also interesting data in relation to adjuvant therapy from the Japan (JASPAC 01) that showed that the 5-year survival for the drug S-1 [an oral 5-fluorouracil (5-FU) prodrug] was 44% which was significantly greater than the 24% seen with gemcitabine. Data on the role of immunotherapy including the role of the PD1 inhibitor Pembrolizumab are also eagerly awaited.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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