### Laparoscopic staging in patients with newly diagnosed pancreatic cancer.

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### Abstract:

Prompt accurate staging is paramount in managing patients with newly diagnosed pancreatic cancer. Initially diagnosis and staging are undertaken using contrast enhanced, multi-detector computerized tomography (CE-MDCT) or magnetic resonance imaging (MRI), supplemented with endoscopic ultrasound in selected cases. Staging laparoscopy (SL) with or without laparoscopic ultrasound (L-LUS) has been found to detect occult disease in 13-28% of patients with pancreatic cancer who are considered potentially resectable on imaging, however, between 1 and 30% of patients thought to be resectable on SL/L-LUS have subsequently been found to have unresectable disease. The clinical utility of SL/L-LUS can be enhanced by adopting a selective approach; only undertaking SL/L-LUS when one or more criteria are present, including: (1) presumed pancreatic primary >3 cm diameter, (2) lesions in the body and tail of the pancreas (3) CA 19-9 > 150 kU/L (>300 when total bilirubin >35 micromol/L), (4) platelet/lymphocyte ratio >150. The judicious use of SL/L-LUS and cross sectional imaging are complementary, however the advent of PET-CT may lead to improvements in the detection of small previously radiologically occult metastases and may reduce the future role of SL/L-LUS.

Keywords pancreas - pancreatic cancer - laparoscopy - laparoscopic ultrasound - diagnosis – staging.

**Introduction**

It is clear that over the last 15 years a combination of better staging, surgical refinement and standard use of adjuvant chemotherapy has achieved an unprecedented increase in survival of patients with pancreatic cancer, who have had surgery to around 30% at 5 years

[1-4]. The importance of diagnosis and staging in the management of pancreas cancer becomes evident when surveying the outcome of patients with localized versus advanced disease.

Given the marked differences in survival between those who undergo potentially curative resection compared to those who cannot, accurate selection of patients for surgery is essential. Accurate selection for potentially curative resection will ensure this is undertaken in only patients who will benefit, and major abdominal surgery avoided in the vast majority of those who will not.

A variety of imaging strategies have been studied to determine the optimal approach to diagnosis and staging of suspected pancreatic cancer

[5-15]. Contrast enhanced multidetector computerized tomography (CE-MDCT), magnetic resonance imaging (MRI with or without magnetic resonance cholangiopancreatograpy, MRCP), endoscopic ultrasound (EUS) and staging laparoscopy with or without laparoscopic ultrasound (SL/L-LUS) have all been compared, and each have their protagonists. Current recommendations

[4,16,17] agree on a standard approach making use of abdominal imaging with CE-MDCT performed according to a defined pancreas protocol with dual arterial and portal venous contrast phases, supplemented selectively with other adjuncts including MRI/MRCP and EUS

[4]. PET-CT is considered an additional diagnostic adjunct to CE-MDCT and MRI, not a substitute for these modalities

[4]. SL/L-LUS is only considered a selective adjunct to diagnosis and is not routinely included in any of the current major international guidelines.

## 1. Background to Staging and Assessment by Radiological Imaging

Contrast enhanced multidetector computerized tomography (CE-MDCT) is the "gold standard" for clinical/radiological staging, since the reported accuracy of CE-MDCT using 2D and 3D algorithms in predicting resectability can exceed 95%, with a sensitivity of 94% and a specificity of 89%

[5,7,11,14,18]. Resectability rates may however, appear artificially high if surgeons adopt a more conservative approach, operating only on easy cases and do not attempt resection in borderline resectable cases. Nevertheless, in the hands of experienced pancreatic radiologists using CE-MDCT, local tumour extension, vascular involvement, lymph node and liver metastases correlate closely with surgical findings

[14].

MRI using ultra-high-field magnetic resonance has been reported to be superior to CT in the detection of non-contour deforming masses (small pancreas cancers) due to its superior soft tissue contrast

[6,8]. MRI may also be preferable for characterizing small liver and peritoneal/omental metastases

[6]. MRI, MRI spectroscopy and MRI functional imaging are under development to distinguish malignant from benign pancreas tumours, using protocols based on signal intensity

[15], but these techniques are yet to gain a place in optimal standard staging approaches.

EUS with or without fine needle aspiration biopsy (FNA) has been found in one study to be highly accurate in diagnosing pancreas cancer (99%) with 88% sensitivity, 100% specificity, 100% PPV and 99% NPV in patients with ambiguous CT findings

[9]. These impressive results, however, were retrospective, and surgical confirmation of diagnoses was available in only a small proportion of these patients. EUS has the advantage of enabling biopsy, but a negative FNA does not exclude cancer and the approach is highly operator-dependent. Although EUS is the preferred biopsy route rather than percutaneous image guided approaches, a decision to operate does not require histological confirmation, although this is required prior to administration of neoadjuvant or palliative chemotherapy

[4,19].

PET-CThas recently emerged as a new imaging modality in pancreatic cancer. PET-CT is found to have a similar sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in evaluating primary tumours as CE-MDCT

[10,20,21], EUS

[13,22] and MRI

[20], Indicating that PET-CT does not add to the determination of resectability of local disease. However, the majority of this evidence is from small, single centre, retrospective studies. The true value of PET-CT may lie in its ability to detect metastatic disease, with studies showing it to have a much greater sensitivity than MDCT or MRI; altering proposed surgical management in 10-45% of patients deemed resectable post MDCT/MRI

[20,23,24]. In addition it has significant advantage in diagnosing invasive transformation within pre-malignant lesions

[25], such as intraductal papillary mucinous neoplasms The full published results of the multi-centre, prospective PET-PANC trial are awaited; however preliminary data demonstrates significantly improved sensitivity (92.7% v 88.5%, p=0.010) and specificity 75.8% v 70.6%, p=0.023) of FDG PET/CT over MDCT in diagnosing pancreatic cancer. FDG PET/CT correctly changed staging in 14% of patients and influenced the management of 45% of patients in the trial, importantly preventing futile attempted resection in 20% of patients due to undergo surgery [26].

Despite these significant advances in imaging techniques, even with state of the art machines, metastatic lesions <5mm may still not be detected, as is often the case in small hepatic and peritoneal deposits. Presence of these deposits would likely render the otherwise radiologically resectable or borderline resectable patient irresectable and thus preclude the need for an ultimately futile laparotomy. This has a cost benefit but more importantly a benefit to the patient allowing prompt initiation of alternative treatment pathways i.e. neoadjuvant or palliative treatment. SL/L-LUS as an adjunct to radiological staging enables direct visualisation of the peritoneal cavity thus providing an opportunity to identify these small lesions and simultaneously assess local resectability particularly with respect to vascular structures. The rational for SL/L-LUS is that it enables: 1) Confirmation of diagnosis when in doubt; 2) The detection of radiological occult metastasis including biopsy of suspicious lesions; 3) Assessment of local resectablity and 4) Peritoneal cytology. SL/L-LUS aims to prevent unnecessary operations which: 5) Decrease patient morbidity; 6) Enables prompt initiation of more appropriate treatment pathway i.e. chemotherapy and 7) Provides more cost effective/patient acceptable disease management.

**2. SL/L-LUS in Potentially Resectable Patients**

As is implicit in the discussion above, SL/L-LUS is an aid to diagnosis and staging, but not a *sine qua non*. It must be remembered that laparoscopy is an invasive procedure requiring general anaesthetic and the relative absence of adhesions from prior disease or interventions to fully inspect the peritoneal cavity. Even then the view of the peritoneum is an extensive sampling rather than a complete inspection, and as regards the liver, small metastases (5 mm diameter or less) are only likely to be identified on the capsular surface. Larger liver metastases can be identified with a laparoscopic ultrasound (LUS) probe, an examination which requires gentle, systematic and complete liver scanning; although, larger metastases should be identified pre-operatively by an up-to-date CE-MDCT or MRI. In addition, LUS can be used as an adjunct when assessing local respectability by helping to delineate vessel encroachment. The guidelines published by the British Society of Gastroenterology and other UK specialist societies in 2005 recommend that when available, SL/L-LUS may be appropriate in selected patients with pancreas and peri-ampullary cancer (recommendation grade B) [27], although the practice is not yet generally incorporated in other international guidelines

[4,16,17]. SL/L-LUS has been found in studies, from specialist pancreatic centres, to identify occult advanced and metastatic disease in 13-58% of patients considered resectable on radiological grounds, the majority of failures to detect occult disease are due to failure to appreciate fully the degree of vascular involvement in locally advanced cases rather than missed liver or peritoneal metastases (see *Table* *1*). Most of these studies are highly selected and designed to answer specific questions: Role of pre-operative cancer antigen 19-9 / sialylated Lewis (a) antigen (CA19.9) in selection of patients for staging

[28,29]; pre-operative inflammatory markers

[30]; sub-sets of peripancreatic cancers

[31] or cost effectiveness

[32]. To date there are no randomised clinical trials looking at the use of laparoscopy. There has been 1 meta-analysis and 3 systematic reviews reviewing the role of laparoscopy following imaging for “resectable” pancreatic cancer. Hariharan et al in 2010

[33] looked at the benefit of SL/L-LUS in 2827 patients across 22 studies with radiologically resectable pancreatic/peripancreatic cancer. Results from this analysis showed the pooled sensitivity and specificity of SL/L-LUS for the detection of liver and peritoneal lesions to be 88% (95% CI 83-92) and 92% (95% CI 84-96) respectively. However, sensitivity for detection of locally advanced disease was poor: 58% (95% CI 51-65). The pooled yield of SL/L-LUS, i.e. proportion of patients in whom unnecessary laparotomy was avoided, was 25%. A Cochrane review, undertaken by Allen el al in 2013 reported similar results

[34]. This included 15 studies with a total of 1015 patients diagnosed with resectable pancreatic/periampullary cancer following initial staging CT scan. They reported a pooled sensitivity for SL/L-LUS of 68.7% (95% CI 54.3% to 80.2%). From the included studies the authors calculated a median pre-test probability for unresectable disease of 0.403.

Table 1. Identification of metastatic disease with SL/L-LUS in patients considered potentially resectable on radiological grounds

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Technique** | **Resectable patients (imaging)** | **Patients undergoing** **L / LUS**  | **Patients unresectable on L /LUS (%)** | **Patients undergoing surgical exploration following L / LUS (%)** | **Non-resected (missed occult disease) following** **L / LUS (%)** | **Patients who underwent resection following L / LUS (%)** |
| Taylor et al. 2001 [35] | L-LUS | 51 | 51 | 21 (41%) | 24 (47%) | 2 (4%) | 20 (39%)\* |
| Menack et al. 2001 [36] | L-LUS | 27 | 27 | 7 (26%) | 20 (74%) | 2 (7%) | 18 (67%) |
| Vollmer et al. 2002 [31] | L-LUS | 157 | 153 | 37 (24%) | - | - | - |
| Nieveen et al. 2003 [37] | L-LUS | 297 | 286 | 39 (13.6%) | Resectable: 197 (69%)Borderline: 31 (11%) | Resectable: 52 (18%)Borderline: 20 (7%) | Resectable: 145 (51%)Borderline: 11 (4%) |
| Doran et al. 2004 [38] | L-LUS  | 190 | 190 | 28 (15%) | 158 (83%) | 33 (17%) | 127 (67%) |
| Thomson et al. 2006 [39] | L-LUS | 154 | 152\*\* | 56 (37%) | 87 (57%) | 25 (16%) | 62 (41%) |
| Doucas et al. 2007 [40] | L-LUS | 75 | 75 | 28 (37%) | 37 (49%) | 22 (29%) | 15 (20%) |
| Halloran et al. 2008 [28] | L-LUS | 164 | 70 | 9 (13%) | Resectable: 37 (53%)Borderline: 24 (34%) | Resectable: 7 (10%)Borderline: 17 (24%) | Resectable: 30 (43%)Borderline: 7 (10%) |
|  |  |  |  |  |  |  |  |
| Ahmed et al. 2006 [41] | L | 59 | 37 | 9 (24%) | 28 (76%) | 4 (11%) | 24 (65%) |
| White et al. 2008 [42] | L | 1045 | 1045 | 145 (14%) | 900 (86%) | 9 (1%) | 891 (85%) |
| Shah et al. 2008 | L | 88 | 19 | 9 (47%) | 8 (42%) | 1 (5%) | 7 (37%) |
| Enestvedt et al. 2008 [32] | L | 298 | 86 | 24 (30%) | 62 (72%) | 16 (19%) | 46 (53%) |
| Contreras et al. 2009 [43] | L | 77 | 25 | 7 (28%) | 18 (72%) | 3 (12%) | 15 (60%) |
| Satoi et al. 2011 [29] | L | 61 | 16 | 5 (31%) | - | - | 11 (69%) |
| Lavy et al. 2012 [44] | L | 52 | 52 | 5 (10%) | 47 (90%) | 9 (17%) | 38 (73%) |
| Garcea et al. 2012 [30] | L | 157 | 137 | 22 (16%) | - | - | - |
| Schnelldorfer et al. 2014 [45] | L | 274 | 136 | 3 (2%) | 133 (98%) | 12 (9%) | - |

Does not include Connor et al, 2005

[46] or Smith et al, 2008

[47] as these reports include patients included in

[28,38]

This would equate to 23% of patients avoiding an unnecessary laparotomy post SL/L-LUS

[34]. The authors recognised the potential impact of advances in CT scan technology and adjusted for this by performing a posthoc meta-regression of studies published before and after the year 2000 and found no statistically significant difference. This was reviewed by the same group again in 2016 [48], with 16 studies, confirming a similar result (avoidance of 21 unnecessary laparotomies). Levy et al. in 2016

[49] performed a systematic review of prospectively conducted studies assessing the accuracy of SL/L-LUS in assessing the resectability of pancreatic tumours, comparing the predicted resection rates of SL/L-LUS with standard preoperative imaging and determining how the accuracy of these modalities has evolved over time. 19 prospective studies met the inclusion criteria including 1,573 patients, 11 of these studies were performed after January 2000 in the MDCT era. Overall SL/L-LUS improved the resection rate of pancreatic malignancies from 55% to 79% over standard preoperative imaging, preventing non-curative laparotomy in 33% of study patients, with no increase in mortality and only a 0.8% complication rate. The added benefit of LUS to staging laparoscopy was directly addressed in 3 studies [50-52], which collectively showed a doubling of the yield of unresectable disease versus non-ultrasound laparoscopy alone. Subgroup analysis of: more recent studies (2009-2014), studies post January 2000 and studies comparing only MDCT imaging all demonstrated comparable findings with resection rates of 100% and 81% (2 studies), 74% and 58% (4 studies) and 100% and 78% (1 study) for SL/L-LUS versus MDCT respectively.

All of these reviews acknowledge significant study heterogeneity, particularly with regard to resectability criteria, requirement to offer surgery for gastric outlet obstruction prior to routine use of duodenal stenting, multimodal imaging protocols and the quality of CT technology.

**2.1 Selective Criteria for SL/L-LUS**

The advent of the MDCT era and more accurate preoperative imaging assessment of resectability results in a larger number of SL/L-LUS required to be performed to prevent one unnecessary laparotomy, Friess et al demonstrate only 1 laparotomy is avoided for every 8 laparoscopies performed in patients with pancreatic cancer resulting in a reduction in the cost benefit relationship associated with SL/L-LUS

[53,54]. These findings led to questioning of the clinical utility of SL/L-LUS on a routine basis and suggested a move towards selective SL/L-LUS. In addition to equivocal radiological staging proposed criteria on which to select patients for SL/L-LUS include: tumour size, tumour location, with clinical and laboratory findings associated with risk of locally advanced disease or metastasis such as hypo albuminaemia, weight loss, raised Ca19.9 and back pain

[55].

2.1.1 CA19.9

Early work by Doran et al (2004) found SL/L-LUS to correctly identify unresectability in 28 (15%) of 190 patients considered potentially resectable on radiological (CE-MDCT) grounds

[38]. Subsequent work by Connor et al (2005), suggested that the utility of SL/L-LUS could be improved to detect unresectability in 20/78 (25%) of those considered potentially resectable, by selecting only those for SL/L-LUS with elevated CA19-9 levels above 150 kU/L, or above 300 kU/L in the presence of an elevated serum bilirubin (>35 micromol/L, to account for the effect of cholestasis)

[46]. This strategy was tested prospectively in a cohort of 164

[28] subsequent patients with potentially resectable disease on CE-MDCT. 94 patients (including 14 who had gastric outlet obstruction and a high CA19.9, who would need surgery regardless) went straight to surgery. 63 of the 80 (79%) with low CA19.9 were resected vs. 2/14 (14%) with high CA19.9 and symptoms. Alternately 70 patients went to L-LUS; this included 55 patients with high CA19.9 and 15 patients with low CA19.9 but with suspicious CT features. 9 patients (13%) were unresectable on L-LUS (1 patient with low CA19.9). 37 patients were considered resectable of whom 30/37 (80%) were resected; 28 with a high CA19.9 and 4 with a low CA19.9. The other 24 patients were thought to have features of borderline respectability (notably vascular contact/distortion); 7/24 (29%) were resected, 5 with a high CA19.9 and 2 with a low CA19.9. The sensitivity of L–LUS for detecting unresectable disease in patients with a high CA19·9 level was 33 per cent. This assumed that all borderline disease seen on L–LUS was resectable (*P* < 0·001). This remained the case even when borderline operable L–LUS disease was assumed to be inoperable, in which case the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for L–LUS in detecting unresectable disease became 52, 93, 79, 79 and 79 per cent respectively (*P* < 0·001)

[28]. These findings are supported by data from the Memorial Sloan-Kettering Cancer Center (MSKCC), in 262 patients with radiologically resectable pancreatic cancer, preoperative Ca19.9 > 130U/ml was strongly associated with the identification of unresectable disease (HR 2.70; 95% CI 1.34–5.44; P = 0.005)

[56].

2.1.2 Pancreatic tumour size and CA19-9

Satoi et al. selected patients for SL/L-LUS with both of the previously established risk factors for unresectable disease tumour size > 3cm

[57,58] and Ca19-9 >150 U/ml

[28,46,59]. Of 61 patients in this cohort, 16 patients underwent laparoscopy, 5 (31%) of which were unresectable. The remaining 11 patients were all resected. Only 4.4% of patients who did not meet the criteria for laparoscopy and went straight to laparotomy were found to have unresectable disease. The combination of tumour size > 3cm and Ca19.9 > 150 U/ml was significantly associated with disease unresectability (p=0.0147). The relatively high rate of vascular resection in this cases series may account for the high resection rates observed with 29% of patients undergoing either portal vein or coeliac trunk resection

[29].

2.1.3 Platelet / Lymphocyte Ratio

Smith et al (2008) hypothetically evaluated the addition of the platelet/lymphocyte ratio to the currently used Ca19-9 selection criteria. Platelet/lymphocyte (P/L) ratio >150 was used as a marker for a pro-systemic inflammatory response associated with tumour invasiveness

[47]. Based on the group of patients selected for SL/L-LUS on the basis of Ca19.9 alone they found the addition of platelet/lymphocyte ratio > 150 could improve both the sensitivity (96% v 51%) and positive predictive value (95% v 83%) of SL/L-LUS beyond that of Ca19-9 alone. This additional criterion would have reduced the number of SL/L-LUS by 21% at the expense of only a 5% false positive rate in those additional patients going straight to laparotomy, which is comparable to that seen in existing cohorts going straight to laparotomy. The combination of indices has still to be tested prospectively.

2.1.4 Pancreatic tumour location

The location of the tumour within the pancreas also affects the rate at which radiologically occult metastatic disease is identified relating to the fact that body and tail lesions usually present later due to a paucity of early symptoms compared with lesions in the pancreatic head

[60,61]. Two studies of SL/L-LUS have identified metastatic lesion twice as frequently when evaluating lesions in the body and tail of the pancreas compared with lesions in the head of the pancreas. Jimenez et al. identified metastasis in 39% of patients with body and tail lesions compared with only 17% of pancreatic head lesions

[62], whereas Liu et al. found metastases in 53% of body and tail lesions and 28% of pancreatic head lesions

[63]. The overall higher rate of metastasis detection by Liu et al reflects that their population only included patients with locally advanced radiologically unresectable pancreatic cancer patients. The utility of SL/L-LUS based on histological diagnosis, has also been analysed. Both found the incidence of radiologically occult unresectable disease was higher for pancreatic head lesions compared with duodenal or ampullary lesions. Vollmer et al. discovered metastatic disease or local invasion of vessels precluding resection in 31% of patients with radiologically resectable pancreatic head cancers at SL/L-LUS, in contrast no patients with carcinomas of the ampulla or duodenum were discovered to have either metastatic disease or locally advanced unresectable disease as a result of SL/L-LUS

[31]. White et al. confirm this observation finding unresectability in 17% of patients with potentially resectable pancreatic head adenocarcinoma imaged outside their institution, and 8% of patients imaged within their institution, in contrast only 4% of patients with “non-pancreatic” tumours were found to have unresectable disease

[42]. Both authors support only using SL/L-LUS in patients with pancreatic head cancers rather than peripancreatic disease, however, often a firm histological diagnosis is a retrospective finding only after the lesion has been resected and subjected to histological analysis and therefore the clinical significance of these studies may be limited.

Shah et al report their experience of selective use of SL/L-LUS in patients with MDCT presumed resectable pancreatic cancer based on 5 criteria: primary tumour >4 cm in diameter, weight loss >20%, ascites, CA19-9 > 1,000 kU/L or ambiguous findings on CE-MDCT. In their study SL/L-LUS avoided unnecessary laparotomy in 11 of 49 (22%) patients. This improved the positive predictive value of their staging protocol from 69% based on MDCT assessment alone to 89% based on MDCT and SL/L-LUS findings combined. Interestingly 49% of patients meeting their criteria for SL/L-LUS had radiologically questionable liver lesions on MDCT and in the current era MRI maybe a more appropriate and non-invasive modality by which to further characterise these lesions rather than SL/L-LUS.

## 3. Peritoneal Cytology at L/LUS

The value of peritoneal cytology obtained at SL/LUS for the staging of pancreatic cancer has been highlighted in work by Warshaw and colleagues at the Massachusetts General Hospital

[60,62,64-66]. This work suggests that the presence of pancreatic adenocarcinoma cells in peritoneal ascites or irrigation fluid (undertaken with 500 ml saline) is a feature of advanced disease (M1 on the TNM system), whether or not there is other evidence of unresectability. Such a classification is consistent with the 7th edition of the American Joint Committee on Cancer (AJCC) staging system, which classifies positive peritoneal cytology as stage IV disease for pancreatic adenocarcinoma [67]. Supporting this Merchant et al. demonstrated that positive peritoneal cytology had a positive predictive value of 94%, specificity of 98% and sensitivity of 25% for determining unresectability

[68]. Although reduced overall survival associated with positive peritoneal cytology has been shown in a number of studies, median survivals are similar to that of patients with stage IV disease

[69]. Yamada et al. demonstrated that resected patients with positive cytology had a significantly better survival (14.3 months) than patients with either cytology negative or positive unresectable disease (7.3 and 6.8 months respectively; both <0.001). Amongst patients with positive cytology, median survival was longer in those who underwent adjuvant chemotherapy rather than those who underwent surgery alone (15.3 v 10.0 months) although this did not reach statistical significance. Positive cytology did not independently predict survival in their study.

[70]. The significance of positive peritoneal cytology on overall and disease free survival has also been questioned in the setting of patients undergoing neoadjuvant chemotherapy prior to resection, although further research is required in this setting

[71] .

## 4. L/LUS in Radiologically Unresectable Patients

Many studies of the utility of SL/L-LUS have included patients with locally advanced unresectable disease

[62,63,66,72]. Two studies have included only patients with radiologically locally advanced unresectable disease due to vascular encasement

[63,73]. These studies found radiologically occult metastases on SL/L-LUS in 34%

[63] and 37%

[73] of patients. This distinction is clinically important in centres where patients with metastatic disease receive chemotherapy whereas those with locally advanced unresectable disease in the absence of metastases receive chemoradiotherapy. By diagnosing radiologically occult metastatic disease patients who will not benefit from chemoradiotherapy are spared the additional toxicity and time expenses associated with this therapy. On a population level correctly staging patients to stage IV disease rather than stage III disease allows a better understanding of treatment protocols and stage specific survival.

[73,74].

## 5. Cost Effectiveness of SL/LUS

An important issue in SL/L-LUS is its operational effectiveness, not least of which is cost. A cost study from the USA found that the use of SL/L-LUS in patients with pancreatic cancer does not add significantly to the overall expense of management: the cost for selective, routine use or no use was found to be $91,805, $90,888 and $93,134, respectively

[32]. By using pre- and post-test probabilities for unresectability

[34] a UK study developed a model based cost-analysis for SL/L-LUS in pancreatic cancer

[75] . Results of this analysis showed that laparoscopy prior to resection incurred similar cost per patient as proceeding straight to laparotomy, with the cost of the laparoscopy (£995) being offset by the savings of an unnecessary laparotomy (£7470; 95% CI £7215 -£7724 vs. £7480 95% CI £7219- £7741). Although, this was only the case if laparoscopy was performed at a separate sitting to the intended laparotomy as a positive SL/L-LUS conducted immediately prior to the intended laparotomy would result in a cancelled operation and thus wasted theatre resources. More importantly, however, this study showed that the Quality Adjusted Life Years (QALYs) were higher for SL/L-LUS compared to direct laparotomy (mean QALYs per patient 0.346 (95% CI 0.346 to 0.347) versus 0.337 (95% CI 0.337 to 0.338)) due to the morbidity associated with an unnecessary laparotomy

[75]. A similar model based cost-analysis using published data on unresectability post-laparoscopy was conducted by a group in the USA

[76]. In this study they also found an improvement in Quality of Life (QoL) when laparoscopy was performed prior to laparotomy and demonstrated a marginal cost saving (US$36,580 vs. US$46,830). As both these cost-analyses rely on pooled estimates from the current literature it’s unclear whether the application of more selective criteria to patient selection of SL/L-LUS as discussed above would result in improved cost-effectiveness.

The current evidence would suggest that SL/L-LUS is at least cost neutral and appears to be associated with a slight improvement in QoL. It would therefore appear that the choice of whether to use SL/L-LUS in staging relates to other practical considerations, such as management priorities and practices, staff, surgical and hospital resources, as well as additional uses to which laparoscopic approaches may be put to use; such as laparoscopic bypass surgery or evaluation of novel techniques or technologies (e.g. nano-device implantation). *Figure 1* indicates where SL/L-LUS sits in current treatment algorithms.

**Conclusion**

Current imaging protocols and technology have resulted in significantly improved sensitivity and specificity for the diagnosis of locally advanced unresectable or metastatic disease. This has resulted in a reduction in the utility of SL/L-LUS; as it correctly identifies unresectable disease in only 15% of an unselected radiologically resectable population with pancreatic cancer. This has led to the selective use of SL/L-LUS in patients considered at higher risk for metastatic or locally advanced cancers based on criteria such as: tumour size and location, elevation of Ca19.9 and questionable radiological findings. This selective use of SL/L-LUS has increased its positive predictive value back to 20-30%. Currently SL/L-LUS is of greatest clinical utility in assessing for liver or peritoneal metastases (sensitivity 88 and 92% respectively) and more limited in assessing locally advanced disease with vascular involvement (sensitivity 58%). The future use of SL/L-LUS will have to be continually re-evaluated in light of advancing imaging technology, namely FDG PET/CT that is shown to improve staging of patients in a large multicentre prospective trial. This improvement in staging is of the same magnitude as that seen for SL/L-LUS and it will be interesting to see if FDG PET/CT replaces the need for SL/L-LUS or finds a complimentary role alongside SL/L-LUS especially when combined with development in novel biomarkers. Development of future laparoscopic instruments, potentially incorporating confocal probes may lead to prospective data on regional and or distant lymph node metastases, potentially even allowing sampling of crucial groups, allowing yet further staging potential.

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*Figure 1.* Outlines a general algorithm to the management of pancreatic cancer, including selective application of L/LUS.

L-LUS = laparoscopy with laparoscopic ultrasound; CA19.9 = cancer antigen 19-9; Plt: Lym ratio = platelet: lymphocyte ratio and IRE = irreversible electroporation “Nanoknife™”.