



The current role of staging laparoscopy for patients with radiographically resectable pancreatic adenocarcinoma

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We read with great interest the paper recently published in the *Annals of Surgical Oncology* entitled “*Reappraisal of Staging Laparoscopy for Patients with Pancreatic Adenocarcinoma (PDAC): A Contemporary Analysis of 1001 Patients*” written by Fong *et al.* of Harvard Medical School (1). In this study, 331 PDAC patients (33%) underwent a staging laparoscopy (SL). Unnecessary laparotomy was prevented for 44.1% of the patients during 2001–2008, and for 24% during 2009–2014. They identified 5 independent predictors for occult metastasis such as (I) male gender (OR 1.8; $P < 0.05$); (II) preoperative resectability (borderline resectable OR 2.1; $P < 0.019$, locally advanced OR 7.6; $P < 0.001$); (III) CA19-9 levels higher than 394 U/L (OR 3.1; $P < 0.0001$); (IV) no neoadjuvant chemotherapy (OR 2.7; $P = 0.012$); and (V) pancreatic body and tail lesions (OR 1.8; $P = 0.063$). In addition, they presented a “laparoscopic score” as follows; (1× male) + (1× borderline resectable) + (1× pancreatic body/tail lesion) + (1× no receipt of neoadjuvant chemotherapy) + (2× CA19-9 > 394 U/L) + (4× locally advanced). A score cutoff at 4 based on the highest Youden index was able to predict 76.1% of occult metastasis. We honor their major and long-lasting contributions to the treatment of patients with PDAC. This study recruited the largest group of PDAC patients to undergo SL so far, and their work is clear and definite; however, I think there are several points that should be discussed further. We would like to address those points in this editorial.

First, regarding its clinical utility, SL can be applied as a minimally invasive procedure to improve the staging of PDAC. SL can prevent an unnecessary laparotomy by

detecting occult metastasis. De Rosa *et al.* (2) reviewed 24 studies assessing the utility of SL for PDAC, and found sensitivities ranging from 44% to 93%, and specificities ranging from 59% to 93%. Fong *et al.* (1) demonstrated that SL could prevent an unnecessary laparotomy for 24.1% of patients with radiographically resectable PDAC. This rate represents a marked decrease from the 35% reported by the same group in 1986 (3); however, SL still prevents an unnecessary laparotomy for almost 1 in 4 patients, which is significant enough to warrant its use in contemporary times.

Needless to say, SL is less invasive than exploratory laparotomy (EL). In a review of 9 studies, Stefanidis *et al.* found that the morbidity of SL ranged from 0 to 3.7%, and mortality from 0 to 0.15% in patients with radiographically resectable PDAC (4). Studies comparing morbidity data of SL and EL are very limited. Conlon *et al.* (5) reported 0% morbidity and mortality for SL, and showed that patients who underwent SL had significantly shorter hospital stays than those undergoing EL (a median of 2 *vs.* 7 days; $P < 0.01$); unfortunately, they did not report the morbidity of EL. In addition, the range of observation in the peritoneal space of SL would be wider than that of EL with a small incision. Washing cytology has been reported to have the important prognostic value in patients with radiographically resectable PDAC and no ascites (6), and laparoscopy would make it easier to collect washed saline during peritoneal lavage from various parts such as Douglas’ pouch.

The reduced invasiveness of SL for patients with radiographically resectable PDAC should be evaluated by quality of life (QOL) after operations compared to EL.

Morris *et al.* reported that SL produced significantly higher mean quality-adjusted life years (QALYs) per patient than EL (0.346 *vs.* 0.337) (7). The QALYs measure combines the length of life and QOL, and is a recommended outcome for use in economic evaluations. They also evaluated the cost-effectiveness of SL, and found that SL incurred similar mean costs per patients as EL (£7,470 *vs.* £7,480); the SL costs (£995) were offset by avoiding the cost of unnecessary laparotomy. This cost-effectiveness of SL disappeared if the SL was performed in the same admission, or in a patient with perianapillary cancers. SL does add time and cost to an operation.

The Harvard group recently reported that SL not only saves patients an incision, but may also help them live longer using the same cohort (8). In that report, 151 PDAC patients (15%) had occult metastases. SL was performed in 89 patients (59%), while 62 patients (41%) underwent EL. The median overall survival (OS) for the SL group (11.4 months) was significantly longer than that for the EL group (8.3 months, $P < 0.001$). Cox regression analysis revealed that SL was independently associated with OS (Hazard ratio 0.53, $P = 0.005$). They attributed this survival advantage to the shorter interval for palliative chemotherapy of SL compared to EL (17.9 *vs.* 39.9 days, $P < 0.001$). We have already reported that SL ($n = 14$) leads to faster induction of palliative chemotherapy compared to the EL ($n = 10$) (3 *vs.* 11 days; $P = 0.006$) (9). The “less invasiveness” of SL would lead to a shorter interval to the starting of palliative chemotherapy, and lead to the better survival impact of SL in patients with radiographically resectable PDAC.

SL, of course, entails extra time and cost in addition to the curative surgery; therefore, we should identify which patients are not likely to have occult metastases before surgery. In short, indication criteria for SL in PDAC patients before surgery should be established. In their recent report (1), they presented a scoring index using 5 variables, and a score cutoff of 4 was able to predict 76.1% of occult metastasis. De Rosa *et al.* suggested an algorithm for selecting patients with radiographically resectable PDAC: CA19.9 ≥ 150 U/mL or tumor size > 3 cm (2). A CA19-9 level ≥ 150 U/mL was chosen based the results of four large studies (10-13), which calculated cut-off values using ROC analysis. These reports presented cut-off values of 130, 150, 150, and 157 U/mL, respectively. Tumor size > 3 cm was chosen based on the results from 2 studies (14,15) that showed that tumors > 3 cm were significantly more likely to have occult metastases at exploration.

Satoi *et al.* performed SL in patients with: CA19-9 level ≥ 150 U/mL; or tumor size ≥ 3 cm (15). They compared the frequency of unnecessary laparotomy in 16 patients (26%) selected for SL based on the above criteria, with 33 patients who underwent laparotomy prior to the SL policy. Of 16 patients, 5 patients (31%) had occult metastasis, and the frequency of unnecessary laparotomy decreased to 15%.

Alexakis *et al.* advocated that high serum CA19-9 but not tumor size should select patients for SL in radiological resectable PDAC (16). They emphasized that even small PDAC in the 2–3 cm range could have metastasis. The concept that patients with a high CA19-9 level should undergo SL to check occult metastasis before curative resection would be widely accepted but for the well-known fact that CA19-9 is undetectable in 4–15% of the population with a Lewis negative (a-, b-) phenotype (17), and is increased in the presence of obstructive jaundice (18). Thus, the scoring index (laparoscopy score) presented by Fong *et al.* (1) which includes 5 variables seems an improvement over previous systems; however, the diagnosis of “borderline resectable” and “locally advanced” sometimes has problems. These categories are clearly defined by the AHPBA/SSAT/SSO Expert Consensus Statement (19); however, actually, the definition of “resectability” for PDAC has changed over time and differs by institutions. Regardless, the clinical utility of this “laparoscopy score” should be validated using another cohort, perhaps one representing ethnic group, and be confirmed by a prospective study including a large number of patients.

The utility of SL for PDAC will decrease if imaging studies improve. The advantage of SL is its detection of small superficial liver metastasis or small peritoneal metastasis (20); therefore, improvements in contrast-enhanced F-18-fluorodeoxyglucose positron emission tomography (PET)/CT would restrict the indication for SL (21). Fong *et al.* reported a false negative rate of 4.2%, comprising mostly metastases located in the posterior segments of the liver (1). To decrease false-negative in SL for PDAC, indocyanine green fluorescence-guided imaging or laparoscopic ultrasound in SL would be a potent tool in detecting small superficial liver metastasis, small peritoneal metastasis, or deep parenchymal liver metastasis (22,23).

We honor again this major and what is likely to be a long-lasting contribution in clinical advancement for the treatment of patients with PDAC. As they say, the clinical utility of SL will change according to the advancement of imaging studies or neoadjuvant chemotherapies. However, SL still has important role, and is recommended for

patients with radiographically resectable but relatively advanced PDAC, because it is difficult to detect small superficial liver metastases or small peritoneal dissemination radiographically. We should understand the merits and demerits of SL per se, and construct optimal indication criteria as soon as possible.

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