

## What's new in oncologic pancreatic surgery

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Cancer of the pancreas is the seventh most frequent cause of cancer death in Italy (1). Prognosis in these patients is poor, with a cumulative 5-year survival rate of 5%, and this is primarily related to the extent of the disease at presentation (1). When pancreatic resection is possible (<20% of cases) the actuarial 5-year survival rate is reported to range only between 15% and 25% (2).

Even if these data advise on the devastating problem of this disease, the low prevalence of pancreatic cancer, the absence of a real screening diagnostic method, and the poor outcomes of surgery, even in early stages, it is currently neither advisable nor cost effective to screen the general population. Actually the efforts are focused on early screening of selected high-risk-cohorts patients (patients with chronic pancreatitis, individuals with a family history of pancreatic cancer, patients with hereditary pancreatitis, Peutz-Jeghers syndrome, cystic fibrosis or familial atypical multiple mole Melanoma, who account for approximately 10% of patients with pancreatic cancer), by a multi-modal-screening approach of endoscopic ultrasound, computed tomography and endoscopic retrograde cholangio-pancreatography (3).

Recent literature has increased the evidence of a direct role of endoscopic ultrasound (EUS) in diagnosis and staging of pancreatic tumors. Has been demostered that for dubious pancreatic lesions EUS has a high negative predictive value (NPV) (4). In a retrospective report from a series of 693 patients with suspicion of pancreatic cancer, 155 of whom had a normal pancreas endosonographically, the NPV of EUS reached 100% (5). In pancreatic lesion smaller than 3 cm EUS has been proven to be more sensitive than CT, as the overall detection rate was shown to be 97% whereas CT only reached 73% (6). EUS-FNA has offered new potential to EUS specially in dubious lesions. The sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) of EUS-FNA vary in published studies, but are generally high (e.g., 83%, 90%, 85%, 100% and 80%, respectively, in one multicenter study) (7).

In addition EUS is more powerful in tumour resectability and vascular invasion assessment, compared to CT, in locally advanced pancreatic tumors. Several studies were summarized in a review which showed that EUS was better than CT when it came to assessment of resectability (91% vs 83%,  $P < 0.05$ ), and was especially more sensitive in diagnosing vascular invasion of the portal venous system (91% vs 64%,  $P < 0.001$ ) (6).

Once resectability is assessed, surgical procedure consisted in an en-bloc resection of the tumor associated to a loco-regional lymphadenectomy. A Cochrane review, analysing the short and long-term after a pancreaticoduodenectomy (classic Whipple) versus a pylorus-preserving pancreaticoduodenectomy (pp Whipple) for surgical treatment of pancreatic carcinoma, found no evidence of relevant differences in mortality, morbidity and survival between the two operations. pp Whipple was associated to a significant reduction of operative time and intra-operative blood loss compared to classic Whipple (8).

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More attention has been recently given to the laparoscopy for pancreatic lesions localized in the distal pancreas. A recent meta-analysis performed at our Institution, showed better results of minimally invasive distal pancreatectomy (MIDP) compared to the open approach (ODP). The mortality and reoperative rates did not differ between MIDP and ODP, however MIDP offers better outcomes in terms blood loss, time to oral intake, and postoperative hospital stay compared to ODP. The MIDP approach had fewer overall complications [odds ratio (OR), 0.49; 95% confidence interval (CI), 0.27–0.89], major complications (OR, 0.57; 95% CI, 0.34–0.96), surgical-site infections (OR, 0.32; 95% CI, 0.19–0.53), and pancreatic fistulas (OR, 0.68; 95% CI, 0.47–0.98) (9).

Vascular venous resection could not be still considered as a contraindication for pancreaticoduodenectomy. The current literature suggests that portal vein/superior mesenteric vein resection combined with pancreatectomy is a safe and feasible procedure, in high-volume centres, that increases the number of patients who undergo curative resection and, therefore, provides important survival benefits to selected groups of patients (10).

Same conclusions cannot be made when we judge vascular arterial resection. A recent German Study compared the outcomes of patients who underwent to pancreatic resection with arterial resection with patients without vascular resection or reconstruction for pancreatic adenocarcinoma. The Authors found no differences in long-term survival rates, but remarked important differences in terms of peri-operative outcomes: mortality rates, complication rates, reintervention rates and R0 rates were respectively, 14% vs 4% ( $p=0.023$ ); 38% vs 19.8% ( $p=0.001$ ); 21% vs 15.1% ( $p=0.422$ ) and 66% vs 85.3% ( $p=0.027$ ), for patients with arterial vascular resection and patient without arterial vascular resection (11).

As described before, survival after surgical resection for pancreatic adenocarcinoma is poor. Several histological prognostic factors as stage, tumor size, lymph node status, grading and status of the surgical resection margin, have been identified. Lymph node involvement has been demonstrated to be significantly related to the prognosis, influencing both early recurrence and poor survival. However, the status of nodal disease (e.g., negative vs positive) has not always been an independent prognostic factor as shown in several studies.

Recent literature highlights the meaning of the lymph node ratio (LNR) as one of the strongest independent prognostic factors, influencing survival after pancreatic resection. Several studies and our experience demonstrated that LNR is a more effective predictor of recurrence and survival than lymph node status, allowing a better patient's stratification and reducing or preventing the stage migration phenomenon (12).

In locally advanced pancreatic cancer, must be highlighted the promising efficacy of neoadjuvant chemotherapy approach. In a recent retrospective review of 458 patients surgically treated for pancreatic adenocarcinoma, the Authors found that the patients underwent neoadjuvant chemotherapy (8,5%) show a significantly low rate of lymph node positivity (45% vs 65%;  $P=0.011$ ) and a better overall survival compared with the adjuvant group (median survival, 34 vs 19 months;  $P=0.003$ ). The Authors conclude that large centers with multidisciplinary expertise have been more aggressive with neoadjuvant therapy for both localized and borderline resectable pancreatic cancer as part of ongoing clinical trials, and that, in light of the morbidity of pancreatic resection and the generally poor oncologic results observed with a resection-first approach, neoadjuvant therapy should be considered a reasonable alternative to upfront surgery and warrants broader application (13).

In patients with unresectable, non-metastatic, pancreatic cancer, an emerging role has been identified for the intra-operative radiofrequency ablation (RFA). Recent publications in fact, emphasize this application as an alternative, effective and feasible palliative treatment, in order to better control the progression of the disease and the chronic associated pain, compared to standard palliation alone (14).

Since the first formal definition and characterisation by the World Health Organization in 1996, intraductal papillary mucinous neoplasm of the pancreas (IPMN), has been the more interesting subject of research in pancreatic oncology. The low prevalence of these lesions explains the lack of high evidence for an agreement in codified international guides lines.

A general consensus supports the evidence that main duct IPMN are more invasive compared to branch duct IPMN. The frequency of malignancy (in situ and invasive) in main duct IPMNs in 8 recent series from Japan, Europe, and the USA has ranged between 60 and 92%, with a mean of 70%. Based on this, Tanaka and Colleagues, recommend to resect all main duct and mixed variant IPMNs as long as the patient is a good surgical candidate with a reasonable life expectancy. For

branch duct IPMN, Tanaka, presenting a well known decision and management algorithm, identified two main prognostic parameters, dimension and “high risk stigmata” (mural nodules, main duct dilatation and positive cytology). Dimensions ranged between 1 to 3 cm associated to a presence of “high risk stigmata” or a dimension > to 3 cm indicate a surgical resection; dimensions < to 1 or 2 cm and the absence of “high risk stigmata” should direct to a radiological surveillance (15).

A minimum postoperative complication rate and an R0 surgical resection is the surgeon's major contribution to the long-term survival of patients with pancreatic cancer.

It is well established that surgeon volume significantly influences the perioperative outcomes and mortality, as well as long-term survival after pancreatic resection. Eppsteiner and colleagues demonstrated a lower postoperative mortality among patients undergoing pancreatic resection by high-volume surgeons compared with less experienced surgeons (2.6% vs. 6.7%). In another study, Birkmayer (16), using the National Surveillance Epidemiology and End Results (SEER) Medicare-linked database, found that 5-year survival rates between low- and high-volume hospitals were 10.8% and 15.9%, respectively.

Surgical resection of pancreatic tumors for cure remains a major challenge; all the data presented emphasize the meaning that pancreatic surgery need specialized centres (experienced radiologist, anaesthesiologist and nurses, apart from experienced surgeons), and a policy of centralization should be strongly considered.

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