

Surgical treatment of pancreatic head cancer: concept revolutions and arguments

Zhe Cao^{1*}, Jianwei Xu^{2*}, Qianqian Shao¹, Taiping Zhang¹, Yupei Zhao¹

¹Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China; ²Department of General Surgery, Qilu Hospital, Shandong University, Jinan 250012, China

*These authors contributed equally to this work.

Correspondence to: Taiping Zhang, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China. Email: tpingzhang@yahoo.com; Yupei Zhao, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China. Email: zhao8028@263.net.

Authors' introduction: Dr. Zhao, M.D. President of Peking Union Medical College Hospital (PUMCH); Member of Chinese Academy of Sciences (CAS); Vice President of Chinese Medical Association (CMA) and Chairman of the Chinese Society of Surgery, CMA; Chairman of Pancreatic Surgery Section of Chinese Society of Surgery; He served as the Chief Editor of "Annals of Surgery" (Chinese version), and the *Chinese Journal of Surgery*.

Dr. Zhang, M.D. Peking Union Medical College; The professor and deputy director of General Surgery Department at Peking Union Medical College Hospital. Currently served as the member and secretary of the Surgery Branch of the Chinese Medical Association and Surgical Study Group.

Dr. Cao, M.D. Department of General Surgery, Peking Union Medical College.



Yupei Zhao



Taiping Zhang



Zhe Cao

Abstract: As we have a deeper and more thorough understanding of the biological behavior of pancreatic head cancer, surgical treatment concepts of this lethal disease are changing all the time. Meanwhile, numerous arguments emerge. Thus, we will probe into the focuses and arguments in the surgical treatment of pancreatic head cancer in this article, including the scope of lymphadenectomy, total mesopancreas excision (TMpE), vascular resection, minimally invasive pancreaticoduodenectomy (PD), palliative resection, surgery for recurrent disease and surgery for primary pancreatic cancer and liver metastasis.

Keywords: Surgical treatment; pancreatic head cancer

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Introduction

Radical resection is a fundamental way to gain long-time survival for the patients with pancreatic cancer. Progresses in surgical techniques and operation methods greatly reduce the perioperative complication rate and mortality. However, the overall survival time does not improve. With a better knowledge of the biological behavior of pancreatic cancer, the concepts of pancreatic surgical treatment have changed. Surgeons have spared no effort to explore the surgical treatment of pancreatic cancer, struggling to make some breakthroughs. Although we have achieved some progress, arguments are going and will never demise.

Lymphadenectomy of pancreatic head carcinoma

Extended lymphadenectomy (ELND) is based on the following theories: adenocarcinoma of the head of the pancreas frequently metastasize to lymph nodes that are beyond the confines of the conventional pancreaticoduodenectomy (PD). Whipple procedure usually leaves out lymph nodes circumferentially from hepatic hilum, celiac trunk (CT) and abdominal aorta, as well as peripancreatic soft tissue, leading to poor prognosis of patients. Arguments about the value of ELND have never ended, and people's understanding of this issue differs in different periods. Regional pancreatectomy was first reported by Fortner in 1973. In the following 10 to 20 years, most retrospective studies in European, America and Japan confirmed that ELND was superior to conventional PD. However, clinical randomized controlled trials carried out in recent 10 years make people to re-recognize the value of ELND. Four prospective, randomized trials comprising some 424 patients and one meta-analysis showed that ELND appears to convey no survival benefit, and may be associated with several complications such as severe diarrhea and delayed gastric emptying postoperatively, which may due to circumferential clearance of the superior mesenteric vessels with severance of parasympathetic nerve fibers (1).

So far, people have not reached an agreement with the scope of lymphadenectomy of the pancreatic head carcinoma. The National Comprehensive Cancer Network (NCCN) practice guidelines suggest that outside of a clinical trial, ELND should not be considered as a routine part of the Whipple procedure. And PD with standard lymphadenectomy is the operation of choice (2). And according to new classification of pancreatic carcinoma of Japan

Pancreas Society (JPS) [2003] (3), the removal should entail the second order nodes (N2), which include peripancreatic lymph nodes, and lymphatic tissue circumferentially from the hepatoduodenal ligament, hepatic artery and the right side of superior mesenteric artery (SMA).

Total mesopancreas excision (TMpE)

Mesopancreas was first recognized by German scholars Gockel and colleagues (4) in 2007, which refers to the perineural lymphatic layer located dorsally to the pancreas and reaching beyond the mesenteric vessels. Mesopancreas is a critical structure associated with incomplete removal and local recurrence of tumor (5), and TMpE gives clinicians a total new understanding of the R0 resection of pancreatic head carcinoma.

Adham *et al.* (6) described the concept of “the mesopancreas triangle” for the first time, and thus characterized the surgical scope of TMpE accordingly. “The mesopancreas triangle” has anatomical boundaries that are represented by a base lying on the posterior surface of the superior mesenteric vein (SMV) and portal vein (PV), a summit lying on the anterior surface of the aorta between CT and SMA origin, and is limited on each side by the right semicircumferences of the CT and SMA plexus. Kawabata *et al.* (7) then proposed the concept of “total mesopancreatoduodenum excision (tMPDe)” on the basis of the above theory. When performing tMPDe, lymphadenectomy with the left side of SMA together with mesopancreas resection is necessary to achieve a complete clearance of the retroperitoneal resection margin. Wu *et al.* extended the concept of mesopancreas further. Uncinate process and pancreatic head divide the mesopancreas into anterior and posterior parts, and the latter has a different surgical scope from “the mesopancreas triangle”. Take the inferior mesenteric artery (IMA) as the lower boundary, and clear the connective tissue circumferentially from the IMA. Take the summit lying from anterior of abdominal aorta proximally to two centimeters distant from the initial of CT as the upper boundary of the dorsal mesopancreas, and clear the connective tissue circumferentially from the CT; take the left vena genialis as the left posterior boundary, and SMV as the left anterior boundary.

There are still a lot of controversies about TMpE. The most obvious question is does “mesopancreas” do exist? No anatomical textbook has mentioned the presence of “mesopancreas” before. And Agrawal *et al.* (8) dissected

20 fresh adult cadavers, but failed to find any fibrous or fascia enveloping the so called “mesopancreas”, neither macroscopically nor microscopically. Thus, it is believed that there does not exist a “mesopancreas” structure in anatomy. Nevertheless, “mesopancreas” plays an important role in the assessment of PD and the prognosis of pancreatic head carcinoma. Studies showed that R0 rate of TMpE was significantly higher, when compared with conventional PD (93% *vs.* 60%) (7). Another question is that is TMpE another kind of regional lymphadenectomy? Although the scopes of lymphadenectomy of TMpE and conventional PD are partly overlapping, each has its own emphasis. Lymphadenectomy focus on clearance of regional lymph nodes, while TMpE attempts to clear all of the soft tissue including nerves, capillaries and lymph nodes; since pancreatic cancer has the tendency of perineural and vessel invasion, clearance of the peripancreatic nerve plexus can significantly improve the radical rate of pancreatic cancer and relieve the intractable pain resulting from the invasion of plexus (9). Furthermore, the latest guidelines make a recommendation that lymphadenectomy should be as far as N2 when performing PD (2), but TMpE always involves N16 (namely lymph nodes circumferentially from abdominal aorta), which seems to go against the current guidelines. The final question is can TMpE benefit patients? Several aspects of TMpE, such as the median operative time and blood loss, perioperative complications rate, mortality and median length of hospital stay, are comparable to other operative methods of pancreatic head carcinoma (6). And TMpE can improve the R0 resection rate. As for median overall survival time, there is not any follow-up data so far. So large scale, randomized controlled trials are needed to clarify the value of TMpE in the future.

Vascular resection

Pancreatic cancer involving adjacent great vessels was once treated as a surgical contraindication. However, with the development of operative skills, narcotic progresses and intensive care medicine, SMV/PV resection and reconstruction at the time of PD has gain positive popularity. A UK multicenter (nine high-volume UK centers) retrospective cohort study comparing 1,588 patients with resectable pancreatic cancer showed that the perioperative mortality did not show significant difference between PD with vascular resection (PDVR), conventional PD and surgical bypass (SB). Both PD and PDVR groups had greater complication rates than the SB group, but with

no difference between PD and PDVR. Overall survival between PD and PDVR groups is similar, but significantly better compared with SB (10). If it is difficult to achieve a negative margin when performing vascular resection (like intensive portal invasion), or distal vascular branches are too many for surgeons to accomplish vascular reconstruction, give up surgical treatment in time!

Arterial resection at the time of PD is technically safe and feasible. Whereas, involving CT and SMA is an indication of intensive infiltration into the surrounding structures. Thus, even if the involved artery is resected meanwhile, there is still high rate of margin positive retroperitoneal resection, and the complication rate will increase significantly. Hence, most scholars do not advocate arterial resection and reconstruction. Since vascular resection and reconstruction at the time of PD requires complex operative procedures and has a high complication rate, operations should be carried out by skilled surgical team in high-volume centers. What's more, only the patients who achieve R0 resection can benefit from the surgery.

Minimally invasive PD

Since Gagner and colleagues reported the first case of laparoscopic PD in the world in 1994 (11), an increasing number of surgeons from high-volume clinical centers showed extremely high passion for minimally invasive surgeries (MIS), including Robot-assisted PD and laparoscopic PD. Laparoscopic PD strictly follows the radical care principle throughout the operation. It can assist the operator to clearly expose PV and SMV, and search for peripancreatic lymph nodes and those circumferentially from abdominal vessels by locally magnifying visual field. But procedures such as dissection of uncinate process of pancreas and reconstruction of digestive tract require exquisite skills, thus only surgeons with abundant experiences at laparoscopy and open surgery can give those surgeries. Vinci robot-assisted surgeries have several advantages, such as more flexible laparoscopic needle holders and superior visualization of the three-dimensional (3D) operative field, which help it gain popularities among clinicians. Unfortunately, expensive cost hinders the spread and wide use of Vinci robot-assisted surgeries in a short time.

A recent meta-analysis (12) was consisted of six studies that included 542 patients (169 MIS and 373 open). This study showed that MIS was associated with a reduction in intraoperative blood loss, significantly higher retrieval

of lymph nodes, significantly lower R1/R2 resection rate, and significantly reduced hospital stay. Postoperative complications rates were comparable, but longer operative times and significantly smaller tumor size were noticed in the MIS group. Although this meta-analysis showed encouraging consequences, there existed great bias. For example, all of the studies included were retrospective and mainly focused on operative and perioperative outcomes, but long-term oncologic results were unavailable, and there were no multicenter studies. Consequently, before randomized controlled trials or prospective cohort studies prove the equivalent or superior of MIS to the open surgery, minimally invasive PD cannot be considered as a routine application.

Palliative resection

In general, people show negative attitude towards palliative resection. Lavu *et al.* (13) found that compared with the patients who underwent palliative surgical bypass (PB), those underwent margin positive PD had a slightly longer length of hospital stay and a significantly reduced median survival time. Gillen *et al.* (14) carried out a systematic review and meta-analysis of four studies. These studies made a comparison between palliative R2 resection and PB procedures. Results showed that compared with PB procedures, palliative R2 resection would lead to a significantly higher complication rate and mortality, as well as significantly longer operative time and hospital stays. Therefore, palliative R2 resection cannot be recommended. And for those with local oppression and obstruction in advanced stage, PB is a standard of care.

Nonetheless, preoperative evaluation of pancreatic cancer for resectability has some limitations, for one can only give an exact judgment after resecting the neck of pancreas during the surgery. And for those involving CT or SMA, R1 or R2 resection is the exclusive option. Therefore, we should make a careful preoperative evaluation of the resectability of tumor, and try hard to avoid R2 resection. Meanwhile, we should not go too far, because over-conservation may wrongly exclude the candidates for regional extended resection or vascular resection.

Surgery for recurrent disease

A total of 80% patients will experience local recurrence in 2 years following resection, and surgical treatment for recurrent disease has never reached an agreement. First

of all, severe postoperative adhesions will increase the complexity as well as the complication rate of secondary operation. Secondly, a large number of tumor recurrences are located close to the CT and SMA therefore not resectable. Finally, it is unclear if secondary surgery can increase the median survival time. Recent studies support the concept of surgical exploration and resection of the local recurrent disease (15) for the following reasons: (I) surgical resection of the recurrence combined with intraoperative radiotherapy of the tumor bed will help to reduce the risk of another recurrence at the resection site; (II) in case of local irresectability, intraoperative radiation can be performed with a palliative intention in terms of tumor reduction and pain control (15); (III) resection of the recurrence may increase the median survival time. A study confirmed that there was a tendency of increased median survival in the group of patients undergoing resection of the recurrence (17.0 months) compared with the bypass group (9.4 months), although this difference was not significant. In addition, patients with a prolonged interval (>9 months) from resection to recurrence were more likely to benefit from resection compared with those with recurrence within 9 months (median survival 7.4 *vs.* 17.0 months, $P=0.004$). Consequently, for patients with recurrence beyond 9 months following operation, secondary surgery can be considered (16).

Surgery for primary pancreatic cancer and liver metastasis

Pancreatic cancer with liver metastasis is seen as a surgical contraindication, but some case reports and small studies indicated that surgical treatment may benefit part patients. Michalski *et al.* (17) performed a systemic review of the literature and identified 103 cases with pancreatic and liver metastasis. Compared with the patients underwent PD without metastasis resection, those underwent PD and hepatectomy had a significantly longer median survival time (11.4 *vs.* 5.9 months, $P=0.038$), and the complication rate and mortality is 24.1-26% and 0-4.3%, respectively. They proposed that experienced pancreatic surgical centers can chose patients with M1 diseases as the candidates for surgery. However, it cannot be ignored that pancreatic cancer is a systemic disease, and tumor cells probably have spread to other organs in patients with liver metastasis, which adds difficulties to R0 resection. And large, prospective studies are needed to further confirm the value of this kind of treatment.

As a conclusion, with a deeper and more thorough

understanding of the biological behavior of pancreatic cancer, our surgical treatment concepts of this lethal disease are changing all the time. However, because of the lack of effective and powerful evidence-based evidences, it is difficult to achieve an agreement in a short time. The revolution of the surgery of pancreatic cancer will progress among endless debates.

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Footnote

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