**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 8109**

**Columns: TOPIC HIGHLIGHT**

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

**Improving outcomes in pancreatic cancer: Key points in perioperative management**

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**Received:** December 14, 2013 **Revised:**February 24, 2014

**Accepted:** June 20, 2014

**Published online:**

**Abstract**

The review is focused in the different perioperative management of the patients with pancreatic cancer in order to improve the outcome of the disease. We consider that most controversial points are jaundice management, vascular resection and neoadyuvant therapy. Preoperative biliary drainage is recommended only in patients with severe jaundice, because in the rest of patients could lead infectious cholangitis, pancreatitis and delay of resection, which can lead to tumoral progression. The development of a phase III clinical trial is mandatory to clarify the role of the neoadjuvant radiochemotherapy in the pancreatic adenocarcinoma. Venous resection doesn’t adversely affect postoperative mortality and morbidity, so the need for venous resection should not be a contraindication to surgical resection in the selected patient. Respect to arterial resection alone, or combined vascular resection at the time of pancreatectomy, reported data are more heterogeneous, so age of patient and comorbidity should be evaluated before take a decision about the operability and respectability. Only the sure R0 resection can move about to performance arterial resections.

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**Key words:** Pancreatic cancer; Obstructive jaundice; Preoperative drainage; Neoadyuvant therapy; Vascular resection

Álamo JM, Marín LM, Suarez G, Bernal C, Serrano J, Barrera L, Gómez MA, Muntané J, Padillo FJ. Improving outcomes in pancreatic cancer: Key points in perioperative management. *World J Gastroenterol* 2014; In press

**INTRODUCTION**

Approximately 45000 people will develop exocrine pancreatic cancer in 2013 in the United States. A high percentage (85%) of diagnosed cases will die which shows the virulent nature of this malignancy[1]. Surgical resection offers the only chance of cure.

Unfortunately, the vast majority of patients are diagnosed with locally advanced unresectable or metastatic disease. Up to 15%-20% of patients are eligible for initial resection[2]. Furthermore, even for those undergoing complete resection (R0) the prognosis is poor, because of most them eventually will relapse and die of their disease.

Reported five-year survival rates following pancreaticoduodenectomy for node-negative and node-positive disease are 25%-30% and 10%, respectively[3].

There are many interesting points in perioperative management in pancreatic cancer to result in an improvement of long-term outcomes in such an aggressive disease, as intraoperative radiation therapy, standard or extend lymphadenectomy and adjuvant chemotherapy, but we consider that most controversial points nowadays are jaundice management, vascular resection and neoadyuvant therapy.

**PREOPERATIVE DRAINAGE IN JAUNDICED PATIENTS**

The most frequent location of pancreatic cancer is the head of pancreas, so obstructive jaundice is a common presenting symptom. Pre-operative biliary drainage has been used to provisionally resolve the obstruction and may reverse the dysfunction resulting from obstruction of biliary flow. This issue has been controversial in recent years. However, this is a controversial therapeutic option because there is not enough evidence at day. Several positive outcomes are observed after preoperative drainage in jaundiced patients: (1) Higher postoperative morbi-mortality are associated to prolonged acute-phase response. More than 10 d of biliary tract obstruction was related to an increase in endotoxin levels, and a positive acute-phase response peak[4]. After biliary drainage a transitory improvement of these alterations was observed, although values remained high 1 wk post-drainage[5]; (2) Malignant obstructive jaundice induces *per se* significant changes in food intake. Anorectic endocrine mediators, liver injury and biliary obstruction are related to protein-caloric malnutrition. This is a reversible situation. Nutritional markers improve after the new beginning of bile flow into the duodenum[6]; (3) Patients with biliary tract obstruction that requires surgery often have protein calorie malnutrition, which is associated with increased peri-operative morbidity and mortality. The internal biliary drainage yields good results, and experimental studies have shown that it may improve nutritional status. The levels of pre-albumin and transferrin improved 10 days after internal biliary drainage for both benign and malignant obstruction[7,8] because nutritional alterations in patients with obstructive jaundice were determined by the intensity of the biliary obstruction[9]; (4) Fluid administration expands the extracellular water compartment before drainage but fails to improve renal function after drainage. Definitive improvement in endocrine and renal function requires the restoration of bile flow into the duodenum[10]; and (5) Plasmatic levels of atrial natriuretic peptide arise from obstruction of the biliary tree[11]. In these cases, it may reflect a subclinical myocardial dysfunction related to the severity of jaundice. There is a measurable improvement of cardiac function after internal biliary drainage[12].

The safety of routine pre-operative biliary drainage has not been established[13]. The pre-operative biliary drainage may increase the rate of serious adverse events, such as the significant increases on the rates of bile culture positive for bacteria and significantly increases the probability of wound infection. In addition, bile cultures positive for bacteria would seem to adversely impact mortality and morbidity after surgery in jaundiced patients[14]. In a large multicenter randomized trial comparing early surgery *vs* preoperative biliary drainage followed by surgery of patients with cancer of the head of the pancreas, the rates of serious complications were 39% (37 of 96 patients) in the early surgery group and 74% (75 of 106 patients) in the patients submitted to preoperative biliary drainage (*P* ≤ 0.001)[15]. A follow-up report from the same trial showed that there was a significant delay in time to surgery (1 wk *vs* 5 wk), but without influence in the survival rate[16]. While there is an increase in overall infectious complications following surgery in the stented group, the detrimental effect of pre-operative biliary stenting is likely limited to those with subsequent bacterial colonization of the biliary tree from stent placement[17].

The rapid and direct proceeding to surgery may limit the number of interventions and thus decrease costs and potential procedure-related complications. Sidiqqui *et al*[18] observed immediate complications such as post-preoperative endoscopic retrograde cholangiopancreatography pancreatitis (*n* = 14), stent migration (*n* = 3), and duodenal perforation (*n* = 3), as well as long-term complications included stent migration (*n* = 9) and hepatic abscess (*n* = 1). Fourteen patients (5.8%) experienced stent occlusion at average 6.6 months (range 1 to 20 mo). A total of 144 of 174 patients (83%) deemed to have resectable cancer at the time of diagnosis subsequently underwent curative surgery. Due to disease progression or the discovery of metastasis after neoadjuvant therapy, only 22 of 67 patients (33%) with borderline-resectable cancer underwent curative surgery.

The pre-operative placement of biliary stents in patients undergoing pancreatoduodenectomy significantly increases blood loss, with non-significant increases in operative time and peri-operative fluid resuscitation. In this cohort, these intra-operative considerations do not translate into increased peri-operative morbidity and mortality, with the data overall showing negligible differences to improved outcomes in stented patients. Consequently, pre-operative biliary stents may complicate the intra-operative surgical management[19].

**NEO-ADJUVANT THERAPY IN PANCREATIC CANCER**

The low rate of resectability and the poor long-term outcomes following pancreatoduodenectomy have led to the investigation of pre-operative chemo-radiation therapy or a combination of pre-operative and post-operative therapies[20]. In this context, neo-adjuvant therapy is defined as any pre-operative therapy aiming to convert un-resectable to resectable tumors and/or to increase microscopic complete tumor resection rates[21]. Given this situation, the rationale for neo-adjuvant therapy in pancreatic cancer are[22]: (1) the main objective is down-staging of the tumor to increase the probability of survival after an R0 resection; (2) a certain percentage of potentially un-resectable tumors may be down-staged to enable surgical resection; (3) radiation therapy is more effective on well-oxygenated cells that have not been devascularized by surgery; (4) pre-operative treatment may prevent implantation and dissemination of tumor cells at laparotomy; (5) patients with metastatic disease on restaging after neo-adjuvant therapy will not be subjected to unnecessary laparotomy; and (6) delayed post-operative recovery will not affect the delivery of neo-adjuvant therapy.

Patients candidates for neo-adjuvant therapy are those with radiographically resectable and biopsy-proven pancreatic adenocarcinoma[23]. Numerous phase II trials have been performed with encouraging results[24-26]. While median survival durations from some uncontrolled trials reported of neo-adjuvant therapy compare favorably to those reported with modern adjuvant therapy approaches[25,27,28], whether pre-operative therapy is better than post-operative therapy is uncertain. No phase III trial between neo-adjuvant and post-operative adjuvant therapy has been performed, however there are many retrospective comparisons using the borderline resectable pancreatic cancer criteria[29] that favor neo-adjuvant therapy for these cancers that almost certainly would have had a positive resection margin if surgery were performed first[30-32]. Moreover, such retrospective studies may have sample selection bias[33].

In this review we distinguish the results on neo-adjuvant therapy between patients with potentially resectable (Group 1) and borderline resectable pancreatic adenocarcinoma (Group 2). In fact, this is one of the main limitations of the different meta-analysis because the criteria for considering borderline carcinoma are heterogenous. The expert consensus statement was published in 2009[34]. The conclusions of the three published meta-analysis (level of evidence 1+ of the SIGN related to the neoadjuvant therapy in pancreatic cancer are showed in Tables 1, 2 and 3[35].

The methods data of the three published meta-analysis on neo-adjuvant therapy in pancreatic carcinoma (Table 1) are different. Gillen *et al*[2] include retrospective and prospective phase I-II trials, as well as cohort studies and case series during an interval of 29 years (from 1980 to 2009) with an important variety of neo-adjuvant regimens.

The authors consider that the heterogeneity of the data is a limiting factor for the extrapolation of the results. However, this first meta-analysis concluded that patients with locally advanced/un-resectable tumors should be included in neo-adjuvant protocols and subsequently be re-evaluated for resection, which is possible in a relevant number of patients. Moreover, the group of resectable tumor patients, resection and survival rates after neo-adjuvant therapy were similar to the ones observed in primarily resected tumor that were treated by adjuvant therapy. Thus, in this group of patients, the current data do not point to an obvious advantage of neo-adjuvant therapy. The study design provided by Assifi *et al*[36] and Andriulli *et al*[37] are less heterogeneous. The data collection is limited only to prospective phase II trials investigating the effects of neoadjuvant therapy on patients with pancreatic cancer during a similar time period. The last study included patients receiving gemcitabine alone or in combination with other drug and/or radiotherapy. The problem of heterogeneity found in all meta-analysis studies was satisfactory handled using the random effects model and a *P* < 0.10 in the Cochran *Q* test in the case of Assifi *et al*[36]. Despite a rigorous selection of studies, Andriulli *et al*[37] founded significant heterogeneity which might indicate that the evidence is biased, confounded or inconsistent. Two factors which could explain at least partly the heterogeneity were identified. First, the patients’ initial disease stage (resectable vs. unresectable) and, second, the study design. We think that one of the main limitations of the meta-analysis is the definition of unresectability and borderline resectability. They are not consistent between the studies, or are not clearly described in the manuscript. Although the definitions have recently undergone standardization[34], the majority of the studies analyzed precede the adaption of such definitions or they have not been utilized by the authors.

A recent meta-analysis of prospective studies published by Festa *et al*[38] involving patients receiving chemotherapy with or without radiotherapy was given before surgery to patients with borderline resectable cancer estimates that the surgically explored and resection rate is higher in patients that received pre-operative treatment with gemcitabine. Promising results in retrospective studies have been reported with neoadjuvant FOLFIRINOX in borderline resectable pancreatic adenocarcinoma followed by radiation[26]. We have assessed the results of the meta-analysis in terms of safety (toxicity of the neoadjuvant regimen and postoperative morbidity), efficacy (response and resection rate), survival and mortality (Tables 2 and 3). Toxicity data was not available in all the studies revised in the three metaanalysis.

However, they are agree on the increasing of the toxicity grade 3-4 with the combined therapy (two or more chemotherapeutic agents or radiotherapy). In spite of the highly estimated heterogeneity on this results, toxicity is higher in the group of borderline resectable than in potentially resectable pancreatic adenocarcinoma[2,36,37].

Postoperative morbidity was only reported by Gillen *et al*[2], and the results are comparable to others series[39,40]. In a systematic review reported by Laurence *et al*[41] neoadjuvant chemoradiotherapy was not associated with a statistically significant increase in the rate of pancreatic fistula formation or total complications. One of the most important aspects of this review is the response and resection rate after neoadjuvant therapy. A 30% of response rate (complete and partial) of the borderline resectable patients provides marginal support to the benefit of preoperative therapy.

The median survival of patients with locally advanced unresectable pancreatic cancer is about 10 to 12 mo. Interest in applying the principles of neoadjuvant or induction therapy to such patients comes from their poor prognosis and the potential for longer term survival if disease can be resected. Both Gillen *et al*[2] and Andriulli *et al*[37] calculated that the 1-year and 2-years estimated survival were 75% and 50%, respectively.

However, these data must be interpreted cautiously given the heterogeneous nature of this group of patients and the treatments given to them. The influence of preoperative therapy on patient survival remains uncertain. Whether the improved median survival times in resected patients should be ascribed to the chemoradiotherapy administered before surgery or to a better selection of patients with nonprogressive disease during the interval from diagnosis to completion of chemoradiotherapy and restaging remains to be addressed in a properly designed randomized trial[37].

Probably, if pancreatic cancer can be clearly completely resected, the best option is still surgical resection; neoadjuvant therapy (chemotherapy or chemoradiotherapy) should be given in those patients with doubts in R0 resection, mostly locally advanced tumors, although this definition is not clearly defined.

**VASCULAR RESECTION IN PANCREATODUODENECTOMY**

The objective of vascular resection in case of vascular tumor invasion is to get a potentially curative resection. We can do this vascular resection only if metastases are absent. Venous invasion affect to superior mesenteric vein (SMV) and portal vein (PV), while arterial invasion use to affect the hepatic artery (HA) and the superior mesenteric artery (SMA). The role and outcomes of arterial resection is today highly controversial.

The purpose vascular resection is to increase the possibility of a curative R0 resection. For most authors curative surgery is the most important prognostic factor that influences in survival patient. This is the reason why to obtain tumor-free resection margins must be the most important objective for vascular resection in pancreatic cancer. In our experience, we have operated 22 patients with pancreatic cancer including vascular resection: 5 with arterial and 17 with venous resection (2005-2013). The mortality associated with the procedure was 8 patients (36.4%), and 6 surviving patients showed tumoral recurrence (27.3%). The 5-year survival is 36.4% (range 1-96 months, median 54).

***Arterial resection***

The narrowing or vessel encasement of SMA, celiac trunk (CT) or splenic artery (SA) visualized in CT scan[42] or intraoperatively is a locally advanced tumor, but differential diagnosis of true vascular tumor infiltration and peritumoral inflammatory fibrosis is very difficult. What is more, if we are sure that this arterial affection indicates irresectability is in order to technical aspects and prognosis, highly debatable.

There are some doubts about arterial infiltration: (1) is arterial infiltration a sign of advanced cancer or is it a consequence of tumor location? (2) are morbidity and mortality rates comparable between patients with and without arterial resection? and (3) does arterial invasion mean that distance metastasis is sure? Several articles show similar long-term survival in patients with arterial invasion compared with patients without vascular invasion. The fact that microscopy evidenced vascular tumor invasion is an adverse factor has been changed by these studies[43-45]. It could be explained because the most important factor in survival in patients with pancreatic carcinoma is the presence or absence of tumoral cells in other organs. Yekebas *et al*[46] showed that pancreatic resection can be safely combined with arterial resection in case of evidenced vascular invasion, and morbidity and mortality rates are comparable with procedures without arterial resections. In this article, vascular reconstruction does not adversely impact in outcomes. When potentially curative resection is performed, 2- and 5- year survival rates in patients with microscopically evidenced vascular invasion is 35% and 15%, respectively, similar to that observed in patients without arterial invasion. The median survival afterarterial resection is between 6-39 mo, much longer than survival in patients treated with chemotherapy or palliative surgery. Although the tumor arterial invasion more than 180º are considered the main criteria to consider unresectable disease in patients with pancreatic cancer according to current guidelines[47], there is no sufficient data in the literature to support this criteria.

The advances in pancreatic surgery together the poor survival of patients who do not undergo surgical resection, have lead to debate regarding the importance of arterial resection in patients without distant metastasis. There are some studies of pancreatectomies with arterial resection with small series of patients but not good results. These articles show overall survival in patients with arterial resection is significantly worse when compared with operated patients without arterial resection. Vascular invasion should be considered an indicator of aggressive tumor biology: the analyses also demonstrated significantly lower long-term survival in patients with arterial resection compared with patients who were made venous resection. When we performance simultaneous venous and arterial resection in these studies, the worst outcome of patients with arterial resection in these uncontrolled studies is rather related to the more advanced tumors with a higher risk of incomplete tumor resection (R1) and a higher incidence of lymph node metastases, which are well-known prognostic factors in patients with pancreatic carcinoma[48-50].

In the meta-analysis published by Mollber *et al*[51] was observed a significantly better survival for patients with arterial resection compared with patients without tumor resection. The results of these analyses has to be interpreted very cautiously, because it is an uncontrolled study: patients without resection could have more advanced tumors with a worse prognosis compared to patients who undergo pancreatic and arterial resection. This metaanalysis observed that patients with arterial resection were associated with more postoperatory complications and a worse long-term survival. This author concludes that the need for arterial resection should be a contraindication to resecability. However, survival benefit offered by pancreatectomy with arterial resection compared to palliative therapy without tumor resection could justify arterial resection in highly selected patients, only if it performed at specialized institutions.

Bachellier *et al*[52] showed that pancreatic resection with arterial resection for locally advanced pancreatic cancer can be performed safely with survival rates similar to patients with locally advanced pancreatic adenocarcinoma without arterial resection (rates of survival 20% at 5 years). This study showed that perineural invasion, number of resected lymph nodes (< 15 *vs* > 15), and the arterial wall invasion were independent prognostic factors for overall survival. Authors give some recommendations: (1) radiological arterial invasion should not be considered a contraindication to pancreatic resection if the resection gets R0 surgery; (2) the specificity of CT scan to predict histological arterial wall invasion is still low; (3) in case of radiological arterial invasion the patient should be candidate for neoadjuvant treatment; (4) after neoadjuvant therapy in absence of cancer progression an exploratory laparotomy should be realized to explore the resecability of the tumor; (5) arterial resection should be performed if we can performance a R0 resection; and (6) pancreatic resection with arterial resection should be performed in specialized centers.

Bockhorn *et al*[53] reported a study with eighteen patients who need reconstruction of HA, eight CT and three SMA. Additional reconstruction of PV was required in 15 patients. Morbidity and mortality index were significatively higher in patients with arterial resection than in patients without arterial resection (*P* = 0.031 and *P* = 0.037 respectively). Venous resection was an independent predictor of morbidity (*P* < 0.001). Although these data median overall survival was similar for both groups (14.0 vs 15.8 months; *P* = 0.152). This article concludes than, in selected patients, overall survival in arterial resection is similar to standard resection and better than palliative treatment.

In conclusion, owing to these doubtful data available, the operative and oncological results of these patients should be documented in centralized patient registries in prospective studies.

***Venous resection***

Portal vein (PV) and superior mesenteric vein (SMV) invasion is frequent because of the intimate relationship of the pancreatic head and uncinate process to these vessels.

For a long time, venous invasion has been considered a contraindication to surgery in pancreatic cancer. Today, the same that arterial resections, there is also controversy about whether pancreatic carcinoma with involvement of the PV/SMV should be resected. The first resections and reconstructions of the PV/SMV when pancreatectomy were reported by Moore *et al*[54] (1951) and by Asada *et al*[55] (1963). In 1973, Fortner[56] proposed “regional pancreatectomy” which involved a systematic resection of the major peripancreatic vessels and wide soft-tissue clearance, to improve the survival rate. Some experiences with this procedure showed no survival benefit associated with high morbidity[57,58]; so, most of surgeons considered tumor invasion of the PV/SMV as a contraindication to curative pancreatic surgery.

However, several reports have confirmed that resection of PV/SMV could be performed with acceptable mortality, morbidity, and survival results, comparable to those observed in pancreatic surgery without venous resection[44,45,59,60]. On the other hand, some authors have reported poor survival results after this surgical procedure[61].

The literature confirms the safety and feasibility of this procedure with mortality rates ranging from 0 to 7.7%, which are similar with perioperative mortality rates for pancreatectomy without PV/SMV resection reported in an analysis of a United States national database[62-64]. Morbidity rates, ranging from 16.7% to 54%, did not differ from morbidity rates reported for standard pancreatectomies by highvolume centers[65,66]. The 5-year survival rate ranged from 9% to 18% is consistent with those reported in large series by experienced centers for patients who underwent standard pancreatic resection for adenocarcinoma of the pancreas[67].

Much studies support PV/SMV resection during pancreatoduodenectomy, although some studies has brought into question the validity of porto-venous resections reporting a low 5-year survival rate, probably in part, the result of advanced stage with a high rate of nodal metastases[68]. A retrospective review of 2 prospective databases of 593 consecutive pancreatic resections for pancreatic adenocarcinoma reported by Martin *et al*[69], 36 patients (18 men and 18 women, range 42-82 years) (6.1%) were submitted to vascular resection at the time of pancreatectomy. Among them, 31 (88%) underwent venous resection alone, 3 (8%) received combined arterial and venous resection; and 2 (6%) arterial resection (superior mesenteric artery resection) alone. The 90-day perioperative mortality and morbidity rates were 0% and 35%, respectively, compared with 2% and 39%, respectively, for the group undergoing nonvascular pancreatic resection (*P* = 0.034). The median survival was 18 (range, 8-42) mo in the vascular resection group compared with 19 mo in the non-vascular resection group.

The current literature suggests that PV/SMV resection combined with pancreatectomy is a safe and feasible procedure, which can be performed for pancreatic carcinoma in experienced centers with acceptable morbidity and mortality rates, comparable to those observed for pancreatectomies without venous resections. Furthermore, this procedure has substantially increased the number of patients undergoing curative resection and provides important survival benefits in selected groups of patients.

Pancreatectomy combined with venous resection should always be considered in case of suspected tumor infiltration of PV/SMV to get good resection margins, in absence of distance metastasis. The R0 resection continues to be the ultimate goal for pancreatic carcinoma, because this is the most important to improve survival, so venous involvement should not contraindicate pancreatic resection, especially with R0 margins are possible and when reasonable reconstructions can be performanced.

**REFERENCES**

1 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]

2 **Gillen S**, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; **7**: e1000267 [PMID: 20422030 DOI: 10.1371/journal.pmed.1000267]

3 **Saif MW**. Controversies in the adjuvant treatment of pancreatic adenocarcinoma. *JOP* 2007; **8**: 545-552 [PMID: 17873458]

4 **Padillo FJ**, Andicoberry B, Muntane J, Lozano JM, Miño G, Sitges-Serra A, Solorzano G, Pera-Madrazo C. Cytokines and acute-phase response markers derangements in patients with obstructive jaundice. *Hepatogastroenterology* 2001; **48**: 378-381 [PMID: 11379313]

5 **Padillo FJ**, Andicoberry B, Muntane J, Lozano JM, Miño G, Sitges-Serra A, Pera-Madrazo C. Factors predicting nutritional derangements in patients with obstructive jaundice: multivariate analysis. *World J Surg* 2001; **25**: 413-418 [PMID: 11344390]

6 **Padillo FJ**, Andicoberry B, Pera-Madrazo C, Sitges-Serra A. Anorexia and malnutrition in patients with obstructive jaundice. *Nutrition* 2002; **18**: 987-990 [PMID: 12431722]

7 **Padillo FJ**, Rodriguez M, Gallardo JM, Andicoberry B, Naranjo A, Minõ G, Sitges-Serra A, Pera-Madrazo C. Changes in the pattern of visceral protein concentrations after internal biliary drainage in patients with obstructive jaundice. *Eur J Surg* 1999; **165**: 550-555 [PMID: 10433138 DOI: 10.1080/110241599750006442]

8 **Padillo FJ**, Andicoberry B, Naranjo A, Miño G, Pera C, Sitges-Serra A. Anorexia and the effect of internal biliary drainage on food intake in patients with obstructive jaundice. *J Am Coll Surg* 2001; **192**: 584-590 [PMID: 11333095]

9 **Padillo FJ**, Andicoberry B, Muntane J, Lozano JM, Miño G, Sitges-Serra A, Pera-Madrazo C. Factors predicting nutritional derangements in patients with obstructive jaundice: multivariate analysis. *World J Surg* 2001; **25**: 413-418 [PMID: 11344390]

10 **Padillo FJ**, Briceño J, Cruz A, Chicano M, Naranjo A, Vallejo J, Martín-Malo A, Pera-Madrazo C, Sitges-Serra A. Randomized clinical trial of the effect of intravenous fluid administration on hormonal and renal dysfunction in patients with obstructive jaundice undergoing endoscopic drainage. *Br J Surg* 2005; **92**: 39-43 [PMID: 15521079 DOI: 10.1002/bjs.4790]

11 **Valverde J**, Martínez-Ródenas F, Pereira JA, Carulla X, Jiménez W, Gubern JM, Sitges-Serra A. Rapid increase in plasma levels of atrial natriuretic peptide after common bile duct ligation in the rabbit. *Ann Surg* 1992; **216**: 554-559 [PMID: 1444646]

12 **Padillo J**, Puente J, Gómez M, Dios F, Naranjo A, Vallejo JA, Miño G, Pera C, Sitges-Serra A. Improved cardiac function in patients with obstructive jaundice after internal biliary drainage: hemodynamic and hormonal assessment. *Ann Surg* 2001; **234**: 652-656 [PMID: 11685028]

13 **Fang Y**, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, Wang C. Pre-operative biliary drainage for obstructive jaundice. *Cochrane Database Syst Rev* 2012; **9**: CD005444 [PMID: 22972086 DOI: 10.1002/14651858.CD005444.pub3]

14 **Garcea G**, Chee W, Ong SL, Maddern GJ. Preoperative biliary drainage for distal obstruction: the case against revisited. *Pancreas* 2010; **39**: 119-126 [PMID: 19940799 DOI: 10.1097/MPA.0b013e3181bd65de]

15 **van der Gaag NA**, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; **362**: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]

16 **Eshuis WJ**, van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, Kuipers EJ, Coene PP, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. *Ann Surg* 2010; **252**: 840-849 [PMID: 21037440 DOI: 10.1097/SLA.0b013e3181fd36a2]

17 **Jagannath P**, Dhir V, Shrikhande S, Shah RC, Mullerpatan P, Mohandas KM. Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. *Br J Surg* 2005; **92**: 356-361 [PMID: 15672425 DOI: 10.1002/bjs.4864]

18 **Siddiqui AA**, Mehendiratta V, Loren D, Kowalski T, Fang J, Hilden K, Adler DG. Self-expanding metal stents (SEMS) for preoperative biliary decompression in patients with resectable and borderline-resectable pancreatic cancer: outcomes in 241 patients. *Dig Dis Sci* 2013; **58**: 1744-1750 [PMID: 23179157 DOI: 10.1007/s10620-012-2482-z]

19 **Coates JM**, Beal SH, Russo JE, Vanderveen KA, Chen SL, Bold RJ, Canter RJ. Negligible effect of selective preoperative biliary drainage on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. *Arch Surg* 2009; **144**: 841-847 [PMID: 19797109 DOI: 10.1001/archsurg.2009.152]

20 **Kleeff J**, Friess H, Büchler MW. Neoadjuvant therapy for pancreatic cancer. *Br J Surg* 2007; **94**: 261-262 [PMID: 17315287 DOI: 10.1002/bjs.5737]

21 **Adler G**, Seufferlein T, Bischoff SC, Brambs HJ, Feuerbach S, Grabenbauer G, Hahn S, Heinemann V, Hohenberger W, Langrehr JM, Lutz MP, Micke O, Neuhaus H, Neuhaus P, Oettle H, Schlag PM, Schmid R, Schmiegel W, Schlottmann K, Werner J, Wiedenmann B, Kopp I. [S3-Guidelines "Exocrine pancreatic cancer" 2007]. *Z Gastroenterol* 2007; **45**: 487-523 [PMID: 17607616 DOI: 10.1055/s-2007-963224]

22 **Wayne JD**, Abdalla EK, Wolff RA, Crane CH, Pisters PW, Evans DB. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. *Oncologist* 2002; **7**: 34-45 [PMID: 11854545]

23 **Wray CJ**, Ahmad SA, Matthews JB, Lowy AM. Surgery for pancreatic cancer: recent controversies and current practice. *Gastroenterology* 2005; **128**: 1626-1641 [PMID: 15887155]

24 **Staley CA**, Lee JE, Cleary KR, Abbruzzese JL, Fenoglio CJ, Rich TA, Evans DB. Preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for adenocarcinoma of the pancreatic head. *Am J Surg* 1996; **171**: 118-24; discussion 124-5 [PMID: 8554125 DOI: 10.1016/S0002-9610(99)80085-3]

25 **Talamonti MS**, Small W, Mulcahy MF, Wayne JD, Attaluri V, Colletti LM, Zalupski MM, Hoffman JP, Freedman GM, Kinsella TJ, Philip PA, McGinn CJ. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol* 2006; **13**: 150-158 [PMID: 16418882 DOI: 10.1245/ASO.2006.03.039]

26 **Hosein PJ**, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A, Narayanan G, Ribeiro A, Portelance L, Merchan JR, Levi JU, Rocha-Lima CM. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 2012; **12**: 199 [PMID: 22642850 DOI: 10.1186/1471-2407-12-199]

27 **Evans DB**, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Wang H, Cleary KR, Staerkel GA, Charnsangavej C, Lano EA, Ho L, Lenzi R, Abbruzzese JL, Wolff RA. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008; **26**: 3496-3502 [PMID: 18640930 DOI: 10.1200/JCO.2007.15.8634]

28 **Meszoely IM**, Wang H, Hoffman JP. Preoperative chemoradiation therapy for adenocarcinoma of the pancreas: The Fox Chase Cancer Center experience, 1986-2003. *Surg Oncol Clin N Am* 2004; **13**: 685-96, x [PMID: 15350942 DOI: 10.1016/j.soc.2004.06.013]

29 **Tempero MA**, Behrman S, Ben-Josef E, Benson AB, Cameron JL, Casper ES, Hoffman JP, Karl RC, Kim P, Koh WJ, Kuvshinoff BW, Melvin WS, Muscarella P, Sasson AR, Shibata S, Shrieve DC, Talamonti MS, Tyler DS, Vickers SM, Warren RS, Willett C, Wolff RA. Pancreatic adenocarcinoma: Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2005; **3**: 598-626 [PMID: 16194453]

30 **Stokes JB**, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, Rich TA, Adams RB, Bauer TW. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. *Ann Surg Oncol* 2011; **18**: 619-627 [PMID: 21213060 DOI: 10.1245/s10434-010-1456-7]

31 **Sahora K**, Kuehrer I, Eisenhut A, Akan B, Koellblinger C, Goetzinger P, Teleky B, Jakesz R, Peck-Radosavljevic M, Ba'ssalamah A, Zielinski C, Gnant M. NeoGemOx: Gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer. *Surgery* 2011; **149**: 311-320 [PMID: 20817204 DOI: 10.1016/j.surg.2010.07.048]

32 **Barugola G**, Partelli S, Crippa S, Capelli P, D'Onofrio M, Pederzoli P, Falconi M. Outcomes after resection of locally advanced or borderline resectable pancreatic cancer after neoadjuvant therapy. *Am J Surg* 2012; **203**: 132-139 [PMID: 21824596 DOI: 10.1016/j.amjsurg.2011.03.008]

33 **Hartwig W**, Schneider L, Diener MK, Bergmann F, Büchler MW, Werner J. Preoperative tissue diagnosis for tumours of the pancreas. *Br J Surg* 2009; **96**: 5-20 [PMID: 19016272 DOI: 10.1002/bjs.6407]

34 **Callery MP**, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009; **16**: 1727-1733 [PMID: 19396496 DOI: 10.1245/s10434-009-0408-]

35 **Harbour R**, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; **323**: 334-336 [PMID: 11498496]

36 **Assifi MM**, Lu X, Eibl G, Reber HA, Li G, Hines OJ. Neoadjuvant therapy in pancreatic adenocarcinoma: a meta-analysis of phase II trials. *Surgery* 2011; **150**: 466-473 [PMID: 21878232 DOI: 10.1016/j.surg.2011.07.006]

37 **Andriulli A**, Festa V, Botteri E, Valvano MR, Koch M, Bassi C, Maisonneuve P, Sebastiano PD. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol* 2012; **19**: 1644-1662 [PMID: 22012027 DOI: 10.1245/s10434-]

38 **Festa V**, Andriulli A, Valvano MR, Uomo G, Perri F, Andriulli N, Corrao S, Koch M. Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. *JOP* 2013; **14**: 618-625 [PMID: 24216547 DOI: 10.6092/1590-8577/1724]

39 **Bhayani NH**, Miller JL, Ortenzi G, Kaifi JT, Kimchi ET, Staveley-O'Carroll KF, Gusani NJ. Perioperative outcomes of pancreaticoduodenectomy compared to total pancreatectomy for neoplasia. *J Gastrointest Surg* 2014; **18**: 549-554 [PMID: 24165872 DOI: 10.1007/s11605-013-2393-0]

40 **Tan WJ**, Kow AW, Liau KH. Moving towards the New International Study Group for Pancreatic Surgery (ISGPS) definitions in pancreaticoduodenectomy: a comparison between the old and new. *HPB (Oxford)* 2011; **13**: 566-572 [PMID: 21762300 DOI: 10.1111/j.1477-2574.2011.00336.x]

41 **Laurence JM**, Tran PD, Morarji K, Eslick GD, Lam VW, Sandroussi C. A systematic review and meta-analysis of survival and surgical outcomes following neoadjuvant chemoradiotherapy for pancreatic cancer. *J Gastrointest Surg* 2011; **15**: 2059-2069 [PMID: 21913045 DOI: 10.1007/s11605-011-1659-]

42 **Bluemke DA**, Fishman EK. CT and MR evaluation of pancreatic cancer. *Surg Oncol Clin N Am* 1998; **7**: 103-124 [PMID: 9443989]

43 **Allema JH**, Reinders ME, van Gulik TM, van Leeuwen DJ, de Wit LT, Verbeek PC, Gouma DJ. Portal vein resection in patients undergoing pancreatoduodenectomy for carcinoma of the pancreatic head. *Br J Surg* 1994; **81**: 1642-1646 [PMID: 7827892]

44 **Harrison LE**, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? *Ann Surg* 1996; **224**: 342-37; discussion 342-37; [PMID: 8813262]

45 **Leach SD**, Lee JE, Charnsangavej C, Cleary KR, Lowy AM, Fenoglio CJ, Pisters PW, Evans DB. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. *Br J Surg* 1998; **85**: 611-617 [PMID: 9635805 DOI: 10.1046/j.1365-2168.1998.00641.x]

46 **Yekebas EF**, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thieltges S, Gawad KA, Schneider C, Izbicki JR. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 2008; **247**: 300-309 [PMID: 18216537 DOI: 10.1097/SLA.0b013e31815aab22]

47 National Comprehensive Cancer Network (NCCN). Guidelines in oncology: pancreatic adenocarcinoma 2008. Available at: http: //www.nccn.org/professionals/ physician\_gls/PDF/pancreatic.pdf. Accessed May 5, 2011

48 **Wagner M**, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004; **91**: 586-594 [PMID: 15122610 DOI: 10.1002/bjs.4484]

49 **Cameron JL**, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006; **244**: 10-15 [PMID: 16794383 DOI: 10.1097/01.sla.0000217673.04165.ea]

50 **Weitz J**, Rahbari N, Koch M, Büchler MW. The "artery first" approach for resection of pancreatic head cancer. *J Am Coll Surg* 2010; **210**: e1-e4 [PMID: 20113929 DOI: 10.1016/j.jamcollsurg.2009.10.019]

51 **Mollberg N**, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011; **254**: 882-893 [PMID: 22064622 DOI: 10.1097/SLA.0b013e31823ac299]

52 **Bachellier P**, Rosso E, Lucescu I, Oussoultzoglou E, Tracey J, Pessaux P, Ferreira N, Jaeck D. Is the need for an arterial resection a contraindication to pancreatic resection for locally advanced pancreatic adenocarcinoma? A case-matched controlled study. *J Surg Oncol* 2011; **103**: 75-84 [PMID: 21105000 DOI: 10.1002/jso.21769]

53 **Bockhorn M**, Burdelski C, Bogoevski D, Sgourakis G, Yekebas EF, Izbicki JR. Arterial en bloc resection for pancreatic carcinoma. *Br J Surg* 2011; **98**: 86-92 [PMID: 21136564 DOI: 10.1002/bjs.7270]

54 **MOORE GE**, SAKO Y, THOMAS LB. Radical pancreatoduodenectomy with resection and reanastomosis of the superior mesenteric vein. *Surgery* 1951; **30**: 550-553 [PMID: 14866700]

55 **Asada S**, Itaya H, Nakamura K, Isohashi T, Masuoka S. Radical pancreatoduodenectomy and portal vein resection. report of two successful cases with transplantation of portal vein. *Arch Surg* 1963; **87**: 609-613 [PMID: 14056238]

56 **Fortner JG**. Regional resection of cancer of the pancreas: a new surgical approach. *Surgery* 1973; **73**: 307-320 [PMID: 4265314]

57 **Sindelar WF**. Clinical experience with regional pancreatectomy for adenocarcinoma of the pancreas. *Arch Surg* 1989; **124**: 127-132 [PMID: 2910241]

58 **Yeo CJ**, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002; **236**: 355-66; discussion 366-8 [PMID: 12192322 DOI: 10.1097/01.SLA.0000027272.08464.0B]

59 **Fuhrman GM**, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, El-Naggar AK, Fenoglio CJ, Lee JE, Evans DB. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. *Ann Surg* 1996; **223**: 154-162 [PMID: 8597509]

60 **Roder JD**, Stein HJ, Siewert JR. Carcinoma of the periampullary region: who benefits from portal vein resection? *Am J Surg* 1996; **171**: 170-14; discussion 170-14; [PMID: 8554135 DOI: 10.1016/S0002-9610(99)80094-4]

61 **Winter JM**, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006; **10**: 1199-210; discussion 1210-1 [PMID: 17114007 DOI: 10.1016/j.gassur.2006.08.018]

62 **Richter A**, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. *World J Surg* 2003; **27**: 324-329 [PMID: 12607060 DOI: 10.1007/s00268-002-6659-z]

63 **Gouma DJ**, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, Obertop H. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 2000; **232**: 786-795 [PMID: 11088073]

64 **McPhee JT**, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME, Anderson FA, Tseng JF. Perioperative mortality for pancreatectomy: a national perspective. *Ann Surg* 2007; **246**: 246-253 [PMID: 17667503 DOI: 10.1097/01.sla.0000259993.17350.3a]

65 **Howard TJ**, Villanustre N, Moore SA, DeWitt J, LeBlanc J, Maglinte D, McHenry L. Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. *J Gastrointest Surg* 2003; **7**: 1089-1095 [PMID: 14675720]

66 **Bachellier P**, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD, Jaeck D. Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? *Am J Surg* 2001; **182**: 120-129 [PMID: 11574081]

67 **Ramacciato G**, Mercantini P, Petrucciani N, Giaccaglia V, Nigri G, Ravaioli M, Cescon M, Cucchetti A, Del Gaudio M. Does portal-superior mesenteric vein invasion still indicate irresectability for pancreatic carcinoma? *Ann Surg Oncol* 2009; **16**: 817-825 [PMID: 19156463 DOI: 10.1245/s10434-008-0281-8]

68 **Siriwardana HP**, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. *Br J Surg* 2006; **93**: 662-673 [PMID: 16703621 DOI: 10.1002/bjs.5368]

69 **Martin RC**, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. *Arch Surg* 2009; **144**: 154-159 [PMID: 19221327 DOI: 10.1001/archsurg.2008.547]

**P-Reviewers:** Borkakoti J, Milella M, Mizuno N, Olah A

**S-Editor:** Zhai HH **L-Editor: E-Editor:**

**Table 1 Methods data of the three published meta-analysis on neoadjuvant therapy in pancreatic carcinoma *n* (%)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Year** | ***n*** | **Type study** | **Mean age (yr)** | **Chemotherapy** | | | **Radiotherapy** | | |
| **Agents Regimen** | | | **Dose (Gy) IORT** | | |
| Gillen 2010 | 80-09 | 111 | 78P-33R | 62.5 | 107 (96.4) | 5FU >GEM>Tax>Others | 44S+48C | 104 (93.7) | 24-63 | 13 (12.5) |
| Assifi 2011 | 93-10 | 14 | 14P-0R | N/P | 14 (100) | GEM>5FU | 3S+11C | 12 (85) | 30-50 | 0 (0) |
| Andriulli 2012 | 97-08 | 20 | 20P-0R | 63 | 20 (100) | GEM>Cis | 13S+7C | 17 (85) | 30-40 | N/P |

P: Prospective; R: Retrospective; 5FU: 5-fluor-uracile; GEM: Gemcitabine; Cis: Cisplatine; Tax: Taxanes; S: Single; C: Combined. IORT: Intraoperative radiotherapy. N/P: Not provided.

**Table 2 Results of the three published meta-analysis on neoadjuvant therapy in pancreatic carcinoma in terms of safety (postoperative morbidity and toxicity) and efficacy (response and resection)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Toxicity (%)** | **Response (%)** | | | **Resection (%)** | | | | **Postoperative Morbidity (%)** |
| **Complete Partial Progression** | | | **Resected R0 Mono Combined** | | | |
| Gillen 2010 | 1: 26.3  2: 31.3 | 3.6  4.8 | 30.6  30.2 | 20.9  20.8 | 73.6  33.2 | 60.4  26.2 | 80.9  27.3 | 66.2  33 | 26.7  39.1 |
| Assifi 2011 | 1: 37  2: 46.2 | 0.8  4 | 9.5  31.8 | 17  21.8 | 65.8  31.6 | 55.9  19.6 | N/P | N/P | N/P  N/P |
| Andriulli 2012 | 1: 29  2: 33 | 12  27 | | 15  32 | 81.2  26.4 | 66.4  16 | N/P | N/P | N/P  N/P |

1: Group of patients with potentially resectable pancreatic adenocarcinoma; 2: Group of patients with borderline resectable pancreatic adenocarcinoma. Toxicity: Only grade 3 and 4; Resection R0: Complete resection of the tumor; Resection Mono: Single chemotherapy drug; Resection Combined: Combined chemotherapy drugs; N/P: Not provided.

**Table 3 Results of the three published meta-analysis on neoadjuvant therapy in pancreatic carcinoma in terms of survival and mortality**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Mean Survival**  **(mo)** | **Mortality (%)** | **Estimated survival (%)** | |
| **1-yr 2-yr** | |
| Gillen 2010 | 1: 23.3  2: 20.5 | 3.9  7.1 | 77.9  79.8 | 47.4  50.1 |
| Assifi 2011 | 1: 15.1  2: 11.2 | N/P | N/P | N/P |
| Andriulli 2012 | 1: 18.8  2: 14 | N/P | 91.7  67.2 | 86.3  54.2 |

Referred only after surgical resection. 1: Group of patients with potentially resectable pancreatic adenocarcinoma; 2: Group of patients with borderline resectable pancreatic adenocarcinoma. N/P: Not provided.