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

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**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

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**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.

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**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: 26.32: 31.3 | 3.64.8 | 30.630.2 | 20.920.8 | 73.633.2 | 60.426.2 | 80.927.3 | 66.233 | 26.739.1 |
| Assifi 2011 | 1: 372: 46.2 | 0.84 | 9.531.8 | 1721.8 | 65.831.6 | 55.919.6 | N/P | N/P | N/PN/P |
| Andriulli 2012 | 1: 292: 33 | 1227 | 1532 | 81.226.4 | 66.416 | N/P | N/P | N/PN/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: 23.32: 20.5 | 3.97.1 | 77.979.8 | 47.450.1 |
| Assifi 2011 | 1: 15.12: 11.2 | N/P | N/P | N/P |
| Andriulli 2012 | 1: 18.82: 14 | N/P | 91.767.2 | 86.354.2 |

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.