Chapter 10

# The Role of Neoadjuvant Therapy in Surgical Treatment of Pancreatic Cancer

## *Dealing with Borderline Resectable Pancreatic Cancer, What Comes First?*

Laura Antolino, Paolo Aurello, Federico Todde, Silvia Amato, Niccolò Petrucciani, Andrea Kazemi Nava, Giuseppe Nigri, Stefano Valabrega, Giovanni Ramacciato and Francesco D'Angelo

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76750

**Abstract**

Pancreatic cancer is a leading cause of cancer-related death worldwide, and its burden is destined to increase. Multimodal treatment is crucial to achieve a cure, but standardization is far to come. Borderline resectable disease is the most challenging situation to face. An anatomically resectable disease may hide a biologically aggressive or undiagnosed systemic disease. Whether the patient has to undergo surgery first or after locoregional or systemic therapy is still unknown. Decision-making stands on low-quality evidences since RCTs are lacking. Neoadjuvant treatment may downstage the tumor and treat an early systemic disease, selecting patients for surgery in order to achieve a margin-free resection and avoid early recurrences and useless pancreatectomies. Resectable patients without other worrisome features may benefit from a surgery-first approach, while all other nonmetastatic patients should be enrolled in trials to rule out the outcomes of neoadjuvant treatments.

**Keywords:** pancreatic cancer, neoadjuvant treatment, pancreatic surgery, borderline resectable, locally advanced

## 1. Introduction

By 2030 pancreatic cancer (PaC) is expected to be the second cancer-related cause of death [1]. Its 5-year survival in nonmetastatic stages currently ranges between 3 and 14% [2] regardless of treatment. Surgery remains the only chance for cure since the 5-year survival in T1 N0 resected patients reaches 55.2% [3]; therefore, the standard of care advocates a surgery-first approach in case of resectable disease followed by adjuvant treatment (ADT), but neoadjuvant approaches are spreading either in resectable or borderline resectable (BLR) and locally advanced (LA) patients. The National Comprehensive Cancer Network (NCCN) states that there is limited evidence to recommend specific neoadjuvant regimens off-study [4]. While the only choice in LA PaC is a locoregional chemoradiation (CRT) or systemic chemotherapy (CHT) and subsequent revaluation, for resectable and BLR, we must choose between a surgery-first approach and a neoadjuvant treatment (NADT). Over 40% of patients who have clinically a resectable disease are found unresectable at surgery, even though this percentage drops to 20% if a diagnostic laparoscopy is added to the preoperative diagnostic panel [5]; one out of five patients are eventually misdiagnosed as resectable or BLR while having a LA disease. Even in a high-volume referral hospital, the percentage of successfully resected patients at surgical exploration is as low as 51% [6]. Results of first-line pancreatectomy may be very poor with only 20% of patients receiving radical surgery and 80% presenting tumor within 1 mm from margin or direct microscopic margin infiltration [7]. In a Korean series, 9.1% of patients presenting with PaC diagnosis were clinically staged as BLR [8], about 27% of whom required a vascular resection (VR) in order to achieve their pancreatectomy [9], but histological invasion of resected vessels is confirmed only in 56.7% of specimens [10]. Finally, up to 28% of successfully resected patients will not undergo ADT because of surgical morbidity, poor performance status, refusal, or early recurrence [10]. As Buchler said, unfortunately available evidences supporting NADT come from retrospective studies in which treatment protocols vary greatly and patient cohorts are often mixed with resectable, BLR, and LA [11].

Whereas features of a metastatic disease are evident, dealing with PaC and NADT, a foreword has to be spent to clarify the terminology "resectable," "borderline resectable," and "locally advanced." To that end, we will first focus on the definition of borderline resectable disease and then analyze the outcomes of NADT from a surgical point of view.

## 2. Definition of borderline resectable pancreatic cancer

In origin the term "marginally resectable" pancreatic cancer was used for tumors without a 180° free fat plane around SMA, SMV, or PV for at least 1 cm [12]; this outlined a tumor with a high probability of positive-margin surgery. In the following years, several revisions took place, and the term "borderline resectable" was adopted, but still there is no universal consensus on its definition.

### 2.1. Anatomic criteria

The pancreatic glands lay in the deepest abdomen in direct contact with several major vascular structures. It is encased between the mesenteric root and the two main splanchnic arteries.

http://dx.doi.org/10.5772/intechopen.76750

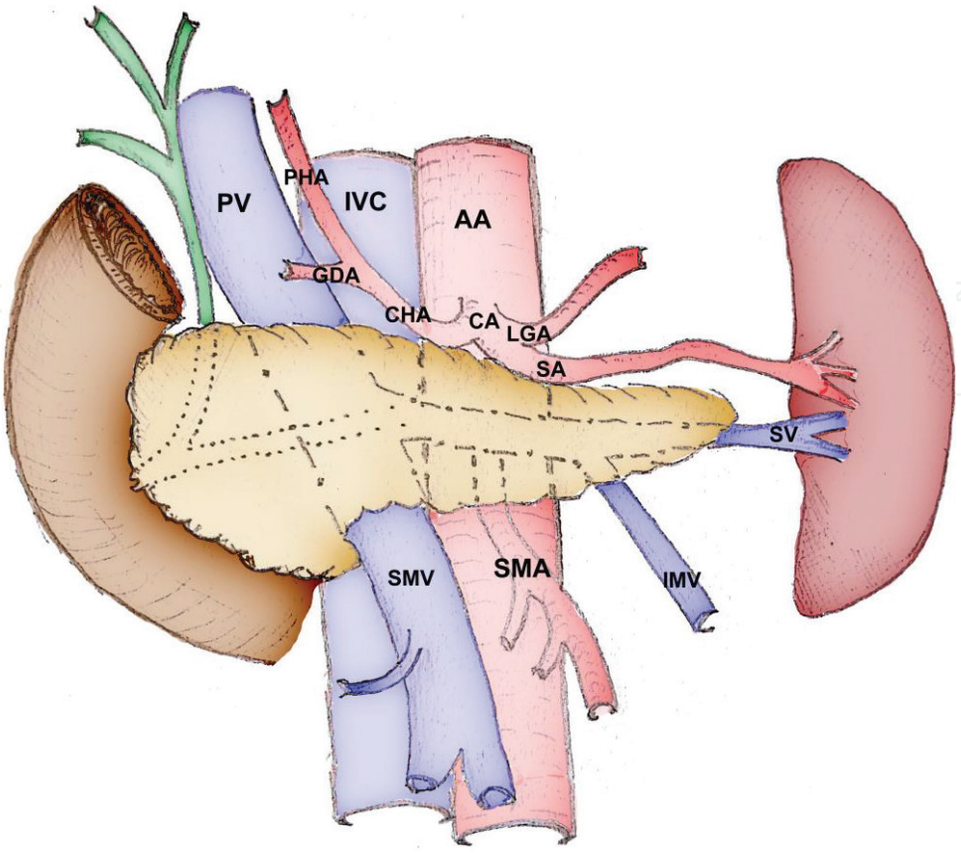


**Figure 1.** Schematic representation of pancreatic vascular relationships. AA, Aorta; IVC, inferior vena cava; PHA, proper hepatic artery; PV, portal vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery; IMV, inferior mesenteric vein; SV, splenic vein; SA, splenic artery; LGA, left gastric artery; CA, celiac axis; CHA, common hepatic artery; GDA, gastro-duodenal artery.

With the PV/SMV-SMA plane being its bed and the celiac trunk being its roof, resectability and thus possibility of cure are played in few millimeters. As shown in **Figure 1**, PaC may arise in the head, body, or tail of the pancreas; therefore, respectability definition differs along with its location whether on the right of the left border of PV/SMV (head) or on the left of the left aortic border (tail) or in between (body). In surgery few things are technically impossible; this is heavily surgeon-dependent because it relies in its skills and will. That is why several institutions/associations have tried and classified PaC resectability depending on its involvement of nearby structures. In **Table 1** the anatomic criteria for definitions of borderline resectable disease from the classifications of five major institutions are shown: MD Anderson Cancer Center [9], American Hepato-Biliary-Pancreatic Association/Society of Surgery of the Alimentary Tract/Society of Surgical Oncology (AHBPA/SSAT/SSO) [13], Alliance A021101 [14], IAP [3], and NCCN [4]. Any situation with a more extensive vascular involvement will obviously be classified under the "locally advanced/unresectable" definition, whereas a less extensive one will define a resectable disease. Despite the effort to standardize definitions and make patients and features comparable among radiologist and surgeons, in some classifications, terms like "allowing for safe reconstruction" still appear increasing confusion among professionals and trials. It is interesting how some may consider a unique SMV/PV <180° involvement that implies a venous resection, as a resectable disease, whereas an arterial involvement is always considered at least borderline resectable; this is due to the surgical

| | |
|---|---|
| International consensus IAP [3] | BR-PV (SMV/PV involvement alone):<br>• SMV/PV: tumor contact 180° or greater or bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum.<br>• SMA, CA, CHA: no tumor contact/invasion.<br>BR-A (arterial involvement):<br>• SMA, CA: tumor contact of less than 180° without showing deformity/stenosis;<br>• CHA: tumor contact without showing tumor contact of the PHA and/or CA. |
| NCCN Guidelines [4] | VENOUS<br>• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but allowing for resection and reconstruction<br>• Solid tumor contact with the inferior vena cava (IVC).<br>ARTERIAL<br>If head/uncinate process:<br>• Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for resection and reconstruction.<br>• Solid tumor contact with the SMA of ≤180°<br>• Solid tumor contact with variant arterial anatomy<br>If body/tail:<br>• Solid tumor contact with the CA of ≤180°<br>• Solid tumor contact with the CA of >180° without involvement of the AA and with intact and uninvolved GDA thereby permitting a modified Appleby procedure. |
| Intergroup criteria Alliance A021101 [14] | • a TVI with SMV or PV ≥180° of the circumference of either vein's wall or short-segment occlusion of either vein amenable to reconstruction;<br>• any TVI with CHA amenable to reconstruction;<br>• a TVI with SMA <180° of the circumference of the vessel wall. |
| AHBPA/SSO/SSAT consensus statement [13] | • Venous involvement of the SMV/PV demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/PV but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but allowing for resection and reconstruction.<br>• GDA encasement up to the CHA with either short segment encasement or direct abutment of the CHA, without extension to the CA.<br>• Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall. |
| MD Anderson Cancer Center [9] | • Tumor abutment (<180° of the circumference of the vessel) of the SMA or CA;<br>• Tumor abutment or encasement (>180° of the circumference of the vessel) of a short segment of the CHA;<br>• Short-segment occlusion of the SMV, PV, or SMV-PV confluence amenable to vascular resection and reconstruction. |

BR, borderline resectable; PV, portal vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery; CA, celiac artery; CHA, common hepatic artery; PHA, proper hepatic artery; AA, aorta; GDA, gastroduodenal artery; IVC, inferior vena cava; TVI, tumor-vessel interface.

**Table 1.** Anatomic criteria for borderline resectable disease.

implications of venous and arterial resections, as the former does not increase either postoperative morbidity or mortality [15].

### 2.2. Biologic criteria

Besides anatomical features, PaC may have an intrinsic undiagnosed risk of early recurrent or micrometastatic disease linked to its biology; indeed, early recurrence occurs in 25% of resected patients [16], thus making surgery ineffective. Herein, some examples of biomarkers are predicting more aggressive disease. Preoperative CA19.9 > 300 U/ml and tumor size >3 cm [16], preoperative CEA >3 ng/ml and CA19.9 > 75 U/ml, N+ disease, and T3–T4 [17] are independent negative prognostic factors. Moreover, patients presenting with local disease have a 22% of SMAD-4 loss versus 78% of patients with metastatic disease [18]. In an era of tailored treatments, it should be reminded that every patient and every disease have their own characteristics that have to be taken into account in the therapeutic decision-making. Lately, circulating tumor cells have been investigated as prognostic biomarkers, three or more CTCs/4 ml were an independent prognostic factor for the overall survival, and it accurately predicted occult metastatic disease [19]. That is why during the 20th meeting of the International Association of Pancreatology held in Sendai in 2016 a consensus of borderline resectable definition has been drawn up that includes biological and conditional criteria. Biological criteria are a CA19.9 above 500 IU/ml and regional lymph node metastasis proven by biopsy or PET-CT. Conditional host-related criteria depends on the patient's performance status defined by a PS score of 2 or more [3]. Thus, patients satisfying at least either an anatomic, biologic, or conditional criteria are classified as borderline resectable.

## 3. Neoadjuvant treatment

### 3.1. Indications

A preoperative treatment has several theoretical advantages. First of all it delivers systemic therapy to all patients: at least 30% of patients do not receive adjuvant therapy after resection for a variety of reasons [20]. Then, it is shed in a highly perfused tumor bed that allows an in vivo testing of the tumor sensibility to the chemotherapeutic agent. Moreover, NADT should increase the probability of negative margin surgery (R0) and decrease the likelihood of nodal involvement and vascular resection (VR). Finally, it identifies tumors with an aggressive biology and picks out patients who would not benefit from surgery because of early progression, recurrence, or previously undiagnosed metastatic disease. Whether those presumed advantages translate into real world is still under investigation. The role of NADT for PaC, especially for primary resectable ones, still remains controversial among other reasons because a quote of those patients undergoing neoadjuvant treatment will experience severe side effects and complications [21]. A comprehensive meta-analysis provides marginal support to the assumed benefit of contemplating neoadjuvant therapies for patients whose tumor was judged resectable at preoperative staging [22]. Neoadjuvant treatment should always be offered to BLR and LA diseases; nevertheless, since preoperative staging in PaC is far from being accurate, with 22.5% of patients brought to the operating room with curative intent found to be metastatic [6], it is crucial to treat every patient within registered trials.

### 3.2. Outcomes

#### *3.2.1. Toxicity*

Unfortunately, every neoadjuvant regimen brings its own risk of toxicity, and a successful resection is more likely in case of completion of NADT [23]. A serious side effect might indefinitely postpone surgery; that is why resectable patients are exposed to a shift from being a surgical patient to never being proposed for cure. This has to be taken into account while proposing such treatment in selected patients. As shown in **Table 2**, it is reported that 29.4–36% of patients will experience grade 3 or 4 adverse effects during preoperative treatment [22, 24, 25], with 6% of patients giving up treatment because of its toxicity [26]. But up to 91% of patients initiated to NADT achieve the intended preoperative protocol [24].

#### *3.2.2. Pathologic response*

As seen in **Table 3**, up to 11.3% of BLR or LA PaC presented a complete pathologic response (ypT0) after NADT [27]. In this paper 83% of patients with ypT0 were dead or relapsed at a

| Author, year | Article type | Grade 3/4 toxicity |
|---|---|---|
| Dhir, 2017 [24] | Metanalysis | 36% |
| Marthey, 2015 [26] | Cohort study | 26% |
| Andriulli, 2012 [22] | Metanalysis | 31% |
| Gillen, 2010* [25] | Metanalysis | 29,4% |
| Kapoor, 2014 [37] | Prospective | 0% |

*PaC AND periampullary tumors.

**Table 2.** Major toxicity.

| Author, year | Article type | Complete pathological response | Partial pathological response | Stable disease | Progression |
|---|---|---|---|---|---|
| Dhir, 2017 [24] | Metanalysis | n.a. | 20% | 59% | 16% |
| Hashemi-Sadraei, 2017 [27] | Retrospective | 11.3% (of resected patients) | n.a. | n.a. | n.a. |
| Marthey, 2015 [26] | Cohort study | 5.2% | 28% | 56% | 16% |
| Addeo, 2015 [40] | Retrospective | 8.8% | n.a. | n.a. | n.a. |
| Andriulli, 2012 [22] | Metanalysis | n.a. | 22%* | 50% | 25% |
| Gillen, 2010† [25] | Metanalysis | 3.9% | 29.1% | 43.9% | 20.8% |
| Heinrich, 2008 [38] | Phase II trial | 0% | n.a. | n.a. | n.a. |
| Kim, 2017 [8] | Retrospective | 0% | 65% | 35% | 0% |

*Including complete path. resp.

†Pancreatic cancers AND periampullary tumors.

**Table 3.** Pathological response.

http://dx.doi.org/10.5772/intechopen.76750

median follow-up of 21.3 months [27], suggesting a systemic undiagnosed or uncontrolled disease. A 2010 meta-analysis shows 3.9% of complete pathologic response, 29.1% partial response, 43.9% stable disease, and 20.8% of progression during NADT [25]. A more recent 2017 meta-analysis confirms those data with partial response or stable disease in 79% of treated patients (20 and 59%, respectively) while in progression in 16% of cases [24]. According to Gillen and coll. Pooled percentages of pathologic response did not vary much in the two groups of initially deemed resectable and non-resectable tumor patients [25]; this may be due to the fact that resectability is defined only by anatomical features, while probably a biological understanding of the disease would enhance clinical staging. Anyhow unfortunately, there are 16–32% of patients that will have to stop treatment because of progression [22, 26].

## 4. Surgery

Surgery is ideally recommended 4 to 8 weeks after neoadjuvant treatment [4] although it has been postulated that patients with a longer (>10 weeks) interval between RT and CHT and surgery could be more likely to have an improved pathological response, R0 resection, and OS [28]. According to a consensus statement drafted in 1999 [29], "standard" pancreatoduodenectomy includes regional lymphadenectomy around the duodenum and pancreas; "radical" pancreatoduodenectomy includes regional lymphadenectomy plus skeletonization of the proper hepatic artery (PHA), common hepatic artery (CHA), superior mesenteric artery (SMA) between the aorta (AA) and inferior pancreaticoduodenal artery, and the CA; dissection of the anterolateral aspect of the aorta and inferior vena cava (IVC) includes Gerota's fascia; and lastly "extended radical" pancreatoduodenectomy includes "radical" pancreatoduodenectomy and clearance of the anterior AA between the diaphragmatic hiatus (around the CA) and the origin of the common iliac arteries. Currently, extended lymphadenectomy is no more recommended as it increases costs [30], blood loss, and operative time without adding survival or staging advantages [31]. For what concerns vascular involvement, venous resection doesn't affect preoperative mortality even if it may slightly increase morbidity; instead, arterial resection is still under major debate since it seems to have acceptable outcomes only in single high-volume centers' reports [32]. In a French experience, patients that received a venous resection but whose tumor did not infiltrate the vessel at final histology, lived longer either than patients whose tumor eventually infiltrate the vein either than patients who did not require a vascular resection (42 months vs. 24 vs 22 respectively $p = .04$) [33]. This may even justify extreme positions such as calling upon routine VR during pancreatectomies. According to the latest staging system of the American Joint Committee on Cancer (8th edition), venous infiltration doesn't modify T stage: indeed T1 to 3 stages relies on tumor's dimension and T4 is defined only in case of arterial involvement [34]; therefore, venous resection should not hold back surgeons from performing a pancreatectomy with curative intent.

### 4.1. Resectability

In a 2010 meta-analysis, surgical exploration after NADT was attempted in 69.5% of patients, but only 50.7% of NADT patients were eventually successfully resected (that is 77.9% of explored patients) [25]. In a more recent meta-analysis, the rate of resected patients raised to

| Author, year | Article type | ITT population | Explored/ITT | Resected/ITT | Vascular resection/ resected |
|---|---|---|---|---|---|
| Epelboym, 2014 [42] | Retrospective | Mixed | ITT=explored | 82.2% | 64.3% |
| Gillen, 2010* [25] | Metanalysis | Mixed | 69.5% | 50.7% | n.a. |
| Sherestha, 2017 [36] | Retrospective | BLR | 54.9% | 44% | n.a. |
| Kim, 2017 [8] | Retrospective | BLR | ITT = explored | 85% | 26.5% |
| D'Angelo, 2017 [35] | Metanalysis | Mixed | n.a. | 65% | n.a. |
| Addeo, 2015 [40] | Retrospective | Mixed | ITT=explored | 77.5% | 97.7% |
| Marthey, 2015 [26] | Cohort study | LA | n.a. | 66% | n.a. |
| Kapoor, 2014 [37] | Prospective | LA | n.a. | 26.7% | n.a. |
| Andriulli, 2012 [22] | Metanalysis | Mixed | 66% | 74% (of explored) | n.a. |
| Heinrich, 2008 [38] | Phase II trial | Resectable | 93% | 89.28% | 12.5% |

ITT, intention to treat; PaC, pancreatic cancer; BLR, borderline resectable; LA, locally advanced.
*PaC AND periampullary tumors.

**Table 4.** Resectability.

65%, but reported percentages vary from 26.7% to 89.28% depending on variability of protocols and patients [35]. In fact resection was more likely in resectable patients (73.6%) than in non-resectable ones (33.2%) [25]. In John Hopkins Hospital's experience, recently published, resection in BLR patients after neoadjuvant treatment was achieved in 44% of cases [36], while it was possible only in 26.7% of LA patients in an Indian report [37] versus 89.28% of pancreatectomies in resectable patients of a Swiss trial [38]. Those are single experiences that cannot reflect general reality, and the few existing neoadjuvant RCTs report a protocol achievement range of 18.18–70% [39]. Anyway, after neoadjuvant treatment between 26.5% [8] and 97.7% [40] of patients successfully receiving a pancreatectomy will require a VR. **Table 4** reports resection's outcomes of selected experiences and meta-analysis.

### 4.2. Morbidity and mortality

According to the recently reported experience of an Italian group with more than 150 pancreatectomies per year, NADT exposes patients to a reduced incidence of postoperative fistula and hemorrhage; unfortunately, in spite of this, the average clinical burden is increased [41]. Back in 2010 a morbidity of 34.2% with a mortality of 5.3% in eventually resected patients was reported as a meta-analytical data after NADT [25]. Some claimed perioperative mortality to be much higher (6.7–7%) after NADT with FOLFIRINOX [26, 40, 42] compared to upfront

resected patients regardless of VR, while others reported mortality in PV/SMV resection to be as low as 3% [33]. In literature a great amount of data make it muddler to understand the picture of the actual situation.

### 4.3. Resection margins

The goal of multimodal treatment is to achieve a margin-free surgery, taking into account that additional resection to achieve negative neck margin after R1 frozen section is not associated to improve survival [43]. In pancreatectomies' specimens the most frequently involved margin is the retroperitoneal one (39%) [6]; that is why VR assumes a central role in academic discussions. In fact among patients requiring VR NADT reduced significantly R1 rate (from 34.9 to 19.6%) [40]. After NADT, intention-to-treat (ITT) R0 rates have been reported to be 23–63% depending on their preoperative assessed resectability [24]. In resected patients R0 rate was estimated by a meta-analysis to be as high as 94%; that is to say that this data comes from nonrandomized trials [35]. Indeed, clear resection margins were present in 40% and 75% of cases in Landry [44] and Palmer's [45] RCTs. Lastly, pathologists have to be aware that after a preoperative treatment what seems to be a tumor-free margin could be only the expression of a reduction of density of tumor cells [46].

## 5. Role of adjuvant treatment

In several trials a significant benefit of ADT after pancreatectomy has been demonstrated [39], but whether additional adjuvant treatment is necessary in preoperatively treated patients is not clear as it may not provide additional survival benefit [40, 47]. In a Korean series 5.9% of patients undergone NADT and pancreatectomy recurred before having the chance to begin ADT [8]. In a Japanese experience, NADT was found to be a negative factor in predicting failure to achieve ADT therapy along with preoperative prognostic nutritional index, intraoperative blood transfusion, organ/space surgical site infections, and advanced UICC stage; however, this association was not confirmed at multivariate analysis, and only poor prognostic nutritional index, intraoperative blood transfusions, and organ/space surgical site infections were confirmed to be significantly associated with ADT dropout [48]. What is the real weight of NADT in precluding the administration of ADT? An American group reported the administration of ADT to 90% of resected patients after a long-term NADT regimen [23]; thus, all that matters is probably only a correct patient selection.

## 6. Survival

Survival goes hand in hand with successful surgical resection with a wide clear (R0) margin (>1 mm) giving the chance for an OS of 35 months, while R0 < 1 mm of 16 months involved margin (R1) resections of 14 months and unresected patients only 11 months ($p < .001$) [6]. Even in case of complete pathologic response (ypT0) after NADT and pancreatectomy cure is not guaranteed; indeed, in a series of ypT0 patients, 83.3% were dead or relapsed after a median of 21.3 months [27]. In NADT patients, resection hangs the scales in survival: in a meta-analysis OS in eventually resected patients was 22.78 months versus 9.89 in non-resected patients with

| Author, year | Type of article | ITT-OS (months) |
|---|---|---|
| Andriulli, 2012 [22] | Metanalysis | 16.4 |
| D'Angelo, 2017 [35] | Metanalysis | 16.7 |
| Sherestha, 2017 [36] | Retrospective | 15.1 |

ITT-OS, intention-to-treat overall survival.

**Table 5.** Survival.

an ITT OS of 16.7 months (please see **Table 5**) [36]. Such results are in line with a high-volume center such as Johns Hopkins Hospital, in which after NADT median overall survival (mOS) of resected patients was 25.8 months versus 11.9 months in eventually non-resected patients [36]. Results in the setting of RCTs aren't equally encouraging with ITT OS ranging 9.9–19.4 months in NADT setting versus 12.5–29.8 months in ADT one [39], but it shouldn't be forgotten that in the former we are dealing with resectable patients, while in the latter with resected ones; therefore, we could make a comparison only including in the latter group also patients who undergone explorative laparotomies. In a retrospective series, thanks to less lymphovascular invasion, less perineural invasion, and lower T and N stages, NADT-treated and NADT-resected patients presented a better median overall survival than primarily resected ones (27.3 months vs. 19.7 months, $p < .05$) [42]. In their experience, concerning vascular resections, there was no difference among NADT patients between VR+ and VR- in terms of OS [42].

## 7. Discussion

Every surgery resident is raised with two warnings:

> *"Eat when you can, sleep when you can, and don't mess with the pancreas."*

and

> *"God put the pancreas in the retroperitoneum so the surgeon won't mess with it."*

Perioperative mortality in pancreatectomies has been as high as 15% in the 1950s–1970s and since then has dropped to 1.5% in selected centers [49]. Nevertheless, pancreatic surgery for PaC has still high in-hospital mortality rates, as highlighted by an analysis of the German national database; it ranges from 12.2% in very-low-volume hospitals (with a median of four resections per year) to 7.1% in high-volume ones (with a median of 105 resections per year) [50]. Surgery is the only chance for cure of patients affected by PaC—and besides it decreases costs compared to palliative treatments [51]—but multimodal treatment is crucial for long-term survival [52]. Therefore, patients' selection has to be accurate since in one hand patients sent to NADT may miss the window for resection and in the other surgical complications may indefinitely postpone systemic treatment. Currently, there are no reliable clinical predictors of resectability [36]: in order not to lose the chance for resection, all patients receiving NADT should be surgically explored unless evident metastatic disease as fibrosis and inflammation can mimic a LA unresectable disease. As Buanes said, "one of the major problems worldwide is the underutilization of surgery in resectable pancreatic cancer" [53], and, especially after NADT, clinical staging

is unreliable. Indeed, there may be relevant tumor regression during NADT around involved vessels despite the absence of radiographic signs of tumor downstaging [54]. Not even PET-CT has shown to be reliable in differentiating benign from malignant disease after NADT [55].

In Miura' study, while in the ITT analysis, clinically BLR disease was an independent poor prognostic indicator, among resected patients OS did not differ between preoperatively classified resectable and BLR patients [56]. Similarly, OS of previously resected patients (20.87 months) was not better than the overall resected ones (22.78 months) in a recent meta-analysis [35]; this reflects the inadequacy of current preoperative staging and confirms that once resected, preoperative staging doesn't influence patients' outcomes. Once more, our efforts have to be straight at bringing patients to a curative surgery.

Supporters claim NADT to increase patients' selection, but unfortunately despite NADT, there is still a proportion of patients early progressing after surgery [8], for those patients we need more accurate staging and prognostic biomarkers in order to avoid useless surgery.

Overall, only 57.7% of PaC patients will receive the intended ADT—of which 24.1% more than 70 days after surgery—and this is mainly due to surgical complications: a wound dehiscence may seem trivial, but it lowers the percentage of patients receiving systemic therapy to 43.6% versus 61.8% in patients without any postoperative morbidity [57]. NADT bypasses this dropout administrating treatment before surgery; the price to pay is that about one-third of patients experiencing major toxicity and about one-fifth progressing, but in resected ones, surgery seems not to be affected by the worst outcomes.

That NADT is safe and helpful in upfront technically unresectable patients and is self-evident, which other choices would they have? But how can we know if it is advisable in resectable patients regardless to vascular (whether venous or arterial) or en bloc multi-organ resections? A German group tried to design an RCT comparing NADT versus upfront surgery, in both cases followed by ADT, to rule out the question. Unfortunately, even if a slight increase in OS, R0, and N0 rates was seen in NADT arm, the trial had to be stopped due to slow recruiting; thus, sample size was not reached and results were not significant [58]. According to Mellon and colleagues, patients with BLR or LA PaC and sufficient response to neoadjuvant multi-agent chemotherapy and stereotactic body radiation therapy have similar or improved perioperative and long-term survival outcomes compared to upfront resected patients [59].

The problem dealing with NADT is that RCTs are lacking; the existing three trials conducted on resectable PaC report a protocol achievement of 18.18–70% and an ITT survival of 9.9–19.4 months [39]. Selected retrospective single-institution experiences over resectable BLR and LA PaC report OS up to 43.4 months in resected patients following chemotherapy or chemo-radiation [60]. In a paper comparing NADT in BLR-LA to upfront resected patients, the ITT analysis showed worse survival for the former (17.0 vs. 22.1 mo, $p = 0.029$); such comparison has little significance because in the first group 61.6% of patients was eventually unresectable, while the upfront surgery group accounted only resected and adjuvant-treated patients [59]. Indeed, there was no significant difference and even a slight trend favoring NADT, in survival between the two groups among only resected patients (33.5 vs. 23.1 mo, $p = 0.057$) [59].

Histological confirmation of the disease is mandatory before administering NADT even though up to 16% of preoperatively cyto−/histologically diagnosed PaC eventually receive a

final pathological diagnosis other than PaC [38], thus receiving a useless neoadjuvant treatment. In Golcher's study pathological diagnosis of PaC at biopsy has been rejected in 4.5% of resected patients (because of the finding of a distal choledochal adenocarcinoma and a duodenal adenocarcinoma) [58].

## 8. Conclusions

The use of different resectability classifications, different NADT protocols, and selective reporting in the past years makes the comparison of literature extremely tricky. Outcomes tend to be better outside an RCT context; literature is influencing our conduct, but strong evidences come only from well-designed randomized trials. The unanimous adoption of the International Association of Pancreatology's classification [3] and standardized protocols and trials might clarify the impact of neoadjuvant treatments on the survival of those patients.

Assuming that patients are unresectable at diagnosis in the vast majority of cases; that even if they are suitable for NADT, more than 20% give up because of progression or toxicity; that barely an half is then resected; that, of those, up to 20% have positive margins; and that nor a negative resection margin nor a complete pathologic response shelters the patient from recurrence, we may say that nowadays PaC treatment desperately needs un upgrading.

Waiting for strong evidences, a reasonable behavior could be to resect all patients primarily resectable without any biologic worrisome feature (high CA19.9, high CEA, tumor >3 cm, positive nodes) and to offer all nonmetastatic patients neoadjuvant treatment in order to select those eligible for surgical exploration. Obviously, this has always to be done in the context of randomized controlled trials.

## Acknowledgements

The authors have no acknowledgement or funding to declare.

## Conflict of interest

The authors have no conflict of interest to declare.

## Abbreviations

| | |
|---|---|
| PaC | Pancreatic cancer |
| ADT | Adjuvant treatment |
| BLR | Borderline resectable |

| | |
|---|---|
| LA | Locally advanced |
| NCCN | National Comprehensive Cancer Network |
| CRT | Chemoradiation |
| CHT | Chemotherapy |
| NADT | Neoadjuvant treatment |
| VR | Vascular resection |
| SMA | Superior mesenteric artery |
| SMV | Superior mesenteric vein |
| PV | Portal vein |
| AA | Aorta |
| IVC | Inferior vena cava |
| GDA | Gastroduodenal artery |
| PHA | Proper hepatic artery |
| CHA | Common hepatic artery |
| AHBPA | American Heptad-Biliary-Pancreatic Association |
| SSAT | Society of Surgery of the Alimentary Tract |
| SSO | Society of Surgical Oncology |
| IAP | International Association of Pancreatology |
| CA19.9 | Carbohydrate antigen 19.9 |
| CEA | Carcinoembryonic antigen |
| CTCs | Circulating tumor cells |
| PS | Performance status |
| R0 | No cancer cells seen microscopically at the resection margin |
| R1 | Cancer cells present microscopically at the resection margin (microscopic positive margin) |
| ypT0 | Complete pathological response after neoadjuvant treatment |
| RCT | Randomized controlled trial |
| ITT | Intention to treat |
| OS | Overall survival |
| mOS | Median overall survival |

## Author details

Laura Antolino[1]*, Paolo Aurello[1], Federico Todde[2], Silvia Amato[1], Niccolò Petrucciani[3], Andrea Kazemi Nava[4], Giuseppe Nigri[1], Stefano Valabrega[1], Giovanni Ramacciato[1] and Francesco D'Angelo[1]

*Address all correspondence to: laura.antolino@uniroma1.it

1 General Surgery Unit, Department of Surgical and Medical Sciences and Translational Medicine, Sapienza University of Rome, Italy

2 Emergency Department, San Pietro Fatebenefratelli Hospital, Rome, Italy

3 Digestive Surgery and Liver Transplantation Unit, Henri Modor Hospital, Creteil, France

4 Liver Transplant Unit, St'Vincent University Hospital, Dublin, Ireland

## References

[1] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Research. 2014;**74**(11):2913-2921

[2] American Cancer Society. Pancreatic Cancer Detailed Guide. Available from: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-survival-rates. [Accessed: March 1, 2018]

[3] Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;**18**(1):2-11

[4] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pancreatic Adenocarcinoma Version 3.2017, 09/11/2017 © National Comprehensive Cancer Network, Inc. 2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

[5] Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database of Systematic Reviews. 2016;**7**:CD009323

[6] Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V, Hong TS, Kwak EL, Lauwers GY, Ryan DP, Wargo JA, Lillemoe KD, Ferrone CR. Pancreatic ductal adenocarcinoma: Is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Annals of Surgery. 2013;**257**(4):731-736

[7] Strobel O, Hank T, Hinz U, Bergmann F, Schneider L, Springfeld C, Jäger D, Schirmacher P, Hackert T, Büchler MW. Pancreatic cancer surgery: The new R-status counts. Annals of Surgery. 2017;**265**(3):565-573

[8] Kim HS, Jang JY, Han Y, Lee KB, Joo I, Lee DH, Kim JR, Kim H, Kwon W, Kim SW. Survival outcome and prognostic factors of neoadjuvant treatment followed by resection for borderline resectable pancreatic cancer. Annals of Surgical Treatment and Research. 2017;**93**(4):186-194

[9] Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF. Borderline resectable pancreatic cancer: The importance of this emerging stage of disease. Journal of the American College of Surgeons. 2008;**206**(5):833-846

[10] Ramacciato G, Nigri G, Petrucciani N, Pinna AD, Ravaioli M, Jovine E, Minni F, Grazi GL, Chirletti P, Tisone G, Napoli N, Boggi U. Pancreatectomy with mesenteric and portal vein resection for borderline resectable pancreatic cancer: Multicenter study of 406 patients. Annals of Surgical Oncology. 2016;**23**(6):2028-2037

[11] Hackert T, Ulrich A, Büchler MW. Can neoadjuvant therapy in pancreatic cancer increase the pool of patients eligible for pancreaticoduodenectomy? Advances in Surgery. 2017;**51**(1):1-10

[12] Metha VK, Fisher G, Ford JA, et al. Preoperative chemoradiation for marginally resectable adenocarcinoma of the pancreas. Journal of Gastrointestinal Surgery. 2001;**5**:27-35

[13] 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. Annals of Surgical Oncology. 2009;**16**(7):1727-1733

[14] Katz MH, Marsh R, Herman JM, Shi Q, Collison E, Venook AP, Kindler HL, Alberts SR, Philip P, Lowy AM, Pisters PW, Posner MC, Berlin JD, Ahmad SA. Borderline resectable pancreatic cancer: Need for standardization and methods for optimal clinical trial design. Annals of Surgical Oncology. 2013;**20**(8):2787-2795

[15] Delpero JR, Boher JM, Sauvanet A, Le Treut YP, Sa-Cunha A, Mabrut JY, Chiche L, Turrini O, Bachellier P, Paye F. Pancreatic adenocarcinoma with venous involvement: Is up-front synchronous portal-superior mesenteric vein resection still justified? A survey of the Association Française de Chirurgie. Annals of Surgical Oncology. 2015;**22**(6): 1874-1883

[16] Matsumoto I, Murakami Y, Shinzeki M, Asari S, Goto T, Tani M, Motoi F, Uemura K, Sho M, Satoi S, Honda G, Yamaue H, Unno M, Akahori T, Kwon AH, Kurata M, Ajiki T, Fukumoto T, Ku Y. Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: A multi-center retrospective study. Pancreatology. 2015;**15**(6):674-680

[17] Distler M, Pilarsky E, Kersting S, Grützmann R. Preoperative CEA and CA 19-9 are prognostic markers for survival after curative resection for ductal adenocarcinoma of

the pancreas—A retrospective tumor marker prognostic study. International Journal of Surgery. 2013;**11**(10):1067-1072

[18] Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, Vilardell F, Wang Z, Keller JW, Banerjee P, Herman JM, Cameron JL, Yeo CJ, Halushka MK, Eshleman JR, Raben M, Klein AP, Hruban RH, Hidalgo M, Laheru D. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. Journal of Clinical Oncology. 2009;**27**(11):1806-1813

[19] Court CM, Ankeny JS, Sho S, Winograd P, Hou S, Song M, Wainberg ZA, Girgis MD, Graeber TG, Agopian VG, Tseng HR, Tomlinson JS. Circulating tumor cells predict occult metastatic disease and prognosis in pancreatic cancer. Annals of Surgical Oncology. 2018;**25**(4):1000-1008

[20] Raigani S, Ammori J, Kim J, Hardacre JM. Trends in the treatment of resectable pancreatic adenocarcinoma. Journal of Gastrointestinal Surgery. 2014;**18**(1):113-123

[21] Del Chiaro M, Valente R, Arnelo U. Neoadjuvant treatment in locally advanced and borderline resectable pancreatic cancer vs primary resectable pancreatic cancer. JAMA Surgery. 2017;**152**(11):1057

[22] 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. Annals of Surgical Oncology. 2012;**19**(5):1644-1662

[23] Rose JB, Rocha FG, Alseidi A, Biehl T, Moonka R, Ryan JA, Lin B, Picozzi V, Helton S. Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. Annals of Surgical Oncology. 2014;**21**(5):1530-1537

[24] Dhir M, Malhotra GK, Sohal DPS, Hein NA, Smith LM, O'Reilly EM, Bahary N, Are C. Neoadjuvant treatment of pancreatic adenocarcinoma: A systematic review and meta-analysis of 5520 patients. World Journal of Surgical Oncology. 2017;**15**(1):183

[25] 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 Medicine. 2010;**7**(4):e1000267

[26] Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terrebonne E, De La Fouchardière C, Manfredi S, Solub D, Lécaille C, Thirot Bidault A, Carbonnel F, Taieb J. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: Results of an AGEO multicenter prospective observational cohort. Annals of Surgical Oncology. 2015;**22**(1):295-301

[27] Hashemi-Sadraei N, Gbolahan OB, Salfity H, O'Neil B, House MG, Shahda S. Clinical characteristics of patients experiencing pathologic complete response following neoadjuvant therapy for borderline resectable/locally advanced pancreatic adenocarcinoma. American Journal of Clinical Oncology. 2017

[28] Chen KT, Devarajan K, Milestone BN, Cooper HS, Denlinger C, Cohen SJ, Meyer JE, Hoffman JP. Neoadjuvant chemoradiation and duration of chemotherapy before surgical resection for pancreatic cancer: Does time interval between radiotherapy and surgery matter? Annals of Surgical Oncology. Feb 2014;**21**(2):662-669

[29] Pedrazzoli S, Beger HG, Obertop H, Andren-Sandberg A, Fernandez-Cruz L, Henne-Bruns D, et al. A surgical and pathological based classification of resective treatment of pancreatic cancer. Summary of an international workshop on surgical procedures in pancreatic cancer. Digestive Surgery. 1999;**16**:337-345

[30] Xu X, Zhang H, Zhou P, Chen L. Meta-analysis of the efficacy of pancreatoduodenectomy with extended lymphadenectomy in the treatment of pancreatic cancer. World Journal of Surgical Oncology. 2013;**11**:311

[31] Yamaguchi K, Okusaka T, Shimizu K, Furuse J, Ito Y, Hanada K, Shimosegawa T, Okazaki K, Committee for Revision of Clinical Guidelines for Pancreatic Cancer of the Japan Pancreas Society. Clinical practice guidelines for pancreatic cancer 2016 from the Japan Pancreas Society: A synopsis. Pancreas. 2017;**46**(5):595-604

[32] Kasumova GG, Conway WC, Tseng JF. The role of venous and arterial resection in pancreatic cancer surgery. Annals of Surgical Oncology. 2018;**25**(1):51-58

[33] Turrini O, Ewald J, Barbier L, Mokart D, Blache JL, Delpero JR. Should the portal vein be routinely resected during pancreaticoduodenectomy for adenocarcinoma? Annals of Surgery. 2013;**257**(4):726-730

[34] AJCC Cancer Staging Manual, Eight Edition 2016 American College of Surgeons

[35] D'Angelo F, Antolino L, Farcomeni A, Sirimarco D, Kazemi Nava A, De Siena M, Petrucciani N, Nigri G, Valabrega S, Aurello P, Ramacciato G. Neoadjuvant treatment in pancreatic cancer: evidence-based medicine? A systematic review and meta-analysis. Medical Oncology. 2017;**34**(5):85. https://doi.org/10.1007/s12032-017-0951-0

[36] Shrestha B, Sun Y, Faisal F, Kim V, Soares K, Blair A, Herman JM, Narang A, Dholakia AS, Rosati L, Hacker-Prietz A, Chen L, Laheru DA, De Jesus-Acosta A, Le DT, Donehower R, Azad N, Diaz LA, Murphy A, Lee V, Fishman EK, Hruban RH, Liang T, Cameron JL, Makary M, Weiss MJ, Ahuja N, He J, Wolfgang CL, Huang CY, Zheng L. Long-term survival benefit of upfront chemotherapy in patients with newly diagnosed borderline resectable pancreatic cancer. Cancer Medicine. 2017;**6**(7):1552-1562

[37] Kapoor R, Khosla D, Gupta R, Bahl A, Shukla AK, Sharma SC. Role of neoadjuvant concurrent chemoradiation in locally advanced unresectable pancreatic cancer: A feasibility study at tertiary care centre. Indian Journal of Cancer. 2014;**51**(2):176-179

[38] Heinrich S, Pestalozzi BC, Schäfer M, Weber A, Bauerfeind P, Knuth A, Clavien PA. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. Journal of Clinical Oncology. 2008;**26**(15):2526-2531

[39] D'Angelo FA, Antolino L, La Rocca M, Petrucciani N, Magistri P, Aurello P, Ramacciato G. Adjuvant and neoadjuvant therapies in resectable pancreatic cancer: A systematic review of randomized controlled trials. Medical Oncology. 2016;**33**(3):28

[40] Addeo P, Rosso E, Fuchshuber P, Oussoultzoglou E, De Blasi V, Simone G, Belletier C, Dufour P, Bachellier P. Resection of borderline resectable and locally advanced pancreatic adenocarcinomas after neoadjuvant chemotherapy. Oncology. 2015;**89**(1):37-46

[41] Marchegiani G, Andrianello S, Nessi C, Sandini M, Maggino L, Malleo G, Paiella S, Polati E, Bassi C, Salvia R. Neoadjuvant therapy versus upfront resection for pancreatic cancer: The actual spectrum and clinical burden of postoperative complications. Annals of Surgical Oncology. 2018;**25**(3):626-637

[42] Epelboym I, DiNorcia J, Winner M, Lee MK, Lee JA, Schrope BA, Chabot JA, Allendorf JD. Neoadjuvant therapy and vascular resection during pancreaticoduodenectomy: Shifting the survival curve for patients with locally advanced pancreatic cancer. World Journal of Surgery. 2014;**38**(5):1184-1195

[43] Kooby DA, Lad NL, Squires MH 3rd, Maithel SK, Sarmiento JM, Staley CA, Adsay NV, El-Rayes BF, Weber SM, Winslow ER, Cho CS, Zavala KA, Bentrem DJ, Knab M, Ahmad SA, Abbott DE, Sutton JM, Kim HJ, Yeh JJ, Aufforth R, Scoggins CR, Martin RC, Parikh AA, Robinson J, Hashim YM, Fields RC, Hawkins WG, Merchant NB. Value of intraoperative neck margin analysis during Whipple for pancreatic adenocarcinoma: A multicenter analysis of 1399 patients. Annals of Surgery. 2014;**260**(3):494-501

[44] Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M, Xu N, Cooper H, Benson AB 3rd. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. Journal of Surgical Oncology. 2010;**101**(7):587-592

[45] Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, Buckels JA, Bramhall SR. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Annals of Surgical Oncology. 2007;**14**(7):2088-2096

[46] Verbeke C, Löhr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: Challenges and uncertainties. Cancer Treatment Reviews. 2015;**41**(1):17-26

[47] de Geus SWL, Kasumova GG, Eskander MF, Ng SC, Kent TS, James Moser A, Vahrmeijer AL, Callery MP, Tseng JF. Is neoadjuvant therapy sufficient in resected pancreatic cancer patients? A national study. Journal of Gastrointestinal Surgery. 2018;**22**(2):214-225

[48] Akahori T, Sho M, Tanaka T, Kinoshita S, Nagai M, Nishiwada S, Nishiofuku H, Ohbayashi C, Kichikawa K, Nakajima Y. Factors associated with failure to complete adjuvant chemotherapy in pancreatic cancer. American Journal of Surgery. 2016;**211**(4):787-792

[49] Castillo C F-d, Morales-Oyarvide V, McGrath D, Wargo JA, Ferrone CR, Thayer SP, Lillemoe KD, Warshaw AL. Evolution of the Whipple procedure at the Massachusetts General Hospital. Surgery. 2012;**152**(3 0 1):S56-S63

[50] Krautz C, Nimptsch U, Weber GF, Mansky T, Grützmann R. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Annals of Surgery. 2018;**267**(3):411-417

[51] Gurusamy KS, Kumar S, Davidson BR, Fusai G. Resection versus other treatments for locally advanced pancreatic cancer. Cochrane Database of Systematic Reviews. 2014;**2**:CD010244

[52] Buanes TA. Role of surgery in pancreatic cancer. World Journal of Gastroenterology. 2017;**23**(21):3765-3770

[53] Buanes TA. Pancreatic cancer-improved care achievable. World Journal of Gastroenterology. 2014;**20**(30):10405-10418

[54] Katz MH, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, Wang H, Abbruzzese J, Pisters PW, Vauthey JN, Charnsangavej C, Tamm E, Crane CH, Balachandran A. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer. 2012;**118**(23):5749-5756

[55] Heinrich S, Schäfer M, Weber A, Hany TF, Bhure U, Pestalozzi BC, Clavien PA. Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cancer without increasing morbidity: Results of a prospective phase II trial. Annals of Surgery. 2008;**248**(6):1014-1022

[56] Miura JT, Krepline AN, George B, Ritch PS, Erickson BA, Johnston FM, Oshima K, Christians KK, Evans DB, Tsai S. Use of neoadjuvant therapy in patients 75 years of age and older with pancreatic cancer. Surgery. 2015;**158**(6):1545-1555

[57] Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, Ko CY, Bentrem DJ. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Annals of Surgery. 2014;**260**(2):372-377

[58] Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C, Jungnickel H, Schreiber S, Grabenbauer GG, Meyer T, Merkel S, Fietkau R, Hohenberger W. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer. Results of the first prospective randomized phase II trial. Strahlentherapie und Onkologie. 2015;**191**(1):7-16

[59] Mellon EA, Strom TJ, Hoffe SE, Frakes JM, Springett GM, Hodul PJ, Malafa MP, Chuong MD, Shridhar R. Favorable perioperative outcomes after resection of borderline resectable pancreatic cancer treated with neoadjuvant stereotactic radiation and chemotherapy compared with upfront pancreatectomy for resectable cancer. Journal of Gastrointestinal Oncology. 2016;**7**(4):547-555

[60] Cloyd JM, Katz MH, Prakash L, Varadhachary GR, Wolff RA, Shroff RT, Javle M, Fogelman D, Overman M, Crane CH, Koay EJ, Das P, Krishnan S, Minsky BD, Lee JH, Bhutani MS, Weston B, Ross W, Bhosale P, Tamm EP, Wang H, Maitra A, Kim MP, Aloia TA, Vauthey JN, Fleming JB, Abbruzzese JL, Pisters PW, Evans DB, Lee JE. Preoperative therapy and pancreatoduodenectomy for pancreatic ductal adenocarcinoma: A 25-year single-institution experience. Journal of Gastrointestinal Surgery. 2017;**21**(1):164-174

IntechOpen