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Primarily resectable pancreatic adenocarcinoma – to operate or to refer the patient to an oncologist?

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ABSTRACT

The aim of this work is to investigate the optimal therapeutic sequence of resectable pancreatic cancer – primary surgery with adjuvant therapy or neoadjuvant followed by resection. Application of the neoadjuvant approach in routine treatment of pancreatic cancer is rapidly growing every year, despite the lack of final results from randomized trials. Recent advancements in the adjuvant therapy, due to the more effective chemotherapy regimens, favor the upfront surgery strategy. On the other hand, theoretical background and metaanalyses favor the neoadjuvant strategy. Currently, primary resection with adjuvant chemotherapy remains the standard approach in resectable pancreatic cancer, but the first recommendations considering the neoadjuvant approach as an option seem to arise among the scientific societies with a global impact. Preliminary results of Prodige 24 study and PREOPANC-1 trial demonstrates that both options are worth further evaluation in clinical trials. Their results should soon provide more answers to this important clinical questions.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth (and estimated for 2018 to be the third) leading cause of cancer-related deaths in Europe and USA (Malvezzi et al., 2017; Siegel et al., 2017; Cronin et al., 2018). In 2012, there were 338,000 new cases of the disease worldwide (Schild and Vokes, 2016). Its incidence increases systematically, while the treatment outcomes remain poor. In the last 30 years, 5-year overall survival rates increased merely from 2% to 5% (Ries et al., 2007), however, the latest SEER (Surveillance, Epidemiology, and End Results) data indicate an increase to 8.5% (Cronin et al., 2018). Based on the growing incidence, demographic data and predicted survival rates, the latest prognoses indicate that after 2020 pancreatic ductal adenocarcinoma may become even the second leading cause of cancer-related deaths (Rahib et al., 2014; De Angelis et al., 2014).

At diagnosis, only 10%–20% of patients are eligible for resection (termed early pancreatic adenocarcinoma) according to the National Comprehensive Cancer Network (NCCN) criteria, defined as the absence of distant metastases along with the lack of evidence of tumor contact with celiac trunk, superior mesenteric artery, common hepatic artery, superior mesenteric vein or portal vein (if subsequent reconstruction is possible, a contact with < 180° of venous vessel circumference does not exclude surgery) (Wagner et al., 2004; Edge and on Cancer AJC, 2010; Al-Hawary et al., 2014).

Radical resection of pancreatic cancer is the only potentially curative treatment method, but the recurrence rate ranges from 46% to 89% (Aoyama et al., 2015; Fischer et al., 2012). In the majority of patients, the recurrence occurs within 2 years after surgery, while in about 20% during the first six months (early recurrence) (Labori et al., 2016; Groot et al., 2018). Such a high failure rate observed in a short time suggests the presence of micrometastases (which are undetectable with current diagnostic imaging techniques) at the time of diagnosis. Recent studies demonstrated that even small, clinically undetectable tumors have a relatively high potential to produce metastases (Rhim et al., 2012; Tuveson and Neoptolemos, 2012). Using a mathematical framework based on radiological and post mortem data, Haeno et al. proposed an exponential model of pancreatic cancer cell growth (Haeno et al., 2012). For pancreatic tumors with the diameters of 1 cm, 2 cm and 3 cm, the risk of micrometastases formation at the time of diagnosis was estimated at 28%, 73% and 94%, respectively. These findings indicate the critical need for a multidisciplinary approach, also at the stage of

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primary resectability. Therefore, surgical treatment along with the systemic therapy, currently principally chemotherapy, are of key importance in the management of pancreatic cancer. The essential question for contemporary medicine is of the optimal sequence: primary resection with adjuvant therapy or neoadjuvant therapy with subsequent resection.

2. Upfront surgery

2.1. Theoretic background

In pancreatic tumors with the suspicion of malignancy and eligibility for primary resection, a radical surgery with complete resection and histopathological assessment enable the prompt diagnosis and initiation of the adjuvant treatment. This strategy has advantages in terms of both diagnosis and therapy. Firstly, to consider a patient eligible for neoadjuvant treatment, it is first necessary to establish a cytological or histopathological diagnosis; the former is preferably based on endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB). The biopsy-based diagnosis may be challenging in case of small tumors and may significantly extend the diagnostic process (as negative biopsy does not rule out malignancy) with a negative effect on the outcome (Hartwig et al., 2009). In contrast, a routine biopsy preceding the pancreatic tumor resection is not recommended (Callery et al., 2009). In summary, in addition to its therapeutic aspect, primary resection may be the only chance to diagnose pancreatic adenocarcinoma.

In some cases surgery is primarily necessary for the immediate problems. Severe alimentary tract obstruction due to tumor-dependent duodenal stenosis or jaundice resulting from bile duct obstruction which cannot be treated with stent implantation are obvious contraindications for the primary systemic therapy (Lim et al., 2012).

Moreover, primary resection is usually considered in patients with good performance status and preoperative results suggesting an early stage of the disease, which may predict an uncomplicated surgery and the possibility to quickly proceed with adjuvant therapy at required doses (Lim et al., 2012). Clearly, the patient should have a significant impact on the decision making process based on a thorough discussion with both surgeon and oncologist.

Overall, surgery has been the main treatment method of pancreatic cancer for more than 100 years. Despite the technical advancement achieved by Allen Whipple in 1941 with the one-stage pancreatic resection, the postoperative complications were frequent and mortality rates reached 30% (Chamberlain et al., 2009). Today, surgery remains the treatment of choice in pancreatic cancer, while the indications for this procedure have been further expanded (Maggino and Vollmer, 2017; Buanes, 2017) and the postoperative mortality rates dropped below 5% (Maggino and Vollmer, 2017). The improved outcomes result from the proper qualification of patients eligible for resection (due to the advances in diagnostic imaging and the centralization of pancreatic surgery), improvements in surgical techniques (e.g. minimally invasive surgery, definitions and standards of pancreatoduodenectomy and lymphadenectomy) and improved post-operative treatment (e.g. Enhanced Recovery After Surgery) (Buanes, 2017; Deplanque and Demartines, 2017). All these factors also contributed to the expansion of indications for resection in patients with tumors infiltrating the vasculature (i.e. superior mesenteric artery, hepatic artery and portal vein) or adjacent organs as well as in patients with distant metastases (Buanes, 2017). The extended resection is typically performed in the setting of cases preoperatively regarded as resectable where further lesions are discovered intraoperatively. Taking into account the aggressive biology of pancreatic cancer, many authors suggest that the imaging may be considered as diagnostic only within 25–32 days prior to surgery, in terms of both vasculature infiltration and liver metastases (Raman et al., 2015; Sanjeevi et al., 2016). Therefore, a resectable tumor may be accompanied by a single metastatic lesion in liver, not yet visible on imaging (Klein et al., 2012; Tachezy et al., 2016). Based on the studies indicating the prolonged survival of M1 patients undergoing the synchronous resection of both primary tumor and metastasis, many surgeons decide to perform such a resection (Klein et al., 2012; Yu et al., 2017; Hackert et al., 2017). Abandoning resection is particularly disputable when the character of liver lesion is ambiguous (i.e. single, small, macroscopically untypical lesions with no possibility to perform intraoperative histopathological examination or with an inconclusive result) (Tachezy et al., 2016; Hackert et al., 2017). Therefore, having excluded other lesions in liver (by intraoperative ultrasonography), a resection should be considered in selected patients taking into account the R0 resection possibility and the risk of surgery (liver metastases that could be easily resected) (Klein et al., 2012; Tachezy et al., 2016; Hackert et al., 2017). Otherwise, the resection is entirely abandoned and the patient is treated with palliative chemotherapy, which, however, often results in a reduced survival (Klein et al., 2012; Hackert et al., 2017). In contrast, cases requiring tumor dissection from the vessel or even venous resection are qualified for surgery based on the NCCN definition of resectable pancreatic cancer (no tumor contact with the superior mesenteric vein or portal vein or $\leq 180^{\circ}$ contact without vein contour irregularity, if subsequent reconstruction is possible) (Tempero et al., 2017). What is crucial, the contiguity between the neoplasm and the vessel is not necessarily synonymous to the vascular infiltration (Mazzeo et al., 2007). According to the on vessel resections, an unequivocal discrimination between the neoplastic and inflammatory character of the perivascular infiltrate is not possible either preoperatively or intraoperatively (Mazzeo et al., 2007; Luketina et al., 2015). Only the final histopathological examination of the resected material may clearly confirm the nature of the infiltrate and (retrospectively) classify the tumor as resectable or borderline resectable (Mazzeo et al., 2007; Zhou et al., 2012). Since the neoplastic infiltration of the vessel is excluded in up to 50% of vessel resections, excision of the tumor seems adequate whenever feasible (Mazzeo et al., 2007; Luketina et al., 2015; Zhou et al., 2012). A tangent excision is performed for the infiltration of portal vein or superior mesenteric vein (which may require a patch e.g. from great saphenous vein) (Luketina et al., 2015). Conversely, for segmental resections, the reconstruction may employ an end-to-end anastomosis, a venous graft (e.g. renal vein, great saphenous vein) or a synthetic prosthesis (Luketina et al., 2015). Arterial resection for pancreatic cancer remains an area of controversy due to their significant complications and lack of unequivocal results confirming their therapeutic effectiveness. According to the International Study Group for Pancreatic Surgery (ISGPS) consensus, arterial infiltration is synonymous to borderline resectability and upfront resection is rarely recommended, even if technically possible (Luketina et al., 2015; Bockhorn et al., 2014).

2.2. Clinical practice

Presently, the consensus regarding resectable pancreatic adenocarcinoma reached by the largest scientific associations such as American Society of Clinical Oncology (ASCO) recommends primary resection with the subsequent adjuvant chemotherapy (Khorana et al., 2017). This strategy has been adopted based on the publication of the CONKO-001 trial results in 2007, which demonstrated the superiority of combined management (surgery + 6 month chemotherapy with gemcitabine) over surgery alone (Oettle et al., 2007). In the adjuvant gemcitabine group, median disease free survival (DFS) was 13.4 months as compared to the surgery alone group with only 6.9 months ($p < 0.001$) (Oettle et al., 2007). In 2013, the long-term outcomes of this study were published (with the median observation time of 136 months) showing the clear superiority of the combined treatment with 5-year overall survival rate of 20.7% in gemcitabine adjuvant therapy and of only 10.4% in the surgery alone group ($p = 0.01$) (Oettle et al., 2013).

At Annual ASCO Meeting in 2016, Neoptolemos et al. presented the results of the ESPAC-4 clinical trial, making a further advancement in

adjuvant therapy (Neoptolemos et al., 2017). This study compared adjuvant gemcitabine monotherapy with adjuvant gemcitabine + capecitabine treatment. Median overall survival (mOS) in monotherapy group was 25.5 months and 28 months in the gemcitabine plus capecitabine group, which was a statistically significant difference ($p = 0.032$). Subgroup analysis demonstrated the biggest difference in patients with a complete resection (R0 subgroup): mOS of 27.9 months for gemcitabine monotherapy and of 39.5 months for gemcitabine + capecitabine treatment (Neoptolemos et al., 2017). The improvement of mOS by an average of 12 months ($p = 0.0001$) achieved only with a modification of the standard adjuvant chemotherapy demonstrates that this path may be worth exploring. At Annual ASCO Meeting in 2018 Conroy et al. presented preliminary results of the Prodige 24 study comparing mFOLFIRINOX and Gemcitabine in the adjuvant setting. The median overall survival was about 54 months with mFOLFIRINOX and 35 months with gemcitabine. In addition, the recurrence free survival was prolonged by 9 months (22 months in mFOLFIRINOX group compared with 13 months in gemcitabine group) (Conroy et al., 2018a). The final results of the study confirmed the preliminary ones and reported the 3-year DFS rate of 39.7% in the mFOLFIRINOX group and 21.4% in the gemcitabine group (Conroy et al., 2018b). These studies show that combined chemotherapy offers superior outcomes and mFOLFIRINOX may be the new standard treatment in the adjuvant approach.

The appropriate timing of adjuvant chemotherapy initiation is the one of the most common problems of everyday clinical practice. It is habitually presupposed that only the early start of adjuvant chemotherapy can be beneficial to the patient. Extrapolating the data from breast or colon cancer studies (where early initiation of chemotherapy is associated with a significant survival benefit (Lohrisch et al., 2006; Alkis et al., 2011; Des Guetz et al., 2010; Biagi et al., 2011)) to pancreatic cancer may support such an approach. Moreover, the prospective adjuvant therapy trials (such as CONKO-001, ESPAC-4 or Prodige 24 (Oettle et al., 2013; Neoptolemos et al., 2017; Conroy et al., 2018b)) were designed to initiate chemotherapy at ≤12 weeks from surgery, making it impossible to analyze the impact of the delayed treatment. On the other hand, a retrospective analysis of the ESPAC-3 trial (comparing gemcitabine and 5-fluororacil in the adjuvant setting (Neoptolemos et al., 2012)), demonstrated no difference in the outcomes for the chemotherapy delayed up to 12 weeks (Valle et al., 2014). Further investigation of this issue revealed that the delayed adjuvant therapy (> 12 weeks) is not associated with poorer survival in comparison to early treatment (≤12 weeks) and both provide survival benefit over surgery alone (Mirkin et al., 2016; Xia et al., 2017). Such results are an important suggestion for the clinicians not to cease to qualify the patients to adjuvant chemotherapy after 12 weeks from surgery. A more widespread awareness of these data might result in a global increase in the number of patients receiving multimodal therapy.

The on-going clinical studies on adjuvant treatment applied in pancreatic adenocarcinoma with such chemotherapy regimens as FOLFIRINOX (NCT02355119 – GIP2), and Gemcitabine + nab-Paclitaxel (NCT01964430 – APACT) will soon provide more data on their effectiveness (Vasile, 2019; Elias, 2019).

Finally, no prospective, randomized clinical trials has demonstrated the superiority of neoadjuvant chemotherapy with subsequent surgery over primary resection followed by adjuvant therapy. Moreover, in 2010 a meta-analysis of treatment outcomes in 4394 patients participating in 111 clinical trials between 1966 and 2009 was published showing comparable survival times in both groups (Gillen et al., 2010). Still, it should be taken into account that it was a retrospective analysis including the times when computed tomography was not available, which undoubtedly hindered the proper selection of patients for primary resection. Similarly, systemic treatment was heterogeneous: the agents used included gemcitabine, 5-fluorouracil, mitomycin C and platinum derivatives, yielding the objective response rate (ORR; the sum of tumor complete and partial remission) of barely 3.6%, which is now considered an unadvisable or suboptimal strategy (Gillen et al., 2010).

3. Neoadjuvant therapy

3.1. Theoretic background

As opposed to other cancers, a clear definition of neoadjuvant therapy in pancreatic cancer has not been established yet. Every preoperative treatment of a resectable cancer as well as treatment to enable surgery in locally advanced cancer may be considered as neoadjuvant (Heinrich and Lang, 2017). Moreover, initial treatment of patients with a synchronous metastatic disease (e.g. liver metastases) has also been termed “neoadjuvant” by some authors if the subsequent resection was considered (Heinrich and Lang, 2017). Nonetheless, as in other neoplasms, it seems optimal to reserve the term “neoadjuvant therapy” for preoperative treatment of the primarily resectable tumors. In contrast, preoperative treatment in patients with locally advanced disease should be termed as induction therapy, while systemic treatment in patients with metastatic cancer as palliative therapy, irrespective of metastasectomy being performed or not.

It is crucial to emphasize that the initiation of the neoadjuvant therapy requires established cytological or histopathological diagnosis. Despite the continuous advancements in the endoscopic ultrasound-guided biopsy techniques (Mukai et al., 2018; Elhanafi et al., 2018; Tian et al., 2018; Fujie et al., 2018), it may still be challenging and the unsuccessful attempts may postpone the therapy initiation. The currently reported sensitivity and specificity rates are 85–92% and 96–98% (Kitano et al., 2019), while the repeat procedure is required in up to 11% of cases (Mitchell et al., 2016). Another potential limitation of the neoadjuvant treatment is that the rare cases of pathologic complete response (pCR) are associated with lack of tumor tissue for further examination. It is crucial in the context of biomarker analysis for subsequent (targeted) therapy qualification, which currently plays a marginal role, but will hopefully gain importance in future. A large study on nearly 600 patients reported major pathologic response (defined as < 5% viable cells) in 13.2% of cases (including pCR in 3.9%) (Cloyd et al., 2017). On the other hand, it was shown that the material obtained with endoscopic ultrasound-guided biopsies is usually adequate for next generation sequencing (Elhanafi et al., 2018).

Starting in the early eighties, several trials have evaluated the feasibility and efficacy of neoadjuvant radiotherapy, chemotherapy and various combinations of these modalities in resectable pancreatic cancer. Radiotherapy concomitant to chemotherapy was the most frequent approach in neoadjuvant setting (Table 1).The introduction of new chemotherapeutic drugs for pancreatic cancer made the administration of chemotherapy alone (Table 1) or followed by chemoradiation (Table 1) an alternative to the upfront chemoradiation.

Further development of multi-agent chemotherapy for the metastatic disease, with the objective response rates of approximately 30% (including such regimens as FOLFIRINOX in 2011 and nab-Paclitaxel in 2013), makes neoadjuvant therapy for pancreatic adenocarcinoma an increasingly promising treatment strategy (Conroy et al., 2011; Von Hoff et al., 2013). In comparison to chemotherapy alone chemoradiotherapy provides better local control at the cost of poorer control of micrometastases. So far, however, these methods have not been prospectively compared in resectable pancreatic adenocarcinoma.

Neoadjuvant therapy is widely applied against malignancies producing micrometastases at the early stage of disease, which depicts pancreatic cancer almost from the very beginning. Taking into account an average time between diagnosis and surgery as well as the time required for the subsequent wound healing (presuming no serious complications), systemic treatment is usually delayed by 2–3 months (Belli et al., 2013). Such a delay can ruin all the potential benefits of more and more effective schedules of systemic treatment.

A frequently quoted argument supporting the neoadjuvant therapy

Table 1
Neoadjuvant trials in pancreatic cancer.

Study	Patients [n]	Regimen	Resection rate [%]	R0 rate [% of resected]	Median OS [months]
Neoadjuvant trials of upfront chemoradiotherapy					
Hoffman et al. (1998)	62	FU + Mitomycin + 50.4 Gy	45.3	70.8	16
Mornex et al. (2006)	41	PF + 50 Gy	63.4	80.7	12
Turrini et al. (2009)	102	PF + 45 Gy	60.8	91.8	23
Evans et al. (2008)	86	Gem + 30 Gy	64.4	86.4	34
Pisters et al. (2002)	37	PXL + 30 Gy (IORT)	54.1	70	19
Golcher et al. (2015)	29	PG + 55.8 Gy	65.5	89.5	25
Pisters et al. (1998)	35	FU + 30 Gy (IORT)	57	51	37
Sho et al. (2013)	61	Gem + 50.4-54Gy	97	92	NR
Van Buren et al. (2013)	59	Gem + Bev + 30 Gy	73	88	17
Neoadjuvant trials of chemotherapy alone					
Palmer et al. (2007)	50	Gem *vs.* PG	37.5 (Gem) 69.2 (PG)	75	28
Heinrich et al. (2008)	28	PG	89.3	80	27
O'Reilly et al. (2014)	38	GemOx	71	74	27
Tajima et al. (2012)	34	Gem + S1	100	85	56% at 24
Neoadjuvant trials of chemotherapy followed by chemoradiation therapy					
Varadhachary et al. (2008)	90	PG - > 30 Gy + Gem	57.8	96.2	31
Talamonti et al. (2006)	20	Gem - > 36Gy	85	80	26 (resected)
Faris et al. (2013)	22	FOLFIRINOX + /-CRT	55	42	NR

Bev - Bevacizumab, CRT - Chemoradiation, FOLFIRINOX - Fluorouracil + Oxaliplatin + Irinotecan + Leucovorin, FU - Fluorouracil, Gem - Gemcitabine, GemOx – Gemcitabine + Oxaliplatin, Gy – Gray, IORT – Intraoperative radiation therapy, NR - not reached, PF - Cisplatin + Fluorouracil, PG - Cisplatin + Gemcitabine, PXL - Paclitaxel, S1 - Tegafur/Gimeracil/Oteracil.

emphasizes the limited probability for the adjuvant treatment to actually be applied. It usually results from the complications of surgery, early local recurrences or distant metastases. Even in the optimally selected groups, the proportion of patients who do not receive the standard combination treatment is dauntingly high. In the pivotal study of the adjuvant gemcitabine-based chemotherapy (CONKO-001), from among patients with good performance status, no laboratory anomalies and postoperative CA19.9 levels 2.5 times lower than the upper normal limit only 62% completed the adjuvant treatment (Oettle et al., 2007). In the prospective clinical studies conducted at large academic centers, the proportion of patients who do not receive postoperative adjuvant therapy, despite being potentially eligible for such a treatment ranges from 26% to 38% (Tzeng et al., 2014; Aloia et al., 2007). At non-academic sites, these rates may reach up to 50% (Mayo et al., 2012).

The potential benefits of neoadjuvant strategy also includes the possible tumor size reduction prior to resection, which may subsequently improve the rate of microscopic surgical completeness. For primary resection, the rate of R0 resections ranges from 25% to even 84%, depending on the surgical technique used and the histopathological criteria (as the definitions of R0 resections may vary) (Verbeke, 2008).

Another factor favoring neoadjuvant therapy is the fact that it allows for an early selection of patients who would not benefit from the surgery. During preoperative treatment there is sufficient time to expose distant metastases associated with the progression of previously undetectable micrometastatic disease. Early treatment of these lesions allows to avoid the extensive surgery, which (if performed at the disseminated stage) is associated with an increased risk of complications and mortality (Tajima et al., 2017). Additionally, in patients with micrometastases, systemic treatment reduces the risk of intraoperative iatrogenic dissemination of cancer cells within the abdominal cavity (Belli et al., 2013; Tajima et al., 2017).

Furthermore, it is often impossible to assess tumor resectability basing on diagnostic imaging with complete certainty. Thus, a crucial issue supporting the neoadjuvant therapy is the possible conversion of tumors with a limited resectability into fully resectable tumors.

With the adjuvant approach, there are no reliable methods of identifying responders to therapy during treatment (Heinrich and Lang, 2017). On the other hand, neoadjuvant strategy may potentially allow for the assessment of tumor response in vivo (Russo et al., 2016). Moreover, considering the commonly accepted definition of PDAC resectability, the assessment of tumor response to neoadjuvant treatment in patients with primarily resectable tumors may be objective, which is helpful in the context of multicenter studies (enabling the higher homogeneity of study groups) (Heinrich and Lang, 2017). Tumor specimens may also be evaluated for the effect of chemotherapy on cancer cells (Tajima et al., 2017).

3.2. Clinical practice

As opposed to the widely accepted consensus on primary resection followed by adjuvant therapy in early pancreatic adenocarcinoma, neoadjuvant treatment with the subsequent surgery is not considered as the standard. In 2013, Belli et al. published a critical review of neoadjuvant therapy in resectable pancreatic cancer with conclusion of no straightforward evidence to support the routine clinical use of this strategy (Belli et al., 2013). Nevertheless, the frequency of preoperative treatment increases.

One of the largest analyses of primarily resectable pancreatic adenocarcinoma subjected to neoadjuvant therapy reported that the metastatic disease was diagnosed on radiological re-evaluation prior to resection eligibility assessment in 14% of patients (Winner et al., 2015). It is noteworthy that only 8% of patients were considered ineligible for surgery for other reasons than the metastatic disease. Among them, 6% were patients who experienced severe adverse effects of neoadjuvant therapy, who moved to different medical center or whose performance status deteriorated considerably. Only 2% comprised patients with a local progression of the disease detected on radiologic re-evaluation (Winner et al., 2015).

The few prospective studies published to date indicate that the rate of R0 resections increases following the neoadjuvant therapy and may reach 90%–95% (Evans et al., 2008; Varadhachary et al., 2008; Talamonti et al., 2006). R1 resections are associated with a shorter overall survival, which is usually below 12 months and not significantly different from the prognosis for patients with a locally advanced disease (Garcea et al., 2008; Neoptolemos et al., 2001; Kuhlmann et al., 2006; Chang et al., 2009).

In 2014, Tzeng et al. published a retrospective analysis comparing the neoadjuvant strategy with the primary resection approach in a group of patients with primarily resectable disease (Tzeng et al., 2014). In the neoadjuvant group, 95 of 115 patients (83%) completed the planned combination treatment, while the same was true for only 29

out of 50 (58%) patients in the primary resection group. Patients who had completed the combined treatment had a better prognosis (36 vs. 11 months, $p < 0.001$). Early progression of the disease was reported as the overall most common cause of the failure to complete the combined treatment (in 11% of patients from neoadjuvant arm and 26% of patients from primary resection arm). The second common cause were serious surgical complications, whose rate was similar in both arms: 18.9% in neoadjuvant group and 16.7% in primary resection group with no statistically significant difference ($p = 0.738$). Postoperative complications had a severe impact on the outcomes of patients treated with primary resection (9.6 vs. 33 months, $p < 0.001$), while only a minor effect on patients who received neoadjuvant therapy (30.1 vs. 35.6 months, $p = 0.936$). These observations demonstrate that the change from adjuvant to neoadjuvant strategy results in an increased proportion of patients who may receive the systemic treatment for early pancreatic adenocarcinoma, which is, thus, related to an improved prognosis (Tzeng et al., 2014).

In 2017, Mokdad et al. presented the comparison of treatment outcomes for primary resection and neoadjuvant therapy in resectable pancreatic adenocarcinoma (Mokdad et al., 2017). 15,237 patients with stage I or II pancreatic head adenocarcinoma who underwent radical surgery between 2006 and 2012 were identified in National Cancer Database. In this group 2005 patients who received neoadjuvant therapy were compared with 6015 patients who underwent upfront resection (ratio of 1:3). Propensity score method was used to achieve proportional standardization of both groups in terms of patients' age, gender, race, date of diagnosis, economic status, performance status, cT and cN stage, cTNM stage and type of surgery. Neoadjuvant therapy group had a longer median overall survival (mOS, 26 months vs. 21 months, $p < 0.01$). Since only 67% of patients received adjuvant therapy in the upfront resection group, an analysis of this subgroup was also performed. What is crucial, even then the neoadjuvant therapy resulted in superior mOS (26 months vs. 23 months, $p < 0.01$). Comparing the outcomes in both groups, patients who underwent upfront resection had higher pTNM stage compared to patients on neoadjuvant therapy (pT3/4: 86% vs. 73%, respectively, $p < 0.01$; pN+: 73% vs. 48% respectively, $p < 0.01$) and higher proportion of microscopically incomplete resections (24% vs. 17%, $p < 0.01$). Multivariate analysis demonstrated that advanced pT stage, positive lymph nodes and positive resection margin were independent negative prognostic factors. Postoperative complications as well as 30-day and 90-day postoperative mortality were similar in both groups (Mokdad et al., 2017). An obvious limitation of this study is its retrospective nature as well as the fact that only patients who had undergone curative-intent resection were included in the analysis. Patients with metastases detected after neoadjuvant therapy in radiological assessment were excluded from the study as well as those with metastases unexpectedly detected during resection (according to literature, these rates range from 18% to 42%), which ultimately made the resection impossible (Wagner et al., 2004; Glant et al., 2011). Nevertheless, this study is a good starting point for the future prospective clinical trials which would finally define the role of neoadjuvant therapy in resectable pancreatic adenocarcinoma.

At Annual ASCO Meeting in 2018 van Tienhoven et al. presented the preliminary results of the PREOPANC-1 trial comparing preoperative chemoradiotherapy vs. immediate surgery for pancreatic cancer. The preoperative chemoradiotherapy consisted of 15 fractions of 2.4 Gy (Gy) combined with gemcitabine, 1000 mg/m2 on days 1, 8 and 15, preceded and followed by a cycle of gemcitabine. The researchers found that those who received chemotherapy plus radiation therapy before surgery had a median overall survival that was about 3 months longer than those who did not. Among the patients in the neoadjuvant group, the tumor was completely removed in 63% and 42% of patients survived more than 2 years. In comparison, in the upfront surgery group, these rates were 31% and 30%, respectively (Van Tienhoven et al., 2018).

The ongoing studies with various treatment regimens such as gemcitabine + oxaliplatin (NCT01314027, NEOPAC), FOLFIRINOX (NCT02172976, NEPAFOX; NorPACT-1), mFOLFIRINOX and Gemcitabine + nab-Paclitaxel (NCT02562716, SWOG S1505) should soon provide more insight into this issue (Clavien, 2019; Al-Batran, 2019; Labori et al., 2017; Sohal, 2019).

4. Summary

The advances seen in systemic treatment of metastatic pancreatic adenocarcinoma with the introduction of such regimens as FOLFIRINOX and gemcitabine + nab-Paclitaxel along with an increasingly dynamic development of immune therapy herald the upcoming changes in the therapy of early pancreatic cancer (Conroy et al., 2011; Von Hoff et al., 2013). An effective systemic control represents the progress in the treatment of this challenging disease. The breakthrough may be sought not only in the type or combination of anti-cancer agents, but also in their optimal timing. The neoadjuvant approach, with a well-established effectiveness in breast cancer, urinary bladder cancer or osteosarcoma, may potentially be the right tool against pancreatic cancer, which obviously requires verification in clinical trials. There are only few recommendations from scientific societies with a global impact taking neoadjuvant setting into consideration. The current ASCO guidelines for potentially curable pancreatic adenocarcinoma include the recommendations for preoperative therapy in patients with the radiographic findings suspicious, but not diagnostic for metastatic disease, with the performance status or comorbidities (potentially reversible) currently not allowing for a major surgery and with the CA19.9 level (in the absence of jaundice) suggestive of metastatic disease (Khorana et al., 2017). In addition, the guidelines indicate that neoadjuvant therapy followed by surgery should be offered as an alternative also to patients meeting all eligibility criteria for primary resection (Khorana et al., 2017). Current NCCN guidelines also consider the neoadjuvant strategy for resectable pancreatic cancer in patients who appear technically resectable, but who have poor prognostic features (i.e., markedly elevated CA19.9, large primary tumors, large regional lymph nodes, excessive weight loss or extreme pain) and therapy should be administered preferably at or coordinated through high volume-centers (Tempero et al., 2017). These recommendations certainly are the starting point to reflect on optimal treatment strategy in the routine clinical practice.

Conflict of interest

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