

Pancreatic Cancer Diagnostics and Treatment – Current State

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) represents permanent and ever rising issue worldwide. Five-year survival does not exceed 3 to 6%, i.e. the worst result among solid tumours. The article evaluates the current state of PDAC diagnostics and treatment specifying also development and trends. Percentage of non-resectable tumours due to locally advanced or metastatic condition varies 60–80%, mostly over 80%. Survival with non-resectable PDAC is 4 to 8 months (median 3.5). In contrast R0 resection shows the survival 18–27 months. Laboratory and imaging screening methods are not indicated on large scale. Risk factors are smoking, alcohol abuse, chronic pancreatitis, diabetes mellitus. Genetic background in most PDAC has not been detected yet. Some genes connected with high risk of PDAC (e.g. BRCA2, PALB2) have been identified as significant and highly penetrative, but link between PDAC and these genes can be seen only in 10–20%. This article surveys perspective oncogenes, tumour suppressor genes, microRNA. Albeit CT is still favoured over other imaging methods, involvement of NMR rises. Surgery prefers the “vessel first” approach, which proves to be justified especially in R0 resection. According to EBM immunotherapy same as radiotherapy are not significant in PDAC treatment. Chemotherapy shows limited importance in conversion treatment of locally advanced or borderline tumours or in case of

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metastatic spread. Unified procedures cannot be defined due to inhomogenous arrays. Surgical resection is the only chance for curative treatment of PDAC and depends mainly on timely indication for surgery and quality of multidisciplinary team in a high-volume centre.

Introduction

Pancreatic cancer represents a permanent and ever rising issue worldwide (www.svod.cz; American Cancer Society, 2013). Nearly in 95% we deal with pancreatic ductal adenocarcinoma. The remaining 5% include acinar cells carcinoma, pancreatic blastoma and certain forms of cystic tumours (American Cancer Society, 2013). PDAC (pancreatic ductal adenocarcinoma) is still considered as the life threatening diagnosis, and despite enormous costs spent, specialists endeavour demonstrated, there virtually exists no effective treatment (Reznik et al., 2014). Statistically PDAC five-year survival rate does not exceed 3 to 6%, which is the worst result among solid tumours (American Cancer Society, 2013; Narayanan, 2015). Since 1977, the incidence of this highly aggressive carcinoma in the Czech Republic (CR) doubled (www.svod.cz) (Figure 1). In the United States, a total of 46 420 patients were diagnosed with PDAC in 2014, and 39 950 patients died of this illness during the same period (Becker et al., 2014; Edderkaoui and Eibl, 2014; Narayanan, 2015). It is expected that by the end of 2020 the number of PDAC cases will double up (Narayanan, 2015). Seriousness of this issue can be seen not only in the fact that the incidence is ever closer to prevalence, but in several other factors. In the USA, PDAC represents the fourth most frequent death causing tumour (7%), similarly to other western countries (placing between fourth and tenth most frequent),

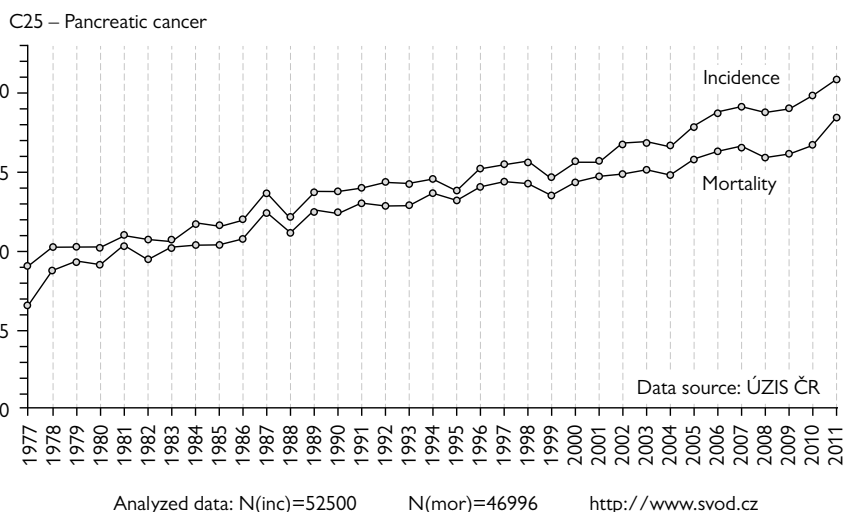


Figure 1 – PDAC incidence in the Czech Republic (array of 100 000 inhabitants, incidence – upper curve, mortality – lower curve).

albeit it represents only 3% of newly diagnosed tumours. Among gastrointestinal malignancies PDAC represents the second most frequent cause of death (www.svod.cz; Siegel et al., 2011; American Cancer Society, 2013; Becker et al., 2014; Edderkaoui and Eibl, 2014; Reznik et al., 2014; Narayanan, 2015). It remains one of the leading causes of cancer-related deaths worldwide, reflected by an incidence of 277 668 new cases and almost the same mortality rate (266 029 cases) per year (Siegel et al., 2011).

A principal difference (considering the chance of survival, yet relative to its length) can be seen, if diagnosis followed by surgical treatment is set in good time, i.e. the patient still benefits from the resection. Percentage of non-resectable tumours due to locally advanced or metastatic condition varies according to the literature from 60 to 96%, mostly over 80% (Lynch et al., 1990; Hoimes et al., 2009; American Cancer Society, 2013; Becker et al., 2014). Survival rate with non-resectable PDAC reaches 4 to 8 months (median value 3.5 months).

Hereditary component can be identified approximately in 10% of cases – familial PDAC, the rest is classified as non-familial sporadic form. Familial aggregation in patients with suspicion of hereditary genetic component was described already in 1973 (MacDermott and Kramer, 1973; Hoimes et al., 2009; Permut-Wey and Egan, 2009; American Cancer Society, 2013; Canto et al., 2013; Conroy et al., 2013). In 1990 Prof. T. Lynch realized the first systematic study involving 18 families with PDAC and confirmed higher risk of its formation (Lynch et al., 1990; American Cancer Society, 2013). Since that moment, the systematic research focuses on this issue (Edderkaoui and Eibl, 2014).

Subject matter

PDAC diagnostics

Provided that the early diagnosis of potentially curative, or rather resectable pancreatic neoplasias, appears to be the only chance for life prolongation, the potential PDAC screening is the logical choice. Nonetheless, due to low PDAC incidence within the population and screening complexity, this method has not been widely recommended so far (Canto et al., 2013). Another reason is because there is no category of individuals within the population defined as a high-risk group (Hruban et al., 2010), except for the familial PDAC cases.

A further intense research aiming at detection and identification particularly among pre-cancerous lesions and especially at the cellular level, might improve screening efficiency. More precise and advanced endoscopic methods, as well as improved imaging of retroperitoneal region, also support the early diagnosis (Kolodcick et al., 2014).

Among risk factors of PDAC formation are not only numerous genetic syndromes, but also modifiable risk factor. Those factors together can increase the PDAC risk up to 132 times (Hoimes et al., 2009; Kolodcick et al., 2014).

Table 1 – Risk factors and PDAC (Becker et al., 2014)

Risk factor	Increased PDAC risk
Current cigarette use	1.7–2.2
Current pipe or cigar use	1.5
> 3 alcoholic drinks per day	1.2–1.4
Chronic pancreatitis	13.3
BMI > 40 kg/m ² , male	1.5
BMI > 40 kg/m ² , female	2.8
Diabetes mellitus, type 1	2.0
Diabetes mellitus, type 2	1.8
Cholecystectomy	1.2
Gastrectomy	1.5
<i>Helicobacter pylori</i> infection	1.4

PDAC – pancreatic ductal adenocarcinomas; BMI – body mass index

Established risk factors include a family history of pancreatic cancer, a medical history of hereditary pancreatitis, diabetes type II and cigarette smoking (Pelzer et al., 2013).

PDAC environmental risks, which involve smoking, diabetes mellitus, obesity, and alcoholism (Table 1) play considerably bigger role in the formation of this tumour than recognized, albeit ever rising number of studies focus on this topic (Go et al., 2005; Canto et al., 2013; Edderkaoui and Eibl, 2014; Kolodecik et al., 2014).

Influence of those elements is a matter of primary prevention.

Other studies in contrast deal with influence of blood types, where negative “impact” has been shown in type A (Pelzer et al., 2013, 2014). Chronic pancreatitis (CP) over a long period has been considered as a significant risk factor of PDAC. Meta-analyses document a relative risk of 13.3% of PDAC formation (Kolodecik et al., 2014). Chronic inflammation connected with CP can induce its progression into a tumour, and also cause development of three pre-cancerous lesion types:

- pancreatic intraepithelial neoplasia (PanIN)
- intraductal papillary mucinous neoplasm (IPMN)
- mucinous cystic neoplasm (MCN).

PanIN are microscopic ductal lesions. Most frequently recognizes as preneoplastic lesions seen in up to 82% of PDAC patients, and also in 16–80% of normal pancreas, albeit late lesions appear exclusively in PDAC patients. PanIN are mostly smaller than 1 cm and usually localized in the head of pancreas. In these cases, the possibility of detection by imaging methods is illusive. Their diagnostic detection is rather accidental or in a section.

The most serious in the three-grade classification is the PanIN 3 – carcinoma *in situ*.

IPMN accounts for 3–5% of pancreatic tumours and their classification derive from the degree of dysplasia. Invasive carcinoma is found in 20–50% IPMN. These

Table 2 – Selected PDAC genetic risk factors (Becker et al., 2014)

Risk factor	Gene	Increases PDAC risk	Other associated cancers
Hereditary breast and ovarian cancer syndrome	BRCA1, BRCA2, PALB2	2–3.5	breast, ovarian, prostate
Lynch syndrome (hereditary non-polyposis colorectal cancer)	MLH1, MSH2, MSH6, PMS2, EPCAM	8.6	colon, endometrium, ovary, stomach, small intestine, urinary tract, brain, cutaneous sebaceous glands
Familial adenomatous polyposis	APC	4.5–6	colon, desmoids, duodenum, thyroid, brain, ampullary, hepatoblastoma
Peutz-Jeghers syndrome	STK11/LKB1	132	esophagus, stomach, small intestine, colon lung, breast, uterus, ovary
Familial atypical multiple mole melanoma pancreatic carcinoma syndrome	P16INK4A/, CDKN2A	47	melanoma
Hereditary pancreatitis	PRSS1, SPINK1	69	
Cystic fibrosis	CFTR	3.5	
Ataxia-telangiectasia	ATM	increased	leukemia, lymphoma
Non-O blood group		1.3	
Familial pancreatic cancer	unknown	9 (1FDR) 32 (3FDRs)	

tumours may occur in the main or in secondary pancreatic outlets; if located in the main outlet, the risk of malignization rises up to 70%.

MCN are less common but relatively bigger tumours (1 to 3 cm), more often seen in females, with greater risk of malignization in 20% (Hruban et al., 2010; Koloddecik et al., 2014). Their development into a malignant tumour depends on several molecular changes. Despite the significant risk factor pancreatic carcinoma develops only in circa 5% of patients (Koloddecik et al., 2014).

About 10% of PDAC has a hereditary component, which complies with the familial incidence, i.e. one affected increases the risk of PDAC in the family by 80% (Becker et al., 2014).

Specific mutations in genes relate to about 10% of PDAC with different penetration and risk degree for each mutation (Table 2; Becker et al., 2014).

T. Koloddecik and his team studied possible pathways of PDAC development. Pancreatitis starts with an initiating insult followed by changes in the cellular environment and premature digestive enzyme activation. Mutations of genes associated with trypsinogen activation/inactivation predispose the pancreas to

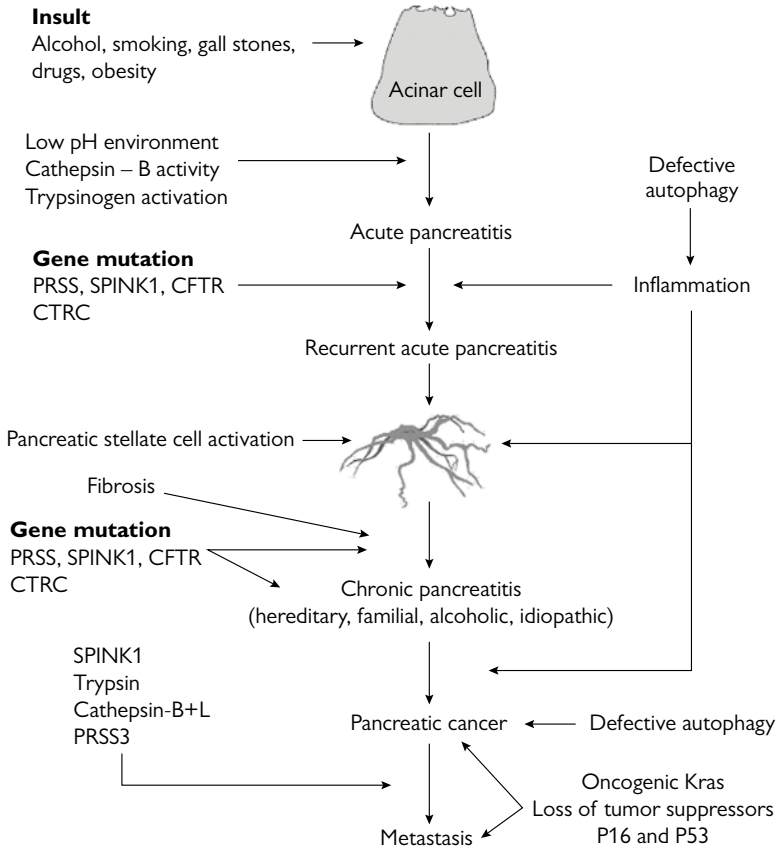


Figure 2 – Common pathways associated with disease progression from acute to chronic pancreatitis and pancreatic cancer.

development of disease. As disease progresses, defective autophagy, increased inflammation, pancreatic stellate cell activation, and fibrosis occur. Advancement toward pancreatic cancer and metastasis is also associated with defective autophagy, as well as extracellular matrix degradation, cell proliferation, expression of oncogenic KRAS and loss of tumour suppressors (e.g. P16 and P53) (Figure 2 – Kolodecik et al., 2014).

Number of studies dealing with gene mutations is on the increase (Conroy et al., 2013; Becker et al., 2014; Reznik et al., 2014). Their attention focuses mainly on DNA alteration of preneoplastic lesions.

Genetic cause in most PDAC has not been discovered so far. There have been some important and highly penetrative genes identified, such as BRCA2, PALB2, connected with the high risk of PDAC; however, the majority of PDAC cannot be explained by known genetic syndromes based on DNA familial testing. This finding

is reflected in the fact that only 10–20% of PDAC with familial aggregation indicate connection with highly penetrative genes. Remaining 80% need to be researched from the aspect of mutual links or by genetic sequencing.

Germinal mutation

Germinal mutation (germ-cell mutation) detectable in family members with PDAC embrace BRCA2 and some other e.g. FANCC and FANCG, PALB, PTEN, TP53, STK11/LKB1, p16CDKN2A, ATM, PRSS1 (influencing DNA in Fanconi anemia).

Somatic mutation

The genetic progression model for PDAC (compared for instance with adenocarcinoma development in CRC – colorectal cancer) represents sequential gain of proto-oncogene KRAS followed by mutation in tumour-suppressor genes, such as p16/CDKN2A/INKA4A, TP53 and SMAD4, that lead to disturbance of cell cycle regulation and initiate progression PanIN to PDAC. We assume that severe genetic mutation leading to sporadic PDAC are in fact mutations in proto-oncogene KRAS, as well as in tumour-suppressor genes p16/CDKN2A/INKA4A, TP53 and DPC4/SMAD4, while alteration in BRCA2, mismatch in repair genes (hMLH1, hMLSH2, and hMSH6), and AKT2 and STK11/LKB1 genes are rare.

Oncogenes

Oncogenesis in PDAC is supported by mutated and activated genes, particularly KRAS (located on 12p chromosome), BRAF (chromosome 7q), AKT2 (chromosome 19q) and AIB I (chromosome 20q). KRAS mutation is detected in up to 90% of PDAC, BRAF in 30%, and AKT2 amplification and overexpression in 10–60% of PDAC. Amplification AIB I in more than 60% of PDAC.

Tumour suppressor genes

These genes are recessive, and if inactivated they support tumour growth. Also, in PDAC a loss of important suppressor gene function can be seen; genes like p16INK4A/CDKN2A, TP53 and SMAD4/DPC4 are inactivated in more than 50% of all PDAC. SMAD4, located on chromosome 18q21, is inactive in about 50–60% PDAC. Also BRCA2 proved to be inactivated, but less frequently. Study focusing on other biomarkers also covers research of EGFG and VEGF expressions. Over the past few years, several studies focussed on assessment whether cytokine panel combination, specifically IL-6, IP-10, PDGF and CA19-9, can be utilised, same as biomarkers, for more precise PDAC diagnostics. According to some researchers, there might be some diagnostic potential (Hruban et al., 2000; Hoimes et al., 2009; Permuth-Wey and Egan, 2009; Delpu et al., 2011; Canto et al., 2013; Edderkaoui and Eibl, 2014; Krška, 2014b; Reznik et al., 2014; Narayanan, 2015). However, the CA (carbohydrate antigen) 19-9, also called sialylated Lewis blood group antigen, found in up to 95% of population in normal pancreatic ductal cells, still remains

the golden standard among laboratory diagnostics. Patients, who are Le^{a-b-} (Lewis blood group) negative do not evince any antigen expression even with large tumours. CA19-9 biomarker was described already in 1979 and still remains the only marker for PDAC diagnostics accepted by FDA (Federal Drug Agency) (Pelzer et al., 2014). CA19-9 serum levels in patients with chronic pancreatitis or benign biliary stricture are often elevated to about the same level as in small-scale PDAC. Another CA19-9 potential, apart from diagnostic importance, is seen in prediction of tumour recurrence after curative resection. Its sensitivity to PDAC varies between 71–81% and specificity between 83–90% at the cut-off level of 34.7 U/ml. The higher the cut-off level is (already 100 U/ml), the bigger the probability of recurrence, the lower the median of survival and percentage of five-year survival. The level is also influenced by high bilirubin or lack of fucosyltransferase (www.pathologyoutlines.com/pancreas.html; Delpu et al., 2011; Edderkaoui and Eibl, 2014; Krška, 2014b; Strobels and Büchler, 2014).

Another monitored marker ranks to microRNAs (miRNA). MicroRNAs are biologically stable and influence carcinogenesis. They are short non-coding RNAs composed of 18–25 nucleotides. They function to impact post-transcript regulation of gene expression leading to mRNA degradation, or possibly repression of mRNA translation, modifying cell proliferation, migration, and invasion and metastasizing.

In relation to PDAC more than 100 miRNAs have been identified. They can be assessed in aspirate, serum, bile or punctured sample. Assessment of suitable miRNA panel, mostly in concordance with other markers monitoring, is performed by many centres. The attention is focussed mainly on miRNA-10b, -155, -106b, -196a, 1290, and others (www.pathologyoutlines.com/pancreas.html; MacDermott and Kramer, 1973; Lynch et al., 1990; Hruban et al., 2000, 2010; Hoimes et al., 2009; Permuth-Wey and Egan, 2009; Delpu et al., 2011; Siegel et al., 2011; Canto et al., 2013; Conroy et al., 2013; Becker et al., 2014; Edderkaoui and Eibl, 2014; Krška, 2014b; Reznik et al., 2014; Narayanan, 2015).

The list of suitable biomarkers monitored for possible assessment of PDAC recurrence after resection is shown in Table 3.

Table 3 – Biomarkers evaluated for predicting recurrence following resection of PDAC (Osayi et al., 2014)

Carbohydrate antigen 19-9 (CA19-9)	Metastin
Carcinoembryonic antigen (CEA)	Phosphate and tensin (PTEN)
Cellular biomarkers	Molecular biomarkers
Circulating tumour cells (CTCs)	CX chemokine receptor 4 (CXCR4)
Neutrophil-lymphocyte ratio (NLR)	Cathepsin B
Gene biomarkers	Vascular endothelial growth factor (VEGF)
P16/CDKN2A, TP53, and SMAD4/DPC4	MicroRNAs (miRNAs)

Pathogenesis of PDAC has been most often correlated with the alterations of KRAS, P16, P53, DPC4 and FHIT (fragile histidina triad protein). Investigation of the alteration together with some of the miRNAs that are intensively investigated now appears as the most promising in this field of diagnosis.

Diagnostics – Imaging methods

Imaging methods play crucial role in PDAC diagnostics. Over the past three decades, some diagnostic methods, such as angiography and hypotonic duodenography, have been abandoned. Also ERCP (endoscopic retrograde cholangiopancreatography) is no longer perceived as necessary and is indicated only selectively. The golden standard in subhepatic region and retroperitoneum examination in case of PDAC suspicion is a multi-detection spiral CT (computed tomography). With each upgraded generation of imaging equipment, the sensitivity and specificity is ever more precise. Application of NMR (nuclear magnetic resonance) for mentioned indication is also wider for its ability to display outlet systems, which is beneficial. PET (positron emission tomography) CT is not applied as standard method in case of primary examination; its benefit is seen at the time of dispensarization (www.pathologyoutlines.com/pancreas.html; Hruban et al., 2000; Go et al., 2005; Delpu et al., 2011; Bockhorn et al., 2014; Diener et al., 2014; Edderkaoui and Eibl, 2014; Krška, 2014b; Osayi et al., 2014; Strobel and Büchler, 2014).

The basic algorithm of examination, which must be fast and as accurate as possible, it is therefore serological (markers as CA19-9) and practically parallel the CT examination rated according to protocol or endosonography with a biopsy. According to the experience of the workplace can CT replace NMR.

Tactics and extent of surgical procedure

Since the forties of the past century, the extent of surgical procedure has not changed significantly. Whipple procedure (pancreaticoduodenectomy) is a major surgical procedure performed if the tumour is located in pancreatic head, comprising resection of pancreatic head and duodenum. When the tumour is located in pancreatic body or tail, then this part is removed. Pancreatectomy is indicated in more developed or diffuse forms of PDAC. The extent of lymphadenectomy (LA) is based on D dissection, D2 or D3; LA does not bring any benefit. Pylorus preserving procedure (ppWhipple), so often referred to in scientific literature, brings almost no benefit in meta-analyses; on the contrary, in the short-term horizon, it represents higher risk of the upper type passage disorder; long-term results are still in the phase of research (Krška, 2014a).

However, overall perspective on the extent of procedure in case of vessel impairment has changed. If R0 (resection border without the presence of macroscopic and microscopic tumour involvement) resection can be expected, procedure on vessel system might be indicated (v. mesenteria superior, v. portae).

In case of arteries infiltration, indication for procedure on hepatic artery is a matter of consideration, yet in case of circulatory impairment of penetration into a. mesenterica superior, the procedure is hardly ever indicated. Some centres do perform this procedure also in the case of recurrence (minor localized recurrence and in a long-term distance from the primary operation), but only if it is reasonable (Bockhorn et al., 2014; Krška, 2014a; Strobel and Büchler, 2014).

Considering the procedure methods an important trend immersed, i.e. vessel first approach consisting in dissection of hepatoduodenal ligament structure, than complete loosening of duodenum and dissecting of the upper mesenteric artery at the point of its clearance from aorta. This technique enables not only to see the extent of tumour spread right in the initial phase, but also to loosen the tumour and surrounding tissue if necessary directly from the artery, i.e. the whole “meso-pancreas”. This way any possible procedure on vessel structures or ligament becomes easier (Bockhorn et al., 2014; Strobel and Büchler, 2014).

Current ISGPS (International Study Group of Pancreatic Surgery) criteria for locally advanced tumour resectability are:

- maximum time-lapse from the last CT of 4 weeks;
- assessment by multi-disciplinary team in large-volume centre.

Technical criteria for possible resectability (i.e. not excluding surgical removal) are:

- constriction or closure of v. portae (VP), v. mesenterica (VMS) and their branching by tumour;
- penetration a. gastroduodenalis or a short part of a. hepatica into tumour, yet without impairment of truncus coeliacus;
- contact of tumour with mesenteric artery superior within circumference under 180 degrees (Hruban et al., 2000; Kelsen et al., 2008; Delpu et al., 2011; Bockhorn et al., 2014; Diener et al., 2014; Edderkaoui and Eibl, 2014; Krška, 2014a; Osayi et al., 2014).

Measures of indication to surgical exploration and resection in case of VP and VMS impairment are:

- evidence of resectability and possible vessel reconstruction;
- no evidence of neoadjuvant treatment;
- possibility of intra-operative decision for resection with vessel reconstruction (only if chance for complete tumour removal);
- type of vessel resection must be classifiable and describable.

General approach of surgeons to indication, exploration and possible resection in case of suspicion of arterial infiltration or occurrence:

- arterial reconstruction – not primary option (lack of evidence about benefits in pancreatic head impairment);
- recommended – surgical explorations should be performed to clarify arterial infiltrations observing the resectability border-line criteria (see above);

- fact that palliative treatment in case of arterial infiltration is the standard;
- concepts of neoadjuvant treatment and non-curative resections should be performed only in the scope of proper clinical trials.

Laparoscopic (LS) techniques are applied particularly in left-side resections or in tumours with possible enucleation. Introduction of staplers and modified transection methods rather increased the number of fistulas. LS procedures in the region of pancreatic head are possible and feasible, however due to complicated dissection with possible vessel involvement they are rarely indicated even in large centres also with respect to R0 resection necessity.

Laparoscopy indicated as the initial surgical step, for more than 20 years already, can confirm or exclude metastatic process, its benefit considering the resectability in locally advanced tumour is questionable. Considerable time parameters, especially for comorbid patient, are not suitable for LS procedures of pancreatic head.

During evaluation of pathological findings from surgically removed section the R-1 definition must be clear, i.e. tumoural cells in the section line (vs. 1 mm or more from the borderline), examination results of all seven evaluated lines, and thorough examination of the vessel wall (in case of its section).

To sum up, based on available data, the primary operation with vessel resection (in patients with locally advanced pancreatic cancer and borderline resectability) can be recommended, on the presumption that all necessary conditions are respected. These complicated procedures should be performed only in specialized high-volume centres with available erudite intensive care (Bockhorn et al., 2014; Diener et al., 2014; Krška et al., 2014; Strobel and Büchler, 2014).

Anastomosis complications, their evaluation and comparison are one “never-ending story”. Considering that pancreatic surgery relates to 3–5% of peri-operative lethality and up to 40% of morbidity, the most serious complication, next to bleeding, is a pancreatic fistula. No existing method can eliminate occurrence of fistulas. The cause for this complication is multi-factorial; it depends on the condition of pancreas, the surgeon, “deep-rooted” operating skill, comorbidities, etc. Existence of this complication led to development and finding of other techniques (3-layer anastomosis, telescopic connection, outlet conversion to stomach, etc.).

Even preventive administration of somatostatin did not bring any change; only highly-developed, sophisticated operation technique of the large-volume centre can have some impact.

The strategy in metastatic PDAC is directed to adjuvant and symptomatic treatment. However, in many centres, an isolated metastasis in liver (in case of tumour resectability) is indicated to surgical section and procedure on pancreas (Diener et al., 2014; Hoskovec et al., 2014; Petruželka, 2014; Strobel and Büchler, 2014).

PDAC system treatment

Neoadjuvant oncological system treatment for resectable PDAC is not indicated. Benefits of this treatment have not been proved; the only chance for the patient is the surgical procedure R0 resection (Bockhorn et al., 2014; Diener et al., 2014; Strobel and Büchler, 2014).

Analysis of PDAC prevalence and incidence curves and their development very clearly shows only a slight effect of the system oncological care in other PDAC forms, despite diverse interpretation of “company trials”. Results of individual trials documenting survival rate differ in weeks, and since the arrays are non-homogenous, meta-analyses can hardly be valid. The wish here is often father to the thought. The era of PDAC chemotherapy (CHT) began in 1996 by introduction of gemcitabine, rather expensive those days, and its global expansion. Results were slightly better than with 5-fluorouracil in the same indication. Before this era, oncologists generally had a very restrained approach towards this treatment.

Gradual development in this field brought combination of gemcitabine with erlotinib (from 2005), however gemcitabine treatment dominated. Situation changed with FOLFIRINOX combination, which suited patients with better performance status. Since 2012, combination of gemcitabine with nab-paclitaxel is used (Gunturu et al., 2013; Petruželka, 2014).

As for the conversion treatment of border-line resectable and locally advanced non-resectable tumour, many studies refer to application of FOLFIRINOX combination in preference to gemcitabine. The most optimistic studies state up to 40% possibility of conversion to resectable state and achievement of 20–30% R0 resection (Hosein et al., 2012).

Such “success rate” is frequently opposed by queries like: 1) primary staging often performed only by means of radiology methods; 2) differences between surgeons; 3) effect of chemotherapy (possibly also chemoradiotherapy) on inflammatory changes around tumour; and many others. It is a fact that conversion therapy must to be a part of oncosurgical team armamentarium.

Sorting of patients with metastasizing PDAC with regard to palliative therapy is described as follows (Petruželka, 2014):

- 1) Patients with good performance status – combined CHT FOLFIRINOX or Nab-paclitaxel/gemcitabine (10–32% patients);
- 2) Patients unsuitable for inclusion in array No. 1 – combination of gemcitabine with oxaliplatin or fluoropyrimidines; or gemcitabine with erlotinib (20–30% patients);
- 3) Patients with poorer performance status, comorbid and biologically older patients – mono-therapy by gemcitabine (20–30% patients);
- 4) Patients on supportive treatment without system therapy (5–30% patients).

Similarly to chemotherapy, radiotherapy apparently also has certain effect to QoL (decrease of tumour and lower pressure to retropancreatic nerve plexus). PDAC radiotherapy (RT) for conversion and adjuvant treatment is widespread

within Asian and American methods and trials. The convention as well as proton radiation, which by the way seems to be theoretically the most promising right now, bring temporary reduction of local impairment. However, there is only a minor influence to possible recurrence or generalization – the crucial cause of lethality.

Generally we can state, that neoadjuvant regimes, radiation and immunotherapy do not play any major role in clinical practice arising from “evidence based medicine” (Strimpakos et al., 2010; Lee et al., 2012).

Locally advanced PDAC – Ablation techniques

Over the several recent decades, some new forms of treatment methods were established (radiofrequency ablation, stereotactic body radiation therapy, high-intensity focused ultrasound, iodine-125-cryosurgery, photodynamic therapy, microwave ablation, irreversible electroporation, and others). Though their application is possible and from the technical aspect relatively easy, there is quite significant risk of serious complications (inflammation, bleeding, and fistulas). They can influence the local impairment, same as radiation therapy, yet the total survival rate remains unaffected. However, by local improvement, achieved for instance by IRE (irreversible electroporation), QoL improves as well (Lee et al., 2012; Boone et al., 2013; Hoskovec et al., 2014; Krška et al., 2014; Pelzer et al., 2014).

Conclusion

The only treatment technique, which in fact can influence not only the survival parameters, but also QoL, remains the R0 surgical resection. All other curative methods are only coarsely palliative and prolong the survival time just temporarily at the most. The principle factor here is timely recognition and indication to surgery. Utilization of diagnostic markers is still subjected to intensive research and we can see huge progress, however unequivocal results unfortunately are not available so far. Radiodiagnostics continues to be one of the principal methods. Primary CT results (not revision ones) should not exceed one month at the time of operation, which unfortunately is still the case in most centres. Main differences between centres can be seen in five-year survival rates and closely relate to arrays of patients and quality of the primary care. High-volume complex centres and highly experienced oncosurgical teams achieve better results. Trophy operations or non-indicated trials in PDAC are highly *non lege artis*. Further research will be directed to high-risk population groups with focus on familial and hereditary detection, onco- and tumour suppressor genes monitoring, and excreted cell parts (sudden formation of diabetes mellitus (DM) type 2, familial occurrence, chronic pancreatitis, and others).

Dedicated to Professor Marie Pešková, DSc. (1935–2008) the significant representative of pancreatic surgery at the occasion of her nearly 80 years birthday anniversary.

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