

Locally advanced pancreatic cancer — new therapeutic challenges

Michał Piątek¹, Sergiusz Nawrocki^{2,3}

The overall survival rate of patients with pancreatic ductal adenocarcinoma remains extremely poor, and the only potentially curative treatment is radical surgery. There are three subgroups among the patients: primary resectable, metastatic and locally advanced pancreatic cancer. The term of locally advanced pancreatic cancer includes borderline resectable pancreatic cancer (BRPC) and unresectable pancreatic cancer (URPC). As in the case of BRPC, the strategy of induction treatment may convert the inoperable tumour into a resectable one. As in the case of URPC, the optimal standard of treatment is unknown. Recent advances in systemic treatment such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel as well as the optimisation of local treatment such as stereotactic radiotherapy (SBRT — stereotactic body radiation therapy) should be incorporated into future trials dedicated for BRPC and URPC.

NOWOTWORY J Oncol 2016; 66, 4: 312–316

Key words: BRPC, URPC, FOLFIRINOX, gemcitabine plus nab-paclitaxel, SBRT

Introduction

Pancreatic cancer is a disease with an extremely high mortality rate — it ranks fifth among the causes of death for malignant cancers in developed countries. It is one of the few cancers in which there has been no significant progress in treatment results for the last few decades. Within the last 30 years, the chances of 5-year survival has grown from about 2% to 5% [1]. At the time of diagnosis, only 10% of patients have a resectable tumour and 60% have distant metastases while in 30% of cases the tumour is locally advanced [2].

Practical clinical division into sub-groups

Primarily the resectable group of patients is characterised by the lack of distant metastases, the lack of infiltration of the vascular structures within the celiac axis (CA), the superior mesenteric artery (SMA), the common hepatic artery (CHA), the superior mesenteric vein (SMV), the portal vein (PV) with the admissible vein infiltration being < 180° of the vessel perimeter with the possibility of reconstruction [3, 4]. Even in the case of R0 resection, the 5-year survival

rate in this group is as low as 15–20%, with median survival being about 20–24 months [5]. In the case of the R1 or R2 resection, survival is usually less than 12 months, being on a comparable level as that of the locally advanced group [6, 7]. The rate of R1 resection reported in publications varied between 20% and 75% [8, 9]. A standard treatment after the radical resection of patients is 6-month adjuvant chemotherapy [10].

Patients with systemic involvement have the worst prognoses. The main treatment method in this group is systemic treatment, mostly with chemotherapy. The clinical benefit over treatment with 5-fluorouracil administered in the form of weekly bolus doses and the slight improvement in overall survival made gemcitabine a standard method of palliative treatment in 1997 [11]. Recent developments in the treatment of metastatic pancreatic cancer with new chemotherapeutic regimens such as gemcitabine plus nab-paclitaxel or FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) led to a significant improvement in treatment results in comparison with gemcitabine in monotherapy [12, 13]. The comparison of FOLFIRINOX (FFX) with gemcitabine

¹Clinical Oncology Division, Prof. K. Gibiński Memorial University Clinical Center, Silesian Medical University, Katowice, Poland

²Radiotherapy Division, Prof. K. Gibiński Memorial University Clinical Center, Silesian Medical University, Katowice, Poland

³Chair of Oncology and Radiotherapy, Silesian Medical University, Katowice, Poland

Table I. The definition of borderline resectable pancreatic cancer according to the Intergroup trial

SMV-PV	SMA	CHA	CA
Tumour — vessel interface > 180° of the vessel perimeter and/or the obliteration of the vessel with the possibility of performing safe resection and reconstruction	Tumour — vessel interface < 180° of the vessel perimeter	Tumour — vessel interface concerning a small segment with the possibility of performing safe resection and reconstruction	Tumour — vessel interface < 180° of the vessel perimeter

showed a significant increase in the objective response rate (31.6% vs 9.4%), a significant prolongation of the survival period (11.1 vs 6.7 months) and a significant prolongation of progression-free survival (6.4 vs 3.3 months). In spite of such intensity of treatment and much larger toxicity in grade 3 and 4, no deterioration of quality of life was observed among the patients treated with FFX [13]. Irrespective of the initial doubts related to the large toxicity of FFX, this regimen was quickly introduced into clinical practice and until today it has been undergoing numerous modifications — these are mFOLFIRINOX (mFFX) which reflect the attempts to reduce toxicity accompanied with the preservation of the treatment efficacy [14–19].

The medium group of patients with a diagnosis of locally advanced neoplastic progress is characterised by the absence of distant metastases. However, some traces of the infiltration of adipose tissue around the arteries (SMA, CHA, CA) and/or the infiltration of veins (SMV, PV) with the involvement of > 180° of the vessel perimeter and the impossibility of its reconstruction is observed [3, 4]. This is the most heterogeneous group of patients among whom there are at the same time possibilities of radical surgery as well as palliative treatment only, and thus there are no definite standards of treatment. Given the above, it was necessary to distinguish a group of patients where the radical treatment could be possible at any stage of the therapeutic process. Eventually the locally advanced pancreatic cancer patients were divided into a group with borderline resectable pancreatic cancer (BRPC) and a group with unresectable pancreatic cancer (URPC).

Borderline resectable pancreatic cancer

The term borderline resectable pancreatic cancer has a relatively short history and it was coined because it became clear that long term survival in pancreatic cancer was only possible in the case of R0 resection. Other developments in this matter were defining venous resections in pancreatoduodenectomy as feasible and safe procedures, accompanied with the first reports of the possibilities of neoadjuvant treatment increasing the rate of R0 resections [20, 21].

The radiological criteria which allow one to distinguish between resectable and non-resectable cancers were described for the first time in 2001 [22]. In 2006, the National Comprehensive Cancer Network (NCCN) introduced the term “borderline resectability” to describe, in the most accurate manner, the tumours which in a limited way involve

the vascular system and whose primary resection, if possible, would leave the positive surgical margins and would require the application of neoadjuvant treatment. Until today no universal definition of BRPC has been coined, which has an adverse effect on the possibilities of comparing the results of the treatment, and, as a result of which no standards in treatment have been created. The most frequently quoted definitions of BRPC were proposed by MD Anderson, America’s Hepatopancreatobiliary Association (AHPBA), the Society for Surgery of the Alimentary (SSO), NCCN and by the Intergroup trial, with the latter deserving special attention, as it does not use any subjective terminology and is easy to apply to the MRI protocols (Tab. I) [4, 23–25].

A great majority of clinical studies carried out so far dealing with BRPC are retrospective, single centred and concern a small group of patients. The value of these reports is limited by a diversity of the definitions of resectability and the multitude of possibilities of neoadjuvant treatment. In one such study, carried out in the MD Anderson Cancer Center, 160 (7%) out of 2454 patients with a diagnosed pancreatic cancer were regarded as BRPC and treated with neoadjuvant therapy. The treatment was completed in 125 patients with 66 undergoing radical resection and 62 of them R0 resection (94%). The median of overall survival in the group of 66 who completed the treatment was 40 months, whilst in the remaining 94 patients who did not go through pancreatoduodenectomy, it was 13 months ($p < 0.001$) [26]. Given the limitations connected with the methodology of studies concerning BRPC, the meta-analyses suggest that neoadjuvant treatment with chemotherapy or chemoradiation, based mostly on gemcitabine or 5-FU, allows for a radical surgery in 1/3 of patients and the prognoses in the group of patients does not differ much from the prognoses among the primarily resectable patients [27, 28]. In light of the new developments in the treatment of metastatic pancreatic cancer, in particular the FFX regimen, some attempts have been made to introduce it to the treatment of locally advanced pancreatic cancer, including BRPC. In 2014, the first published results on this issue concerned a prospective clinical trial with 18 patients with a diagnosis of BRPC, who first underwent neoadjuvant chemotherapy with FFX followed by a consecutive chemoradiation (50.4 Gy + gemcitabine or capecitabine). In the consecutive stage, 12 patients (66%) underwent radical surgery and in all of the cases the R0 was obtained (100%). With regards to the too short follow-up period, the final treatment results

are missing; nevertheless 7 patients (58.3%) out of the 12 who completed the treatment are still alive and 5 of them (41.7%) are free from progression (18–35 months from diagnosis), whereas 6 patients who did not complete the treatment, died (6.9–17.5 months from diagnosis). It must also be stressed that the adverse event rate in the 3rd and 4th grade was relatively low. The most frequent complications comprised nausea/vomiting (35.7%), neutropenia (14.3%) and diarrhoea (14.3%), and a large emphasis was laid on supportive care, such as, among others, the prophylactic application of granulocyte growth factor and antiemetic therapy with aprepitant — yet the toxicity of FFX did not have any negative influence on the completion of chemoradiation or mortality or peri-operative complications [29]. The largest undertaking devoted to BRPC is a multicentre pilot study, Alliance A021101, initiated by the Intergroup trial in 2013, in which the neoadjuvant treatment was based on 4 mFFX cycles followed by a consecutive chemoradiation with capecitabine. The results of this study are hoped to be a reference point for future BRPC studies [25].

Definitely non-resectable pancreatic cancer

The distinction of BRPC from patients with a locally advanced pancreatic cancer resulted in the appearance of a group of patients with cancers with URPC — unresectable pancreatic cancer. The reports of the two carefully performed studies in this subject showed that in such cases, as opposed to BRPC, the possibility of obtaining resectability is extremely rare (1/87 and 6/114 patients respectively), which, in consequence, means that long-term survival in this group is exceptionally rare [30, 31]. Given the above, the main objectives of treatment in patients with URPC is improvement of quality of life and the improvement of the survival period, as the course of the disease in this group of patients differs significantly from metastatic pancreatic cancer and requires analysis in separate protocols of clinical studies [32].

The optimal therapeutic standard in URPC is highly controversial with many questions still remaining unanswered. The role of radiotherapy or chemotherapy in the treatment of URPC, now increasingly in use, as well as the effect of such treatment on overall survival is undoubtedly one of these questions. The data from the two largest trials carried out so far are contradictory. The first of them (FFCD/SFRO) compared chemoradiation (60 Gy + cisplatin and 5-fluorouracil) with gemcitabine in monotherapy. In the group of patients treated with chemoradiation, the average overall survival time was only 8.6 months, whilst in the group treated with chemotherapy alone, it was 13 months ($p < 0.03$). It must be stressed that the treatment with radiotherapy was burdened with significant toxicity, which was caused by an extensive irradiation area and a large radiation dose — and finally this was the main cause of the deterioration of treatment

outcomes in this group [33]. In the second trial (ECOG 4201) chemoradiation (50.4 Gy + gemcitabine) was compared with gemcitabine in monotherapy. The average overall survival in the group of patients treated with chemoradiation was 11 months, whilst in the group treated with chemotherapy alone it was 9.2 months ($p = 0.017$). Significantly greater toxicity of treatment was observed in the chemoradiation arm: as GI tract complications G3/4 (38 vs 14%, $p = 0.03$) and fatigue G3/4 (32 vs 6%, $p = 0.006$) [34]. Summarising the two above trials, it seems that adding radiotherapy to chemotherapy has some insignificant effects on the improvement of overall survival, yet it is burdened with large toxicity. The final attempt to establish the role of radiotherapy in the treatment of URPC was made in the RTOG 1201 trial, currently in progress, where after an initial 3-month chemotherapy: gemcitabine + nab-paclitaxel and the exclusion of the group with the disease progression, the patients were randomly assigned to consecutive chemoradiation (50.4 Gy + capecitabine) or chemoradiation (63 Gy + capecitabine) or the continuation of chemotherapy [35].

Another issue related to the problems in the treatment of URPC is the optimal sequence of chemotherapy and chemoradiation. The recent analyses concerning the treatment with primary chemotherapy followed by consecutive chemoradiation in comparison with primary chemoradiation followed by consecutive chemotherapy point to the advantage of the first method of treatment over the latter. Primary chemotherapy carried for 2–3 months allows for the correct selection of the patients who could benefit from consecutive chemoradiation — the progression is observed in about 30% of patients after primary chemotherapy [36, 37]

The selection of an adequate cytostatic agent for treatment with radiation, as the radio-sensitiser, is also controversial among investigators. The largest meta-analysis so far, containing 229 patients and comparing gemcitabine with 5-fluorouracil associated with radiation, has proven the advantage of gemcitabine over 5-fluorouracil with regards to 1-year survival (27.9–56.2% vs 18.3–31.6%, $p = 0.03$), however, with regards to 6-month and 2-year survival, no differences were found between the groups [38]. A recent prospective clinical study, (SCALOP trial) comparing chemoradiation based on capecitabine (2x 830 mg/m² on irradiation days) as opposed to gemcitabine (300 mg/m² every 7 days, 6 doses in total) preceded by a primary 3-month chemotherapy, showed a significant prolongation of the survival period in the group with capecitabine (15.2 vs 13.4 months, $p = 0.01$); moreover, the treatment with capecitabine was characterised with a more favourable toxicity profile, both haematological (0 vs 18%), and non-haematological one (12 vs 26%). Contrary to gemcitabine, the administration of capecitabine during radiation could also affect the control of the disease from a systemic

Table II. Selected clinical studies with SBRT in combination with chemotherapy (GEM, gemcitabine; 5-FU, 5-fluorouracil; GTX, gemcitabine, docetaxel, capecitabine) in locally advanced pancreatic cancer

Study	Number of subjects	Treatment regimen	Months	1-year local control	Early toxicity G3/4	Late toxicity G3/4
Mahadevan (2010)	36	8–12 Gy x 3 + GEM	14.3	78%	8% G3	6% G3
Lominska (2011)	28	4–8 Gy x 3–5 + 5-Fu/GEM	5.9	86%	0	7.1% G3
Chuong (2012)	16	5–10 Gy x 5 + GTX	15.0	81%	0	5.3% G3
Tozzi (2013)	30	8 Gy x 5	11.0	86%	0	0
Gurka (2014)	10	5 Gy x 5				
+ GEM	12.2	40%	0	0		
Herman (multi- center, 2015)	49	6.6 Gy x 5				
+ GEM	13.9	78%	12.2%	10.6%		

point of view, which finally could translate into the improvement of overall survival. Irrespective of the initially small number of patients participating in the above study (74 subjects), capecitabine is now the most frequently associated with radiation in new protocols of pancreatic cancer chemotherapy [39]. The discussion of URPC treatment must point to the attempts of SBRT — stereotactic body radiation therapy alone or in combination with chemotherapy (Table II) [40–45]. The trials which have been carried out point to an effective local disease control in this method. The data concerning the safety of SBRT show very high late toxicity (ulceration, bleeding, perforation, mainly in the duodenal area), in the case of a single dose of SBRT. In the case of fractionation SBRT, the efficacy of treatment is comparable to conventional radiation with the safety of treatment kept at an acceptable level [40–48].

Conclusions and future directions for development

Resection, carried out with healthy margins, still remains the only chance for curing pancreatic adenocarcinoma. In the group of patients with locally advanced tumours, there is a distinction between the radical treatment (BRPC) and palliative approach (URPC). Preoperative treatment is not a standard approach in the treatment of pancreatic cancer, nevertheless in the case of BRPC, the application of preoperative therapy naturally seems to be the only possibility of obtaining R0 resection. Given the above, a careful qualification of the patients into specific groups is critical for the selection of the therapeutic strategy.

Distant metastases remain the main cause of the treatment failure in pancreatic cancer. The improvement of the treatment results must be found first of all in better systemic treatment. The progress in treatment obtained in metastatic pancreatic cancer, gained in such methods as FFX/mFFX or gemcitabine + nab-paclitaxel should be used for the treatment protocols of clinical studies in both BRPC and URPC [12, 13]. Given the autopsy results pointing to

the 30% rate of deaths resulting from local progression, one must not forget about the necessity of local control improvement. In spite of many controversies concerning the adequacy of irradiation in locally advanced pancreatic cancer, both conventionally fractionated chemoradiation and SBRT are frequent constituents of treatment in the protocols of clinical studies. Although there have not been any studies comparing the two methods of irradiation, SBRT is growing in frequency. This reflects the improvement of the quality of life resulting from very effective and fast pain control (less use of analgesic agents) in SBRT and a shorter treatment period than in conventional chemoradiation (1–5 days vs 5–6 weeks) [50]. There are reports which are based on molecular profiling, that point to the most probable method of disease progression. In one of the studies, it was shown that the loss of the DPC4 tumour suppressor gene was connected with an increased risk of metastatic disease, whilst its presence in the tumour tissues resulted in a more frequent local progression ($p = 0.007$) [49]. The possibility of predicting the method of disease progression (local vs distant) may in future be a justification for the use of local and/or systemic methods of treatment. Currently, the treatment strategy both in BRPC and URPC, apart from surgical intervention (if it is possible), comprises the combination of systemic treatment and irradiation. So far the combination of FFX or mFFX with SBRT has not been studied. Such a combination may prove to be very effective in the treatment of locally advanced pancreatic adenocarcinoma and definitely requires some further clinical research.

Conflict of interest: not declared

Michał Piątek, MD

*Uniwersyteckie Centrum Kliniczne im. prof. K. Gibińskiego
Oddział Kliniczny Chemioterapii
ul. Ceglana 35, 40–952 Katowice*

Received: 8 Mar 2016

Accepted: 29 Jun 2016

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