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CURRENT TOPIC • АКТУЕЛНА ТЕМА

Pancreatic carcinoma – diagnosis and modern multimodal treatment

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SUMMARY
Pancreatic cancer is one of the most aggressive tumors and is among the top ten most common malignancies in the world. This is a disease of older adults, and men get it more often. Pancreatic carcinomas risk factors are obesity and type II diabetes, smoking, and alcohol consumption. Symptoms of the disease include obstructive jaundice, loss of appetite, weight loss, fatigue, and back pain. The diagnosis of pancreatic cancer involves computed tomography of the thorax, abdomen and pelvis or magnetic resonance imaging of the abdomen and pelvis, and endoscopic ultrasound with biopsy. The most common histological type of pancreatic cancer is ductal adenocarcinoma. The TNM classification is used to determine the stage of the disease. Pancreatic cancer treatment is complex, multidisciplinary, and multimodal, and involves the use of surgery, chemotherapy, and radiotherapy, alone or in different combinations. Surgery is the main treatment modality for these tumors, especially in localized stages. Chemotherapy is applied in all forms in the treatment of pancreatic cancer as neoadjuvant, adjuvant, and systemic. Immunotherapy, as the newest type of treatment, is used in a limited way in the metastatic phase of pancreatic cancer. The role of radiotherapy in the treatment of pancreatic cancer is still debated, and it is most often applied in a neoadjuvant and palliative approach. Palliative therapy and care are an indispensable part of the treatment of patients with pancreatic cancer.
Keywords: pancreatic cancer; treatment; surgery; chemotherapy; radiotherapy

INTRODUCTION

Pancreatic carcinomas are considered one of the deadliest malignancies because they are usually in advanced stage at the time of diagnosis.

EPIDEMIOLOGY AND ETIOLOGY

Pancreatic cancer is among the top ten cancers in the world in terms of incidence and the seventh most common cause of death from cancer [1]. In the Republic of Serbia, pancreatic cancer is the sixth most common cancer.

Pancreatic cancer is a multifactorial disease. Genetic factors include a positive family history. Demographic risk factors, age and sex, indicate that the disease is more common over the age of 50 and with a male predominance. Acquired risk factors include obesity, type II diabetes, smoking and alcohol consumption [2].

SYMPTOMS AND DIAGNOSIS

Early-stage pancreatic cancer rarely causes symptoms, and when symptoms develop, it is usually at an advanced stage. Symptoms includes obstructive jaundice, loss of appetite, fatigue, weight loss, and abdominal or back pain.

At the time of diagnosis, about 50% of patients have metastatic disease, about 35% have locally advanced disease, and 15% have local disease [3].

Diagnostics of pancreatic cancer includes computerized tomography (CT) of the thorax, magnetic resonance (MR) or CT of the abdomen and pelvis, MR cholangiopancreatography, endoscopic ultrasound (EUS) with biopsy and pathohistological analyses.

CT is widely accepted in the diagnosis of pancreatic cancer. With modern multiphase and multidetector high-resolution CT with multiplanar reconstructions and contrast, the sensitivity of pancreatic cancer detection is 89%, and the specificity is 90% [4].

MR of the abdomen and pelvis provides a much better image of the soft tissues, especially in cases where the CT findings are inconclusive. MR with using diffusion sequences, the sensitivity increases to 92–96%, and the specificity to 97–99% [4].

EUS is not used as a routine method in the detection of pancreatic cancer, but for the detection of small tumors that are not visible on CT and are suspected on MR. EUS is primarily used to biopsy suspicious changes in the head of the pancreas to obtain pathohistological findings. The sensitivity of this method is 89–91% and the specificity is 81–86% [5].

Pancreatic carcinomas form a very heterogeneous group of tumors and ductal adenocarcinomas make about 90% of all pancreatic carcinomas [6]. Although histopathology remains the most reliable method for establishing

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a definitive diagnosis, it may be difficult to distinguish pancreatic carcinomas from metastases without immunohistochemistry [7]. Progress in molecular biology and pathology have led to more precise diagnosis, subtyping, tumor classification and prediction of therapeutic response. Pancreatic cancer genome is very heterogeneous and includes gene mutations and abnormalities (*BRCA1*, *BRCA2*, *TP53*, *KRAS*, etc.), microsatellite instability as well as impaired expression of growth factors (*HER2*) [8].

STAGING

The TNM classification is used to present the stage of pancreatic cancer [9]. The lymphovascular and perineural invasion of pancreatic carcinoma is prominent. The most common sites of pancreatic cancer metastasis are the liver (90%), lymph nodes and lungs (25%), peritoneum (20%) and bones (10–15%) [10].

TREATMENT

Five-year survival of a patient with pancreatic cancer is very modest, about 30% in the local stage, about 10% in the locally advanced stage, and 5% in the metastatic stage of the disease [8]. Pancreatic cancer treatment is multidisciplinary and multimodal. The basic type of treatment for early pancreatic cancer involves surgery, for locally advanced cancers a combination of chemotherapy (HT) with/or without radiotherapy (RT) and surgery, and for metastatic cancers, HT and RT are used. The most widely used recommendations in the treatment of pancreatic cancer are the National Comprehensive Cancer Network [11] and the European Society of Medical Oncology [12].

SURGERY

The primary approach in the treatment of pancreatic cancer is radical surgery and involves complete removal of the visible tumor and obtaining histologically free margins, i.e., microscopically negative margin means a distance of less than 1 mm from cancer cells.

In terms of resectability, pancreatic cancers can be estimated as resectable, borderline resectable, or unresectable [11].

The treatment is surgical for resectable tumors. Borderline resectable and locally advanced tumors are operated upon after neoadjuvant therapy and conversion to a resectable stage. Radical surgical procedures are pancreaticoduodenectomy (Kausch–Whipple procedure), distal pancreatectomy and total pancreatectomy.

Pancreaticoduodenectomy (Kausch–Whipple procedure) is a cancer operation of the head of the pancreas that includes the removal of the distal part of the stomach, duodenum, the end of the common bile duct, the gallbladder and the head of the pancreas with at least a 1 cm margin from the tumor. Reconstruction can be achieved in the form of pancreaticojejunostomy or pancreaticogastrostomy [13]. Lymphadenectomy involves dissection of the associated lymph nodes and standard dissection includes the infra- and suprapyloric lymph nodes, along the common hepatic artery, lymph nodes in the hepatoduodenal ligament, around the pancreatic head, and around the proximal part of the superior mesenteric artery and superior mesenteric vein. Distal pancreatectomy is an operation for carcinoma of the pancreas body and tail with "en-block" splenectomy, and involves mobilization of the body and tail of the pancreas, ligation of the splenic artery and splenic vein, lymphadenectomy, transection of the pancreas and ligation of the pancreatic duct. Total pancreatectomy is a combination of pancreaticoduodenectomy and distal pancreatectomy in patients with multilocular, large, and centrally located pancreatic tumors. It includes "en bloc" resection of the pancreas, gallbladder, duodenum and spleen with accompanying lymphadenectomy and reconstruction with hepaticojejunostomy and duodenojejunostomy.

The operation can be classic (open) and minimally invasive (laparoscopic and robotic). The minimally invasive techniques in the treatment of pancreatic cancer are not inferior comparing to open surgery in terms of surgical and oncological outcome. Laparoscopic technique may lead to a reduced hospital stay and postoperative complications and increased percentage of marginal clearance resections and harvested lymph nodes [14]. Robotic surgery is a promising technique that may lead to shorter hospitalization and lower postoperative complications but longer operative time [14]. Minimally invasive technique should be performed by experienced surgeons in high-volume centers and randomized trials with a large number of patients are necessary to examine the benefits of new technique, especially robotic surgery.

CHEMOTHERAPY

In the treatment of pancreatic cancer, HT is applied in almost all stages of the disease (except in early stages), as preoperative (neoadjuvant), postoperative (adjuvant) and systemic (palliative).

The role of neoadjuvant HT is manifested in marginally resectable pancreatic cancers because it significantly improves overall survival (OS) compared to "up-front" surgery (median OS 19 months *vs.* 29 months with neoadjuvant HT) [15], usually in combination with RT. In locally advanced unresectable pancreatic cancer with median OS of about 11–14 months [16], neoadjuvant HT is essentially induction, with the aim of reducing the size of the tumor and regional lymph nodes, to facilitate resection rate (up to 28%) and increase the chance of achieving R0 resection (up to nearly 70%), thus prolonging OS [17]. It can be combined with RT. Neoadjuvant HT can be applied as polytherapy with 5-fluorouracil plus leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) or as doublet therapy with gemcitabine-cisplatin / gemciatbin-nabpaclitaxel (GP/GN). FOLFIRINOX provides a slightly greater benefit to OS survival (median OS 33.4 months with FOLFIRINOX and

surgery *vs*. 27.9 months with GN and surgery) [17], but also slightly more pronounced toxic effects, so it is used in patients with preserved performance [Eastern Cooperative Oncology Group performance status (ECOG PS)] 0–1, and for more fragile patients gemcitabine-based HT is a good alternative.

Adjuvant HT is indicated in operated patients with pancreatic cancer regardless of resection margin status, in poor prognostic factors such as younger patients, poor tumor differentiation (grade 3–4), T3 and T4 disease stage and positive ln (N+). In patients with preserved ECOG PS, modified (m) FOLFIRINOX is used as standard. PRODIGE 24/CCTG PA6 trial [18] is the most relevant study on the role of adjuvant HT and demonstrated significantly longer survival with (m) FOLFIRINOX (median OS 53.5 months *vs*. 35.5 months in group with gemcitabin), which is much longer OS than those patient with only observation after resection (median OS is 22.3 months) [19]. A good alternative to standard HT is GP doublet, while mono-gemcitabine and fluorouracil and leucovorin (5FU-LV) is reserved for ECOG PS 2–3 patients [12].

Systemic HT is applied in the metastatic phase of the disease and has a palliative purpose. The same types of cytostasis are used. In the first line, in good ECOG PS 0–1, FOLFIRINOX is preferred over GN (median OS 9.6 months with FOLFIRINOX *vs*. 6.1 months with GN) [20], which is not a significant increase of OS (median OS in metastatic pancreatic cancer is 4.6–8.1 months) [21]. In fragile patients, mono-gemcitabine or mono-capecitabine is given [11, 12]. In the second line, in patients with ECOG PS 0–1, who were previously treated with FOLFIRINOX, GN can be used, while in patients who received gemcitabine-based HT in the first line, nanoliposomal irinotecan-5FU-LV is used. Other cytostatic combinations in the metastatic phase of the disease are GP, capecitabine-oxaliplatin and oxaliplatin-5FU-LV [11, 12].

New developments in cytotoxic HT imply that a combination of liposomal irinotecan, fluoracil, leucovorin and oxaliplatin) and it is possible option for frontline therapy in previously untreated patients with metastatic pancreatic cancer [22]. Some of ongoing trials include an efficiency assessment of combination of small molecule and cytotoxic drug in therapy of metastatic pancreatic cancer, like AVENGER 500 trial (mFOLFIRINOX and CPI-613) and NCT03126435 trial (endoTAG-1 and gemcitabine) [23].

IMMUNOTHERAPY

Immunotherapy in the treatment of pancreatic cancer is limited and for the time being is only used in metastatic disease. Poly adenosine diphosphate ribose polymerase enzyme inhibitors (PARP inhibitors) such as olaparib are used, followed by "checkpoint" inhibitors such as pembrolizumab (they act on receptors for programmed cell death-1 (PD-1) and PD-L1 protein in the tumor cell). Olaparib is administered as maintenance therapy in patients with metastatic pancreatic cancer harboring a *BRCA* gene mutation (about 4% of patients) after first-line platinum-based HT [24]. Pembrolizumab in unresectable pancreatic cancers can lead to a good partial remission of the disease [25].

CAR T-cell therapy is a promising development in immunotherapy of pancreatic cancer and is driving future clinical trials. Ongoing immunotherapy trials include combination of PARP inhibitors and PD-1 inhibitor (SWOG2001 trial) and PD-1 inhibitor and small molecule (SX-682) (NCT04477343 trial) [22].

RADIOTHERAPY

The role of radiation in the treatment of pancreatic cancer is still insufficiently defined. State-of-the-art RT techniques such as intensity modulated RT, volumetric modulated arc therapy, and stereotactic "body" RT are used [26]. Four-dimensional CT planning and image-guided RT are recommended. However, there is still no consensus regarding the fractionation of RT in the treatment of pancreatic cancer. RT in the treatment of pancreatic cancer can be preoperative (neoadjuvant), postoperative (adjuvant), and palliative, usually at the same time as HT to enhance the effect of the therapy.

The real role of neoadjuvant HT (HRT) is in marginally resectable pancreatic cancers because they are at increased risk of R1 resection, and RT can lead to downsizing and/or downstaging of the tumor, which increases the chance of achieving R0 resection. Landmark study on the role of neoadjuvant HRT is the PREOPANC study with 250 patients that compared the five-year OS of two groups of patients, treated with surgery alone plus adjuvant HT or a combination of preoperative HRT plus surgery and adjuvant HT (HT with gemcitabine and RT with tolerance dose 36 Gy in 15 fractions). The percentage of R0 resection was 72% *vs*. 43%, five-year OS rate was 20.5% *vs*. 6.5% (HRT and surgery group *vs*. surgery group) [27]. Today, standard therapy includes induction HT for 2–3 months, FOLFIRINOX or GN, and then concomitant HRT with 5-FU or capecitabine or gemcitabine [12]. RT doses of neoadjuvant HRT for borderline resectable pancreatic cancer are varied starting from standard fractionation (45–54 Gy in 25–30 fractions), through hypofractionation (36 Gy in 15 fractions, 30 Gy in 10 fractions) to stereotaxy (28–30 Gy in five fractions, 33–40 Gy in five fractions) [28]. In locally advanced unresectable pancreatic cancer, neoadjuvant therapy can lead to conversion to potentially resectable cancer. It was demonstrated in the CONKO-007 trial with over 300 patients that compared the OS of two groups of patients, treated with induction HT and sequential HT or preoperative HRT plus surgery (induction HT with gemcitabine/FOLFIRINOX and RT with tolerance dose 50.4 Gy in 28 fractions) [29]. The percentage of R0 resection was 25% *vs*. 18%, pathological complete response was 10% *vs*. 0% and two-year OS rate was similar (HT and surgery group *vs*. HRT and surgery group) [29]. The optimal therapeutic approach in the treatment of locally advanced unresectable pancreatic cancer remains controversial, with conversion induction HT followed by neoadjuvant HRT being more commonly used in the US, while induction

HT is favored in most European countries. RT doses of neoadjuvant HRT of locally advanced unresectable pancreatic cancer are also different starting from standard fractionation (50.4–54 Gy in 28–30 fractions) which is less frequently used, through hypofractionation (36 Gy in 15 fractions, 30 Gy in 10 fractions) and ablative RT (67.5 Gy in 15 fractions and 75 Gy in 25 fractions) to stereotaxy (30 Gy in five fractions, 33–35 Gy in five fractions and 45 Gy in six fractions) [28].

Adjuvant HRT is not a therapeutic standard in operated patients with pancreatic cancer because the role of adjuvant RT in the modern era of new and more effective systemic therapies remains unclear [30]. Adjuvant HRT can be considered in pT3 stage and pN+ cases, and RT doses would be 50–55 Gy in 25–30 fractions [28].

Palliative RT is carried out in order to control local symptoms and improve the quality of life of patients in an advanced stage of malignant disease. Indications are pain, bleeding, bone and brain metastases, and RT doses are 8 Gy in one fraction, 16 Gy in four fractions, 20 Gy in five fractions or 30 Gy in 10 fractions.

PALLIATIVE THERAPY AND CARE

Palliative therapy and care are very important parts of pancreatic cancer treatment. It encompasses drug therapy (non-opioid, opioid, and co-analgesics), palliative surgical interventions or endoscopic placement of stents in case of obstruction (gastrojejunostomy or biliary-digestive anastomosis) and palliative RT for bone and brain metastases.

CONCLUSION

Pancreatic cancer is an aggressive invasive tumor with a modest five-year survival. The treatment of these cancers is complex and challenging, and involves the use of surgery, HT and immunotherapy as well as RT, alone or in different combinations. Surgery is the main way of treating pancreatic cancer, especially in the early stages of the disease. Various HT regimens are indispensable in the treatment of pancreatic cancer in the neoadjuvant, adjuvant and systemic approach. Immunotherapy as the newest type of therapy is emerging in the treatment of selected cases of these cancers, especially in systemic disease. RT has an unclear role in the treatment of these tumors, and it is used in marginally resectable and locally advanced cancers in a neoadjuvant approach, usually in combination with HT, but also in a systemic approach. Palliative therapy is complementary and important part of pancreatic cancer therapy.

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Карцином панкреаса – дијагноза и савремено мултимодално лечење

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САЖЕТАК

Карцином панкреаса је један од најагресивнијих тумора и налази се међу првих десет најчешћих малигнитета у свету. Ово је болест старијих особа, а мушкарци обољевају чешће. Карциноми панкреаса су тумори са утицајем генетских наследних синдрома и стечених фактора као што су гојазност и дијабетес тип II, пушење и алкохол. Симптоми болести укључују опструктивни иктерус, губитак апетита, умор, губитак тежине, инсуфицијенцију панкреаса, бол у трбуху, бол у леђима и умор. Дијагноза карцинома панкреаса подразумева компјутеризовану томографију торакса, компјутеризовану томографију / магнетну резонанцу абдомена и мале карлице, ендоскопски ултразвук са биопсијом. Најчешћи хистолошки тип карцинома панкреаса је дуктални аденокарцином. За одређивање стадијума болести користи се ТНМ класификација. Лечење карцинома панкреаса је мултидисциплинарно и мултимодално, а подразумева примену хирургије, хемотерапије и радиотерапије, самостално или у различитим комбинацијама. Хирургија је основна метода лечења ових тумора, нарочито у раном стадијуму. Хемотерапија се у лечењу карцинома панкреаса примењује као неоадјувантна, адјувантна и системска. Имунотерапија се као најновији вид лечења ограничено примењује у метастатској фази карцинома панкреаса. Улога радиотерапије у лечењу карцинома панкреаса је врло контроверзна, о њој се још увек дискутује, а најчешће се примењује у неоадјувантном и палијативном приступу. Палијативна терапија и нега су незаобилазни део лечења болесника са карциномом панкреаса.

Кључне речи: карцином панкреаса; лечење; хирургија; хемиотерапија; радиотерапија