Automatic Segmentation of Pancreas and Pancreatic Tumor: A Review of a Decade of Research

Dr V MAHENDER[1], GANGASANI SOUMYA[2]

[1]Asst.Professor, ECE Department, Kakatiya University, Warangal, Telangana, India.

[2]M.Tech Student, ECE Department, Kakatiya University, Warangal,Telangana, India.

Abstract: In the current era of gadget learning and radiomics, one of the challenges is the automatic segmentation of organs and tumors. Tumor detection is in most cases based on a radiologist's manual reading, which necessitates a excessive level of expert capabilities and scientific revel in. Moreover, growing the high volume of photos makes radiologists' assessments extra challenging. Artificial intelligence (AI) can assist clinicians in diagnosing most cancers at an early degree by way of presenting an answer for assisted clinical photograph analysis. The automated segmentation of tumor is better realized through traditional segmentation strategies and, these days, via system studying and deep learning strategies. The segmentation of belly organs and tumors from diverse imaging modalities has gained tons attention in latest years. Among those, pancreas and pancreatic tumor are the maximum hard to segment and have currently drawn lots of enchantment. The main objective of this paper is to provide a summary of different computerized techniques for the segmentation of pancreas and pancreatic tumors and to perform a comparative evaluation using various indices such as cube similarity coefficient (DSC), sensitivity (SI), specificity (SP), precision (Pr), don't forget and Jaccard index (JI), and so on. Finally, the limitations and destiny studies perspectives of pancreas and tumor segmentation are summarized.

I. INTRODUCTION

In clinical practice, radiologists help in the visual analysis of various anatomical structures. Small changes in form, size, or structure can indicate illness and aid in the confirmation of a diagnosis. Manual readings with radiographic images, such as computer tomography scan (CT) or magnetic resonance imaging (MRI), are tedious and can lead to inter and intra-operator variability. Moreover, for quantitative radiographic image analysis with machine learning which has shown widespread application in clinical decision making, segmentation of organs or tumor plays an important role. Automatic systems with artificial intelligence can assist radiological experts in detecting and diagnosing disease and thus improve treatment management. One such disease that requires automated segmentation is pancreatic cancer. One of the most serious illnesses, pancreatic cancer, is becoming more common. According to the global cancer observatory (GLOBOCAN) 2020 statistics, pancreatic cancer accounted for approximately 466,003 deaths worldwide, with 54,277 fatalities reported in the United States in the same year [1]. The most prevalent kind of pancreatic cancer, pancreatic

ductal adenocarcinoma (PDAC), arises from the exocrine glands and ducts of the pancreas [2]. Despite improvement in treatment techniques for cancer care, five year survival rate for PDAC is only 10% [3] due to its late diagnosis and lack of effective treatment. More than half of the patients are with metastasis, and 30% with locally advanced disease at the time of diagnosis. As the mortality and incidence rate of pancreatic cancer is continually rising globally, there is an unmet need to enhance the survival outcomes of individuals affected by this disease through the implementation of advanced diagnostic and therapeutic interventions. Recent studies show that patients diagnosed at stage-I can have the most favorable outcome, with a 5-year survival rate reaching up to 80% [4]. Thus, better detection of early-stage disease is a tremendous opportunity to improve PDAC prognosis. However, detection and segmentation of PDAC is often challenging and vary due to irregular contours and ill-defined margins [5], as shown in FIGURE 1. In addition, in the past decade, with the advancement of imaging technology, radiographic images are being widely investigated with machine learning to develop imaging biomarkers of diagnosis, progression, outcome, and response prediction [6]. However, these techniques highly depend on manual segmentation. As compared to the liver, spleen, and other abdominal organs, the segmentation of the pancreas is challenging as pancreas shape, size, and position are different between individuals [7], [8], [9]. Automated segmentation of pancreas and pancreatic tumor techniques thus can help radiologists not only in proper detection and diagnosis but also in developing more generalized imaging biomarkers for pancreatic cancer. Several approaches have been proposed for automated segmentation of pancreas and pancreatic tumor using different techniques. However, the methods with unsupervised learning, such as clustering, region growing, threshold based methods, etc., did not provide satisfactory performance. Deep learning-based segmentation techniques have recently seen widespread implementation and have outperformed traditional segmentation techniques in terms of performance. These models consist of hierarchical architecture with different layers. Deep learning with convolutional neural networks (CNN) is the most successful architecture for image analysis. Neural networks, consisting of neurons with parameters and activation functions, have been utilized to extract and combine image features, enabling the development of diagnostic models. The neural network is composed of neurons with parameters and activation functions to extricate and merge the image features, enabling the development of diagnostic models. In diagnosis and segmentation of various diseases such as diabetic retinopathy [10], liver masses [11], and skin cancer [12] CNN has achieved a better accuracy than conventional methods. Discovering the practicality of CNN in pancreatic cancer segmentation has major implications discussed in pertinent sections. This paper aims to comprehensively review the studies based on the segmentation of the pancreas and pancreatic tumor by using various conventional, unsupervised and supervised approaches, including deep learning methods. The paper also discusses the current challenges in pancreatic tumor segmentation and the future scope of such techniques. FIGURE 2 represents the detailed outline of the literature

review paper. The subsequent sections of the paper are as follows. Section II focuses on the database selection method. Section III describes the statistical analysis of AI in pancreatic cancer segmentation. Section IV addresses various imaging modalities. Section V presents a detailed revie of various pancreas and pancreatic tumor segmentation techniques. Section VI describes the evaluation metrics used in segmentation. Section VII provides an overview of the experimental datasets. Section VIII discusses the findings and insights derived from the review. Section IX summarizes the overall review. Finally, Section X concludes the paper by outlining the future approaches for pancreas and tumor segmentation.

1. Pancreas and pancreatic cancer

1.1 Pancreas: structure and function

The pancreas functions as an accessory gland of the digestive system and is composed anatomically and functionally of a mixed, exocrine, and endocrine component. Most of the pan- creatic tissue (99%) is made up of exocrine tissue that is composed of closely packed serous acini that secrete digestive enzymes (proteases, lipases, and amylases). Some of the enzymes (e.g., trypsinogen, chymotrypsinogen, and proelastase) are secreted as inactivated precursors, to prevent pancreatic cell damage, and are activated upon release in the duodenum. Other key digestive enzymes, such as α-amylase and lipase, are present in the pancreas in their active forms. The duct cells secrete a watery, bicarbonate-rich fluid that carries the enzymes and neutralizes the acidity in the small intestine. The endocrine pancreas is composed of islets of Langerhans, clusters of about 3000 cells supported by reticulin fibers, in close contact with fenestrated capillaries. They contain three types of cells that secrete the three pancreatic hormones: α cells secrete glucagon that rises the glucose blood levels, while β cells secrete insulin that decreases the glucose blood levels and Δ cells secrete somatostatin that regulates the endocrine system and afects the neurotransmission and cell proliferation. The islet cells appear paler on hematoxylin and eosin stain (**Figure 1**) [5].

1.2 Pancreatic cancer

The incidence of PC continuously raised in the past years, and it is estimated to become the second leading cause of cancer-related deaths by 2030 [6]. The highest PC incidence occurred in Northern America (7.4 per 100,000 people) and Western Europe (7.3 per 100,000 people), followed by other regions of Europe and Australia (equally about 6.5 per 100,000 people). The lowest rates (about 1.0 per 100,000 people) were observed in Middle Africa and South-Central Asia. More than half of new cases (55.5%) were registered in the more developed regions [7]. PC has been correlated to exposure to risk factors concerning lifestyle, such as obesity, or the environ- ment [8]. The incidence of PC is higher in men than in women [9]. PC is a disease of the elderly, with most of the cases being diagnosed after the age of 55 [10]. African-Americans have the high- est incidence rate of PC, that is 28-59% higher than those of other racial/ethnic groups [11]. Most pancreatic tumors are derived from the exocrine tissue. More than 80% of the exocrine PCs are classified as pancreatic adenocarcinomas (PAs). Microscopically, these cancers are characterized by infiltrating small glands that are lined with low-columnar, mucin-containing

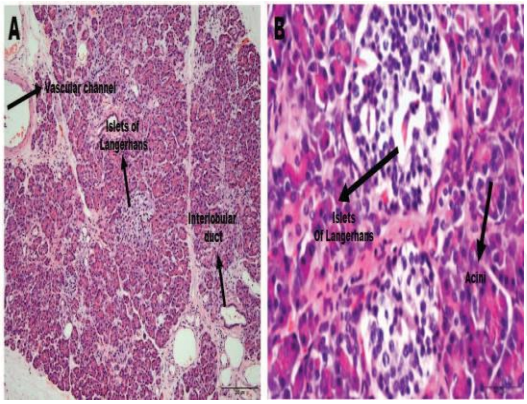

Figure 1. Representative pictures from hematoxylin and eosin staining of pancreatic tissue. (A) Pancreatic parenchyma composed in the vast majority by the exocrine pancreas composed of tightly packed acini that secrete enzymes via a duct system in the duodenum. The endocrine pancreas is composed of islets of Langerhans, which appears as clusters of pale colored cells (10×). (B) High magnification of pancreatic tissue shows exocrine tightly packed acini and endocrine islets of Langerhans. The islets appear pale due to less intracytoplasmic ribosomal content (40×).

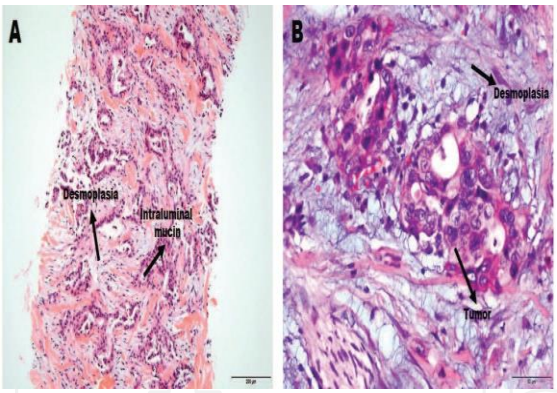

Figure 2. Representative pictures from hematoxylin and eosin staining of PC tissue. (A) Biopsy of pancreatic adenocarcinoma. The malignant glands invade tissue eliciting a strong desmoplastic reaction. Focally intraluminal mucin may be seen (10×). (B) Higher magnification of pancreatic adenocarcinoma shows malignant irregular glands composed of cell with loss of polarity, large nuclei with high nuclear-to-cytoplasmic ratio. The nuclei show irregular shape and are hyperchromatic or vesiculated with prominent nucleoli (40×).

cells. Cell nuclei often show polymorphism, hyperchromasia, loss of polarity, and proeminent nucleoli [12]. PA shows strong desmoplastic reaction that occurs around cancer cells, which is considered a hallmark for this cancer type and may account to up to 90% of the tumor vol- ume (**Figure 2**). The stroma surrounding the cancer cells is actively involved in tumor growth and dissemination. Desmoplastic stroma is composed of extracellular matrix (ECM), cancer- associated fibroblasts, stellate and inflammatory cells, and small blood vessels. Desmoplastic stroma shows high levels of cytokines and growth factors. The desmoplastic stroma creates a barrier for chemotherapeutic drug delivery. Targeted therapies against PC stromal compo- nents have so far failed to translate into significant clinical benefits [13].

Pancreatic neuroendocrine tumors (PNETs), representing 1–2% of PC, are commonly called islet cell carcinomas. Functional PNET secretes biologically active hormones (insu- lin, glucagon, somatostatin, or vasoactive intestinal peptide), causing a clinical syndrome. Nonfunctioning PNET does not cause clinical symptoms [14]. Other types of exocrine PC include acinar cell carcinomas, adenosquamous carcinomas, colloid carcinomas, hepatoid carcinomas, intraductal papillary mucinous neoplasms and pancreatoblastomas [15].

The majority of PC develops silently from pancreatic intraepithelial neoplasia (PanIN) over a long period of time that highlights the importance and the challenge for early diagnosis [16]. Survival of patients with PC depends on the tumor stage at the time of diagnosis. The American Joint Commitee on Cancer staging system has defined the relationship of pancre- atic tumor with surrounding tissues, lymph nodes, vessels, and distant organs [17]. The first clinical stage of PC refers to tumors that are confined within the pancreas. The second stage involves PC that is spread to the adjacent tissues, especially to the lymph nodes. In Stage 3, the disease has already spread to the blood vessels, while in Stage 4, the metastasis has occurred in distant organs. Unfortunately, at the time of diagnosis, most of the patients have already invasion of vascular, lymphatic, and perineural tissue. The most common sites for distant metastasis are the liver, lung, pleura, peritoneum, and adrenal glands. Surgery may be ofered to <20% of patients with PC. An additional challenge is that surgery success rate is gravely limited by the extent of early or occult micro metastases [18].

2. Risk factors for pancreatic cancer

There are several factors that pose high risk for PC, such as obesity, chronic pancreatitis, diabetes, tobacco, and alcohol usage, exposure to chemicals, such as dyes and pesticides, age, and epigenetic changes. High-fat diets activate oncogenic Kras and Cox-2, causing inflammation and ibrosis in the pancreas, leading to PanINs and PC onset. Fat diet that induces pancreatic faty iniltration could play an important role in PC. Moreover, the presence of PanINs was associated with intralobular fat accumulations [19]. The risk of PC increases with age, more than half of new cases occur in patients over 70 years old. ABO blood types and genetic variants may also inluence PC risk [20]. Cigarete smoking increases the risk for PC by 75% when compared with nonsmoking individuals, and the risk persists for 10 years after smoking cessation [7]. Although several risk factors have been identiied, the causes of PC are not well known. Understanding the mechanisms through which the risk factors might affect PC progression and survival is the key to develop a prevention strategy for this disease.

2.1 **Obesity**

Obesity is pandemic in the USA and has been associated with poor prognosis of several malig- nancies, including prostate, colon, breast, endometrial cancer, and PC. Both general and abdom- inal obesity are associated with increased PC risk. Moreover, physical inactivity has been linked with increased PC risk [7]. Obesity was linked with increased mortality from PC [21] and the promotion of stromal desmoplasia [22]. The most common method for obesity detection is the determination of the body mass index (BMI) that is calculated based on the relationship between body height and weight (BMI 18.5–24.9, nor- mal; 25.0–29.9, overweight; ≥30, obese). Obesity strongly correlates with body fat levels. Adipose tissue has a very strong endocrine function, secreting various adipokines that are involved in cancer development and progression, and insulin resistance. Leptin, IL-6, and tumor necrosis factor-alpha (TNF-α) are inflammatory factors increased

in cancers, but adiponectin is protective against tumorigenesis, and its serum levels are usually decreased. Cancer patients show higher baseline levels of C-reactive protein and soluble TNFα receptor 2. Lipocalin 2 was associated with tumor invasiveness. Resistin, another proinflammatory adipokine, was increased in colon, breast, and prostate cancer. To date, many adipokines have been associated with cancer, contributing to enhanced inflammation, angiogenesis, cellular proliferation, and tumorigenesis [23].

IV RESULTS AND DISCUSSION

The standard database images of lungs are taken from the available Database from IMBA Home (VIA-ELCAP Public Access)[5]. Fig2 contains the standard database image of lung and fig3 contains the image that we get after thresholding. But after thresholding we cannot get exact tumor area in some cases.

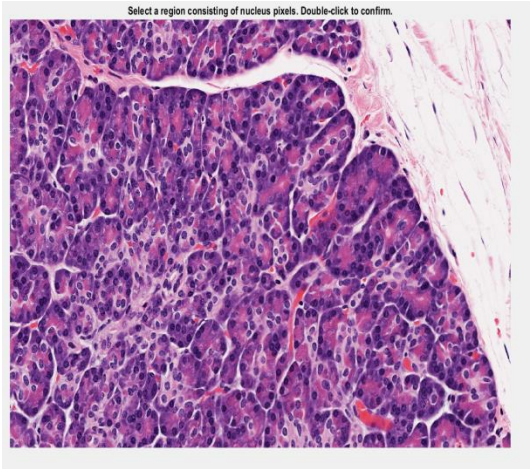

Fig 5. Image After Thresholdin

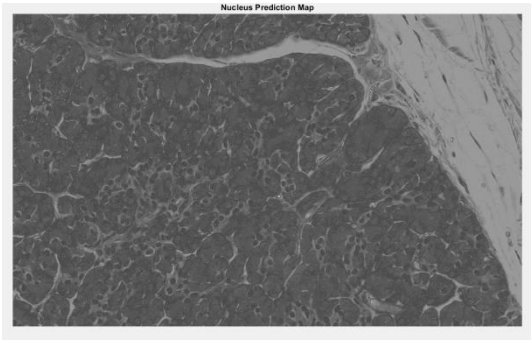

Fig 5. Image After Thresholding

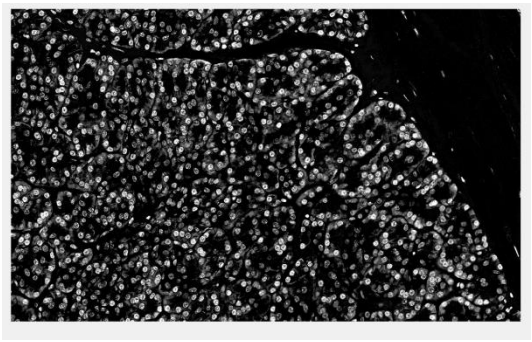

Fig 5. Image After Thresholding

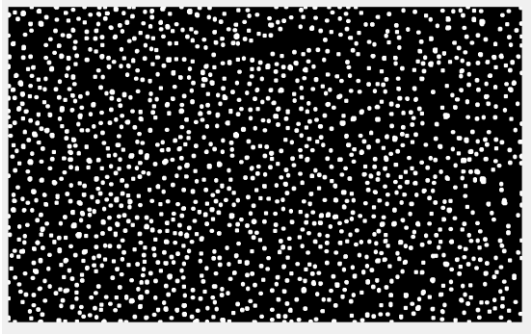

Fig 5. Image After Thresholding

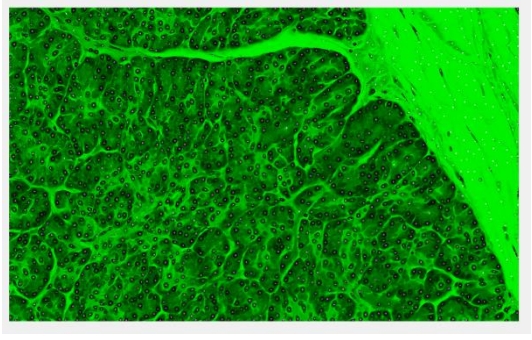

Fig 5. Image After Thresholding

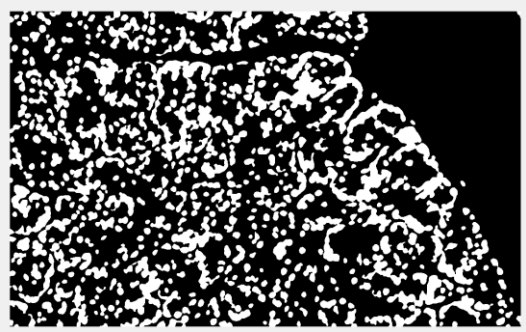

Fig 2. Lung Image

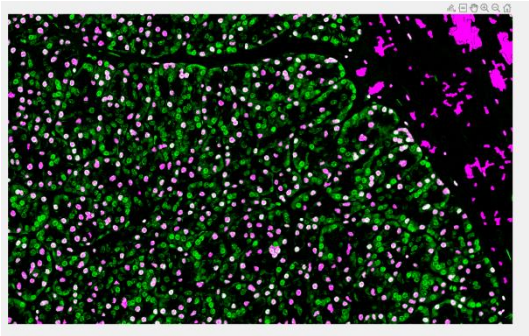

Fig 3. Image obtained after thresholding

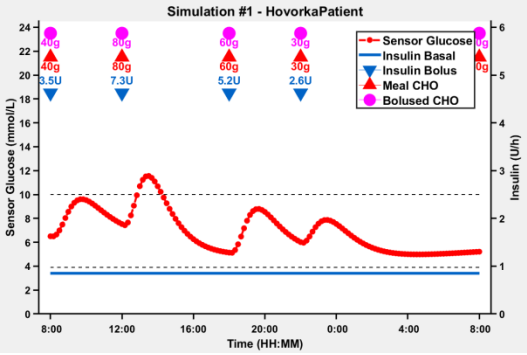

Fig 4. Lung image

V CONCLUSION

PC is a lethal systemic disease that is difficult to detect and treat. This is mainly due to the fact that even patients diagnosed with early stages eventually develop metastasis. The deep abdominal position of the pancreas is an additional factor that delays the onset of specific PC symptoms. Early PC diagnosis and potential cure remain important challenges due to the lack in screen- ing methods and specific biomarkers. PC risk factors, such as high-fat diet, obesity, tobacco, and alcohol consumption, can be modified, leading to prevention of disease occurrence and increased survival. PC desmoplastic stroma, which decreases chemotherapeutic drug delivery to the tumor, is an another current challenge to improve PC survival. Currently, combined che- motherapy strategies are used in selected patients with PC metastatic disease. The identification of novel PC targets is the key for the development of new individualized strategy for prevention and treatment. An emerging and promising area is the relationship between obesity and leptin- induced prooncogenic efects in PC, which could also afect chemoresistance and metastasis. In this respect, the use of leptin signaling antagonists as a novel sensitization adjuvant for current chemotherapeutic drugs appears as a potential new strategy to improve treatment efective- ness and patients' survival. The use of leptin signaling antagonists could also make possible the reduction of drug dosage and the improvement of patient quality of life.

VI REFERENCES

[1] Li D, Xie K, Wolf R, Abbruzzese JL. Pancreatic cancer. Lancet. 2004;363(9414):1049-1057. DOI: 10.1016/S0140-6736(04)15841-8

[2] Amrutkar M, Gladhaug IP. PC chemoresistance to gemcitabine. Cancers (Basel). 2017; 9(11):157-180. DOI: 10.3390/cancers9110157 [3] Pelosi E, Castelli G, Testa U. PC: Molecular characterization, clonal evolution, and cancer stem cells. Biomedicines. 2017;5(4):65-122. DOI: 10.3390/biomedicines5040065

[4] Gharibi A, Adamian Y, Kelber JA. Cellular and molecular aspects of PC. Acta Histochemica.

2016;118(3):305-316. DOI: 10.1016/j.acthis.2016.01.009

[5] Pandol SJ. The Exocrine Pancreas. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. DOI: 10.4199/C00026ED1V01Y201102ISP014

[6] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and

pancreas cancers in the United States. Cancer Research. 2014;74(11):2913-2921. DOI: 10.1158/0008-5472.CAN-14-0155

[7] Ilic M, Ilic I. Epidemiology of PC. World Journal of Gastroenterology. 2016;22(44):9694-9705. DOI: 10.3748/wjg. v22.i44.9694

[8] Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, English DR, Folsom AR, Freudenheim JL, Fuchs CS, Giles GG, Giovannucci E, Horn- Ross PL, et al. A pooled analysis of 14 cohort studies of anthropometric factors and PC risk. International Journal of Cancer. 2011;129(7):1708-1717. DOI: 10.1002/ijc.25794

[9] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015;136(5):E359-E386. DOI: 10.1002/ijc.29210

[10] Boseti C, Bertuccio P, Negri E, La Vecchia C, Zeegers MP, Bofeta P. PC: Overview of descriptive epidemiology. Molecular Carcinogenesis. 2012;51(1):3-13. DOI: 10.1002/ mc.20785

[11] PC Action Network. Available from: https://www.pancan.org/wp-content/uploads/2016/ 02/2016-GAA-PC-Facts.pdf

[12] Winter JM, Maitra A, Yeo CJ. Genetics and pathology of PC. HPB: The Oicial Journal of the International Hepato Pancreato Biliary Association. 2006;8(5):324-336. DOI: 10.1080/13651820600804203

[13] Solomon BL, Garrido-Laguna J. Novel therapies in PC: Opportunities and challenges for precision medicine. In: 2018 Gastrointestinal Cancer Symposium. Available from: https://gicasym.org/daily-news/novel-therapies-pancreatic-cancer-opportunitiesand- challenges-precision-medicine

[14] Ro C, Chai W, Yu VE, Yu R. Pancreatic neuroendocrine tumors: Biology, diagnosis, and treatment. Chinese Journal of Cancer. 2013;32(6):312-324. DOI: 10.5732/cjc.012.10295

[15] Cancer.net. Available form: htps://www.cancer.net/cancer-types/pancreatic-cancer/ introduction

[16] Kaur S, Baine MJ, Jain M, Sasson AR, Batra SK. Early diagnosis of PC: Challenges and

new developments. Biomarkers in Medicine. 2012;6(5):597-612. DOI: 10.2217/bmm.12.69

17] Russo S, Ammori J, Eads J, Dorth J. The role of neoadjuvant therapy in PC: A review. Future Oncology. 2016;**12**(5):669-685. DOI: 10.2217/fon.15.335

[18] Rahman SH, Urquhart R, Molinari M. Neoadjuvant therapy for resectable PC. World Journal of Gastrointestinal Oncology. 2017;**9**(12):457-465. DOI: 10.4251/wjgo.v9.i12.457

[19] Rebours V, Gaujoux S, d'Assignies G, Sauvanet A, Ruszniewski P, Lévy P, Paradis V, Bedossa P, Couvelard A. Obesity and faty pancreatic iniltration are risk factors for pancreatic precancerous lesions (PanIN). Clinical Cancer Research. 2015;**21**(15):3522-3528. DOI: 10.1158/1078-0432.CCR-14-2385

[20] Amundadotir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Zheng W, Albanes D, et al. Genome-wide association study identiies variants in the ABO locus associated with susceptibility to PC. Nature Genetics. 2009;**41**(9):986-990. DOI: 10.1038/ng.429

[21] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. The New England Journal of Medicine. 2003;**348**(17):1625-1638. DOI: 10.1056/NEJMoa021423

[22] Incio J, Liu H, Suboj P, Chin SM, Chen IX, Pinter M, Ng MR, Nia HT, Grahovac J, Kao S, Babykuty S, Huang Y, Jung K, et al. Obesity-

induced inlammation and desmoplasia promote PC progression and resistance to chemotherapy. Cancer Discovery. 2016;**6**:852- 869. DOI: 10.1158/2159-8290.CD-15-1177

[23] Lee CH, Woo YC, Wang Y, Yeung CY, Xu A, Lam KS. Obesity, adipokines and cancer: An update. Clinical Endocrinology. 2015;**83**(2):147-156. DOI: 10.1111/cen.12667

[24] Candelaria PV, Rampoldi A, Harbuzariu A, Gonzalez-Perez RR. Leptin signaling and cancer chemoresistance: Perspectives. World Journal of Clinical Oncology. 2017;**8**(2):106- 119. DOI: 10.5306/wjco.v8.i2.106

[25] Gonzalez RR, Caballero-Campo R, Jasper M, Mercader A, Devoto L, Pellicer A, Simon C. Leptin and leptin receptor are expressed in the human endometrium and endometrial leptin secretion is regulated by the human blastocyst. The Journal of Clinical Endocrinology & Metabolism. 2000**8**;**5**(2):4883-4888. DOI: 10.1210/jcem.85.12.7060

[26] Wauman J, Zabeau L, Tavernier J. The Leptin receptor complex: Heavier than expected? Frontiers in Endocrinology (Lausanne). 201**8**7:;30. DOI: 10.3389/fendo.2017.00030

[27] Guo S, Liu M, Wang G, Torroella-Kouri M, Gonzalez-Perez RR. Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells. Biochimica et Biophysica Acta. 2012;**1825**(2):207-222. DOI: 10.1016/j.bbcan.2012.01.002

[28] Harbuzariu A, Rampoldi A, Daley-Brown DS, Candelaria P, Harmon TL, Lipsey CC, Beech DJ, Quarshie A, Ilies GO, Gonzalez-Perez RR. Leptin-notch signaling axis is involved in PC progression. Oncotarget. 2017;**8**(5):7740-7752. DOI: 10.18632/oncotarget.13946

[29] Duta D, Ghosh S, Pandit K, Mukhopadhyay P, Chowdhury S. Leptin and cancer: Pathogenesis and modulation. Indian Journal of Endocrinology and Metabolism. 2012;**16**(Suppl 3):S596-S600. DOI: 10.4103/2230-8210.105577