INDEX COPERNICUS INTERNATIONAL

MEETING REPORT

# Pancreatic cancer – summary of the session of the 6th International Pancreatic Days in Gdynia, 27-30 October 2016

**Caroline S. Verbeke[1], Marcus W. Büchler[2], Marek Dobosz[3], Stanisław Hać[4]**

[1]Department of Pathology, University of Oslo, Norway
[2]Department of General, Visceral and Transplantation Surgery at the University Hospital Heidelberg, Germany
[3]Department of Surgery, Copernicus Hospital, Gdańsk, Polska
[4]Department of General Endocrine and Transplant Surgery Medical University of Gdańsk, Poland

Article history: Received: 14.11.2018 Accepted: 14.11.2018 Published: 15.11.2018

**ABSTRACT:** The session participants were Prof. Caroline Verbeke from The Department of Pathology of Oslo University and Prof. Marcus Wolfgang Büchler from the Department of General, Visceral and Transplantation Surgery at the University Hospital Heidelberg. The participants discussed the problem of surgical treatment of pancreatic cancer with regard to radicality.

**KEYWORDS:** pancreatic cancer, surgical treatment, pathology, staging

## CAROLINE VERBEKE

The role of pathology in pancreatic cancer. The characteristic features of ductal adenocarcinoma include: desmoplastic stroma, dispersed growth and morphological heterogeneity. These are important factors distinguishing the pancreatic cancer from other carcinomas. Desmoplastic stroma constitutes from 40% to 80% of the tumor mass. [1] So far, stroma has not been an important role in diagnostic or prognostic criteria, but intensive research is being carried out in that field. In simple light microscopy it is evident that stroma is not uniform in different tumors or even in different areas of the same tumor. It has been found that the morphology of the central part of the tumor differs from that observed in the periphery. The distance between cells on the periphery of the tumor is much larger than in the central part of the cancer. Another important feature of pancreatic adenocarcinoma is dispersing growth. No other cancer shows the distance between cells higher than 1.5 mm. On a cellular level it means miles. This was confirmed by a morphometric analysis. Colorectal and pancreatic cancer revealed a completely different morphology [2]. The border of the tumor in pancreatic cancer is difficult to recognize macroscopically. It is not uncommon to see different morphologies within the same tumor. It is probably true that morphological heterogeneity accompanies the molecular heterogeneity which is an important phenomenon in the treatment strategy [3]. This leads to discordant treatment results. The role of a pathologist is to provide data necessary for The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT). Pathomorphological study is a gold standard in diagnostics and TNM criteria classification. However, the data analysis shows that T and N as well as margin involvement criteria do not correspond with the disease morphology and require revision. Another important morphological phenomenon of pancreatic cancer is the infiltration along tubular structures without their destruction. The role of margin status in pancreatic cancer treatment is frequently discussed. The results of a small single-center study from 2006 showed that positive margins remained strongly underestimated in standard examinations of pancreatoduodenectomy specimens. Two years later, in 2008, a larger study confirmed these results. The lack of standardization and significant differences between the centers were pointed to. So far, there has been no consensus on the pathological protocol, except for the one concerning the nomenclature of the specimen surfaces. The technique based on the actual protocol and the axial way of analysis of specimens give the best results in positive margin detection [4]. An important problem in pancreatic cancer is also specimen analysis after neoadjuvant treatment and distinction between fibrosis and residual tumor. Another important feature is the minimal radical resection margin. One millimeter is not really applied after neoadjuvant treatment because of the distance between cancer cells and disperse growth. Due to the features of desmoplastic stroma of pancreatic cancer, it is difficult to obtain a representative biopsy and to recognize the residual tumor. The R1 feature after neoadjuvant therapy does not apply to the same criteria as in case of the primary resection without prior chemotherapy. After chemotherapy, the distance between cancer cells increases. The post-neoadjuvant tumor regression grading in pancreatic cancer based on the volume of residual tumor compared to the tumor after chemotherapy does not correspond to the real morphology of the tumor [5]. The American Pathologist Society recommends grading based on residual tumor fibrosis; however, the primary tumor includes a lot of stroma. It is important to include a pathologist in the local pancreatic team to improve and control the results of pancreatic cancer treatment [5].

## WOLFGANG MARCUS BÜCHLER

I would like to refer to pathologists; they only look at what they receive. The surgery has changed dramatically in the last few years. We analyzed the history of the last 250 patients and half of them were R1. I agree that we need a new classification for pancreatic cancer.

Please remember these two important numbers – 40 and 40. Forty months of median survival and 40 percent of 5-year survival rate in pancreatic cancer. I will try to present it to you. There is a discussion going on about pancreatic cancer surgery; many surgeons ask about the sense of surgical treatment. In my opinion we have much to do as it comes to surgery in pancreatic cancer.

There is the "old" surgery, I was trained in, and the "new" surgery. Surgery is twice as effective as the best systemic chemotherapy with Gemcytabine of FOLFIRINOX, regarding the survival time. Surgery is the only chance for cure [6]. Pancreatic surgery is dangerous, and it is closely related to the education in surgery. The mean mortality in pancreatic cancer surgery in German hospitals is 10%. The reason for this is no proper education in surgery. The total in-hospital mortality in pancreatoduodenectomy is 21%. The pancreatic surgery is dangerous but if you want to do it you have to learn it and to train to become good enough to operate [7]. The old surgery based on cutting the pancreas above the vessels and resecting the pancreatic head. The "new" surgery is to explore all large vessels i.e. superior mesenteric vein and artery and to remove the artery completely at its origin from the aorta. You need to visualize all vessels. Remember what Caroline Verbeke said yesterday: if you leave some tissue between the vessels, you will get a recurrence. "The artery first" approach in pancreatic surgery is of uttermost importance [8]. We have learnt this from Japanese surgeons. First, deal with the superior mesenteric artery and celiac trunk and then move on to resection. The first step is to go up along the superior mesenteric artery. This is completely different from what you have learnt, with the Whipple procedure. Another important difference is the uncinated process preparation without cutting the pancreas, as you and I have learnt. At the end of this procedure the pancreas is transected [9]. Thanks to that procedure you obtain much better clearance. In 2011 we published the results of 1000 pancreatic cancer resections. What have we learnt? We learnt that pancreatic cancer is not one pancreatic cancer.... All former opinions that every pancreatic cancer patient will die are absolutely wrong. We observed essential differences in the survival rates of patients. It means that pancreatic cancer is not uniform from a clinical and molecular point of view. We have identified at least 4 different groups of pancreatic adenocarcinomas. And in our groups, the 5-year survival rate was up to 60% [10]. Now, why did I tell you that Caroline Verbeke is the best pancreatic pathologist in the world? She is really a pioneer; she came up with a new classification. My coworker Oliver Strobel has shown recently that a 1-mm margin is connected with a median survival of 41% and with a five-year survival rate of 37.7%. And this is what I told you about at the beginning: 40/40 [11]. This is a result we can expect in pancreatic cancer with a good surgery. According to this new R0 classification, even the R1 resection, i.e. cancer is within the 1mm margin, the 5-year survival is quite good. If you really apply the new R0 resection criteria you can expect fantastic results in the treatment of the true pancreatic adenocarcinoma. You need a correct radical surgery. How to manage vascular involvement? The medical oncology usually says – vascular involvement means palliative chemotherapy. This is completely wrong. Vascular involvement does not mean there is no place for surgery. Portal vein resection is no longer a major achievement. It is a kind of a standard procedure in pancreatic cancer resection. Much more demanding for surgeons is arterial infiltration. We have learnt much about the management of arterial infiltration from Japanese surgeons. We can replace the common hepatic artery with the splenic artery. You should not be afraid of arterial resection to achieve R0 resection. Arterial resection is connected with a higher perioperative mortality but a better one- and three-year survival rate. How about lymphadenectomy in pancreatic cancer surgery? According to the recent data from Oliver Strobel, we need to revise the N status. Nowadays, there is only the N0 and N1 status.

According to our observations, no lymph node involvement and one lymph node involved show the same fife-year survival. Next group is constituted by 2-4 lymph node metastases, and another prognostic group includes more than 8 lymph nodes involved. This shows that in a new TNM classification we need at least three N categories. It is not correct to put all metastatic lymph nodes in one group [12]. Extended pancreatic resection i.e. vascular resection and multiorgan resection shows a much better fife-year survival rate than chemotherapy alone. Neoadjuvant chemotherapy in resectable patients does not help, while in non-resectable patients the neoadjuvant therapy helps. The best option in neoadjuvant therapy is FOLFIRINOX and the secondary resection rate is more than 60% after that treatment [13]. Also, resection of single liver metastases in pancreatic cancer seems reasonable. I personally invite all interested surgeons to come to Heidelberg and to learn the modern pancreatic cancer surgery.

## SUMMARY

The pancreatic cancer is a morphologically unique tissue. A high amount of stroma disperse growth and infiltration along tubular structures are characteristic for this tumor and determine the treatment modalities and outcomes. From the pathological point of view, the disperse growth and large distance between cells make it difficult to obtain a reliable biopsy material. The aggressiveness and growth along tubular structures gives the grounds for the revision of the extent of traditional surgery. It seems reasonable to give a chance to pancreatic cancer patients to be treated in high-reference centers experienced in this kind of procedures and in vascular infiltration management. The results of oncological treatment as well as perioperative mortality are also arguments for pancreatic surgery centralization. Taking into account the latest data on five-year survival rates, it seems evident that the current TNM classification of pancreatic cancer requires a profound revision of the T, N and M criteria.

## REFERENCES:


1. Moffitt R.A, Marayati R., Flate E.L., Volmar K.E., Loeza S.G.H., Hoadley K.A., Rashid N.U., Williams L.A., Eaton S.C., Chung A.H., Smyla J.K., Anderson J.M., Kim H.J., Bentrem D.J., Talamonti M.S., Iacobuzio-Donahue C.A., Hollingsworth M.A., Yeh J.J.: Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet 2015; 47 (10): 1168–1178.
2. Verbeke C.S.: Resection margins in pancreatic cancer. Surg Clin North Am 2013; 93 (3): 647–62.
3. Verbeke CS, Knapp J, Gladhaug IP. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. Histopathology 2011; 59 (6): 1111–21.
4. Verbeke C.S., Gladhaug I.P.: Dissection of Pancreatic Resection Specimens. Surg Pathol Clin. 2016; 9 (4): 523–538.
5. Verbeke C., Löhr M., Karlsson J.S., Del Chiaro M.: Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev 2015; 41 (1): 17–26.
6. Conroy T., Desseigne F., Ychou M., Bouché O., Guimbaud R., Bécouarn Y., Adenis A., Raoul J.L., Gourgou-Bourgade S., de la Fouchardière C., Bennouna J., Bachet J.B., Khemissa-Akouz F., Péré-Vergé D., Delbaldo C., Assenat E., Chauffert B., Michel P., Montoto-Grillot C., Ducreux M.: Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364 (19): 1817–1825.
7. Nimptsch U., Krautz C., Weber G.F., Mansky T., Grützmann R.: Nationwide In-hospital Mortality Following Pancreatic Surgery in Germany is Higher than Anticipated. Ann Surg 2016; 264 (6): 1082–1090.
8. Weitz J., Rahbari N., Koch M., Büchler M.W.: The „artery first" approach for resection of pancreatic head cancer. J Am Coll Surg 2010; 210 (2): 1–4.
9. Hackert T., Werner J., Weitz J., Schmidt J., Büchler M.W.: Uncinate process first--a novel approach for pancreatic head resection. Langenbecks Arch Surg 2010; 395 (8): 1161–1164.
10. Hartwig W., Hackert T., Hinz U., Gluth A., Bergmann F., Strobel O., Büchler M.W., Werner J.: Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg 2011; 254 (2): 311–319.
11. Strobel O., Hank T., Hinz U., Bergmann F., Schneider L., Springfeld C., Jäger D., Schirmacher P., Hackert T., Büchler M.W.: Pancreatic Cancer Surgery: The New R-status Counts. Ann Surg 2017; 265 (3): 565–573.
12. Strobel O., Hinz U., Gluth A., Hank T., Hackert T., Bergmann F., Werner J., Büchler M.W.:
13. Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. Ann Surg 2015; 261 (5): 961–969.
14. Gillen S., Schuster T., Meyer Zum Büschenfelde C., Friess H., Kleeff J.: Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010 Apr 20; 7(4)



Word count: 2120 Page count: 3 Tables: – Figures: – References: 14

DOI: 10.5604/01.3001.0012.7408 Table of content: https://ppch.pl/issue/11483





Competing interests: The authors declare that they have no competing interests.





Corresponding author: Prof. dr hab. n. med. Stanisław Hać; Katedra i Klinika Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej Gdańskiego Uniwersytetu Medycznego; e-mail: sthac@gumed.edu.pl



Cite this article as: Verbeke C. S., Büchler M. W., Dobosz M., Hac S.: Pancreatic cancer – summary of the session of the 6th International Pancreatic Days in Gdynia, 27-30 October 2016; Pol Przegl Chir 2018: 90 (6): 43–45