Interview with Prof. Jörg Kleeff during the 2018 13th IHPBA Congress

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Expert introduction

Jörg Kleeff (*Figure 1*), MD, FACS, FRCS, is Professor and Chair of Visceral Surgery at Martin-Luther-University Halle-Wittenberg and Director of the Department of Visceral, Vascular and Endocrine Surgery at the University Hospital Halle (Saale), Germany.

He started his scientific career 1997 as a postdoctoral research fellow at the University of California in Irvine, USA with Murray Korc. Following two years of research work, he started his clinical training with Markus Büchler at the Department of Visceral and Transplantation Surgery at the University of Bern, Switzerland. From 2001 to 2007 he worked at the Department of Surgery at the University of Heidelberg and from 2007 to 2015 at the Department of Surgery, Technical University Munich, Germany. From 2015–2016 he worked as a Consultant in Hepatobiliary & Pancreatic Surgery at the Royal Liverpool University Hospital and as Honorary Professor at the University of Liverpool, UK. He has published more than 250 peer-reviewed articles in internationally recognized medical journals as well as over 150 review articles and book chapters. His clinical work focuses on oncological surgery of the hepato-pancreato-biliary system and his basic and translational scientific research focuses on pancreatic diseases specifically on pancreatic carcinogenesis and tumor biology, stromal reaction, and inflammation.

Figure 1 Prof. Jörg Kleeff.

Interview

ATM: As the 13th World Congress of International Hepato-Pancreato-Biliary Association (IHPBA) is around the corner, could you share with us the cutting-edge development in hepato-biliary-pancreatic (HPB) surgery?

Prof. Jörg Kleeff: There are many exciting and novel developments in HPB surgery, and only a narrow selection can be outlined here.

There is a continuous focus and novel achievements in laparoscopic and robotic surgery. In pancreatic surgery, for example, we have moved from proof of concept studies and analyses to evidence-based strategies. The LEOPARD-1 trial of the Dutch Pancreatic Cancer Group has demonstrated that minimally invasive distal pancreatectomy for left-sided pancreatic tumors without vascular involvement reduces time to functional recovery without compromising safety. In contrast, the LEOPARD-2 trial of minimally invasive versus open pancreatoduodenectomy was stopped early because of increased mortality in the laparoscopic arm (10% versus 2%), which is in contrast to previous data (e.g., the PADULAP randomized controlled trial), highlighting the importance of well-designed multicenter trials. Further trials on the minimally invasive approach for pancreatic cancer are ongoing and more and more data are available on robotic pancreatic surgery, especially with respect to safety and efficacy.

There have been important developments in the multimodal therapy for pancreatic cancer. New adjuvant protocols (most recently the PRODIGE 24 trial using mFolfirinox) prolong median survival after resection to

more than 50 months. Robust data from randomized controlled trials of neoadjuvant therapy in pancreatic cancer (e.g., the PREOPANC-1 trial) are emerging, challenging the role of upfront surgery in resectable and borderline resectable disease. Personalized medicine by stratifying subtypes of pancreatic cancer (e.g., the Precision-Panc initiative) will lay the basis for future trials in the palliative and (neo)adjuvant setting.

There are also new and exciting developments in laparoscopic and robotic liver surgery, and the jury is still out, which approach is superior.

There is also ongoing progress in the management of hilar cholangiocarcinoma. Recent data point towards a survival benefit of liver transplantation as compared to resection for hilar cholangiocarcinoma (if smaller than 3 cm and lymph-node negative), although it remains to be shown in randomized controlled trials if transplantation is superior to resection, especially in R0 resectable disease in patients without primary sclerosing cholangitis.

According to the Nagoya group around Masato Nagino, there is no role of solitary hilar resection and lymphadenectomy in Bismuth type I and II tumors; instead extended resection, i.e., right hepatectomy offers superior survival. The same group is also advocating an aggressive surgical approach to Bismuth type IV tumors with vascular resections in the majority of patients. This is particularly important because many surgeons have so far considered these tumors irresectable. However, we must be cautious in interpreting data from Asian patients—as patients from Europe or the USA might tolerate extensive surgery less well.

There are controversies regarding preoperative management for hilar cholangiocarcinoma. Is portal vein embolization necessary/beneficial in all patients with planned extended resections? Is biliary drainage necessary for all cases, or only in those with expected small future liver remnant? In this context, a recent trial from the Netherlands of endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma had to be stopped because of a higher mortality rate (all causes) in the percutaneous biliary drainage group.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an established but still debated procedure. Recent evidence suggests that it offers higher resection rates compared to classical two-stage hepatectomy in patients with colorectal liver metastasis, with comparable morbidity/mortality rates. Better patient selection and new techniques such as less invasive approaches at the first stage, as for example laparoscopic ALPPS or mini-ALPPS, can further improve outcomes and decrease morbidity from the procedure.

Precision oncology is another cutting-edge development that will also impact on the surgical management of patients. In a seminal study, Sean P. Pitroda and co-workers identified by integrative molecular analysis a subgroup of patients with metastatic colorectal cancer that achieved prolonged survival after resection of liver metastases, pointing towards true oligometastatic rather than diffuse metastatic disease. It is therefore conceivable that molecular subtyping will aid in deciding which patients with (colorectal) liver metastasis to resect and which not.

ATM: With your training experience both in USA and Europe, could you please share with us your impression of the training system in different institutes? Throughout the training process, what impressed you most?

Prof. Jörg Kleeff: As a medical student, I have studied mainly in Germany, but also for some period in Switzerland, the USA and Canada. I have received my clinical training in Germany (and to a lesser extent in Switzerland) under the guidance of Markus Büchler (University of Heidelberg). I spent two years of basic and translational research in the USA (University of California, Irvine) with mentoring of Murray Korc. As a surgeon I have worked in Switzerland, Germany and the UK.

Surgical training has evolved both in the USA and Europe. Although surgical curricula exist everywhere, the surgical training is more structured in the USA and the UK as compared to Germany. It very much depends on the center how well the training is and at what level of expertise you are once you have finished your training. In the USA and the UK, training is mainly based and organized at universities (with possible rotation to other health care providers). In Germany, training can be done in university hospitals but also in primary care community hospitals. It is possible to be only trained at a tertiary referral university center, but also only at smaller community hospitals. Thus, the level of experience and the exposure to surgical procedures varies greatly.

Another important difference is that there are no official fellowship programs in Germany (in contrast to the US and UK). For further sub-specialization, one must work in a hospital with a special focus on the area of interest (or go abroad).

During my training, I was impressed by the passion for teaching in the USA and to a lesser extent also in

the UK. I have seen a genuine desire to teach in both countries. In Germany, teaching is of course part of the university curriculum and there a certainly dedicated clinical teachers. In general, however, it depends much more on your individual motivation and effort, to learn and get training in Germany. This means on one side more freedom (less school-like), on the other side more self-responsibility. Nowadays, strict working time regulations pose further challenges to effective teaching and training in all mentioned countries.

ATM: How did you become involved in your research field, and how would you describe the particular challenges, setbacks, and successes you've encountered along the way?

Prof. Jörg Kleeff: My doctoral thesis was about the prevalence of the human T-cell leukemia virus type 1 (HTLV-1) in Germany—a topic far away from pancreatic cancer. One of my last clinical rotations as a medical student was in the Department of Visceral and Transplantation Surgery at the Inselspital, University of Bern, Switzerland. There, the group of Markus Büchler and Helmut Friess was international renowned and had an impressive track record in translational and clinical research of pancreatic diseases—that is how I became involved in this field.

Pancreatic cancer remains one of the most challenging tumors to treat. The prognosis is still unsatisfactory, and most patients that we aim to cure by surgery (i.e., resection) will finally succumb to their disease. When I was starting to perform research in this field—molecular, translational, and clinical—there was widespread pessimism and nihilism with respect to standard therapeutic options, surgery, chemotherapy, and radiotherapy (i.e., "does not change the natural course of the disease"). This has considerably changed: surgery has evolved into a safe procedure in experienced hands and more advanced procedures including vascular resections are routinely carried out. Effective adjuvant protocols have increased 5-year survival rates from less than 10% two decades to approaching 50% nowadays. Further, multimodal therapies and aggressive surgery made it possible to resect patients that were previously deemed unresectable.

When I was entering the field of molecular biology, we started to understand the genetic makeup of pancreatic cancer, specific mutations (e.g., DPC4/Smad4) were discovered that raised the hope of early detection and targeting. Ours and other studies showed aberrant expression of a number of tumors promoting factors and their receptors and it was hoped that—similar to other cancers (e.g., breast cancer)—this would result in successful targeted therapies. However, we have learned the hard way that this approach had largely failed and we had to realize that pancreatic cancer is more complex and more resistant to "easy" approaches, with multiple redundant pathways driving carcinogenesis. We have appreciated the complex genetic makeup and the equally complex and heterogenous microenvironment, that influences tumor prognosis and therapy responses. Currently, we are finally able to identify subgroups of patients that benefit from specific therapies and we are at the beginning on an era, where immunotherapy might change also pancreatic cancer therapy substantially.

ATM: Where do you see your research leading in the future?

Prof. Jörg Kleeff: As a surgeon, we are particularly close to the patient (and its diseased organs). Translational research that involves patients' tissue and cells is therefore a logical approach. We are currently establishing patients derived organoids that can serve as a tumor model to, for example, predict response to chemotherapy in pancreatic cancer.

We are also using genetically engineered mouse models to better understand early steps in pancreatic carcinogenesis, especially inflammation driven processes.

Another focus is the tumor microenvironment. We have established a large biobank of pancreatic stellate cells (from cancer patients as well as from patients with cystic pancreatic tumors and chronic pancreatitis). The interaction of the microenvironment, especially pancreatic stellate cells with tumor cells greatly influences a variety of aspects like chemoresistance and metastasis. We are also analyzing genetic and epigenetic alterations that occur in pancreatic stellate cells during inflammation and carcinogenesis.

From a clinical perspective, we have learned that we are able to safely perform extended resections, i.e., vascular resection, metastasis resection etc. However, we urgently need better patient stratification to identify the subgroups of patients that will benefit. Integrative molecular analysis of patient derived tissues and/or organoids will be most important for better patient selection in the future.

To advance clinical knowledge multicenter trials are necessary. Here, international cooperation is the key, as single center studies are inherently biased and patient cohorts are generally too small. As an example, the Scientific & Research Committee of the E-AHPBA has initiated several international projects such as one analyzing

the outcomes and risk score of distal pancreatectomies with celiac axis resection for pancreatic cancer. Another example is the European consortium on Minimally Invasive Pancreatic Surgery that aims—beside other activities—to establish an international registry on minimal-invasive pancreatic surgery.

ATM: You have written lots of articles and many of them have high citation. What do you think would be important factors for a paper to be liked by peers?

Prof. Jörg Kleeff: "To be liked" is an interesting term; the key aspect is whether the work is cited by peers, meaning that it is deemed a valuable and reliable source of information. The number one aspect is that it has to be good scientific work, either novel original work or a comprehensive overview. The best papers most often tell a complete story, in contrast to piecemeal publications. This aspect is not trivial as there is continuous pressure (Universities, funding agencies, postdoctoral researchers, competitors etc.) to publish more and/or faster. Further, publishing (in general) has become easier with online submission processes and a larger selection of potential journals (not counting predatory ones).

The number two aspect is that the topic must be timely and interesting; obviously, this is difficult to "plan", and it is also not advisable in most circumstances. Hot topics usually have the toughest competition, and whether or not a topic is of general interest at the time of publication is usually not clear at the beginning of a project.

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For example, around 1999/2000 we were interested in glypican-3 and liver diseases and from our (RNA based) analysis we suggested glypican-3 as a specific marker for hepatocellular carcinoma (HCC). The paper was rejected several times (mainly because of lack of interest), and when it finally got published it initially got very few citations. A few years later (with specific antibodies being available), there was a "rediscovery" with several high-impact papers being published on this topic by other groups and an increasing number of citations on our original article. Glypican-3 is now an established marker for HCC and is currently being investigated as a diagnostic and therapeutic target.

I believe that one should not start a scientific career calculating high citations. In contrast, one should focus on the science and personal interests. At the end, to succeed in publishing highly cited papers, one needs good mentoring, stamina and luck.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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