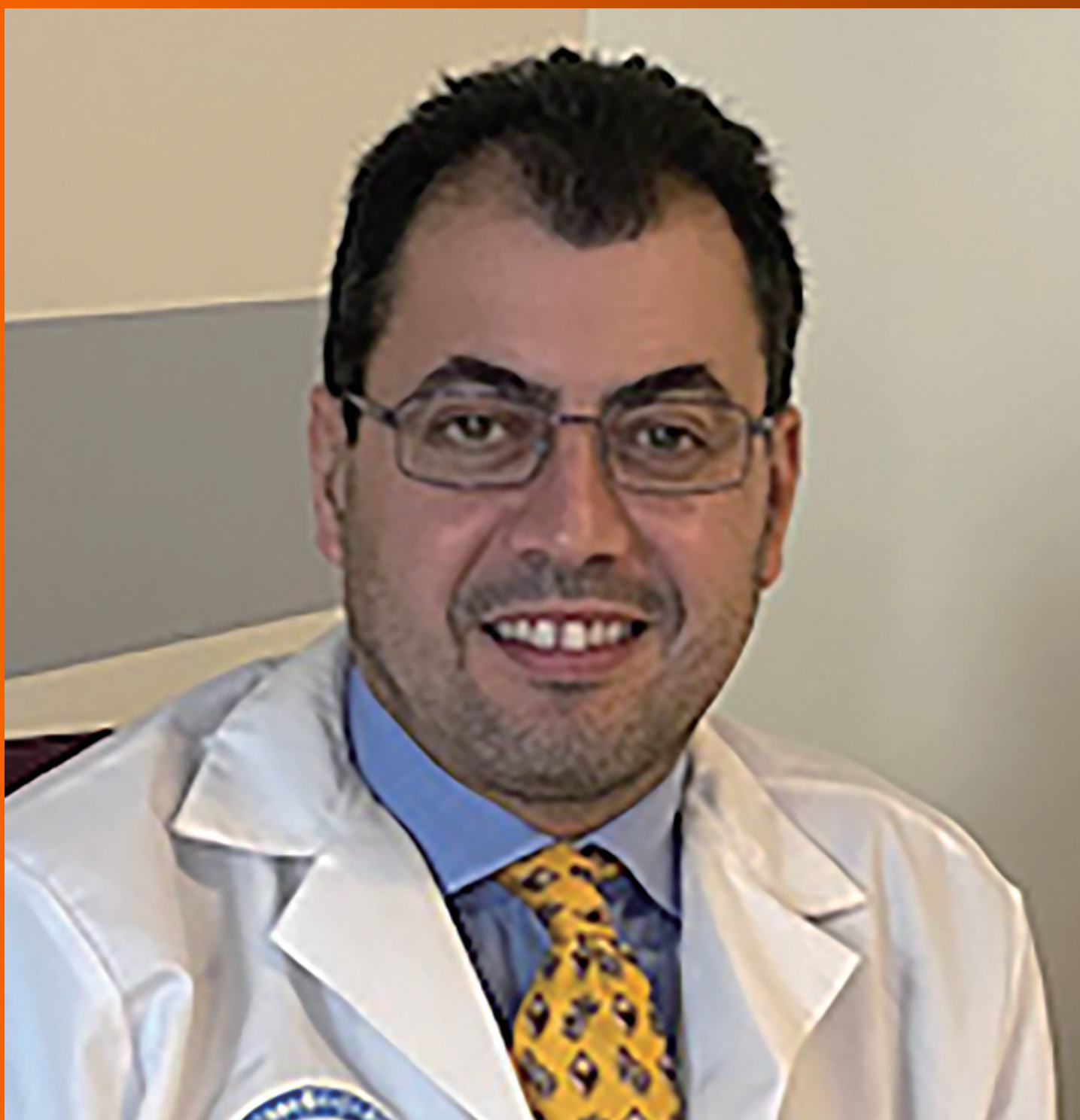


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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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## Patient-centered developments in colon- and rectal cancer with a multidisciplinary international team: From translational research to national guidelines

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and co-conduction of FOGT-2; Maulbecker-Armstrong C was leading partner for the public campaign for preventive colonoscopies; Danenberg P and Danenberg K were partners in the design of translational research projects; Ji ZL, Li JT and Peng SY are in close research and clinical collaboration with the FOGT members; all coauthors contributed substantially to scientific developments and reviewed the paper which was written by Link KH and Traub B; Danenberg P performed language edition.

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## Abstract

Rarely, scientific developments centered around the patient as a whole are published. Our multidisciplinary group, headed by gastrointestinal surgeons, applied this research philosophy considering the most important aspects of the diseases "colon- and rectal cancer" in the long-term developments. Good expert cooperation/knowledge at the Comprehensive Cancer Center Ulm (CCCU) were applied in several phase III trials for multimodal treatments of primary tumors (MMT) and metastatic diseases (involving nearly 2000 patients and 64 centers), for treatment individualization of MMT and of metastatic disease, for psycho-oncology/quality of life involving the patients' wishes, and for disease prevention. Most of the targets initially were heavily rejected/discussed in the scientific communities, but now have become standards in treatments and national guidelines or are topics in modern translational research protocols involving molecular biology for e.g., "patient centered individualized treatment". In this context we also describe the paths we had to tread in order to realize our new goals, which at the end were highly beneficial for the patients from many points of view. This description is also important for students and young researchers who, with an actual view on our recent developments, might want to know how medical progress was achieved.

**Key Words:** Colon- and rectal cancer; Translational research; Interdisciplinary treatment; Personalized treatment; National guidelines

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**Core Tip:** Interdisciplinary innovative research projects centered on the needs of patients with either colon- or rectal cancer were initiated under the leadership of gastrointestinal-surgeons. Phase III- and translational research trials were applied. Quality of life and disease prevention were involved. The projects initially were heavily criticized, but now are routine methods of treatment or goals of modern translational research. The paths may be interesting for the scientific community, and for young researchers, even students.

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## INTRODUCTION

Diagnosis and treatment of patients with colon- and rectal cancer has improved significantly in the last three decades. A multidisciplinary approach was the main driving force leading to higher cure rates[1]. In recent years treatment individualization/personalized medicine contributed to better treatment results in both adjuvant and palliative therapies, e.g., respecting the mutational status of microsatellite stability (MSI), as outlined in current guidelines such as from the German Cancer Society[2]. Surgery of colon- and rectal cancer also has improved, avoiding local relapses[3,4]. Minimal invasive surgery in both tumor entities improved the quality of life[5-7]. The lethal fate of patients with metastasis, e.g., to the liver[8,9] or to the peritoneum[10,11]

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has been stepwise diminished, but not abolished. In the late 1980's surgery was the only treatment of choice for patients with primary colon- and rectal tumors in Germany. The 5-year survival rates of patients with advanced tumor stages, *e.g.*, in stage UICC III was 49% for colon cancer and 38% for rectal cancer at our university hospital[1,12,13], with the surgeon and hospital being significant prognostic factors for survival[13-15]. The local relapse rate for rectal cancer patients exceeded 30% at our hospital in a long-term review, despite them being originally operated on in curative attempt[16]. Only the minority of the patients with liver metastases were resected for cure[8], and patients with peritoneal carcinosis received palliative therapy only with 5-fluorouracil (5-FU) or 5-FU + folinic acid (FA) at median survival times below 15 mo [10,11]. Early detection of high-risk colon adenomas or early stage curable cancers by screening colonoscopy was not yet the standard to improve incidences and overall survival (OAS) rates of colon and rectal cancers. Psycho-oncology was unknown in cancer treating units and palliative homecare as well.

These unsatisfactory results encouraged us to seek significant improvement. The first author (Link KH), with grants from the German research foundation [Deutsche Forschungsgemeinschaft (DFG)], studied tumor biology at the department of basic research, USC Cancer Center in Los Angeles, as a postdoctoral student with the late Charles Heidelberger, who had developed 5-FU. International exchanges and the recommendation of Ch. Heidelberger led to the use of multimodal therapy for colon- and rectal cancer patients and to seek a possibility to individualize systemic treatment. The cooperation with the French group of the late Professor Jacquillat C and his successor, Professor Khayath D at Hospital Salpêtrière, Univ.Paris, France initiated the idea to downstage advanced primarily nonresectable metastases by neoadjuvant chemotherapy. After suggestion of Link KH to P.V. and Danenberg K, then leading the "Fluoropyrimidine" laboratory of Ch. Heidelberger, they were able to show in cooperation with the medical oncologists at the USC cancer center that low expression of the thymidylate synthase (TS) in human metastatic tumor cells could predict a beneficial response to 5-FU ( $\pm$  FA)[17]. Previous work had already shown that the quantitative expression of TS correlates with the cytotoxicity of the 5-FU-anabolite FdUMP.

Subsequently, since 1987, under the leadership of Link KH, a multidisciplinary team at the Ulm University Cancer Center was established in cooperation with oncologic teams in 64 hospitals in Germany nationwide ["Forschungsgruppe Onkologie Gastrointestinale Tumoren" (FOGT) (= Multidisciplinary Study Group on Oncology of Gastrointestinal Tumors)]. At the Department of Surgery I (General and Visceral surgery) of the University Hospital of Ulm (Head: Professor Beger HG) a translational research project with a cell culture laboratory under continuous funding by research grants from the German Research Society "DFG" was established and integrated to modernize the traditional surgical treatment of primary tumors and metastases.

In addition, the demand for a better care for patients in the outpatient setting, either after curative surgery or in the palliative situation, became increasingly obvious. Psycho-oncologic expertise (MSch) was integrated into patient care. With the rising evidence of the significant benefit of screening colonoscopies, we initiated public awareness events on cancer prevention, including better nutritional habits (Maulbecker-Armstrong C, Link KH).

All efforts were initiated with a mindset of putting the patients in the center of our team's efforts. With this we succeeded to establish many significant innovations in our country, with relevance worldwide.

During a time of eminence- and not evidence-based medicine, these provocative results were initially disregarded by many colleagues, but the significantly improved survival of patients with advanced colon- and rectal cancers prompted the field to integrate the new treatment concepts in their programs.

In this paper we want to summarize the results of our teamwork and therewith motivate research teams in oncology to perform multidisciplinary treatment approaches and to stimulate translational teams in basic and clinical research for the benefit of patients with colon- and rectal cancer. For example, an experienced biometician is an essential member of the team.

The developments and results of multidisciplinary treatments included translational research with efforts towards a better outcome for patients with colon- and rectal cancer, including prevention of the disease.

## PRIMARY TUMORS

We were trained in best quality procedures when operating on patients with primary tumors or metastases. We reported our results regularly and demanded quality control and benchmarking. We participated in corresponding expert groups and boards of the German Cancer Society and the Convent Leading Hospital Surgeons[1,12,14,18].

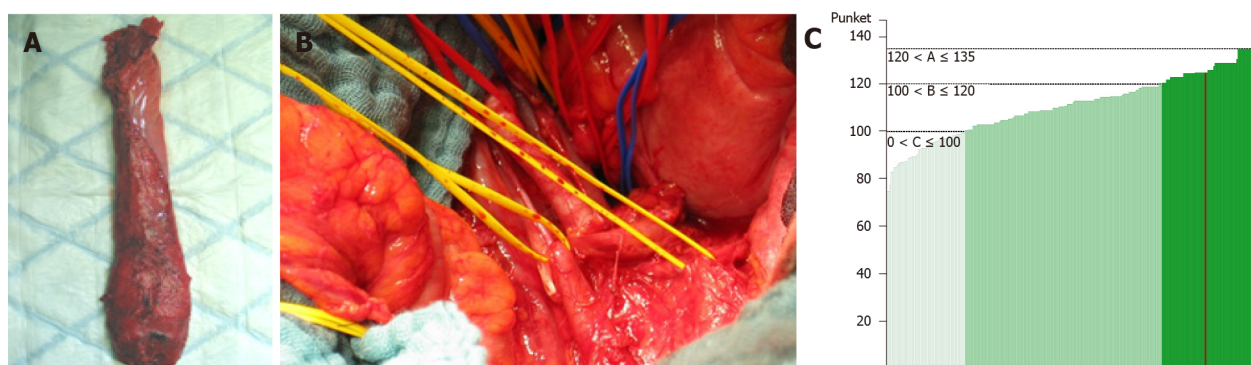
The team initiated the first nationwide multicenter phase III prospective controlled randomized trials for adjuvant chemotherapy of colon cancer patients with UICC stages II B (T4N0M0) and III (TxN1-2M0) (FOGT-1, 855 patients), and adjuvant radiochemotherapy of rectal cancer patients with UICC stages II + III (FOGT-2, 796 patients) involving three systemic treatment arms, after United States-research teams had shown that multimodal treatment improved the survival in both tumor entities and reduced local relapse rates in rectal cancer (reviewed in[13]). In both trials the patients received postoperative adjuvant systemic chemotherapy in the three arms: A: 5-FU, B: 5-FU + FA, C: 5-FU + interferon alpha (IFN- $\alpha$ ). Rectal cancer patients were treated with radiochemotherapy (50.4 Gy + 5-FU) before the systemic chemotherapy arms were started with the same protocols as in FOGT-1. In FOGT-1, 5-year OAS was significantly improved by 11.5% from 60.5% (the control arm result corresponded to the results of the initiating United States trial of Ch. Moertel) to 72%; the 5-year OAS was not improved by adding IFN- $\alpha$  to 5-FU (61.7%)[19]. In rectal cancer stages UICC II + III, local relapse rates of 16.7%, 13.6%, and 17.1% in arms A, B, and C, respectively, were not differing in significance, but due to the radiochemotherapy and to the modern protocol-standardized (TME) surgery, turned out to be significantly lower than the 33% in historic controls[15,16]. Importantly, in FOGT-2 the 5-year overall survival rates showed no difference between treatment arms A (60.2%), B (60.3%), and C (59.9%)[20]. These findings were similar even after 7 years of observation. We were the first to show a lack of benefit in terms of OAS time improvement in rectal cancer patients in comparison to colon cancer patients treated with the same systemic chemotherapy[21]. In addition, we clearly demonstrated that the patient's age did not influence the outcome of colon cancer patients[22]. However, in rectal cancer, the 5-year OAS survival of aged patients was even reduced in the more intensive arm B (5-FU + FA)[21]. Regarding this and other differences between colon- and rectal cancer patients, we reviewed our FOGT data and the data from the literature and were among the first worldwide to make the statement that from many points of view (epidemiology, carcinogenesis, prevention, response to treatment *etc.*) colon cancer is different from rectal cancer, and the term "colorectal cancer" should be abandoned[13, 23,24].

Adjuvant (and neoadjuvant) therapy can be a considerable overtreatment in a subset of patients that either never develop metastases or local relapses due to early tumor stages, or patients who progress despite of multimodal treatment (resistant micrometastases). Therefore, we searched for ways of predicting a patient's response towards 5-FU based multimodal treatment with molecular biology tests. Vital primary tumor biopsies were collected and then tested for the quantitative expression of the enzyme set TS and dihydropyrimidine dehydrogenase (DPDH), both involved in cell proliferation (TS) or 5-FU catabolism (DPDH). The analysis of samples from 295 patients was performed at the leading laboratory of Peter Danenberg at USC/Los Angeles. Most interestingly, and other than expected, patients with high TS had significantly higher survival rates than those with low TS; Low DDPH seemed to increase the survival rates[25-27].

With study groups from the universities of Heidelberg and Mainz we tested samples from the multimodal treatment study FOGT-4 for the predictive potency of the MSI status[28] and the VEGFR/EGFR expression[29]. It could be shown that expression of both in primary tumors correlates with survival under 5-FU based multimodal therapy. MSI meanwhile has been integrated into the national guidelines [13,23,24]. With this step towards personalization of multimodal treatment in colon- and rectal cancer patient, we were among the first three groups worldwide to start interdisciplinary research on this issue. In summary, reviewing our own experience and regarding the possibilities of treatment individualization in multimodal therapy, the 5-year survival rates was increased in colon cancer UICC III from 49% *via* 72% (FOGT-1 Arm B) to potentially > 85%[1,26].

In our team and in the FOGT protocols we always delineated the surgical procedures corresponding to the best standard (CME in colon cancer[3], TME in rectal cancer)[4,30], being in productive scientific exchange with Hohenberger *et al*[3] and Heald[4], who developed and propagated these techniques and attended several of the meetings of our International Colon- and Rectal Cancer Club (ICRCCs; [www.ICRCC.de](http://www.ICRCC.de)) (Figure 1). When we compared the FOGT-1 and -2 survival curves among hospitals,





**Figure 1** Examples for surgical treatment recommendations in the FOGT protocols and quality level of one participant's surgical team applying these recommendations (Link KH) in the benchmarking of German Cancer Society Bowel Centers. A: The best standard-of-care in rectal resection was total mesorectal excision according to Heald RJ; B: Lateral nerve preserving lymph node dissection could be applied in cases with lateral LN-metastasis (diagnosed in the preoperative MRI) according to Mori T; C: The variation of results of quality control in German Bowel Centers is demonstrated [marked in red color is the position of APK Wiesbaden under leadership of the first author; dark green = bowel units that were rated as top groups (Link KH)].

we could not find significant differences in hospital volume categories — due to the strict surgical guidelines and repetitive discussion of those in study group- and ICRCC-meetings[13,23,24].

We also aimed at improving the standards of therapy in metastatic diseases. Our scientific strategy of involving translational research as consequently as possible, and the inherent initial difficulties in convincing surgical and medical oncologic colleagues at top level positions are described in the following.

## METASTASES

### *Treatment individualization in colorectal liver metastases*

At the time we started our multidisciplinary treatment concept, patients with liver metastases either were resectable according to standard indications[8] or they received palliative chemotherapy with 5-FU + FA either by systemic or by hepatic arterial infusion (HAI) chemotherapy. Systemic treatment with additional FA was even opposed by some medical oncologists at the Ulm Cancer Center at that time. HAI was performed due to the low effectiveness of systemic 5-FU or 5-FU + FA, the therapeutic standard at our surgical department at that time in the late 1980s and early 1990s. Response and survival with HAI were twice as good as with systemic treatment[8,31].

Therefore, a rationally designed program for HAI in nonresectable “colorectal liver metastases” (CRLM) was developed with a translational research program. Two metastatic human colon cancer cell lines and individual cell suspensions from human metastatic tissue (mostly CRLM) in the human tumor colony assay (HTCA, first described by Hamburger A and Salmon S (for details see[32,33]) were established. Available drugs were tested for their concentration response behavior and for the optimal treatment time[34,35]. Similar approaches to find out best basic treatment conditions using patient-derived cell lines and *in vitro* cytotoxicity tests are standard practice today. These extensive *in vitro* experiments revealed a broad variability of cancer cell sensitivity between individual patients (as it is the factual dilemma *in vivo*) and offered first cues on how chemotherapeutic treatment may be optimized for the individual patient. We successfully translated these findings into clinical action by adding the *in vitro* active drugs, Mitomycin C and Mitoxantrone, to our primary HAI-protocol with 5-FU + FA according to their potential effectiveness at the same conditions *in vivo* as tested *in vitro* (calculated drug kinetics in the arterial blood during infusion time was matched to the optimal *in vitro* conditions)[32,34-37]. The response rates and survival times achieved by these protocols increased from 45%/20 mo (HAI with 5-FU + FA) to 54%/26 mo (HAI with the combination of 5-FU + FA + Mitoxantrone + Mitomycin C (MFFM)[31,36,38]. The combination of Mitomycin C and Epirubicin, with high *in vitro* phase II response rates at 10 µg/mL, was used for chemoembolization [39].

An important step in gaining confidence in our following study protocols using *in vitro* tests with assumed relevance for *in vivo* treatment was the *in vitro* confirmation of the immediate drug effects on tumor cell viability seen *in vivo* after isolated liver

perfusion (ILP) with high drug concentrations in a reconstruction experiment: For this experiment in CRLM patients, we did an incision biopsy of a metastasis and performed an HTCA drug cytotoxicity test as described above. After 1h of ILP (*e.g.*, with 5-FU + Mitomycin C), another metastasis was excised and the cell suspension was tested for its colony forming efficiency. To our great satisfaction, the colony growth inhibition rates after drug exposition *in vitro* correlated to those after *in vivo* treatment[33]. This made us hopeful to be able to individualize HAI by *in vitro* drug testing in the HTCA. First, being cautious, we correlated the *in vitro* results with the individual clinical responses to HAI, and then we used the drugs effective *in vitro* to add to 5-FU + FA for HAI *in vivo*[40,41]. After we had seen that patients with low TS responded very well to HAI with 5-FU[27,42] and that drug selection with the HTCA was possible[40] we finally added TS determination to our prospective *in vitro* individualization trial. With this strategy we were able to show an impressive response rate of 77% and median survival time of 32 mo in *in vitro* sensitive patients *vs* 9%/17 mo of the *in vitro* resistant patients receiving the standard MFFM protocol (Table 1)[42].

In the meantime, systemic chemotherapy had improved with major steps (FOLFIRI or FOLFOX). In a subsequent phase III decision aiding trial, supported by the European Organization for Research in Treatment of Cancer (EORTC), we tested if “TS-low” patients with multiple, unresectable metastases from colon and rectal cancer primaries could be selected to receive systemic i.v. chemotherapy with 5-FU-FA only without inferiority compared to the more toxic combination of 5-FU + FA + Irinotecan (FOLFIRI). TS quantitative expression was determined from diagnostic fresh biopsies by the Danenberg P and Danenberg K laboratories, and the results were reported timely to the treating center before the protocol assigned therapy was started. In this decision-aiding trial (FOGT-5), the TS-low patients treated with 5-FU + FA i.v. had nearly the same response rates as the (TS-low) FOLFIRI patients. Response towards FOLFIRI was comparable in TS-high and -low patients but significantly superior to 5-FU + FA in TS high patients, demonstrating the potential of TS in selecting patients that can profit from the more aggressive FOLFIRI protocol (Table 2)[27].

### **Downstaging and resection of CRLM**

Since HAI with our stepwise concepts for personalized chemotherapy using cell culture and molecular biology methods resulted in higher response rates, and, compared to HAI with 5-FUDR, with only low hepatotoxicity[43], we started to resect patients with good responses (“downstaged CRLM’s”). By this decision, we were able to achieve long term survivors (survival  $\leq$  81 mo, median survival 39.2 mo) in some cases exceeding 5-years and achieving even cures. Together with the Paris group of Professor Henry Bismuth we were the first worldwide with a major patient number reported to demonstrate that this treatment concept is possible and successful[38,44]. This treatment concept soon became standard for primarily nonresectable patients in our department in case of adequate responses and resectability, and meanwhile has become (the demanded) standard for systemic chemotherapy of CRLM in the national guidelines[2].

### **Split time resection of unresectable CRLM**

The question of resectability sometimes was highly controversial and experts denied resectability of some patients, either at their first presentation or after relatively good responses. One young patient in the year 1992 was sent home from a renowned German liver transplantation unit judged to be nonresectable and recommended to have palliative chemotherapy at home with 5-FU + FA. According to our assessment, she was not suitable for primary HAI aiming at downstaging/resection. Since she was 35 years old and had two small children, we decided to resect the huge metastasis reaching into the pelvis by extensive right hepatectomy. Then we performed individualized HAI of the metastases remaining in the left liver segments. After 3 HAI cycles the patient had recovered well, the metastases had responded and the liver had regenerated as expected. The two metastases were resected for cure and the patient received additional HAI with the same protocol applied initially. She remained tumor free for seven years. Fatefully, she returned with jaundice due to lymphangiosis of the hepatoduodenal ligament, a noncurable situation. This split time liver resection with interim individual HAI was the first case reported worldwide (Figure 2)[8]. We (Link KH) applied this concept several times, even resulting in individual cures. One patient, received his second resection of a segment I metastasis by Link KH together with the top specialist for segment I resections from China, Professor Peng SY from the Department for Liver and Transplantation Surgery at Zhejiang University, Hangzhou, China, on occasion of his participation in an ICRCC-congress in Wiesbaden, and the

**Table 1 Individualized response prediction in patients with hepatic artery infusion[42]**

Response predictor	Clinical outcome		Median survival (mo, range)
	Beneficial response (%)	No response (%)	
HTCA			
Sensitive	58	42	28 (3-75)
Resistant	33	67	19 (5-48)
TS			
Sensitive	64	36	26 (6-48)
Resistant	20	80	26 (3-75)
HTCA + TS			
Sensitive	77	23	32 (5-75)
Resistant	9	91	17 (3-28)

HTCA: Human tumor colony assay; TS: Thymidylate synthase.

**Table 2 Influence of quantitative thymidylate synthase expression in individual metastatic biopsies on response rates and median survival times in patients with metastatic colon- or rectal cancer[27]**

	TS low		TS high	
	5-FU + FA	5-FU + FA + Irinotecan	5-FU + FA	5-FU + FA + Irinotecan
Patients ( <i>n</i> = 119)	39	38	23	19
Median survival (95%CI)	18.4 (12.1-25.2)	18.8 (12.0-23.2)	19.2 (5.6-33.3)	15.2 (8.4-26.0)
Beneficial response <sup>1</sup> (%)	33	45	22	47, <i>P</i> = 0.077 <sup>3</sup>
No response <sup>2</sup> (%)	67	55	78	53

<sup>1</sup>Complete and partial response.

<sup>2</sup>Stable and progressive disease.

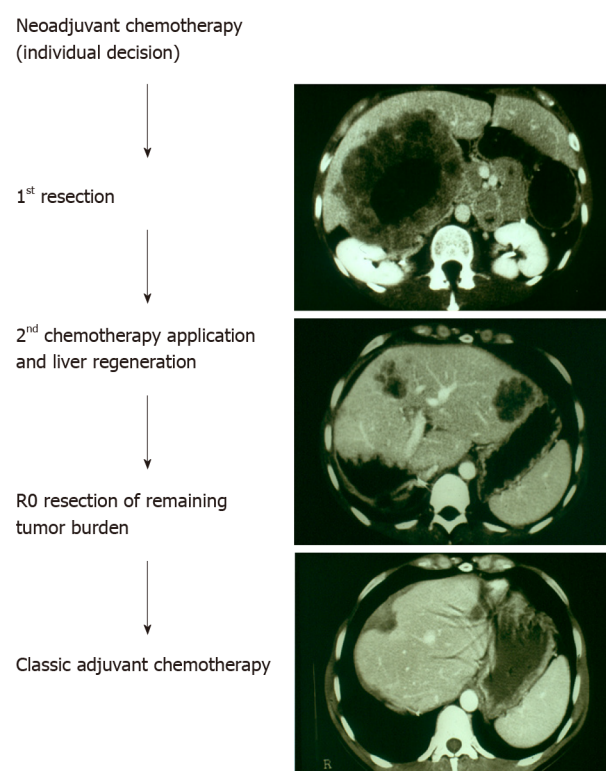
<sup>3</sup>Fisher's exact test (one-sided).

TS: Thymidylate synthase; 5-FU: 5-Fluorouracil; FA: Folinic acid; CI: Confidence interval.

patient remained tumor free for the rest of his life exceeding 5 years. Split time resection thus was the precursor of TSH (Two Stage Hepatectomy) and ALPPS (Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy), both of which have become the treatment of choice in specialized surgical liver units[9,45, 46].

### **Peritoneal carcinosis and malignant ascites**

Peritoneal carcinosis at the time of our team formation was a death sentence to the patients. Sugarbaker P initiated the treatment "Peritonectomy with Hyperthermic Intraabdominal Chemotherapy" (HIPEC). The convincing data reported by several groups including a phase III trial and our own experience in Ulm, as one of the first teams in Germany and in Europe starting to apply this very extensive procedure, led us to propagate peritonectomy and HIPEC[10,11] on occasion of international meetings, actively involving Professor Sugarbaker P (*e.g.*, "ICACT"/Professor Khayath D/Paris, "ICRCC-meetings", *etc.*). After initial opposition, the procedure finally has been taken up into the S-3 guidelines of the German Cancer Society to be recommended as treatment in "isolated" peritoneal carcinosis in qualified patients[2] We used Mitoxantrone due to the excellent *in vitro* phase II results and applied the drug for HIPEC at the test concentration of our HTCA-tests with individual tumor cell suspensions from colon-, rectal-, and ovarian cancer metastases[32,47,48]. Later, Oxaliplatin was suggested by expert groups. Although qualified according to basic research experiments[49], we were reluctant to use oxaliplatin since the drug may exert severe systemic toxicity due to its significant peritoneal resorption, which did not occur with Mitoxantrone.



**Figure 2 Individualized multistep treatment of a patient with primarily nonresectable isolated colorectal liver metastasis.** A 35-yr-old woman with bi-lobal metastatic disease in the first step was partially resected by extended right hemihepatectomy, then treated with individualized hepatic artery infusion chemotherapy (HAI), then R0 resected by atypical resections on the left side. She then received three cycles of postoperative adjuvant chemotherapy applying the same HAI protocol. The resected metastases on the left side had shown nearly complete pathological responses. The patient lived tumor free for 7 yr and then presented with obstructive lymphangiosis in the hepatoduodenal ligament. She died due to disease progression after treatment with systemic chemotherapy.

Malignant ascites occurs in peritoneal carcinosis, and the palliative primary treatment option is diuretic therapy. Based on our *in vitro* phase II results, we used Mitoxantrone at 10 µg/mL for 1 h exposure as repeating intraperitoneal instillation therapy at 1-mo intervals as second line option after failure of diuretic drugs. Since this treatment was very effective and very well tolerated, we propagated it and then conducted a retrospective study on the effect of Mitoxantrone instillation therapy together with the gynecological department of the University Heidelberg. The data of the examination were convincing, and the treatment was approved by the German Drug Commission[32,47,50].

## PREVENTION

Since Link KH at the Charles Heidelberger laboratory had a research project on carcinogenesis and tumor biology, we were interested on carcinogenesis and risk factors for colon- and rectal cancer. We were the first in Germany to organize a conference together with the CCCU on the topic "Nutrition and Cancer" in 1996 and the conference presentations were published in a book. At that time, we proposed a beneficial effect of a mediterranean diet. Although the idea was initially rejected by gastroenterologists, it was later approved by the European Prospective Investigation into Cancer and Nutrition (EPIC) with participation of the German Institute of Nutritional Science (Dr. Boeing HH). Now this primary preventive measure among others is recommended in the S3 guideline[2].

In parallel, we became very interested in the benefit of (secondary) preventive colonoscopy and continuously supported propagating initiatives, which have been actively conducted by Professor Riemann J, a participant of the ICRCC-meetings, who, as a most renowned gastroenterologist, has established the preventive colonoscopy to be recommended and paid for by the health insurances for all Germans (males at 50-year-old, females at 55-year-old, persons at risk earlier ages and in closer intervals). We (Maulbecker-Armstrong C and Link KH) co-founded the campaign "du bist kostbar" ("you are of great value") in Germany for the German Cancer Society and



others to promote prevention of various cancers, *e.g.*, involving Professor zur Hausen H, Nobel Prize Winner 2008 for his development of a vaccine against Human Papilloma Virus (HPV)/cervical cancer, and other preventive activities (Maulbecker-Armstrong C) together with Professor Riemann J (Mannheim) and Professor von Knebel-Doeberitz M, Director of the Department of Applied Tumor Biology at the University and German Cancer Center, Heidelberg. With “du bist kostbar” in 2013/2014 we conducted a wide initiative to improve the participation of male (in parallel, of course, also female) candidates for preventive colonoscopy, involving gastroenterologists, surgeons and prominent supporters from the field of sports such as a multiple Olympic gold medal winner and a soccer World Cup- and European Championship winner. The 1-year public initiative “1000 brave males” in Wiesbaden, the capital of the German state Hessen, convinced 1645 males and 1588 females to have a preventive colonoscopy. Regarding the usual frequency of high-risk adenomas and early cancers being detected and removed, potentially > 150 lives were saved by this 1-year campaign. The campaign gained political momentum and public interest initially in the state of Hessen and subsequently in Germany (German Cancer Society, *e.g.*, special session on the congress of the German Cancer Society 2018, organized by Link KH) (Figure 3).

But prevention measures shouldn't only include secondary preventive measures. Although thankfully preventive colonoscopies can detect and treat colon adenomas that might develop into invasive cancer, many colonoscopies without tumor symptoms still detect early stage lesions.

By understanding carcinogenic drivers in our everyday environment, we can take measures of primary prevention by reducing exposure and thus reducing the overall incidence of colon and rectal cancer.

Molecular pathologic epidemiology (MPE) is a novel approach in identifying those endogenous and exogenous exposures[51]. The computational integration of big-data consisting of potentially modifiable factors like dietary lifestyle, environment and also microbiome with pathological data of genome, transcriptome and metabolome of neoplasia can identify personal strategies for risk reduction[51,52].

Furthermore, MPE could identify patients with an increased stochastic risk tumor development and offer more intensive screening measures to this subpopulation.

Obviously, primary preventive measures are the most effective in reducing the threat that arises from neoplastic diseases, but the combination of both primary and secondary, yet even tertiary preventive measures offers the best chances in early stage detection of cancer.

## PATIENT'S QUALITY OF LIFE

The patient's interests have always been in our focus, not only regarding the gain in their life expectancy by improving our therapeutic possibilities, but also with respect to their personal quality of life[53-55]. We early organized high-quality homecare by nurses from our Ulm University Hospital, including home parenteral nutrition (which in the beginning 1990's was not yet available from companies at that time). A psycho-oncologist (MSch) joined our team. We also involved the patient's wishes on the decision for multimodal therapy and received a national prize for this step[56]. Taking various high level and responsible positions in cancer societies and surgical societies in Hessen and in Germany, we (Link KH) also supported the psycho-oncological and social support of tumor patients and their families. With a 1 million Euro initial grant and then successive grants from the German Cancer Aid Fund (Deutsche Krebshilfe), we established 5 counseling units for patient support, accessible for free (Link KH).

Besides advocating for the patient's quality of life, we were also demanding surgical and oncological treatment quality with low morbidity/mortality in nationwide campaigns[14] and by participating in structure and S-3 guideline commissions of the German Cancer Society (Link KH: German Cancer Society S-3 guideline and structure commissions for “colorectal” cancer, pancreatic cancer, and for psycho-oncology). We took part in the benchmarking for treatment and structure quality of more than 260 “Bowel Centers”, that had been certified by independent auditors according to the guidelines of the German Cancer Society (for a benchmarking result see Figure 1C). The patient's opinions towards neoadjuvant radiochemotherapy in rectal cancer were evaluated and disseminated by publications and oral presentations[57,58]. Quality of life was not diminished in our FOGT 1 + 2 Arms A and B chemotherapy protocols. By using the 2 h infusion of 5-FU, based on the cell culture experiment results, we soon recognized, that this treatment timing caused less toxicity than bolus injections. The





**Figure 3** German action for secondary prevention of colon- and rectal cancers by colonoscopy/polyp excision. Public action “1000 brave men” (left, “1000 Mutige Männer”) with support of public personalities in sports (left, Otto K, Olympic gold medal champion) and politics (right, Bouffier V, Hessian state prime minister).

toxicity in FOGT-1 + 2 were relatively low and the patients’ acceptance rates of the full protocol treatment, indicating a good quality of life in Arms A (5-FU) and B (5-FU + FA) for 1 year, was high; however, IFN- $\alpha$  in arm C (5-FU + IFN- $\alpha$ ) had to be interrupted frequently[56].

## DISCUSSION

The success of our team’s consistent multidisciplinary scientific work with several original innovations for the benefit of patients, together with our research philosophy, could be a model for young academic cooperative research teams. We always regarded the patient with the disease as a whole and were rewarded with good and satisfying results on all levels.

Our developments over many years are influenced by the available research- and clinical tools and processes. Nowadays the necessities and tools of prevention and personalization involving molecular diagnostics have become the major pacemakers to limit the lethal threat of the diseases colon- and rectal cancer. Recently one of the authors was elected to be “Ambassador of the year 2021” of “Stiftung Lebensblicke (SLB)”, the German foundation that has established preventive colonoscopy as a routine examination. SLB, founded and headed by Professor Riemann J, aims to propagate the acceptance and the continuous improvement of prevention and early detection to reduce the burden of this type of cancer, with high incidences in the nations with western lifestyle such as dietary habits with fat and meat consumption, obesity, diabetes, and alcohol consumption.

The strategy of SLB aims both at achieving a high acceptance of the preventive colonoscopy and stool tests, as well as public information on the impact of lifestyle on polyp formation and cancer development in the colon and the rectum. Many environmental, dietary, and lifestyle factors, their influence on the microbiome and the immune system and on bowel habits contribute to the carcinogenesis in the colon and rectum. Cancer development is influenced by the consumption or intra-bowel formation of carcinogenic substances and their effect on molecular targets in the large bowel epithelium (gene-by-environment interactions). Patient exposures towards exogenous and endogenous factors like the gut microbiome and their influence on cancer development combined with pathological and epidemiological data is studied in molecular pathological epidemiology (MPE)[51,52]. These epidemiologic findings go hand in hand with molecular findings of personalized diagnostics in determining a patient’s individual risk. Known genetic risk factors like loss of tumor suppressor genes and overexpression of tumor promoters might help to detect patients in need of more frequent preventive measures like colonoscopy or stool examinations. In the future, epidemiologists, nutritionists, molecular pathologists, human geneticists, immunologists should be integrated in the modern teams to reduce the still unnecessary high incidences of colon- and rectal cancers. Furthermore, treatment individualization by inclusion of nutritionists *etc.* should also be included in secondary and tertiary disease prevention to reduce the elevated risk for the development of second primary cancers in the colon or rectum.

With our group we initiated several new treatment options for patients with colon and rectal cancer in both primary tumors and metastases, and discussed our new developments continuously in oncological societies[59]. After recognizing the possibilities for multimodal therapy from a few trials[13], we introduced multimodal treatment of colon and rectal cancer patients in Germany in two nationwide trials

involving 64 hospitals and 1651 patients (FOGT-1: 855 pts., FOGT-2: 796 pts.). In these phase III trials, the 5-year-survival rates in colon cancer UICC IIB and UICC III were improved significantly. Unexpectedly, the same therapies led to no survival improvement in the stage II+III rectal cancer patients receiving postoperative adjuvant radiochemotherapy in FOGT-2. In FOGT-2 the local relapse rates in the three arms were similar, but significantly lower than after surgery only (13.8%, 10.7%, and 13.5% (in arms A, B, and C) *vs* > 30%, respectively)[20]. We regularly followed the possibilities of multimodal treatment in rectal cancers[60,61]. To our knowledge, neither modern combination protocols (*e.g.*, FOLFOX), nor neoadjuvant radiochemotherapy led to an increase of survival rates. In the comparison of preoperative *vs.* postoperative radiochemotherapy the local relapse rates were reduced by the preoperative (neoadjuvant) treatment, however with the insecurity of preoperative tumor staging and thus possible overtreatment. We established that colon- and rectal cancers are differing in response to chemotherapy besides many other parameters[21,23]. This had also been demonstrated by other groups[62]. We were the first to conduct a colon- and a rectal multimodal trial in parallel with identical adjuvant systemic treatment arms. The realization of the FOGT-1 and FOGT-2 trials helped, that multimodal therapy was included in national guidelines.

In case of metastatic disease, *e.g.*, nonresectable CRLM, 5-year survivors still are very rare with chemotherapy only[63]. Resection of primarily nonresectable CRLM after adequate response to systemic chemotherapy nowadays is demanded in the guidelines. Together with the group of Professor Henry Bismuth (Paris), we were among the first worldwide to show that downstaging and resection is possible in primarily nonresectable CRLM, improving median survival times significantly[38]. This later has been confirmed with large prospective controlled trials[64].

We were the first worldwide to perform “split time liver resections” in case of far advanced CRLM. TSH and ALPPS later followed our first report in 1993 (see in[13,23,24]) and is now routinely practiced in surgical liver units[9,45,46,65,66]. We have observed several patients who live > 5 years after this exceptional surgical treatment with added chemotherapy.

Our group successfully translated laboratory-based knowledge into clinical applications. We designed the optimal treatment timing of cytotoxic drugs by evaluating the impact of exposure concentration and time of 5-FU and other drugs[35], and applied this knowledge successfully in our clinical protocols for multimodal treatment of the primary tumors and for (regional) chemotherapy of metastases to the liver and peritoneum. By conducting dose response and *in vitro* phase II trials (testing the response rates of drugs tested in the HTCA with tumor cell suspensions deriving from *e.g.*, CRLM's of several patients) with individual metastatic tumor cell suspensions we identified active drugs for successful chemotherapeutic protocols of CRLM, peritoneal carcinosis, and malignant ascites. Response rates were high and exceeded the standard systemic treatment with 5-FU or 5-FU + FA at the corresponding time period. Meanwhile, to our great pleasure, systemic protocols were significantly improved by French oncological groups (FOLFIRI/FOLFOX ± MAB), so that we abandoned HAI, which can only be performed by surgical catheter implantation with high levels of special expertise. For chemoembolization we had established a combination protocol in Ulm [Mitomycin C + Epirubicin (+ Lipiodol)], based on our *in vitro* phase II results at the drug concentrations of 10 µg/mL, which are achievable by chemoembolization. Chemoembolization, in Germany promoted by a surgical friend, Professor Schultheis KH, is still standard in nonresectable liver tumors nonresponsive to the low concentration systemic i.v. chemotherapy, and applied as rescue therapy in CRLM[9].

Most importantly, we were the first group to show, that individual drug selection for (HAI-) chemotherapy of nonresectable CRLM is effective (this originally had been suggested to Link KH by Professor Charles Heidelberger, developer of 5-FU, in 1982). The individualized treatment of our patients, based on *in vitro* results (HTCA, TS-determination), induced significantly higher response rates and median survival times than the treatment with standard protocols or in the “*in vitro* resistant” patients. These results were published in “Cancer” and awarded “Best Paper of the Year 2000”[42]. With this paper we were able to show that personalization of chemotherapy in the HAI set-up is possible. Our success was based on the fact that we used exactly the same pharmacologic parameters (concentration and time of drug exposure) *in vitro* as those which had been either measured or calculated for the arterial blood concentrations. Our reconstruction experiment in ILP confirmed this hypothesis. Individual response, besides K-ras status and SMAD status is now also a prognosticator for the benefit of downstaging/resection, ALPPS or orthotopic liver transplantation in CRLM [9,64,67]. To our knowledge, up to now there is no test to individually select effective chemotherapeutic drugs for systemic chemotherapy, but research is ongoing[68,69].

The benefit of adding anti EGFR-monoclonal antibodies to chemotherapeutic combination protocols can be predicted by pathology immuno-assays.

We were one of the first three groups addressing the importance to select patients for multimodal therapy in resectable primary tumors to avoid a significant overtreatment. We retrospectively confirmed the usual prognostic parameters in our FOGT-1 + 2 trials and, as incidental information, showed that due to the outlined surgical standards in our FOGT protocols (which has not always been the case in other multimodal treatment protocols) the surgeons or hospitals were not prognostic factors [70]. Most importantly, in cooperation with Danenberg P and Danenberg K we obtained evidence, that TS- and DPDH-expressions seemed to be predictors of survival of the FOGT-1 + 2 patients [26]. In the meantime, we and many others have tried to define a reliable test of either single or a combination of parameters for personalization of multimodal therapy [68,69]. Up to now, only the MSI-status is influencing the decision for multimodal therapy in the S3 guidelines [2]. Most recently in adjuvant therapy of early node positive breast cancer, the large prospectively controlled trial RxPONDER successfully defined the benefit of chemotherapy by applying the Oncotype DX<sup>®</sup> test. First results from the study conducted by the independent SWOG Cancer Research Network, and sponsored by the National Cancer Institute, identified the majority of women with 1-3 nodes who received no benefit from chemotherapy. The prospective randomized controlled phase III study at 632 sites has involved > 5000 women. The data was just recently presented at the 2020 San Antonio Breast Cancer Symposium (December 10, 2020) [71]. The Oncotype DX<sup>®</sup> test, scheduled soon to be published (in 2021) in a peer reviewed journal, was said to have redefined personalized medicine by making genomics a critical part of cancer diagnosis and treatment. According to our findings, colon and rectal cancer patients differ in profiting from adjuvant chemotherapy, so that these tumor entities must be studied separately in future phase III trials similar to the RxPONDER trial in breast cancer.

Which are the principal conclusions for young (surgical) researchers and for translational research teams? First, you must be fully motivated to conduct research involving basic and clinical research. This can be described by the saying of Winston Churchill “We make a living by what we get-we make a life by what we give”. The improvement of surgical techniques influenced the quality of life (*e.g.*, reducing local relapses by TME/Heald or applying minimally invasive- and robotic surgical techniques), but rarely improved overall survival. The findings of basic research must be translated earlier into clinical application. You must believe what you find *in vitro*, then cross check your hypothesis derived from the *in vitro* results, *e.g.*, with reconstruction experiments and then use these new findings in clinical applications. If you have new ideas, you have to reflect on them and then work on their realization. To recognize problems and deduct solutions is an individual intellectual process, as the German philosopher Kant I described in his major work “Kritik der reinen Vernunft” (philosophical reflections and discoveries on the process of getting a new own opinion/conviction) [72]. Popper K, the late contemporary Austrian/British philosopher (1902-1994) even demanded that you always have to proof your conviction by excluding the possibility of a truth with an opposite solution (Popper 1994). Kant, as cited by Popper said “Be brave and use your (scientific) sense” [73].

Your new strategy needs to be backed up by enough general experience so that you and your intentions are generally accepted. Broadening your research spectrum and applying these approaches can further increase the trust put into your research, *e.g.*, Link KH together with HGB also contributed to new developments in pancreatic cancer research [74]. We decided to translate the cell culture experiments into clinical practice, since we were convinced that the laboratory conditions are representative for the conditions *in vivo* in HAI of CRLM and HIPEC. Our reconstruction experiment (Popper: Is it really true?) fully supported our translational strategy and resulted in innovative findings to the benefit of the patients [33].

Once you have started your programs and generated first results that are better than the conventional practices, the way forward can get rocky, as Arthur Schopenhauer has described in his viewpoint on scientific developments: “First you are ridiculed, then you are heavily criticized, then your achievements are captured by others”. When we initiated the multimodal FOGT-1 + 2 trials, we faced skepticism from both highly rated university surgeons (“In Ulm they cannot operate, they need additional chemotherapy and radiotherapy”) and the medical oncologists, still stuck to 5-FU monotherapies for many GI-tumors (“Surgeons do not understand chemotherapy, they should perform surgery only”). Backed by the team at the CCCU and by the convinced head of the Department (HGB) (and by significant/protocol fixed support of companies (medac, Roche, Aventis, Sanofi, Pfizer, Baxter, Tyco), who also helped to generate interest in many German hospitals), we finally were able to finish the high

level FOGT-1, 2, 4 and 5 trials. After other groups confirmed the beneficial effects of multimodal therapies in colon and rectal cancer, these schemes were included into the German guidelines[8].

Similar critics were voiced after we promoted “downstaging and resection” in primarily nonresectable CRLM. Renowned liver surgeons were stating that “they (the Ulm group) can’t operate on the liver”. Most liver surgeons did not believe in our split time resection we originally performed in a young patient rejected for resection or transplantation at a top liver unit. International specialists for chemotherapy and surgery awarded the poster presentation with admiration and the poster prize at an international meeting in 1993. It took years and many oral presentations from our group (with increasing patient numbers), until another strategy, also taking liver regeneration into account, led to TSH/ALPPS[9,45].

So, Schopenhauer was right with his prediction on the fate of new scientific developments. However, sometimes findings, in spite of being significant, unfortunately are not accepted by *e.g.*, supporting companies or colleagues: Our published and addressed findings, that rectal cancer metastases/micrometastases seem to be less responsive to chemotherapy, so that adjuvant chemotherapy is less effective than in colon cancer (arm B FOGT-1 survival improvement, arm B FOGT-2 no survival improvement, or even harmful to patients > 70 years), are waiting to be included into clinical practice/guidelines. These findings relevant for the patient’s benefit are not disputed: they are simply ignored, for whatever reason.

Besides our research we tried to perform the best possible surgery and to consider the guidance of the patients. We not only looked just at the organ to be operated/treated, but predominantly at the patient and his/her disease as a whole. We were continuously trying to improve the palliative situation at the patients’ homes or to create professional psycho-oncological care and social advice to the patients and their families, not only during palliative care, but also after curative treatment. We and the patients, including their relatives, estimated this part of care also as “good treatment” [53,58,75].

## CONCLUSION

What can be deducted from our “Patient-centered developments in colon and rectal cancer with a multidisciplinary international team converting translational research into national guidelines?” Surgery is important in modern human societies to promote the health of our peoples. Scientific developments are important to improve the medical armamentarium against diseases, also in surgery. New ideas and structures, with promise to achieve major achievements to fight diseases in terms of prevention, treatment, and posttreatment care – all to the benefit of the patient should be in the center of multidisciplinary efforts, avoiding the propagation of the status quo.

A surgeon participating or leading this kind of science in his academic profession can be assumed to be a good scientist but must not necessarily be a bad surgeon. A surgeon performing good studies on a surgical methodological or outcome question may be assumed to be a good surgeon, but isn’t so necessarily. Young academic researchers should be accepted and supported by their older department colleagues and heads. Translational research is not always understood by doctors who prefer “surgery only”. Basic and translational research should be regarded as equally important in the estimation of the surgeons/researchers. “Translational researchers” can also be good surgeons and even surgical academic department heads. Older experienced surgeons/department heads can take up molecular biology/translational research easily, if interested (like HGB). Thankfully, nowadays new developments from basic research areas are adopted more easily, and young surgeons are encouraged to also follow a research path.

Our research developments were clearly patient-centered and not oriented toward industrial or academic career interests. To our great amazement, some of our findings were rejected due to personal interests with withdrawn support of companies in cases when the presented data didn’t match expectations. Treatment of rectal cancer patients > 70 years still includes intensified adjuvant schemes despite the findings of FOGT-2, and, additionally, of recent large randomized controlled trials that failed in showing positive effects of intensified adjuvant treatment[76,77]

The society of basic researchers in cancer research in Germany (SEK) was unreceptive towards our findings when we initially submitted abstracts on our translational research findings at their annual meeting in Heidelberg. The abstracts were accepted as posters but drew little attention from non-clinician basic scientists. This



thankfully has changed into a more constructive discourse between tumor biologists and clinicians leading to optimal cooperation without losing ideas and time to realize them. The US basic research association AACR was, in contrast, highly interested in our translational research, admitting several abstracts as oral presentations – and the posters were always well discussed. Even former presidents of the AACR and top basic researchers visited our regular “International Charles Heidelberger Symposia on Cancer Research” to exchange ideas between clinicians and basic researchers (1997 and 2012 at the Cancer Center in Ulm with researchers like Professors Bertino J, former AACR president, and Curtis Harris (first description of p53 with relevance in colon- and rectal cancer tumor biology/carcinogenesis, National Cancer Institute/United States).

Besides conducting translational research, we were always highly interested in involving the patients in treatment decisions and monitoring/improvement of the quality of life which has been rewarding on a very personal level.

Young academic surgeons nowadays are sharing this opinion and will use these developments for their future work. Even established surgeons in surgical societies now are integrating such developments, which we had very early in our minds, into their research programs. Old-fashioned attitudes are gradually changing, as shown by the following statement (in this case, however, mainly relating to modern surgical management tasks): “Surgery is more than operating” (*H. Bauer, General Secretary em. of the German Surgical Society, 3/17*). We recommend to “See the problems of the patients as a whole, build up your philosophy and strategy for improvements, apply modern translational and interdisciplinary research, control your paths stepwise, take into account but not be frustrated by criticism, keeping your aim in mind and above all never give up”.

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