International Journal of Colorectal Disease (2018) 33:1559–1567
https://doi.org/10.1007/s00384-018-3146-z

ORIGINAL ARTICLE

Benefit of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy in patients with isolated peritoneal metastases from colorectal cancer

Pompiliu Piso[1,2] · Kathrin Stierstorfer[3] · Michael Gerken[3] · Monika Klinkhammer-Schalke[3]

Accepted: 13 August 2018 / Published online: 21 August 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

Background Ever since Sugarbaker has established the cytoreductive surgery (CRS) in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), there is a chance of cure for selected patients with peritoneal metastases from colorectal cancer. Objective of this study was to investigate the benefit of CRS and HIPEC compared to other therapy options in patients with isolated synchronous and metachronous peritoneal metastases of colorectal origin in terms of long-term overall survival.

Methods A retrospective population-based cohort study, including 370 patients diagnosed with isolated synchronous and metachronous peritoneal metastases of colorectal origin, was carried out. Therefore, data were acquired from the cancer registry at the Regensburg Tumor Center in Bavaria, Germany. Patients' overall survival (OAS) according to their therapy received was analyzed by means of Kaplan-Meier method and multivariable Cox regression.

Results Overall median survival was 41.6 months for patients treated with CRS and HIPEC, compared with surgery and chemotherapy (24.0 months, log-rank $p = 0.015$), chemotherapy only (14.1 months, $p < 0.001$), surgery only (11.4 months, $p < 0.001$), and best supportive care (7.9 months, $p < 0.001$). This benefit persisted after adjustment for further risk factors in multivariable analysis.

Conclusion The effect of CRS and HIPEC stands out significantly in comparison to all other therapies. The multimodality approach should be a regular option for patients with isolated peritoneal metastases.

Keywords Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Colorectal cancer · Peritoneal metastases · Survival analysis · Population-based analysis

✉ Pompiliu Piso
pompiliu.piso@barmherzige-regensburg.de

Kathrin Stierstorfer
kathrin.stierstorfer@outlook.com

Michael Gerken
michael.gerken@ur.de

Monika Klinkhammer-Schalke
monika.klinkhammer-schalke@ur.de

[1] Department of General and Visceral Surgery, Barmherzige Brueder Hospital Regensburg, Pruefeninger Str. 86, 93049 Regensburg, Germany

[2] Klinik für Allgemein- und Viszeralchirurgie, Krankenhaus Barmherzige Brueder Regensburg, Pruefeninger Str. 86, 93049 Regensburg, Germany

[3] Tumor Center – University Institute of Quality Assurance and Health Services Research, Am BioPark 9, 93053 Regensburg, Germany

Introduction

Peritoneal metastases represent a significant clinical problem, affecting around 10% of all patients with a colorectal cancer [1]. As this entity is associated with a poor prognosis, it is of great importance to find out if selected patients may benefit from other treatment options than best supportive care or palliative systemic chemotherapy [1, 2]. Little is known about the impact of modern systemic chemotherapy on survival of patients with isolated peritoneal metastases [3, 4]. These patients are rarely included in studies because peritoneal metastases cannot be visualized in CT or MRI scans to monitor the therapeutic effect, as compared to liver metastases [5]. Survival data of these patients suggest, nevertheless, that we can achieve with modern systemic chemotherapy today at least 22 months median survival time [6]. This is similar to the experimental arm (CRS and HIPEC) of the only prospective

randomized trial performed for peritoneal metastases—published 13 years ago [7].

The acceptance in the medical oncologic community is limited due to a lack of other high-quality prospective randomized trials [8–10]. Good survival data presented by single institutions obviously is of limited value due to a selection bias. Last year, a first group from the Netherlands presented initial data of a population-based analysis on patients with synchronous peritoneal metastases, showing that about 10% of all patients nationwide were able to receive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with a median survival of 32.3 months. Considering data from the randomized trial, the median survival time was improved by about 10 months [11].

Therefore, we considered of great importance to analyze data available in Eastern Bavaria, as this area has a good functioning cancer registry with regular updates of follow-up data. Similar analyses have been done for liver metastases with relevant data that had enabled the Tumor Center to implement clinical pathways in order to improve the offered treatment options, e.g., increase resectability [12].

Methods

Study design

For an evaluation of the benefit of CRS and HIPEC in patients with peritoneal metastases of colorectal origin in terms of overall survival, a retrospective cohort study was carried out. Therefore, clinical data were obtained from the population-based clinical cancer registry at the Regensburg Tumor Center in Eastern Bavaria, Germany. Following the declaration of Helsinki [13] and the Bavarian Law of Cancer Registration [14], only unidentified information concerning any patient data was used.

Background and data collection

Epidemiological and clinical data from all patients suffering from malignancies, which have been diagnosed and treated in Oberpfalz and Niederbayern (Eastern Bavaria), are collected and registered in the cancer registry of the Regensburg Tumor Center since 1991, covering a population of 2.2 million inhabitants.

Definition and numbers of study group

In the present study, 16,225 patients with colorectal neoplasia, diagnosed between January 2004 and December 2014 and classified with the ICD-10-Code C18-20, by ICD-10-GM-2016 [15], constituted the basic cohort in the present study. Due to incomplete follow-up data or histology of the primary other than adenocarcinoma (e.g., sarcoma, lymphoma, and malignant melanoma), 2575 patients were excluded. Out of the remaining 13,650 patients with histologically confirmed colorectal carcinoma, 648 developed peritoneal metastasis during a median follow-up of 59.8 months (5-year cumulative rate 5.7%). While in 226 patients (34.9%) also other organs had been affected, 422 (65.1%) showed peritoneal tumor spread only (Fig. 1).

Fifty-two (12.3%) patients died within the first 30 days after diagnosis of peritoneal metastases and thus had no chance of receiving an adequate kind of treatment (37 had no therapy, 8 palliative surgery, 7 start of chemotherapy). Since their early death would distort the survival analysis, they were excluded. Eventually, 370 (87.7%) were considered in the survival analysis, comprising 219 patients (59.2%) with synchronous and 151 patients (40.8%) with metachronous peritoneal metastases.

Additionally to the available registry data, details of the treatment were accomplished by reviewing hospital discharge letters from all patients. Two hospitals within the register region are specialized in treatment of peritoneal metastases. Eight hospitals are certified as colorectal cancer centers from German Cancer Society, which perform treatment of peritoneal metastases too.

For a reliable comparison, these patients were divided into five groups according to their therapy received: (1) macroscopically complete cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC), (2) combined surgery and chemotherapy, (3) chemotherapy only, (4) surgery only, and (5) best supportive care (Fig. 1).

Details and selection criteria for treatment by CRS, HIPEC, and systemic chemotherapy

Generally, only affected areas of the abdominal cavity were removed during cytoreductive surgery. This may have included a parietal peritonectomy and/or a visceral resection, mostly as right colectomy, anterior rectal resection, hysterectomy, cholecystectomy, or splenectomy. An omentectomy was mandatory. Common selection criteria for CRS and HIPEC were peritoneal cancer index PCI < 20, score of complete cytoreduction CC 0/1 (no residual nodules or remaining nodules < 2.5 mm, respectively), no extraperitoneal metastases, and no progression under systemic chemotherapy. The common chemotherapy agents intraperitoneally employed were mytomycin C (1 h) and oxaliplatin (30 min), predominantly complemented by systemic administration of 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX), or capecitabine and oxaliplatin, the latter replaced by irinotecan in some cases.

All patients in the groups 2 “combined surgery and chemotherapy” and 4 “surgery only” underwent cytoreductive surgery too (mandatory omentectomy and optional parietal peritonectomy and/or a visceral resection), but information on completeness of cytoreduction was not sufficient for most of the cases.

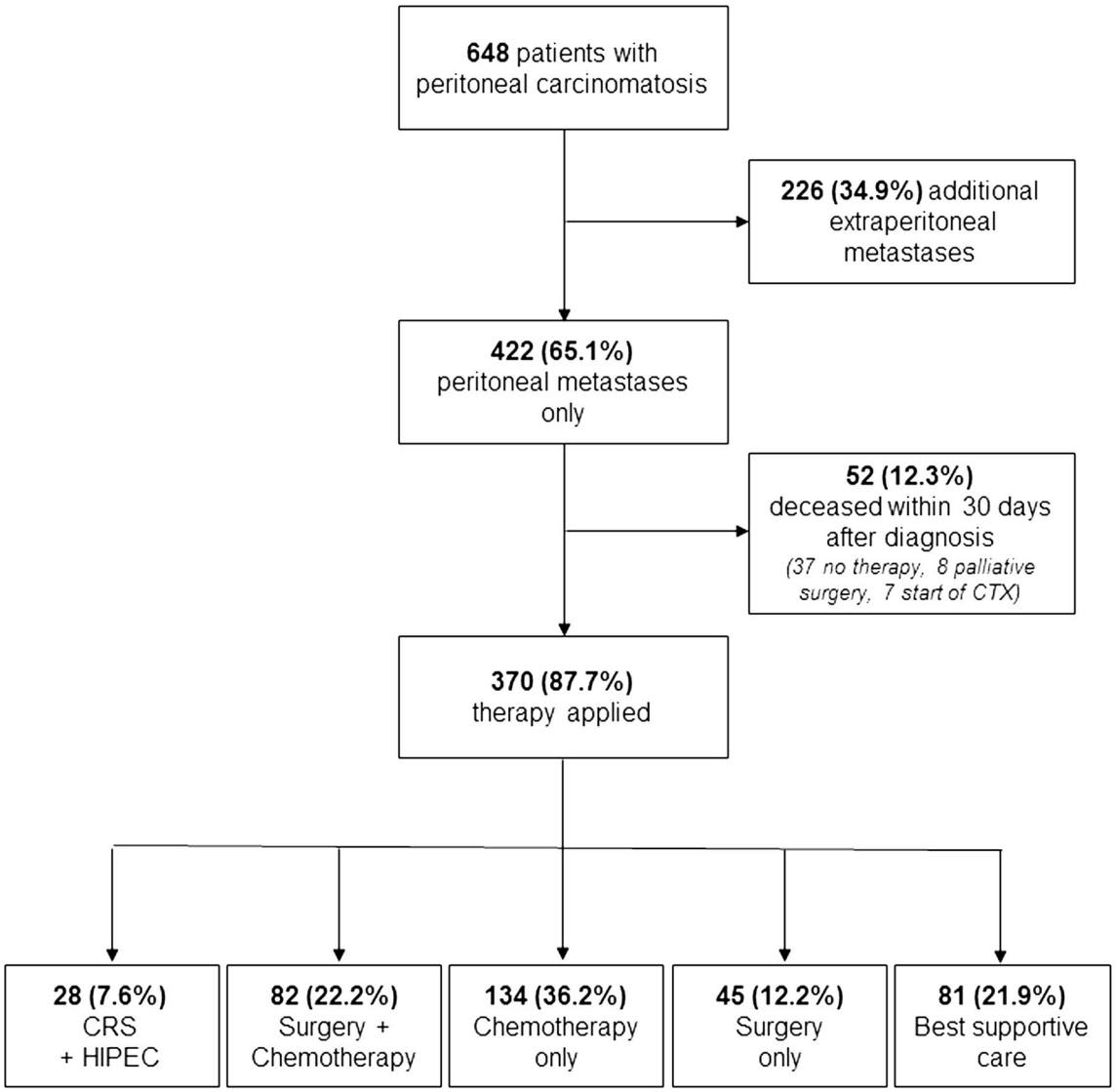

Fig. 1 Study flowchart showing percentages of eligible patients, patients excluded from analysis, and distribution of therapy groups

Fluorouracil and folinic acid (FuFol) was the predominant combination in systemic chemotherapy (76.8% of all patients), a fewer portion receiving the oral fluorouracil prodrug capecitabine (15.3%). In 39.1%, FuFol was complemented with oxaliplatin, and irinotecan was added in 29.8%. Antibody-based target therapy was administered in 34.4% of all cases, predominantly as second-line therapy.

Statistical analysis

For a comparison of the patients' characteristics, *t* test was used for continuous data in case of normal distribution; otherwise, Mann-Whitney *U* test was applied. Pearson's chi-square test was applied for testing independence of categorical variables, and Fisher's exact test in case of small numbers.

To identify factors that are correlated with treatment by CRC and HIPEC, multivariable analysis with binary logistic regression was performed. Estimated odds ratios show the chance of receiving CRC and HIPEC vs. other treatments in dependence on various variables.

Life status and corresponding dates of death and last follow-up of the patients were found out from medical documents, death certificates, and registration offices. Overall survival time was calculated starting from the date of diagnosis of peritoneal metastases until date of death, last date of follow-up, or cut-off date, whichever came first. The follow-up period and survival times were right censored using 30th of June 2015 as a cut-off date, resulting in a median follow-up time of 53.8 months (mean 56.9) in patients with peritoneal metastases only. The overall survival rates (OAS) in the

five different therapy groups were estimated with the Kaplan-Meier method. Survival differences were tested for statistical significance by the two-sided log rank test; the level of significance was set to 0.05.

To determine the influence of further variables on overall survival, we performed multivariable regression analysis using Cox proportional hazard models. The hazard ratios (HR) of the different therapies versus best supportive care as reference category were estimated and subsequently adjusted for the variables sex, age at diagnosis and year of diagnosis, time of metastases, tumor localization and morphology, grading, tumor stage T, and nodal stage N of primary. All analyses were performed using IBM SPSS Statistics, version 23.0.

Results

Patient characteristics and therapy

The therapies administered to the 370 patients showing peritoneal metastasis only were grouped into five categories (Fig. 1): The two largest groups are comprised of chemotherapy only (36.2%) and surgery combined with chemotherapy (22.2%). Surgery only was applied to 45 patients (12.2%), and 28 (7.6%) received a combination of CRS and HIPEC. Nevertheless, the use of HIPEC and CRS has increased in the last 20 years: When between 2004 and 2011, only 6.0% of patients were treated with CRS and HIPEC, and the rate has risen to 9.4% in the period from 2011 to 2014 ($p = 0.216$).

Table 1 Patients' demographic and clinicopathological characteristics according to therapy

		Therapy groups of peritoneal carcinomatosis										
		CRS + HIPEC		Surgery + chemotherapy		Chemotherapy only		Surgery only		Best supp. care		Chi-square
		N	%	*N*	%	*N*	%	*N*	%	*N*	%	*p**
	Total	28	100.0%	82	100.0%	134	100.0%	45	100.0%	81	100.0%	
Sex	Men	14	50.0%	47	57.3%	78	58.2%	19	42.2%	37	45.7%	0.199
	Women	14	50.0%	35	42.7%	56	41.8%	26	57.8%	44	54.3%	
Age at diagnosis (years)	<50	7	25.0%	13	15.9%	12	9.0%	5	11.1%	3	3.7%	
	50–59	10	35.7%	14	17.1%	25	18.7%	6	13.3%	9	11.1%	<0.001
	60–69	9	32.1%	29	35.4%	28	20.9%	7	15.6%	17	21.0%	
	>70	2	7.1%	26	31.7%	69	51.5%	27	60.0%	52	64.2%	
Year of diagnosis	2004–10	12	42.9%	51	62.2%	66	49.3%	24	53.3%	47	58.0%	0.252
	2011–14	16	57.1%	31	37.8%	68	50.7%	21	46.7%	34	42.0%	
Time of carcinomatosis	Synchronous	20	71.4%	53	64.6%	75	56.0%	27	60.0%	44	54.3%	0.389
	Metachronous	8	28.6%	29	35.4%	59	44.0%	18	40.0%	37	45.7%	
Tumor localization	Colon	26	92.9%	71	86.6%	101	75.4%	40	88.9%	69	85.2%	0.048
	Rectum	2	7.1%	11	13.4%	33	24.6%	5	11.1%	12	14.8%	
Tumor morphology	Adenocarcinoma	13	46.4%	59	72.0%	102	76.1%	37	82.2%	70	86.4%	
	Mucinous ca	13	46.4%	19	23.2%	24	17.9%	8	17.8%	7	8.6%	0.004
	Neuroendocrine	2	7.1%	2	2.4%	2	1.5%	0	0.0%	2	2.5%	
	Signet-ring cell	0	0.0%	2	2.4%	6	4.5%	0	0.0%	2	2.5%	
Grading	G1/2	10	35.7%	45	54.9%	68	50.7%	24	53.3%	49	60.5%	
	G3/4	17	60.7%	37	45.1%	64	47.8%	17	37.8%	26	32.1%	0.012
	GX/ns	1	3.6%	0	0.0%	2	1.5%	4	8.9%	6	7.4%	
T stage of primary	T1–3	12	42.9%	27	32.9%	53	39.6%	16	35.6%	42	51.9%	
	T4	14	50.0%	52	63.4%	60	44.8%	23	51.1%	33	40.7%	0.023
	TX/ns	2	7.1%	3	3.7%	21	15.7%	6	13.3%	6	7.4%	
N stage of primary	N0	6	21.4%	19	23.2%	18	13.4%	6	13.3%	16	19.8%	
	N1/2	19	67.9%	56	68.3%	91	67.9%	32	71.1%	56	69.1%	0.395
	NX/ns	3	10.7%	7	8.5%	25	18.7%	7	15.6%	9	11.1%	

X/ns not measurable/not specified

**p* value based on Pearson's chi-square test and Fisher's exact test in case of small numbers

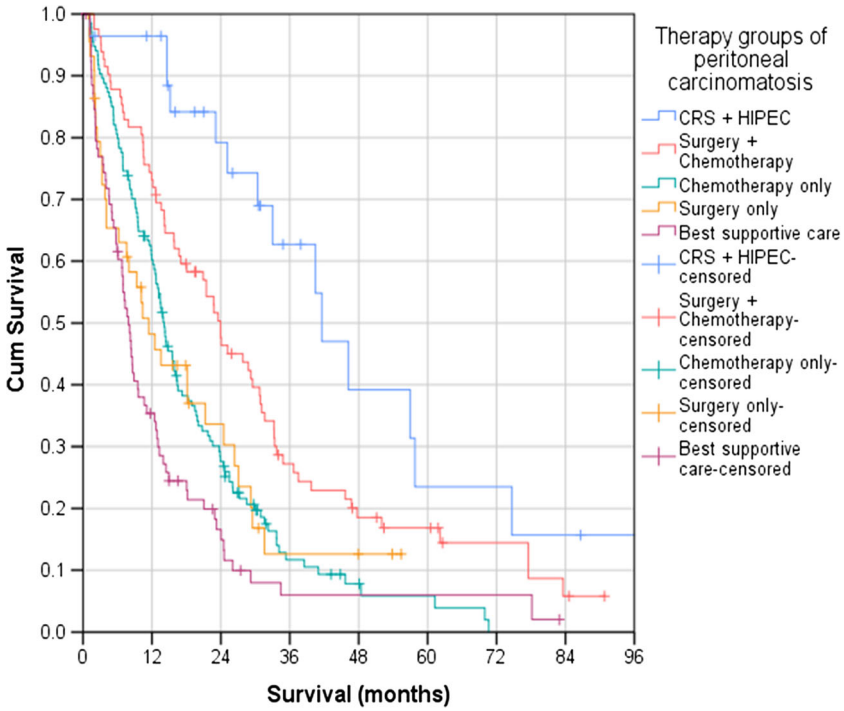

Fig. 2 Overall survival according to treatment with CRS + HIPEC and other therapies in 370 patients diagnosed with isolated synchronous and metachronous peritoneal metastases

The distribution of patient characteristics according to therapy is presented in Table 1. The results are confirmed by a multivariable analysis with binary logistic regression showing the following factors that contributed to the decision whether CRS and HIPEC or a different approach was chosen as a treatment for patients. The chance of being given CRS and HIPEC decreased with the age at diagnosis, although only age above 70 years showed an influence that was statistically significant compared to the youngest group (OR 0.04, $p < 0.001$). In all groups, more synchronous than metachronous metastases of the peritoneum occurred in the patients, yet the highest percentage was found in the CRS and HIPEC therapy set. In terms of the primary tumor, localization in the colon—in contrast to rectum—meant a stronger probability of receiving CRS and HIPEC (OR for rectum 0.24, $p = 0.084$).

Overall survival according to therapy

Overall median survival was 41.6 months for patients treated with CRS and HIPEC, compared with surgery and chemotherapy (24.0 months, log-rank $p = 0.015$), chemotherapy only (14.1 months, $p < 0.001$), surgery only (11.4 months, $p < 0.001$), and best supportive care (7.9 months, $p < 0.001$, Fig. 2, Table 2).

HIPEC and CRS were by far the most successful therapy, although after 5 years, the differences of the overall survival rates were less obvious and diminished.

The gradient between therapy groups seen in univariable Kaplan-Meier analyses persisted when multivariable analysis using Cox proportional hazard model was performed (Table 3). Using best supportive care as reference, CRS and HIPEC yielded the greatest benefit (HR 0.19, CI 0.10–0.36), followed by surgery combined with chemotherapy (HR 0.40,

Table 2 Kaplan-Meier estimates of median, 2-year, and 5-year overall survival according to treatment with CRS + HIPEC and other therapies

Therapy group	Total *N*	*N* death	Median OAS (months)	2-year-OAS (%)	5-year-OAS (%)
CRS + HIPEC	28	15	41.6	79.2	23.5
Surgery + chemotherapy	82	68	24.0	47.7	16.8
Chemotherapy only	134	117	14.1	27.6	5.8
Surgery only	45	33	11.4	33.6	12.6
Best supportive care	81	71	7.9	16.6	6.0
Overall	370	304	14.4	34.2	10.5

OAS overall survival

Table 3 Results of multivariable analysis of overall survival according to therapy and other variables, using Cox proportional hazard model

Variable	Category	Hazard ratio	Lower 95% CI	Upper 95% CI	*P* value*
Therapy group	Best supportive care	1.000	Reference		< 0.001
	CRS + HIPEC	0.191	0.101	0.362	< 0.001
	Surgery + chemotherapy	0.403	0.279	0.582	< 0.001
	Chemotherapy only	0.565	0.407	0.783	0.001
	Surgery only	0.579	0.371	0.906	0.017
Sex	Men	1.000	Reference		
	Women	1.328	1.045	1.686	0.020
Age at diagnosis	< 50	1.000	Reference		0.011
	50–59	0.799	0.485	1.314	0.376
	60–69	1.004	0.628	1.605	0.988
	> 70	1.383	0.883	2.164	0.156
Year of diagnosis	2004–10	1.000	Reference		
	2011–14	0.934	0.727	1.200	0.593
Time of carcinomatosis	Synchronous	1.000	Reference		
	Metachronous	1.595	1.223	2.081	0.001
Tumor localization	Colon	1.000	Reference		
	Rectum	1.025	0.750	1.400	0.876
Tumor morphology	Adenocarcinoma	1.000	Reference		0.643
	Mucinous carcinoma	1.220	0.897	1.661	0.206
	Neuroendocrine carcinoma	0.990	0.375	2.611	0.983
	Signet-ring cell carcinoma	1.133	0.558	2.301	0.730
Grading	G1/2	1.000	Reference		0.006
	G3/4	1.488	1.164	1.901	0.002
	GX/ns	1.094	0.557	2.151	0.794
T stage of primary	T1–3	1.000	Reference		0.319
	T4	1.224	0.942	1.591	0.131
	TX/ns	1.202	0.583	2.481	0.618
N stage of primary	N0	1.000	Reference		0.023
	N1/2	1.436	1.032	1.998	0.032
	NX/ns	2.323	1.174	4.598	0.016

CI confidence interval, *X/ns* not measurable/not specified

**P* value based on Likelihood ratio test

CI 0.28–0.58), and again, similar results were seen for chemotherapy (HR 0.57, CI 0.41–0.78) and surgery only (HR 0.58, CI 0.37–0.91).

Among the variables adjusted for, sex affected the survival time, thus women showing a hazard ratio of 1.33 (CI 1.05–1.69). Age at diagnosis was significant in the whole model, but not between categories of age ($p = 0.011$). Moreover, the time when metastases were diagnosed played an important role. Metachronous metastases were accompanied by worse survival than synchronous ones (HR 1.60, CI 1.22–2.08). Year of diagnosis, localization, T stage, and morphology of the primary tumor did not correlate significantly with death rate. In comparison to that, high-grading G3/4 (HR 1.49, CI 1.16–1.90) and positive nodal stage N1/2 (HR 1.44, CI 1.03–2.00) showed significant effects on overall survival.

Discussion

Paul Sugarbaker and Francois Gilly have introduced in the clinical practice at the End of the 80s cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as a new and innovative method to treat peritoneal metastases which otherwise were considered to be a fatal condition as most patients died within 1 year [16, 17]. The German Society of General and Visceral Surgery has founded a Peritoneal Group for the study and implementation of this multimodality treatment strategy [18]. This group was responsible for the training of new centers, for studies, e.g., COMBATAC study, for the implementation of a national HIPEC registry including data of all treated patients nationwide [19]. Finally, a recommendation for cytoreductive surgery and HIPEC in selected patients

was formulated. This is published in the present S3 guideline for colorectal cancer with direct impact for the daily routine as all patients should be discussed within a Multi-Disciplinary Team of certified centers [20].

The area of Eastern Bavaria includes about 2.2 Mio inhabitants, and the data of all patients is recorded by the Tumor Center Regensburg in a regional Cancer Registry. This is one of the most accurate Cancer Registries nationwide including all patients affected by colorectal cancer.

One of the first and meanwhile the largest center for the treatment of peritoneal metastases is located in Regensburg. This had for certain influenced the regional accessibility of patients for this treatment option and had increased the awareness towards this method within the medical community. The percentage of patients treated by cytoreductive surgery and locoregional chemohyperthermia increased due to this implementation to 9.4% of all patients with isolated peritoneal metastases. A slightly stronger rise is described in the newest study of Razenberg from 2016: While from 2005 to 2009, 10% of the patients received this multimodal treatment approach, in the years between 2010 and 2014, the number increased to 23% [21].

Having mentioned that, one can realize that the selection criteria for appropriate patients were defined and well-known in the area, nevertheless, due to several personal interactions of different medical teams [22]. Patients offered cytoreductive surgery and hyperthermic intraperitoneal chemotherapy had isolated peritoneal metastases and limited extent of peritoneal spread, in whom a complete (macroscopic) surgical cytoreduction seemed to be achievable [23]. Most of the patients with CRS and HIPEC had synchronous metastases (71%) and a colon cancer (93%). Therefore, the regional treatment consisting of chemotherapy and hyperthermia was considered to be effective only in such patients and not in those with bulk residual disease, being in line with available literature data [24].

The impressive median survival data of patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in our study (42 months) reflects a good patient selection and is better than the population-based data from the Netherlands (32 months) or data published by national or multi-institutional registries [25].

There are several national and international published registry studies, matched pair analysis, large multi-institutional studies, and reports on CRS and HIPEC from many single institutions [26]. They all show median survival data of up to 48 or even 60 months with correspondent 5-year survival rates of 30 to 50% [5, 27–35]. However, even the survival of patients treated by surgery and systemic chemotherapy was better than historical data and similar to single institution reports, e.g., from Bordeaux in France [30, 36]. There may be an explanation for this: In patients responding to systemic chemotherapy, due to the prolonged survival and motivation for further treatment, surgery including debulking resection has been performed not only for both relief of symptoms but also for prolongation of survival. This is a relevant finding as 22% of all patients received this treatment in our series. However, most of the patients were treated either by best supportive care (22%), by palliative systemic chemotherapy (36%) or surgery only (12%).

One important prognostic factor was HIPEC. The hazard ratio as compared to best supportive care (HR = 1) and other therapies ranging from 0.40 to 0.58 was 0.19. The impact of HIPEC on survival was positive; however, treated patients had a limited and resectable disease. Regarding HIPEC itself: a prospective phase III trial that investigated and randomized HIPEC (PRODIGE 7) showed no significant differences in postoperative mortality, and long-term overall and recurrence-free survival between the HIPEC and non-HIPEC arm [30].

Metachronous metastases had a poorer prognosis (HR 1.6); however, rectal cancer as primary tumor was not having a negative impact on prognosis as compared to colon cancer ($p = 0.88$). This was one of the initial presumptions, not confirmed by further studies, therefore concordant to our results.

The treatment of peritoneal metastases reminds us of how things evolved in the treatment of isolated liver metastases. Without any prospective randomized trial, resection became standard treatment option. Liver metastases are, however, more frequent than peritoneal ones, resectability can be achieved in half of all patients, and the awareness within the medical community regarding then importance of surgery as being first choice therapy is much higher than for peritoneal metastases. This was shown by a recent analysis of our group with concern to liver metastases and long-term results [12]. According to surveys performed among medical and surgical oncologist, just half of them are aware that CRS and HIPEC exists at all and can be offered patients with colorectal cancer and peritoneal metastases [37].

Being aware of the selection bias in this retrospective analysis, the survival of patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is so much better compared to other options that clinicians have to asses every patient with stage IV colorectal cancer according to meanwhile known and accepted criteria—also presented in the present study [38]. A MDT will discuss patients with synchronous and metachronous peritoneal metastases and therefore have to be aware of selection criteria and long-term results following multimodality treatment strategies consisting of CRS, HIPEC, and systemic chemotherapy [39, 40].

References

1. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, François Y, Vignal J, Gilly FN (2000) Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 88(2):358–363
2. Piso P, Glockzin G, von Breitenbuch P, Sulaiman T, Popp F, Dahlke M, Esquivel J, Schlitt HJ (2009) Patient selection for a curative approach to carcinomatosis. Cancer J 15(3):236–242
3. Piso P, Arnold D (2011) Multimodal treatment approaches for peritoneal carcinosis in colorectal cancer. Dtsch Arztebl Int 108(47): 802–808
4. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ III (2010) Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer 116(16):3756–3762
5. Klaver CEL, Musters GD, Bemelman WA, Punt CJA, Verwaal VJ, Dijkgraaf MGW, Aalbers AGJ, van der Bilt JDW, Boerma D, Bremers AJA, Burger JWA, Buskens CJ, Evers P, van Ginkel RJ, van Grevenstein WMU, Hemmer PHJ, de Hingh IHJT, Lammers LA, van Leeuwen BL, Meijerink WJHJ, Nienhuijs SW, Pon J, Radema SA, van Ramshorst B, Snaebjornsson P, Tuynman JB, te Velde EA, Wiezer MJ, de Wilt JHW, Tanis PJ (2015) Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial. BMC Cancer 15:428
6. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, Saltz L, Punt CJA, Koopman M, Tournigand C, Tebbutt NC, Diaz-Rubio E, Souglakos J, Falcone A, Chibaudel B, Heinemann V, Moen J, De Gramont A, Sargent DJ, Grothey A, Analysis and Research in Cancers of the Digestive System (ARCAD) Group (2016) Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol 17(12):1709–1719
7. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H (2008) 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 15(9):2426–2432
8. Chua TC, Yan TD, Saxena A, Morris DL (2009) Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. Ann Surg 249(6):900–907
9. Beckert S, Struller F, Horvath P, Falcke A, Königsrainer A, Königsrainer I (2015) Overall morbidity but not mortality is increased in elderly patients following cytoreductive surgery and HIPEC. Langenbeck's Arch Surg 400(6):693–698
10. Simkens GA, van Oudheusden TR, Braam HJ, Wiezer MJ, Nienhuijs SW, Rutten HJ, van Ramshorst B, de Hingh IH (2016) Cytoreductive surgery and HIPEC offers similar outcomes in patients with rectal peritoneal metastases compared to colon cancer patients: a matched case control study. J Surg Oncol 113(5):548–553
11. Razenberg L, van Gestel Y, Creemers G-J et al (2015) Trends in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of synchronous peritoneal carcinomatosis of colorectal origin in the Netherlands. Eur J Surg Oncol 41(4):466–471
12. Hackl C, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ (2014) Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. BMC Cancer 14:810
13. Word Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/20activities/10ethics/10helsinki/DoH-Oct2013-JAMA.pdf. Accessed 25 May 2016
14. Landtag des Freistaates Bayern. Gesetz über das bevölkerungsbezogene Krebsregister Bayern (BayKRG). http://www.krebsregister-bayern.de/Documents/baykrg2005.pdf. Accessed 27 May 2016
15. DIMDI: Deutsches Institut für Medizinische Dokumentation und Information. ICD-10-WHO. https://www.dimdi.de/static/de/klassi/icd-10-who/kodesuche/index.htm. Updated May 10, 2016. Accessed 26 May 2016
16. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, de Simone M, Barone R, Yonemura Y, Cavaliere F, Quenet F, Gutman M, Tentes AAK, Lorimier G, Bernard JL, Bereder JM, Porcheron J, Gomez-Portilla A, Shen P, Deraco M, Rat P (2004) Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 22(16):3284–3292
17. Sugarbaker PH (1995) Peritonectomy procedures. Ann Surg 221(1):29–42
18. Glockzin G, Rochon J, Arnold D, Lang SA, Klebl F, Zeman F, Koller M, Schlitt HJ, Piso P (2013) A prospective multicenter phase II study evaluating multimodality treatment of patients with peritoneal carcinomatosis arising from appendiceal and colorectal cancer: the COMBATAC trial. BMC Cancer 13:67
19. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A (2012) Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg 99(5):699–705
20. Pox C, Aretz S, Bischoff SC, Graeven U, Hass M, Heußner P, Hohenberger W, Holstege A, Hübner J, Kolligs F, Kreis M, Lux P, Ockenga J, Porschen R, Post S, Rahner N, Reinacher-Schick A, Riemann JF, Sauer R, Sieg A, Scheppach W, Schmitt W, Schmoll HJ, Schulmann K, Tannapfel A, Schmiegel W, Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e. V, Deutschen Krebshilfe e. V (2013) S3-guideline colorectal cancer version 1.0. Z Gastroenterol 51(8):753–854
21. Razenberg, Lieke GEM, Lemmens et al (2016) Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: results of a population-based study. Eur J Cancer 65:113–120
22. Van Oudheusden TR, Braam HJ, Bienhuijs SW et al (2015) Poor outcome after cytoreductive surgery and HIPEC for colorectal peritoneal carcinomatosis with signet ring cell histology. J Surg Oncol 111:237–242
23. Jacquet P, Sugarbaker PH (1996) Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH (ed) Peritoneal carcinomatosis: principles of management; Cancer treatment and research vol. 82. Springer US, Boston, pp 359–374
24. Piso P, Leebmann H, Marz L et al (2015) Cytoreductive surgery for malignant peritoneal tumors. Chirurg 86(1):38–46
25. Ceelen WP, Bracke ME (2009) Peritoneal minimal residual disease in colorectal cancer. Mechanisms, prevention, and treatment. Lancet Oncol 10(1):72–79
26. Tabrizian P, Jayakrishnan TT, Zacharias A, Aycart S, Johnston FM, Sarpel U, Labow DM, Turaga KK (2015) Incorporation of diagnostic laparoscopy in the management algorithm for patients with peritoneal metastases: a multi-institutional analysis. J Surg Oncol 111: 1035–1040
27. Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, Pitot HC, Grothey A, Alberts SR, Sargent DJ (2012) Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment

group phase III trials N9741 and N9841. J Clin Oncol 30(3):263–267
28. Goere D, Malka D, Tzanis D et al (2013) Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg 257(6):1065–1071
29. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, Ferron G, Guilloit JM, Meeus P, Goéré D, Bonastre J (2009) Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 27(5):681–685
30. Quenet F, Elias D, Roca L et al (2018) A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol 36 (suppl; abstr LBA3503)
31. Elias D, Mariani A, Cloutier A-S, Blot F, Goéré D, Dumont F, Honoré C, Billard V, Dartigues P, Ducreux M (2014) Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. Eur J Surg Oncol 40(11):1467–1473
32. Elias D, Honore C, Dumont F et al (2011) Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. Ann Surg 254(2):289–293
33. Braam HJ, van Oudheusden TR, de Hingh et al (2014) Patterns of recurrence following complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. J Surg Oncol 109(8):841–847
34. Desolneux G, Maziere C, Vara J et al (2015) Cytoreductive surgery of colorectal peritoneal metastases: outcomes after complete cytoreductive surgery and systemic chemotherapy only. PLoS One 10(3):e0122816
35. Elias D, Faron M, Iuga BS, Honoré C, Dumont F, Bourgain JL, Dartigues P, Ducreux M, Goéré D (2015) Prognostic similarities and differences in optimally resected liver metastases and peritoneal metastases from colorectal cancers. Ann Surg 261(1):157–163
36. Pelz JOW, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL, Maeder U, Germer CT, Kerscher AG (2010) Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. BMC Cancer 10:689
37. Braam HJ, Boerma D, Wiezer MJ, van Ramshorst B (2015) Cytoreductive surgery and HIPEC in treatment of colorectal peritoneal carcinomatosis: experiment or standard care? A survey among oncologic surgeons and medical oncologists. Int J Clin Oncol 20(5):928–934
38. Piso P, Arnold D, Glockzin G (2015) Challenges in the multidisciplinary management of stage IV colon and rectal cancer. Expert Rev Gastroenterol Hepatol 9(3):317–326
39. Goere D, Souadka A, Faron M et al (2015) Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. Ann Surg Oncol 22(9):2958–2964
40. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP (2006) Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg 243(2):212–222