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Did the uptake of new treatment options change the treatment strategy in patients with colorectal cancer and primary non-resectable metastases?

The results of large population-based survey in Germany 2005-2007

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Abstract

Objectives: The survey was initiated to gain insights into the changes of treatment patterns In treatment of metastatic colorectal cancer and the implementation of the results of clinical trials in daily practice.

Patients and methods: A representative sample of centres (82) was selected with regard to the distribution of treated prevalence in colorectal cancer in institutions (university hospitals, community hospitals, office based oncologists) and regional population density. The physicians reported all pts. with a treatment decision in colorectal cancer in the respective reporting period May 06-April 07. The database contains 3254 pts. with a retrospective record of their entire treatment history. The treatment patterns were analysed in the whole patient group and in subgroups according to resectability of metastases, the treatment objectives (esp. secondary resectability of metastases), used systemic treatment regimen, age, concomitant diseases and performing institution type. The statistics were performed in SPSS by bivariate analyses with two-sided Chi-square test. In the next step the decisive parameters for treatment choice were defined by logistic regression in multivariate analysis.

Results: The clinical trial data was taken up very soon in clinical reality. The correlation of drug efficacy and resectability of metastases was transferred into the disease management of colorectal cancer. The patient share with treatment objective "secondary resection of metastases" increased significantly (18% 2004 vs 27% 2006-07, p=0,000%). In this subgroup the patient share treated with targeted therapy was significantly higher than in patients with other treatment objectives (34% vs. 19%, p=0,000%).

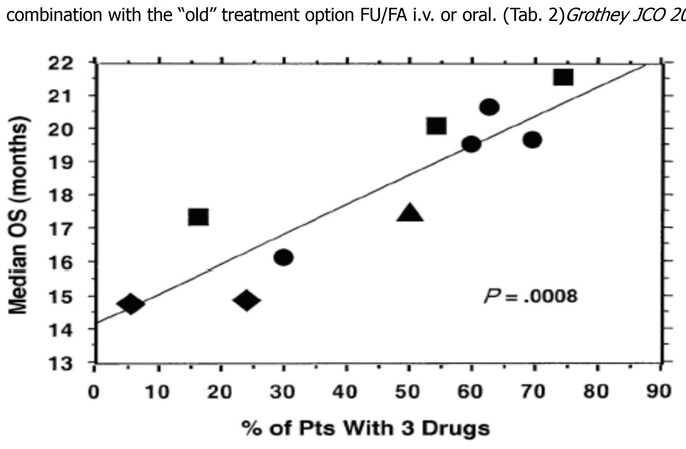
Conclusion: The method used for creation of the database and for the statistic analyses has been proven as appropriate for the objectives of this survey. The resectability of metastases is recognized as an important treatment objective. Therefore, targeted therapy was implemented more frequently in treatment regiments for patients deemed secondary resectable, compared to other treatment aims.

Background

Since the 90s treatment options in metastatic colorectal cancer have developed rapidly. (Tab. 1)

Year	Available effective drugs
< 1995	5FU/FA
> 1995	5FU/FA iv or oral
> 2000	5FU/FA iv or oral, Oxaliplatin, Irinotecan
> 2005	5FU/FA iv or oral, Oxaliplatin, Irinotecan Bevacizumab, Cetuximab

The new anticancer agents Ironotecan and Oxaliplatin displayed impressive effectiveness in clinical trials and led to longer median overall survival of pts with metastastic colorectal cancer when used in combination with the "old" treatment option FU/FA i.v. or oral. (Tab. 2) *Grothey JCO 2004*



Liver metastases are the most frequent localisation of metastases in pts. with metastatic colorectal cancer (75%). The majority of them (80%) are not primary resectable. 30-40% of patients with primary resection of liver metastases live >= 5 years after the diagnosis of metastatic cancer. The secondary resection enables a survival benefit comparable with the primary resection. With the availability of new effective anticancer agents secondary resectability became the focus of clinical research in order to increase the overall survival of patients without primary resection of liver metastases. Tab.3

year	Development of Treatment Objective „Secondary Resectability of Metastases"
1999	5-yr survival in pts. with primary resectability 30-40%
2002	Comparable survival in pts. with secondary resectability reported
2004-5	Definition of secondary resection as Therapy Objective (i.e. „Oncosurge")
2005	Retrospective analysis shows the correlation of effectiveness (Response Rate, RR) und resectability (R0-Rate)
2005-6	Clinical Trials Phase II- III : increased RR-Rate with Cetuximab und Bevacizumab

Fong et al. 1999, Adam et al. 2002, Poston et al., 2005, Folprecht et al. 2005

With this background the following questions were posed:

1. Were the results of clinical trials implemented into clinical reality in Germany?
2. Did the treatment strategy of 1st line therapy of metastatic colorectal cancer change between 2005-2007?
3. Were biologicals as new treatment options implemented more frequently in patients with the new treatment strategy in the 1st line?

TherapyMonitor as a large population based survey offered a convincing method of answering these questions.

Method

Since 1998 O.I.s) has consistently conducted TherapyMonitor for metastatic colorectal cancer and many other cancer types. The analysis published here is based on data from annual TherapyMonitor surveys in 2004 (698 pts.), 2005 (678 pts.) and monthly continuous surveys in 5/2006-4/2007 (1079 pts.).(Tab.4)

Parameter	TM 2004	TM 2005	TM 2006-2007
Age Median (years)	65	65	65
Metastases %			
Liver	68	78	74
Lung	23	22	24

The sample in all TherapyMonitor surveys is representative and based on the structural analysis of treated prevalence in metastatic colorectal cancer in Germany regarding type of treatment institution, specialty and regional density of population. The centres in the sample represented ~10% of treated prevalence with metastatic colorectal cancer in Germany.

Therapy Monitor	2004		2005		5/2006-4/2007	
Sample	*Pts*	*Centres*	*Pts*	*Centres*	*Pts*	*Centres*
UICC 0-III (M0)	493	46			1775	82
UICC IV (M1)	698	48	678	73	1476	
Total	1191	95	678	73	3254	82

Each case history was reported retrospectively based on patient records by physicians or nurse on site. O.I.s) offered EDC (SecuTrial™) or optionally CRF on paper for patient recording in order to avoid a technological bias. The patient records were checked by O.I.s) monitors with regard to plausibility and completeness ensuring that the data base contained only completed and plausible patient records. O.I.s) performed the analysis in SPSS. The CRF method and results were evaluated by Prof. Arnold (University Hamburg)and Prof. Schmoll (University of Hale/Salle). Analysis of independent variables in the collected data and comparison with published data indicated that the TherapyMonitor sample was highly consistent and representative and supported the reliability of the reported results.

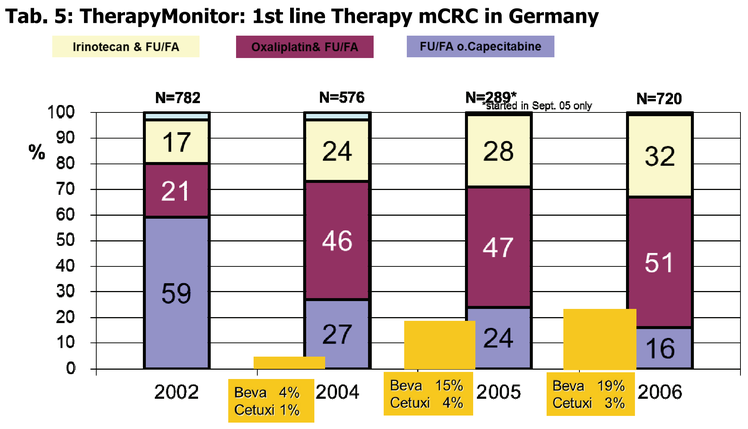
Results

1. Were the results of clinical trials implemented into clinical reality in Germany?

Since 2002 the 1st line therapy of metastatic colorectal cancer has changed significantly. The extended overall survival following the use of all available treatment options was reported in multiple clinical trials up to 2002.

TherapyMonitor survey in Germany (Tab.5) in 2002 demonstrated the predominant use of classical treatment options FU/FA i.v. or mono. (59% pts. with 1st line chemotherapy). Only a minority of pts (32%) received the new agents irinotecan or oxaliplatin in the 1st line, generally combined with FU/FA. The treatment algorithm reversed completely from 2002 to 2004. TherapyMonitor 2004 demonstrated the predominant use of the new agents irinotecan or oxaliplatin in the 1st line (70% pts with chemotherapy) with only 27% receiving FU/FA i.v. or oral in a mono therapy. Use of the most innovative treatment options – the biologicals bevacizumab and cetuximab – was only reported in TherapyMonitor 2004 in clinical trials (4%/1% pts.) The approval of bevacizumab for the 1st line therapy of metastatic colorectal cancer followed in January 2005. The results of clinical trials resulted in the fast uptake of pts. treated with bevacizumab in to the treatment algorithm – up to 19% in the Therapy Monitor sample 2006-2007.

Tab. 5: TherapyMonitor: 1st line Therapy mCRC in Germany



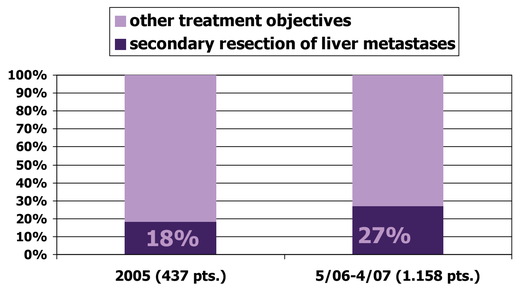
TherapyMonitor thus verified that the results of clinical trials were quick to be introduced into clinical reality in the treatment of metastatic colorectal cancer in Germany. The majority of patients in the 1st line treatment of metastastic colorectal cancer had access to the effective new agents promising the benefit of extended overall survival.

2. Did the treatment strategy of 1st line therapy of metastatic colorectal cancer change between 2005-2007?

The TherapyMonitor 2006-07 sample contained 25% of pts with primary resectable liver metastases – this proportion corresponds with the published data, i.w. van Velde, ESMO 2005 .

Secondary resection of liver metastases as a treatment objective was defined and focused on following approval of the new effective anticancer agents in the 1st line treatment of metastatic colorectal cancer. Clinical trials of biologicals with treatment endpoint „resectability of liver metastases" verified the effectiveness with an impressively increased R0-Rate. The results of clinical trials had an immediate impact, in clinical reality, on the development of treatment strategy in 1st line treatment of patients without primary resection of liver metastases in 2005-2007. Oncologists accept that secondary resection is an important treatment objective.

According to TherapyMonitor 2005 there were only 18% of pts. with secondary resection of liver metastases in Germany. Only 1 year later the rate of patients with secondary resection increased significantly to 27%. (p=0,00, Fisher's Exact Test). (Tab 6)

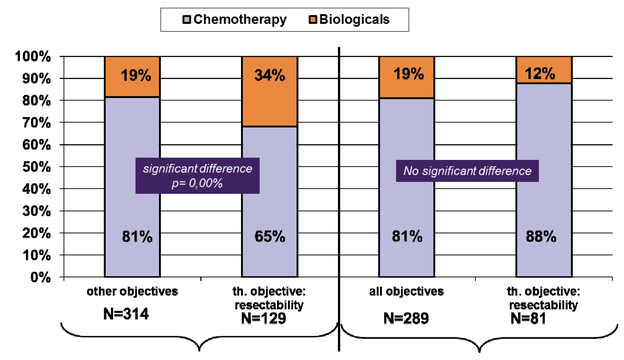


3. Were biologicals as new treatment options implemented more frequently in patients with the new treatment strategy in the 1st line?

The results of clinical trials regarding the effectiveness of bevacizumab or cetuximab in non primary resectable liver metastases had not yet been published in 2005. Both biologicals were used in 12% of pts. with non resectable liver metastases (7% bevacizumab, 5% cetuximalb) in 1st line treatment without any significant difference regarding treatment objectives.

The publication of CRYSTAL and NO 16966 results had an immediate impact, not only on the treatment strategy, but on the choice of the anticancer agents too. In TherapyMonitor 2006-07 27% of patients were treated with the treatment objective "secondary resectability of liver metastases"and 34% of them were treated with biologicals (24% bevacizumab, 8% cetuximab, 2 % others). The use of biologicals in pts. with non resectable liver metastases and other treatment objectives was significantly lower at 19% (16% bevacizumab, 3% cetuximab). (p=0,00%, % Chi-Square Test, Fisher´s Exact Test)

Tab 6: Therapy Monitor mCRC: 1st line Therapy in pts without primary resection of liver metastases: Use of Biologicals by Treatment Objective (2005 vs.´06-´07)



TherapyMonitor dealt with all individual, diagnostic and clinical variables available which could have an impact on the treatment choice in the 1st line treatment of metastatic colorectal cancer. Therefore, it was decided to check the treatment objective "resectability of liver metastases" and other variables with respect to their impact on the use of biologicals.

TherapyMonitor data allowed the building of profiles for patients with different treatment options in1sline therapy regarding individual characteristics and treatment management factors, (Tab. 7) including the treatment objective "resectability of liver metastases". The analysis was based on 690 pts. with 1st line systemic treatment without primary resection of metastases.

Variable	Bevacizumab (n=218)	Cetuximab (n=30)	Oxaliplatin +FU/FA (n=480)	Capecitabine (n=48)
Age (Median)	65	58	67	78
KI% (Median)	90	90	90	70
Concomitant disease reported %	55	37	60	79
CHD reported %	11	13	17	50
Th. objective: Resectability of M.%	37	53	25	8
1 localisation of M. %	55	53	43	48
Th. initiated in non-univ. cancer centres %	65	85	85	56
Th. initiated by office based oncologists %	31	0	13	20

The established profiles differed significantly in characteristics and variables and should therefore be considered as parameters for the choice of treatment. In order to find out the variable with the highest impact on the choice of biologicals a bivariate analysis was performed and significant parameters were identified. (Tab.8)

Variable	Significant impact on the choice of biologicals in the 1st line therapy	p-value
Age (on 31.12.2006)	+	0,0%
Concomitant diseases reported	-	2,7%
> 1 metastases	-	2,0%
CHD	-	0,1%
COPD	-	1,7%
Metastases in lymph nodes reported	-	1,0%
Treatment objective „Resectability of metastases"	+	0,0%

We considered multiple factors to have a simultaneous impact on treatment choice. From all the significant factors (detected in bivariate analysis) it was demonstrated in a simultaneous multivariate analysis (logistic regression) that only the factors „age" (median 65 y.,p=0,1%) and „treatment objective resectability of metastases" (p=2,7%) had a significant impact on the treatment choice of biological. The patients with the treatment objective „resectability of liver metas- tases" were treated signifycantly more frequently with the new biologicals than patients with other treatment objectives. This treatment strategy was based on the results of clinical trials.

On the other hand, patients older than 65 had significantly limited access to the new biologicals – without any evidence in clinical trials. In clinical reality the age >=65 y. (=median age) seemed to be a threshold for the use of biologicals in 1st line treatment of metastatic colorectal cancer in Germany.

Conclusions

1. The 1st line treatment of metastatic colorectal cancer has changed fundamentally since 2000. Clinical trials demonstrated the increased effectiveness of new anticancer agents leading to extended overall survival. The new agents were included into the treatment algorithm from the be ginning in the 1st line. The majority of patients in Germany benefited from these innovations immediately.

2. The next stage demonstrated that the new agents and especially the biologicals were effective in non-resectable liver metastases. The new therapy strategy for secondary resection of liver metastases was developed and was adopted in clinical reality following impressive data from clinical trials. TherapieMonitor surveys in 2005 and 2006-07 in Germany demonstrated the fast uptake of results from clinical trials regarding new agents and a new treatment strategy, "secondary resections of liver metastases", in clinical reality.

3. TherapyMonitor, furthermore, showed that the choice of 1st line therapy resulted from multiple factors acting simultaneously. Following the results of clinical trials the biologicals were used significantly more frequently in patients with the treatment objective, "secondary resectability of metastases", than in patients with other treatment objectives in 1st line treatment. In addition to the results of clinical trials and the established effectiveness of a new treatment approach, there are individual characteristics, such as the age of a patient, that were demonstrated to have a significant impact on the treatment choice. In order to avoid limited access to the innovative treatment approach for the majority of cancer patients, the median age of cancer patients should be considered as an important factor in clinical trial design.

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