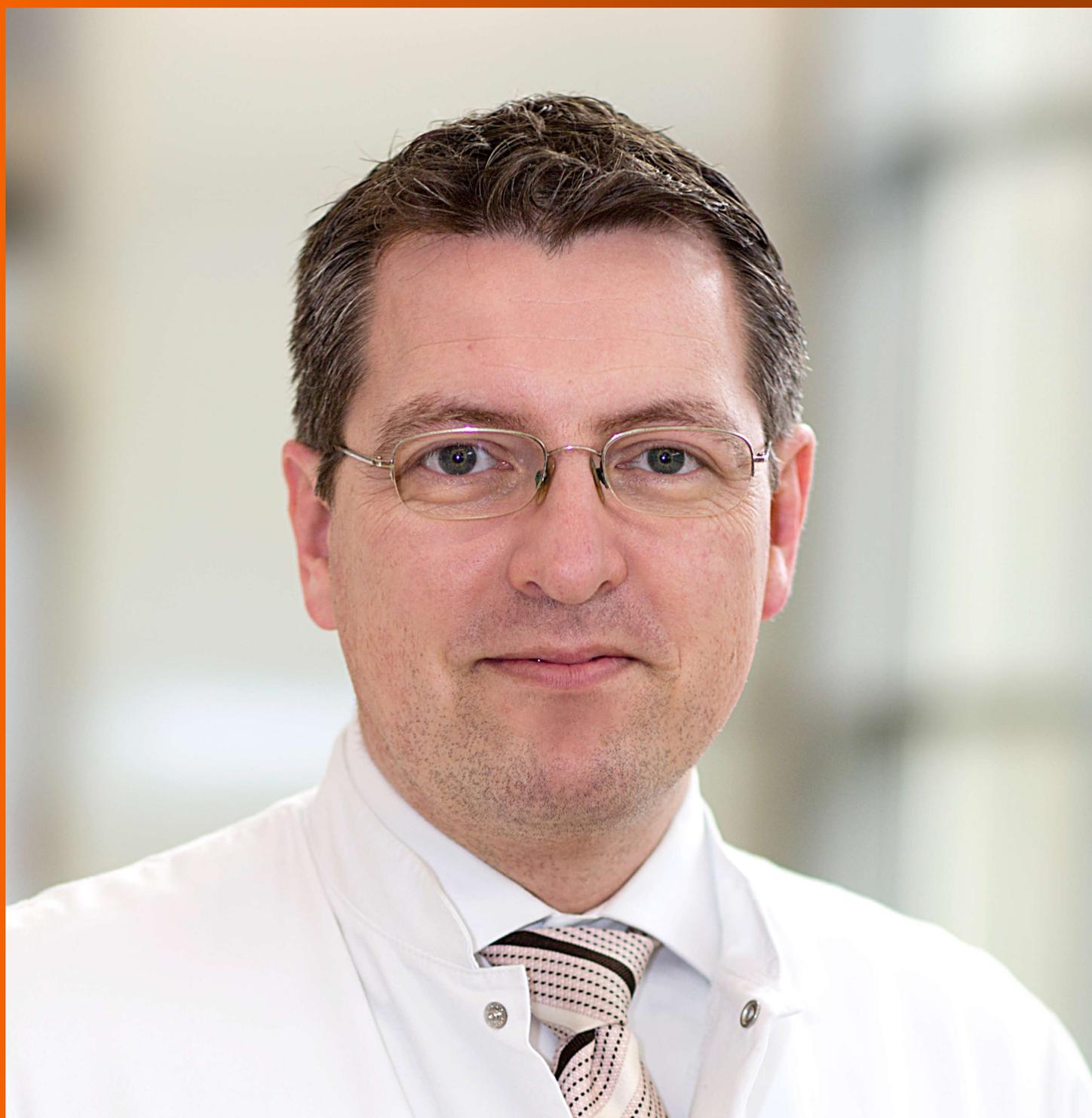


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Retrospective Study

Impact of homogeneous pathologic response to preoperative chemotherapy in patients with multiple colorectal liver metastases

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Abstract

AIM

To analyze the homogeneity of pathologic response to preoperative chemotherapy (PRPC) after chemotherapy in patients with multiple liver metastases (LM).

METHODS

From September 2011 to August 2014, patients with at

least two LM undergoing preoperative chemotherapy prior to resection were included in this retrospective, single-center study. The endpoints were PRPC homogeneity (according to both the Rubbia-Brandt and MD Anderson classifications), the impact of PRPC on the MDT decision, factors associated with homogeneous PRPC and overall survival of patients with *vs.* without homogeneous PRPC.

RESULTS

seventy-three patients with a total of 88 liver resections (including 15 two-stage procedures) were included in the study. The homogeneous PRPC rate was 55% according to the Rubbia-Brandt classification and 53% according to the MD Anderson classification. The MDT decision was modified by the PRPC in only 2.7% of patients ($n = 2$).

CONCLUSION

The PRPC was homogeneous in only one half of patients and had very little influence on the MDT decision.

Key words: Liver metastases; Pathological response; Homogeneity; Preoperative chemotherapy; Colorectal cancer

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Core tip: Pathologic response to preoperative chemotherapy (PRPC) is correlated with survival after resection of liver metastases. This study analyzed the homogeneity of PRPC after chemotherapy in patients with multiple liver metastases. The study underlines that homogeneous PRPC rate was low (55% according to the Rubbia-Brandt classification and 53% according to the MD Anderson classification) and has little impact on the multidisciplinary team meeting decision (modified by the PRPC in only 2.7% of patients).

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INTRODUCTION

One half of patients with colorectal cancer develop liver metastases (LM) with a 5-year overall survival rate of 50%^[1,2]. The curative management of LM includes surgical resection and chemotherapy (combined with targeted therapies, in some cases)^[3-5].

Three main classifications of pathologic response to preoperative chemotherapy (PRPC) have been described (Rubbia-Brandt classification^[6], MD Anderson

classification^[7] and the Sebahg classification)^[8]. Two of these classifications, the Rubbia-Brandt classification and the MD Anderson classification, are used in routine clinical practice in our institution. The Rubbia-Brandt classification^[6] is based on whether or not chemotherapy induces fibrosis in the metastasis, whereas the MD Anderson classification reflects the proportion of metastatic tumor cells that remain viable after chemotherapy^[7]. A complete PRPC is defined as the absence of tumor cells at the liver site in both classifications^[7]. However, the two classifications differ markedly in patients with multiple LM. The Rubbia-Brandt classification is based on the worst nodule, whereas the MD Anderson classification is based on the mean PRPC of all the nodules. Furthermore, the best category (in terms of survival) in the Rubbia-Brandt classification includes both complete tumor regression (tumor regression grade 1, TRG1) and a major response (TRG2), whereas the best category in the MD Anderson classification consists solely of a complete response^[9-11].

PRPC scores appear to be correlated with survival after LM resection^[6] but the really use of PRPC is a daily question. PRPC may be useful in three situations in which adjuvant chemotherapy may be required in patients with multiple LM, provided a homogeneous response is observed for all LM: (1) after neoadjuvant chemotherapy in a perioperative management setting; (2) between surgical stages in patients scheduled for two-stage hepatectomy for bilobar LM; and (3) in the case of recurrence. In these situations, PRPC could help to guide modification of the chemotherapy regimen when necessary.

For example, in the two-stage hepatectomy setting, Mentha *et al.* addressed this question by studying the difference in TRG grade between the two operative specimens from a given individual patient as a measure of chemotherapy resistance due to interruption of treatment or as a result of the immunosuppression that follows a surgical procedure^[12]. However, Sebahg *et al.*^[8] did not assess the homogeneity of the PRPC in individual patients or whether a homogeneous PRPC had an impact on prognosis. Recently, Sebahg *et al.* reported for the first time a 19.7% rate of PRPC heterogeneity.

The objective of the present study was therefore to analyze the homogeneity of PRPC after chemotherapy and to assess the impact of PRPC on the multidisciplinary team meeting (MDT) decision, on survival and on the management of two-stage procedures.

MATERIALS AND METHODS

Population

From September 2011 to August 2014, patients undergoing resection of at least two colorectal cancer LMs, who had received preoperative chemotherapy and for whom both PRPC classifications were available

Table 1 Details of the Rubbia-Brandt and MD Anderson classifications

The Rubbia-Brandt classification	The MD Anderson classification
TRG1: Absence of residual cancer and large amount of fibrosis	Complete response: No residual cancer cells
TRG2: Rare residual cancer cells scattered throughout the fibrosis	Major response: 1%-49% of residual cancer cells
TRG3: More residual tumor cells but fibrosis predominates	Minor response: More than 50% of residual cancer cells
TRG4: Residual cancer cells predominate over fibrosis	
TRG5: No signs of regression.	

TRG: Tumor regression grade.

were included in the present study.

Study design

This was a retrospective, single-center study. Data were extracted from a single-center database. The study was initiated following systematic use of PRPC by our institution (according to the MD Anderson and Rubbia-Brandt classifications) in pathology reports and MDTs.

Criteria studied

Patient-related: Age, gender, body mass index (BMI), and comorbidities. Tumor-related: Number of metastases, size of the metastases (after chemotherapy on pathological exam), site in the liver (central or peripheral), primary tumor stage (according to the TNM classification) and site (colon or rectum), and tumor markers (CEA, CA 19.9). Treatment-related: Type of chemotherapy, number of cycles, and association with targeted therapy. Related to surgery: The type of liver resection (minor or major). Related to pathologic response: A homogeneous PRPC (defined as the same classification for all metastases resected in a given patient, for example all metastases were classified as having a major regression when Rubbia-Brandt classification is considered and for example all metastases had a minor response to PRPC when the MD Anderson classification is considered). A heterogeneous PRPC was determined if in a single specimen, one metastasis had a major regression and others have partial regression or no regression in the Rubbia-Brandt classification or if in a single specimen, one metastasis had a major PRPC and others have complete or minor PRPC in the MD Anderson classification. The homogeneity of PRPC was assessed separately for each classification (Rubbia-Brandt and MD Anderson), but the two classifications were not compared in terms of homogeneity of PRPC.

Endpoints

The primary endpoints were homogeneity of the PRPC according to the Rubbia-Brandt classification and the MD Anderson classification, and the impact of PRPC on the MDT decision.

The secondary endpoints were factors associated with homogeneous PRPC and the PRPC between the two surgical procedures for patients who underwent two-

stage hepatectomy with preoperative chemotherapy.

Pathologic examination

Only operative specimens and no biopsies were examined. All specimens were examined independently by two pathologists (DC + AC). Tumors less than 2 cm in diameter were fully embedded, while an average of 5 slides were taken from tumors measuring more than 2 cm. All data were reported on a standardized pathology report form and included the Rubbia-Brandt and MD Anderson classifications for all LM^[6,7]. The pathologists were blinded from each other for the analysis but in the event of disagreement between the two pathologists, a consensus was reached.

Rubbia-Brandt classification: The Rubbia-Brandt classification scores patients from TRG 1 to TRG 5 (Table 1)^[6]. Patients were then categorized into three groups, defined as major regression (TRG1 or TRG2), partial regression (TRG3) or no regression (TRG4 or TRG5). Patients with multiple liver metastases and heterogeneous PRPC scores were categorized according to the poorest response.

MD Anderson classification: The MD Anderson classification scores patients as having complete, major or minor PRPC (Table 1)^[7]. Patients with multiple liver metastases and heterogeneous PRPC scores were categorized according to the mean response.

Multidisciplinary team meeting

All operated patients were discussed at the MDT meeting before and after liver surgery. In the situation of liver metastases, at our institution, all patients had preoperative chemotherapy except for patients with small LM that could disappear with preoperative chemotherapy or patients with a limited number of metastases who had the resection of the primary tumour during the same procedure than liver resection. The decision to use a target agent was considered on a case-by-case basis. The MDT records were standardized and accessed with in-house software. The MDT decision (withdrawal from postoperative chemotherapy or modification of the chemotherapy regimen) was noted by the team leader (JPJ) in a register. The MDT records and decisions were analyzed retrospectively. The reason for modifying chemotherapy

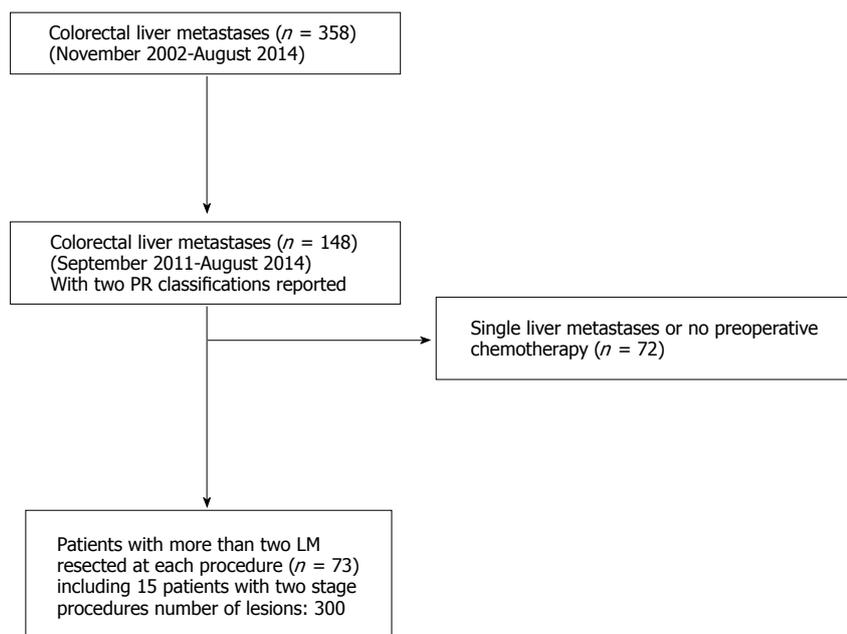


Figure 1 Study flowchart.

was always reported (disease progression, treatment response, or toxicity), thereby identifying all cases in which, the MDT decision was modified by either a complete PRPC or no PRPC.

Statistical analysis

Data are expressed as mean \pm SD, median (range) or number (percentage). Logistic regression analysis was then performed to identify risk factors for homogeneous PRPC, with homogeneous PRPC as dependent variable. Only variables with a *P*-value < 0.2 in univariate analysis were included as independent variables in a multivariate model. Variables with a *P* value ≤ 0.1 in the multivariable model were considered to be risk factors. Statistical analyses were performed by a datamanager with SAS 9.2 statistical analysis software (SAS Institute Inc., Cary, NC, United States).

Ethical authorizations

The present study was reviewed and approved by the Commission Nationale de l'information et des libertés (CNIL) with the number DRCI T135.

RESULTS

Population

Seventy-three patients (with a total of 300 LM, including 15 two-stage procedures) met the inclusion criteria and were included in the study (Figure 1). The study population had a median age of 62.5 years (range: 40-80) and included 45 men (61%). The primary tumor was located in the colon in 66% of patients ($n = 48$). It was on the ascending colon in 14% ($n = 14$), on the transverse colon in 7% ($n = 5$), on the descending colon in 45% ($n = 45$) and in the rectum in 34% ($n =$

25). The primary tumour was resected in 98% ($n = 72$) of the cases with a mean delay between the primary tumour resection and the first liver resection of 15.2 mo (range: 2-60). The median number of LM was 3 (range: 1-14), and metastases were synchronous with the primary tumor in 75% of patients ($n = 55$). The rate of patients with BRAF mutation was 5% ($n = 4$). The rate of patients with KRAS mutation was 9.5% ($n = 7$). The sites of LM are detailed in Table 2. The chemotherapy regimen included targeted therapy in 45% of cases ($n = 40$). The median number of preoperative cycles was 12 (range: 4-38) and the median number of overall cycles was 17 (range: 4-42) (Table 2). Median follow-up was 17 mo (ext: 2-78).

According to the Rubbia-Brandt classification, 15% of patients ($n = 13$) displayed major response, 14% ($n = 12$) displayed partial response and 71% ($n = 63$) had no response. The rate of concordance between the two pathologists for the Rubbia-Brandt classification was 98% ($n = 86$).

According to the MD Anderson classification, 9% of patients ($n = 8$) displayed a complete response, 30% ($n = 26$) displayed a major response and 61% ($n = 54$) displayed a minor response. The rate of concordance between the two pathologists for the MD Anderson classification was 96% ($n = 85$). A concordance was observed between the two classifications in 69% of cases ($n = 61$).

Primary endpoint

Homogeneity of PRPC: According to the Rubbia-Brandt classification, 55% of patients ($n = 48$) obtained a homogeneous PRPC. According to the MD Anderson classification, 53% of patients ($n = 47$) obtained a homogeneous PRPC.

Table 2 Characteristics of the study population *n* (%)

Variable	Study population
Demographic data	
Male gender	45 (61)
Age, median (range), yr	62.5 (40-80)
body mass index, mean \pm SD, kg/m ²	25.36 \pm 4.42
Tumor markers	
CEA level, mean \pm SD (mg/L)	17 \pm 3.5
Ca 19.9 level, mean \pm SD (UI/L)	23 \pm 5.2
Primary tumor site	
Ascending colon	10 (14)
Transverse colon	5 (7)
Descending colon	33 (45)
Rectum	25 (34)
Liver metastases	
Median (range) number of preoperative LM	3 (1-14)
Synchronous LM	55 (75)
Surgical procedure	
Right hepatectomy	15 (16)
Left lobectomy	4 (4)
Right lobectomy	3 (3)
Posterior segmentectomy	8 (11)
Wedge	58 (66)
Two-stage hepatectomy	15 (17)
Site of the 300 metastases (%)	
I	2.5
II	10
III	17.5
IV	11
V	16
VI	20
VII	13
VIII	10
Preoperative chemotherapy	
Regimen	
Folfox	28 (32)
Folfiri/Folfox and bevacizumab	28 (32)
Folfiri with or without cetuximab	8 (9)
Campto or folfiri with or without cetuximab	20 (23)
Folfirinox	4 (4)
Median (range) number of preoperative cycles	12 (4-38)
Pathology	
T stage	
2	7 (9)
3	56 (77)
4	10 (14)
N stage	
0	18 (24)
1	37 (51)
2	11 (15)
X	7 (10)
Median (range) size of metastases, cm	3.1 (0.2-5)
PRPC	
Rubbia-Brandt classification	
Major response	13 (15)
Partial response	12 (14)
Absence of response	63 (71)
MD Anderson classification	
Complete response	8 (9)
Major response	26 (30)
Minor response	54 (61)

Impact of PRPC on the MDT decision: The PRPC changed the MDT decision in only 2 cases (2.7%; withdrawal of chemotherapy in both cases). For both patients, the PRPC was classified as major in the Rubbia-Brandt classification or complete in the MD

Anderson classification. The PRPC was homogeneous in both patients and according to both classifications. Both patients had severe (grade III) oxaliplatin-induced peripheral neuropathy. The absence of PRPC or the presence of heterogeneous PRPC did not change the MDT decision in any of the other cases.

Secondary endpoints

Factors associated with a homogeneous PRPC:

For the Rubbia-Brandt classification, only the use of bevacizumab [OR (95%CI): 3.5 (1.2- 10.5); $P = 0.02$] was associated with a homogeneous PRPC (Table 3).

For the MD Anderson classification, no factor was associated with a homogeneous PRPC (Table 3).

PRPC in two-stage procedures: After the first stage of hepatectomy, a homogeneous PRPC was observed in 100% of cases ($n = 15$) with the Rubbia-Brandt classification and 73% of cases ($n = 11$) with the MD Anderson classification. After the second stage of hepatectomy, a homogeneous PRPC was observed in 53% of cases ($n = 8$) with the Rubbia-Brandt classification and 53% of cases ($n = 8$) with the MD Anderson classification.

DISCUSSION

A homogeneous PRPC was obtained in only 55% of cases according to the Rubbia-Brandt classification and in only 53% of cases according to the MD Anderson classification and PRPC had little impact on the MDT decision and patient survival. This study is the second to report these findings and to have identified factors associated with a homogeneous PRPC.

Recently, Sebahg *et al.*^[8] reported a heterogeneous PRPC in 19.7% of cases. In their study, the authors considered PRPC to be heterogeneous when at least 50% of metastases did not present the same PRPC. They also demonstrated the lack of impact of homogeneous PRPC on survival. In another study by the same group, the authors emphasized the limited impact of PRPC on survival according to the definition of heterogeneous PRPC. Thus, according to the MD Anderson classification, PRPC was not a prognostic factor when based on the mean value but tended towards significance when based on the median PRPC^[8].

The high proportion of major or complete PRPC (*i.e.* similar to the rates reported in the literature) and the high quality of examination of our specimens support the robustness of the present study. Our findings therefore question the real value of PRPC in everyday practice. In our series, the PRPC influenced the MDT decision in only 2 cases. In everyday practice, the decision to prescribe adjuvant chemotherapy is based on laboratory data (decreased tumor marker levels), morphological data (RECIST score) and clinical data (postoperative performance status and tolerability of chemotherapy) and randomized controlled clinical

Table 3 Univariate and multivariate analyses of factors associated with a homogeneous pathologic response to preoperative chemotherapy

Variable	Homogeneity (Rubbia-Brandt)				Homogeneity (MD - Anderson)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR [95%CI]	P value	OR [95%CI]	P value	OR [95%CI]	P value	OR [95%CI]	P value
Age	2.33 [0.89-6.07]	0.82	/	/	1.5 [0.61-3.67]	0.37	/	/
Gender	1 [0.48-2.09]	0.99	/	/	1 [0.48-2.09]	0.99	/	/
Hypertension	1.13 [0.43-2.92]	0.81	/	/	1.13 [0.43-2.92]	0.81	/	/
Body mass index	0.99 [0.98-1.02]	0.95	/	/	1.01 [0.98-1.03]	0.86	/	/
Rectal cancer	1.14 [0.56-2.34]	0.72	/	/	1.73 [0.82-3.63]	0.15	/	/
Number of peroperative LM	0.96 [0.86-1.07]	0.45	/	/	0.99 [0.89-1.10]	0.87	/	/
Time interval between chemotherapy and surgery	3 [0.31-28.84]	0.34	/	/	1.5 [0.53-4.21]	0.44	/	/
Folfiri-based chemotherapy	0.007 [0.09-0.6]	0.90			0.8 [0.3-2.0]	0.60		
Metachronous liver metastases	2.11 [0.96-4.67]	0.14	2.8 [0.92-8.5]	0.06	1.33 [0.63-2.82]	0.45	/	/
T stage	1.26 [0.73-2.18]	0.41	/	/	1.17 [0.68-2.01]	0.58	/	/
N0 stage	0.8 [0.22-2.98]	0.74	/	/	0.8 [0.22-2.98]	0.74	/	/
ASA score	1.05 [0.88-1.25]	0.62	/	/	1.05 [0.88-1.26]	0.56	/	/
MSI	1.9 [0.2-18.3]	0.90			1.5 [0.2-9.8]	0.60		
RAS status	1.05 [0.0-99]	0.90			4.5 [0.8-23.9]	0.30		
Braf mutation	1.6 [0.0-120]	0.90			3.3 [0.32-34.6]	0.30		
Use of bevacizumab	3.20 [1.17-8.74]	0.02	3.5 [1.2-10.5]	0.02	1.33 [0.56-3.16]	0.51	/	/
Metastases in the left lobe of the liver	0.67 [0.24-1.87]	0.44	/	/	0.67 [0.24-1.87]	0.44	/	/
Number chemotherapy cycles	1.79 [0.93- 3.44]	0.12	1.06 [0.97-1.1]	0.10	1.44 [0.76- 2.72]	0.27	/	/

LM: Liver metastases.

trials and cohort studies have such a major impact on the decision to prescribe perioperative and adjuvant chemotherapy^[5,13], that the potential impact of the PRPC in the MDT decision is negligible.

However, the proportion of patients with a homogeneous PRPC in our series was much lower than that published in the initial report by Rubbia-Brandt *et al*^[6] (90%). Firstly, this disparity might be due to differences in chemotherapy regimens. In the study by Rubbia-Brandt *et al*^[6] none of the patients received targeted therapies vs 61% of the patients in the present study. Secondly, the studies differed in terms of the number of slides prepared per metastasis. In the study by Rubbia-Brandt *et al*, specimens were prepared as 0.5-cm-thick slices. In the present study, a mean of 10 slides per metastasis were prepared, and metastases measuring less than two centimeters were fully embedded. One can argue that the retrospective design of the study is a limitation since no special analysis or additional slide for each metastasis was performed. Furthermore, no information on the distribution of the residual tumour cells in a single metastasis is available since there is no classification for that particular point.

Our findings concerning the proportion of patients with a homogeneous PRPC also question the conclusions reached by Mentha *et al*^[12] on interval treatment in patients undergoing two-stage hepatectomy. Mentha *et al*^[12] found that, when comparing the PRPC after the first and second stages, 10 out of 22 patients (45%) had a poorer PRPC at the second stage (compared with 23% in the present study). These authors suggested that this difference in PRPC might

be due to interruption of treatment for 5-15 wk of chemotherapy^[12]. Our results suggest another possible explanation for the difference in PRPC between the two stages of hepatectomy, as a heterogeneous PRPC was observed in one-half of our patients. The difference in PRPC classification therefore cannot be solely attributed to putative chemoresistance between the two stages of hepatectomy. Data on homogeneity also reflect the biological heterogeneity of liver metastases, derived from independent colonies with their own biological profile^[14] and information on PRPC homogeneity is crucial regardless of the impact of PRPC on survival as it shows that the treatment strategy does not need to be adapted to the PRPC, which is variable from one metastasis to another.

Bevacizumab is known to be associated with an increased likelihood of complete PRPC. The present study is the first to report the association between bevacizumab and an increased likelihood of homogeneous PRPC^[15]. One possible explanation is related to the mechanism of action of bevacizumab (necrosis and modification of vasculogenesis)^[16]. The outcomes of this analysis should nevertheless interpret with caution, since there was a lot of tested variable of a limited number of patients and events^[17]. An interesting extension of this work would be to perform the same analysis on patients who have received intra-arterial chemotherapy (which is known to influence the PRPC).

Although it has been clearly established that a complete PRPC is a major prognostic factor^[6,7], it is a static variable (like age or the presence of metachronous vs synchronous metastases) in contrast

with the dynamic nature of tumor markers and the RECIST score, and therefore constitutes another limitation to the practical value of PRPC.

The present study nevertheless presents a number of limitations, due to the heterogeneous characteristics of liver resections, preoperative chemotherapy, inclusion of patients receiving targeted therapy and the number of preoperative cycles. Moreover, as previously demonstrated in the series published by Rubbia-Brandt *et al*^[6] and Kishi *et al*^[7], complete PRPC (but not homogeneous PRPC) is a prognostic factor but the presence of two classifications is disturbing^[9] and contributes to the poor understanding and correct use of PRPC. All these points could have a direct impact on the homogeneity of PRPC.

In conclusion, the PRPC was homogeneous in only half of patients with multiple LM and had little impact on the MDT decision. Routine use of PRPC to guide treatment may be questionable (due to differences between classifications and the heterogeneity of the PRPC for multiple LMs in the same patient). Further investigations are therefore necessary in order to improve the value of the PRPC.

COMMENTS

Background

Pathologic response to preoperative chemotherapy scores appears to be correlated with survival after liver metastases (LM) resection. Pathologic response to preoperative chemotherapy may be useful in situations in which adjuvant chemotherapy may be required in patients with multiple LM. However a little is known about the homogeneity rate of pathologic response to preoperative chemotherapy and on its use in daily practice.

Research frontiers

Fifty percent of patients with colorectal cancer will develop LM with a 5-yr overall survival rate of 50%. The curative management of LM includes surgical resection and chemotherapy (combined with targeted therapies, in some cases).

Innovations and breakthrough

The study underlines that homogeneous PRPC rate was low and has little impact on the multidisciplinary team meeting decision.

Applications

Doing a liver biopsy to know the pathological response to preoperative chemotherapy is useless. Pathological response to preoperative chemotherapy is not a crucial point in MDT discussions.

Peer-review

The authors review a cohort of 73 patients undergoing liver resection for colorectal LM after systemic chemotherapy in order to assess the impact of homogeneity of pathological response to chemotherapy on survival and routine management of patients. They conclude that pathological response to chemotherapy is not a powerful prognostic factor and do not influence treatment or management in patients with advanced resectable LM. Overall this is a concise and well written manuscript.

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