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Conversion Chemotherapy for Technically Unresectable Colorectal Liver Metastases

A Retrospective, STROBE-Compliant, Single-Center Study Comparing Chemotherapy Alone and Combination Chemotherapy With Cetuximab or Bevacizumab

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Abstract: The response rate of patients with unresectable liver-limited metastases of colorectal cancer can be improved by converting inoperable disease to operable disease. However, the benefits of conversion chemotherapy for survival are still controversial.

Patients considered to have technically inoperable disease by a multidisciplinary team were retrospectively analyzed. Patients were stratified based on the treatment they received, into the chemotherapy only (G1), chemotherapy plus bevacizumab (G2), or chemotherapy plus cetuximab (G3) groups. The primary endpoint was the resection rate. The secondary endpoint was the overall survival (OS), according to both the treatment received and liver surgery status.

In total, 104 patients were included: 30 in the G1, 39 in the G2, and 35 in the G3 groups. All G3 patients had the wild-type *KRAS* exon 2. The surgical resection rates for patients in the G1, G2, and G3 groups were 43.3% (13/30), 30.7% (12/39), and 51.4% (18/35), respectively. Disease-free survival did not show significant differences among the 3 groups. The median OS was 35.2 months in the G1, 28.8 months in the G2, and 42.1 months in the G3 ($P=0.25$) groups. The OS was significantly higher in patients who underwent surgical resection than those who did not. The median OS was 28.4 months in patients who did not undergo resection, whereas it had not been reached after a median follow-up period of 37.5 months for patients who underwent surgical resection (events: 21/43).

Our data confirmed that the conversion of initially inoperable disease to operable disease conferred a survival benefit, even in patients

who relapsed after surgery. The addition of cetuximab to chemotherapy improved the objective response and resection rates, conferring a potential survival benefit even in patients whose diseases were not converted to operable disease, compared to chemotherapy alone or in combination with bevacizumab.

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Abbreviations: Bev = bevacizumab, Cet = cetuximab, CR = complete response, Chemo = chemotherapy, CRC = colorectal cancer, CT = computed tomography, DFS = disease-free survival, FOLFIRI regimen = leucovorin 200 mg/m² administered as a 2-h infusion immediately followed by a bolus of 5-fluorouracil 400 mg/m² and subsequent continuous 46-h infusion 2400 mg/m² plus irinotecan 180 mg/m², FOLFOX regimen = leucovorin 200 mg/m² administered as a 2-h infusion immediately followed by a bolus of 5-fluorouracil 400 mg/m² and subsequent continuous 46-h infusion 2400 mg/m² plus oxaliplatin 100 mg/m², G1 = group 1, patients treated with chemotherapy alone, G2 = group 2, patients treated with chemotherapy plus bevacizumab, G3 = group 3, patients treated with chemotherapy plus cetuximab, *KRAS* = Kirsten rat sarcoma viral oncogene homolog, LOM = liver-only metastases, mOS = median overall survival, MRI = magnetic resonance imaging, MTD = multidisciplinary team, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, R0 = radical resection, R1 = microscopic involvement of margins, R2 = macroscopic residual, RECIST = Response Evaluation Criteria In Solid Tumors, RR = resection rate, SD = stable disease.

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INTRODUCTION

Until recently, patients with liver-only metastases (LOM) of colorectal cancer (CRC) were mostly considered eligible only for palliative chemotherapy, excluding approximately 10% to 20% considered eligible for surgery at diagnosis. However, the 5-year survival rate was poor.¹ Surgery was demonstrated to be curative in the subgroup of patients with easily resectable tumors.^{2,3} In the light of the increasing evidence suggesting that combination chemotherapy could be effective in converting inoperable disease to operable disease, many efforts have been made to develop more aggressive chemotherapy regimens for maximizing response rates and resectability.^{4–11} Nevertheless, the benefits of conversion chemotherapy are still controversial because the survival data obtained from the patients with easily operable diseases are not strictly comparable to those with initially inoperable ones, and no randomized study has

addressed this issue to date. Moreover, the role of molecular targeted therapies in the treatment of initially unresectable liver metastases is still controversial. Recently, a randomized study demonstrated that the addition of cetuximab to chemotherapy improved resection rate and overall survival (OS) in comparison to chemotherapy alone in patients with unresectable liver-limited metastases of CRC without *KRAS* mutations.¹² In addition, this study showed that, in patients who underwent resection, the median OS was significantly longer than that in those who did not undergo resection. This small-scale study included only 70 patients per arm, with approximately 20 patients who underwent resection. Therefore, these results cannot be considered conclusive. In addition, the use of cetuximab with chemotherapy before surgery in resectable patients has shown a detrimental effect in a recent trial.¹³ There are no prospective randomized studies using bevacizumab in combination with chemotherapy in conversion or neoadjuvant therapy of liver metastases.

In the last decade, surgeons have been more aggressive about the resectability of liver metastases. This has increased resection rates in some specialized centers; however, it has also enhanced differences in resectability criteria both among hepatic surgeons and between the hepatic and general surgeons. In fact, in randomized clinical trials focusing on conversion therapy, resectability retrospectively reviewed by a panel of surgeons had resulted in a significant disagreement.⁷

In spite of numerous trials, the real benefit of conversion therapy in patients with initially technically unresectable LOM is still partially controversial. The introduction of molecular targeted drugs has increased uncertainty, because the expectation of higher resection rates and OS was not always satisfied. Therefore, we planned a retrospective study, in patients with initially technically unresectable LOM, to evaluate the benefits of conversion to resectable disease on OS, and to compare different chemotherapeutic strategies. In this single-center study, the same surgeon took part in the multidisciplinary team (MDT) and performed liver resections, thereby reducing the risk of variability in the assessment of technical nonresectability.

METHODS

This retrospective study was conducted at the Catholic University of Sacred Heart in Rome and was approved by the local ethics committee. Clinical records of patients affected by CRC with LOM between 2006 and 2014 were reviewed. The eligibility criteria included histologically confirmed colon cancer, measurable LOM (according to RECIST 1.1 criteria) considered technically unresectable by the local MDT, and no serious concomitant illnesses (uncontrolled hypertension, recent myocardial infarction, unstable angina, heart disease grade ≥ 2 according to New York Heart Association criteria, uncontrolled diabetes, renal or liver failure) that could have affected treatment duration, survival, or the possibility of surgery at the time of diagnosis. Only patients who underwent computed tomography (CT) at regular intervals, for < 3 months, were considered. Consent for chemotherapy was obtained from all patients, also including consent for the retrospective analysis of all clinical data. Patients were excluded in case of previous treatment for metastatic disease, known extra-hepatic disease at the time of diagnosis, or other cancers (with the exception of nonmelanoma skin cancers and in situ cervical cancer) diagnosed within the past 5 years. All eligible patients were consecutively included.

Treatment

Patients were divided into 3 groups depending on the chemotherapy regimen they received. Group 1 (G1) chemotherapy only patients were administered 200 mg/m² leucovorin as a 2-h infusion, immediately followed by a bolus of 400 mg/m² 5-fluorouracil and a subsequent continuous 46-h infusion of 2400 mg/m², plus either 180 mg/m² irinotecan or 100 mg/m² oxaliplatin (FOLFIRI or FOLFOX6 regimens, respectively). Group 2 (G2) patients, who received chemotherapy plus bevacizumab, received FOLFIRI or FOLFOX6 (as described for G1 patients) plus bevacizumab (5 mg/kg every 2 weeks). Group 3 (G3) patients, who received chemotherapy plus cetuximab, received FOLFIRI or FOLFOX6 (as described for G1 patients) plus cetuximab (initial dose of 400 mg/m² and then 250 mg/m² weekly).

The Assessment Procedures

Patients with LOM of CRC were diagnosed using contrast-enhanced CT or magnetic resonance imaging (MRI). Therapeutic decisions concerning each patient were taken by the same MDT, which included 2 hepatic surgeons, 2 medical oncologists, a radiologist, and an interventional radiologist. Only patients who underwent CT or MRI followed by MDT evaluation at diagnosis, and at regular intervals of ≤ 3 months, were included.

There were no predefined criteria of resectability with regard to the number, size, and bilaterality of metastases. Patients were considered to have resectable tumors when the entire tumor could be removed with negative margins, leaving an adequate amount of healthy liver. Unresectability was defined by the MDT as technical unresectability, based on the inadequate amount of healthy liver tissue, or the technical inability to remove all metastases through a 1- or 2-stage procedure. The main causes of technical unresectability were multinodular bilobar disease, inoperable lesions considering the size, and ill-located lesions. Although the presence of extra-hepatic disease did not represent a contraindication to liver surgery, these patients were not enrolled in this study in order to ensure homogeneity.

Objective response was assessed using RECIST 1.1 criteria to define complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).¹⁴

Surgery

Liver resection was considered feasible when an R0 resection was technically possible with adequate residual healthy liver tissue to ensure adequate function. Intraoperative ultrasonography was always performed to assess the number of metastases and their interaction with the major vascular structures. In case of CR to chemotherapy, the locations of the metastases were carefully evaluated in order to resect all the potentially residual neoplastic tissue. Liver resection was defined as R1 when microscopic margin involvement was demonstrated, while it was considered R2 when macroscopic disease was not removed. Surgery had to be performed within 8 weeks of the last chemotherapy dose.

Statistical Analysis

Disease-free survival (DFS), progression-free survival (PFS), and OS were retrospectively assessed for each patient group. DFS was defined as the interval between liver surgery (only R0 patients) and the first documented postoperative relapse or death. OS was calculated from the diagnosis of

TABLE 1. Baseline Characteristics

	Pts, %	G1	G2	G3
Total pts	104	30 (29)	39 (37)	35 (34)
Age, median (range)	62 (36–82)	61	59	64
Sex				
Male/female	63 (60.5)/41 (39.4)	19/11	19/20	25/10
Performance status				
0	59 (56.7)	18	21	20
1	45 (43.3)	12	18	15
Primary site				
Ascending colon	29 (27.8)	10	12	7
Descending colon/sigmoid	49 (51.0)	11	18	20
Transverse	8 (7.8)	3	3	2
Rectum	18 (18.7)	6	6	6
Diagnosis of metastases				
Synchronous	84 (80.8)	24	31	29
Metachronous	20 (19.2)	6	8	6
Number of metastases				
≤3	29 (27.9)	9	11	9
>3	75 (72.1)	21	28	26
Unresectability reason				
Bilobar, multinodular	62 (59.6)	15	24	23
Ill-located	25 (24.0)	8	7	10
Size	17 (16.3)	7	8	2
Chemotherapy administered				
FOLFOX4	46 (44.2)	18	20	8
FOLFIRI	58 (55.8)	12	19	27
KRAS exon 2 mutational status				
Wild type	65 (62.5)	13	17	35
Mutant	31 (29.8)	11	20	–
Not assessed	8 (7.7)	6	2	–

FOLFIRI = leucovorin 200 mg/m² administered as a 2-h infusion immediately followed by a bolus of 5-fluorouracil 400 mg/m² and subsequent continuous 46-h infusion 2400 mg/m² plus irinotecan 180 mg/m², FOLFOX = leucovorin 200 mg/m² administered as a 2-h infusion immediately followed by a bolus of 5-fluorouracil 400 mg/m² and subsequent continuous 46-h infusion 2400 mg/m² plus oxaliplatin 100 mg/m², KRAS = Kirsten rat sarcoma viral oncogene homolog.

metastatic disease until death or last follow-up. PFS was defined as the interval between the beginning of chemotherapy and documented disease progression. OS, PFS, and DFS were estimated according to the Kaplan–Meier method and compared using the log-rank tests. Multivariate analysis was performed using a Cox proportional hazards model in order to detect independent prognostic factors for survival. On multivariate analysis, a *P* value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS v.22.0 software (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

In total, 104 patients with liver-limited metastatic CRC, diagnosed between 2006 and 2014 and defined to have technically unresectable disease on a multidisciplinary evaluation, were included in this single-center retrospective study. The median age was 62 years (range, 36–82 years). A very high proportion of patients had synchronous metastatic diseases (80.8%). Only 29 patients (27.9%) had ≤3 metastases. The 3 main reasons for technical unresectability were the presence of multinodular bilobar disease (62 patients, 59.6%); inoperable

lesions considering the size (17 patients, 16.3%); and ill-located lesions (25 patients, 24.0%). Most patients (62.5%) had the wild-type *KRAS* exon 2, whereas 29.8% carried a mutation on codon 12 or 13. The *KRAS* mutational status of 8 (7.7%) patients was not known. Among the 104 patients, 30 were treated with chemotherapy alone (G1 group), 39 with chemotherapy plus bevacizumab (G2), and 35 with chemotherapy plus cetuximab (G3). All G3 patients had wild-type *KRAS*, whereas 36.7% (11/30) of patients in G1 and 51.3% (20/39) in G2 had a *KRAS* exon 2 mutation. Detailed patient characteristics are listed in Table 1.

Efficacy

Among the 104 patients, 64 (61.5%) achieved PR according to the RECIST 1.1 criteria, and 2 (1.9%) patients achieved CR. The overall response rate was 63.5%. Twenty-six patients (25%) had SD as the best response, while 12 (11.5%) had PD after first-line chemotherapy.

Overall, the resection rate was 41.3% (43/104) for patients who underwent resection with radical intent. Radical resection (R0) was achieved in 33 patients (31.7%), whereas histological analysis showed microscopic involvement of margins (R1) in 7 patients, and macroscopic residual disease (R2) in 3 patients. The resection rate was 43.3% (13/30) for G1, 30.7% (12/39) for

TABLE 2. Resection and Response Rate (RECIST) According to Treatment Groups

	G1-Chemo-only- n (%)	G2-Chemo+Bev-n (%)	G3-Chemo+Cet- n (%)
RR	13/30 (43.3)	12/39 (30.7)	18/35 (51.4)
CR	1 (3.3)	0	1 (2.8)
PR	13 (43.3)	25 (64.1)	26 (74.3)
SD	11 (36.6)	10 (25.6)	5 (14.3)
PD	5 (16.6)	4 (10.2)	3 (8.5)

Bev = bevacizumab, Cet = cetuximab, Chemo = chemotherapy, CR = complete response, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, RR = resection rate, SD = stable disease.

G2, and 51.4% (18/35) for G3, with no statistically significant differences identified by the Pearson chi-squared test among the groups, although a trend in favor of G3 was observed when compared to G2 (hazards ratio [HR], 0.42; 95% confidence interval [CI], 0.14–1.20; $P = 0.07$). The resection and response rates according to treatment are summarized in Table 2.

The median OS was 35.2 months in G1 (22/30 events), 28.8 months in G2 (27/39 events), and 42.1 months in G3 (20/35 events). The Kaplan–Meier survival curves are shown in Figure 1. The differences in OS did not reach statistical significance, probably because of the sample size ($P = 0.252$). The 3-year survival rates were 36.7%, 20.5%, and 45.7% for G1, G2, and G3, respectively; data on 5-year survival rates are still immature. The median PFS was 13.6, 13.0, and 15.4 months for G1, G2, and G3, respectively, with overall 96/104 events observed. The differences in OS and PFS among the 3 groups did not reach statistical significance. The median DFS was 9.8, 11.0, and 5.5 months for G1, G2, and G3, respectively, with no statistically significant differences. The median OS for liver surgery was 28.4 months in the patients who did not undergo resection (48/61 events; $P = 0.26$) without significant differences according to systemic treatment (29.3, 25.3, and 32.0 months). The OS in patients who underwent resection had not been reached yet at a median follow-up of 37.5 months (estimated 47.0 months, with 21/43 events; Figure 2). The differences in survival between the patients who underwent and did

not undergo resection reached a high level of statistical significance (HR, 0.32; 95% CI, 0.19–0.51; $P < 0.0001$).

Chemotherapy

Chemotherapy was well tolerated and the adverse events observed were those typically observed with the particular regimens. The median number of cycles administered was 9.3 for G1, 10.7 for G2, and 10.8 for G3 patients, without statistically significant differences. The dose intensity was 90% in G1, 87% in G2, and 84% in the G3 groups, respectively. In the patients who underwent resection, the median number of cycles before surgery was 9.1 for G1, 10.4 for G2, and 9.5 for G3 patients, respectively.

Following surgery, 53.8% (7/13) for G1, 58.2% (7/12) for G2, and 38.8% (7/18) for G3, further underwent the same chemotherapy regimen as adjuvant therapy. The median number of cycles administered under this setting was 5.4 for G1, 5.2 for G2, and 5.4 for G3 patients. The main reasons for chemotherapy withdrawal after the surgery were patient refusal, postoperative complications, and investigator decision based upon the number of cycles received before surgery.

Liver Surgery

In patients who converted to operable disease, surgery was planned according to the volume of healthy residual liver

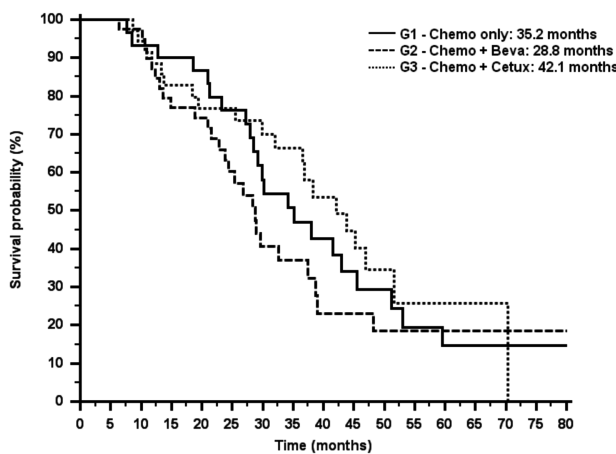


FIGURE 1. Overall survival according to treatment groups. G1: chemo only—35.2 mo (events: 22/30). G2: chemo + bevacizumab—28.8 mo (events: 27/39). G3: chemo + cetuximab—42.1 mo (events: 20/35). P value = 0.252.

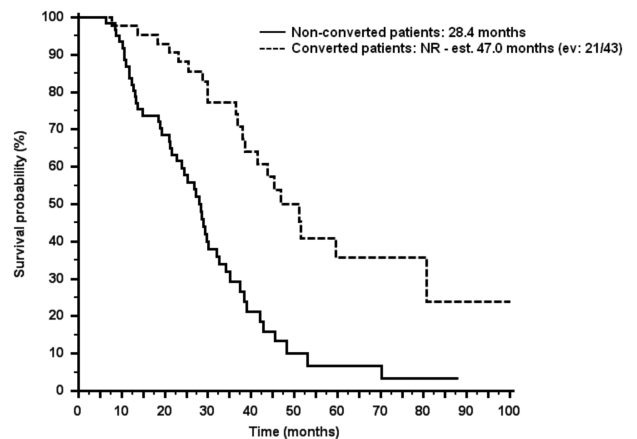


FIGURE 2. Overall survival according to metastases conversion. Nonconverted patients: 28.4 mo (events: 48/61). Converted patients: not reached (events: 21/43)—estimate 47.0 mo at a median follow-up of 37.5 mo. Hazards ratio 0.32 (95% confidence interval 0.19–0.51). P value < 0.0001 .

required to obtain an R0 resection. This approach proved feasible in 43 out of 104 treated patients. In 9 patients (20.9% of the interventions), equally distributed among the 3 groups, a 2-stage resection strategy was planned, for which a second resection was considered only for DFS evaluation. Among the 33 patients who underwent single-stage surgery, 21 (48.8%) were subjected to multiple segmental resections, 11 (25.6%) received right hepatectomy, while 2 patients underwent left hepatectomy (4.6%). For those who underwent the 2-stage surgery, all 9 patients (21.1%) underwent multiple segmental resections in the left lobe in the first step, whereas in the second step a right hepatectomy was performed. Radiofrequency ablation was never used in combination with surgery.

No postoperative mortality was observed in the 2 months following surgery. The morbidity rate was 20.9% (9 patients; 2 with mild liver failure, 2 with bile leak, 1 with abdominal abscess, 1 with bronchopneumonia, 2 with bowel obstruction/intestinal perforation, and 1 with bleeding) in the whole population of patients who underwent resection, without statistically significant differences between the groups. The patient who experienced bleeding had received bevacizumab.

Oxaliplatin-related liver sinusoidal injury (bleu liver) was relatively more frequent among the G1 and G2 patients (4 patients), compared with G3 (1 patient) patients, because the backbone chemotherapy was FOLFIRI in most G3 patients. Steatohepatitis was rare and did not differ significantly among the 3 groups.

DISCUSSION

It is challenging to design a large multicenter randomized clinical study involving patients with unresectable colorectal liver metastases for several reasons. The most important is the definition of unresectability that might differ among the surgeons and might differ for the same surgeon depending on the clinical situation. Another issue is the choice of the chemotherapy schedule, because there is no consensus on both the best regimen to be administered and the biological therapies to be combined with. Furthermore, the choice of the control arm is extremely critical. In the light of these difficulties, we conducted a single-center study in order to minimize variability on the definition of unresectability (all patients were evaluated and operated on by the same group of surgeons). Moreover, we restricted our analysis to patients who could not undergo resection because of technical concerns, thereby limiting the bias of nonhomogeneous criteria for assessing resectability. Finally, the retrospective nature of the study allowed us to avoid ethical issues around the choice of a control arm. Patients were retrospectively analyzed based on the treatment they received. We evaluated not only the R0 resection rate (which was our primary endpoint) but also other efficacy endpoints including the DFS, PFS, and OS for different treatment regimens.

With a 63.4% overall response rate, resectability was achieved in 41.3% of patients, with R0 resection achieved in most of them (33/43). Overall, our results are consistent with those reported by other authors for patients with unresectable LOM of CRC.^{15,16} We obtained the best response rate, although statistically insignificant, with the cetuximab plus chemotherapy combination in wild-type *KRAS* patients. The response rate we obtained was similar to results reported for a more aggressive and complex combination therapy regimen involving cetuximab.¹¹ Overall, our results support the

opinion that in selected *KRAS* patients, cetuximab-based therapy is the regimen with the highest resection rate and tumor shrinkage.^{17,18}

Consistent with the results of previous studies, our findings confirm that patients whose diseases converted to operable disease, experience a statistically significant survival benefit compared with those who did not undergo surgery.¹⁹ In our study, the median OS achieved for patients with inoperable diseases that did not convert, was 28.4 months, while the median OS for patients whose disease converted to operable disease had not been reached yet after a median follow-up time of 37.5 months (21/43 events, estimated 47.0 months; $P=0.0001$). Interestingly, if the total number of patients in our study is considered, the median OS was higher, although statistically insignificant, in patients treated with cetuximab plus chemotherapy than those treated with bevacizumab or with chemotherapy alone (35.2, 28.8, and 42.1 months for G1, G2, and G3, respectively; $P=0.252$). Generally, with the higher resection rate observed in the G3 group (51.4%) compared with the G1 (43.3%) and the G2 (30.7%) groups, these results indicate that combining cetuximab with chemotherapy not only offers the highest likelihood of converting inoperable disease to operable disease (that might confer a survival benefit) but also the opportunity to have better survival independent from the surgery, as also reported by other authors in nonselected patients.^{20,21} The suggestion that chemotherapy plus cetuximab might confer a survival benefit compared with other groups requires confirmation through further randomized and larger clinical trials. For patients with mature survival data, cetuximab treatment might also confer a survival advantage in the converted patients compared with those who received bevacizumab or no biological therapy; however, survival data for these patients are still immature.

Among the 43 converted patients, 37 (86%) relapsed. In addition, the DFS of patients who underwent resection was only approximately 8.3 months, which indicates that most patients with initially unresectable, even when converted, quickly relapse. Therefore, the curative capacity of surgery in these patients is poor. However, it still prolongs survival and might be considered an adjunctive line of therapy in these patients, as also suggested by other authors.²²

The strength of our study is that it was a single-center study. Although this helped avoid some of the problems inherent to prospective studies in patients with unresectable LOM, 4 main biases were identified: the “aggressiveness” of the surgeon increased over the study period; the year of diagnosis affected the choice of chemotherapy, that is, patients diagnosed earlier were more likely to receive chemotherapy alone without biologics; the sample size was small; and molecular selection was variable; in the G3 group, only wild-type *KRAS* patients were included.

CONCLUSIONS

Our retrospective study confirmed that patients whose diseases converted from inoperable to operable disease had a significant survival benefit, even in those patients with technical concerns for resectability at diagnosis. The combination of chemotherapy with cetuximab appears to be the most effective strategy in converting the inoperable disease of the patients with wild-type *KRAS* mutations to operable disease. In addition, the treatment schedule also appeared to confer a major survival benefit, although this has to be confirmed in a larger series.

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