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Treatment Response After Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastases of Colorectal Originf

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Objective: The objective of this study is to analyze oncological outcomes of patients with peritoneal metastases (PM) of colorectal origin treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC).

Background: PIPAC has been demonstrated to be a feasible and safe novel treatment for patients with PM of various origins. Only small series reports on survival after PIPAC by disease entity.

Methods: International retrospective cohort study of consecutive patients with PM of colorectal origin. Outcome measures were overall survival (OS), radiological response according to Response Evaluation Criteria in Solid Tumors (RECIST), histological response (peritoneal regression grading score [PRGS]: complete response: 1–4: no response), change of peritoneal cancer index (PCI), and symptom control.

Results: Seventeen eligible centers compiled 256 non-selected patients (mean age 61 [50.6–69.2], 43% female) and 606 procedures. Sixty-three percent were treated after 2 lines of chemotherapy, median PCI at PIPAC1 was 18 (interquartile range [IQR] = 10–27). Median OS was 19.00 months (IQR = 12.9–29.8) from diagnosis and 9.4 months (IQR = 4.5–16.8) from PIPAC1. One hundred and four of 256 patients (40.6%) had ≥3 procedures (per protocol [pp]) with the following outcomes at PIPAC3: RECIST: 59.3% partial response/stable, 40.7% progression; mean PRGS: 2.1 ± 0.9. Median PCI was 21 (IQR = 15–29) at baseline and 20 (IQR = 12–27) at PIPAC3 (P = 0.02). Fifty-six (54%) and 48 (46%) patients were symptomatic at baseline and PIPAC3, respectively (P = 0.267). Median OS for the pp cohort was 11.9 months (IQR = 10.7–15.0) from PIPAC1. Independent predictors for survival were radiological response (HR = 3.0; 95% CI = 1.6–5.7) and no symptoms (HR = 4.5, 95% CI = 2.2–9.1) at PIPAC3.

Conclusions: Objective treatment response and encouraging survival were demonstrated after PIPAC for colorectal PM. Prospective registry data and comparative studies are now needed in to confirm these data.

Keywords: chemotherapy, peritoneal metastasis, PIPAC, PRGS, RECIST, survival

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INTRODUCTION

Treatment of peritoneal metastases (PM) offers limited options and prognosis for most entities remains dismal.[1–4] In addition, assessment of treatment response is challenging and frequently unsatisfying when mainly considering imaging modalities.[5–7] For colorectal primary, PM show a worse response to systemic chemotherapy than solid organ metastases.[8] Best results are obtained by multimodal treatment including perioperative chemotherapy and complete cytoreductive surgery (CRS), which can be combined with Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) in selected patients offering median overall survival (OS) of about 42 months and a potential for cure in up to 16% of patients.[9,10] However, only fit patients with limited disease can be treated by this multimodal approach. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) has been proposed as an alternative treatment in patients not eligible for CRS ± HIPEC and having insufficient response or intolerance to systemic chemotherapy.[11–13] PIPAC treatment foresees repeated laparoscopy and biopsies offering unique opportunity to assess treatment response also by intraoperative evaluation including peritoneal cancer index (PCI),[14] cytology (ascites or washing), and histological assessment by use of the validated 4–grade peritoneal regression grading score (PRGS).[15] Recent systematic reviews confirmed feasibility, safety, and excellent tolerance of PIPAC overall in patients with PM.[12,13,16] However, large-scale multimodal evaluation of oncological efficacy by disease entity is still missing.

The aim of this study was to assess survival outcomes after PIPAC for colorectal PM and to study the different aspects of

clinical response, laparoscopic exploration, radiological and histological response.

METHODS

The target population for this international retrospective cohort study were non-selected patients who received PIPAC treatment for colorectal PM. For this purpose, all active PIPAC centers (>60 procedures performed) were invited to participate and to enter all eligible patients in an anonymized online database. Eligible were all patients who received PIPAC treatment in line with the currently recommended indications.[13] Patients who refused to participate were excluded from the analysis. Appendicular tumors were not considered due to their different tumor biology, treatment and prognosis (separate analysis). The study was approved by the respective institutional review boards (#ICM-ART-2020/05) and patients provided consent as needed according to national requirements.

PIPAC Treatment

PIPAC technique, safety guidelines, and treatment protocol are highly standardized and have been previously described in detail.[13,17–19] The diagnostic part included documentation of disease extent (PCI), removal of ascites (volume) or in its absence washing for cytology. Three to four biopsies were taken during each PIPAC aiming to compare histological response (specified below) under PIPAC treatment. Oxaliplatin was the drug of choice with the empirical dose of 92 mg/m^2. Patients were scheduled per protocol (pp) for 3 PIPAC administrations with 4- to 8-week intervals in between, allowing to intercalate additional cycles of systemic chemotherapy if combined treatment was decided by the multidisciplinary tumor board.

Clinical Evaluation, Quality of Life, and Survival

Main outcome of interest was OS counted in separate analyses from first PIPAC and from first diagnosis of PM. Symptoms were accounted as dichotomous variables including abdominal pain, distension, nausea, and altered intestinal transit (including obstruction).[13,20] Quality of life (QoL) was assessed by use of the validated EORTC QLQ-C30 survey analyzing overall QoL as well as its components and main symptoms.[21]

Assessment of Histological Response and Cytology

Conversion of positive (presence of malignant cells) to negative cytology was counted as treatment response. In addition, 3 to 4 representative biopsies of PM were performed during PIPAC procedures and analyzed according to institutional standards.

Use of the PRGS was strongly propagated and encouraged after its proposal in 2016[15] and validated recently showing a moderate-good/substantial interobserver variability and a good-excellent/almost perfect intraobserver variability.[22] PRGS evaluates the histological response after treatment on PM by evaluating the number of tumor cells, fibrosis, acellular mucin pools and necrosis. As described by Solass et al,[15,22] the PRGS is defined as follows: 1 corresponds to a complete regression with absence of tumor cells; 2 to major regression features with only a few residual tumor cells; 3 to minor regression with predominance of residual tumor cells and only few regressive features; and 4 corresponds to an absence of response to therapy and where the tumor cells are not accompanied by any regressive features. A PRGS was assessed for each biopsy taken during PIPAC. The mean PRGS (out of a minimum of 4 biopsies) was calculated to illustrate overall histological response according to current recommendations.[15,22]

Assessment of Radiological Response

Repeated imaging was performed before, during (mostly after PIPAC2), and after treatment, mainly by computed tomography or by magnetic resonance imaging and positron emission tomography/computed tomography if indicated. Treatment response was assessed by use of the Response Evaluation Criteria In Solid Tumors (RECIST).[23]

Statistics and Analysis

For the descriptive analysis, Student *t* test for continuous data, Kruskal-Wallis test for non-continuous data, and a χ^2 test for categorical data were performed. Descriptive statistics are expressed as mean ± SD, mean (interquartile range [IQR]), or n (%). Repeated measures *t* test was performed for comparing means before and after treatment. The Kaplan–Meier method was used to calculate OS from the time of diagnosis to the first PIPAC. Variables for each of the survival outcomes were fitted to univariate Cox models. The forward selection strategy was used to create multivariate Cox models. The assumption of proportional hazard was tested. The statistical significance level was considered as <0.05. For all the statistical analysis Statistical software RStudio (Version 1.4.1106) was used. Percentage was calculated based on the availability of information and not on the total number of patients per group.

RESULTS

Study Cohort

Seventeen eligible centers agreed to participate and collected a total of 256 consecutive patients meeting the inclusion criteria (Supplemental Appendix 1, http://links.lww.com/AOSO/A165). The patient flow chart (Fig. 1) details drop-outs, number of PIPACs, and patients lost to follow-up. Median follow-up from diagnosis of PM and first PIPAC was 18.6 (IQR = 12.6–29.3) and 9.4 (IQR = 4.9–17.0) months, respectively.

Patients' characteristics and details on tumor and prior treatments are given in Tables 1 and 2 for patients having 1 or 2 PIPACs versus those having ≥3 PIPACs as foreseen pp. Median PCI at PIPAC1 was 18 (IQR = 10–27). Overall, 142 patients (63%) were treated in the third-line situation, and PIPAC was combined with intermittent systemic chemotherapy in 133 patients (52%).

Response After Full PIPAC Treatment

Treatment response for the pp cohort is displayed in Table 3. Objective radiological and histological response (PRGS1-2) was observed in 59.3% and 72.7% of analyzed patients, respectively. Mean PRGS at PIPAC3 was 2.1 ± 0.9. Negative cytology was found in 44.9% and 69.4% of patients at PIPAC1 and PIPAC3, respectively (P = 0.006; Supplemental Appendix 2a, http://links.lww.com/AOSO/A165). Median PCI was 21 (IQR = 15–29) at baseline and 20 (IQR = 12–27) at PIPAC3 (P = 0.02). Symptoms improved in 56 (53.8%) versus 48 (46.2%) patients, respectively (P = 0.267; Supplemental Appendix 2b, http://links.lww.com/AOSO/A165). QoL was available for only 71 patients (28%) and could hence not be analyzed.

Survival After PIPAC Treatment and Predictors for Survival

Survival of patients is provided from diagnosis of PM and from start of PIPAC treatment for the overall cohort in Figure 2A, B. Figure 2C illustrates the OS from first PIPAC of the pp cohort versus those who underwent <3 procedures. Cox regression analysis identified radiological progression HR 3.0 (95% CI = 1.6–5.7) and symptoms HR 4.5 (95% CI = 2.2–9.1) at PIPAC3 as negative

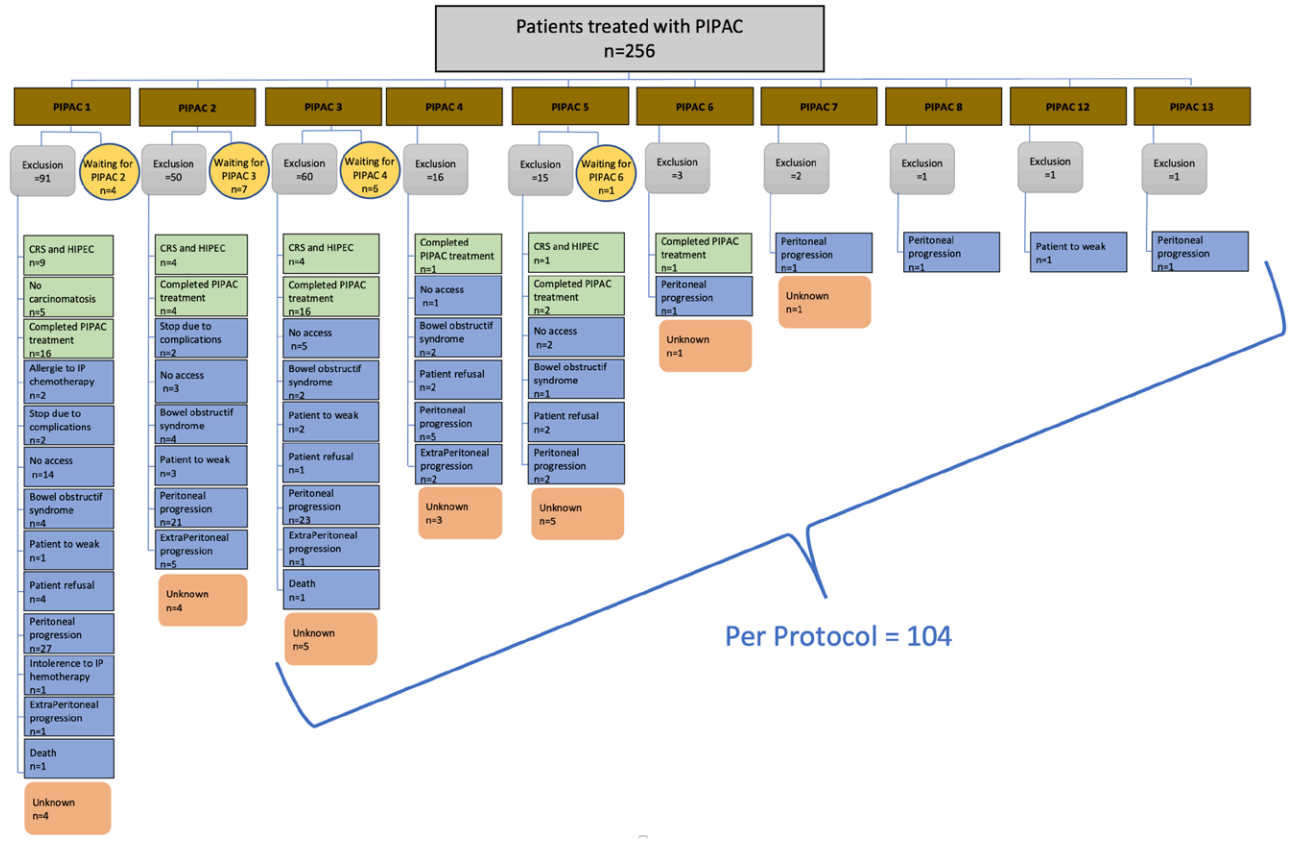

FIGURE 1. Patient flow chart. IP indicates IntraPeritoneal chemotherapy.

predictors for OS. Of note, potential surrogates such as histological response, cytology, and PCI had no predictive value.

DISCUSSION

This large retrospective cohort study demonstrated objective response to PIPAC treatment in patients with PM of colorectal origin. OS was encouraging for patients mostly in the third line of treatment. Potential surrogates for treatment response were not predictive of OS in this study.

Objective tumor response in patients with colorectal PM was observed after PIPAC. The primary outcome of the present study was to determine OS in patients with colorectal PM treated at different PIPAC centers. We found a median OS from PIPAC1 of 9.4 and 11.5 months for the whole patient population and pp cohort, respectively. Remarkably, 2 earlier retrospective publications in patients with colorectal PM report OS ranging from 15 to 21 months from PIPAC1.[24,25] However, the mean PCI score in these smaller single center studies was considerably lower compared with the present study of non-selected all-comers. The present study is the first that compiled survival data of most of active PIPAC centers and clearly extends previous knowledge on OS from PIPAC1. Most importantly, we first describe median OS data starting from PM diagnosis as earlier research did not specify the baseline time-point or calculated OS from PIPAC1.[16] In patients with isolated PM colorectal cancer given first-line systemic chemotherapy, Franko et al[8] found a median OS of 16.3 months starting from PM diagnosis, which is in line with our findings. However, the PCI score was not assessed and this patient population may thus differ from our study. Therefore, definitive conclusions on the added value of PIPAC in terms of OS from PM diagnosis cannot be drawn from this study alone. In metastatic colorectal cancer, the optimal drug regimen and sequence in third line or beyond is currently unknown.[26] Median OS for third line ranges from 6.2 to 7.6 months and no data on survival of patients with isolated PM are available.[27] As almost two-third of our patients were treated with PIPAC (± systemic chemotherapy) after 2 lines of prior chemotherapy, an added benefit of PIPAC appears to be probable.

Our findings revealed that radiological response and symptoms at PIPAC3 are predictive of survival while other promising surrogates failed. However, radiological response according to RECIST was effective in predicting survival in this study. A few earlier studies merely used RECIST to assess change in tumor burden after PIPAC.[28–30] We must emphasize that this is the first PIPAC study performed to show that symptoms at PIPAC3 affect survival. Both observations enable clinicians to make informed estimates on the patients' treatment response and prognosis. It was not surprising to find that PRGS and peritoneal cytology had no independent prognostic value. Furthermore, also PCI at PIPAC3 was not predictive of survival. This differs from prior research in CRS and HIPEC, demonstrating that PCI score was an independent prognostic indicator.[31] It is important to underline that the PCI score was despite the known risk of moderate underestimation a valuable tool to describe the extent of PC at PIPAC1. However, PCI after repeated PIPAC is challenging as a subjective macroscopic assessment cannot differentiate between therapy-induced regression and viable tumor lesions (possible overestimation of disease extent under treatment).

Note that almost half of patients received PIPAC as monotherapy. The reason for this is partially unclear but we assume that most patients had refractory disease and no further systemic chemotherapeutic options. PM had a reduced response to systemic chemotherapy and earlier implementation of PIPAC must be strongly considered. It is, however, important to note that no survival data are available in the literature for colorectal cancer patients receiving either PIPAC as monotherapy or PIPAC with concomitant systemic chemotherapy. Moreover, no previous PIPAC research stratified survival outcomes of colorectal cancer

TABLE 1.

Demography Characteristics of Patients Undergoing PIPAC for Peritoneal Metastases of Colorectal Origin

Parameter	All Patients (n = 256)	<3 PIPACs (n = 152)	≥3 PIPACs (n = 104)	*P*
Median age (IQR)	61.0 (50.6–69.2)	59.6 (50.3-68.0)	62.0 (51.0–71.6)	0.820
Age group, n (%)				
≤30	7 (2.7)	4 (2.7)	3 (2.9)	0.964
31–40	17 (6.5)	9 (6)	8 (7.7)	
41–50	40 (15.8)	26 (17.3)	14 (13.4)	
51–60	62 (24.3)	39 (25.5)	23 (22.1)	
61–70	75 (29.4)	46 (30.2)	29 (27.9)	
>70	55 (21.3)	28 (18.3)	27 (25.9)	
Gender, n (%)				
Male	145 (57)	79 (52)	66 (63)	0.084
Female	111 (43)	73 (48)	38 (37)	
Median BMI (kg/m^2) (IQR)	23.4 (21.1–26.2)	23.6 (21.2–26.3)	23.0 (21.0–25.5)	**0.031**
ASA				
1	15 (7%)	9 (7%)	6 (7%)	0.906
2	137 (62%)	83 (63%)	54 (61%)	
3	68 (31%)	39 (30%)	29 (33%)	
ECOG				
0	73 (37%)	48 (41%)	25 (31%)	0.337
1	93 (47%)	53 (45%)	40 (49%)	
2 + 3	33 (17%)	17 (14%)	16 (20%)	
Symptoms pre-PIPAC				
No	131 (52%)	79 (53%)	48 (46%)	0.636
Yes	122 (48%)	70 (47%)	56 (54%)	
Pain				
No	160 (67%)	98 (69%)	62 (65%)	0.599
Yes	78 (33%)	45 (31%)	33 (35%)	
Ascites				
No	182 (77%)	114 (82%)	68 (71%)	**0.044**
Yes	53 (23%)	25 (18%)	28 (29%)	
Dysphagia				
No	212 (96%)	126 (95%)	86 (97%)	0.665
Yes	9 (4%)	6 (5%)	3 (3%)	
Obstructive symptoms				
No	189 (81%)	108 (77%)	81 (88%)	**0.029**
Yes	44 (19%)	33 (23%)	11 (12%)	
Nausea				
No	199 (85%)	120 (85%)	79 (86%)	0.872
Yes	34 (15%)	21 (15%)	13 (14%)	

BMI indicates body mass index; ECOG, Eastern Cooperative Oncology Group.

patients by line of palliative treatment,[16] demonstrating a need for further research, ideally in the sense of prospective studies.

Not surprisingly, patients in the pp cohort had less frequently obstructive symptoms than those who had <3 PIPAC procedures. The development of obstructive symptoms signals in most patient's disease progression with consecutive stop of PIPAC therapy. Hence, early prediction of treatment response is a priority of ongoing research to better select PC patients for PIPAC treatment.

The present analysis provides an honest report on the real-world experience with PIPAC in a large cohort of patients with colorectal PM and constitutes an important piece of evidence in a field with high clinical need for but chronic lack of data. Nonetheless, heterogeneity, missing data and lack of control group make definitive conclusions impossible and further prospective investigation a priority as outlined in the following. The retrospective study design entails a risk of reporting bias and patient selection. Therefore, all expert centers were invited and only cohorts of non-selected consecutive patients were accepted. Definition of outcomes and follow-up was heterogeneous among the institutions, and missing data had to be dealt with. Finally, and despite multicenter analysis, we acknowledge that the patient sample remains still limited and heterogeneous. And most importantly, no control group was available to compare the study cohort versus an adequately matched cohort of patients treated with standard of care. Further confirmation of oncological efficacy will require prospective registry data including non-selected patients treated for PM with or without PIPAC. Eventually, randomized controlled trials are inevitable and they should pay particular attention to outcomes of PIPAC as monotherapy versus PIPAC with intermittent systemic chemotherapy, including stratification of survival data according to line of chemotherapy and tumor biology.

The present study offers at the time being the best available evidence on efficacy of PIPAC in patients with colorectal PM. Objective tumor response could be demonstrated and survival compares favorably to reports on patients under systemic treatment only. These results can justify the use of PIPAC for colorectal PM in the third-line situation and stimulate prospective evaluation of PIPAC for this and other indications within the framework of clinical studies with appropriate control groups.

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TABLE 2.

Oncological Characteristics of Patients Undergoing PIPAC for Peritoneal Metastases of Colorectal Origin

Parameter	All Patients (n = 256)	<3 PIPACs (n = 152)	≥3 PIPACs (n = 104)	*P*
Pathology				
Metachronous <1 y	20 (23%)	16 (25%)	5 (13.5%)	0.387
Metachronous >1 y	67 (77%)	47 (75%)	32 (86.5%)	
Synchronous	156 (61%)	89 (35%)	67 (26%)	0.344
Metachronous	100 (39%)	63 (25%)	37 (14%)	
Histology				
G1	106 (41%)	64 (42%)	42 (40%)	0.711
G2	41 (16%)	27 (18%)	14 (13%)	
G3	42 (16%)	24 (16%)	18 (17)	
RAS				
No	71 (44%)	37 (42%)	34 (46%)	0.575
Yes	92 (56%)	52 (58%)	40 (54%)	
BRAF gene				
No	98 (88%)	49 (86%)	49 (91%)	0.434
Yes	13 (12%)	8 (14%)	5 (9%)	
Previous CRS + HIPEC				
No	238 (93%)	140 (92%)	98 (94%)	0.514
Yes	18 (7%)	12 (8%)	6 (6%)	
Previous CRS				
No	129 (50%)	74 (49%)	55 (53%)	0.509
Yes	127 (50%)	78 (51%)	49 (47%)	
Previous first chemo line				
No	0 (0%)	0 (0%)	0 (0%)	
Yes	256 (100%)	152 (100%)	104 (100%)	0.788
Oxaliplatin-based	146 (63%)	85 (67%)	61 (58%)	0.166
Biological therapy	147 (64%)	89 (67%)	58 (60%)	0.267
Total cycle (IQR)	7 (5–12)	8 (6–12)	6 (5–12)	0.492
Previous 2 lines of chemotherapy	142 (63%)	82 (63%)	60 (63%)	0.931
Previous 3 lines of chemotherapy	63 (28%)	43 (33%)	20 (22%)	0.054
Total cycles (IQR)	11 (6–14)	10 (6–14)	11 (6–16)	0.668
Bimodal (PIPAC + IV/oral chemo)	133 (52%)	61 (40%)	72 (69%)	**0.001**
Total cycles				
≤12	128 (68%)	77 (68%)	51 (67%)	0.881
>12	61 (32%)	36 (32%)	25 (33%)	
Ca19.9 (U/mL) (SD)	336 ± 1930	522 ± 2553	94 ± 194	0.089
Ca125 (U/mL) (SD)	104 ± 147	132 ± 169	77 ± 118	**0.004**
Creatinine (µmol/L) (SD)	76 ± 27	76 ± 26	76 ± 28	1.00
Albumin (g/L) (SD)	38 ± 7	38 ± 8	37 ± 7	0.303
PCI (IQR)	18 (10–27)	18 (9–26)	21 (14–29)	0.202

TABLE 3.

Treatment Response of the PP Cohort of Patients Having ≥PIPAC Treatments for Peritoneal Metastases of Colorectal Origin

	PP Cohort (n = 104)		
Parameter	Baseline	≥3 PIPACs	*P*
RECIST (n = 59)			
Partial response/stable		35 (59.3%)	
Progression		24 (40.7%)	
PRGS (n = 66)			
1–2		48 (72.7%)	
3–4		18 (27.3%)	
Cytology (n = 49)			
Positive	27 (55.1%)	15 (30.6%)	**0.006**
Negative	22 (44.9%)	34 (69.4%)	
ΔPCI (PIPAC1 vs 3) (n = 81)			
≥3 decrease		24 (29.6%)	0.503
<3 decrease or increase		57 (70.4%)	
Any symptoms (n = 104)ti			
Yes	56 (53.8%)	48 (46.2%)	0.267
No	48 (46.2%)	56 (53.8%)	

Surrogates for treatment response were available for a variable no. of patients as specified (n=). This number was used as denominator for the consecutive percentage calculation of outcomes.

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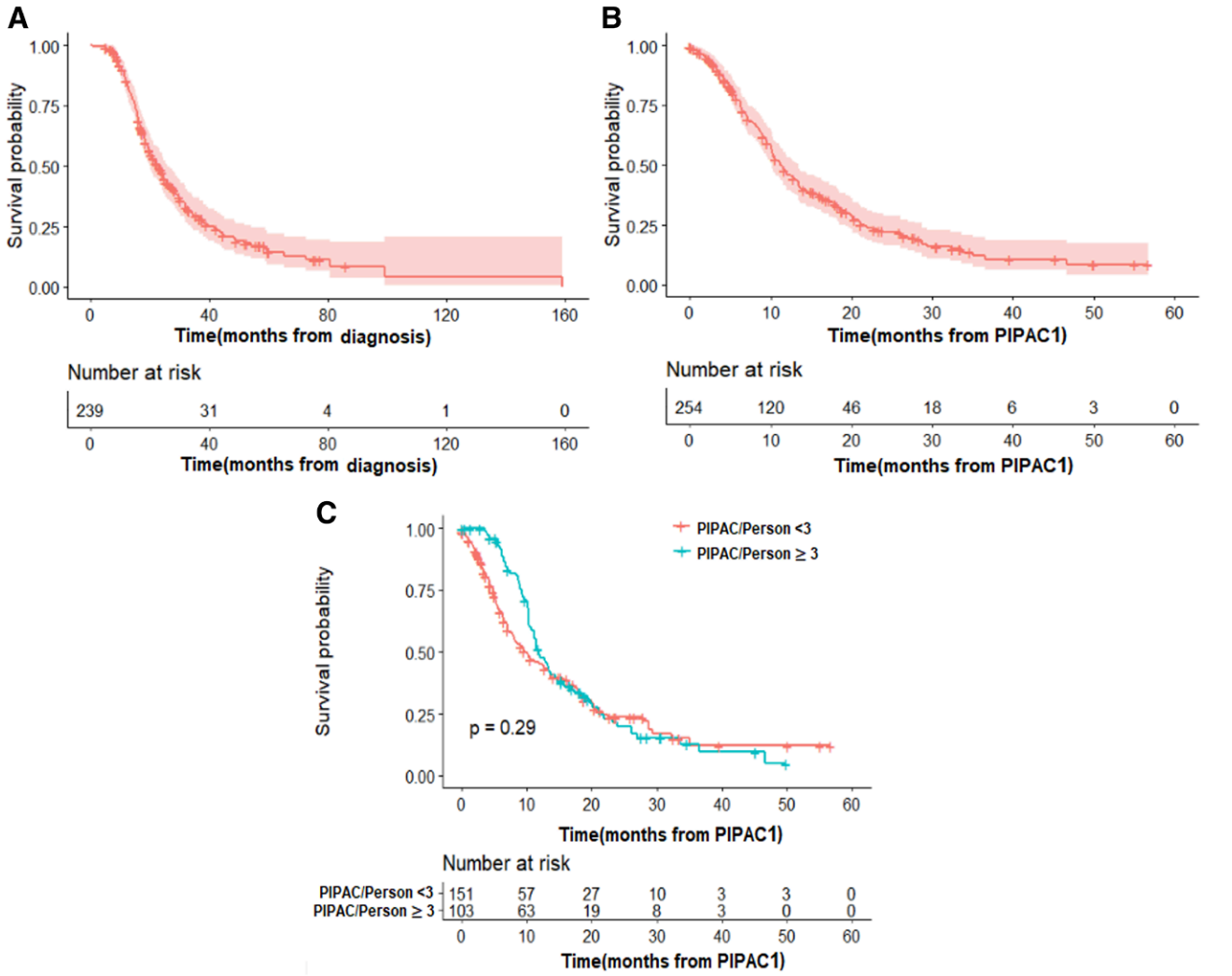

FIGURE 2. Survival of patients undergoing PIPAC for peritoneal metastases of colorectal origin. OS for the entire cohort from time of diagnosis of PM (A) and first PIPAC (B). By protocol analysis versus <3 PIPACS in terms of OS (C) from first PIPAC.

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REFERENCES

1. Lemmens VE, Klaver YL, Verwaal VJ, et al. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011;128:2717–2725.
2. Segelman J, Granath F, Holm T, et al. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2012;99:699–705.
3. Narasimhan V, Ooi G, Michael M, et al. Colorectal peritoneal metastases: pathogenesis, diagnosis and treatment options - an evidence-based update. ANZ J Surg. 2020;90:1592–1597.
4. Sasson AR, Kim J. Many challenges of peritoneal carcinomatosis. J Oncol Pract. 2017;13:435–436.
5. Yan TD, Morris DL, Shigeki K, et al. Preoperative investigations in the management of peritoneal surface malignancy with cytoreductive surgery and perioperative intraperitoneal chemotherapy: expert consensus statement. J Surg Oncol. 2008;98:224–227.
6. Koh JL, Yan TD, Glenn D, et al. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. Ann Surg Oncol. 2009;16:327–333.
7. Cortés-Guiral D, Hübner M, Alyami M, et al. Primary and metastatic peritoneal surface malignancies. Nat Rev Dis Primers. 2021;7:91.
8. Franko J, Shi Q, Meyers JP, et al; Analysis and Research in Cancers of the Digestive System (ARCAD) Group. 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. 2016;17:1709–1719.
9. Goéré D, Malka D, Tzanis D, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg. 2013;257:1065–1071.
10. Quénet F, Elias D, Roca L, et al; UNICANCER-GI Group and BIG Renape Group. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:256–266.
11. Solass W, Kerb R, Mürdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21:553–559.
12. Grass F, Vuagniaux A, Teixeira-Farinha H, et al. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. Br J Surg. 2017;104:669–678.
13. Alyami M, Hübner M, Grass F, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20:e368–e377.
14. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–374.
15. Solass W, Sempoux C, Detlefsen S, et al. Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the Peritoneal Regression Grading Score (PRGS). Pleura Peritoneum. 2016;1:99–107.
16. Lurvink RJ, Rovers KP, Nienhuijs SW, et al. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC-OX) in patients with colorectal peritoneal metastases-a systematic review. J Gastrointest Oncol. 2021;12(Suppl 1):S242–S258.
17. Hübner M, Grass F, Teixeira-Farinha H, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy - practical aspects. Eur J Surg Oncol. 2017;43:1102–1109.
18. Sgarbura O, Villeneuve L, Alyami M, et al; ISSPP PIPAC study group. Current practice of pressurized intraperitoneal aerosol chemotherapy (PIPAC): still standardized or on the verge of diversification? Eur J Surg Oncol. 2021;47:149–156.
19. Sgarbura O, Eveno C, Alyami M, et al. Consensus statement for treatment protocols in pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pleura Peritoneum. 2022;7:1–7.
20. Nowacki M, Alyami M, Villeneuve L, et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: an international survey study. Eur J Surg Oncol. 2018;44:991–996.
21. Teixeira Farinha H, Grass F, Kefleyesus A, et al. Impact of pressurized intraperitoneal aerosol chemotherapy on quality of life and symptoms in patients with peritoneal carcinomatosis: a retrospective cohort study. Gastroenterol Res Pract. 2017;2017:4596176.
22. Solass W, Sempoux C, Carr NJ, et al. Reproducibility of the peritoneal regression grading score for assessment of response to therapy in peritoneal metastasis. Histopathology. 2019;74:1014–1024.
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–247.
24. Demtröder C, Solass W, Zieren J, et al. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis. 2016;18:364–371.
25. Ellebæk SB, Graversen M, Detlefsen S, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)-directed treatment of peritoneal metastasis in end-stage colo-rectal cancer patients. Pleura Peritoneum. 2020;5:20200109.
26. Fernández-Montes A, Grávalos C, Pericay C, et al. Current options for third-line and beyond treatment of metastatic colorectal cancer. Spanish TTD group expert opinion. Clin Colorectal Cancer. 2020;19:165–177.
27. Vogel A, Hofheinz RD, Kubicka S, et al. Treatment decisions in metastatic colorectal cancer - beyond first and second line combination therapies. Cancer Treat Rev. 2017;59:54–60.
28. Struller F, Horvath P, Solass W, et al. Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal metastasis: a phase II study. Ther Adv Med Oncol. 2019;11:1758835919846402.
29. Tempfer CB, Winnekendonk G, Solass W, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol. 2015;137:223–228.
30. De Simone M, Vaira M, Argenziano M, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with oxaliplatin, cisplatin, and doxorubicin in patients with peritoneal carcinomatosis: an open-label, single-arm, phase II clinical trial. Biomedicines. 2020;8:E102.
31. Glehen O, Gilly FN, Boutitie F, et al; French Surgical Association. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer. 2010;116:5608–5618.