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ORIGINAL ARTICLE

Chasing Rainbows? the Possibility of "Cure" in Patients with Colorectal Peritoneal Metastases Undergoing Cytoreductive Surgery and HIPEC—a Retrospective Study by INDEPSO

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Abstract

Cytoreductive surgery (CRS) and HIPEC results in a median disease-free survival (DFS) of 12–15 months, overall survival (OS) of 23–63 months, and cure in around 15% of patients with colorectal peritoneal metastases (CPM). The wide variation in OS may largely be attributed to different criteria for patient selection employed by different investigators. To evaluate outcomes of CRS and HIPEC for CPM in patients enrolled in the Indian HIPEC registry. A retrospective analysis of patients enrolled in the registry since its inception in March 2016 was performed. The impact of various prognostic factors on DFS and OS was evaluated. From Jan 2013 to Dec 2017, 68 patients underwent CRS with HIPEC at six Indian centers. The median PCI was nine [range 3–35]. Twenty-two (32.3%) had mucinous tumors. A CC-0 resection was performed in 53 (77.9%) and CC-1 in 14 (20.5%). The median DFS was 12 months [95% CI 11.037–12.963 months] and the median OS 25 months [95% CI 18.718–31.282]. The DFS was inferior in patients with right upper quadrant involvement ($p = 0.02$) and 90-day major morbidity ($p = 0.002$) and OS inferior in those with 90-day major morbidity ($p < 0.001$) and mucinous tumors with a PCI > 20. The DFS compares well with results obtained by pioneering teams but we have no "cured" patients. Better patient selection and utilization of systemic therapies could in the future improve the OS. There is a compelling need to identify subgroups of CPM that benefit from the addition of HIPEC to CRS.

Keywords Colorectal cancer · Peritoneal metastases · Cytoreductive surgery · HIPEC · Mucinous tumors

Introduction

Surgical treatment comprising of cytoreductive surgery and HIPEC can cure selected patients with colorectal peritoneal metastases (CPM) [1]. The recent PRODIGE 7-ACCORD 15 trial (NCT00769405) underlined the survival benefit of surgical resection of CPM that has previously been demonstrated by other studies [2, 3]. This trial did not show a benefit of adding oxaliplatin hyperthermic intraperitoneal chemotherapy (HIPEC) to complete cytoreductive surgery (CRS) in a large proportion of patients with CPM who had responded to neo-adjuvant systemic chemotherapy [3]. In the light of these results, it should be borne in mind that the benefit of any form of intraperitoneal chemotherapy in addition to CRS will remain marginal and subgroups that derive the maximum benefit from intraperitoneal therapies remain undefined.

Most studies report a similar disease-free survival following CRS and HIPEC of 12–15 months but the overall survival

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ranges from 23 to 63 months [4]. The disease extent according to the PCI and completeness of cytoreduction are the two most important prognostic factors [5]. Other factors that have a negative impact on survival are the presence of lymph node metastases, extensive disease on the small bowel, signet ring cell histology, and BRAF-mutation-positive tumors [4]. A recent study demonstrated that patients with early onset of metachronous metastases after chemotherapy develop early recurrence after CRS and HIPEC [6]. The results in patients with colorectal PM are evaluated for the combined modality largely and it is difficult to quantify the benefit of each. Colorectal PM at large is a heterogeneous group of patients and it is not clear if the outcomes in patients with colonic versus rectal tumors, right-sided versus left-sided tumors are different [7, 8]. The molecular subtype commonly found in colorectal PM is the one with the worst prognosis [9]. While comparing different studies or subgroups within one study, it is possible to balance only the known prognostic factors and hence the homogeneity of subgroups remains questionable.

Colorectal cancer is an uncommon cancer in India [10]. The oncological practices in India commonly follow western trends in the setting of the clinician's own experience, the socioeconomic status of the population being treated, and their expectations. In this manuscript, we look at outcomes of CRS and HIPEC for colorectal PM in patients enrolled in the Indian HIPEC registry.

Methods

A retrospective analysis of prospectively collected data was performed. Indian Network for Development of Peritoneal Surface Oncology (INDEPSO) is a collaborative group of Indian surgeons specializing in the management of peritoneal surface malignancies. All patients with colorectal PM enrolled in the Indian HIPEC registry since its inception in March 2016 were included in the study.

Demographic data, clinical findings, operative findings, and perioperative outcomes and details of systemic therapy were recorded.

All patients undergoing CRS with or without HIPEC were included. CRS was performed with the goal of obtaining a complete cytoreduction (CC-0). Patients with a predicted peritoneal cancer index (PCI) of less than 17–20 and absence of unresectable extraperitoneal metastases were taken up for surgery [11]. The other criteria for patient selection like the use of prognostic scores and response to systemic chemotherapy depended on the individual surgeons/institutions. HIPEC was performed by the closed, semi-open or open technique using an oxaliplatin or mitomycin-C based regimen. The Elias protocol of 460 mg/m^2 of oxaliplatin for 30 min with intravenous 5-FU infused over 1 h just before starting HIPEC was followed for oxaliplatin HIPEC [12]. Mitomycin C was used as a single agent (25–35 mg/m^2) or in combination with Adriamycin (15 mg/m^2) with or without bidirectional chemotherapy [13, 14]. The use of perioperative systemic chemotherapy and targeted therapies was at the discretion of the treating surgeon/institution. Complications were reported according to the common terminology criteria for adverse events (CTCAE) classification version 4.0 and the 90-day morbidity was also recorded [15].

Patients were followed up every 3 months for the first 2 years and every 6 months thereafter. Thoracoabdominopelvic (or whole-body) imaging was performed every 6 months or as clinically indicated.

In addition, we looked at the distribution of PM based on the detailed PCI score provided by each surgeon and the impact of histology on survival. The terms right upper quadrant (RUQ) and left upper quadrant (LUQ) were used for regions 1 and 3 of Sugarbaker's peritoneal cancer index, respectively. Regions 5, 6, and 7 were categorized as "lower region"; regions 8, 0, and 4 as "middle region"; and regions 1, 2, and 3 as "upper region." Mucinous tumors were defined as tumors with > 50% extracellular mucin and signet ring cell tumors as those with > 50% signet ring cells [16].

All patients were followed-up till death from any cause. Survival was calculated from the day of surgery.

Statistical Analysis

Categorical data were described as number (%). Abnormally distributed continuous data were expressed as the median and range. Categorical data were compared with the × 2 test. Multivariate Cox proportional hazard regression was used to describe the association between individual risk factors and morbidity, disease-free survival (DFS) and overall survival (OS) both, in terms of hazard ratio and its 95% confidence interval (CI). Survival curves were calculated using the Kaplan–Meier method and compared using the two-tailed log-rank test. SPSS Version 20 (SPSS Inc., Chicago, IL) and MedCalc Version 12.2 were used for analysis. A p value of < 0.05 was considered statistically significant. Disease-free survival and overall survival were both calculated from the date of surgery.

Results

From Jan 2013 to Dec 2017, 68 patients underwent CRS with HIPEC at six Indian centers (Table 1). Thirteen (19.1%) patients were under 40 years of age. Fifty-seven (83.8%) had colonic primary tumors and 11 (16.2%) had rectal primaries. The PM were synchronous in 30 (44.1%). Forty-seven (69.1) patients had received systemic chemotherapy before CRS of which 23 (48.9%)

Table 1 Patient and disease characteristics and perioperative outcomes in patients undergoing CRS and HIPEC

Characteristic		Overall (%)	Right side	Left side	*p* value
Age	Less than 40	13 (19.1)	4	9	0.172
	More than 40	55 (80.9)	25	23	
Sex	Male	31(45.5)	11	18	0.152
	Female	37 (54.5)	18	14	
Synchronous vs metachronous	Synchronous	30 (44.1)	14	14	0.229
	Metachronous	31 (45.5)	11	17	
	Info missing	07 (10.2)	4	01	
Chemotherapy before PM	Yes	47 (69.1)	17	25	0.100
	No	21 (30.9)	12	07	
NACT for PM	Yes	23 (33.8)	11	9	0.415
	No	45 (66.2)	18	23	
Prior surgery	Yes	45 (66.2)	15	25	0.03
	No	23 (33.8)	14	7	
PCI	< 12	43 (63.2)	18	22	0.714
	> 12	25 (66.8)	10	10	
Histology	Mucinous	22 (32.3)	12	8	0.295
	Non-mucinous	36 (52.9)	2	5	
	Signet ring	07 (10.2)	14	19	
	Mucinous+signet	3 (4.5)	1	0	
CC-score	CC-0	53 (77.9)	20	27	0.225
	CC-1	14 (20.5)	08	05	
	CC-2/3	01 (1.4)			
Ovarian metastases	Present	17 (25.5)	7	8	0.938
	Absent	51 (75.5)	22	24	
Diverting stoma	Yes	9 (13.2)			
	No	59 (86.8)			
90-day grade 3–4 morbidity	Yes	24 (35.2)	10	12	0.806
	No	44 (64.8)	19	20	
90-day mortality	Yes	05 (7.3)	3	1	0.255
	No	63 (92.7)	26	31	
Failure to rescue	Yes	05 (7.3)	2	2	0.919
	No	63 (92.7)	27	30	
Early recurrence (within 9 months)	Yes	20 (29.4)	11	7	0.170
	No	48 (70.6)	18	25	
Adjuvant therapy after CRS	Yes	20 (29.4)	10	8	0.417
	No	48 (70.6)	19	24	

patients received it for PM (neoadjuvant chemotherapy). The median PCI was nine [range 3–35]. Thirteen (19.1%) patients had a PCI > 20. Twenty-two (32.3%) patients had mucinous tumors and 7 (10.2%) patients had signet ring cell tumors. A complete cytoreduction was obtained in 53 (77.9%) patients, CC-1 in 14 (20.5%), and CC-2/3 in 1 (1.4%) patient. HIPEC was performed in 64 (94.1%) patients. The drug used was mitomycin C in 38 (55.8%) patients, mitomycin C and Adriamycin in 4 (5.8%), and oxaliplatin in 20 (29.4%). The median ICU stay was 3 days [range 0–39 days] and the median hospital stay was 14 days [range 5–49 days]. 64.1% completed 6 months of perioperative systemic chemotherapy. Only 12% received targeted therapies.

Morbidity and Mortality

Grade 3–4 complications developed in 20 (29.4%) patients at 30 days and in 27 (39.7%) at 90 days. The commonest complications were respiratory complications in 4 (5.8%), anastomotic leak in 3 (4.4%), spontaneous bowel perforations in 2 (2.9%), systemic sepsis in 2 (2.9%), and intraperitoneal hemorrhage in 2 (2.9%). Four (5.8%) patients died within 90 days of surgery. The cause of death was spontaneous bowel perforations in one patient, intraabdominal sepsis in one, respiratory failure in one, and acute renal failure in one. Eighteen (26.4%) patients had positive regional nodes. In five patients, adjuvant chemotherapy was delayed due to complications. In 19 patients, it was not planned. Patients with a PCI > 12 had a

higher incidence of complications at 30 days ($p = 0.08$) and 90 days ($p = 0.08$) and also increased mortality ($p = 0.06$) though these were not statistically significant (Table 2). Patients with no diverting stoma in the presence of a bowel anastomosis ($p = 0.02$) and diaphragmatic surgery ($p = 0.08$) had a higher incidence of grade 3–4 complications at 30 days. Patient with diaphragmatic surgery also had an increased incidence of mortality ($p = 0.002$).

Survival Outcomes

At a median follow-up of 13 months [range 3–72 months], the median DFS was 12 months [95% CI 11.037–12.963 months] and the median OS was 25 months [95% CI 18.718–31.282]. On univariate analysis, patients with PCI < 12 ($p = 0.04$), without RUQ involvement ($p = 0.01$), female sex ($p = 0.04$), and without grade 3–4 morbidity at 30 days ($p = 0.005$) and 90 days ($p < 0.001$) experienced a prolonged DFS (Table 3). Only RUQ involvement ($p = 0.02$) and 90-day major morbidity ($p = 0.002$) were independent predictors of an inferior DFS. Patients with PCI < 12 ($p = 0.01$), without RUQ involvement ($p = 0.02$) and without grade 3–4 morbidity at 30 ($p < 0.001$) and 90 days ($p < 0.001$) experienced a longer OS but only absence of 90-day grade 3–4 morbidity was an independent predictor of a superior OS ($p < 0.001$). Other factors like lymph node involvement, mucinous histology, side of the primary tumor, colonic versus rectal primary tumor and use of HIPEC had no significant impact on either the DFS or OS.

Distribution of Peritoneal Metastases

Ovarian metastases were present in 16 (23.5%) patients. Small bowel involvement was seen in 24 (35.2%) patients of which 14 (58.3%) had a small bowel PCI > 3. The RUQ was involved in 31 (45.5%) patients. In patients with RUQ involvement, the lower regions (regions 5, 6, and 7) were involved in all patients except one. Patients with RUQ involvement had a higher median PCI (18 versus 6), higher small bowel PCI ($p < 0.001$), higher proportion of mucinous tumors ($p < 0.01$) and CC-1 versus CC-0 resections ($p = 0.03$), and received more neoadjuvant chemotherapy ($p < 0.001$). All patients without RUQ involvement had a PCI of less than 12 compared to 22.5% with RUQ involvement. Left upper quadrant involvement (region 3) was associated with RUQ involvement in all except two patients. The 90-day grade 3–4 morbidity ($p = 0.08$) and 90-day mortality ($p = 0.52$) was similar between patients with and without RUQ involvement. Involvement of the RUQ was an independent predictor of an inferior DFS [Hazard ratio 2.097 (95% CI 1.067–4.122); $p = 0.03$] (Fig. 1). The median OS was inferior ($p = 0.02$) in these patients though it did not reach statistical significance on multivariate analysis.

Outcomes in Patients with Mucinous Tumors

There were 25 (36.7%) patients with mucinous tumors of which 3 (4.4%) had a rectal primary tumor. Seventeen (77.2%) colonic tumors were right sided and five were left sided. The proportion of ovarian metastases ($p = 0.01$) was higher in the mucinous group ($p = 0.02$). The mucinous group had a median PCI of 13 [range 4–35] compared to 8 [range 3–27] in the non-mucinous group and more patients with a PCI > 12 ($p = 0.01$). All patients except one in the mucinous group had a complete cytoreduction (CC-0/1). HIPEC was performed in 92% in the mucinous and 90.6% in the non-mucinous group ($p = 0.85$). 88% in the mucinous and 88.3% in the non-mucinous group received 6 months of perioperative

Table 2 Factors affecting morbidity and mortality

Characteristic	30-day morbidity	90-day morbidity	Grade 3–4 morbidity
Age < 65 and > 65	0.148	0.373	0.448
Sex	0.910	0.333	0.379
Synchronous versus metachronous	0.580	0.184	0.431
Right versus left sided tumors	0.960	0.962	0.400
Prior surgery	0.766	0.898	0.496
Prior chemotherapy	0.542	0.417	0.407
PCI < 12 versus > 12	0.081	0.082	0.006
PCI < 20 versus > 20	0.012	0.016	0.002
Stoma formation	0.022	0.094	0.406
Mucinous versus non-mucinous tumors	0.307	0.056	0.542
RUQ disease	0.081	0.139	0.026
HIPEC versus no HIPEC	0.103	0.241	0.558
Drug-oxaliplatin versus Mitomycin C	0.359	0.521	0.499
Duration of surgery more than 480 min	0.820	0.400	0.617

Table 3 Factors affecting disease free and overall survival

Variable	Disease-free survival		Overall survival	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age < 40 versus > 40	0.111	NA	0.101	NA
Male versus female	0.048		0.346	NA
Metachronous versus synchronous	0.859	NA	0.167	NA
PCI < 12 versus > 12	0.042		0.012	
PCI < 20 versus > 20	0.003		0.001	
CC-0/1 versus CC-2/3		NA		
Mucinous vs non-mucinous vs signet ring	0.195	NA	0.515	NA
Right sided versus left sided	0.898	NA	0.620	NA
Colonic versus rectal primary	0.892	NA	0.467	NA
Right upper quadrant involvement (region 1)	0.013	0.024	0.027	Not significant
Ovarian metastases versus no metastases	0.235	NA	0.974	NA
NACT for PM	0.696	NA	0.972	NA
Adjuvant chemotherapy after CRS	0.296	NA	0.011	Not significant
Lymph node involvement	0.604	NA	0.901	NA
Grade 3–4 morbidity	0.005		0.000	
90-day morbidity	0.000	0.002	0.000	0.000

Abbreviations: *NA* not applicable

chemotherapy. The DFS was 12 months in both groups and the median OS was 26 months for mucinous and 20 months for non-mucinous tumors ($p = 0.51$). Patients with mucinous tumors with a PCI of > 20 had a median DFS of 6 months compared to 24 months in those with a PCI of < 20 ($p = 0.016$). As with non-mucinous tumors, patients with a PCI >12 had an inferior survival compared to patients with PCI<12 (p=0.08) though the difference was not statistically significant (Fig. 2). A PCI < 20 [hazard ratio (HR) 0.109; 95% confidence interval (CI) 0.021–0.570; $p < 0.001$] was the only independent predictor of a longer OS.

Discussion

The median DFS (12 months) in this group of patients is similar to that reported by other studies whereas the median OS (25 months) is inferior to the best results obtained worldwide [17, 18]. It is difficult to determine the reasons for the inferior OS since the patient population is heterogeneous and the selection criteria for surgery are not uniform. But even the 95% confidence interval is not very large with the longest survivors averaging only 32 months.

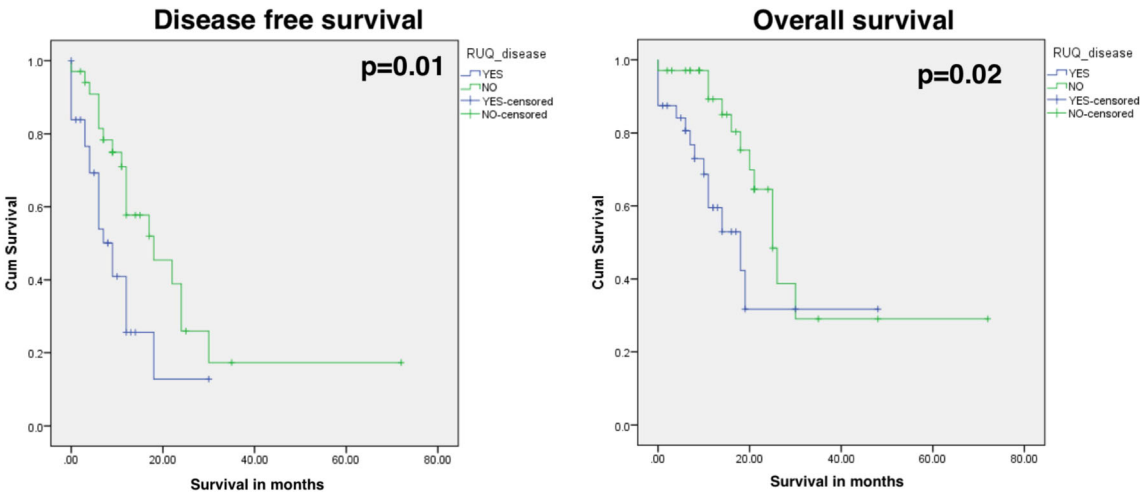

Fig. 1 Disease-free survival and overall survival in patients with and without RUQ involvement

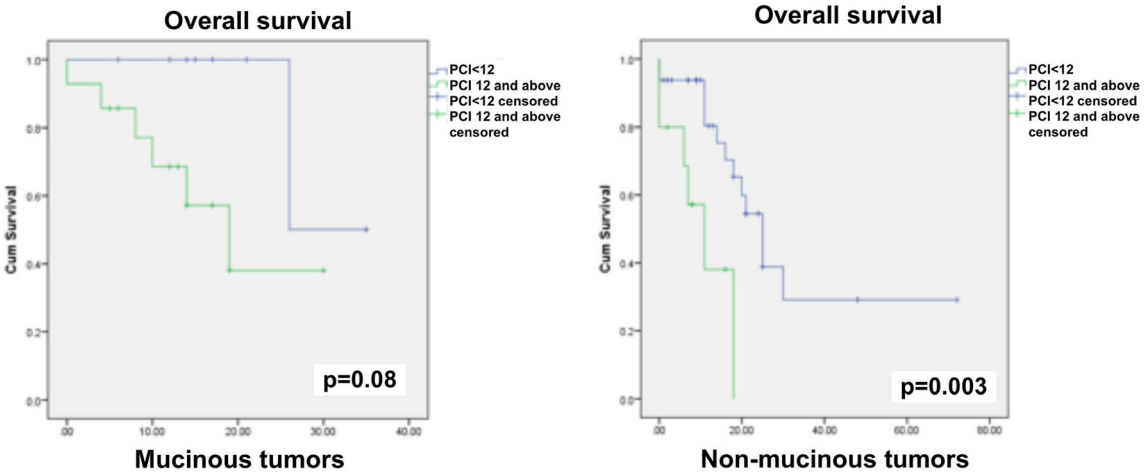

Fig. 2 Impact of PCI on survival in patients with mucinous and non-mucinous tumors

Though the 90-day grade 3–4 morbidity (39.7%) is comparable to published reports, 5 patients did not receive the planned chemotherapy due to complications [19, 20]. The benefit of adding HIPEC has to be weighed against the risk of morbidity especially where resources are limited. The same can be utilized for biological/systemic therapy. 64.4% of the patients completed 6 months of perioperative chemotherapy but only 12% received targeted therapy. Though the role of systemic chemotherapy remains undefined, the high survival outcomes reported in the PRODIGE-7 trial also underline the benefit of systemic chemotherapy [21]. The median progression-free survival in this trial was only 14 months while the overall survival was 43 months [2]. Even if systemic chemotherapy is not given as adjuvant therapy, it will invariably be used at the time of recurrence which will develop in over 75% of the patients [22].

The other question is of cure. In our experience, we had no "cured" patients. Patients who are disease-free at 5 years are considered to be cured [1]. All "cured" patients have a PCI of < 10. It would be interesting to know if the pathological response to chemotherapy had an impact on cure but such information is unavailable. Less than 10% of patients receiving NACT experience a complete response [23]. A complete/near complete pathologic response to systemic chemotherapy may be one of the important factors leading to cure. And in such patients, surgery may have a role in resection of residual disease or staging but HIPEC may not have much of a role [24]. Though over 2/3 of our patients received 6 months of perioperative chemotherapy, we do not have an evaluation of the pathological response to chemotherapy. Detractors of systemic chemotherapy argue that it may lead to the exclusion of patients with potentially resectable disease from surgery and add to the toxicity without benefit in poor responders. Most studies including ours do not have information on patients that are excluded due to toxicity and disease progression. It is possible that many such patients never reach a specialized center and hence it may not be unreasonable to recommend that all patients with PM are evaluated by a specialized team even if the initial plan is to administer systemic chemotherapy [25]. It is not just the surgical management that requires expertise but also administration of systemic chemotherapy and radiological and pathological evaluation.

There is also a need to develop biomarkers for selecting patients for chemotherapy. If the patients who are likely to respond could be identified, the selection process could become more homogenous across centers.

The high rate of complete cytoreduction (98.1%) in this series reflects good patient selection in terms of resectability alone. But other prognostic factors need to be taken into account while selecting patients for surgery. The important information that is missing in this study is the *KRAS* and *BRAF* mutation status and the MSI status. At times, these investigations are performed only when targeted therapy is planned. This is one aspect of practice that needs to undergo change. It has been shown that the survival in patients with *KRAS* and *BRAF* mutations is inferior with CRS and HIPEC [26]. Though CRS and HIPEC may still have a benefit over systemic chemotherapy alone in this subgroup, the survival is inferior to that in patients with non-mutated tumors and this information can be used for counseling patients of the expected benefit in survival.

The OS was non-inferior in 7 patients with signet ring cell tumors in this study. The peritoneal surface disease severity score (PSDSS) may be useful in selecting patients with signet ring cell tumors for surgery and could be used [27].

The proportion of mucinous tumors is higher but that reflects a selection bias as these patients are more commonly referred for surgery and surgeons take up patients with a high PCI for surgery as well. The survival in mucinous and non-mucinous tumors was also similar which has been reported by other investigators too [28]. Patients with mucinous tumors and PCI > 20 had a significantly inferior survival compared to those with a PCI < 20. However, another series of 58 patients with

CPM did not show any difference in survival between patients with PCI < or > 16. This data needs confirmation in larger prospective series [29].

Our results show the negative prognostic impact of RUQ involvement on survival. Involvement of the RUQ was seldom associated with localized disease—most patients had extensive disease. It was predictive of an inferior DFS and OS following complete CRS and HIPEC that were not offset by the use of systemic chemotherapy. Involvement of this region can be determined on pre-op imaging or staging laparoscopy and could be incorporated into patient selection tools and nomograms as a poor prognostic factor.

This study is retrospective with a small number of patients and the median follow-up is short, which are its major limitations. This study design is not ideal for establishing the proposed conclusions. Though the data collection is prospective, some important prognostic information is missing. Nevertheless, it provides a snapshot of the real-time situation in the country. There is a need to have not just specialist surgeons but multidisciplinary teams to improve outcomes in patients with peritoneal metastases.

In light of existing evidence, the role of CRS and HIPEC should be considered individually. There is level 1 evidence for performing cytoreductive surgery by "specialist surgeons" for colorectal PM [30]. HIPEC can be performed in selected subgroups of patients where the risk of morbidity is low, after consultation in multidisciplinary meetings taking into consideration the patients' socioeconomic status and education level. Some of the subgroups that benefit from HIPEC are patients with PCI 10–15, those that have limited disease that is poorly responding to chemotherapy or when systemic chemotherapy is not planned, and in patients with mucinous tumors. Further analysis of the outcomes of the PRODIGE-7 [2] and the results of the CAIRO-6 (NCT02758951) trial will largely influence the future of HIPEC for colorectal PM.

Conclusions

CRS and HIPEC can be performed with an acceptable morbidity in Indian patients with a DFS comparable to that reported by experienced centers across the world though there were no "cured" patients. Prognostic scores should be developed and used to stratify patients according to the expected survival benefit which in turn should be used for patient selection and counseling. Optimizing the use of systemic therapies is essential for obtaining long-term survival and cure. Patients with colorectal PM represent a heterogeneous group in which there is a compelling need to identify subgroups that benefit from the addition of HIPEC to complete cytoreductive surgery.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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References

1. Goéré D, Malka D, Tzanis D, Gava V, Boige V, Eveno C, Maggiori L, Dumont F, Ducreux M, Elias D (2013) Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg 257:1065–1071
2. Quenet F, Elias D, Roca L, Goere D, Ghouti L, Pocard M, et al (2018) A UNICANCER phase III trial of hyperthermic intraperitoneal chemotherapy (HIPEC) for col- orectal peritoneal carcinomatosis (PC): PRODIGE 7 [Internet]. J Clin Oncol. [cited 2018 Jul 17];36:LBA3503-LBA3503 Available from. http://ascopubs.org/doi/10.1200/JCO.2018.36.18_suppl.LBA3503
3. Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M (2016) Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015. A systematic review. Crit Rev Oncol Hematol 100:209–222
4. Bhatt A, Mehta S, Quenet F. Multimodality treatment for colorectal peritoneal metastases. In book: Management of peritoneal metastases- cytoreductive Surgery, HIPEC and beyond https://doi.org/10.1007/978-981-10-7053-212
5. Glehen O, Kwiatkofski F, Sugarbaker PH, Elias D et al (2004) Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 22:3284–3292
6. Sluiter NR, Rovers KP, Salhi Y, Vlek SL, Coupé VMH, Verheul HMW, Kazemier G, de Hingh IHJT, Tuynman JB (2018) Metachronous peritoneal metastases after adjuvant chemotherapy are associated with poor outcome after cytoreduction and HIPEC. Ann Surg Oncol 25(8):2347–2356. https://doi.org/10.1245/s10434-018-6539-x
7. Péron J, Mercier F, Tuech JJ, Younan R, Sideris L, Gelli M, Dumont F, Le Roy B, Sgarbura O, Lo Dico R, Bibeau F, Glehen O, Passot G, on behalf BIG-RENAPE working groups (2018) The location of the primary colon cancer has no impact on outcomes in patients undergoing cytoreductive surgery for peritoneal metastasis. Surgery:S0039-6060(18)30483-5. https://doi.org/10.1016/j.surg.2018.07.027
8. Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S et al (2017) Pri- mary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Ann Oncol 28:1862–1868
9. Ubink I, van Eden WJ, Snaebjornsson P, Kok NFM, van Kuik J, van Grevenstein WMU, Laclé MM, Sanders J, Fijneman RJA, Elias SG, Borel Rinkes IHM, Aalbers AGJ, Kranenburg O (2018 Jan) Histopathological and molecular classification of colorectal cancer and corresponding peritoneal metastases. Br J Surg 105(2):e204–e211. https://doi.org/10.1002/bjs.10788
10. BFact sheets by population-CRC India ASRs. [Online]. Available: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx
11. Goéré D, Souadka A, Faron M, Cloutier AS, Viana B, Honoré C, Dumont F, Elias D (2015) Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not

offer survival benefit: a comparative study. Ann Surg Oncol 22: 2958–2964

12. Elias D, Bonnay M, Puizillou JM, Antoun S, Dermirdjian S, El Otomany A et al (2002) Heated intra- operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmaco- kinetics and tissue distribution. Ann Surg Oncol 13: 267–272
13. Van der Speeten K, Stuart OA, Chang D et al (2011) Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis. Cancer Chemother Pharmacol 68:147. https://doi.org/10.1007/s00280-010-1460-4
14. Witkamp AJ, van Coevorden F, Kaag MM, van Slooten GW, Beijnen JB, Boot H et al (1998) Dose finding study of hyperthermic intraperitoneal chemotherapy with mitomycin C in patients with carcinosis of colorectal origin. Eur J Surg Oncol 24:214
15. Pande R, Sunga A, Levea C, Wilding GE, Bshara W, Reid M, Fakih MG (2008) Significance of signet-ring cells in patients with colorectal cancer. Dis Colon Rectum 51:50–55
16. United States Department of Public Health and Human Services, NIH, NCI: Common Toxicity Criteria for Adverse Events (CTCAE). National Cancer Institute, June 2010. http://evs.nci.nih.gov/ftp1/CTCAE_Vers._4.03_2010-06-14;_QuickReference_5x7.pdf
17. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ III (2010) Cytoreductive surgery and hyperthermic intraperitoneal chemo- perfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer 116:3756–3762. https://doi.org/10.1002/cncr.25116
18. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dubè P, Glehen O (2010) Peritoneal colorec- tal carcinomatosis treated with surgery and periop- erative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 28:63–68
19. Saxena A, Yan TD, Morris DL (2010) A critical evaluation of risk factors for complications after cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis. World J Surg 34:70–78
20. Glockzin G, Zeman F, Croner RS, Königsrainer A, Pelz J, Ströhlein MA, Rau B, Arnold D, Koller M, Schlitt HJ, Piso P (2018) Perioperative systemic chemotherapy, cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy in patients with colorectal peritoneal metastasis: results of the prospective multicenter phase 2 COMBATAC Trial. Clin Colorectal Cancer
21. Rovers KP, Simkens GA, Punt CJ, van Dieren S, Tanis PJ, de Hingh IH (2017) Perioperative systemic therapy for resectable colorectal peritoneal metastases: sufficient evidence for its widespread use? A critical systematic review. Crit Rev Oncol Hematol 114:53–62. https://doi.org/10.1016/j.critrevonc.2017.03.028
22. Golse N, Bakrin N, Passot G, Mohamed F, Vaudoyer D, Gilly FN, Glehen O, Cotte E (2012) Iterative procedures combining cytoreductive surgery with hyperther- mic intraperitoneal chemotherapy for peritoneal recurrence: postoperative and long-term results. J Surg Oncol 106(2):197–203
23. Passot G, You B, Boschetti G, Fontaine J, Isaac S, Decullier E, Maurice C, Vaudoyer D, Gilly FN, Cotte E, Glehen O (2014) Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol 21:2608–2614
24. Sugarbaker PH (2016) Preoperative assessment of cancer patients with peritoneal metastases for complete cytoreduction. Indian J Surg Oncol 7(3):295–302
25. Jacobson R, Sherman SK, Dadaleh F, Turaga KK (2018 Aug) Peritoneal metastases in colorectal cancer. Ann Surg Oncol 25(8): 2145–2151
26. Roth L, Schneider M, Eden J, Pache B, Laminger F, Lopez-Lopez V, Steffen T et al (2018) Mutation of RAS/RAF-proto-oncogenes impair survival after cytoreductive surgery and HIPEC for peritoneal metastases of colorectal origin. Pleura Peritoneum 1(Special Suppl):sA6–sA463
27. Pelz JOW, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J (2009) Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol 99:9–15. https://doi.org/10.1002/jso.21169
28. Huang Y, Alzahrani NA, Liauw W, Arrowaili A, Morris DL (2018) Survival difference between mucinous vs. non-mucinous colorectal cancer following cytoreductive surgery and intraperitoneal chemotherapy. Int J Hyperth 21:1–7
29. Brandl A, Weiss S, von Winterfeld M, Krannich A, Feist M, Pratschke J, Raue W, Rau B (2018) Predictive value of peritoneal cancer index for survival in patients with mucinous peritoneal malignancies treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a single centre experience. Int J Hyperthermia 34(5):512–517
30. Cashin PH, Mahteme H, Spång N, Syk I, Frödin JE, Torkzad M, Glimelius B, Graf W (2016) Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: a randomised trial. Eur J Cancer 53:155–162. https://doi.org/10.1016/j.ejca.2015.09.017