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Therapeutic efficacy of systemic therapy for colorectal peritoneal carcinomatosis: Surgeon's perspective

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Abstract: Treatment choices for colorectal peritoneal carcinomatosis/metastases include systemic therapy and increasingly cytoreductive surgery with intraperitoneal chemotherapy delivery. These options are best considered as complementary and not exclusive alternatives. Two prospective randomized trials support use of peritonectomy procedures and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis. This overview examines efficacy, limitations and landscape of systemic therapy focusing on colorectal peritoneal carcinomatosis. Observations from literature support notions that (1) systemic therapy provides survival benefit for all prototypical patients with mCRC irrespective of metastatic disease site; (2) the magnitude of this benefit is considerably reduced among patients with peritoneal metastases who consequently experience significantly shorter overall survival; (3) efficacy of systemic therapy improved over time but at a slower pace for those with carcinomatosis; (4) this therapeutic difference has not diminished with introduction of targeted therapy, but perhaps widened; (5) further research of cytoreductive surgery and/or intraperitoneal regional therapies is thus a multidisciplinary responsibility of the entire oncology community; (6) peritonectomy procedures with intraperitoneal regional therapy are not scientifically supported in absence of systemic therapies.

Keywords: cytoreduction, hyperthermia, intraperitoneal therapy, intraperitoneal chemotherapy, peritoneal surface, peritonectomy

Introduction

Contemporary landscape of treatment options in metastatic colorectal cancer (mCRC) includes systemic agents (cytotoxic, targeted and immunotherapy) and regional therapies (hepatic resection, ablation, regional chemo/radiotherapy delivery and similar). Comprehensive management of metastatic colorectal cancer patients is based on individual patient performance status, metastatic disease extent and treatment-related risk–benefit ratio. Thus, in context of systemic tumor dissemination (or risk thereof), prescription of systemic therapy until disease progression, unacceptable toxicity or disease complications is experienced by most patients. Outlook of mCRC patients has vastly improved in past decades, yet cure (long-term disease-free survival) remains restricted to a limited subgroup of those with resectable liver or lung metastases [1–6].

Peritoneal metastases in colorectal cancer (pmCRC) develop after coelomic metastatic spread as opposed to hematogenous route in hepatic or pulmonary metastases. Peritoneal metastases (or carcinomatosis) are associated with markedly worsened prognosis [7–15], perhaps due to progressive gastrointestinal dysfunction culminating in cachexia from carcinomatosis syndrome [16, 17]. Peritoneal surface lesions are difficult to radiologically detect, often do not meet RECIST criteria to qualify for "measurable disease" and thus are often excluded from response evaluation. Carcinomatosis deposits have a dense extracellular matrix causing elevated interstitial fluid pressure. Such environment forms an unfavorable therapeutic gradient resulting in diminished drug bioavailability and amplified drug clearance from peritoneal nodules after intravenous delivery [16, 18]. Nevertheless, a minority of authors would consider patients with limited peritoneal carcinomatosis as potentially curable if approached by combination of systemic and regional therapy [19–21]. Peritonectomy, abdominal cytoreduction and regional chemotherapy have been cautiously yet increasingly accepted by major guidelines both in Europe [22] and the United States [3] after some 30 years of liberal clinical experience, nevertheless controversy on this treatment modality is far from over [23].

Comparative studies of systemic therapy and its combination with surgical cytoreduction demonstrate reliable improvement in clinical outcomes (Table 1) [19–21, 24, 25],

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Table 1: Overall survival of colorectal peritoneal carcinomatosis patients treated with systemic chemotherapy alone or in combination with cytoreductive surgery and intraperitoneal chemotherapy. Listed are all four available comparative studies with internal control.

Study type Origin [citation]	Overall median survival (months)		Hazard ratio
	Systemic therapy-only	Systemic therapy and CS + IP therapy	
Prospective Amsterdam [21]	12.6	22.3	0.55
Retrospective France [19]	23.9	62.7	0.38 (estimate)
Retrospective Pittsburgh [24]	16.8	34.7	0.42
Prospective Sweden [20][a]	18.0	25.0	0.51

[a]Scandinavian trial delivered intraperitoneal and systemic therapy through intraperitoneal port and did not use hyperthermia, which was used in other three studies. CS + IP , cytoreductive surgery plus intraperitoneal therapy.

despite differences in histological type and disease volume burden [26–28]. Another important, yet often overlooked feature of colorectal peritoneal metastases/carcinomatosis, is its consistently worse survival as compared to unselected mCRC patients or those with absence of peritoneal involvement. Meaningful (by about 30–40 %) and statistically significant overall survival reduction was observed in population reports, retrospective institutional series as well as pooled studies of prospective randomized trials (Table 2, Figures 1, 2, 3) [7–11, 29–32].

While systemic therapy approaches are largely agnostic of mCRC disease site, regional approaches, such as hepatectomy, lung resection, and peritoneal cytoreduction with intraperitoneal chemotherapy capitalize on subtle phenotypic regions-specific characteristics. Optimal treatment of pmCRC must therefore require a combination of systemic and regional therapies in harmony to ensure synergy and long-term disease control [2, 19–21, 33]. To this end it is important to study effectiveness of systemic therapy specifically for peritoneal metastases, if one desires to meticulously examine the role of peritoneal-directed regional approaches, such as cytoreduction ± hyperthermic intraperitoneal chemotherapy (HIPEC) [19, 21, 24], extended postoperative intraperitoneal

Table 2: Overall survival of patients with colorectal peritoneal metastases (pmCRC) treated in prospective studies by systemic therapy only (no regional therapies).

Population sample/study	N *pmCRC only*	Systemic therapy	Hazard ratio *pmCRC vs. other mCRC*	median OS *months*	Weighted average (median OS)
[12]	45	5-FU	NR	6.0	7.2 months
Royal Marsden Hospital [7]	91	5-FU ± interferon	1.46	NR	HR = 1.27
EVOCAPE-1 [15]	118	5-FU	NR	5.2	
[21, 41] *(some appendix cancers)*	51	5-FU (±IRI)	NR	12.6	
[8]	326	5-FU	1.38	6.9–7.8	
[8]	71	5-FU+IRI	1.19	17.9	13.2
[9]	364	5-FU/OX/IRI	1.32	12.7	months HR = 1.27
CAIRO [11]	34	Cap±IRI→Cap+Ox	1.66[E]	10.4	
CAIRO2 [11]	47	Cap+Ox+Bev ± cetuximab	1.32 [E]	15.2	
Peritoneum-only ARCAD[10]	193	5-FU/Ox/IRI/bio	1.28 vs. non-pmCRC with 1 site	16.3	
Peritoneum + another site(s) [10]	1181	5-FU/Ox/IRI/bio	1.24 vs. non-pmCRC with ≥ 1 site	12.6	

5-FU, 5-fluorouracil; IRI, irinotecan; OX, oxaliplatinum; Cap, ceptacibine; Bev, bevacizumab; bio, biologic/targeted agent; [E], estimated hazard ratio; OS, overall survival; NR, not reported.

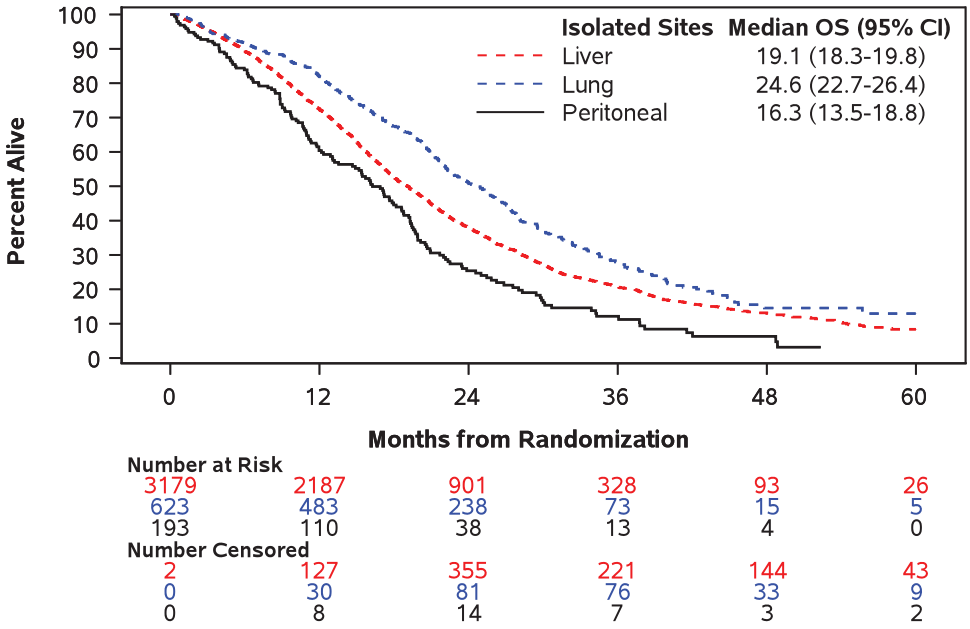

Figure 1: Overall survival in patients with metastatic colorectal cancer with metastases in a single organ. Adapted with permission from [10].

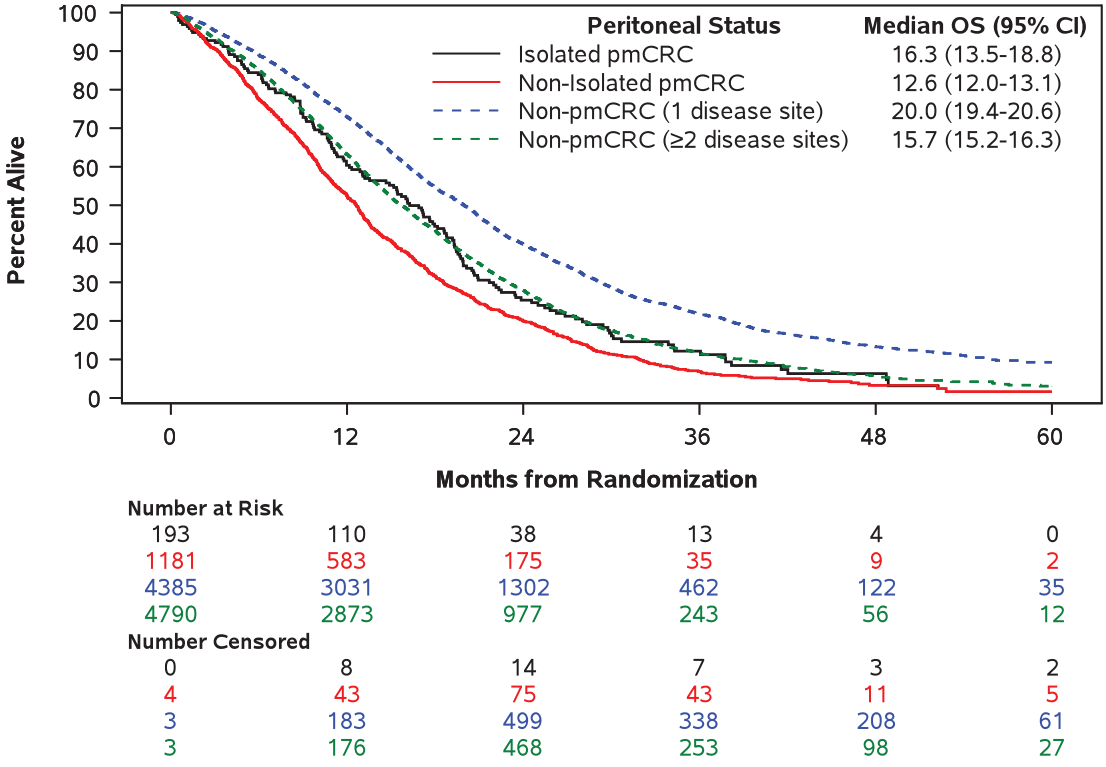

Figure 2: Overall survival of mCRC treated by first-line systemic therapy in 14 prospective randomized trials. Individual groups are selected by peritoneal involvement (solid lines - mCRC with peritoneal involvement; dashed lines – mCRC without peritoneal involvement) and number of metastatic disease sites (1 or ≥ 2). Adapted with permission from [10].

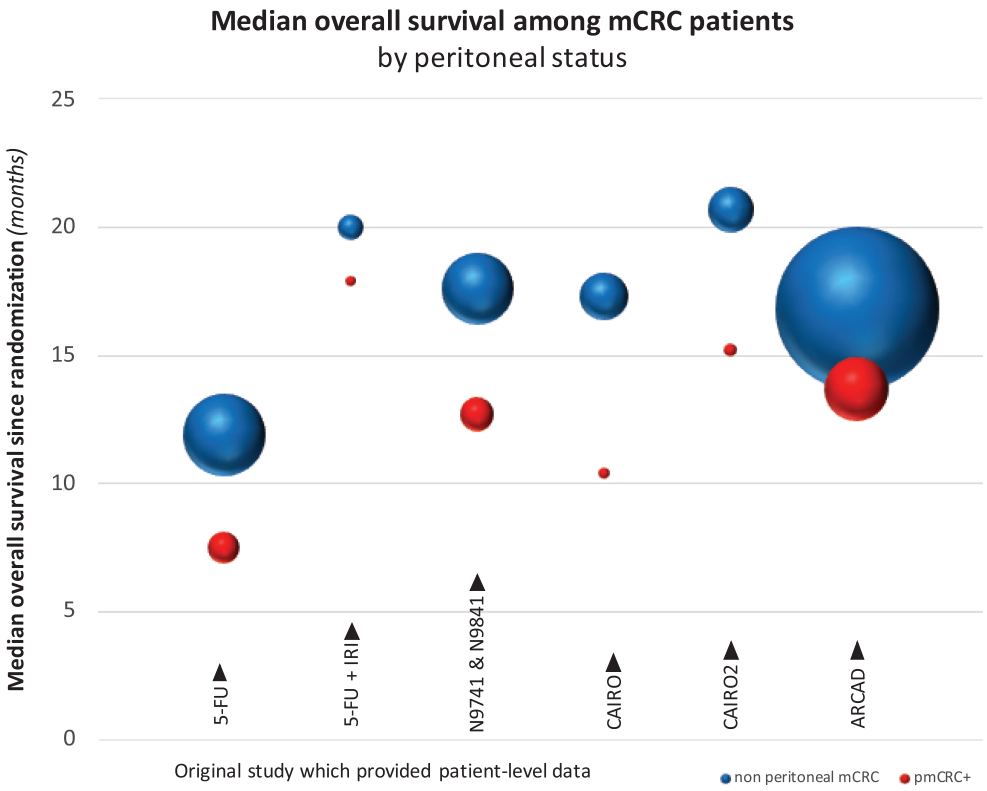

Figure 3: Median overall survival in selected studies of systemic chemotherapy published after adoption of oxaliplatinum and irinotecan. All presented studies are secondary/retrospective analysis of individual patient data collected prospectively on randomized trials of systemic therapy for mCRC. Larger size of circle corresponds to larger dataset. Blue circles = mCRC patients without peritoneal involvement, red circles = patients with colorectal peritoneal carcinomatosis (pmCRC +).

chemotherapy (EPIC) [20] or pressurized intraperitoneal chemotherapy (PIPAC) [33]. This overview examines efficacy, characteristics and limitations of systemic therapy for colorectal peritoneal carcinomatosis.

Era of 5-fluorouracil

5-fluorouracil has been a backbone of cytotoxic chemotherapy for colorectal cancer for decades and the first widely used drug for metastatic colorectal cancer. Folprecht et al. provided excellent evidence of clinically meaningful outcome differences between cases with and without peritoneal metastases in 2007 [8]. Analyzing 2,568 patients treated by first-line 5-FU chemotherapy in randomized prospective trials an overall survival benefit was observed for infusional 5-FU as compared to patients treated by 5-FU bolus (14.6 versus 10.8 months, $p < 0.0001$). However, no survival difference between infusional and bolus 5-FU application was observed among patients with peritoneal metastases (7.8 versus 6.9 months, $p = 0.44$). Additionally, pmCRC patients demonstrated markedly shorter median survival when compared to mCRC without carcinomatosis, although it was not commented upon by authors. In agreement with survival data, there was a significant difference in response rates based on peritoneal status and mode of 5-FU delivery. Patients without peritoneal involvement enjoyed substantially better objective response rates (36.2 % and 19.9 % for infusional and bolus 5-FU, respectively; $p < 0.001$) as compared to pmCRC cases (19 % and 12.6 % for infusional and bolus 5-FU, respectively; $p = 0.14$).

Many authors observed that peritoneal disease sites were radiologically less responsive as compared to hepatic metastases in mCRC [7, 27, 34, 35]. Assersohn et al. [7] pooled data obtained from trials of 5-FU based therapy conducted before approval of modern cytostatics. This analysis of Royal Marsden Hospital prospective data demonstrated substantially lower objective response of metastases in peritoneum as compared to other metastatic sites. Any response was observed among 10 % of peritoneal metastases, while liver metastases had 40 % response rate. Additionally, progressive disease was noted among 20 % of pmCRC patients over the study period as compared to 10 % of colorectal liver metastases (Figure 4).

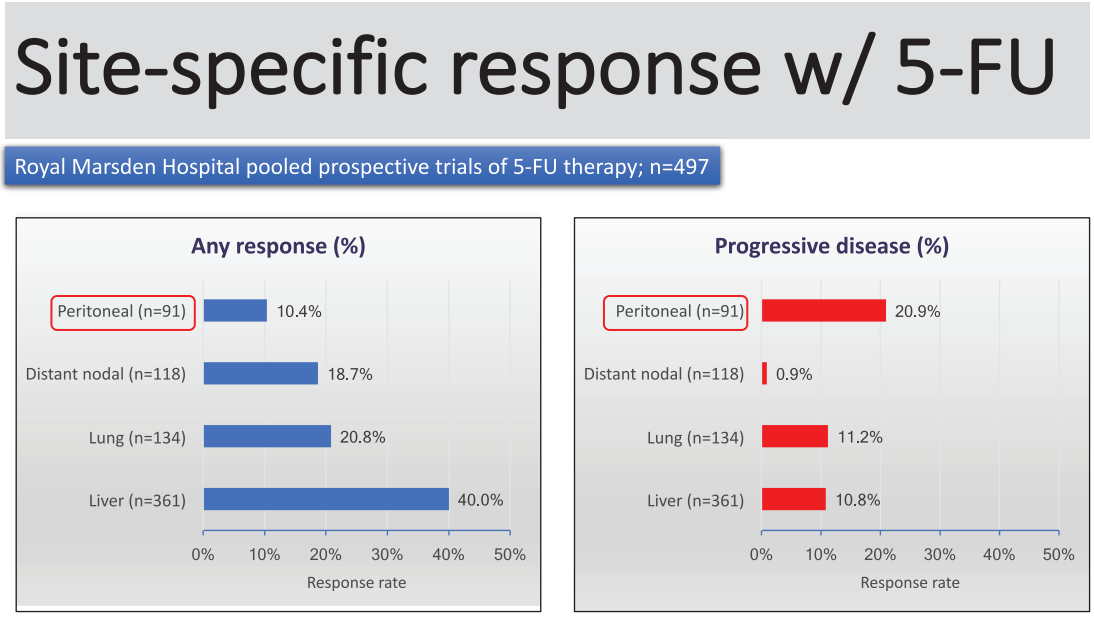

Figure 4: Response rates depending on site of metastases in mCRC patients treated with historical 5-FU combinations. Data from Royal Marsden Hospital studies [7].

Era of modern cytostatics: oxaliplatinum and irinotecan

Widespread approval of oxaliplatinum and irinotecan around 2004 led to a meaningful improvement in survival of patient population with mCRC as a whole (Figure 3). Importantly, there is virtually no clinical difference observed when administering all cytotoxic drugs concurrently in a very intense regimen as compared to sequential treatment started with less toxic combination first [36–38]. Survival is improved as long as all available cytotoxic agents are used during disease course [39].

However, the Eindhoven cancer registry study suggested that while survival for patients with colorectal liver metastases was longer in 2005–2008 period as compared to earlier periods, there was no significant improvement in overall survival among registered patients with isolated peritoneal disease, even when analysis was limited to chemotherapy recipients [29]. Because only 10 out of 904 patients with peritoneal-only metastases received peritoneal cytoreduction and HIPEC, this regional therapy has not confounded study results. A nearly identical conclusion came from a two-decade retrospective German institutional review with 2,406 patients; while mCRC patients all together experienced substantial survival gain over time, this benefit was not realized among those with carcinomatosis [32].

Survival advantage of irinotecan combined with 5-FU was suggested by separating survival curves, but was not statistically significant in a limited sample of patients with peritoneal carcinomatosis ($n = 71$; 17.9 versus 9.8 months for 5-FU + irinotecan versus 5-FU only, $p = 0.17$). Response rates were again higher among non-peritoneal mCRC and irinotecan combination as compared to pmCRC or 5-FU only [8]. Reported objective response rate among mCRC with no peritoneal metastases were 56 % for 5-FU+irinotecan versus 32 % for 5-FU ($p < 0.001$). Lower response rates were reported among those with colorectal peritoneal metastases (39 % for 5-FU + irinotecan versus 14 % 5-FU alone; $p = 0.03$).

A larger and detailed analysis of clinical outcomes of modern cytotoxic chemotherapy among patients with peritoneal involvement was provided by our group in an analysis of the North Central Cancer Treatment Group trials (N9741 trial, first-line therapy and N9841 trial, second-line therapy after first progression) [9]. There were 364 patients with peritoneal metastases among 2,101 patients extracted from databases of these prospective randomized studies. Hazard ratio for earlier death among pmCRC patients was consistently some 30 % higher as compared to cases without carcinomatosis, even after multiple adjustments. Of note, peritoneal metastases were more frequent among more advanced disease patients (22.6 % among patients in second-line versus 15.9 % in first-

line treatment trial, $p < 0.001$). Even greater survival difference between patients with and without peritoneal metastases was observed subsequently by re-analysis of CAIRO (estimated HR 1.6 for pmCRC patients as compared to those without peritoneal involvement) and CAIRO2 studies (estimated HR 1.4). This survival difference was judged to be related to intrinsic features of peritoneal involvement and not undertreatment, because median number of chemotherapy cycles was not statistically different between patients with and without peritoneal carcinomatosis [11].

Histological subtype has been a recognized survival predictor among CS-HIPEC patients [24, 26]. Regrettably, there is a remarkable paucity of information on histological features of mCRC among patients enrolled to randomized trials. Nonetheless, adjusted retrospective analyses suggest that non-mucinous tumors are 3.4 times more likely to respond as compared to mucinous and that non-peritoneal metastases are 2.7 times more likely to respond as compared to peritoneal metastases [27]. Based on nearly 6000 autopsies mucinous and signet-ring cell tumors metastatize to peritoneum more frequently as compared to more favorable adenocarcinoma with no other specification [28]. Possible link between proximal colon cancer, mucinous or signet-ring-cell histology and peritoneal dissemination represents an opportunity for further research [10, 28, 40].

Era of targeted therapies

A comprehensive evaluation of cytotoxic chemotherapy alone and in combination with targeted (biologic) therapy was facilitated by the availability of the ARCAD Project (Aide et Recherche en Cancérologie Digestive; www.fondationarcad.org).

One ARCAD endeavor adopted included prospective randomized studies of first-line systemic therapy, which either solicited request for peritoneal involvement in their protocol or performed peritoneum-specific review of original computed tomography scans to ascertain whether peritoneum was or was not involved [10]. Trial inclusion criteria scrutiny was so tall that we did not include N9741 trial forming basis of our prior report of colorectal peritoneal carcinomatosis [9]. The final study involved individual patient-level data from 14 prospective randomized studies with known peritoneal status and included 10,533 patients [10]. There were 1181 patient with peritoneal metastases in addition to other metastatic disease sites and 194 patients with metastases isolated to peritoneum. We reconfirmed in the largest dataset that peritoneal involvement among mCRC patients recruited to randomized trials is associated with shortened overall survival and progression free survival. Additionally, survival difference between patients with peritoneal involvement and disease-free peritoneum widened (Figures 1, 2, 5), data which was previously suggested by secondary analysis of CAIRO2 trial [11]. Median overall

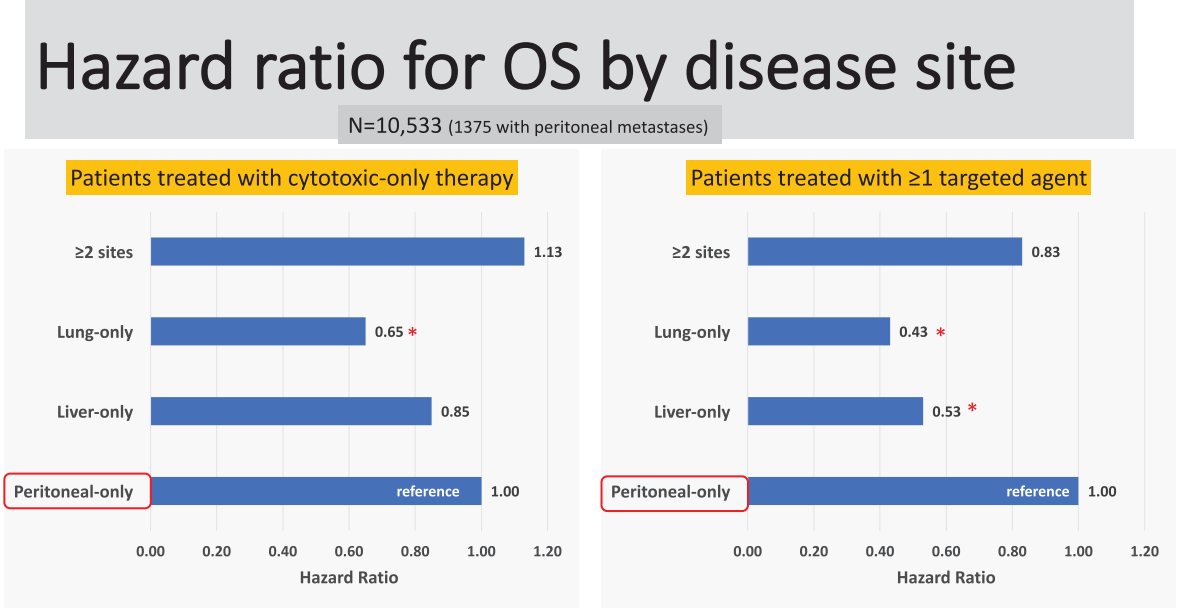

Figure 5: Hazard ratios for overall survival by site of metastases in cytotoxic-only therapy (left panel) and combined therapy including at least one targeted agent (right panel). * denotes statistical significance at least $p < 0.05$. Data from [10].

survival of patients with isolated peritoneal-only metastases was 16.8 months, whether cytotoxic chemotherapy was used alone or in combination with targeted agents (of note they were only 25 patients with peritoneal-only metastases and targeted therapy). On the contrary, there was trend toward longer survival among colorectal liver metastases patients treated by targeted agent as compared to those treated by cytotoxic chemotherapy only (20.4 months versus 18 months). Interestingly, remarkably similar survival of cetuximab-treated patients without peritoneal metastases (20.7 months) was observed in CAIRO2 study [11].

Discussion

There are multiple prospective data based [7–12, 15, 21, 41] and purely retrospective studies [27, 29, 32, 42] examining therapeutic efficacy of systemic therapy for colorectal peritoneal carcinomatosis. The largest prospective data-based studies confirmed both therapeutic efficacy of systemic chemotherapy but also consistently demonstrated inferior survival of patients affected by colorectal carcinomatosis in early 5-FU period [8], oxaliplatinum/irinotecan era [9, 11] and current era of targeted biologic therapy [10, 11]. Nevertheless, the literature recorded survival improvement of all forms of mCRC, including for those with peritoneal surface metastases (Table 2, Figure 3).

Meaningful survival improvements, and sometimes even cure, have been observed among those with resected or ablated liver metastases, typically in combination with systemic therapy [1, 2, 4–6]. On the other hand, failure to demonstrate clear survival benefit of well-designed liver-directed approaches, like Y90-based selective internal radiation or hepatic arterial infusion, reveals the complexity of metastatic colorectal cancer [43, 44].

Systemic therapy approaches are agnostic of metastatic site. On the contrary, regional approaches involving surgery and regional chemotherapy have been designed for specific metastatic site since their conception. Clinicians faced with historically poor prognosis developed peritoneal surface surgery combined with hyperthermic intraperitoneal chemotherapy [17, 21, 25, 45]. After years of research both the European and the United States National Comprehensive Cancer Network guidelines carefully recognized a restricted role of peritoneal cytoreduction and HIPEC in colorectal peritoneal carcinomatosis in addition to established role of systemic therapy [3, 22].

There are notable limitations of this review. Data from most studies examining peritoneal status come from older studies, and thus we lack information on efficacy of modern cytostatics (e. g. TAS-102). On the contrary, fairly good agent-specific data are available for 5-FU, oxaliplatinum and irinotecan [8, 9, 37–39]. Much less granularity is available for six approved targeted therapies by the end of 2017: bevacizumab, cetuximab, panitumumab, ziv-aflibercept, regorafenib, ramucirumab. The ARCAD agreements make it impossible to study drug versus drug, and therefore only class of drugs may be compared within ARCAD projects, i. e. antiangiogenic class as opposed to individual effect of bevacizumab or ziv-aflibercept. No peritoneum-specific facts are available on immunotherapy for advanced mCRC, such as approved pembrolizumab or not-yet-approved ipilimumab. Notably, contemporaneous immunotherapy is applicable exclusively to patients with mismatch repair deficient genome.

There are no uniformly accepted and clinically useful prognostic tumor biomarkers for mCRC. *Consensus Molecular Subtypes* classification has identified clinical differences in overall survival, relapse-free survival and survival after relapse among four defined subtypes, but has not been applied to peritoneal or other site-specific metastases [46]. While *BRAF* mutations have been associated with worsened survival among mCRC patients, it became clear that survival shortening is specifically associated with mutations in codon 600 (^{V600E}*BRAF*-mutant mCRC), while $^{non\text{-}V600}$*BRAF* mutations feature clinical course superior to that seen among wild-type *BRAF* mCRC patients [47]. Recent data, however, support even simpler clinical characteristics as powerful biomarkers – both peritoneal involvement and sidedness of primary colon tumor, with right-sided tumors featuring shorter survival and inefficacy of epithelial growth factor blocking therapies. Increased proportion of right-sided tumors and peritoneal carcinomatosis was observed in the ARCAD study in the whole population and wild-type BRAF mCRC patients alike [10].

In the author's interpretation, systemic treatment forms a backbone of modern therapy for metastatic colorectal cancer, including among patients with peritoneal metastases. Two randomized trials of surgical cytoreduction and intraperitoneal chemotherapy were conducted on background of systemic chemotherapy [20, 21, 41], as were both retrospective studies with internal control supporting the therapeutic role of CS-HIPEC in colorectal peritoneal carcinomatosis [19, 24]. Despite proven efficacy of systemic therapy in all forms of mCRC, clinical outcome among those with peritoneal metastases is consistently inferior to unselected mCRC population [7–11]. Therefore, it is imperative to explore adjuncts in peritoneal carcinomatosis treatment such as surgical cytoreduction and various intraperitoneal therapies (HIPEC, EPIC, PIPAC). Yet those adjunct approaches must evolve in

addition to and not instead of systemic therapy. Moreover, surgeons must maintain knowledge of therapeutic effectiveness of colorectal systemic therapy, and related risks and benefits for patients in surgical consideration.

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