European Journal of Surgical Oncology 45 (2019) 2003–2008

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Colic and rectal tumors with peritoneal metastases treated with cytoreductive surgery and HIPEC: One homogeneous condition or two different diseases? A systematic review and meta-analysis

Marco Tonello*, Antonio Sommariva, Giovanni Pirozzolo, Genny Mattara, Pierluigi Pilati

Unit of Surgical Oncology of the Esophagus and Digestive Tract, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy

A R T I C L E I N F O

Article history:
Received 17 December 2018
Received in revised form
11 May 2019
Accepted 12 June 2019
Available online 12 June 2019

Keywords:
Colo-rectal peritoneal metastases
HIPEC
CRS

A B S T R A C T

Colorectal cancer (CRC) peritoneal metastasis (PM) is one of the most important cause of cancer-related death in world. CRC PM is considered as a homogeneous disease without differentiating colonic or rectal origin. Aim of this study is to analyze survival of patients treated with cytoreductive surgery and HIPEC, according to the origin of PM.

Literature search was performed to identify relevant articles. All meta-analysis were performed using mean difference and log of HR, when appropriate. The I^2 statistic was used to determine the heterogeneity of included studies.

Out of 349 selected records, 9 articles (1308 patients, 1153 colon PM and 155 rectal PM) have been included. OS and DFS is higher in patients affected by colon PM (OS mean difference: 24,49 months [95% CI: 14,70-34,28 months, p < 0,000001]; DFS mean difference: 7,75 months [95% CI: 1,37-14,13 months, p: 0,02]) and pooled Hazard Ratio for disease-related death in rectal PM is 1.62 [95% CI: 1,01-2,59, p: 0,05] compared to colon PM). Heterogeneity among selected studies is high in two subgroups and low in one (OS subgroup A I^2: 98%, p < 0,000001; DFS subgroup I^2: 91%, p < 0,000001; OS subgroup B I^2: 25%, p: 0,26).

Our analysis, with all the limitations related to included studies, suggests that peritoneal metastasis of rectal tumors treated with CRS and HIPEC have a worst prognosis of colon tumors PM. Larger studies are required to confirm those results and therefore we invite all Authors in considering also tumor localization when reporting data on CRC peritoneal metastasis treatment.

Background

Colorectal cancer (CRC) is the third tumor in Western population with a significant impact on cancer-related mortality. It has been estimated that 10-15% of CR cancers present with peritoneal metastasis (PM) and that 20-25% of patients will develop PM at some point of disease evolution, making the peritoneum one of the most important site of CRC metastasis [1].

PM-affected patients' prognosis, if not treated, is poor with a median survival time of 6–9 months. Modern systemic chemotherapy can increase survival, but cannot be curative [1,2]. In the last 20 years, cytoreductive surgery (CRS) and hypertermic intraperitoneal chemotherapy (HIPEC) has been used as a curative-intent treatment for CRC peritoneal metastasis in selected patients [2].

Considering the impact of CRS and HIPEC, selection of patients (good performance status and "favorable" prognosis) is of paramount relevance. Many Authors have proposed risk stratification and prognostic factors. Among others, performance status and the burden of intraperitoneal disease, calculated before surgery as peritoneal cancer index (PCI) or after CRS, as completeness of cytoreduction (CC score) are most important ones [3].

It is well known that also primary tumor that generates PM (e.g. pancreato-biliary, ovarian or gastric cancer) is critical in differentiate patients' prognosis [3]. Nevertheless, the vast majority of papers treats CRC peritoneal metastasis as a homogeneous disease without differentiating colonic or rectal (extraperitoneal) origin. There are a very few papers analyzing this topic and only a minority

* Corresponding author.
E-mail address: marco.tonello@iov.veneto.it (M. Tonello).

https://doi.org/10.1016/j.ejso.2019.06.020

of works have reported, as a marginal result of larger survival analysis, different biological behavior and survival according colonic and rectal origin of PM.

The aim of this study is to review published works searching for papers reporting survival according to primary tumor origin to verify if colon and rectal PM have different biological behavior and clinical outcome.

Material and methods

Design

The present analysis was performed according to the Cochrane Collaboration and PRISMA statements [4].

Eligibility criteria

Inclusion criteria for this meta-analysis were: (1) patients with colo-rectal peritoneal metastases with pathological confirmation, treated with cytoreductive surgery (CRS) and hypertemic intraperitoneal chemotherapy (HIPEC) (every chemotherapy regimen, e.g. Oxaliplatin “bidirectional”, Cisplatin and Mytomicin C, Mytomicin C alone, etc.) or CRS and early post-operative intraperitoneal chemotherapy (EPIC) or CRS and HIPEC followed by EPIC; (2) complete cytoreduction (CC0 or CC1 score); (3) reported complete survival data: overall survival (OS) and/or disease free survival (DFS) or hazard ratio (HR) with confidence interval (CI); (4) data reported dividing primary tumor origin (colon vs rectum, considering rectum only the extraperitoneal section of bowel).

Exclusion criteria were: (1) incomplete cytoreduction (CC2 or CC3) regardless the association of HIPEC/EPIC; (2) review and duplicated articles (if needed, it has been chosen the largest sample size and/or the latest work), editorials and non-English papers, radiologic or pharmacokinetics research, quality of life assessment articles, commentary, letter, book, etc; (3) studies that did not separate results according to primary tumor site; (4) incomplete data on survival.

Search strategy

A literature search was performed on the 10th of August 2018 using PubMed, EMBASE, and Web of Science to identify relevant articles. Search terms (alone or in combination using Boolean operators) were: “colorectal cancer”,” colon cancer”, “rectal cancer”, “peritoneal carcinomatosis”, “peritoneal carcinosis”, “peritoneal metastases”, “hyperthermic chemotherapy”, “hyperthermic intraperitoneal chemotherapy”, “HIPEC”, “EPIC”, The combined application of “key words terms” and “MeSH terms” were conducted to improve the efficiency and accuracy of literature search. References from selected relevant studies were manually searched to add others potentially pertinent publications.

Meta-analysed endpoints

Included studies were used to identify data on two main endpoints: overall survival (OS) and disease free survival (DFS) after CRS and HIPEC procedure. All relevant text, tables and figures were reviewed for data extraction.

Statistical analysis

All meta-analysis were performed with Review Manager 5.3 [5], using mean difference and log of HR, when appropriate. A p value of 0,05 or less has been considered significative. Overall survival (OS) and disease-free survival (DFS), hazard ratios (HR) and confidence intervals (CI) were extracted from included studies.

In case of incomplete or not accurate data, hazard ratios (HR) for time-to-event outcomes with 95% confidence intervals (95% CI) in two groups (colon vs rectum) were estimated using Tierney's method [6]. In case of incomplete data on mean/median survival and survival ranges, missing values were estimated using Hozo's method [7] and following modifications by Wan [8].

The I^2 statistic was used to determine the heterogeneity of the included studies. I^2 values of 25–49%, 50 - 74%, and above 75% were considered as low, moderate and high heterogeneity levels, respectively [9]. If I^2 statistic was lower than 50%, fixed effect model has been used to get pooled HR and 95% CI and mean difference analysis; otherwise, random effects model has been used.

Forest and funnel plots were used for graphical description of the statistical results. Final elaboration was revised by a statistician of our Unit of Clinical Research.

Results

Studies selection and systematic review process

After literature search, 337 relevant records have been identified. 12 more articles have been added from other sources (e.g. after references check of the most relevant publications). Of these 349 records, 281 have been excluded because not relevant or pertinent for the ongoing analysis. 68 full-text articles have been extensively checked for survival data (mean, median OS and DFS, HR and CI) and finally 9 articles have been included in the analysis because of the completeness of data.

Main authors of potentially eligible studies with minor missing or incomplete data, have been directly contacted and invited for additional information and data. Studies from Authors that have answered with updated and complete data, have been included in the analysis [10,17].

The studies are summarized in Table 1 and selection process depicted in Fig. 1.

Level of evidence and study quality (assessed using Newcastle-Ottawa Score) have been summarized in Table 2.

Meta-analysis: survival analysis

Cumulatively, 1308 patients have been evaluated, of which 1153 affected by PM of colonic origin (88,15% of the total sample) and 155 affected by rectal origin PM (11,85%).

Survival analysis has been divided in two main sections: overall survival (OS) and disease-free survival (DFS). Both survival periods have been calculated started from CRS and HIPEC procedure. OS survival has been further divided in two sub-groups because 5 articles reported mean OS (subgroup A), whereas 3 articles reported only survival HR of rectal PM compared to colonic PM (subgroup B).

Survival analysis demonstrates that colonic origin of PM relates with a longer overall survival and disease free survival, compared to rectal origin of PM.

OS is longer in patients with PM arising from colonic primary tumor, compared to rectal one. Actually OS mean difference is 24,49 months greater for colonic PM [95% CI: 14,70 - 34,28 months, $p < 0,000001$] and pooled Hazard Ratio for rectal PM is 1.62 [95% CI: 1,01 - 2,59, p: 0,05] compared to colonic PM. Similarly, disease free survival is greater for colon PM, as mean difference is 7,75 months greater [95% CI: 1,37 - 14,13 months, p: 0,02]. Data and results are shown in Fig. 2

Sensitivity analysis and publication bias

Heterogeneity is high among studies in OS subgroup A analysis

Table 1
Characteristics of the selected studies.

Author, year, country	Period	N. of centers	Design	Number of patients. Total (colon, rectum)	Treatment strategy	Systemic treatment before CRS+HIPEC (% of pts receiving)	Liver metastases (% of patients)	PCI value and PM presentation	Systemic treatment after CRS+HIPEC (% of pts receiving)
Chua - Morris, 2011, Australia [10] (Updated data directly from last Author)	1997–2018	1	Prospective	268 (244,24)	HIPEC: mitomycin C (10–12.5 mg/m2). EPIC: POD 1-5 5-FU (650–800 mg/m2)	n.r	n.r	PCI < 20 (inclusion criteria)	n.r
DaSilva, 2005, USA [11]	1981–2004	1	Retrospective	70 (64,6)	HIPEC: mitomycin C at 10 mg/m2 in females and 12.5 mg/m2 in males; EPIC: POD 1-5: 5-FU 650 mg/m2	rectal: 100% CT colon: n.r.	none (exclusion criteria)	mean PCI rectal pts: 8.4 ± 5.8; colon pts: 15 ± 7.2 metachronous: 100% rectal pts colon pts n.r.	rectal: 45% RCT, 45% CT, 10% none colon pts: n.r.
Elias, 2010, France [12]	1989–2007	23	Retrospective	368 (341,27)	HIPEC: mitomycin C at 35 mg/m2 ± Cisplatin 100 mg/m2 or oxaliplatin 460 mg/m2 ± irinotecan 200 mg/m2 + 5FU, leucovorin e.v.; EPIC: POD 1: mitomycin C 10mg/m2, POD 2-5: 5FU 600 mg/m2	n.r.	rectal: 17% colon: 15%	median rectal PCI: 6 (range n.r.)	rectal: 50% CT colon: 44% CT
Froysnes, 2016, Norway [13]	2004–2013	1	Retrospective	119 (109,10)	HIPEC: mitomycin C 35 mg/m2 for 90 min in three fractions	81% of all pts	1.7% of all pts	median PCI 9 (0-28) of all pts metachronous PM in 39% of all pts	n.r.
Huang, 2014, China [14]	2004–2013	1	Case-control	33 (21,12)	HIPEC: cisplatin 20 mg/ml, mitomycin C 5 mg/ml	n.r.	6% of all pts	median rectal PCI: 21 (6-36), median colon PCI: 21 (6-39) metachronous 39.4% of all pts	100% (colon >6 cycles 42%, rectal >6 cycles 58%). Regimen: oxaliplatin or irinotecan based
Tonello, 2018, Spain [15]	2003–2015	1	Retrospective	36 (31,5)	HIPEC: mitomycin C at 35 mg/m2 ± Cisplatin 100 mg/m2 or oxaliplatin 460 mg/m2 + 5FU, leucovorin e.v.; EPIC: POD 1-5 5-FU (650–800 mg/m2)	rectal: 60% RCT (syncronous PM), colon 25% Regimen: oxaliplatin or irinotecan based	rectal: 20%, colon: 19.3%	median rectal PCI: 10 (2-30), median colon PCI: 9 (9-26) metachronous rectal: 40%, metachronous colon: 58.3%	rectal: 60%, colon 72.2% Regimen: oxaliplatin or irinotecan based
Verwaal, 2004, Netherlands [16]	1995–2002	1	Prospective	87 (82,5)	HIPEC with mitomycin C 35 mg/m2 for 90 min in three fractions	n.r.	none (exclusion criteria)	SPC score: modal value 6	100% of all pts. Regimen: 5FU-LV
Yonemura, 2013, Japan [17] (Updated data directly from Author)	2004–2018	1	Prospective	240 (203,37)	HIPEC with mitomycin C at a dose of 20mg/m2 and cisplatin 100mg/m2	77.5% of all pts Regimen: oxaliplatin, irinotecan or S1-paclitaxel based	n.r.	PCI <10: 52.8% of all pts metachronous PM: 58.5% of all pts	n.r.
Simkens, 2016, Netherlands [21]	2004–2015	1	Case-Control	87 (58,29)	HIPEC: mitomycin C at 35 mg/m2 ± Cisplatin 100 mg/m2 or oxaliplatin 460 mg/m2 + 5FU (400mg/m2), leucovorin e.v. (20 mg/m2)	rectal: 48%, colon: 12.1%	rectal: 10.3%, colon 12.1%	mean rectal PCI: 9.3 ± 4.7, colon PCI: 9.0 ± 5.1 metachronous rectal 34.5%, colon 46.6%	rectal: 27.6%, colon: 13.8%

List of abbreviations: pts: patients; n.r.: not reported; PCI: peritoneal cancer index; SPC: simplified peritoneal cancer (a simplified PCI score ranging from 0 to 21, using 7 abdominal regions); CT: chemotherapy; RCT: radio-chemotherapy.

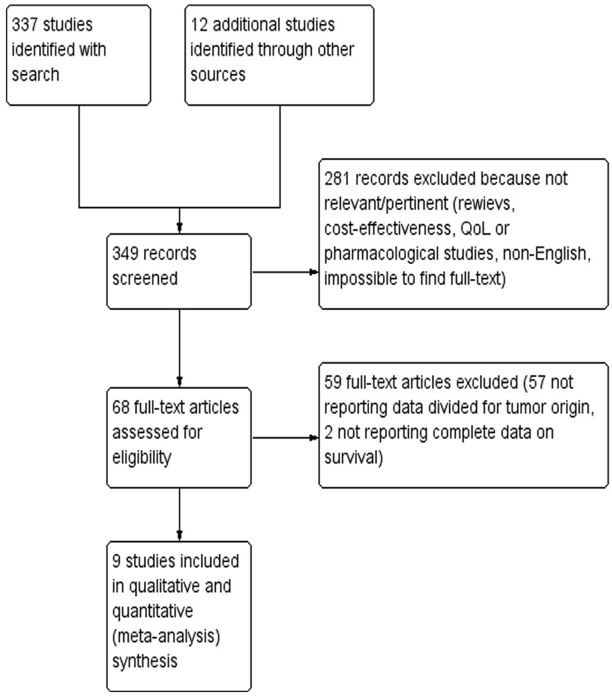

Fig. 1. Flowchart of the literature search and selection process.

(I^2: 98%, $p < 0{,}000001$) and in DFS analysis (I^2: 91%, $p < 0{,}000001$); whereas among studies in OS subgroup B analysis is low (I^2: 25%, p: 0,26). Publication bias was evaluated with funnel plot analyses, as shown in Fig. 3, and the funnel plot was symmetric only in OS subgroup B.

Discussion

The present study evaluated the relation between survival (as overall survival and disease free survival) and primary tumor site in colorectal peritoneal metastases treated with CRS and HIPEC with curative intent. We defined colon as the intraperitoneal large bowel portion and rectum as the extraperitoneal one.

Many studies reported location of primary tumor in a descriptive section, but a very few used location as a survival-related variable in their analyses. In all series, rectal origin PM represents a minority of cases; the sample numeric discrepancy between the two groups, with the cultural background of considering CRC PM as an homogeneous disease, might explain the lack of interest in analyzing this factor.

Data obtained from this meta-analysis confirms the working hypothesis that colon and rectum PM are two different diseases with different biological behavior. Almost all studies included, support this concept reporting higher survival (OS and DFS) rates for colon PM.

The exceptions are Huang [14] and Simkens [21] papers. Huang showed an higher survival period for rectal PM, eventhough both survivals are significantly shorter compared to other papers (only 13 months for colon PM). Simkens, in its case-matched studied, showed an higher OS for colon PM (median 35,1 months for colon PM vs 26 months for rectal PM), but the observed difference was not statistically relevant. Interestingly, using adjuvant systemic chemotherapy after CRS and HIPEC as stratification factor, the same Author demonstrated that colon PM patients have a significant increase in overall survival (43,2 vs 14,5 months, $p < 0{,}001$) in contrast with rectal PM patients (26,3 vs 20,9 months, p 0,17). Clearly, the decision of administrating adjuvant CT could be a confounding factor (reflecting perhaps patients' performance status or oncological history), but considering that almost the same proportion of patients in the two groups (about 70%, p 0,74) received systemic CT, the different response to adjuvant therapy could be speculatively considered as a marker of major biological aggressiveness of rectal cancer.

In contrast with our results, there is a French retrospective multi-institutional registry published in 2004 (that cannot be included in our analysis because of missing data), that reports a median survival of 19.2 months for all CRC PM patients, with rectal PM of 19 months [18].

Disease free survival analysis could be performed only in four studies, because other included works do not report DFS. Also this analysis confirms an incremented disease-free period in colon PM. In contrast, Froysnes at al [13] reported only HR of recurrence and being the only paper with that kind of data, cannot be included in the quantitative DFS analysis; the result of Froysnes work is that rectal PM have a slightly lower risk of recurrence compared to colon PM (HR 0.93 [CI 95%: 0.39–2,23]), eventhough overall survival favors colon PM.

A potential bias of included studies could be year of publication, because colorectal cancer treatment has rapidly evolved in the last years and patients in older series have been treated with EPIC plus

Table 2
Level of evidences and quality assessment of the selected studies.

Study Author, year, reference	Newcastle-Ottawa Score							LoE
	Cohort study			Case-control study			Scores	
	Selection	Comparability	Outcome	Selection	Comparability	Exposure		
Chua - Morris, 2011 [10],	****		***				7	II
DaSilva, 2005 [11],	****	**	***				9	III
Elias, 2010 [12],	****	*	***				8	III
Froysnes, 2016 [13],	****	*	***				8	III
Huang, 2014 [14],				****	**	***	9	II
Tonello, 2018 [15],	****	**	***				9	III
Verwaal, 2004 [16],	****	*	***				8	II
Yonemura, 2013 [17],	****		***				7	II
Simkens, 2016 [21],				****	**	***	9	II

Newcastle-Ottava Scale for Case-Control studies (Selection: 1. Adequacy of case definition, 2.Representativeness of the cases, 3.Selection of controls, 4.Definition of Controls; Comparability: 1.Comparability of cases and controls on the basis of the design or analysis (two items: PCI and pre and post CRS+HIPEC systemic treatment); Exposure: 1.Ascertainment of exposure, 2.Same method of ascertainment for cases and controls, 3.Non-Response rate) and Cohort studies (Selection: 1.Representativeness of the exposed cohort, 2.Selection of the non exposed cohort, 3.Ascertainment of exposure, 4.Demonstration that outcome of interest was not present at start of study; Comparability: 1.Comparability of cohorts on the basis of the design or analysis (two items: PCI and pre and post CRS+HIPEC systemic treatment); Outcome: 1.Assessment of outcome, 2.Was follow-up long enough for outcomes to occur, 3.Adequacy of follow up of cohorts). LoE: Level of evidence.

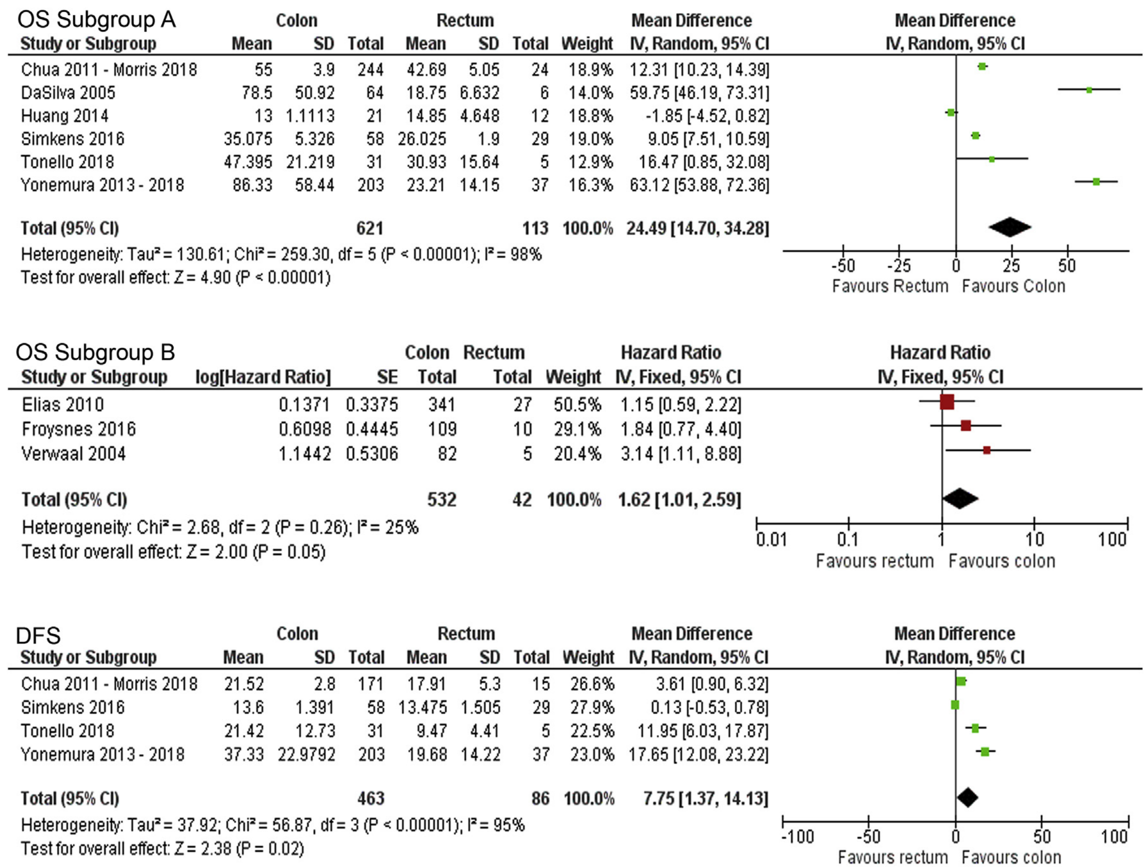

Fig. 2. Forest plots of survival analysis.

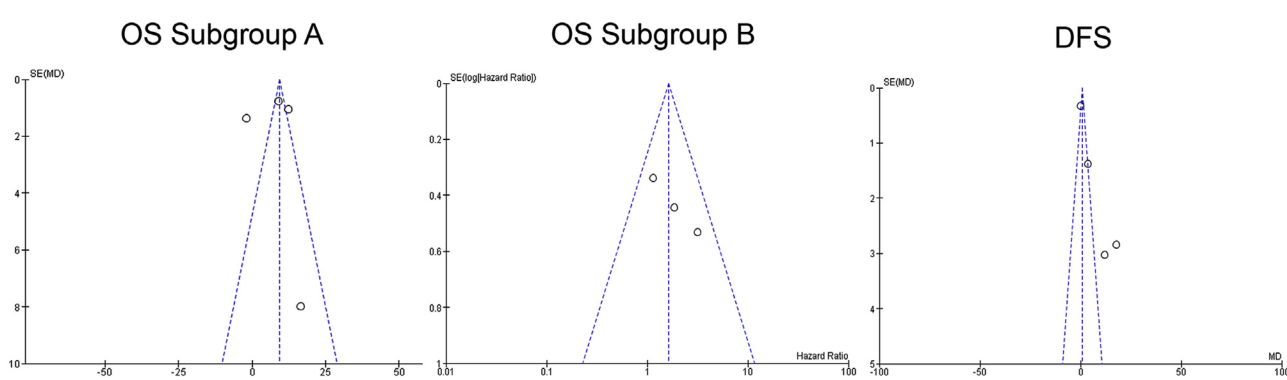

Fig. 3. Funnel plots of the analysed subgroups.

HIPEC, but, considering the small number of included studies and the fact that only 2 studies have been published earlier than 2010, a sub-analysis according to post-CRS treatment or publication year could not be performed.

We are well aware of the limitations of this study (high heterogeneity in two analysis out of three, quite low level of evidence) and of the ongoing discussion in scientific community after recent RCTs preview on CRC PM treated with CRS and HIPEC [19]. It is also possible that in a not-far future we will be able to have diagnostic (namely molecular) tools to stratify pre-operatory risk in a better way than comparing only peritoneal tumor burden and primary tumor site, as recent works report [20].

Considering all the previous aspects, we therefore cannot claim with absolute certainty that rectal PM is a completely different disease from colon origin PM, but we would like to raise strong a claim of considering these results when evaluating rectal PM patients for curative CRS and HIPEC.

Our results underline the need of further and larger multicentric studies and to do so we also would warmly invite all Authors to publish their clinical experience and data, focusing also on primary tumor localization.

Conclusions

Our analysis, with all the limitations related to included studies, suggests that peritoneal metastasis of rectal tumors treated with

CRS and HIPEC have a worst prognosis than colon tumors PM. Larger studies are required to confirm those results and therefore we invite all Authors in considering also tumor localization when reporting data on CRC peritoneal metastasis treatment.

Acknowledgments

We wish to thank Dr. Y. Yonemura and Dr. D.L. Morris for their active collaboration in providing missing and updated data, Dr. S. Gonzalez-Moreno for his support and advices, Dr. P. Del Bianco (Unit of Clinical Research at Veneto Institute of Oncology) for statistical review and suggestions and Dr. V. Bozzato for bibliographic assistance and articles retrieving.

References

[1] Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg 2002;89:1545–50.
[2] Glehen O, Osinsky D, Beaujard AC, Gilly FN. Natural history of peritoneal 1550 carcinomatosis from nongynecologic malignancies. Surg Oncol Clin 2003;12: 729–39 [xiii].
[3] Sugarbaker PH. Cytoreductive surgery and intraperitoneal chemotherapy for peritoneal surface malignancies. In: Markman M, editor. Regional chemotherapy. Current clinical Oncology. Totowa, NJ: Humana Press; 2000.
[4] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–94.
[5] Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
[6] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8: 16.
[7] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5(13).
[8] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14(135).
[9] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–66.
[10] Chua TC, Liauw W, Saxena A, Al-Mohaimeed K, Fransi S, Zhao J, et al. Evolution of locoregional treatment for peritoneal carcinomatosis: single-center experience of 308 procedures of cytoreductive surgery and perioperative intraperitoneal chemotherapy. Am J Surg 2011;201:149–56.
[11] Gomes da Silva R, Cabanas J, Sugarbaker PH. Limited survival in the treatment of carcinomatosis from rectal cancer. Dis Colon Rectum 2005;48:2258–63.
[12] Elias D, Glehen O, Pocard M, Quenet F, Goéré D, Arvieux C, et al. A comparative study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. Ann Surg 2010 May;251(5):896–901.
[13] Frøysnes IS, Larsen SG, Spasojevic M, Dueland S, Flatmark K. Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastasis in Norway: prognostic factors and oncologic outcome in a national patient cohort. J Surg Oncol 2016 Aug;114(2):222–7.
[14] Huang CQ, Feng JP, Yang XJ, Li Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves 55680 survival of patients with peritoneal carcinomatosis from colorectal cancer: a case-control study from a Chinese center. J Surg Oncol 2014;109:730–9.
[15] Tonello M, Ortega-Perez G, Alonso-Casado O, Torres-Mesa P, Guiñez G, Gonzalez-Moreno S. Peritoneal carcinomatosis arising from rectal or colonic adenocarcinoma treated with cytoreductive surgery (CRS) hyperthermic intraperitoneal chemotherapy (HIPEC): two different diseases. Clin Transl Oncol 2018 Oct;20(10):1268–73.
[16] Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated byaggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. Br J Surg 2004 Jun;91(6):739–46.
[17] Yonemura Y, Canbay E, Ishibashi H. Prognostic factors of peritoneal metastasis from colorectal cancer following cytoreductive surgery and perioperative chemotherapy. Sci World J 2013;2013:978394.
[18] Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004 Aug 15;22(16): 3284–92.
[19] Quenet F, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol 2018;36(18):1.
[20] Schneider MA, Eden J, Pache B, Laminger F, Lopez-Lopez V, Steffen T, et al. Mutations of RAS/RAF proto-oncogenes impair survival after cytoreductive surgery and HIPEC for peritoneal metastasis of colorectal origin. Ann Surg 2018 Nov;268(5):845–53.
[21] Simkens GA, van Oudheusden TR, Braam HJ, Wiezer MJ, Nienhuijs SW, Rutten HJ, et al. Cytoreductive surgery and HIPEC offers similar outcomes in patients with rectal peritoneal metastases compared to colon cancer patients: a matched case control study. J Surg Oncol 2016 Apr;113(5):548–53.