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**Outcome following incomplete surgical cytoreduction combined with intraperitoneal chemotherapy for colorectal peritoneal metastases**

Heaney RM *et al.* Incomplete cytoreduction and colorectal peritoneal metastases

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**Abstract**

Cytoreductive surgery combined with intraperitoneal chemotherapy can improve survival in appropriately selected patients with colorectal peritoneal metastases. Outcomes are best in those patients in whom a complete cytoreduction can be achieved. Unresectable disease is however encountered in approximately one-quarter of patients at laparotomy. The merits, or otherwise, of proceeding with an incomplete cytoreduction in this setting are unclear. We performed a review of published outcomes following incomplete cytoreduction for colorectal peritoneal metastases. Using the electronic databases, PubMed and MEDLINE, a systematic search of available literature published during the period January 1997 to September 2014 was conducted. Following application of exclusion criteria, 19 papers were identified and included in this review. These comprised fifteen case series, 3 case control studies and one randomised control trial. In the nineteen studies included in, 2790 patients underwent cytoreductive surgery with or without intraperitoneal chemotherapy for peritoneal metastases of colorectal origin. Of these, 1732 (62%) underwent a complete cytoreduction while 986 (35%) patients underwent an incomplete cytoreduction. Median survival in the complete cytoreduction group ranged from 11 to 62 mo while survival in the latter group ranged from 2.4 to 32 mo. Of the 986 patients with an incomplete cytoreduction, 331 patients received intraperitoneal chemotherapy and survival in this cohort ranged from 4.5 to 32 mo. An incomplete cytoreduction, with or without intra-peritoneal chemotherapy, does not appear to confer a survival benefit. The limited available data points to a palliative benefit in a subset of patients. In the absence of high quality data, the decision as to whether or not to proceed with surgery should be made on an individual patient basis.

**Key words:** Colorectal carcinoma; Peritoneal metastases; Carcinomatosis; Incomplete cytoreduction; Intraperitoneal chemotherapy

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**Core tip:** Cytoreductive surgery combined with intraperitoneal chemotherapy for colorectal peritoneal metastases improves survival in appropriately selected patients following complete cytoreduction. The merits of an incomplete cytoreduction, with or without intra-peritoneal chemotherapy, are unclear. The available evidence is heterogenous and of poor quality. The current review has not shown a benefit to surgery in the setting of unresectable disease. Certain patients, particularly those with ascites may however gain from a quality of life point of view.

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**INTRODUCTION**

Peritoneal metastases (PM) are found in approximately 10% of individuals undergoing resection for colorectal cancer[1] and ultimately occur in up to 35% patients[2-4]. After hepatic metastases, the most common site of cancer recurrence after curative primary resection is the peritoneum[5,6]. Peritoneal metastases have traditionally been associated with a poor prognosis, with patients frequently referred for palliative care. In this setting, median survival in the order of five to seven months was typical[1,7,8]. Recent advances have allowed the introduction of new, more targeted approaches combining systemic chemotherapy with biological agents such as bevacizumab. However, best survival rates achieved with these combinations rarely exceed twenty months[9-11].

Over the past 20 years, a number of studies have shown a survival benefit following combined cytoreductive surgery (CRS) and intraperitoneal chemotherapy for patients with colorectal peritoneal metastases. The primary aim of cytoreductive surgery is to eliminate all macroscopic disease through peritonectomy procedures, as described by Sugarbaker, and multi-visceral resections if necessary[12,13]. Cytoreductive surgery is combined with intraperitoneal chemotherapy with the aim of irradicating residual microscopic disease[14,15]. A 2003 randomized control trial by Verwaal *et al*[16], showed that patients treated with cytoreduction and heated intraperitoneal chemotherapy (HIPEC) had a median survival of 22.4 mo compared with 12.6 mo for those assigned to systemic chemotherapy alone. Favourable outcomes using this approach have since been demonstrated in a number of case series, including a 2010 multicentre study of 523 patients in which patients undergoing cytoreduction and HIPEC had a median survival of 30.1 mo[17]. The results of a recent meta-analysis by Mirnezami *et al*[18] further supported these encouraging outcomes, with patients undergoing CRS and HIPEC having superior two and five year survival rates when compared to those receiving systemic chemotherapy alone.

In patients undergoing surgery for colorectal peritoneal metastases, a correlation between the completeness of cytoreduction and survival has been shown in a number of studies and confirmed in a recent meta-analysis[18]. Verwaal *et al*[19] found that patients with a complete cytoreduction had a median survival of fifty-two months compared with an eight month median survival in patients with an incomplete cytoreduction. A complete cytoreduction is more likely to be possible and beneficial in the absence of biliary, ureteric, or multilevel bowel obstruction and in patients with lower volume disease [Peritoneal Carcinomatosis Index (PCI) less than twenty][20].

Unfortunately, the pre-operative prediction of those patients in whom a complete cytoreduction will be achievable is difficult. It is well accepted that CT scanning and conventional imaging techniques have a poor sensitivity for identifying peritoneal metastases[21,22]. This can lead to underdiagnosis and understaging, with the result that unresectable disease is first discovered at laparotomy. In an attempt to overcome these limitations, many centres now utilise staging laparoscopy to pre-operatively assess operability and calculate the PCI. A 2012 cohort study by Iversen *et al*[23] found that while pre-operative laparoscopy reduced the rates of open and closed laparotomy, it understaged peritoneal tumour in 56% of patients. Furthermore, in patients with metachronous disease, post-operative adhesions may reduce the ability of this approach to accurately determine the extent and site of recurrent tumour[23]. Ultimately, the tumour burden, PCI, and resectability can only be reliably calculated at laparotomy[24].

While it is evident that a complete cytoreduction combined with intraperitoneal chemotherapy confers a survival benefit, it is not clear what impact, if any, an incomplete cytoreduction has on overall survival and quality of life. In this paper we aim to review the current literature to address the question of whether surgery should be abandoned if a complete cytoreduction cannot be achieved or, would the patient benefit in terms of symptomatic relief or prolongation of life, from an incomplete cytoreduction combined with intraperitoneal chemotherapy.

**LITERATURE SEARCH STRATEGIES**

A systematic search of available literature using the PubMed and MEDLINE databases provided by the National Library of Medicine was conducted. Search terms included the following keywords, or combinations thereof: “colorectal,” “peritoneal,” “metastases,” “cytoreductive surgery,” “intraperitoneal”, “HIPEC” and “chemotherapy.” The ‘related citations’ function was utilised to broaden the search. Additional relevant publications were obtained by reviewing the reference sections of all selected articles.

***Inclusion/Exclusion criteria***

Only papers published in the English language during the period January 1997 to September 2014 were included.Only original research articles that studied peritoneal metastases of colorectal origin were included. Papers that omitted the breakdown of survival data according to the primary cancer and a completeness of cytoreduction score (CC-score) were excluded. Studies reporting iterative cytoreductive procedures were also eliminated.

The full text articles of 165 publications were obtained and their relevance assessed. 143 papers were excluded based on the aforementioned criteria. A total of 22 eligible publications were identified. Further review of these papers identified likely overlap between study centres and patient cohorts. Best efforts were made to eliminate any duplication however this was not possible with regard to one paper, in which one-quarter of patients were included in a separate retrospective multicentre study[6,17]. Following this further analysis, 19 papers were ultimately deemed appropriate for inclusion in the current study. This comprised 15 case seriesp[6,17,25-37], 3 case control studies[38-40] and one randomised control trial (RCT) (16). Figure 1 summarises the selection process.

***Completeness of Cytoreduction Score***

Eleven of the nineteen studies utilised the CC - score as described by Jacquet *et al*[41] in which a CC-0 score indicates that no macroscopic peritoneal tumour remains after cytoreduction, a CC-1 score indicates that persisting tumour nodules are < 2.5 mm, a CC-2 score indicates residual tumour nodules between 2.5mm and 2.5 cm and finally a CC-3 score indicates tumour nodules > 2.5 cm or a confluence of unresected tumour. The remaining eight studies used four different scoring systems, which for the purpose of this review, were analysed and assigned the most appropriate Completeness of Cytoreduction Score (CC-Score) based on the size of the remaining tumour nodules[6,29,30,33,35-37,40]. Three of the papers utilised the R-score, where R0 indicates complete cytoreduction, R1 indicates the persistence of microscopic disease, and R2a, R2b and R2c indicate residual tumour nodules measuring < 5 mm, 5 mm – 2 cm and > 2 cm respectively[16,29,37]. Five studies failed to identify specific tumour measurements. Two of these classified resections as: no evidence of macroscopic disease, persisting microscopic disease and persisting macroscopic disease and for comparison purposes, these were assigned scores of CC-0, CC-1 and CC-2/3 respectively[30,33]. The other three studies used the categories; macroscopically complete or macroscopically incomplete, and were assigned appropriate CC scores[35,36,40]. Complete cytoreduction refers to a CC-0 or 1 score whereas a CC-2 or 3 score is classified as incomplete.

**LITERATURE SEARCH RESULTS**

***Patients***

In the nineteen studies analysed, a total of 2790 patients underwent cytoreductive surgery and intraperitoneal chemotherapy for peritoneal metastases of colorectal origin during the period 1997 to 2014. Median age provided in seventeen of the studies ranged from 47–67 years. Of the 2790 patients, a CC-0/1 cytoreduction was achieved in 1732 (62%) while a CC-2/3 resection was achieved in 986 (35%). The 986 patients who had final resection scores of CC-2/3 form the basis of our review. The remaining 72 patients are not included in our analysis as a result of unknown or unassigned CC-scores and patients who were lost to follow up or not included in the original analyses.

***Synchronous vs metachronous disease***

Five studies included patients with synchronous peritoneal metastases only[27,30,35-37]. The study by Peistieau *et al*[26] included patients undergoing resection for both synchronous and metachronous disease, with all but one of the patients in the incomplete cytoreduction group having metachronous peritoneal metastases. The remaining studies included patients with both synchronous and metachronous disease.

***Use of neo-adjuvant chemotherapy***

No data was provided regarding the delivery of neo-adjuvant therapy in eighteen of the included studies. The remaining study included only patients who had not received systemic treatment prior to surgery[31].

**FACTORS ASSOCIATED WITH AN INCOMPLETE CYTOREDUCTION**

***Extent of disease***

Twelve studies included patients with intra-abdominal disease only[6,16,17, 25,26,28,29,32,37-40] and five of these included patients with peritoneal metastases alone[16,28,32,38,40]. In the seven studies that included patients with non-peritoneal intra-abdominal metastases (hepatic metastases), only one paper included the resection of hepatic metastases in the overall CC-score[29]. In three of these seven studies[6,17,37], the CC-score referred to resection of peritoneal disease only and the remaining three studies did not specify whether the resection of hepatic metastases affected the final CC-score[25,26,39]. Cavaliere *et al*[25] found that the presence of extensive disease at the porta hepatis increased the likelihood of an incomplete cytoreduction. Four of the other studies included patients with extra-abdominal distant metastases (lung and supraclavicular nodes[27], lung only[31], and the other two studies did not specify the site of distant disease[30,36]. The remaining three studies did not specify whether patients also had non peritoneal distant metastases[33-35].

Only two of the studies provided information regarding the actual PCI, or equivalent, in patients in whom a complete cytoreduction was not possible[26,34]. The 55 patients in the study by Pestieau *et al*[26] in whom a complete cytoreduction was not possible, had a median PCI of 20.7 ± 7.6 compared to a PCI of 15.4 ± 7.6 in patients in whom a CC-0/1 was possible.

Chua *et al*[34] reported a series of three patients with colorectal peritoneal metastases who underwent incomplete cytoreduction. Two of the patients had a PCI of 11 while the third had a score of 39.The reasons for failure to clear all macroscopic disease in this study were extensive small bowel involvement, liver metastases, and extensive involvement of the lesser sac and diaphragm[34]. Similarly, Winer *et al*[32] found that extensive small bowel involvement or small bowel mesenteric deposits resulted in an aborted or incomplete resection in their 4 patients. Finally, Park *et al*[31] identified the presence of metastases covering a substantial amount of the peritoneal surface as the reason for failure of cytoreduction in the 5 patients in the incomplete cytoreduction group.

***Tumour histology***

One study specifically reported outcomes in patients with signet ring histology only[32]. Winer *et al*[32] found that tumours with signet ring histology responded poorly to CRS and HIPEC and their five CC-2/3 patients had a median survival of 2.4 mo. In the remaining studies no correlation between completeness of cytoreduction and tumour histological subtype or differentiation was reported.

**TREATMENT OF PATIENTS WITH UNRESECTABLE PERITONEAL METASTASES**

***Extent of surgical resection***

In the nineteen studies analysed, 986 patients underwent a CC-2/3 or incomplete resection. No study reported the specific resections that were undertaken in the incomplete cytoreduction group. Two studies reported that in the presence of distant metastases or extensive disease not amenable to a complete cytoreduction, a radical resection of peritoneal disease was not pursued and palliative surgery was performed[30,31]. This, in one study involved the removal of gross tumour deposits or disease that was likely to cause gastrointestinal obstruction, without the administration of intraperitoneal chemotherapy[30] and in the other entailed omentectomy with EPIC[31]. Four studies included patients with extra-abdominal distant metastases. In one study, 10/27 patients had extra-abdominal distant metastases, of whom 5 patients underwent resection of extra-abdominal disease[27]. In another study no patient had resection of their distant disease[30] and the other two studies did not document whether distant metastases were resected[31,36].

***Systemic chemotherapy***

In three studies[28,38,39], all patients received some form of systemic therapy (neoadjuvant, adjuvant or both). Three series did not document whether their patient cohort received chemotherapy or not and in the remaining thirteen studies the number of the CC-2/3 patients who received systemic therapy was not documented.

***Intraperitoneal chemotherapy***

In twelve studies[6,16,17,26,28,29,31,33,34,37,39,40] all patients following incomplete cytoreduction (331) received intraperitoneal chemotherapy (EPIC, IPHC or both). In one study the number of patients receiving intraperitoneal chemotherapy was not specified[27]. In the series reported by Huang *et al*[38], a comparison of intraperitoneal chemotherapy *vs* no intraperitoneal therapy following incomplete cytoreduction was performed. Five studies did not utilise this treatment modality. Mitomycin C was the most frequently used chemotherapeutic agent[16,26,27,31,34,37,38] followed by fluorouracil[6,28,40].

**OUTCOMES**

***Survival***

A breakdown of survival by completeness of cytroreduction is outlined in Table 1. All studies reported survival using the Kaplan Meier method. Patients in whom a CC-0 resection was achieved had a median survival of 25 to 62 mo, whereas following CC-1 median survival ranged from 11 to 35 mo. In studies where the CC-0 and CC-1 groups were analysed together, a median survival of 15.8 to 42 mo was reported. The 986 patients in whom a CC-2/3 cytoreduction was achieved had a median survival ranging from 2.4 to 32 mo. From the data reported, it is possible to identify only 63 patients in the CC-2/3 group who definitively had peritoneal metastases only and median survival in this cohort ranged from 2.4 to 11 mo. Further analysis of survival data for the CC-2/3 group is outlined in Table 2. Ten of the nineteen studies calculated 5 year survival rates. Two studies documented 5 year survival rates of 3%[30] and 4.7%[36] while the others reported no 5 year survival following incomplete cytoreduction.

***Morbidity/Mortality***

The randomised control trial by Verwaal *et al*[19] was the only study to report perioperative mortality for the incomplete cytoreduction group. Seven out of ten patients in the CC-2/3 group died in comparison to 1/18 (5.5%) patients in the CC-0 group. Furthermore, 80% of the grade 4 toxicities and complications occurred in the CC-2/3 group. The treatment related mortality for the experimental arm (complete and incomplete cytoreduction) was 8%.

**DISCUSSION**

It is now broadly accepted that the treatment modality of complete cytoreductive surgery with intraperitoneal chemotherapy confers a survival benefit for appropriately selected patients with peritoneal metastases of colorectal origin. It is also accepted that a complete cytoreduction is associated with better outcomes than an incomplete resection. It is less clear however, whether an incomplete cytoreduction is of benefit with respect to survival or quality of life when compared to non-operative approaches. This question is particularly relevant in the setting of unresectable disease first encountered at laparotomy for planned CRS and HIPEC. Despite advances in staging, this situation arises in up to one quarter of patients[23,42,43] and poses a dilemma for the surgeon; should they proceed and remove resectable disease, combining it with HIPEC, or should the procedure be abandoned?

From the current literature review it is not possible to make firm conclusions as to the merits or otherwise of persisting with CRS and HIPEC when it is apparent that it will not be possible to resect all disease. This difficulty arises mainly due to the heterogeneity of patients and reported approaches, most of which has been taken from uncontrolled studies. In the only RCT in the series, the 10 patients in the incomplete group had a median survival of 5 mo compared with 12.6 mo for those undergoing systemic chemotherapy[16]. Perioperative mortality in the incomplete group was high however, impacting significantly on overall survival for this group. Similar results were obtained in the case control series by Mahteme *et al*[40] who reported median survival of 10 mo in those undergoing CRS *vs* 14 mo for those in the standard chemotherapy group. It is however noteworthy that sixteen of the nineteen studies in the current review reported median survival of 12 mo or less following incomplete cytoreduction. While most of the studies were non-comparative, it is clear that these outcomes are no better than historical controls, or those reported with best systemic treatment. These outcomes suggest no survival advantage to an incomplete cytoreduction. There was however great heterogeneity of patients (many of whom had non-peritoneal distant disease), the extent of surgery, use of HIPEC, and the delivery of systemic treatment. From the literature it is noted that peritoneal metastases of appendiceal adenocarcinoma origin tend to have a better overall survival when compared to true colorectal peritoneal metastases[13,44].

The value of intraperitoneal chemotherapy after CC-2/3 is also unknown. For the twelve studies in the current review in which all patients received intraperitoneal chemotherapy, median survival for the patients with incomplete cytoreduction ranged from 4.1 to 32 mo and, for the five without intraperitoneal chemotherapy, from 2.4 to 15 mo[25,30,32,35,36] (Table 3). In a case-control study, Huang *et al*[38] compared outcomes in CRS/HIPEC with CRS alone. Those in the HIPEC group had a median survival of 11 mo *vs* 5 mo in those who underwent CRS alone. It is important to note that the cut off point, with respect to the size of residual tumour, for use of intraperitoneal chemotherapy varied across the studies in this review, varying from > 1 mm[17] to > 5 mm[6].

While its impact on survival remains debatable, an incomplete cytoreduction with HIPEC may provide symptom relief. Malignant ascites results in abdominal distension and dyspnoea and symptomatic relief with paracentesis is transient at best as failure to treat the cause of the ascites results in rapid reaccumulation of the fluid[45]. Chua *et al*[34] specifically assessed a small number of patients who underwent CC-2/3 resections for colorectal PM. Two out of the three patients reported resolution of their symptoms (abdominal pain, anorexia, distension) postoperatively. Randle *et al*[46] found that partial cytoreduction and HIPEC was successful in treating malignant ascites (no radiological evidence of ascites three months post-operatively) in 84% (243/288) of patients with peritoneal metastases from a variety of primary tumours. This suggests a potential role for intraperitoneal chemotherapy in controlling ascites and improving symptoms. Garofalo *et al*[47] found that laparoscopic HIPEC successfully treated debilitating ascites in 3 patients with PM of colorectal origin. Valle *et al*[48] showed a benefit (at least in the short term) to laparoscopic HIPEC with mitomycin C in patients with PM of colorectal origin. At one month post-operatively, forty-nine out of fifty-two patients (94%) were free of ascites. Eleven of these patients had PM of colorectal origin. These findings suggest a potential benefit, in the presence of unresectable disease at laparotomy, from intraperitoneal chemotherapy. Patients may also benefit, albeit temporarily, from formation of an ostomy, intestinal bypass or adhesiolysis[49].

Factors associated with unresectability have been documented in the literature. The two main causative factors are 5-7 abdominal regions affected by PM and extensive small bowel or mesenteric involvement[50,51]. Only three of the studies in the current review documented the reasons for unresectability. These included extensive small bowel involvement, hepatic metastases and extensive disease involving the diaphragm and lesser sac[31,32,34]. Similar causative factors were identified in a series reported by van Oudheusden and colleagues[43], however, the main factor was found to be a high PCI with 50% (41/82) of patients undergoing an open and closed laparotomy upon the discovery of a PCI exceeding 20. The literature suggests that a complete cytoreduction confers little survival benefit in patients with a PCI > 17[52] and the association between a high PCI and poor outcomes is documented in eight of the studies[6,16,17,25-28,38] in this review. However, while there are reports showing favourable outcomes in a subset of these patients[53,54], selecting which patients with a high PCI to operate on remains a challenge.

It appears that tumour biology can impact on resectability and outcomes in peritoneal carcinomatosis. Winer *et al*[32] reported outcomes in patients with poorly differentiated tumours. They found that PM was a common finding in patients with signet ring cell subtype in the primary tumour and accounted for 14% of the cytoreductive surgeries performed in their institute. Tumours with signet ring histology are more likely to have metastasised at initial presentation and have an extremely poor prognosis despite advances in systemic chemotherapy[55,56] .The median survival for patients with an incomplete cytoreduction in Winer’s series was 2.4 mo. Winer *et al*[32] and Ceelen *et al*[33] concluded that aggressive histological subtypes, including signet ring, are particularly resistant to cytoreductive surgery and this finding is also reported by Chua *et al*[57]. PM with signet ring histology is also associated with an increased risk of death in those undergoing open and closed laparotomy[43] as well as an increased risk of recurrence[58]. These results suggest that patients with signet ring subtype and peritoneal metastases should be approached with caution, particularly when there is a question regarding resectability.

From the published literature it would appear that there is a survival benefit to the delivery of adjuvant systemic treatment following incomplete cytoreduction. Chua *et al*[39] compared outcomes of patients with peritoneal metastases who received systemic chemotherapy *vs* patients who underwent an incomplete cytoreduction, intraperitoneal chemotherapy and systemic chemotherapy. Those in the systemic chemotherapy group alone had median survivals of 11 to 23 mo (depending on the chemotherapy regimen delivered - standard, modern and modern chemotherapy with biological agents) while the median survival of patients who underwent an incomplete cytoreduction was 32 mo. Overall, they found that the administration of a modern chemotherapy regimen improved survival in patients who underwent an incomplete CRS/HIPEC when compared with standard chemotherapy and that an incomplete cytoreduction conferred a survival benefit over systemic chemotherapy alone. Similarly, Glehen *et al*[6] found that adjuvant chemotherapy (irinotecan or oxaliplatin) following incomplete cytoreduction significantly improved survival, when compared with no adjuvant chemotherapy.

 Klaver *et al*[59] and Hompes *et al*[50] specifically assessed the impact of palliative chemotherapy (without cytoreductive surgery or HIPEC) on survival in patients with colorectal PM. In a population based study, Klaver *et al*. found that patients who received systemic chemotherapy survived for up to 66 weeks *vs* 11 weeks for those who didn’t. They also found that peritoneal metastases are somewhat resistant to fluorouracil monotherapy but may be sensitive to modern, multi-agent chemotherapy regimens[59]. Hompes *et al*[50] reported a series of 43 patients with unresectable PM in whom no resection was performed at laparotomy. The overall median survival for these patients was 6.3 mo with those who received palliative chemotherapy having a slightly improved survival of 9.3 mo *vs* 3.1 for those without.

Verwaal *et al*[16] showed particularly adverse peri-operative outcomes associated with an incomplete cytoreduction. More recent studies do not provide sufficient data to support or refute this finding. It is however clear that the morbidity associated with CRS and HIPEC has improved significantly and is now comparable with other major gastrointestinal procedures[60]. This factor must be taken into account if a decision is to be made to proceed on an individual patient basis, even when a complete cytoreduction will not be possible.

**CONCLUSION**

It is generally accepted that the preoperative diagnosis of unresectable peritoneal carcinomatosis precludes an attempt at cytoreductive surgery and patients should not routinely be exposed to an unnecessary laparotomy. In the setting of unresectable peritoneal disease discovered at laparotomy, there is currently no evidence that an incomplete cytoreduction, with or without HIPEC, will improve survival. However, the available data is of poor quality and the decision to proceed must be made on an individual patient basis, taking into account the site and extent of disease, tumour biology and any palliative benefit that may result, and balancing this with the risk of morbidity. Certain patients, particularly those with ascites may receive a quality of life benefit following incomplete cytoreduction and intraperitoneal chemotherapy.

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**Figure 1 Study flow chart.**

**Table 1 Survival according to completeness of cytoreduction in patients undergoing surgery for colorectal peritoneal metastases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author** |  | **Year** | **Study size,*****n =*** |  | **CC-0,*****n =*** | **Median survival****(mo)** |  | **CC-1,*****n =*** | **Median survival,****(mo)** |  | **CC-0/1,*****n =*** | **Median survival****(mo)** |  | **CC-2/3,*****n =*** | **Median survival****(mo)** |
|  |  |  |  |  |
| Pestieau[26] |  | 2000 | 104 |  | - | - |  | - | - |  | 44 | 24 |  | 55 | 12 |
| Verwaal[16] |  | 2003 | 49 |  | 18 | - |  | 21 | 20 |  | - | - |  | 10 | 5 |
| Glehen[6] |  | 2004 | 506 |  | 271 | 32.4 |  | 106 | 24 |  | - | - |  | 129 | 8.4 |
| Carmignani[27] |  | 2004 | 27 |  | - | - |  | - | - |  | 15 | 20.6 |  | 12 | 9 |
| Mahteme[40] |  | 2004 | 18 |  | - | - |  | - | - |  | 11 | 32 |  | 7 | 10 |
| Fuzun[28] |  | 2006 | 29 |  | 8 | 62 |  | 18 | 21 |  | 26 | 37 |  | 3 | 7 |
| Shen[29] |  | 2008 | 77 |  | 13 | NR |  | 35 | 15.2 |  | - | - |  | 29 | 4.5 |
| Varban[37] |  | 2009 | 14 |  | - | - |  | - | - |  | 9 | 23 |  | 5 | 15.4 |
| Chua[34] |  | 2010 | 58 |  | - | - |  | - | - |  |  |  |  | 3 | 19 |
| Elias[17] |  | 2010 | 523 |  | 439 | 33 |  | 53 | 20 |  | - | - |  | 22 | 7 |
| Cavaliere[25] |  | 2011 | 146 |  | 124 | 25 |  | 11 | 11 |  | - | - |  | 11 | 8 |
| Mulsow[30] |  | 2011 | 125 |  | - | - |  | - | - |  | 31 | 25 |  | 94 | 8 |
| Chua[39] |  | 2011 | 110 |  | 72 | 46 |  | 27 | 35 |  | - | - |  | 11 | 32 |
| Matsuda[35] |  | 2012 | 153 |  | - | - |  | - | - |  | 31 | 42 |  | 122 | 10 |
| Park[31] |  | 2013 | 29 |  | 24 | - |  | 0 | - |  | - | - |  | 5 | 12 |
| Winer[32] |  | 2013 | 30 |  | 14 | - |  | 9 | - |  | 23 | 15.8 |  | 4 | 2.4 |
| Huang[38] with HIPEC |  | 2013 | 33 |  | - | - |  | - | - |  | 14 | 21.7 |  | 19 | 11 |
| Huang[38] without HIPEC |  | 2013 | 29 |  | - | - |  | - | - |  | 9 | 18.3 |  | 20 | 5 |
| Kobayashi[36] |  | 2014 | 564 |  | - | - |  | - | - |  | 160 | 30.5 |  | 404 | 12 |
| Ceelen[33] |  | 2014 | 166 |  | 79 | 49 |  | 66 | 22 |  | - | - |  | 21 | 12 |

NR: Not reached

**Table 2 Survival following incomplete cytoreduction**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author** |  | **Year** |  | **Study size,*****n =*** | **Control1****median survival** **(mo)** | **CC-2/3,*****n =*** | **Median survival (mo)** | **1 yr** | **2 yr** | **3 yr** | **4 yr** | **5 yr** |
|  |  |
| Pestieau[26] |  | 2000 |  | 104 | - | 55 | 12 | - | - | - | - | 0.0% |
| Verwaal[16] |  | 2003 |  | 49 | 12.6 | 10 | 5 | - | - | - | - | - |
| Glehen[6] |  | 2004 |  | 506 | - | 129 | 8.4 | 38.0% | - | 6.0% | - | 0.0% |
| Carmignani[27] |  | 2004 |  | 27 | - | 12 | 9 | - | - | - | - | - |
| Mahteme[40] |  | 2004 |  | 18 | 14 | 7 | 10 | - | - | - | - | - |
| Fuzun[28] |  | 2006 |  | 29 | - | 3 | 7 | - | - | - | - | - |
| Shen[29] |  | 2008 |  | 77 | - | 29 | 4.5 | - | - | 6.0% | - | 0.0% |
| Varban[37] |  | 2009 |  | 14 | - | 5 | 15.4 | - | 40.0% | - | 20.8% | - |
| Chua[34] |  | 2010 |  | 58 | - | 3 | 19 | - | - | - | - | 0.0% |
| Elias[17] |  | 2010 |  | 523 | - | 22 | 7 | - | - | 8.5% | - | 0.0% |
| Cavaliere[25] |  | 2011 |  | 146 | - | 11 | 8 | - | 0.0% | - | - | 0.0% |
| Mulsow[30] |  | 2011 |  | 125 | - | 94 | 8 | 39.0% | 17.0% | - | - | 3.0% |
| Chua[39] |  | 2011 |  | 110 | - | 11 | 32 | - | - | - | - | - |
| Matsuda[35] |  | 2012 |  | 153 | - | 122 | 10 | - | - | - | - | 0.0% |
| Park[31] |  | 2013 |  | 29 | - | 5 | 12 | - | - | 0.0% | - | 0.0% |
| Winer[32] |  | 2013 |  | 30 | - | 4 | 2.4 | - | - | - | - | - |
| Huang[38] with HIPEC |  | 2013 |  | 33 | - | 19 | 11 | - | - | - | - | - |
| Huang[38] without HIPEC |  | 2013 |  | 29 | - | 20 | 5 | - | - | - | - | - |
| Kobayashi[36] |  | 2014 |  | 564 | - | 404 | 12 | - | - | - | - | 4.7% |
| Ceelen[33] |  | 2014 |  | 166 | - | 21 | 12 | - | - | - | - | - |

1Control: No surgery group/patients treated with systemic chemotherapy alone.

**Table 3 Survival following incomplete cytoreduction, with or without intraperitoneal chemotherapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Author** |   | **CC-2/3,** | **Median survival (mo)** |
|  | ***n =*** |
| With intraperitoneal chemotherapy |  |  |  |
| Shen[29] |  | 29 | 4.5 |
| Verwaal[16] |  | 10 | 5 |
| Elias[17] |  | 22 | 7 |
| Fuzun[28] |  | 3 | 7 |
| Glehen[6] |  | 129 | 8.4 |
| Carmignani[27]1 |  | 12 | 9 |
| Mahteme[40] |  | 7 | 10 |
| Huang[38] with HIPEC |  | 19 | 11 |
| Park[31] |  | 5 | 12 |
| Ceelen[33] |  | 21 | 12 |
| Pestieau[26] |  | 55 | 12 |
| Varban[37] |  | 5 | 15.4 |
| Chua[34] |  | 3 | 19 |
| Chua[39] |  | 11 | 32 |
| Without intraperitoneal chemotherapy |  |  |  |
| Winer[32] |  | 4 | 2.4 |
| Huang[38] without HIPEC |  | 20 | 5 |
| Cavaliere[25] |  | 11 | 8 |
| Mulsow[30] |  | 94 | 8 |
| Matsuda[35] |  | 122 | 10 |
| Kobayashi[36] |  | 404 | 12 |

1An unspecified number of patients received HIPEC.