Meta-analysis of oncologic effect of primary tumor resection in patients with unresectable stage IV colorectal cancer in the era of modern systemic chemotherapy

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INTRODUCTION

Approximately 20%–25% of patients with colorectal cancer present with metastases at the time of diagnosis. Most patients with metastatic colorectal cancer have unresectable disease, but may benefit from chemotherapy or primary tumor resection (PTR) with palliative intent followed by systemic chemotherapy [1]. PTR may improve quality of life and may prevent or ameliorate complications caused by growth of the primary tumor, such as obstruction, perforation or bleeding [2-5]. These complications require emergency surgery, which is associated with high morbidity and mortality rates and less favorable long-term outcomes. Despite the benefits of PTR, it delays the start of systemic chemotherapy, which also provides survival advantages [6,7]. Systemic chemotherapy regimens that contain agents such as irinotecan, oxaliplatin, and targeted agents have improved the prognosis of these patients. Administration of systemic chemotherapy to most patients who lack symptoms related to primary tumors may be sufficient to control the asymptomatic primary lesions, as chemotherapy can shrink tumors and/or control tumor spread [8-11]. Moreover, PTR may lead to postoperative morbidity and mortality, making resection questionable even in patients with asymptomatic tumors.

It is therefore unclear whether PTR with palliative intent...
is safe or provides actual survival benefit. Although three previous meta-analyses reported oncologic outcomes of PTR [2,12,13], 2 of those analyses assessed overall survival (OS) alone, and did not consider the survival outcomes of subgroups. Furthermore, all of these analyses included studies published prior to the introduction of chemotherapeutic regimens that contained irinotecan or oxaliplatin. The current meta-analysis therefore evaluated the survival benefits of PTR in patients with unresectable metastatic colorectal cancer in the era of modern chemotherapy.

**METHODS**

This meta-analysis followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [14]. Multiple comprehensive databases were searched for studies that assessed the oncologic outcomes of PTR in patients with unresectable metastatic colorectal cancer. The study protocol was based on Cochrane Review Methods [15].

**Data and literature sources**

PubMed (January 1, 1976 to November 23, 2016), Embase (January 1, 1985 to November 23, 2016), and the Cochrane Central Register of Controlled Trials (CENTRAL: January 1, 1987 to November 23, 2016) were searched. There were no restrictions on year or language of publication. The search terms used were "colorectal cancer," "metastatic," "stage IV," "palliative resection," and "survival." After the initial electronic search, articles were manually searched to identify additional studies. All articles were assessed individually before inclusion.

**Study selection and data extraction**

Article titles and abstracts were screened, and full texts were reviewed independently by 2 reviewers (GWH and MRL), based on the selection criteria. Discrepancies were resolved by discussion between these reviewers.

Included studies assessed the survival outcomes, including OS and progression-free survival (PFS), of patients with metastatic colorectal cancer who did and did not undergo PTR. Studies were excluded if they: (1) assessed patients who had tumor pathology other than adenocarcinoma; (2) assessed patients who were not treated with modern cytotoxic agents, such as irinotecan or oxaliplatin, or were diagnosed with metastatic colorectal cancer before 2000, the beginning of the modern chemotherapy era; (3) assessed patients who underwent simultaneous or subsequent metastasectomy; (4) assessed only specific groups of patients (e.g., elderly or obese patients); (5) had no extractable data and the authors could not be reached to provide additional information; (6) were case series with fewer than 10 patients; and (7) were not published in English.

All eligible studies were reviewed, and all relevant data were extracted independently by 2 reviewers using a predefined data extraction form. The variables recorded were: (1) basic publication information, including name of the first author, year of publication, and number of patients; (2) demographic, clinical, and treatment characteristics of the patients; and (3) patient outcomes (OS and PFS).

**Assessment of methodological quality**

The methodological quality of the included studies was assessed using the Newcastle-Ottawa quality scale (NOS), which allocates a maximum of 9 points to each study: a score ≥ 6 indicated high quality [16]. The quality of included studies was determined by examining three factors: patient selection, comparability of the study groups and assessment of outcomes.

**Statistical analysis**

The meta-analysis determined the hazard ratio (HR) with its variance and 95% confidence interval (CI). The presence and extent of heterogeneity were assessed using the Q test and I^2 index, respectively, with a P-value less than 0.1 considered statistically significant [17]. The DerSimonian-Laird random effects model (REM) was used for pooling data in anticipation of cross-study heterogeneity [18]. If sufficient data were available, planned subgroup analyses were performed to evaluate oncologic effects of PTR. Sensitivity analyses were also performed to assess the robustness of the meta-analysis findings [19,20]. Publication bias was assessed by visually inspecting funnel plots of the outcome. and using the Egger weighted linear regression test, in which a P-value less than 0.1 was considered significant [21,22].

All data were analyzed using Review Manager (RevMan 5.3, Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis ver. 3 (Englewood, NJ, USA).

**RESULTS**

**Description of studies**

The predefined searching strategy and manual searching identified 13,577 potentially relevant articles; of these, 2,436 articles were excluded because they were duplicates and 11,070 were excluded because their titles and abstracts did not fulfill the selection criteria. After full text review of the remaining 71 articles, 54 were excluded due to the exclusion criteria of these studies. Therefore, a total of 17 nonrandomized studies were deemed suitable for inclusion (Fig. 1). These studies examined a total of 18,863 patients. 9,575 of whom underwent PTR without metastasectomy. All 17 studies evaluated OS [23-39], whereas only two evaluated PFS [24,35]. Three studies examined patients with colon cancer exclusively [28,32,38].
one examined patients with rectal cancer exclusively [25], and 13 examined patients with colorectal cancer [23,24,26-35,39]. In three of the latter studies, data on patients with colon cancer could be separated from data on patients with rectal cancer [34,37,39]. Thirteen studies evaluated patients who received targeted chemotherapy [23,24,26-35,39]. In eight studies, all patients who did not undergo PTR received systemic chemotherapy [23,24,28,30,32,33,35,36]. Four studies evaluated oncologic outcomes using large databases [34,36-38]. Seven studies assessed HR for OS using propensity score analysis [27,29,31,32,36-38].

Evaluation of methodological quality showed that 14 studies scored high (≥6) on the NOS [24-28,30-36,38,39].

Tables 1 and 2 summarize the characteristics of all 17 included studies.

**Outcome measures**

Analysis of oncologic outcomes after PTR indicated that all 17 studies, involving 18,863 patients, reported data on OS. Pooled analysis showed that PTR increased OS rate (HR, 0.65; 95% CI, 0.57–0.70; I² = 19%).

Sensitivity analyses, performed using predefined methods, indicated the robustness of all OS results of this meta-analysis. Reanalysis of the data using an alternative statistical effects model (HR, 0.54; 95% CI, 0.52–0.56; I² = 83%), analysis of high-quality studies (NOS ≥ 6) (HR, 0.62; 95% CI, 0.54–0.70; I² = 81%), analysis of studies reported by surgeons (HR, 0.62; 95% CI, 0.51–0.75; I² = 75%) and analysis of studies reported by medical oncologist (HR, 0.64; 95% CI, 0.57–0.72; I² = 36%), and analysis of studies using large databases (HR, 0.64; 95% CI, 0.50–0.83; I² = 96%) all showed that PTR was associated with increased OS. Finally, analysis of studies using HRs for OS from propensity score analysis showed that PTR was associated with increased OS (HR, 0.64; 95% CI, 0.52–0.80; I² = 88%). Table 3 summarizes the results of these subgroup and sensitivity analyses.

**Publication bias**

Publication bias was analyzed using the Egger weighted linear regression test, which assesses the asymmetry of funnel plots. The funnel plot for OS (P = 0.01) was found to be asymmetric, indicating publication bias (Fig. 4).

**DISCUSSION**

To our knowledge, this is the first meta-analysis to assess the oncologic effect of PTR for patients diagnosed with unresectable stage IV colorectal cancer in the era of modern chemotherapy.
| Study                | Design                | Study period  | PTR (n) | Non-PTR (n) | Symptomatic resections (%) | Primary site (rectum, %) | Outcome measures | NOS scale |
|----------------------|-----------------------|---------------|---------|-------------|---------------------------|--------------------------|------------------|-----------|
| Ahmed [39] 2016      | RCS, Single           | 2006–2010     | 232     | 248         | 55                        | 28                       | 41               | OS        |
| Alwadi [38] 2016     | RCS, Large database   | 2003–2005     | 5,332   | 3,010       | 0                         | 0                        | 0                | OS        |
| Gulack [37] 2016     | RCS, Large database   | 2003–2006     | 231     | 1,215       | NR                        | 8.2                      | 46.7             | OS        |
| 't Lam-Boer [36] 2016| RCS, Large database   | 2008–2011     | 1,484   | 3,177       | NR                        | 13                       | 32               | OS        |
| Wang [35] 2016       | PCS, Single           | 2011–2013     | 118     | 73          | 0                         | 38                       | 42.5             | OS, PFS   |
| Wong [34] 2016       | RCS, Large database   | 2009–2015     | 216     | 394         | NR                        | 3                        | 36               | OS        |
| Kodaz [33] 2015      | RCS, Single           | 2007–2013     | 34      | 44          | NR                        | 0                        | 0                | OS        |
| de Mestier [32] 2014 | RCS, Single           | 2004–2008     | 69      | 27          | NR                        | 0                        | 0                | OS        |
| Gresham [31] 2014    | RCS, Multi            | 2006–2008     | 378     | 139         | NR                        | 18.3                     | 39.6             | OS        |
| Miyamoto [30] 2014   | RCS, Single           | 2005–2011     | 68      | 63          | NR                        | 42                       | 30               | OS        |
| Yoon [29] 2014       | PCS, Single           | 2000–2007     | 195     | 66          | 43                        | 34.9                     | 63.6             | OS        |
| Boselli [28] 2013    | RCS, Single           | 2010–2011     | 17      | 31          | 0                         | 0                        | 0                | OS        |
| Park [27] 2013       | RCS, Single           | 2000–2009     | 527     | 320         | 27                        | NR                       | NR               | OS        |
| Kim [26] 2012        | RCS, Single           | 2000–2009     | 63      | 83          | 93                        | 35.2                     | 44.8             | OS        |
| Verbeeme [25] 2012   | RCS, Single           | 2002–2006     | 26      | 62          | 7                         | 100                      |                  | OS        |
| Verderbosch [24] 2011 | RCS, Multi           | 2003–2004     | 258     | 141         | NR                        | 22                       | 34               | OS, PFS   |
| Verderbosch [24] 2011 | RCS, Multi           | 2005–2006     | 289     | 159         | NR                        | 18                       | 27               | OS, PFS   |
| Tanoue [23] 2010     | RCS, Single           | 2005–2009     | 38      | 36          | NR                        | 42                       | 53               | OS        |

PTR, primary tumor resection; RCS, retrospective cohort study; PCS, prospective cohort study; Single, single center study; Multi, multicenter study; OS, overall survival; PFS, progression free survival; NOS, Newcastle-Ottawa quality scale; NR, not reported.
Table 2. Clinical characteristics of included studies

| Study          | Metastatic spread                        | Chemotherapy regimens                                      | CTx received (%) | Radiation therapy (%) | Median survival (mo) |
|----------------|------------------------------------------|-------------------------------------------------------------|------------------|-----------------------|---------------------|
|                |                                          |                                                             | PTR | Non-PTR | PTR | Non-PTR | PTR | Non-PTR |
| Ahmed [39] 2016| Liver, lung, peritoneum, bone, brain     | FOLFOX/FOLFIRI ± bevacizumab, cetuximab, panitumumab         | 64   | 50      | 14  | 18      | 27  | 14      |
| Alwadi [38] 2016| NR                                       | NR                                                           | 61.7 | 46.2    | 0   | 0       | 20.3| 10      |
| Gulack [37] 2016| NR                                       | NR                                                           | 46.2 | 66      | 6.1 | 47.9    | 9.2 | 7.6     |
| 't Lam-Boer [36] 2016| Liver, lung, peritoneum | NR                                                           | 54   | 100     | NR | NR      | 20.7| 11.9    |
| Wang [35] 2016  | NR                                       | FOLFOX/XELOX/FOLFIRI + bevacizumab                         | 100  | 0       | 0   | 11      | 22.5| 17.8    |
| Wong [34] 2016  | Liver, other distant                     | Oxaliplatin/irinotecan ± bevacizumab, cetuximab             | 78   | 74      | NR | NR      | 21  | 17      |
| Kodaz [33] 2015 | Liver, lung, other distant              | FOLFOX/FOLFIRI ± bevacizumab                                | 97   | 100     | NR | NR      | 25  | 16      |
| de Mestier [32] 2014| Liver, lung, other distant | FOLFOX/FOLFIRI ± bevacizumab                               | 100  | 0       | 0   | 0       | 23.1| 22.1    |
| Gresham [31] 2014| Liver, extrahepatic                   | FOLFOX/FOLFIRI ± bevacizumab, capecitabine, 5FU             | 68   | 50.4    | NR | NR      | 17.9| 7.9     |
| Miyamoto [30] 2014| Liver, lung, other distant             | FOLFOX/FOLFIRI ± bevacizumab, capecitabine                  | 100  | 100     | NR | NR      | 30.4| 24.1    |
| Yoon [29] 2014  | Liver                                    | FOLFOX/FOLFIRI/XELOX/XELIRI/FL/capecitabine ± bevacizumab, | 85.1 | 71.2    | NR | NR      | 21  | 10      |
| Boselli [28] 2013| Liver                                   | FOLFOX ± bevacizumab                                        | 64.7 | 100     | 0   | 0       | 4   | 5       |
| Park [27] 2013  | Liver, lung, peritoneum, other distant   | Oxaliplatin/irinotecan/capecitabine ± bevacizumab, cetuximab| 91   | 86.9    | NR | NR      | 21.4| 14.1    |
| Kim [26] 2012   | Liver, lung, peritoneum, other distant   | FOLFOX/FOLFIRI ± bevacizumab                                | 58.1 | 74      | 4.8 | 25      | 14  | 8       |
| Verberne [25] 2012| Liver, lung, other distant              | NR                                                           | 58   | 34      | 0   | 19      | 10  |         |
| Verderbosch [24] 2011 (1)| Liver, extrahepatic                   | Capecitabine/irinotecan/oxaliplatin                      | 100  | 0       | 0   | 0       | 16.7| 11.4    |
| Verderbosch [24] 2011 (2)| Liver, extrahepatic                   | Capecitabine/oxaliplatin/bevacizumab ± cetuximab           | 100  | NR      | NR | NR      | 20.7| 13.4    |
| Tanoue [23] 2010 | Liver, lung, peritoneum                 | FOLFOX/FOLFIRI ± bevacizumab, cetuximab                     | 100  | NR      | NR | NR      | 30.6| 20.8    |

CTx, chemotherapy; PTR, primary tumor resection; NR, not reported.
This meta-analysis found that PTR was associated with increased OS in patients with unresectable metastatic colorectal cancer. This result is similar to that of previous meta-analyses [2,12,13]. However, these previous analyses included studies that evaluated patients diagnosed with colorectal cancer before the introduction of modern chemotherapy regimens which led to a major transition in the treatment of metastatic colorectal cancer [40]. Irinotecan was introduced in 1996, and it was reported that irinotecan provided survival benefits in patients with metastatic colorectal cancer in 2000 [41]. Therefore, we chose a time period of diagnosis beginning in 2000. The number of new chemotherapeutic agents has increased significantly over the past decade, with these new agents playing an important role in the treatment of metastatic colorectal cancer. Therefore, the present meta-analysis included studies that assessed patients treated with modern cytotoxic agents, such as irinotecan or oxaliplatin, or assessed patients diagnosed with metastatic colorectal cancer after 2000.

The present study provides a more detailed assessment of oncologic outcomes, using subgroup and sensitivity analyses, than previous studies. We found that PTR was associated with increased OS from the analysis of studies including patients who received target agents, and from the analysis of studies in which all patients in non-PTR group received chemotherapy. Despite selection bias, these results suggest that PTR may be an independent prognostic factor for OS, similar to a study that reported that PTR itself was an independent predictor of response to bevacizumab [42]. PTR may reduce the concentrations of tumor-derived protumorigenic chemotactic cytokines that regulate cancer metastasis [43,44]. Primary tumors may have unique attributes that support tumor progression. Primary tumors frequently exhibit greater genetic variability than metastases and, therefore, may have greater

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**Fig. 2.** Forest plot and meta-analysis of the effects of primary tumor resection on overall survival. SE, standard error; CI, confidence interval; df, degree of freedom.

**Fig. 3.** Forest plot and meta-analysis of the effects of primary tumor resection on progression-free survival. SE, standard error; CI, confidence interval; df, degree of freedom.
capacity to generate new metastatic clones resistant to ongoing treatments [40,45,46]. Additionally, we tried to separately analyze patients with colon cancer and rectal cancer, because the natural history, complications and therapeutic options differ in these 2 groups. We found that PTR was associated with increased OS in patients with colon cancer. However, it was impossible to analyze patients with rectal cancer, because only one of the 17 included studies separately analyzed patients with rectal cancer.

This meta-analysis had several limitations. There was potential heterogeneity among the included studies, despite our use of definite exclusion criteria and our performance of subgroup and sensitivity analyses. Because all included studies were nonrandomized, selection bias was likely. Patient performance status, presence of symptoms, tumor burden, and various surgical techniques may have influenced the oncologic outcomes of PTR. Moreover, most studies included in this analysis did not specify reasons or criteria for nonresection. The included studies were retrospective in design, suggesting a possible bias in decision-making for individual patients, which may have influenced oncologic outcomes. Although the factors that may have influenced the selection of patients for surgery remain unclear, patients who were younger in age and had fewer comorbidities and metastases were more likely to undergo PTR, whereas patients who were older, sicker and had many metastatic foci were less likely to undergo surgery. Finally, Publication bias was found in the analysis of OS. However, using the Trim-and-Fill method, under both of the fixed effects model and the REM for the outcomes, our results were not affected by this bias.

In conclusion, surgical resection of the primary tumor without metasactomy may have survival benefits in patients with unresectable stage IV colorectal cancer. Continued advances in modern chemotherapy and appropriate local

Table 3. Subgroup and sensitivity analyses of overall survival

| Variable                          | No. of studies | No. of cases | HR    | 95% CI          | Heterogeneity | Cochrane Q | df (Q) | I² (%) | P-value | P-value |
|-----------------------------------|----------------|--------------|-------|-----------------|---------------|------------|--------|--------|---------|---------|
| All studies                       | 17             | 18,863       | 0.63  | 0.56–0.71       | <0.001        | 101.85     | 17     | 83     | <0.001  | <0.001  |
| Subgroup analyses                 |                |              |       |                 |               |            |        |        |         |         |
| Colon cancer alone                | 6              | 9,751        | 0.63  | 0.48–0.85       | <0.001        | 49.16      | 5      | 90     | <0.001  | <0.001  |
| Target agent                      | 13             | 3,927        | 0.65  | 0.58–0.73       | <0.001        | 18.93      | 12     | 37     | 0.090   | 0.090   |
| All chemotherapy in non-PTR group | 8              | 6,126        | 0.63  | 0.57–0.70       | <0.001        | 9.85       | 8      | 19     | 0.280   | 0.280   |
| Sensitivity analyses              |                |              |       |                 |               |            |        |        |         |         |
| Fixed effect model                | 17             | 18,863       | 0.54  | 0.52–0.76       | <0.001        | 101.85     | 17     | 83     | <0.001  | <0.001  |
| High-quality studies              | 14             | 17,082       | 0.62  | 0.54–0.70       | <0.001        | 73.29      | 14     | 81     | <0.001  | <0.001  |
| Surgeons                          | 14             | 15,197       | 0.62  | 0.51–0.75       | <0.001        | 70.42      | 14     | 89     | <0.001  | <0.001  |
| Medical oncologist                | 9              | 3,666        | 0.62  | 0.57–0.72       | <0.001        | 12.50      | 9      | 36     | 0.130   | <0.001  |
| Large database analysis           | 4              | 15,059       | 0.64  | 0.50–0.83       | <0.001        | 75.96      | 3      | 96     | <0.001  | <0.001  |
| Sensitivity analyses              |                |              |       |                 |               |            |        |        |         |         |
| Fixed effect model                | 17             | 18,863       | 0.54  | 0.52–0.70       | <0.001        | 101.85     | 17     | 83     | <0.001  | <0.001  |
| High-quality studies              | 14             | 17,082       | 0.62  | 0.54–0.70       | <0.001        | 73.29      | 14     | 81     | <0.001  | <0.001  |
| Surgeons                          | 14             | 15,197       | 0.62  | 0.51–0.75       | <0.001        | 70.42      | 14     | 89     | <0.001  | <0.001  |
| Medical oncologist                | 9              | 3,666        | 0.64  | 0.50–0.83       | <0.001        | 12.50      | 9      | 36     | 0.130   | <0.001  |
| Large database analysis           | 4              | 15,059       | 0.64  | 0.52–0.80       | <0.001        | 75.96      | 3      | 96     | <0.001  | <0.001  |

HR, hazard ratio; CI, confidence interval; df (Q), degree of freedom.

Fig. 4. Funnel plots of included studies in the analysis for the effects of primary tumor resection on overall survival. SE, standard error.
treatments including PTR would improve survival outcomes. Randomized controlled trials are needed to determine the optimal treatment for these patients.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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