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# To resect or not to resect: The hamletic dilemma of primary tumor resection in patients with asymptomatic stage IV colorectal cancer

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ABSTRACT

Primary tumor resection (PTR) in advanced asymptomatic colorectal cancer (CRC) has been a matter of intense debate for long time. With the advances in systemic treatments, this practice has decreased over the years, although it remains still pervasive. Although the removal of primary tumor has been extensively interrogated both in retrospective and prospective studies, it still remains a clinical conundrum. There are many arguments for and against PTR in CRC both from the preclinical and the clinical point of view. Two scoring models have been published aiming at identifying patients who are suitable candidate for PTR, but they deserve further investigations in larger datasets. While awaiting the results of ongoing randomized clinical trials (RCTs) on this controversial topic, both upfront systemic treatment and PTR followed by chemotherapy should be considered valid options in patients with asymptomatic mCRC. Clinical selection and a shared-decision making approach are the keys to success.

## 1. Introduction

CRC represents one of the leading causes of cancer-related death worldwide (Siegel et al., 2018). Despite widespread of screening procedures, even today approximately 20% of patients with CRC are found to have distant metastases at the time of diagnosis (Nitzkorski et al., 2012).

Historically, patients diagnosed with mCRC were managed with the resection of primary tumor with the aim to avoid deleterious complications such as massive bleeding, perforation or obstruction. However, the improved outcomes with the introduction of new chemotherapeutics and targeted agents in the therapeutic armamentarium led to a paradigm shift towards a non-operative management of patients with asymptomatic primary tumor. Indeed, while there is no doubt that patients with potentially resectable metastatic disease should receive PTR with synchronous or staged resection of all metastatic lesions, its role in patients with unresectable metastatic disease (that unfortunately represent the majority of patients) remains controversial (Hu et al., 2015; Adam, 2003).

The concept of PTR in metastatic disease comes from renal cell carcinoma. Cytoreductive nephrectomy (CN) became an established paradigm since many retrospective series and randomized clinical trials (RCTs), conducted both in the era of immunotherapy and targeted therapies, demonstrated a survival advantage compared to patients who received only systemic therapies (Flanigan et al., 2001; Mickisch et al., 2001; Flanigan et al., 2004; Choueiri et al., 2011; Heng et al., 2014). These data have fueled a large amount of retrospective analyses and RCTs across a variety of solid tumors, but the results were conflicting (Steuber et al., 2017; Ristau et al., 2016; Dittmar et al., 2012; Fujitani et al., 2016; Lane et al., 2017; Badwe et al., 2015; Seisen et al., 2016).

Further complicating this scenario is the fact that preclinical evidences point out that surgery represents a potential trigger for tumor progression by increasing shedding of tumor cells into circulation and suppressing antitumor immunity, thus suggesting a potential deleterious effect of PTR also in the context of metastatic disease (Tohme et al., 2017).

This narrative review aims at summarizing the literature data and discussing the arguments for and against PTR in CRC, both from a preclinical and clinical point of view, providing a useful algorithm for oncologists treating these patients.

## 2. Time trends of PTR in CRC

In 1999 Scoggins and colleagues published a retrospective review of

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**Table 1**
Summary of systematic reviews, meta-analysis and propensity-scored adjusted analyses about PTR mCRC.

| Author | type of study | Number of studies (pts) | Outcome |
|---|---|---|---|
| Stillwell (Stillwell et al., 2010) | meta-analysis | 8 (1062) | PTR associated with longer OS and less complications |
| Anwar (Anwar et al., 2012) | systematic review | 21 (N.A.) | PTR associated with longer OS in most studies |
| Cirocchi (Cirocchi et al., 2012) | systematic review (and meta-analysis) | 7 (1086) | PTR not associated with longer OS or less complications |
| Clancy (Clancy et al., 2014) | meta-analysis | 21 (44,226) | PTR associated with longer OS |
| Faron (Faron et al., 2015) | pooled analysis | 4 (1155) | PTR associated with longer OS |
| t Lam-Boer ('t Lam-Boer et al., 2016) | propensity-scored adjusted analysis | N.A. (10,371) | PTR associated with longer OS |
| Nitsche (Nitsche et al., 2017) | meta-analysis | 56 (140,151) | PTR associated with longer OS |
| van Rooijen (van Rooijen et al., 2018) | meta-analysis | 8 (3423) | PTR associated with longer OS |

N.A.: not available.

their series of patients with stage IV CRC observing that only 8.7% of patients managed without resection (non-resection group) developed obstruction at the primary site requiring emergent diversion, while in the resection group the operative morbidity was 30.3% and the perioperative mortality rate was 4.6%, without any difference in terms of survival between the two groups (Scoggins et al., 1999).

Furthermore, another retrospective analysis of patients with stage IV CRC diagnosed between 1988 and 2000 demonstrated that 66% of patients underwent PTR, which was more frequent in younger patients with right-sided tumors (Cook et al., 2005).

Subsequently, other retrospective analyses of the Surveillance, Epidemiology and End Results (SEER) database showed that this practice has decreased over the years, although it remains still pervasive (Shapiro et al., 2015; Stillwell et al., 2010). This trend should probably be attributed to the addition of new chemotherapeutics (Oxaliplatin, Irinotecan) and targeted agents (anti-VEGF monoclonal antibodies, anti-EGFR monoclonal antibodies, multi-target tyrosin-kinase inhibitors) to 5-fluorouracil that, alone or variably combined with each other, lead to an improvement in clinical outcomes of patients with mCRC, both in terms of response and survival. In fact, in the study by Hu and colleagues, despite a trend towards decreased use of PTR, an improvement of survival rate was observed, which probably temporally coincides with the introduction of new chemotherapeutics agents that started in 2000 (Hu et al., 2015). However, this remains only a speculation, since SEER database does not provide information about systemic treatments. In addition, in vitro and in vivo studies demonstrated that primary colonic tumors were more chemosensitive compared to matched metastases (Takebayashi et al., 2013; Cameron et al., 2009).

## 3. Clinical data on PTR in CRC

The usefulness of PTR in patients with stage IV CRC has been extensively investigated in many retrospective series and systematic reviews, often coming to opposite conclusions (Stillwell et al., 2010; Anwar et al., 2012; Clancy et al., 2014; Eisenberger et al., 2008; Scheer et al., 2008a; Cirocchi et al., 2012; Faron et al., 2015; Alawadi et al., 2017; Nitsche et al., 2017). Most of these studies suggest a potential benefit of PTR in terms of survival compared to patients managed only with systemic therapy, but these conclusions are tainted by concerns of selection bias inherent in retrospective series, since patients who underwent PTR were frequently fitter and had less extensive disease. Furthermore, other unaccounted clinical factors could have influenced the results of these studies.

For example, Clancy and colleagues performed a meta-analysis of 21 eligible studies (19 retrospective series, 2 cohort studies) demonstrating a lower mortality risk and a gain of 6.4 months in terms of survival in patients undergoing PTR (Clancy et al., 2014). Nevertheless, obvious selection bias affected the results of this study, since patients who received PTR had more frequently liver-limited disease, a lower number of metastases and less frequently rectal cancer as compared to the non-operative group of patients.

In addition, cohort studies using propensity scored-matched analysis came to the same conclusions ('t Lam-Boer et al., 2016). However, albeit propensity-scored matched analyses can be used to reduce the risk of bias, the scientific evidence deriving from them will not have the same dignity of a RCT (Søreide, 2016).

Recently, an individual patient data analysis of 3423 patients enrolled into 8 RCTs of first-line systemic therapy in the ARCAD database was performed (van Rooijen et al., 2018). Of note, patients analyzed in this study were enrolled in modern clinical trials, most of them including treatment with targeted agents. Patients with synchronous mCRC who underwent PTR were roughly 50%, thus confirming PTR as a common practice also in the context of modern systemic treatments. The authors demonstrated that patients with unresected synchronous disease had a significantly worse median progression-free survival (PFS) and overall survival (OS) as compared to patients with synchronous disease who received PTR or with metachronous disease. Nevertheless, these results may be subject to selection bias, since reasons for (non)resection were not available.

Table 1 provides an overview of the main systematic reviews, meta-analysis and propensity-scored adjusted analyses published on this issue.

Furthermore, since anti-angiogenic therapies have become part of the therapeutic repertoire of CRC, some concerns raised about an increased risk of complications, such as perforation, with the use of these drugs in patients with metastatic disease and an intact primary tumor. The NSABP trial C-10 was therefore specifically conceived to address this clinical question (McCahill et al., 2012). In this prospective, multicenter phase II trial of patients treated with chemotherapy (mFOLFOX6) combined with bevacizumab, the rate of major morbidities related to the primary tumor was 14%, which might be substantially considered within the same range of complications of patients treated with chemotherapy alone (Ruo et al., 2003; Tebbutt et al., 2003; Sarela et al., 2001).

One of the main topics of discussion among oncologists treating CRC concerns the prognostic and potentially predictive role of tumor sidedness both in early-stage and advanced disease. Differences in the microbiome, clinical, chromosomal and molecular characteristics have been reported between the right and left side of the colon. In fact, there is now strong evidence about the prognostic role of tumor sidedness, with right-sided tumors marked by worst prognosis than left-sided ones and resistance to anti-EGRF antibodies (Missiaglia et al., 2014; Benedix et al., 2010; Boisen et al., 2013; von Einem et al., 2014; Loupakis et al., 2015; Tejpar et al., 2016; Holch et al., 2017; Moretto et al., 2016). In this regard, the study conducted by Zhang and colleagues was the only one able to demonstrate a prolonged median OS in patients with-left-sided CRC who underwent PTR as compared to patients with right-sided CRC (Zhang et al., 2017). Nevertheless, since it was a retrospective analysis of a small series of patients with the associated risk of selection bias, these results cannot be considered conclusive and warrant further confirmation in prospective studies.

One of the factors that could guide the selection of patients who could benefit from PTR is the mutational status of genes such as RAS or BRAF. Kodaz and colleagues observed in a cohort of 78 patients with

**Table 2**
Summary of ongoing RCTs about PTR in mCRC.

| Trial name | Trial number [reference] | population | Primary endpoint |
|---|---|---|---|
| CAIRO-4 | NCT01606098 (J1 et al., 2014) | colorectal cancer | OS, 5 yrs |
| GRECCAR-8 | NCT02314182 (Cotte et al., 2015) | rectal cancer only | OS, 2 yrs |
| SYNCHRONOUS* | ISRCTN30964555 (Rahbari et al., 2012) | colon cancer only | OS, 3 yrs |
| Chinese trial | NCT02149784 | colorectal cancer | OS, 3 yrs |
| Korean trial* | NCT01978249 | colon and upper rectal cancer | OS, 2 yrs |

Adapted('t Lam-Boer et al., 2016).
* accrual closed.

unresectable mCRC that median OS was 28 months in KRAS mutant patients who underwent PTR and 14 months in KRAS mutant patients without PTR (P = 0.002) (Kodaz et al., 2015). However, these data need further validation in larger prospective clinical trials.

To the best of our knowledge, two scoring models have been published aiming at predicting post-operative survival using variables in order to identify patients who are the most suitable candidate for PTR. Dorajoo and colleagues identified preoperative clinical, pathological and laboratoristic variables (advanced age, poorly differentiated tumor, liver, lung, bone and peritoneal metastases, hypoalbuminaemia and elevated carcinoembryonic antigen levels) which significantly shorten post-operative survival. The scoring model segregates patients into three prognostic groups with distinct median survival lengths of 4.8, 12.4 and 18.6 months, respectively (p < 0.0001) (Dorajoo et al., 2016). In the work by Li and colleagues, age, alkaline phosphatase, ascites and platelet/lymphocyte ratio (PLR) were subsequently combined to form the so-called AAAP scoring system. Patients were classified into high, medium and low risk groups according to the score obtained with significant differences in terms of OS between the three groups (Li et al., 2016). Nevertheless, further confirmation of the reliability of these models in larger datasets is awaited.

Table 2 summarizes the ongoing RCTs which will hopefully clarify the role of PTR in patients with unresectable mCRC ('t Lam-Boer et al., 2014; Cotte et al., 2015; Rahbari et al., 2012).

## 4. Clinical data on PTR in other malignancies

A large body of literature has been published across a variety of solid tumors supporting the notion that the removal of primary tumor can improve the outcome of patients with established metastases.

Following the results of two pioneering RCTs, CN followed by systemic therapy with interferon-α (IFN-α) proved to be superior to IFN-α alone and became a paradigm in the management of metastatic renal cell carcinoma (Flanigan et al., 2001; Mickisch et al., 2001; Flanigan et al., 2004). Thereafter, the tumultuous developments in the treatment landscape of renal cell carcinoma led to a lower use of CN (Tsao et al., 2013). More recently, retrospective data from patients with synchronous metastatic renal cell carcinoma from the International Metastatic Renal Cell Carcinoma Database Consortium (IDMC) demonstrated a survival benefit of CN, even after adjusting for prognostic factors, although patients with estimated survival times < 12 months or adverse prognostic factors seem to derive no benefit from CN (Heng et al., 2014). Data from ongoing RCTs will hopefully clarify the therapeutic role and the optimal timing of CN, albeit recruitment to these studies has been hugely challenging (NCT, 2018a,b).

Similarly, register-based and case-control studies suggest that cytoreductive prostatectomy may improve survival and reduce local symptoms in patients with metastatic prostate cancer, but the interpretation of these results may be limited by their retrospective nature and a number of potential biases (Steuber et al., 2017; Ristau et al., 2016; Culp et al., 2014; Antwi and Everson, 2014; Heidenreich et al., 2015).

Furthermore, since several retrospective series yielded conflicting results regarding the potential benefit of locoregional treatment in patients with metastatic breast cancer (Lane et al., 2017; Rapiti et al., 2006; Gnerlich et al., 2007; Cady et al., 2008; Leung et al., 2010), a RCT was conducted. In this trial, 350 patients presenting with *de novo* metastatic breast cancer were randomized to receive or not locoregional treatment directed at their primary breast tumour and axillary lymph nodes. Of note, no difference in terms of survival was observed between the two groups (Badwe et al., 2015).

Analogously, an open-label RCT in patients with advanced gastric cancer with a single non-curable factor confined to either the liver, peritoneum, or para-aortic lymph nodes, demonstrated that the removal of the primary tumor (gastrectomy plus D1 lymphadenectomy) without any resection of metastatic lesions followed by chemotherapy does not improve survival over chemotherapy alone (Fujitani et al., 2016).

Collectively, these data show the enormous efforts of the clinical research to shed light on this issue which, with the sole exception of CN in renal cell carcinoma, remains a clinical conundrum and warrants further investigations across a broad spectrum of malignancies.

## 5. Pros and cons of PTR in mCRC

### 5.1. The preclinical point of view

Despite surgery represents the mainstay of the treatment of early-stage disease in the majority of tumors and in selected cases of metastatic disease, a growing number of publications suggest a potential detrimental effect by creating a pro-tumorigenic environment and increasing the formation of new metastatic foci.

In their comprehensive review, Tohme and colleagues analyzed the complex mechanisms behind this phenomenon (Tohme et al., 2017). Firstly, surgical manipulation seems to increase the shedding of tumor cells into the blood and lymphatic circulation (Yamaguchi et al., 2000). Secondly, surgery may impair antitumor immunity enabling circulating tumor cells to survive (Rushfeldt et al., 1999; Oosterling et al., 2005). Thirdly, surgery may increase the invasion and migration properties of tumor cells and enhance their entrapment at metastatic site (Tohme et al., 2016). Fourthly, the local and systemic inflammation induced by surgical trauma can accelerate the growth of micrometastatic foci (Michelson, 1994; Chiarella et al., 2012). Furthermore, perioperative factors, such as anesthesia, transfusions, hypothermia and post-operative complications, may contribute to cancer progression (Horowitz et al., 2015; Ohtsuka et al., 2009).

The ability of a primary tumor to exert a controlling action on its metastases is called "concomitant tumor resistance" and has been extensively studied by numerous observations showing that the removal of primary tumor may be followed by an increase in metastatic growth (Chiarella et al., 2012). In this regard, studies in patients with liver metastases from CRC demonstrated that PTR may result in an increase of peritumoral and intratumoral vascular density, proliferation rate and metabolic activity assessed by 18F-FDG PET and a decrease of apoptosis (Peeters et al., 2004, 2006; Scheer et al., 2008b).

On the other hand, there are some arguments in favour of PTR which can explain the potential benefit observed in many retrospective studies. Turner and colleagues, for example, examined a cohort of 145 consecutive patients with de novo mCRC who had undergone PTR, analyzing the neutrophil/lymphocyte ratio (NLR) as a biomarker of systemic inflammation and comparing OS between patients groups according the pre- and post-PTR NLR. They observed that patients with elevated baseline NLR (> 5) who had a low NLR after PTR had an improved survival (hazard ratio, 0.53; P = .017). The reversal of this systemic inflammatory response was more frequent in patients with larger primary tumors and good performance status (Turner et al., 2015).

Furthermore, while the spread of cancer cells from a primary tumor was historically seen as a unidirectional process, experimental evidences demonstrated the existence of a process called “tumour self-seeding”. According to this theory, circulating tumor cells can re-colonize their tumor of origin, thus accelerating tumor growth and angiogenesis and leading to a more aggressive disease (Kim et al., 2009). PTR could therefore influence the prognosis of these patients by interrupting this vicious circle.

Moreover, accumulating evidence shed light on the existence of cancer stem cells (CSCs) in CRC. In this model, CSCs represent a minor fraction of cancer cells, which are implicated in tumor initiation, heterogeneity and resistance to systemic treatments and radiation. By removing the primary tumor, one can theoretically eliminate this source of resistance, thus providing a benefit in terms of survival (Hatano et al., 2017).

### 5.2. The clinical point of view

Besides the questionable advantage in terms of survival, one of the main arguments in favour of PTR in asymptomatic stage IV CRC is the reduction of the risk of morbidity and mortality in the elective setting compared to emergency surgery, which can be particularly deleterious in patients with chemotherapy-induced myelosuppression (Stillwell et al., 2010; Ruo et al., 2003; Kleespies et al., 2009). Nevertheless, since an emergency intervention may be necessary only in 7–22% of cases, elective PTR could be spared in the majority of patients (Scheer et al., 2008a; Kleespies et al., 2009; Poultsides et al., 2009).

Moreover, elective PTR may be itself the cause of a subsequent urgent intervention for complications like adhesions or anastomotic leakages. In fact, in the work by Tebbutt and colleagues, 13.2% of the patients with mCRC who had undergone elective PTR developed post-operative complications requiring an intervention (Tebbutt et al., 2003). This figure is substantially in the same range of patients managed with systemic therapy and who require an intervention due to complications related to an intact primary tumor, thus supporting the thesis that PTR could be avoided for the majority of patients with mCRC.

Several studies demonstrated that PTR in mCRC confers more morbidity as compared to surgery in less advanced disease (Nitzkorski et al., 2012; Scoggins et al., 1999; Rosen et al., 2000). In their prospective database, Kleespies and coworkers analyzed 233 patients who were electively operated for non-curable stage IV CRC between 1996 and 2002. They reported an overall post-operative morbidity of 41.7% in colon cancer patients and 54.5% in rectal cancer patients, which was much higher than in series of patients with early-stage disease (Kleespies et al., 2009).

Analogously, the perioperative mortality rate ranges between 1.7 and 8% (Stillwell et al., 2010; Eisenberger et al., 2008; Scheer et al., 2008a). When selecting patients candidate to PTR, it is of crucial importance to minimize both morbidity and mortality risks, since most of the patients in this palliative setting die from metastatic disease rather than for complications related to the primary tumor.

One of the arguments against PTR in mCRC is the delayed initiation of chemotherapy. In this regard, Temple and coworkers reported a difference of nearly 3 weeks in the time to initiation of chemotherapy (38 vs 58 days after diagnosis between the non-resection and the resection group, respectively) (Temple et al., 2004). However, nowadays this delay can be minimized by using laparoscopic procedures, which allow a faster post-operative recovery. Moreover, safe procedures such as segmental colonic resection can reduce complications rate and allow a quicker start of chemotherapy (Nitsche et al., 2017).

Furthermore, there is a much higher use of PTR in patients with colon cancer rather than in those with rectal cancer. This is thought to be due to the higher complexity of rectal surgery, with a higher risk of complications, to the patient fear of a permanent stoma, particularly for low-lying rectal tumors, and to the improved local control with the use of multimodality therapy (Hu et al., 2015). This factors need to be considered and discussed with patients with metastatic rectal cancer who are eligible for PTR.

Another option that should be considered in patients with malignant bowel obstruction is the placement of a self-expandable metal stent (SEMS). In fact, earlier studies demonstrated lower early morbidity and mortality, shorter lengths of hospital stay, lower stoma formation rate and earlier initiation of chemotherapy with the use of SEMS compared to surgery (Ahn et al., 2016; Vemulapalli et al., 2010; Lee et al., 2011). However, subsequent studies raised some concerns about long-term efficacy and safety of SEMS (van den Berg et al., 2015; Abbott et al., 2014). Therefore, placement of SEMS seems preferable to PTR in patients with poor clinical conditions and short life expectancy.

Of note, several retrospective series reported an increased risk of perforation in patients with palliative stent treated with the anti-angiogenetic monoclonal antibody bevacizumab (Small et al., 2010; Manes et al., 2011; Cennamo et al., 2009). For this purpose, a meta-analysis demonstrated an increase of perforation rate in patients receiving bevacizumab (12.5%), while chemotherapy without bevacizumab was not associated with an increased risk of stent perforation (7.0%) (van Halsema et al., 2014). Despite the lack of evidence, the increased risk of perforation can be reasonably extrapolated to other anti-angiogenic drugs, such as Aflibercept, Ramucirumab and Regorafenib. Therefore, in patients candidate to receive these drugs the use of SEMS should be discouraged (van Hooft et al., 2014).

Another argument in favour of PTR in stage IV CRC is the more accurate staging, especially regarding peritoneal carcinomatosis, by the direct visualization of the peritoneal cavity.

Table 3 summarizes the main arguments for and against PTR in mCRC both from a preclinical and a clinical point of view.

**Table 3**
Arguments for and against PTR in mCRC.

| | |
|---|---|
| **Preclinical point of view** | |
| **pros** | **cons** |
| PTR may reverse systemic inflammatory response | PTR may increase the shedding of tumor cells in the blood and lymphatic vessels |
| PTR may interrupt the vicious circle of “tumor self seeding” | PTR may increase the invasion and migration of tumor cells and enhance their entrapment at metastatic site |
| PTR may reduce CSCs | PTR may impair antitumor immunity |
| | local and systemic inflammation can accelerate the growth of micrometastatic foci |
| | perioperative factors (anesthesia, transfusions, hypothermia) and postoperative complications, may contribute to cancer progression |
| | PTR may result in an increase of vascular density, proliferation rate and metabolic activity and a decrease of apoptosis |
| **Clinical point of view** | |
| **pros** | **cons** |
| survival advantage (?) | an emergency operation may be necessary only in a small fraction of patients |
| more accurate staging | elective PTR may not entirely avoid the risk of a urgent intervention for complications |
| reduction of morbidity and mortality in the elective setting | PTR confers more morbidity and mortality compared to surgery in less advanced disease |
| | PTR may delay the initiation of chemotherapy |

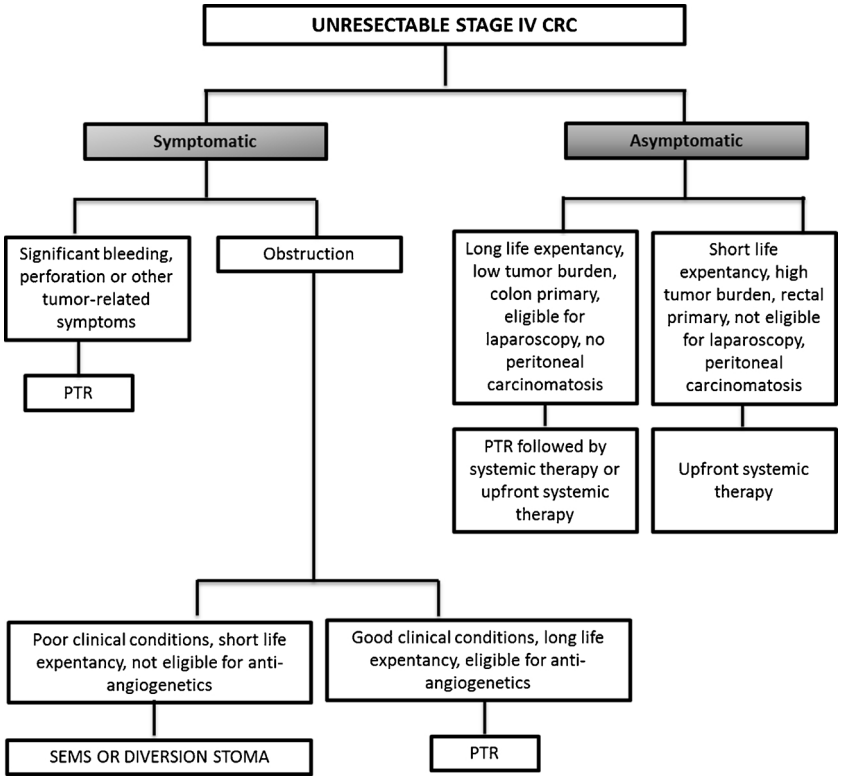


**Fig. 1.** A therapeutic algorithm for unresectable stage IV CRC.

## 6. Conclusions and future perspectives

The potential benefit of PTR in mCRC has been a matter of intense debate for long time. While for symptomatic patients the decision to treat the primary tumor is straightforward, for those with asymptomatic primary tumor both upfront systemic chemotherapy and PTR followed by medical treatment can be considered appropriate strategies and the decision should be made on a case-by-case basis after a careful discussion with the patient.

Despite current guidelines do not recommend PTR in asymptomatic patients, it represents a common practice even in recent series of patients treated with modern systemic therapies. Retrospective series seem to support the thesis that removal of the primary tumor may yield a survival benefit, but the molecular mechanisms that underlie this phenomenon are not well understood and need to be further clarified. Besides its questionable survival advantage, the benefits of PTR (more accurate staging, reduction of morbidity and mortality in the elective setting) must be carefully weighed against its potential drawbacks (delay of chemotherapy, low risk of an urgent operation in patients with intact primary tumor).

Furthermore, what is clear from the literature is the complete lack of data about quality of life in patients who underwent PTR. This represents a crucial point, especially in the setting of patients with incurable disease and deserves further evaluations.

As today, two scoring models which correlate clinical, pathological and laboratoristic variables to post-operative survival have been published. However, since their reliability deserves further validation, they cannot help clinicians facing this crucial decision in daily clinical practice. Ongoing RCTs will hopefully provide a definitive solution to this clinical dilemma. Until results from these trials are available, clinical judgment and discussion within a multidisciplinary team should guide the selection of patients who are candidate for PTR. Clinicians should take into account various factors, both related to the patients (performance status, age, comorbidity, eligibility to laparoscopic surgery, patient's wishes) and to the disease (burden of metastatic disease, location of primary tumor, RAS e BRAF mutational status). Fig. 1 provides a useful algorithm for clinicians treating patients with unresectable stage IV CRC.

Finally, patients managed without PTR should be closely observed and educated to monitor for signs of obstruction or bleeding, in order to offer a prompt treatment of these potential life-threatening complications.

## Author contribution

FG conceived and designed the manuscript. All authors analysed and interpreted the data, and drafted the article. All authors revised it critically for important intellectual content and finally approved the version to be submitted.

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None.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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