Diagnostic and therapeutic algorithm for colorectal peritoneal metastases. A consensus of the peritoneal surface malignancies onco-team of the Italian society of surgical oncology

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Aim: the surgical workup for colorectal cancer peritoneal metastases (CRCPM) is complex and should be managed in specialized centers. Diagnostic and therapeutic algorithms (DTA) have been proposed to balance optimal patients management and correct use of resources. Aim of this study was to establish a consensus on DTA for CRCPM patients in Italy.

Method: a panel of 18 delegated members of centers afferent to Peritoneal Surface Malignancies Onco-team of the Italian Society of Surgical Oncology was established. A list of statements regarding the DTA of patients with CRCPM was prepared according to different activities and decision-making nodes with a defined entry and exit point. Consensus was obtained through RAND UCLA methodology.

Results: two different DTA were defined and approved according to the modality of presentation of CRCPM (synchronous and metachronous). A consensus was also obtained on 17 of the 19 statements related to DTA.

Conclusion: a shared model of DTA is now available for healthcare providers to monitor appropriateness in diagnosis and treatment of patients with isolated peritoneal metastases from CRC.

Introduction

Colorectal cancer (CRC) represents the third most common...
cancer in men and the second most common in women worldwide [1]. During the last decade, the median overall survival for patients with CRC metastatic disease have improved significantly and is currently estimated around 30 months [2]. Although peritoneum is a rare site of CRC spread (4.8–8.3%) [3–5], peritoneal metastases (PM) are associated with the worst prognosis compared to other metastatic sites (liver, lung, lymph nodes), with a median overall survival of 16.3 months [6]. Systemic chemotherapy, alone or combination with targeted therapy, represents a standardized approach of CRCPM [7,8]. In selected patients, cytoreductive surgery associated (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to be effective in prolonging survival compared to systemic treatment alone [9–12]. Patient selection remains crucial to obtain satisfactory results after CRS-HIPEC. Optimal cytoreduction with less than 2.5 mm (so called cytoreduction grade 0 or 1) and limited tumor diffusion inside the peritoneal cavity (expressed by the peritoneal cancer index, PCI) represent the most important prognostic factors for recurrence and survival in CRCPM treated with CRS-HIPEC [13,14].

Health requirements of the oncologic population becomes more and more complex every. In this scenario, diagnostic and therapeutic algorithms (DTA) allowing the definition of the most viable pathway within a single organization and network [15] for a particular disease or clinical problem are crucial. In this perspective, a defined DTA for CRCPM is needed for several reasons [16]. Most CRCPM patients are diagnosed outside a tertiary referral center, frequently in an emergency setting. When PM are discovered by colorectal surgeons during abdominal exploration, surgical strategy is neither clear nor standardized [17]. It is possible that a significant number of patients with peritoneal disease who may benefit from a multimodal approach such as CRS-HIPEC are undertreated, and every effort should be made to define the best clinical pathway for diagnosis and treatment of this group of patients. Moreover, CRS-HIPEC is a very complex procedure that is available in a limited number of specialized centers. Evaluation of CRCPM patients in these centers allows to select those who would benefit more from surgery in terms of morbidity and mortality, therefore optimizing the costs of treatment and improving patient quality of life [18,19].

Aim of this study is to establish a consensus on a DTA model viable for CRCPM patients.

**Method**

The consensus panel included 18 delegated members of centers afferent to Peritoneal Surface Malignancies Onco-team of the Italian Society of Surgical Oncology. The steering committee was charged of constructing a DTA considering the best evidence-based treatment options for CRCPM. During a first meeting (Siena, May 17, 2019), after widespread review of national or society guidelines and results of randomized controlled trials, phase I and II clinical studies, the committee determined that low quality evidence data were of little help to drive decision making. Thus, consensus on list of statements, based on the available literature and expert opinion, and appropriate to create a DTA for CRCPM was designed. DTA was diagrammed into a pathway which covers CRCPM patient care from the initial diagnosis through curative and palliative treatments. DTA was divided in two main clinical scenarios (synchronous and metachronous CRCPM) and organized according to different activities and decision-making nodes with a defined entry and exit point. A list of 19 statements regarding the different activities and decision-making nodes of the DTA were discussed and modified during a second meeting (Ca’furlia September 9, 2019). Definitive achievement of consensus was obtained through the RAND/University of California Los Angeles Appropriateness Methodology [20]. Appropriateness was scored from 1 (inappropriate) to 9 (completely appropriate). For each statement the appropriateness median score (AMS) was calculated. Statements were classified into three levels of appropriateness: appropriate (AMS, in range 7–9), uncertain (AMS, in range 4–6) and inappropriate (AMS, in range 1–3). Agreement among panelists on each statement was established according to an Interpercentile Range (IPR) of 0.3–0.7. If the IPR obtained was in range 7–9, this was considered indicative of agreement for that statement. Each panellist ranked anonymously via web each statement for appropriateness as reported above. The same method has been used for obtaining consensus of the diagram of DTA. Statistical analyses (median and IPR) were conducted with SPSS 17.0 (SPSS Statistics, Release 17.0.0).

**Results**

The statements were related to different decision-making points in the clinical algorithm of CRCPM patients: 7 (1–7) the management of patients diagnosed with synchronous disease, 7 the multidisciplinary evaluation (8–14), 1 (15) the HIPEC regimen, 4 the role of perioperative systemic chemotherapy (16–19) (Table 1). All the statements proposed for consensus were considered appropriate with an AMS ranging between 7 and 9. Statements 14 and 19, although scored as appropriate (AMS 7.5 and 7 respectively) didn’t reach consensus with an IPR lower than limit of 7 (both 6). Statement 13 obtained an AMS of 7 but the IPR was 7–8. The voting results on statements are summarized in Table 2.

The two DTA diagrams for synchronous (Fig. 1) and metachronous CRCPM (Fig. 2) obtained both an IPR of 9 and an IPR of 8–9.

**Discussion**

The current study reports on a consensus obtained for a DTA in CRCPM patients. In oncology, DTA represents an organizational health pathway, distinct for specific tumors and stages, in which every step of the process is codified and the responsibility for its execution and implementation are clear and defined. The main objectives of DTA is to provide timely patient management, quality of care and patient satisfaction, continuity and equity in terms of access of care and an optimal use of resources. CRCPM is a typical clinical situation in where the complexity of the diagnostic and therapeutic process determines circumstances favouring the heterogeneity of care and facilitate inappropriate behaviors and/or errors, thus causing adverse effects on cancer prognosis and an increase in treatment costs [18,19]. In a Dutch population study, a large variation in treatment approach for synchronous CRCPM was observed at individual hospital level (teaching versus non-teaching center), with significant differences in the chance to undergo CRS-HIPEC and to obtain a favorable survival outcome [21].

The consensus was reached for two main clinical situations, synchronous and metachronous CRCPM (Figs. 1 and 2). In around 10% of cases, PM occur at the time of primary presentation (synchronous) [3,5]. If primary tumor is asymptomatic/uncomplicated, patients with suspected synchronous peritoneal involvement should be directly evaluated by a peritoneal tumor referral center (PTRC) and considered for curative CRS [22] (statement 1). However, PM are more difficult to be detected by conventional imaging (CT or MRI scan) compared to other metastatic sites (liver, lung and lymph nodes) and PM can be an unexpected event (around 4%) during surgery for primary CRC [5]. Intra-operative diagnosis of PM during treatment of primary CRC occurs in most of cases in non-specialized centers. The correct strategy in this situation is still matter of debate. Small retrospective studies showed that the 5-year overall survival of patients treated with surgical resection of the primary and synchronous PM is about 30%, which is lower than that obtained by specialized centers in patients operated with CRS
with or without HIPEC [23,24]. Moreover, primary tumor resection seems to determine extended bowel resections and permanent colostomy respect to patients treated with a one-stage procedure [25]. Even if, one stage curative in PTRC is preferable, in presence of nodules limited and close to the tumor, resection of the primary and the peritoneum involved, it is an acceptable option. However, one-stage curative treatment with HIPEC in referral centers is preferable whenever possible [26].

PM can be an unexpected event during surgery for primary CRC. In this case, if the nodules are limited and close to the tumor, resection of the primary and the peritoneum involved, it is an acceptable option. However, one-stage curative treatment with HIPEC in referral centers is preferable whenever possible [26].

PM can be an unexpected event during surgery for primary CRC. If the tumor load is high, with multiple and diffuse nodules, a simple histological confirmation and an accurate intra-operative staging (PCI and unresectability causes) is the best choice, before sending the patient to a peritoneal referral center. If the patient is symptomatic and peritoneal metastases is suspected, surgery should be performed according to the urgency to intervene before sending the patient to a peritoneal referral center. When surgery is emergent and peritoneal metastases are diffuse, a limited palliation (primary resection only, stoma formation) with peritoneal biopsy and staging (PCI and unresectability causes) are indicated, before sending the patient to a peritoneal referral center. Every patient potentially eligible for CRS-HIPEC should be evaluated by a referral center and discussed in dedicated colorectal multidisciplinary meetings. During colorectal multidisciplinary meetings a complete medical history, abdominal/thoracic CT scan and blood tumor markers should be available.

CT scan with contrast enhancement medium represents the gold standard for stage patients with colorectal peritoneal metastases. MRI and PET scan should be considered complementary imaging for stage patients with colorectal peritoneal metastases.

Laparoscopy is a complementary method for stage patients with colorectal peritoneal metastases and it is crucial that is performed by surgeons with experience in CRS-HIPEC. Only patients with pre-operative Peritoneal Cancer Index <16 and with the possibility of obtain a CCO/1 resection should be selected for CRS-HIPEC. Molecular gene mutation testing (RAF/RAS mutation) and microsatellite status (stable or not) are important selection factors for CRS-HIPEC. Molecular gene mutation testing (RAF/RAS mutation) and microsatellite status (stable or not) are important selection factors for CRS-HIPEC. Performance status, extraperitoneal metastases (liver, lymph nodes), tumor site (right versus left colon) tumor differentiation, signet ring histology, ascites, symptoms of obstruction and lymph node status (N2a) of the primary in case of metachronous PM should be carefully considered potentially exclusion criteria for CRS-HIPEC.

In patients selected for CRS-HIPEC Mitomycin C based regimen is recommended. Before selecting patients to CRS-HIPEC pre-operative chemotherapy should be always considered especially in presence of synchronous disease. Peritoneal progression during systemic chemotherapy should not be considered an absolute contraindication for CRS-HIPEC, if the selection criteria are still met. In very selected patients with limited metachronous peritoneal metastases and no risk factors, perioperative systemic chemotherapy could be omitted in favour of a front-line CRS-HIPEC.

In the sub-group of patients with peritoneal metastases who have mismatch repair-deficient (dMMR) and/or microsatellite instability-high (MSI-H), the treatment with immune checkpoint inhibitor should be considered as first choice. Performance status, extraperitoneal metastases (liver, lymph nodes), tumor site (right versus left colon) tumor differentiation, signet ring histology, ascites, symptoms of obstruction and lymph node status (N2a) of the primary in case of metachronous PM should be carefully considered potentially exclusion criteria for CRS-HIPEC.

Table 1
Selected statements for consensus.

<table>
<thead>
<tr>
<th>Statements</th>
<th>Appropriateness</th>
<th>Interpercentile Range (IPR, 0.3–0.7)</th>
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<tr>
<td>1</td>
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<td>19</td>
<td>7</td>
<td>6–8</td>
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After primary curative treatment, the rate of metachronous PM can reach 19% of cases [31]. Multidisciplinary discussion of CRCPM patients is mandatory for selecting the best therapeutic approach. In this setting, a complete medical history, abdominal/thoracic CT scan and blood tumor markers should be available (statement 8). Every patient with a diagnosis of CRC should undergo CT scan with contrast enhancement medium which represents the gold standard not only for diagnosis but also for staging those with PM (statement 9). Sensitivity and specificity of CT scan in CRCPM is estimated 83 and 86%, respectively [32]. The diagnostic performance of CT scan for PM is dependent on the radiologist’s experience and can be suspected in presence of defined radiological features (ascites, organ invasion) [33]. The role of MRI and PET-CT as complementary investigations are still under investigation and should be reserved in selected cases and performed by experienced radiologists in PM diagnosis (statement 10) [32]. Diffusion-weighted MRI is promising for estimation of PCI and prediction of operability but its role is still under study [34,35]. Laparoscopic exploration is an important tool.
Fig. 1. Diagnostic and therapeutic pathway for synchronous CRCPM.

Fig. 2. Diagnostic and therapeutic pathway for metachronous CRCPM.
for confirming the diagnosis of peritoneal involvement, allowing a histological definition of all suspected nodules [29]. Laparoscopic exploration can assess the peritoneal cancer index (PCI) more accurately than the preoperative radiological investigations [36]. Moreover, during laparoscopy, any potential cause of unresectability (mesenteric retraction or infiltration of the hepatic hilum, suprahepatic veins and Treitz ligament) can be easily identified under direct vision [37]. Therefore, it is crucial that laparoscopy should be performed by skilled surgeons in peritoneal surgery, it being the most accurate staging tool in patients selected for surgery (statement 11).

Despite notable advances in systemic treatments, patients with isolated PM treated only with cytotoxic/targeted agents show a significantly worse survival (16.3 months) as compared to patients with isolated non-peritoneal sites (liver, lung, lymph nodes) [6]. CRS-HIPEC allows to provide a long-term survival of up to 40 months in selected patients treated in PTRC and is widely adopted worldwide and included in several national guidelines [38–42]. However, the real added value of HIPEC over CRS alone is still under investigation. A recent French multi-institutional randomized controlled trial (Prodige 7) presented at the ASCO annual meeting confirms the relevant role of surgery to treat patients with PM but with notable survival advantage when adding HIPEC to radical surgery [24]. The study is not yet published and it is difficult to assess all aspects and bias, but an important point is that in the subgroup analysis of patients with PCI less than 16, overall survival is significantly better in the HIPEC arm, confirming previous results on the impact of this benchmark in patient prognosis [43]. Therefore, only patients with PCI <16 in which a complete surgery can be obtained (grade of cytoreduction or residual disease zero or less than 2.5 mm) (statement 12).

The role of additional selection factors and their weight within the pre-operative evaluation is unclear and also the panelist didn’t reach a consensus on this point. Among these, mutations in the RAS lymph node status (N2a) of the primary [44], are not considered important selection factors (statement 13). Other selection factors as performance status (Eastern Cooperative Oncology Group, ECOG), extraperitoneal metastases (liver, lymph nodes) which should be performed by skilled surgeons in peritoneal surgery, it being the most accurate staging tool in patients selected for surgery (statement 11).

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Conclusion

A consensus on DTA for CRCPM patients have been reached in Italy. The document will be an important tool for healthcare providers to monitor appropriateness in diagnosis and treatment of CRC patients with isolated peritoneal metastases.

Conflict of interest and authorship confirmation form

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

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CRediT authorship contribution statement

Antonio Sommariva: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Project administration, Writing - original draft, Writing - review & editing. Luca Ansaloni: Writing - original draft, Writing - review & editing. Gian Luca Baiocchi: Writing - original draft, Writing - review & editing. Stefano Cascini: Writing - original draft, Writing - review & editing. Roberto Cirocchi: Writing - original draft, Writing - review & editing. Federico Coccolini: Writing - original draft, Writing - review & editing. Marcello Deraco: Conceptualization, Investigation, Supervision, Project administration, Writing - original draft, Writing - review & editing. Giannmaria Fiorentini: Writing - original draft, Writing - review & editing. Roberta Gelmini: Writing - original draft, Writing - review & editing. Andrea Di Giorgio: Writing - original draft, Writing - review & editing. Piero Vincenzo Lippolis: Writing - original draft, Writing - review & editing. Enrico Maria Pasqual: Writing - original draft, Writing - review & editing. Cinzia Sassaroli: Writing - original draft, Writing - review & editing. Antonio Macrì: Writing - original draft, Writing - review & editing. Paolo Sammartino: Supervision, Writing - original draft, Writing - review & editing. Stefano Scaringi: Writing - original draft, Writing - review & editing. Mario Valle: Conceptualization, Investigation, Project administration. Marco Vaira: Writing - original draft, Writing - review & editing.

Declaration of competing interest
None of the authors have any conflicts of interest.

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