Editorial

Past, present and future of adjuvant HIPEC in patients at high risk for colorectal peritoneal metastases

Peritoneal metastases (PM) from colorectal cancer (CRC) still represent a huge health-care problem. Recent population-based studies report an overall 3.5—4.2% incidence of CRC-PM after potentially curative primary surgery [1,2]. These rates can reach up to about 25% in locally advanced CRC penetrating visceral peritoneum (pT4a), or directly infiltrating surrounding organs (pT4b) [1—3]. Accordingly, the peritoneum is one of the most common site of metastatic spread for CRC, following the liver and lung, even though incidences may be likely underestimated because PM are more difficult to detect than liver or lung metastases.

A strategy involving local-regionally delivered chemotherapy to prevent the outgrowth of occult peritoneal seeding into macroscopic metastases is supported by a strong rationale: first, cytoreductve surgery (CRS) combined with hyperthermic intraperitoneal chemotheray (HIPEC) improve CRC-PM survival, but most patients are not suitable for this demanding treatment due to extensive peritoneal involvement, systemic metastases, and/or poor clinical conditions. Second, CRS/HIPEC is maximally effective and safe when small-volume disease is treated. Third, in the palliative setting, modern systemic chemotherapy (s-CT) and targeted agents appear to be less effective for peritoneal metastatic CRC than non-peritoneal metastatic CRC. Finally, the absence of symptoms, as well as current limitations of imaging, hamper early diagnosis and treatment [3].

On these bases, the use of HIPEC for the prevention or early treatment of CRC-PM has been tested at different time-points, either simultaneously with primary surgery [3—5], at the time of second-look surgery after adjuvant s-CT [6], or as a staged procedure at 5—8 weeks postoperatively [7]. Since we were amongst the first groups to investigate the role of adjuvant HIPEC, we were surprised to read that in the COLOPEC randomized trial such a treatment approach failed to demonstrate improved peritoneal-free survival in pT4a/b or perforated CRC [7].

The Dutch investigators randomly assigned patients to oxaliplatin-based HIPEC given either at primary resection in 9% of patient, or 5—8 weeks later in the remaining 91%, and followed by adjuvant s-CT. Patients assigned to the control arm received standard adjuvant s-CT only. All patients showing no recurrent disease at 18 months underwent diagnostic laparoscopy. There was no difference in 18-month peritoneal-free survival between groups: 80.9% (95% confidence interval [CI] 73.3—88.5) for the experimental arm vs. 76.2% (95%CI 68—84.4) for the control arms (log-rank two-sided P = 0.28) [7]. Analogously, the randomized French trial Prophylochip failed to demonstrate a survival benefit associated with a strategy of systematic second-look surgery plus HIPEC in high risk patients, as compared with standard surveillance. The French

trial was done in a different clinical setting than the COLOPEC trial, as high risk to develop CRC-PM was defined as history of ovarian or low-volume peritoneal metastases resected with the primary, or perforated primary tumor [6].

Investigators in Rome and Milan have completed two pilot studies to test oxaliplatin-based HIPEC, and mitomycin plus cisplatin-based HIPEC, respectively. In both studies, HIPEC was given at the same time as primary resection [3,4]. Limiting the analysis to patients with pT4a/b or perforated CRC (the same population as in COLOPEC trial), PM occurred in one of seven patients treated in Rome, with a median follow-up of 48 months [4]. After an up-dated follow-up of more than 10 years (median 128.0 months), PM has occurred so far in one of 14 patients treated in Milan, and another patient has died of liver metastases (Baratti D, unpublished data). The study by Tentes et al. is the third relevant literature series of simultaneous adjuvant HIPEC. The authors report no PM occurring in 15 patients treated with either oxaliplatin or mitomycin, with a median follow-up of 17 months [5].

Putting together these three series of adjuvant HIPEC delivered at primary resection, PM occurred in 2 of 36 patients (5.6%) [3—5]. This figure compares favourably with the peritoneal failure rate of 19% following staged adjuvant HIPEC in the experimental arm of the COLOPEC trial, and also the 23% rate in control arm [7]. Although it may be not scientifically sound to compare outcome results across different trials, it has to be taken into consideration that patients were included in both COLOPEC trial and the aforementioned series essentially on the base of pT4 primary stage, with minimal likelihood that a selection bias could have occurred. In this aspect, the adjuvant setting is different from the setting of clinically manifest PM, where multiple variables, such as peritoneal disease extent and distribution, response to previous therapies, and patient conditions, may influence appropriate physician judgment in the selection of such therapies outside the context of a randomized controlled trial.

The simultaneous time setting for adjuvant HIPEC is further supported by a pharmacological rationale (i.e. better exposure to antiblastic agents before viable tumor cells are entrapped in postoperative adhesions) [3]. Also, it is worth to note that 9% of patients in COLOPEC trial were found with PM at surgical exploration preceding intentional adjuvant HIPEC, and these patients could have been potentially cured by HIPEC at primary surgery [7]. Finally, bilateral adnexectomy and greater omentectomy were routinely performed in Milan and Rome series [3,4]. These procedures may have contributed to improved peritoneal control by ensuring better drug circulation throughout the abdominal cavity,

and removing target organs of peritoneal dissemination.

Drawbacks of the simultaneous setting are logistic issues, difficult preoperative/intraoperative identification of T4 tumors, and potential toxicity of HIPEC. However, three independent studies have demonstrated that in an appropriate environment simultaneous adjuvant HIPEC is feasible [3—5]. Regarding safety issues, five anastomotic leaks (5.7%) and three HIPEC-related toxicities, namely two transient grade 3 renal failures, and one grade 2 pancreatitis (3.4%), were observed in the total of 87 patients from the three series of simultaneous HIPEC, that included also pT3 primaries and completely resected ovarian or low-volume peritoneal metastases.

This incidence of anastomotic leaks may be slightly higher than common elective colorectal surgery, but this has to be seen not only in light of the potentially adverse impact of HIPEC on anastomotic healing, but also of the more extensive surgery performed in patients with more advanced disease. Such a complication rate appears to be compatible with the potential benefit, and even the risk of overtreatment for those patients in which a locally advanced primary stage should be erroneously diagnosed by preoperative studies, analogously to preoperative radiation in rectal cancer.

Oxaliplatin efficacy have become matter of intense debate after the negative results of COLOPEC and Prophylochip trials in the adjuvant setting, and Prodige-7 trial in patients with clinically manifest CRC-PM [8]. Although oxaliplatin is one of the drugs of choice for metastatic CRC, factors such as insufficient exposure time (30 minute), adverse effects of carrier solution (Dextrose 5%), and potential drawbacks of hyperthermia have been related to the lack of survival benefit [8]. Patients undergoing simultaneous adjuvant HIPEC were treated according to different protocols (open vs. close-abdomen technique, mitomycin with or without cisplatin vs. oxaliplatin, isotonic vs. hypotonic carrier solution, 30 vs. 60 vs. 90 minute perfusion time), thus precluding any meaningful comparison [3—5].

In conclusion, we believe that future trials of adjuvant HIPEC should not be discouraged. Besides oxaliplatin efficacy issues, future trial design must address the question whether staged vs. simultaneous adjuvant HIPEC, and prophylactic resection of target organs may impact outcomes.

Accordingly, the PROMENADE (NCT02974556) trial is open in seven Italian high-volume centers. Patients with cT3c/d CRC (depth of invasion beyond the outer border of the muscularis propria >5—15 mm, and >15 mm, respectively), and cT4a/b CRC (any N, M0), selected by multidetector computed tomography (MDCT) will be randomized between standard surgery vs. proactive surgical management. The latter includes greater omentectomy, appendectomy, resection of the liver round ligament and bilateral adnexectomy in post-menopausal women, plus oxaliplatin-based simultaneous adjuvant HIPEC. The choice to include cT3c/d CRC is not only based on the accuracy of MDCT to discriminate between pT1-2 and pT3-4 tumors, but also to correctly identify pT3c or more advanced disease [9]. On the other hand, differentiating between pT3 and pT4 tumors on imaging still remains challenging. Furthermore, pT3 tumors invading the peritoneal elastic lamina (30% of the cases) have a prognosis that approximates those of pT4 cancers [10]. Ninety-seven patients will be enrolled in each arm. In both groups, postoperative adjuvant s-CT will be given. The primary study endpoint is the incidence of peritoneal recurrence at 36 months from randomization.

A Spanish collaborative study with a similar design (HIPECT4, NCT02614534) is actively enrolling patients with cT4a/b CRC to test mitomycin-based adjuvant HIPEC plus resection of target organs at primary surgery.

Declaration of competing interest

The authors have no financial interests to disclose.

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Dario Baratti*
Peritoneal Malignancy Program, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian, 1, 20133, Milan, Italy

Paolo Sammartino
Cytoreductive Surgery and HIPEC Unit, Department of Surgery "Pietro Valdoni", Azienda Policlinico Umberto I, Sapienza University, Viale del Policlinico, 155, 00161, Rome, Italy

Shigeki Kusamura, Marcello Deraco
Peritoneal Malignancy Program, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian, 1, 20133, Milan, Italy

The Peritoneal Surface Malignancy Onco-team of the Italian Society of Surgical Oncology (SICO)

Luca Ansaloni
Department of Surgery, General and Emergency Surgery Unit, Bufalini Hospital, Cesena, Italy

Salvatore Asero
Division of Surgical Oncology, Ascoli Tomaselli Hospital, Catania, Italy

Gianluca Baiocchi
Department of General Surgery, Spedali Civili di Brescia, Brescia, Italy

Pietro Bagnoli
Emergency and General Surgery Unit, Istituto Clinico Città di Milano, Milano, Italy

Davide Cavaliere, Massimo Framarini
General Surgery and Surgical Oncology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

Roberto Cirocchi
General and Oncological Surgery Unit, University of Perugia, Terni, Italy

Federico Coccolini
Department of General, Emergency and Trauma Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy

Franco Decian
Department of General Surgery, Policlinico San Martino, University of Genoa, Genoa, Italy

Paolo Delrio, Cinzia Sassaroli
Abdominal Oncology Department, Fondazione Giovanni Pascale, IRCCS, Naples, Italy

Michele De Simone, Manuela Robella, Marco Vaira
Department of Surgical Oncology, Candiolo Institute for Cancer Research and Treatment, Torino, Italy

Andrea Di Giorgio
Division of General Surgery, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

Anna Fagotti, Domenica Lorusso
Department of Obstetrics and Gynecology, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, Rome, Italy

Orietta Federici
Department of Surgery, Surgical Oncology, National Cancer Institute Regina Elena, Rome, Italy

Giammaria Fiorentini
Department of Oncology and Hematology, Ospedali Riuniti Marche Nord, Pesaro, Italy

Massimiliano Fambrini, Stefano Scaringi
Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy

Alfredo Garofalo, Mario Valle
Department of Digestive Surgery, Regina Elena National Cancer Institute, IRCCS-IFO, Rome, Italy

Roberta Gelmini, Francesca Cabry, Nicola Cautero, Lorena Sorrentino
Department of Surgery, Policlinico of Modena, University of Modena and Reggio Emilia, Modena, Italy

Luigina Graziosi
Department of General and Emergency Surgery, Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy

Marcello Guaglio, Matteo Montenovo, Valentina Bartolini
Peritoneal Malignancy Program, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Piero Vincenzo Lippolis
Department of Surgery, Azienda Ospedaliero Universitaria Pisana (AOUP), S.D. General and Peritoneal Surgery, Pisa, Italy

Antonio Macrì
Department of Surgery, Peritoneal Surface Malignancy and Soft Tissue Sarcoma Program, University of Messina, Italy

Enrico Maria Pasqual
Department of Surgery, AOU Santa Maria della Misericordia, Udine, Italy

Francesco Roviello, Daniele Marrelli
Department of Medical, Surgical and Neuroscience, University of Siena, Siena, Italy

Elena Orsenigo
Department of Surgery, San Raffaele Scientific Institute, Milan, Italy

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

[*] Corresponding author. Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian,1, 20133, Milano, Italy.
E-mail address: dario.baratti@istitutotumouri.mi.it (D. Baratti).