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Prospective, randomised, multicentre, open-label trial, designed to evaluate the best timing of closure of the temporary ileostomy (early versus late) in patients who underwent rectal cancer resection and with indication for adjuvant chemotherapy: the STOMAD (STOMa closure before or after ADjuvant therapy) randomised controlled trial

Correspondence to
Dr Paolo Massucco;
pmassucco@mauriziano.it

Paolo Massucco [ORCID],[1] Andrea Fontana,[1] Michela Mineccia,[1] Serena Perotti,[1] Giovannino Ciccone,[2] Claudia Galassi,[2] Maria Carmela Giuffrida,[3] Donatella Marino,[4] Igor Monsellato,[5] Myriam Katja Paris,[6] Roberto Perinotti,[7] Patrizia Racca,[8] Chiara Monagheddu,[2] Fabio Saccona,[2] Elisa Ponte,[9] Massimiliano Mistrangelo [ORCID],[10] Mauro Santarelli,[11] Francesco Tomaselli,[12] Rossella Reddavid,[13] Simone Birolo,[14] Marcello Calabrò,[15] Nicoletta Pipitone,[15] Luca Panier Suffat,[16] Monica Carrera,[17] Francesco Potente,[18] Marco Brunetti,[19] Roberto Rimonda,[20] Vincenzo Adamo,[21] Domenico Piscioneri,[5] Francesca Cravero,[22] Alberto Serventi,[23] Eliana Giaminardi,[24] Luca Mazza,[25] Paolo Bellora,[26] Fabio Colli,[27] Clemente De Rosa,[28] Francesco Battafarano,[29] Renza Trapani,[30] Alfredo Mellano,[31] Enrico Gibin,[32] Paola Bellomo[33]

ABSTRACT

Introduction Temporary ileostomy is a valuable aid in reducing the severity of complications related to rectal cancer surgery. However, it is still unclear what is the best timing of its closure in relation to the feasibility of an adjuvant treatment, especially considering patient-reported outcomes and health system costs. The aim of the study is to compare the results of an early versus late closure strategy in patients with indication to adjuvant chemotherapy after resection for rectal cancer.

Methods and analysis This is a prospective multicentre randomised trial, sponsored by Rete Oncologica Piemonte e Valle d'Aosta (Oncology Network of Piedmont and Aosta Valley-Italy). Patients undergone to rectal cancer surgery with temporary ileostomy, aged >18 years, without evidence of anastomotic leak and with indication to adjuvant chemotherapy will be enrolled in 28 Network centres. An early closure strategy (between 30 and 40 days from rectal surgery) will be compared with a late one (after the end of adjuvant therapy). Primary endpoint will be the compliance to adjuvant chemotherapy with and without ileostomy. Complications associated with stoma closure as well as quality of life, costs and oncological outcomes will be assessed as secondary endpoints.

Ethics and dissemination The trial will engage the Network professional teams in a common effort to improve the treatment of rectal cancer by ensuring the best results in relation to the most correct use of resources. It will take into consideration both the patients' point of view (patient-reported outcome) and the health system perspective (costs analysis). The study has been approved by the Ethical Review Board of Città della Salute e della Scienza Hospital in Turin (Italy). The results of the study will be disseminated by the Network website, medical conferences and peer-reviewed scientific journals.

Trial registration number NCT04372992.

Strengths and limitations of this study

► The study will involve all the referral centres for the treatment of colorectal cancer in the Northwestern area of Italy in a joint effort to improve the quality of rectal cancer care.
► It will have a high external validity given the large multicentric territorial context and the pragmatic approach with large inclusion criteria.
► The results will be analysed taking into account both the point of view of patients (patient-reported outcome analysis) and the costs for the health system.
► The main weakness of the study is the relative rarity of the patient population that could slow the accrual rate.

INTRODUCTION

The temporary ileostomy is effective in reducing the severity of anastomotic complications in anterior resections for tumours of the rectum at risk of dehiscence and is therefore widely used, particularly after radiotherapy treatment.[1] In patients with indication for adjuvant chemotherapy, current practice consists of closing the stoma after the end of treatment.

The prolonged presence of the stoma can however favour the onset of stoma-related complications, such as prolapse, parastomal hernia, mechanical ileus, high-flow dehydration and damage to kidney function. Ostomy-related complications may require unscheduled hospitalisations and result in increased costs.[2] In addition, the presence of the stoma impacts on patients' quality of life (QoL), causing alteration of the body image and imposing changes in the daily routine, lifestyle and sexual sphere.[3 4] Therefore, early closure of the ileostomy has been proposed in patients without signs of postoperative fistula.

The early closure (within 1 month of surgery) of the temporary ileostomy resulted not inferior to late closure (over 12 weeks) in two randomised studies that evaluated postoperative complications as an outcome.[5 6] Early closure saves days of life with ileostomy for the patient and costs related to ostomy care for the health system and could represent the most desirable and convenient choice.[7] It was also associated with better long-term functional results in a secondary analysis of a randomised study.[8] However, in patients with indication for adjuvant therapy, it is not known what the best timing is for closing the stoma (before the start, during or at the end of the treatment) in terms of therapy tolerability, QoL and overall costs.[9]

Both a start date delayed more than 8 weeks from surgery[10] and a received dose <70% of that planned[11] have been reported to reduce the effectiveness of adjuvant therapy in colorectal cancer patients. The presence of a stoma or the consequences of its early closure may interfere with an optimal delivery of chemotherapy. A recent multicentre retrospective study reported an increase in gastrointestinal toxicity in chemo-treated patients with stoma, with significant reduction in treatment compliance.[12] On the other hand, early closure of the stoma could reveal an low anterior resection syndrome (LARS) before chemotherapy, with a potential negative impact on the tolerability of the treatment itself,[13] or delay its initiation due to postoperative complications.[14]

This randomised study aims to identify the best timing for the stoma closure in relation to adjuvant therapy in terms of compliance to chemotherapy, complications, costs and QoL.

METHODS AND ANALYSIS

STOMAD is a multicentre open-label randomised phase III trial designed to evaluate the best timing of the closure of temporary ileostomy in patients operated on for rectal cancer and with indication for adjuvant chemotherapy.

Objectives

1. Primary objective
   – To compare the compliance with adjuvant therapy between early and late closure of temporary ileostomy.
   – The compliance with adjuvant chemotherapy in relation to the timing of ileostomy closure (before the start or after the end of treatment) will be assessed considering any therapeutic delay or dose reduction compared with the initially planned.
2. Secondary objectives
   – To compare patients with early and late closure of temporary ileostomy in terms of:
   – Surgical morbidity.
   – Chemotherapy toxicity.
   – Patient-reported QoL.
   – Costs.
   – Progression-free survival (PFS).
   – Overall survival (OS).

Target population and setting

Patients undergone to rectal resection (±neoadjuvant therapy) for cancer with protective ileostomy and candidates for adjuvant chemotherapy in the Centres for the treatment of colorectal neoplasms recognised by Rete Oncologica Piemonte e Valle d'Aosta.

The list of participating centres is reported in table 1.

Enrolment

Inclusion criteria

► Patients undergone to radical intestinal resection (R0) for rectal neoplasia with protective ileostomy.
► Age ≥18 years.
► Absence of fistula (enema and/or endoscopy).
► Indication to adjuvant chemotherapy.
► Informed consent.

Exclusion criteria

► ASA >3.
► UICC stage IV.
► ECOG Performance Status ≥2.
► Severe and non-controlled systemic, oncological or infectious disease.

Table 1 List of participating centres

Local PI	Local trial manager	Centre	Location
Paolo Millo	Elisa Ponte	AUSL Aosta–Surgical Unit–Parini Hospital	Aosta
Mario Morino	Massimiliano Mistrangelo	AOU Città Salute e Scienza–Academic Surgical Unit–Molinette Hospital	Torino
Paolo De Paolis	Mauro Santarelli	AOU Città Salute e Scienza–Surgical Unit–Molinette Hospital	Torino
Alessandro Ferrero	Paolo Massucco	AO Ordine Mauriziano–Surgical Unit–Umberto I Hospital (Coordineting centre)	Torino
Maurizio Degiuli	Rossella Reddavid	AOU S. Luigi Gonzaga–Academic Surgical Unit–S. Luigi Hospital	Orbassano (TO)
Roberto Saracco	Francesco Tomaselli	ASL Città Torino–Surgical Unit–Martini Hospital	Torino
Mauro Garino	Simone Birolo	ASL TO3–Surgical Unit–Infermi Hospital	Rivoli (TO)
Andrea Muratore	Marcello Calabrò Nicoletta Pipitone	ASL TO3–Surgical Unit–Agnelli Hospital	Pinerolo (TO)
Lodovico Rosato	Luca Panier Suffat	ASL TO4–Surgical Unit–Civile Hospital	Ivrea (TO)
Eraldo Personnettaz	Monica Carrera	ASL TO4–Surgical Unit–Ciriè Hospital	Ciriè (TO)
Pietro Cumbo	Francesco Potente	ASL TO5–Surgical Unit–S. Croce Hospital	Moncalieri (TO)
Felice Borghi	Maria Carmela Giuffrida	AO S. Croce e Carle–Surgical Unit–S. Croce Hospital	Cuneo
Franco Bertolino	Marco Brunetti	ASL CN1–Surgical Unit–SS. Annunziata Hospital	Savigliano (CN)
Andrea Gattolin	Roberto Rimonda	ASL CN1–Surgical Unit–Regina Montis Regalis Hospital	Mondovì (CN)
Marco Calgaro	Vincenzo Adamo	ASL CN2–Surgical Unit–S. Lazzaro Hospital	Alba (CN)
Fabio Priora	Igor Monsellato Domenico Piscioneri	AO SS. Antonio e Biagio e Cesare Arrigo-Surgical Unit–SS. Antonio e Biagio Hospital	Alessandria
Marco Amisano	Francesco Cravero	ASL AL–Surgical Unit–S. Spirito Hospital	Casale Monf.to (AL)
Alberto Serventi	Alberto Serventi	ASL AL–Surgical Unit–Mons. Galliano Hospital	Acqui Terme (AL)
Carmine Di Somma	Eliana Giaminardi	ASL AL–Surgical Unit–S. Giacomo Hospital	Novi Ligure (AL)
Vincenzo Sorisio	Luca Mazza	ASL AT–Surgical Unit–Cardinal Massaia Hospital	Asti
Sergio Gentilli	Paolo Bellora	AOU Maggiore Carità–Academic Surgical Unit–Maggiore Hospital	Novara
Raffaele Romito	Fabio Colli	AOU Maggiore Carità–Surgical Unit–Maggiore Hospital	Novara
Roberto Polastri	Roderto Perinotti	ASL BI–Surgical Unit–Infermi Hospital	Biella
Silvio Testa	Clemente De Rosa	ASL VC–Surgical Unit–S. Andrea Hospital	Vercelli
Sandro Zonta	Francesco Battafarano	ASL VCO–Surgical Unit – S. Biagio Hospital	Domodossola (VB)
	Renza Trapani	ASL VCO–Surgical Unit – Castelli Hospital	Verbania (VB)
Dario Ribero	Alfredo Mellano	FPO–Colorectal Surgical Unit – IRCCS	Candiolo (TO)
Renzo Leli	Paola Bellomo	Surgical Unit–Humanitas Gradenigo Hospital	Torino
Carlo Bima	Enrico Gibin	Surgical Unit–Cottolengo Hospital	Torino

PI, Principal Investigator.

Before enrolment, the patient shall not show signs of ongoing complications. The integrity of the colorectal anastomosis will be confirmed with an enema and/or endoscopy according to local standards starting 15 days after surgery.

The presence of a discontinuation of the anastomotic rhyme in endoscopy or of a spreading of any entity of the contrast medium on the enema will represent an exclusion criterion. All patients will simultaneously perform an oncological evaluation to establish the indication for adjuvant therapy in the presence of the definitive histological examination. Patients without signs of anastomotic complications and with indication for adjuvant therapy will be enrolled for study by the local investigators. Enrolment and randomisation must take place within 21 days of the intervention.

The subjects who are eligible for the study, after the informed consent has been signed, will be stratified by previous neoadjuvant treatment (yes or no) and by the proposed adjuvant chemotherapy scheme (with or without platinum derivatives), and then randomised to one of the following arms:

► Arm A (experimental): closure of the stoma between 30 and 40 days after surgery on the rectum, before starting adjuvant therapy.

► Arm B (standard): closure of the stoma starting from 15 days and within 60 days from the end of the adjuvant therapy. The anastomosis instrumental evaluation will be repeated after the end of chemotherapy in this group.

Endpoint definition

1. Primary endpoint.
   – Proportion of patients with adequate compliance with adjuvant treatment.
   – Compliance with adjuvant therapy will be considered adequate if both of the following criteria are met: start of adjuvant therapy within the 70th day (≤10 weeks) after surgery on the rectum; and total cumulative dose delivered, compared with the theoretical planned, ≥70%.
   – Failure to adhere to at least 1 of the two criteria will correspond to a failure (inadequate compliance).
   – Patients with missing or non-performed assessment of compliance for any reason will also be considered unsuccessful adherence.

2. Secondary endpoints.
   – Morbidity. Incidence of complications related to the presence or to the closure of the ileostomy, during the hospitalisation or after discharge, using the Clavien-Dindo classification. Individual patient events, hospitalisations and reoperations will be recorded.
   – Chemotherapy toxicity. All adverse events according to CTCAE V.5.0 classification will be considered.
   – QoL. Patient-reported QoL will be measured at the baseline and at defined time points using validated questionnaires (EORTC C30 and CR29, EQ5D). Bowel function will be evaluated at 12 months from randomisation by means of the LARS score.
   – Costs. The costs related to hospitalisation, outpatient visits, ostomy care supplies and the management of complications and toxicity will be assessed.
   – PFS defined as the time elapsed between the randomisation date and the date of progression/death for any cause or the latest follow-up available.
   – OS defined as the time elapsed between the randomisation date and the date of death for any cause or the latest follow-up available

Patients will be followed for the duration of the study, regardless of the clinical course, and will conclude the active follow-up with a final evaluation 12 months after randomisation in both study arms. A longer follow-up, based only on routinely recorded data, will be conducted

to assess long term OS. Enrolment is expected to start in September 2020.

The study flow diagram is depicted in figure 1.

Surgical technique and medical therapy

Hospitalisation will normally take place the day before or the morning of surgery. Antibiotic prophylaxis (usually short term with cefazoline within half an hour after skin incision) and thrombus embolic prophylaxis will be performed according to national guidelines.

The stoma closure will be performed manually or mechanically according to the surgeon's judgement. The suture of the skin incision will be linear or purse string according to the local standards.

The postoperative management will be based on the ERAS strategy (early feeding and mobilisation). Discharge criteria will be passage of gas, adequate oral feeding and good pain control.

Adjuvant chemotherapy will be administered, in terms of indications, drugs and schedules, according to the national guidelines (AIOM) and according to the consensus documents of the Colorectal Study Group of the Oncology Network (http://www.reteoncologica.it/area-operatori/gruppi-per-patologie/raccomandazioni-di-rete).

The ideal temporal target for the start of chemotherapy will be within 8 weeks of surgery on the rectum; the maximum time within 10 weeks. Randomised patients starting after this term are still followed up and evaluated until the end of follow-up for the evaluation of the other endpoints.

Endpoints assessment and follow-up
Morbidity

Complications related to stoma closure surgery, which occurred both during and after hospitalisation, will be recorded according to the Clavien-Dindo classification. Their overall weight per patient will be calculated through the CCI. Management problems and complications from the stoma presence will also be recorded. All reinterventions and hospitalisations during the study period will be captured.

Adjuvant therapy

Chemotherapy toxicity will be evaluated according to the CTC-EORTC. Prophylaxis and treatment of side effects and dose reductions will be applied according to international standards (NCI-CTCAE criteria). Starting date of the treatment, dose reductions and therapeutic scheme variations, suspensions or interruptions will be recorded. In relation to the total dose and the total number of programmed cycles, the percentage of completeness of the adjuvant therapy will be calculated. Grade and type of adjuvant therapy toxicity will be recorded for each patient.

Quality of life

QoL will be measured using the EORTC C30, CR29 and EQ5D validated questionnaires. The questionnaires will be administered, in both arms, on enrolment (baseline),
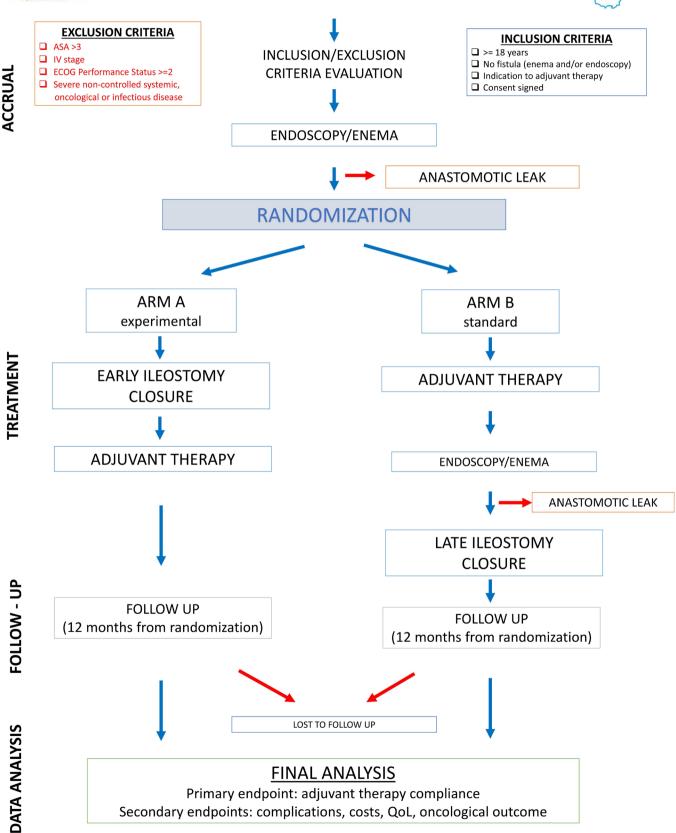
Figure 1   Study flow diagram. QoL, quality of life.

at the beginning of the fourth cycle of adjuvant therapy and at 12 months after the intervention on rectal cancer.

The LARS score will be used to evaluate intestinal and sphincter function at 12 months after the rectal intervention in both arms (in the control group if ostomy closed since at least 2 months).

Costs

The costs will be estimated considering the days of hospitalisation related to the closure of the stoma, the treatment of complications or toxicity, the outpatient visits during the study period and the amount of supplies for stoma care. Regional averages costs will be used as the basic cost unit.

Statistical considerations
Sample size

The sample size was calculated in relation to the main objective. The null hypothesis (proportion of patients with adequate compliance to the adjuvant treatment in patients with closure of the stoma after treatment) was inferred from data of randomised trials of adjuvant chemotherapy after rectal cancer resection[15 16] and studies on chemotherapy toxicity directly related to the presence of an ostomy,[12] and was set at 0.70. The alternative hypothesis is an increase in the proportion up to 0.85, with an absolute increase of 0.15. This increase is considered clinically relevant. With a two-tailed alpha error of 0.05 and a power of 0.80, the sample size required is at least 242 patients (121 for each treatment arm). Taking into account a maximum drop-out rate of approximately 10%, the total number of patients enrolled and randomised will be 270. The estimated study duration is 36 months.

Randomisation

The randomisation list, stratified by neoadjuvant therapy (yes/no) and by type of planned adjuvant chemotherapy (fluoropyrimidine±platinum derivatives) will be generated by the Clinical Epidemiology Unit of Città della Salute e della Scienza University Hospital in Turin, using a block procedure of variable length in random order, completely concealed to clinicians. The 1:1 randomisation will be done online. After entering the inclusion/exclusion criteria and the stratification variables into the database, the patient will be randomised and registered in arm A or B. The computerised randomisation system will be accessible continuously.

Analysis

The principal analyses will be carried out on all subjects randomised according to the assigned treatment arm (intention to treat principle). The demographic and baseline characteristics will be described for the whole study population and for each treatment arm. Discrete variables will be summarised by frequencies and percentages. The continuous variables will be summarised with the use of standard measures of central tendency and dispersion (mean and SD or median deviation and IQR). The analysis of the primary endpoint will be based on

the comparison of treatment compliance between the two arms by means of a stratified χ^2 test. As a sensitivity analysis, further potential confounders detected at the baseline will be included in a logistic regression model. OS and PFS, calculated from the randomisation date, will be assessed with the Kaplan-Meier method and the differences in survival (overall and disease free) will be tested using the stratified Log-rank test. The 95% CI will be calculated for all the study endpoints. HR, adjusted for the stratification criteria and the main prognostic factors, will be estimated using the Cox model. Planned subgroup analyses will be carried out for the two stratification factors of the randomisation (neoadjuvant treatment and adjuvant chemotherapy) and by age (divided into three classes according to the tertiles) using interaction terms between treatment arm and the subgroup variable in the regression models. Multiplicity adjustments for secondary outcomes and subgroup analyses will not be performed because these results will be considered exploratory and no claims will be made on them. The incidence of individual adverse events during hospitalisation will be compared using the χ^2 test or the Fisher's exact test, as appropriate. The comparison on the QoL will be evaluated by comparing the average score between the two groups with the Student's t-test (or with a non-parametric test and quartile regression, if necessary) and with generalised linear mixed model to take into account the repeated measurements over time on the same subjects. Per-protocol analyses will be performed for exploratory purposes.

Data collection

The data will be collected in each participating centre by filling in an electronic CRF. A local study manager will be identified for each participating centre. The completeness and congruity of the data will be checked periodically by a central study monitor and overviewed the study's Steering Committee. The central monitor and Steering Committee will refer to the local managers for any request for clarification.

ETHICS AND DISSEMINATION

The Rete Oncologica Piemonte e Valle d'Aosta is a multidisciplinary organisation that includes specialists involved in the treatment of cancer disease in the north-western territory of Italy. The aim of the Oncology Network is to reduce the variability of treatments, guarantee uniform access to and improve the quality of cancer care. To this end, the Network issues recommendations, drafted through a peer-review process by its members, and defines the criteria for the designation as referral centres for cancer specific procedures.

STOMAD is a non-profit study conducted within the Network centres and is part of the research branch aimed at improving the healthcare delivery system. It is proposed to investigate which is the best adjuvant treatment delivery strategy in relation to the presence of the stoma for patients operated on for rectal cancer, taking into consideration both

the patient's point of view (patients reported outcome) and the health system perspective (costs analysis).

The study will be conducted according to the principles of the Helsinki Declaration and the ICH Guideline for Good Clinical Practice. It will be approved by the reference Ethics Committee of each participating centre. Each enrolled patient must express a written consent (the consent form in original language is provided as online supplemental material). Consent can be revoked at any time. Patients data will be collected on an existing online platform created by the clinical epidemiology unit of the main centre in the region, which will also be responsible for all statistical analyses. The data collected for the study will be processed in accordance with current national legislation (personal data protection code). The trial steering committee may request the premature termination of the study in case of adverse events with severity and frequency significantly higher than expected or if the primary end point in the experimental group is significantly worse than the control group before the end of the study. For these evaluations, the steering committee will not use predefined statistical criteria (statistical stopping rules) but will base the decision on a careful quantitative and qualitative evaluation of the events that will be discussed in scheduled meetings.

This trial will engage the Network professional teams in a common effort to improve the treatment of rectal cancer by ensuring the best results in relation to the most correct use of resources (value-based healthcare). Other positive effects could be the strengthening of collaboration relationships between the Network centres and the definition of a common platform for future Network research.

The results of this study will be presented at national and international meetings and reported in the Network website. A manuscript with the final results will be submitted for publication in a peer-reviewed journal.

Author affiliations
[1]Department of General and Oncological Surgery, Azienda Ospedaliera Ordine Mauriziano, Torino, Italy
[2]Clinical Epidemiology Unit, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza, Torino, Italy
[3]Department of Surgery, Azienda Ospedaliera S Croce e Carle, Cuneo, Italy
[4]Department of Oncology, Azienda Ospedaliera Ordine Mauriziano, Torino, Italy
[5]Department of Surgery, Azienda Ospedaliera Nazionale SS Antonio e Biagio e C Arrigo, Alessandria, Italy
[6]Department of Oncology, Ospedale degli Infermi, Ponderano (BI), Italy
[7]Department of Surgery, Ospedale degli Infermi, Ponderano (BI), Italy
[8]Colorectal Cancer Unit, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza, Torino, Italy
[9]Department of Surgery, Ospedale Regionale Umberto Parini, Aosta, Italy
[10]Department of Surgical Science, Turin University, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza, Torino, Italy
[11]Department of General and Emergency Surgery, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza, Torino, Italy
[12]Department of Surgery, Ospedale Martini, Torino, Italy
[13]Department of Surgical Oncology and Digestive Surgery, Turin University, Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano (TO), Italy
[14]Department of Surgery, Ospedale degli Infermi, Rivoli (TO), Italy
[15]Department of Surgery, Ospedale Edoardo Agnelli, Pinerolo (TO), Italy
[16]Department of Surgery, Ospedale di Ivrea, Ivrea (TO), Italy
[17]Department of Surgery, Ospedale di Ciriè, Ciriè (TO), Italy
[18]Department of Surgery, Ospedale Santa Croce, Moncalieri (TO), Italy
[19]Department of Surgery, Ospedale SS Annunziata, Savigliano (CN), Italy
[20]Department of Surgery, Ospedale Regina Montis, Mondovì (CN), Italy
[21]Department of Surgery, Ospedale San Lazzaro, Alba (CN), Italy
[22]Department of Surgery, Ospedale Santo Spirito, Casale Monferrato (AL), Italy
[23]Department of Surgery, Ospedale Mons. Galliano, Acqui Terme (AL), Italy
[24]Department of Surgery, Ospedale San Giacomo, Novi Ligure (AL), Italy
[25]Department of Surgery, Ospedale Cardinal Massaia, Asti, Italy
[26]Department of Surgery, Eastern Piedmont University, Azienda Ospedaliera Maggiore della Carita, Novara, Italy
[27]Department of Surgery, Azienda Ospedaliera Maggiore della Carità, Novara, Italy
[28]Department of Surgery, Presidio Ospedaliero Sant'Andrea, Vercelli, Italy
[29]Department of Surgery, Ospedale S. Biagio, Domodossola (VB), Italy
[30]Department of Surgery, Ospedale Castelli, Verbania (VB), Italy
[31]Colorectal Surgical Unit, IRCCS, Candiolo (TO), Italy
[32]Department of Surgery, Presidio Sanitario Ospedale Cottolengo, Torino, Italy
[33]Department of Surgery, Humanitas Gradenigo, Torino, Italy

ORCID iDs
Paolo Massucco http://orcid.org/0000-0003-1620-0464
Massimiliano Mistrangelo http://orcid.org/0000-0001-8506-6794

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