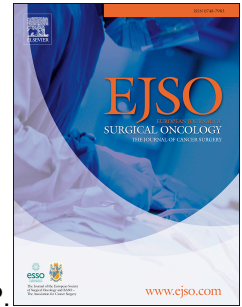


# Journal Pre-proof

Mid-transverse colon cancer and extended versus transverse colectomy: Results of the Italian society of surgical oncology colorectal cancer network (SICO CCN) multicenter collaborative study



M. Milone, M. Degiuli, M.E. Allaix, C.A. Ammirati, G. Anania, A. Barberis, A. Belli, P.P. Bianchi, F. Bianco, C. Bombardini, M. Burati, D. Cavaliere, C. Coco, A. Coratti, R. De Luca, G. De Manzoni, P. De Nardi, M. De Rosa, P. Delrio, A. Di Cataldo, A. Di Leo, A. Donini, U. Elmore, A. Fontana, G. Gallo, S. Gentilli, S. Giannessi, A. Giuliani, L. Graziosi, M. Guerrieri, G. Li Destri, R. Longhin, M. Manigrasso, M. Mineccia, M. Monni, M. Morino, M. Ortenzi, F. Pecchini, C. Pedrazzani, M. Piccoli, S. Pollesel, S. Pucciarelli, R. Reddavid, D. Rega, M. Rigamonti, G. Rizzo, V. Robustelli, F. Rondelli, R. Rosati, F. Roviello, M. Santarelli, F. Saraceno, S. Scabini, G.S. Sica, P. Sileri, M. Simone, L. Siragusa, S. Sofia, L. Solaini, A. Tribuzi, M. Trompetto, G. Turri, E.D.L. Urso, S. Vertaldi, A. Vignali, M. Zuin, M. Zuolo, D. D'Ugo, G.D. De Palma

PII: S0748-7983(20)30006-8

DOI: <https://doi.org/10.1016/j.ejso.2020.01.006>

Reference: YEJSO 5599

To appear in: *European Journal of Surgical Oncology*

Received Date: 7 August 2019

Accepted Date: 3 January 2020

Please cite this article as: Milone M, Degiuli M, Allaix ME, Ammirati CA, Anania G, Barberis A, Belli A, Bianchi PP, Bianco F, Bombardini C, Burati M, Cavaliere D, Coco C, Coratti A, De Luca R, De Manzoni G, De Nardi P, De Rosa M, Delrio P, Di Cataldo A, Di Leo A, Donini A, Elmore U, Fontana A, Gallo G, Gentilli S, Giannessi S, Giuliani A, Graziosi L, Guerrieri M, Li Destri G, Longhin R, Manigrasso M, Mineccia M, Monni M, Morino M, Ortenzi M, Pecchini F, Pedrazzani C, Piccoli M, Pollesel S, Pucciarelli S, Reddavid R, Rega D, Rigamonti M, Rizzo G, Robustelli V, Rondelli F, Rosati R, Roviello F, Santarelli M, Saraceno F, Scabini S, Sica GS, Sileri P, Simone M, Siragusa L, Sofia S, Solaini L, Tribuzi A, Trompetto M, Turri G, Urso EDL, Vertaldi S, Vignali A, Zuin M, Zuolo M, D'Ugo D, De Palma GD, Mid-transverse colon cancer and extended versus transverse colectomy: Results of the Italian society of surgical oncology colorectal cancer network (SICO CCN) multicenter collaborative study, *European Journal of Surgical Oncology* (2020), doi: <https://doi.org/10.1016/j.ejso.2020.01.006>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Ltd.

## Mid-transverse colon cancer and extended versus transverse colectomy: results of the Italian Society of Surgical Oncology Colorectal Cancer Network (SICO CCN) multicenter collaborative study

Milone M<sup>1</sup>, Degiuli M<sup>2</sup>, Allaix ME<sup>3</sup>, Ammirati CA<sup>4</sup>, Anania G<sup>5</sup>, Barberis A<sup>6</sup>, Belli A<sup>7</sup>, Bianchi PP<sup>8</sup>, Bianco F<sup>7</sup>, Bombardini C<sup>5</sup>, Burati M<sup>1</sup>, Cavaliere D<sup>9</sup>, Coco C<sup>10</sup>, Coratti A<sup>11</sup>, De Luca R<sup>12</sup>, De Manzoni G<sup>13</sup>, De Nardi P<sup>14</sup>, De Rosa M<sup>15</sup>, Delrio P<sup>16</sup>, Di Cataldo A<sup>17</sup>, Di Leo A<sup>13</sup>, Donini A<sup>18</sup>, Elmore U<sup>14</sup>, Fontana A<sup>19</sup>, Gallo G<sup>20</sup>, Gentili S<sup>21</sup>, Giannessi S<sup>22</sup>, Giuliani A<sup>8</sup>, Graziosi L<sup>18</sup>, Guerrieri M<sup>23</sup>, Li Destri G<sup>17</sup>, Longhin R<sup>6</sup>, Manigrasso M<sup>1</sup>, Mineccia M<sup>19</sup>, Monni M<sup>21</sup>, Morino M<sup>3</sup>, Ortenzi M<sup>23</sup>, Pecchini F<sup>24</sup>, Pedrazzani C<sup>25</sup>, Piccoli M<sup>24</sup>, Pollesel S<sup>26</sup>, Pucciarelli S<sup>27</sup>, Reddavid R<sup>2</sup>, Rega D<sup>16</sup>, Rigamonti M<sup>28</sup>, Rizzo G<sup>10</sup>, Robustelli V<sup>22</sup>, Rondelli F<sup>15</sup>, Rosati R<sup>14</sup>, Roviello F<sup>26</sup>, Santarelli M<sup>29</sup>, Saraceno F<sup>30</sup>, Scabini S<sup>4</sup>, Sica GS<sup>31</sup>, Sileri P<sup>30</sup>, Simone M<sup>12</sup>, Siragusa L<sup>31</sup>, Sofia S<sup>2</sup>, Solaini L<sup>9</sup>, Tribuzi A<sup>11</sup>, Trompetto M<sup>20</sup>, Turri G<sup>25</sup>, Urso EDL<sup>27</sup>, Vertaldi S<sup>1</sup>, Vignali A<sup>14</sup>, Zuin M<sup>27</sup>, Zuolo M<sup>28</sup>, D'Ugo D<sup>32</sup>, De Palma GD<sup>1</sup>.

<sup>1</sup> Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy

<sup>2</sup> Department of Oncology, Surgical Oncology and Digestive Surgery Unit, San Luigi University Hospital, Orbassano, Turin, Italy

<sup>3</sup> Department of Surgical Sciences, University of Turin, Turin, Italy

<sup>4</sup> Oncologic Surgical Unit, Hospital Policlinic San Martino, Genova, Italy

<sup>5</sup> Department of Morphology, Experimental Medicine and Surgery, Section of General and Thoracic Surgery, University of Ferrara, Italy

<sup>6</sup> Unit of General and Hepatobiliopancreatic Surgery, Galliera Hospital, Genova, Italy

<sup>7</sup> Division of Surgical Oncology, Department of Abdominal Oncology, IRCCS Fondazione "G. Pascale", Naples, Italy

<sup>8</sup> Department of General and Minimally Invasive Surgery, Misericordia Hospital, Grosseto, Italy

<sup>9</sup> General and Oncologic Surgery, Morgagni-Pierantoni Hospital, Forlì, Italy

<sup>10</sup> Department of General Surgery, Sacred Heart Catholic University, Rome, Italy

<sup>11</sup> Division of Oncological and Robotic General Surgery, Careggi University Hospital, Florence, Italy

- <sup>12</sup> Department of Surgical Oncology, National Cancer Research Center, Giovanni Paolo II Tumor Institute, Bari, Italy
- <sup>13</sup> Department of Surgery, General and Upper GI, Surgery Division, University of Verona, Verona, Italy
- <sup>14</sup> Division of Gastrointestinal Surgery, San Raffaele Scientific Institut, Milan, Italy
- <sup>15</sup> Department of General Surgery, San Giovanni Battista Hospital, Foligno, Italy
- <sup>16</sup> Colorectal Abdominal Surgery Division, IRCCS Fondazione "G. Pascale", Naples, Italy
- <sup>17</sup> Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy
- <sup>18</sup> Department of General and Emergency Surgery, University of Perugia, Perugia, Italy
- <sup>19</sup> Department of HPB and Digestive Surgery, Ospedale Mauriziano Umberto I, Turin, Italy
- <sup>20</sup> Department of Colorectal Surgery, Santa Rita Clinic, Vercelli, Italy
- <sup>21</sup> Department of General Surgery, Maggiore della Carità Hospital, Novara, Italy
- <sup>22</sup> Operative Unit of General Surgery, San Jacopo Hospital, Pistoia, Italy
- <sup>23</sup> Department of General Surgery, Università Politecnica delle Marche, Ancona, Italy
- <sup>24</sup> Department of General and Emergency Surgery, Azienda Ospedaliera Universitaria Modena, Modena, Italy
- <sup>25</sup> Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Unit of Colorectal Surgery, University of Verona, Verona, Italy
- <sup>26</sup> Department of General Surgery and Surgical Oncology, University of Siena, Italy
- <sup>27</sup> Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, Padova, Italy
- <sup>28</sup> Operative Unit of General Surgery, Valli del Noce Hospital, Cles, Trento, Italy
- <sup>29</sup> Division of General and Emergency Surgery, Molinette Hospital, Turin, Italy
- <sup>30</sup> Department of General Surgery, University of Rome Tor Vergata, Rome, Italy
- <sup>31</sup> Department of Minimally Invasive and GI Surgery, Policlinico Tor Vergata, Rome, Italy
- <sup>32</sup> Department of Surgery, Università Cattolica del Sacro Cuore, Rome, Italy

**Corresponding Author:** Marco Milone, MD, PhD, Department of Clinical Medicine and Surgery, Federico II University of Naples, Via Sergio Pansini, 5, 80131, Naples, Italy

E-mail: milone.marco.md@gmail.com

Telephone: +39-0817463064

## Abstract

**Introduction:** Transverse colon cancer (TCC) is poorly studied, and TCC cases are often excluded from large prospective randomized trials because of their complexity and their potentially high complication rate. The best surgical approach for TCC has yet to be established. The aim of this large retrospective multicenter Italian series is to investigate the advantages and disadvantages of both hemicolectomy and transverse colectomy in order to identify the best surgical approach.

**Materials and methods:** This was a retrospective cohort study of patients with mid-transverse colon cancer treated with a segmental colon resection or an extended hemicolectomy (right or left) between 2006 and 2016 in 28 high-volume (more than 70 procedures/year) Italian referral centers for colorectal surgery.

**Results:** The study included 1529 patients, 388 of whom underwent a segmental resection while 1141 underwent an extended resection. A higher number of complications has been reported in the segmental group than in the extended group (30.1% versus 23.6%;  $p$  0.010). In 42 cases the main complication was the anastomotic leak (4.4% versus 2.2%;  $p$  0.020). Recovery outcomes also showed statistical differences: time to first flatus ( $p$  0.014), time to first mobilization ( $p$  0.040), and overall hospital stay ( $p$  <0.001) were significantly shorter in the extended group. Even if overall survival were similar between the groups (95.1% versus 97%;  $p$  0.384), 3-year disease-free survival worsened after segmental resection (78.1% versus 86.2 %;  $p$  0.001).

**Conclusions:** According to our results, an extended right colon resection for TCC seems to be surgically safer and more oncologically valid.

**Keywords:** transverse colon cancer, extended hemicolectomy, segmental colectomy, transversectomy

## Introduction

Ten per cent of colorectal cancers are located in the transverse colon<sup>1</sup>. To the best of our knowledge, compared to other colon neoplasms transverse colon cancer (TCC) is poorly studied, and TCC cases are often excluded from large prospective randomized trials because of their complexity and potentially high complication rate<sup>2</sup>.

Surgery is a key point in the treatment of colonic tumors<sup>3</sup>. For TCC, either a transverse colectomy or an extended hemicolectomy can be performed. A colonic resection for TCC, to be complete, requires technically complicated passages to perform a lymph-node dissection around the middle colic artery and a difficult reconstruction of the bowel continuity. At present, the best surgical approach for TCC has yet to be established. Due to the lack of consistent data comparing the two approaches, the choice of which to perform has to be based on the surgeon's preference and experience.

The aim of this large retrospective multicenter Italian series is to investigate the advantages and disadvantages of hemicolectomy and transverse colectomy in order to determine which is the best surgical approach.

## Materials and methods

### Study population and design

This was a retrospective cohort study of patients with mid-transverse colon cancer treated with a segmental colon resection or an extended hemicolectomy (right or left) between 2006 and 2016 in 28 high-volume (more than 70 procedures/year) Italian referral centers for colorectal surgery. The study was approved by the institutional review board of all participating centers. All items required by the STROBE checklist for reports of observational studies have been included.

Mid-transverse colon cancer is defined as a tumor located in the mid part of the transverse colon, excluding the 10-cm distal third in the left colonic angle (splenic flexure) and the 10-cm proximal part in the right colonic angle (hepatic flexure) of the transverse colon. The mid-transverse location was determined by surgical exploration.

A comparative analysis was performed, including 388 patients with a mid-transverse colon cancer who underwent segmental transverse colectomy compared with 1141 matched patients who underwent extended hemicolectomy during the same period. All consecutive procedures were included in our analyses. All patients were operated by expert surgeons. In order to minimize the

bias related to the different surgical techniques, only procedures performed according to the standardized criteria were included in the study.

Transverse colectomy is defined as the resection of a variable length of bowel included between the hepatic and splenic flexures, together with its lymph vascular supply along the middle colic pedicle, the ligation of which is done at its origin. Usually both flexures are mobilized and the continuity of the bowel is restored by fashioning an end-to-end or side-to-side anastomosis. An extended hemicolectomy can be performed on the right colon or on the left. To perform an extended right hemicolectomy, middle colic vessels must be ligated at their origins along with the ileocolic pedicle. In the left extended hemicolectomy, the left colic pedicle and the left branch of the middle colic pedicle are ligated (ligation of the whole middle colic pedicle may be necessary in a few cases).

Segmental or extended resection was performed according to the clinical advice of each individual surgeon. An attempt was made to verify whether patients were matched based on the probability (propensity) of undergoing segmental or extended colectomy. The predicted probability of undergoing one of the two procedures was estimated for each patient using a multivariate logistic regression model in which the surgical procedure was the dependent variable while baseline patient and tumor characteristics—age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) score and TNM stage—were the independent variables. The two treatment groups were entirely matched for the analyzed characteristics. Thus, no propensity matching was needed for further analysis.

The postoperative period was homogenized. Patients who received different medical and nursing cares were excluded. An enhanced recovery-after-surgery (ERAS) perioperative care protocol was applied when consent was given<sup>4</sup>.

Data were collected prospectively. Gender, age, BMI, ASA, tumor stage, operative time, conversion, postoperative pain, intraoperative complications, number of lymph nodes harvested, time to first flatus, time to mobilization, and hospital discharge were all included. We also collected data about postoperative surgical complications according to the Clavien–Dindo classification<sup>5</sup>; these included surgical wound complications, anastomotic leakage, bowel obstruction and abdominal or bowel bleeding. We defined as complications all the adverse events that occurred within 30 days from surgery. The anastomotic leakage was defined as a condition of clinical or radiological anastomotic dehiscence that either needed or didn't need surgical revision.

We considered as bleeding the cases that required blood transfusion. Pain was considered if rescue analgesia was needed. Discharge occurred with the absence of symptoms, passage of stools, and tolerance of meals.

Pathological outcomes included the length of the specimen and the distance of the tumor from the proximal and the distal margins, all measured in centimeters. We also reported the number of lymph nodes harvested and how many of these contained metastases. Overall survival and disease-free survival were evaluated during the follow-up.

Separate analyses comparing extended right colectomy versus segmental colectomy and extended left colectomy versus the segmental one were performed.

Statistical analysis was performed using the SPSS 20 system (SPSS Inc., Chicago, IL, USA).

Continuous data were expressed as the means  $\pm$  SDs, while categorical variables were expressed as percentages. Continuous variables were compared by an independent sample *t* test. The Wilcoxon test for paired samples was employed as a non-parametric similar of the paired samples *t* test used for continuous variables. Categorical data were analyzed by the chi-square test. Fisher's exact test was employed when the minimum expected value was  $<5$ . All the results were presented as two-tailed values with statistical significance if  $p < 0.05$ .

## Results

One thousand five hundred and twenty-nine patients responded to the characteristics and could account for at least 1 year of follow-up, so they were included in the study. Of these, 759 have completed a 3-year follow-up. Demographic characteristics are shown in Table 1. Patient and tumor characteristics (age, ex, BMI, ASA, pTNM) showed no statistically significant difference. A segmental conservative resection was carried out in 388 patients, while 1141 patients underwent an extended resection; of these, 1017 were right hemicolectomies, 117 left hemicolectomies, and seven total colectomies. Among the colonic segmental resections, 164 (42.3%) were laparoscopic segmental resections, while 224 (57.7%) were open segmental resections with a significant difference. Speaking of the extended resection, 632 (55.4%) were performed laparoscopically and 509 (44.6%) were open procedures. Thus, statistical analysis showed a significant difference in terms of surgical approach (laparoscopic versus open) between the two groups ( $p < 0.001$ ). In the majority of cases, the procedures were elective; in particular, 360 (92.8%) were segmental resections and 1049 (91.9%) were extended resections ( $p = 0.812$ ). Only 92 (8.1%) were emergency procedures for extended resections, and 28 (7.2%) were



emergency segmental colectomies (Table 2). Conversion occurred in 23 cases (5.9%) in the segmental resection group and 38 cases (3.3%) in the extended resection group, showing a statistical difference between the two groups in favor of extended resection ( $p < 0.001$ ).

Mean operative time was  $153.61 \pm 70.83$  minutes for segmental resections and  $170.07 \pm 77.99$  minutes for hemicolectomies ( $p < 0.001$ ).

Recovery outcomes (Table 3) showed statistically significant differences: time to first flatus, time to first mobilization, and overall hospital stay were significantly shorter in the extended group. Complications (Table 4) occurred in 117 (30.1%) segmental resection and 269 (23.6%) extended ones ( $p < 0.010$ ). In particular, anemia occurred in eight patients (2.1%) who underwent a segmental resection and five patients (0.4%) of the hemicolectomy group ( $p < 0.025$ ); wound infection was reported in 17 cases (4.4%) after transverse colectomy and in 32 cases (2.8%) after a hemicolectomy ( $p < 0.026$ ). Anastomotic leak occurred after 17 segmental procedures (4.4%) and after 25 extended ones (2.2%) ( $p < 0.020$ ).

Complications were grouped according the Clavien–Dindo classification as shown in Table 5. A smaller number of complications for each of the five grades has been registered in the hemicolectomy group ( $p < 0.005$ ). In particular, of the 70 patients who presented pain, 64 were treated with rescue analgesia. All the 49 patients who presented wound infection were treated with antibiotics, and in just eight cases surgical debridement was needed; 69 cases of bleeding were registered, and in 23 reintervention was necessary. In 42 cases the main complication was anastomotic leakage; of these, 24 were treated with reintervention while in 18 cases a conservative radiological drainage was decisive.

Pathological outcomes (Table 6) also showed significant differences between the two groups: specimens in the extended group were significantly longer ( $22.84 \pm 11.49$  versus  $35.05 \pm 15.09$ ;  $p < 0.001$ ), and both proximal and distal margins had greater lengths ( $8.25 \pm 6.45$  versus  $10.16 \pm 9.13$ ;  $p < 0.001$ ;  $10.55 \pm 8.54$  versus  $20.84 \pm 13.27$ ;  $p < 0.001$ ). The mean number of lymph nodes harvested was also significantly greater in the hemicolectomy group ( $15.03 \pm 9.93$  versus  $24.58 \pm 13.90$ ;  $p < 0.001$ ).

Finally, mean follow-up was  $3.6 \pm 2.4$  years with an overall survival (OS) of 95.1% for segmental resection and 97% for extended resection ( $p < 0.384$ ) (Figure 1). Three-year DFS showed a significant difference, being 78.1% for transverse colectomy and 86.2% for hemicolectomy ( $p < 0.001$ ).

Of interest, by analyzing separately the extended right colectomy versus the segmental one we can confirm the advantages of an extended resection. Conversion occurred in 23 cases (5.9%) in the segmental resection group and in 32 (3.1%) in the extended right colectomy group, showing a statistical difference in favor of extended resection ( $p$  0.016).

Recovery outcomes also showed significant differences: time to first flatus ( $3.44 \pm 1.74$  versus  $3.74 \pm 1.60$ ;  $p$  0.003), time to first mobilization ( $1.41 \pm 0.90$  versus  $1.56 \pm 0.85$ ;  $p$  0.004), and overall hospital stay ( $8.31 \pm 5.35$  versus  $9.76 \pm 6.24$ ;  $p$  <0.001) were all shorter in the extended group.

Complications occurred in 117 cases (30.1%) in the segmental resection group and in 230 cases (22.6%) in the extended right colectomy group ( $p$  0.003). Specifically, anemia occurred in eight cases (2.1%) after transverse colectomy versus four cases (0.4%) after an extended right colectomy ( $p$  0.002); wound infection was reported in 17 patients (4.4%) in the segmental group and in 32 patients (2.4%) in the extended group ( $p$  0.045); anastomotic leakage occurred after 17 segmental procedures (4.4%) and after 23 extended ones (2.3%) ( $p$  0.033).

Finally, the OS for segmental resections was 95.3% and for extended resection it was 96.5%, with a significant statistical difference ( $p$  0.095). Three-year disease-free survival (DFS) also showed a significant difference, being 78.1% in case of transverse colectomy and 86.1% for right extended colectomy ( $p$  <0.001). The advantage of an extended resection was lost when the segmental resection and extended left colectomy were analyzed separately. In fact, there were no significant statistical differences between the segmental and the extended group as regards conversion rates ( $p$  0.290), complications ( $p$  0.762) and recovery outcomes (time to first flatus,  $p$  0.545; time to mobilization,  $p$  0.213; overall hospital stay,  $p$  0.229). Even the overall survival was similar for segmental resections (95.3%) and extended left colectomy (96.6%), showing no significant difference ( $p$  0.568). By contrast, 3-year DFS showed a statistical difference, being 78.1% in case of transverse colectomy and 87.2% for left extended colectomy ( $p$  0.031).

## Discussion

Although one out of ten colonic cancers occur in the transverse colon<sup>6</sup>, little is known about the short- and long-term outcomes of transverse cancer surgery. Recent publications have reported its 5-year survival rate to be between 28% and 50%, rather low compared to other colon cancer survival rates<sup>2,7,8</sup>. According to Chong et al. this is due to the possibility of these tumors giving rise to lymph-node metastases through both superior and inferior mesenteric vessels. Another reason for the poor survival rates could be the proximity to other organs which often requires a more

aggressive surgery<sup>9</sup>. These are potential sources of complications after surgery and have led to the exclusion of transverse tumor cases in many large prospective randomized trials<sup>10</sup>.

Few publications have compared transverse colon surgical techniques, and because of the lack of consistent data there is no unanimous opinion upon which is the most advisable. A more conservative and less aggressive procedure is advised by a few authors<sup>11,12</sup>, while many others support an extended hemicolectomy to achieve a more complete lymphadenectomy.

Furthermore, even if the minimally invasive surgery is nowadays considered the gold standard approach for colorectal cancers<sup>13,14</sup>, and the intracorporeal anastomosis seems to be related with better postoperative outcomes<sup>15-17</sup>, data about minimally invasive approaches for the TCC are scarce. Thus, at present, the lack of a 'gold standard' technique leaves the surgeon the choice of which technique to perform, based on his preferences.

In the medical literature, only a few studies have concentrated on surgical approaches and outcomes among TCC cases. Among these examples we find Leijssen and colleagues<sup>18</sup> who analyzed the outcomes of transverse colectomy and hemicolectomy groups in a total of 103 patients who underwent colonic surgery for mid-transverse colon cancer. Although fewer lymph nodes were harvested in the transverse colectomy group, there was no difference in the postoperative morbidity between the two approaches, so the authors concluded that transverse colectomy was oncologically safe for stage I–III mid-transverse colon cancer. However, this study, had some limitations, such as the sample of patients, which was small. Moreover, it is not clear whether the colectomies analyzed were always performed by expert surgeons.

Another cohort of 103 patients was analyzed by van Rongen et al.<sup>19</sup> In their study they stated that transverse colon surgery carries a high risk of postoperative complications, independently of the type of surgical approach. Nevertheless, they considered the results after transverse colectomy satisfactory, and so concluded that a conservative approach could be an option for treating TCC. Matsuda et al.<sup>20</sup> analyzed retrospectively 38 and 34 patients who received extended right hemicolectomy or transverse colectomy, concluding that both procedures provided similar oncological outcomes. It is important to highlight that in this case also the size of the sample was small, and the study was retrospective, meaning that a selection bias cannot be excluded.

Chong et al.<sup>9</sup> collected one of the largest cohorts of patients (1066), of whom 939 underwent an extended colon resection while 127 underwent a transverse colectomy. For the authors, the two techniques did not differ in terms of safety and oncological outcomes. However, only 127

conservative resection cases were included, which were compared with as many extended resections. Thus, even with a large cohort the series analyzed was small.

To the best of our knowledge, the largest study was published by Guan et al.<sup>21</sup> who analyzed data from 10,334 cases of TCC. Despite the harvested lymph nodes being fewer after a transverse colectomy, their positivity was similar in the two groups. Moreover, 5-year cancer-free survival was similar. The authors' conclusions were that, although transverse colectomy is a less aggressive surgical approach, it can be advisable in some TCC cases. The major limitation of this study lies in data collection: the authors identified patients in the Surveillance, Epidemiology and End-Results (SEER) registry, in which no information about perioperative or postoperative complications, type of surgical approach, and short-term outcomes can be found.

We recently carried out a meta-analysis<sup>22</sup> of data from 11,687 patients, of whom 4664 underwent transverse segmental colectomy and 7023 underwent extended hemicolectomy. Although the results showed that a conservative approach is feasible and safe, and oncological outcomes of the two procedures are comparable, a definitive conclusion cannot be made because the metanalysis was limited owing to included studies not having sufficient statistical power for the small sample size; moreover, no data could be extracted about technical aspects of each surgical procedure, and no comparison could be made between laparoscopic and open approaches.

The results of our study compared to those in the current medical literature are controversial; nevertheless, it is important to underline that, to date, this is the largest cohort comparing short- and long-term results of different surgical approaches for transverse colon cancer. Furthermore, we were able to collect the most representative sample of transverse colectomy, since we analyzed the largest number of cases up to the present.

The current investigation yielded three key results. First of all, a paradoxical protective impact on the occurrence of complications in extended hemicolectomy was observed. Second, another paradoxical effect was that recovery after surgery was better after an extended approach. Third, and most importantly, DFS and OS worsened after conservative transverse colectomy.

Postoperative complications, in fact, occurred after 30.1% of transverse segmental resections, compared with 23.6% of hemicolectomies. In particular we have reported a more consistent number of bleeding cases, wound infections and anastomotic leaks after transverse colectomy compared to hemicolectomy. This could be explained by the particular location of TCC. Tumors located in the transverse colon expand into the regional lymph nodes alongside the middle, right and left colic vessels. This particular lymphatic invasion pattern makes adequate

lymphadenectomy technically difficult in the transverse colectomy approach. It must be said that previous studies<sup>21</sup> have already shown that the number of lymph nodes harvested during hemicolectomy is much higher than that harvested during transverse colectomy, but still both procedures provided an adequate number of lymph nodes for a proper staging.

Another possible explanation for the major rate of complications after transverse colectomy is that the conservative resection of the transverse colon requires the mobilization of both splenic and hepatic flexures. The mobilization of both flexures is a technically difficult step in every colon resection. Therefore, the double mobilization required in transverse colectomy leads to a higher grade of risk in terms of the development of complications.

Recovery also seems better after an extended resection. Time to first flatus, time to mobilization, and duration of hospital stay seem shorter in the hemicolectomy group, probably because of the minor incidence of complications after a hemicolectomy.

It is very important to underline the statistically significant difference in OS and DFS found in the two groups. This is a path-changing finding, in contrast with all previous literature concluding that OS and DFS after the two procedures are similar so both surgical approaches were safe and feasible in selected cases. Even if overall survival were similar ( $p$  0.384) in the transverse resection group (95.1%) and extended resection group (97%), DFS worsened after segmental resection (78.1% versus 86.2%;  $p$  0.001). This sheds new light on the decision concerning the correct surgical approach, opening the way for a gold standard for the surgical treatment of transverse colon cancer.

Of interest, we were also able to identify that an extended right colectomy has to be preferred. The advantages of an extended resection were lost when the results obtained after an extended left colectomy were evaluated.

In conclusion, as far as we know our study sheds new light on the significant differences between transverse resection and extended hemicolectomy. The two procedures, in fact, might not be comparable, and choosing one approach compared to another could influence the surgical and oncological outcomes, taking into account that the advantages have to be related to performing a right colectomy. According to our results, for TCC cases an extended right colon resection seems to be surgically safer and more oncologically valid. Therefore, well-designed prospective multicenter trials and RCTs with homogeneous parameters are needed to draw a final conclusion

and set a gold standard for surgical procedures for treating transverse colon cancer in order to improve surgical and oncological safety.

### **Author contributions**

Milone M: conception, design, interpretation of the data and drafting of the article; Milone M, Degiuli M, Allaix ME, Ammirati CA, Anania G, Barberis A, Belli A, Bianchi PP, Bianco F, Bombardini C, Burati M, Cavaliere D, Coco C, Coratti A, De Luca R, De Manzoni G, De Nardi P, De Rosa M, Delrio P, Di Cataldo A, Di Leo A, Donini A, Elmore U, Fontana A, Gallo G, Gentilli S, Giannessi S, Giuliani A, Graziosi L, Guerrieri M, Li Destri G, Longhin R, Manigrasso M, Mineccia M, Monni M, Morino M, Ortenzi M, Pecchini F, Pedrazzani C, Piccoli M, Pollesel S, Reddavid R, Rega D, Rigamonti M, Rizzo G, Robustelli V, Rondelli F, Rosati R, Roviello F, Santarelli M, Saraceno F, Scabini S, Sica GS, Sileri P, Simone M, Siragusa L, Sofia S, Solaini L, Tribuzi A, Trompetto M, Turri G, Urso EDL, Vertaldi S, Vignali A, Zuin M, Zuolo M: acquisition, analysis and interpretation of the data; D'Ugo D, De Palma GD: interpretation of the data and critical revisions; D'Ugo D, De Palma GD: critical revisions and final approval.

### **Funding**

The authors have no financial support to declare or financial ties to disclose.

### **Conflict of interest statement**

The authors have no conflicts of interest to declare.

### **References**

1. Lê P, Mehtari L, Billey C. [Carcinoma of the transverse colon]. *J Chir (Paris)*. 143(5):285-293. <http://www.ncbi.nlm.nih.gov/pubmed/17185954>.
2. Sjo OH, Lunde OC, Nygaard K, Sandvik L, Nesbakken A. Tumour location is a prognostic factor for survival in colonic cancer patients. *Colorectal Dis*. 2007;0(0):070802113755001 doi:10.1111/j.1463-1318.2007.01302.x
3. Clinical Outcomes of Surgical Therapy Study Group, Nelson H, Sargent DJ, et al. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. *N Engl J*

- Med. 2004;350(20):2050-2059. doi:10.1056/NEJMoa032651
4. Vignali A, Elmore U, Cossu A, et al. Enhanced recovery after surgery (ERAS) pathway vs traditional care in laparoscopic rectal resection: a single-center experience. *Tech Coloproctol.* 2016;20(8):559-566. doi:10.1007/s10151-016-1497-4
  5. Makuuchi; PCB de OVDS de SPSBGVPC. The Clavien-dindo Classification of Surgical Complications: Five-year Experience. *Ann Surg.* 2009;250(2):187-196. doi:10.1097/sla.0b013e3181b13ca2
  6. Wray CM, Ziogas A, Hinojosa MW, Le H, Stamos MJ, Zell JA. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. *Dis Colon Rectum.* 2009;52(8):1359-1366. doi:10.1007/DCR.0b013e3181a7b7de
  7. Ueno H, Kajiwara Y, Shimazaki H, et al. New criteria for histologic grading of colorectal cancer. *Am J Surg Pathol.* 2012;36(2):193-201. doi:10.1097/PAS.0b013e318235edee
  8. Kim MK, Won D-Y, Lee J-K, et al. Laparoscopic Surgery for Transverse Colon Cancer: Short- and Long-Term Outcomes in Comparison with Conventional Open Surgery. *J Laparoendosc Adv Surg Tech.* 2015;25(12):982-989. doi:10.1089/lap.2015.0122
  9. Chong CS, Huh JW, Oh BY, et al. Operative Method for Transverse Colon Carcinoma. *Dis Colon Rectum.* 2016;59(7):630-639. doi:10.1097/DCR.0000000000000619
  10. Lee YS, Lee IK, Kang WK, et al. Surgical and pathological outcomes of laparoscopic surgery for transverse colon cancer. *Int J Colorectal Dis.* 2008;23(7):669-673. doi:10.1007/s00384-008-0471-7
  11. Kim CW, Shin US, Yu CS, Kim JC. Clinicopathologic characteristics, surgical treatment and outcomes for splenic flexure colon cancer. *Cancer Res Treat.* 2010;42(2):69-76. doi:10.4143/crt.2010.42.2.69
  12. Morikawa E, Yasutomi M, Shindou K, et al. Distribution of metastatic lymph nodes in

- colorectal cancer by the modified clearing method. *Dis Colon Rectum*. 1994;37(3):219-223. <http://www.ncbi.nlm.nih.gov/pubmed/8137667>.
13. Milone M, Manigrasso M, Burati M, Velotti N, Milone F, De Palma GD. Surgical resection for rectal cancer. Is laparoscopic surgery as successful as open approach? A systematic review with meta-analysis. *PLoS One*. 2018 Oct 9;13(10):e0204887. doi: 10.1371/journal.pone.0204887
14. Milone M, Elmore U, Vignali A, Mellano A, Gennarelli N, Manigrasso M, Milone F, De Palma GD, Muratore A, Rosati R. Pulmonary Complications after Surgery for Rectal Cancer in Elderly Patients: Evaluation of Laparoscopic versus Open Approach from a Multicenter Study on 477 Consecutive Cases. *Gastroenterol Res Pract*. 2017;2017:5893890. doi: 10.1155/2017/5893890.
15. Milone M, Angelini P, Berardi G, Burati M, Corcione F, Delrio P, Elmore U, Lemma M, Manigrasso M, Mellano A, Muratore A, Pace U, Rega D, Rosati R, Tartaglia E, De Palma GD. Intracorporeal versus extracorporeal anastomosis after laparoscopic left colectomy for splenic flexure cancer: results from a multi-institutional audit on 181 consecutive patients. *Surg Endosc*. 2018 Aug;32(8):3467-3473. doi: 10.1007/s00464-018-6065-8.
16. Milone M, Elmore U, Vignali A, Gennarelli N, Manigrasso M, Burati M, Milone F, De Palma GD, Delrio P, Rosati R. Recovery after intracorporeal anastomosis in laparoscopic right hemicolectomy: a systematic review and meta-analysis. *Langenbecks Arch Surg*. 2018 Feb;403(1):1-10. doi: 10.1007/s00423-017-1645-y. Epub 2017 Dec 12. Review.
17. Milone M, Elmore U, Di Salvo E, Delrio P, Bucci L, Ferulano GP, Napolitano C, Angiolini MR, Bracale U, Clemente M, D'ambra M, Luglio G, Musella M, Pace U, Rosati R, Milone F. Intracorporeal versus extracorporeal anastomosis. Results from a multicentre comparative study on 512 right-sided colorectal cancers. *Surg Endosc*. 2015 Aug;29(8):2314-20. doi:



10.1007/s00464-014-3950-7.

18. Leijssen LGJ, Dinaux AM, Amri R, Kunitake H, Bordeianou LG, Berger DL. A Transverse Colectomy is as Safe as an Extended Right or Left Colectomy for Mid-Transverse Colon Cancer. *World J Surg.* 2018;42(10):3381-3389. doi:10.1007/s00268-018-4582-1
19. van Rongen I, Damhuis RAM, van der Hoeven JAB, Plaisier PW. Comparison of extended hemicolectomy versus transverse colectomy in patients with cancer of the transverse colon. *Acta Chir Belg.* 113(2):107-111. <http://www.ncbi.nlm.nih.gov/pubmed/23741929>.
20. Matsuda T, Sumi Y, Yamashita K, et al. Optimal Surgery for Mid-Transverse Colon Cancer: Laparoscopic Extended Right Hemicolectomy Versus Laparoscopic Transverse Colectomy. *World J Surg.* 2018;42(10):3398-3404. doi:10.1007/s00268-018-4612-z
21. Guan X, Zhao Z, Yang M, et al. Whether partial colectomy is oncologically safe for patients with transverse colon cancer: a large population-based study. *Oncotarget.* 2017;8(54):93236-93244. doi:10.18632/oncotarget.21275
22. Milone M, Manigrasso M, Elmore U, et al. Short- and long-term outcomes after transverse versus extended colectomy for transverse colon cancer. A systematic review and meta-analysis. *Int J Colorectal Dis.* 2019;34(2):201-207. doi:10.1007/s00384-018-3186-4

**Table 1.** Patient characteristics

	<b>Segmental</b>	<b>Extended</b>	<b>p value</b>
<b>Age</b>	71.72 ± 12.88	70.46 ± 11.03	0.063
<b>Sex</b>	194/388 (50.3%)	617/1141 (54.1%)	0.023
<b>Male</b>	192/388 (49.7%)	524/1141 (45.9%)	
<b>Female</b>			
<b>BMI</b>	43.69 ± 68.14	42.56 ± 175.98	0.902
<b>ASA score</b>	42/388 (11.1%)	129/1141 (11.2%)	0.738
<b>I</b>	189/388 (49.2%)	594/1141 (51.9%)	
<b>II</b>	142/388 (36.9%)	394/1141 (34.5%)	
<b>III</b>	11/388 (2.8%)	27/1141 (2.4%)	
<b>IV</b>			
<b>T stage</b>	26/388 (6.7%)	71/1141 (6.2%)	0.384
<b>T0</b>	31/388 (8.2%)	114/1141 (9.9%)	
<b>T1</b>	55/388 (14.4%)	193/1141 (16.9%)	
<b>T2</b>	210/388 (54.6%)	567/1141(49.5%)	
<b>T3</b>	62/388 (16.1%)	200/1141 (17.5%)	
<b>T4</b>			
<b>N stage</b>	258/388 (67.3%)	755/1141 (65.9%)	0.515
<b>N0</b>	92/388 (23.7%)	265/1141 (23.2%)	
<b>N1</b>	34/388 (9%)	125/1141 (10.9%)	
<b>N2</b>			

<b>M stage</b>	348/388 (89.7%)	1058/1141 (92.7%)	0.175
<b>M0</b>	40/388 (10.3%)	83/1141 (7.3%)	
<b>M1</b>			

---

Journal Pre-proof

**Table 2.** Recovery after surgery

	<b>Segmental</b>	<b>Extended</b>	<b>p value</b>
<b>Time to flatus</b>	3.74 ± 1.61	3.49 ± 1.76	0.014
<b>Time to food tolerance</b>	4.02 ± 1.60	3.90 ± 2.02	0.216
<b>Time to mobilization</b>	1.55 ± 0.85	1.44 ± 0.90	0.040
<b>Hospital stay</b>	9.69 ± 6.17	8.42 ± 5.27	<0.001

**Table 3.** Complications

	Segmental	Extended	p value
<b>Complications:</b>			0.010
Yes	117/388 (30.1%)	269/1141 (23.6%)	
No	271/388 (69.9%)	872/1141 (76.4%)	
<b>Anemia:</b>			0.025
Yes	8/388 (2.1%)	5/1141 (0.4%)	
No	380/388 (97.9%)	1134/1141 (99.6%)	
<b>Nausea:</b>			0.416
Yes	11/388 (2.8%)	47/1141 (4.1%)	
No	377/388 (97.2%)	1092/1141 (95.9%)	
<b>Wound infection:</b>			0.026
Yes	17/388 (4.4%)	32/1141(2.8%)	
No	371/388 (95.6%)	1107/1141 (97.2%)	
<b>Bleeding:</b>			0.746
Yes	19/388 (4.9%)	50/1141 (4.4%)	
No	369/388 (95.1%)	1080/1141 (95.6%)	
<b>Anastomotic leak:</b>			0.020
Yes	17/388 (4.4%)	25/1141 (2.2%)	
No	371/388 (95.6%)	1114/1141 (97.8%)	
<b>Prolonged ileus:</b>			0.316
Yes	3/388 (0.8%)	22/1141 (1.9%)	
No	385/388 (99.2%)	1117/1141 (98.1%)	

**Table 4.** Complications according to Clavien–Dindo classification

	Complications	Segmental	Extended	p value
<b>Grade</b>				0.005
<b>0</b>		230/388 (59.3%)	827/1141 (72.5%)	
<b>I</b>	<b>Pain</b>	59/388 (15.2%)	124/1141 (10.9%)	
	<b>Nausea and vomiting</b>	24/388 (6.2%)	46/1141 (4.1%)	
	<b>Wound infections</b>	11/388 (2.8%)	47/1141 (4.1%)	
	<b>Others</b>	13/388 (3.3%)	22/1141 (1.9%)	
		11/388 (2.8%)	9/1141 (0.8%)	
<b>II</b>	<b>Wound infections</b>	54/388 (13.9%)	101/1141 (8.9%)	
	<b>Bleeding</b>	4/388 (1%)	10/1141 (0.9%)	
	<b>Others</b>	10/388 (2.6%)	27/1141 (2.4%)	
		40/388 (10.3%)	64/1141 (5.6%)	
<b>III</b>	<b>Anastomotic leak</b>	33/388 (8.5%)	63/1141 (5.5%)	
	<b>Bleeding</b>	17/388 (4.4%)	25/1141 (2.2%)	
	<b>Others</b>	9/388 (2.3%)	23/1141 (2%)	
		7/388 (1.8%)	15/1141 (1.3%)	
<b>IV</b>	<b>ICU management</b>	2/388 (0.5%)	10/1141 (0.9%)	
		0/388 (0%)	2/1141 (0.2%)	
<b>V</b>	<b>Mortality</b>	8/388 (2%)	16/1141 (1.4%)	

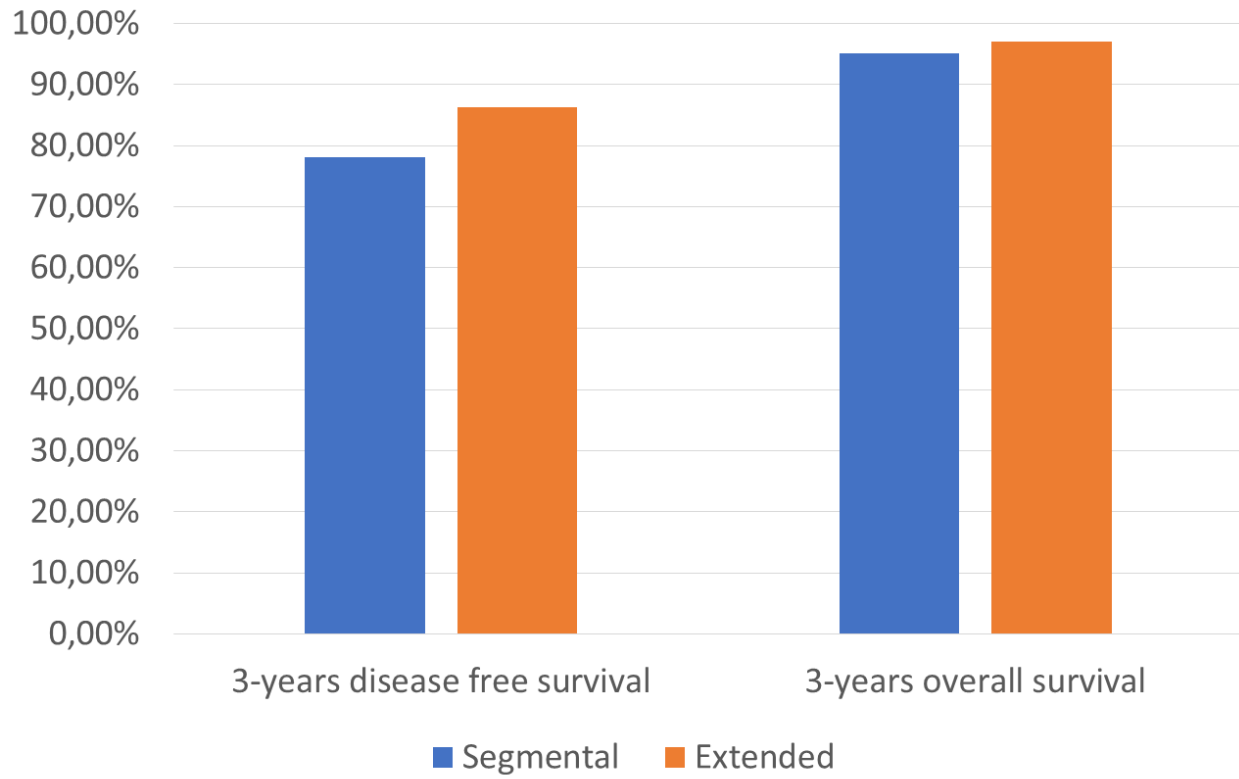
**Table 5.** Pathological outcomes

	<b>Segmental</b>	<b>Extended</b>	<b>p value</b>
<b>Lymph nodes harvested</b>	15.03 ± 9.93	24.58 ± 13.90	<0.001
<b>Metastatic lymph nodes</b>	1.05 ± 2.33	1.25 ± 2.90	0.216
<b>Specimen length</b>	22.84 ± 11.49	35.05 ± 15.09	<0.001
<b>Proximal margin</b>	8.25 ± 6.45	10.16 ± 9.13	<0.001
<b>Distal margin</b>	10.55 ± 8.54	20.84 ± 13.27	<0.001

**Figure 1.** Three-year disease free survival and overall survival.

Journal Pre-proof





Journal