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***Basic Study***

**Plasma MMP-2 and MMP-7 levels are elevated first month after surgery and may promote growth of residual metastases**

Shantha Kumara H *et al*. Plasma MMP-2 and MMP-7

HMC Shantha Kumara, Hiromichi Miyagaki, Sajith A Herath, Erica Pettke, Xiaohong Yan, Vesna Cekic, Richard L Whelan

**HMC Shantha Kumara, Xiaohong Yan, Vesna Cekic, Richard L** **Whelan,** Division of Colon and Rectal Surgery, Department of Surgery, Lenox Hill Hospital, Northwell Health, New York, NY 10028, United States

**Hiromichi Miyagaki,** Department of Gastroenterological Surgery, Osaka University, Suita 565-0862, Osaka, Japan

**Sajith A Herath,** Analytic Department, Novartis, Morris Plains, NJ 07905, United States

**Erica Pettke,** Department of Surgery, Swedish Medical Center, Seattle, WA 98122, United States

**Richard L Whelan,** Department of Surgery, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY 11549, United States

**Author contributions:** Shantha Kumara H contributed to the conception, design, sample processing, statistical analysis and interpretation of data, and revision of the articles; Miyagaki H, Herath SA and Yan X contributed to collection of human material clinical data, revision of the article; Pettke E and Cekic V contributed to human sample collection, processing, analysis and interpretation of data; Whelan RL contributed to the conception, design, interpretation of data, critical revision of the article; all authors drafted the article and made critical revisions and approved the submitted final version of the article to be published.

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**Corresponding author:** **Richard L Whelan, FACS, MD, Professor,** **System Chief,** Division of Colon and Rectal Surgery, Department of Surgery, Lenox Hill Hospital, Northwell Health, Suite 1B, 122 East, 76th Street, New York, NY 10028, United States. rwhelan1@northwell.edu

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**Abstract**

BACKGROUND

MMP-2 also known as gelatinase A and MMP-7 (matrilysin) are members of the zinc-dependent family of MMPs (Matrix metalloproteinase). MMP-2 and MMP-7 are remodeling enzymes that digest extracellular matrix; MMP-2 is extensively expressed during development and is upregulated at sites of tissue damage, inflammation, and in stromal cells of metastatic tumors. MMP-7 is expressed in the epithelial cells and in a variety of cancers including colon tumors. Plasma MMP-2 and MMP-7 levels were assessed before and after minimally invasive colorectal resection for cancer pathology.

AIM

To determine plasma MMP-2 and MMP-7 levels before and after minimally invasive colorectal resection for cancer pathology.

METHODS

Patients enrolled in a plasma bank for whom plasma was available were eligible. Plasma obtained from preoperative (Preop) and postoperative blood samples was used. Only colorectal cancer (CRC) patients who underwent elective minimally invasive cancer resection with preop, post-operative day (POD) 1, 3 and at least 1 late postop sample (POD 7-34) were included. Late samples were bundled into 7 d blocks (POD 7-13, 14-20, *etc.*) and treated as single time points. Plasma MMP-2 and MMP-7 levels were determined *via* enzyme-linked immunosorbent assay in duplicate.

RESULTS

Total 88 minimally invasive CRC resection CRC patients were studied (right colectomy, 37%; sigmoid, 24%; and LAR/AR 18%). Cancer stages were: 1, 31%; 2, 30%; 3, 34%; and 4, 5%. Mean Preop MMP-2 plasma level (ng/mL) was 179.3 ± 40.9 (*n* = 88). Elevated mean levels were noted on POD1 (214.3 ± 51.2, *n* = 87, *P* < 0.001), POD3 (258.0 ± 63.9, *n* = 80, *P* < 0.001), POD7-13 (229.9 ± 62.3, *n* = 65, *P* < 0.001), POD 14-20 (234.9 ± 47.5, *n* = 25, *P* < 0.001), POD 21-27 (237.0 ± 63.5, *n* = 17, *P* < 0.001,) and POD 28-34 (255.4 ± 59.7, *n* = 15, *P* < 0.001). Mean Preop MMP-7 level was 3.9 ± 1.9 (*n* = 88). No significant differences were noted on POD 1 or 3, however, significantly elevated levels were noted on POD 7-13 (5.7 ± 2.5, *n* = 65, *P* < 0.001), POD 14-20 (5.9 ± 2.5, *n* = 25, *P* < 0.001), POD 21-27 (6.1 ± 3.6, *n* = 17, *P* = 0.002) and on POD 28-34 (6.8 ± 3.3, *n* = 15 *P* < 0.001,) *vs* preop levels.

CONCLUSION

MMP-2 levels are elevated for 5 wk and MMP-7 levels elevated for weeks 2-6. The etiology of these changes in unclear, trauma and wound healing likely play a role. These changes may promote residual tumor growth and metastasis.

**Key Words:** Effects of surgery; Colorectal resection; Colorectal cancer; Plasma MMP-2 and MMP-7 levels; Angiogenesis

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**Core Tip:** Our past studies have shown that the levels of 9 plasma proteins that play a role in angiogenesis have been shown to be elevated, vs baseline levels, for 2-5 wk after minimally invasive colorectal cancer resection (MICR). This group of proteins includes vascular endothelial-derived growth factor, placental growth factor, angiopoietin-2, soluble vascular adhesion molecule-1, monocyte chemo-attractant protein-1, chitinase 3-like-1, interleukin-8, CXCL16 and MMP-3 (matrix metalloproteinase-3). We have demonstrated that postoperative plasma from colorectal cancer (CRC) patients stimulates *in vitro* endothelial cell proliferation, migration, and invasion. This manuscript is to demonstrate that proangiogenic proteins, plasma MMP-2 and MMP-7 in CRC patients remain elevated for month after MICR.

**INTRODUCTION**

Colorectal cancer (CRC) accounts for almost 900000 deaths per year worldwide[1,2]. Despite advances in surgery as well as in medical and radiation oncology, recurrence and mortality rates remain high. As regards surgery, there is evidence that tumor resection may indirectly or directly stimulate the growth of residual cancer early postop *via* unclear mechanisms[3-8]. Among other suggested explanations, persistently elevated blood levels of proangiogenic proteins during the early postoperative (Postop) period[9,10] has been proposed as a potential cause of increased tumor growth post-surgery.

In the past decade the levels of at least 9 plasma proteins that play a role in angiogenesis have been shown to be elevated, *vs* baseline levels, for 2-5 wk after minimally invasive CRC resection. Included on this list are vascular endothelial-derived growth factor (VEGF), angiopoeitin-2 (Ang-2), placental growth factor (PIGF), soluble vascular adhesion molecule-1 (sVCAM-1), monocyte chemotactic protein-1 (MCP-1), and matrix metalloproteinase-3 (MMP-3), chitinase 3-like 1 (CHI3L1), interleukin 8 (IL-8) and CXCL16[11-15]. The added finding that plasma from the second and third postop weeks stimulates *in vitro* endothelial cell (EC) proliferation, migration and invasion (all critical to angiogenesis) suggests that post resection plasma is proangiogenic[16,17]. It has been suggested that these systemic changes may stimulate tumor angiogenesis in patients who harbor unknown micrometastases after the primary tumor has been removed.

MMP-2 and MMP-7 are two proteins that play a role in angiogenesis whose postop levels have not been thoroughly studied. Both are members of the diverse zinc dependent MMP family that breaks down extracellular matrix (ECM) proteins. Based on their specific substrate specificities MMP-2 and MMP-7 are grouped in the gelatinase and matrilysin sub families, respectively[18,19]. MMP-2 degrades gelatin and the following ECM components; collagen (types IV, V, VII and X), decorin, elastin, and fibronectin[20,21]. MMP-2 promotes tumor cell invasion and metastasis because of its high specificity for type IV collagen[22,23]. MMP-2 ECM degradation releases VEGF and transforming growth factor β (TGF-β), thus, increasing their bioavailability[24,25]. Transformation of TGF-β into its active form is further supported by MMP-7[26]. Of note, MMP-2 overexpression has been noted in a variety of cancers and has been associated with tumor progression[27-30].

Most MMPs are synthesized in the stroma, however, MMP-7 is produced in normal large bowel epithelium as well as in cancer cells and is associated with tumor invasion and metastasis by virtue of the damage it incurs to the basement membrane. MMP-7, like MMP-2, has a high affinity for numerous ECM proteins[31,32]. MMP-7 is capable of shedding of bioactive cell-surface molecules such as epidermal growth factor (EGFR)[33], heparin binding EGFR (HB-EGFR)[34], Fas-Ligand[35,36] and E-cadherin[32,37]. MMP7 related vascular basement membrane degradation has been shown to facilitate hematogenous metastasis[38].

Elevated MMP-2 and MMP-7 activity has been linked to a poor prognosis in many cancers including CRC[27,28,38-47]. As mentioned, the impact of MICR for CRC on plasma levels of MMP-2 and MMP-7 is unknown. This study’s purpose was to evaluate plasma MMP-2 and MMP-7 levels during first month after MICR for CRC.

**MATERIALS AND METHODS**

***Study population***

CRC patients undergoing elective minimally invasive colorectal resection (MICR) at Mount Sinai West Hospital and New York Presbyterian Hospital between 2007 and 2014 who were enrolled in an IRB approved data/plasma bank (Institutional Review Board of the Mount Sinai School of Medicine, New York; IRB reference NO: GCO1: 16-2619 and Institutional Review Board of the Columbia university medical center, New York; IRB reference NO: AAAA4473) for whom adequate plasma samples were available were included in the study. This tissue bank’s purpose was to assess the physiologic, immunologic, and oncologic ramifications of MIS large bowel resection. Patients included in the current study underwent either laparoscopic-assisted (LAP) or hand assisted laparoscopic colorectal resection. Exclusion criteria included perioperative blood transfusion, recent radio- and/or chemotherapy, and immunosuppression (medication-related, HIV+, *etc.*). Demographic, operative, pathologic, and short term outcome data were prospectively collected. Blood samples were collected preoperative (Preop) and at varying Postop time points.

***Blood sampling and processing***

Blood samples were collected Preop, on post-operative day (POD) 1, 3 and at 1 or more late timepoint (POD 7-34). Only patients for whom sufficient volumes of frozen plasma were available were included in the study. Since most late specimens were obtained post hospital discharge the timing of the samples varied. Consequently, it was necessary to ‘bundle’ late samples into 7 d time blocks (POD7-13, POD14-20, POD21-27, and POD 28-34) that, collectively, were considered as single time points. Blood was collected in heparin-containing tubes and processed within 5-6 h. After centrifugation, plasma samples were stored at -80 °C until utilized.

***Plasma MMP-2 and MMP-7 analysis***

Plasma MMP-2 and MMP-7 levels were analyzed in duplicate using commercially available enzyme-linked immunosorbent assays (ELISA) (R and D Systems, Minneapolis, MN, United States) according to the manufacturer's instructions. MMP-2 and MMP-7 concentrations (ng/mL) were calculated using a standard curve made for each ELISA plate and were reported as mean ± SD.

***Statistical analysis***

Demographic and clinical data are expressed as the mean ± SD for continuous variables. As regards analysis of the MMP-2 and MMP-7 data (Preop *vs* Postop comparisons) the Wilcoxon signed rank test was used. Other comparisons (males *vs* females, surgical methods, *etc.*) were carried out using the Mann Whitney test. Correlation between plasma MMP-2/MMP-7 Levels and age, T, N, M stage, incision size and length of surgery were assessed by the Spearman's rank correlation coefficient (rs). Data analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, United States).

**RESULTS**

A total of 88 CRC patients were studied [44 males/44 female; mean age 66.38 ± 12.83 years; colon cancer, 67 patients (76%); rectal cancer, 21 (24%)]. Sixty-two percent underwent laparoscopic assisted resection [mean incision length (IL), 7.3 ± 3.7 cm] whereas 38% had a hand-assisted MIS procedure (mean IL 10.8 ± 4.3 cm) (Table 1). The types of resection performed were; right (37%), sigmoid (24%) and rectal resection (18%). The cancer stage breakdown was: Stage 1, 31%; Stage 2, 30%; stage 3, 34%; and stage 4, 5%. There were no perioperative deaths, anastomotic leaks or intraabdominal abscesses. There was 2 superficial SSI’s, 1 pneumonia, 1 pulmonary edema, 1 acute renal failure, 1 seroma, 7 ileus, 4 UTI’s, 1 phlebitis, 3 atelectasis, 6 cases urinary retention, and 4 other complications.

The mean Preop MMP-2 level (ng/mL) was 179.3 ± 40.9 (*n* = 88). Significantly elevated mean plasma levels were noted on POD 1 (214.3 ± 51.2, *n* = 87, *P* ≤ 0.001), POD 3 (258.0 ± 63.9, *n* = 80, *P* ≤ 0.001), POD 7-13 (229.9 ± 62.3, *n* = 65, *P* ≤ 0.001), POD 14-20 (234.9 ± 47.5, *n* = 25, *P* ≤ 0.001), POD 21-27 (237.0 ± 63.5, *n* = 17, *P* < 0.001) and on POD 28-34 time point (255.4 ± 59.7, *n* = 15, *P* < 0.001) (Figure 1). The mean Preop MMP-7 level (ng/mL) was 3.9 ± 1.9 (*n* = 88). When compared to Preop levels, no significant differences were noted on POD 1 or 3, however, significantly elevated mean plasma levels were noted on POD 7-13 (5.7 ± 2.5, *n* = 65, *P* ≤ 0.001), POD 14-20 (5.9 ± 2.5, *n* = 25, *P* ≤ 0.001), POD 21-27 (6.1 ± 3.6, *n* = 17, *P* = 0.002) and on POD 28-34 (6.8 ± 3.3, *n* = 15, *P* < 0.001) when compared to Preop levels (Figure 2).

Of note regarding the results, because the “*n*” for each time point varied for both MMP-2 and MMP-7, the Preop mean protein values are different at each time point. Because of this, as regards the bar graph figures, at each timepoint, in addition to a bar showing the postop result, there is an adjacent bar (on the left) providing the mean preop result.

Of note, when the postop results of the rectal and colon cancer subgroups were compared, no significant differences were noted for either protein. Likewise, the choice of surgical method (laparoscopic *vs* hand-assisted laparoscopic) did not significantly influence the Postop plasma levels of these 2 proteins.

Correlation of MMP-2 and MMP-7 Preop and Postop (POD) time point data *vs* (T), (N) and pathological stage were carried out. Of note, there were only four (*n* = 4) stage 4 patients in the study. No significant correlation was found between preop or Postop time point MMP-2 levels with (T), (N) or pathological stage except at the POD 14-21 time point. MMP-2 levels on POD 14-21 significantly correlated with T stage (*P* = 0.002) N stage (*P* = 0.02) and with final pathological stage (*P* = 0.01). Regarding MMP-7, no significant correlation between Preop and Postop levels and (T), N or pathological stage was found.

Preop and Postop levels of MMP-2 and MMP-7 in node positive and node negative patients were compared. MMP-2 levels of node negative group was significantly higher at POD 14-21 time point compared to node positive group. No other significant difference between the node positive and node negative subgroups were found at any other time points for either MMP-2 or MMP-7.

**DISCUSSION**

As mentioned, whereas the vast majority of surgery-related blood protein alterations resolve in 2-5 d, plasma levels of at least 8 proteins have been shown to be persistently elevated for up to 5 wk after MICR[11-15]. Of note, all of these proteins have proangiogenic effects and plasma from the 2nd and 3rd postop weeks has been shown to stimulate EC invasion, migration, and proliferation which are critical steps in neovascularization[16,17]. These findings raise the possibility that the proangiogenic postop plasma might stimulate tumor angiogenesis in residual metastases, thus stimulating tumor growth early Postoply. This study was undertaken to determine the impact of colorectal resection on blood levels of 2 other proteins that, amongst other effects, play a role in angiogenesis.

Plasma MMP-2 and MMP-7 levels were determined Preop and for over one month post-operatively in CRC patients who underwent MICR. Mean MMP-2 levels were found to be significantly elevated during weeks 1 through 5 after surgery (change from mean baseline varied from 22% to 43%). MMP-2, therefore, fits the pattern noted for almost all of the other blood proteins noted to have long duration elevations, namely both early and late postop increases. MMP-7 is unique because although its levels are significantly increased during weeks 2-5 (change from mean baseline varied from 41%-46%), during the first 3 d after surgery plasma levels were not significantly altered. The MMP-7 results support the concept that, perhaps, that the etiology of the early and late protein elevations are different.

As mentioned, the vast majority of surgery related blood protein compositional changes resolve in 1-7 d. IL-6, IL-2, tumor necrosis factor, C-reactive protein, fibroblast growth factor, hepatocyte growth factor, angiostatin and endostatin are examples of proteins whose levels are transiently elevated early after surgery[48]. The etiology of these short lived blood protein elevations is likely to include anesthesia, surgical trauma, and the acute inflammatory response. As mentioned, longer duration plasma elevations have been noted for VEGF, Ang-2, PIGF, sVCAM-1, MCP-1, CHI3L1, MMP-3 and IL-8[11-15]. The etiology of the later postop plasma changes is unclear, however, there is evidence that at least 1 source of the added proteins are the healing wounds. In a study that simultaneously measured perioperative levels of 8 proangiogenic proteins in both the blood and fluid from surgical wounds for up to 3 wk after MICR, it was noted that wound fluid protein levels were 3-40 times higher than plasma levels which, in turn, were significantly elevated from preop plasma baseline levels[49]. It is postulated that the notably increased levels of these proteins in the wounds are the result of healing related angiogenesis; as a result of diffusion along concentration gradients, blood levels of these proteins subsequently increase. The persistent wound fluid elevations of these proteins also confirms that angiogenesis plays a prominent role in wound healing. Because both MMP-2 and MMP-7 play roles in neovascularization[50-52], the authors conjecture, without evidence, that the 4-5 wk long plasma elevations of these proteins postop are likely related to the surgical wounds.

Of note, all of the long duration proteins mentioned above are capable of supporting cancer growth and metastasis[11-15,16]; most have also been noted to be overexpressed by a variety of human cancers[50-62]. Further, the mean pre-resection plasma levels of almost all of the long duration proteins have been shown to be significantly higher in cancer patients than in cancer-free patients. MMP-2 and MMP-7 are similar in these regards.

In separate studies from our lab, preop MMP-2 and MMP-7 plasma levels were determined and compared in CRC and benign disease patients (MMP-2, CRC *n* = 168, Benign *n* = 128; MMP-7, CRC and Benign groups, *n* = 120 each). The mean preop levels in the cancer groups were significantly higher for both MMP-2 (24.5% higher than benign group) and MMP-7 (51.1% increase).

Further, increased expression of MMP-2 has been noted in CRC and other cancers[27,28]. Of note, a shortened relapse-free survival has been noted in early stage non-small cell lung cancer patients whose tumor expression of MMP-2 was high[27]. Further, it has been shown that elevated serum levels of MMP-2 are an independent predictor of overall survival in node positive breast cancer[63].

As regards *in vitro* studies, it has been shown that decreasing MMP-2 expression in CRC cell lines by adding lentiviral-mediated shRNA markedly reduced tumor cell proliferation and invasiveness[22]. The same group showed that protein levels of VEGF and MT1-MMP were markedly reduced in MMP-2-expression suppressed CRC cells *vs* control cells; thus, MMP-2 impacts tumor cell proliferation and invasion[64-66]. MMP-2 also plays a role in wound healing. Using a double knockout mouse model, Hingorani *et al*[67] have shown that MMP-2 and MMP-9 are involved in multiple overlapping activities critical to both epithelial wound healing and tumor progression *in vivo.* Karim *et al*[68] showed that MMP-2 expression is a reliable indicator of clinical wound healing. Thus, MMP-2 plays a role in both cancer development and wound healing.

As regards MMP-7, it has been shown that upregulation of MMP-7 and other MMPs in tumors as well as increased blood levels of these proteins have an adverse association with cancer survival[69-72]. Decreasing MMP-7 levels *via* antisense RNA mediated knockdown or by knockout in mice reduces tumor incidence, while increased MMP-7 expression leads to increased tumor formation[73-75]. MMP-7 also plays a role in the shedding of cell-surface molecules including EGFR[33], HB-EGF[34], E-cadherin[37] and Fas ligand[35,36] which suggests that MMP-7 plays a role in tumor invasion and metastasis. Also, elevated MMP-7 expression is associated with aggressive CRC tumor cell behavior, *in vitro*[39,75-78]. Recombinant MMP-7 accelerates EC proliferation in a dose dependent manner which confirms its role in angiogenesis which is critical to both wound healing and tumor growth[79].

To summarize, blood levels of MMP-2 and MMP-7, which play roles in both wound healing and tumor growth are elevated after surgery for over 1 mo. There are now a total of 10 proangiogenic proteins shown to be elevated post MICR for up to 5 wk. It is the authors’ position that the first month after MICR (or any major operation) may be a dangerous period for cancer patients with residual disease. Of note, a number of investigators have suggested that cancer excision[80] and/or surgical trauma[81] may stimulate the development of recurrences or the growth of residual lesions early postoperatively[3-8,81]. Kaibori *et al*[5] noted, within a short period of time after surgery, new liver lesions in 31% of CRC patients presenting with synchronous liver metastases who underwent resection of the colon primary alone. Similarly, Yoshidome *et al*[6], as regards a similar patient population (CRC patients with synchronous liver lesions), noted new liver lesions on computed tomography in 43% of patients who underwent staged resection (median time between surgery and scan 2.4 mo). Also, Slesser *et al*[3] noted that resection of the colon tumor alone in similar synchronous disease patients was associated with disease progression. A variety of mechanisms for accelerated tumor growth/development have been proposed and include: Immunosuppression, removal of primary tumor generated circulating growth suppression factors, surgery induced spread of viable cancer cells and stimulated tumor angiogenesis[82].

Perhaps, the administration of anti-cancer agents during the first month after surgery would make sense. Presently, adjuvant chemotherapy is usually started 4-8 wk after surgery. The use of standard chemotherapeutic agents is problematic since these agents may interfere with wound and anastomotic healing. Immunotherapies (vaccines, select monoclonal antibodies, immunomodulators) and other anti-cancer agents that do not interfere with wound healing, however, might be given during the first month after surgery.

***Limitations of study***

Obtaining post hospital discharge blood samples is a challenge from several perspectives. These specimens are mainly obtained during follow up office visits and since the timing of these visits vary, it was not possible to get late samples on the same postop days. Therefore, by necessity, late samples were grouped into 7 d time blocks that were considered as individual timepoints. Also, because contact between MD and patients wane after the first follow up appointment, there were fewer opportunities to obtain late first month samples. One result is that the “*n*” for weeks 2-5 time is substantially less than the starting number and is ever diminishing. Also, ideally, open (lengthy incision) patients would have been included so that the impact of the abdominal wall trauma element of these operations on plasma MMP2/7 levels could be determined. Lastly, because there is no long term outcome data it is not possible to correlate postop MMP 2/7 levels with recurrence rates or the time to recurrence.

**CONCLUSION**

Significant and enduring plasma elevations over baseline were noted for 5 wk after MICR for MMP-2 (entire period) and for MMP-7 (weeks 2-5 only). No correlation between postop levels and cancer location (rectal *vs* colon), disease stage, or MIS surgical method used was noted. MMP-2 and 7 join the list of proteins with proangiogenic and tumor promoting effects and associations that are persistently elevated during the first month after MICR. Although unproven, these conditions may stimulate the growth of residual tumor deposits early after surgery. Further studies are warranted to further investigate the postop time period and to determine the clinical importance, if any, of these systemic changes.

**ARTICLE HIGHLIGHTS**

***Research background***

Major abdominal surgery is known to results a brief period of immunosuppression and short lived plasma protein alterations. In past decade it has been shown that minimally invasive colorectal cancer resection (MICR) is associated with elevated levels of at least 8 plasma proteins after surgery that play major role in angiogenesis. Angiogenic proteins included on this list are vascular endothelial-derived growth factor (VEGF), angiopoeitin-2, placental growth factor, soluble vascular adhesion molecule-1 (sVCAM-1), monocyte chemotactic protein-1 (MCP-1), interleukin 8 (IL-8) and matrix metalloproteinase-3 (MMP-3). The plasma from the second and third postoperative weeks stimulates *in vitro* endothelial cell proliferation, migration and invasions which are critical for angiogenesis suggests that post colorectal surgery plasma bears proangiogenic property. The impact of MICR for colorectal cancer (CRC) on plasma levels of MMP-2 and MMP-7 is unknown.

***Research motivation***

MMP-2 and MMP-7 are two proteins that play a key role in angiogenesis whose postoperative blood levels have not been thoroughly studied investigated. Both proteins are members of the large zinc dependent MMP family that breaks down extracellular matrix (ECM) proteins. Based on their substrate specificities MMP-2 and MMP-7 are grouped in the gelatinase and matrilysin sub families, respectively. MMP-2 degrades gelatin and the following ECM components; collagen (types IV, V, VII and X), decorin, elastin, and fibronectin. MMP-2 ECM degradation releases increase bioavailability of angiogenic VEGF and transforming growth factor β. MMP-2 promotes tumor cell invasion and metastasis because of its high specificity for type IV collagen. MMP-7 is produced in normal large bowel epithelium as well as in cancer cells and is associated with tumor invasion and metastasis by virtue of the damage it incurs to the basement membrane. MMP-7, like MMP-2, has a high affinity for numerous ECM proteins. MMP-7 related vascular basement membrane degradation has been shown to facilitate hematogenous metastasis. Overexpression of MMP-2 and MMP-7 activity has been linked to a poor prognosis in many cancers including CRC has been associated with tumor progression. The impact of MICR for CRC on plasma levels of MMP-2 and MMP-7 is unknown. Motivation of this study was to assess plasma MMP-2 and MMP-7 levels during first month after MICR for CRC.

***Research objectives***

The objective of this study was to determine plasma MMP-2 and MMP-7 levels during first month after minimally invasive colorectal resection at various postoperative time points, which include the first blood draw on the day of operation before surgery, the second on post-operative day 1 (POD 1), the third on POD 3, and additional four time points between POD 7 and POD 34. The hypothesis was that if blood levels of proangiogenic MMP-2 and MMP-7, which play major roles in wound healing, remain elevated for month after surgery would confirm that surgery has long lasting systemic manifestations that have the potential to influence growth in residual cancer after surgery and metastasis.

***Research methods***

This study analyzed colorectal patients who underwent elective surgery for cancer pathology. Plasma was obtained from IRB approved perioperative tissue and data bank. The clinical, demographic and pathologic data was prospectively gathered. Blood samples were obtained preoperative (Preop) and at varying postop time points and were stored at -80 °C. Blood samples were obtained from consented patients Preop and at varying postop time points. Late post op samples were collected during follow-up visits. Because of the fewer specimens taken after POD 3, the 7 d blocks were bundled and considered as single time points (POD 7-13, POD 14-20, POD21-27, and POD 28-34). Plasma MMP2 and MMP7 protein levels were determined in duplicate *via* highly specific commercially available Enzyme-linked Immunosorbent Assays. Demographic and clinical data are expressed as the mean ± SD for continuous variables. As the Wilcoxon signed rank test was used for MMP-2 and MMP-7 data preop *vs* postop comparisons. Other comparisons (males *vs* females, surgical methods, *etc.*) were carried out using the Mann Whitney test. Correlation between plasma MMP-2/MMP-7 levels and age, incision size and length of surgery were assessed by the Spearman's rank correlation coefficient (rs).

***Research results***

A total of 88 CRC patients were studied. Majority of patients (62%) underwent laparoscopic assisted resection whereas 38% had a hand-assisted MIS procedure. The most common resection performed was right colectomy (37%) followed by sigmoid (24%) and rectal resection (18%). The cancer stage breakdown was: Stage 1, 31%; Stage 2, 30%; stage 3, 34%; and stage 4, 5%. The mean Preop MMP-2 level (ng/mL) was 179.3 ± 40.9. Significantly elevated mean plasma levels were noted on POD 1 (214.3 ± 51.2, *P* ≤ 0.0001), POD 3 (258.0 ± 63.9, *P* ≤ 0.0001), POD 7-13 (229.9 ± 62.3, *P* ≤ 0.0001), POD 14-20 (234.9 ± 47.5, *P* ≤ 0.0001), POD 21-27 (237.0 ± 63.5, *P* = 0.0008) and on POD 28-34 time point (255.4 ± 59.7, *P* = 0.0002). The mean Preop MMP-7 level (ng/mL) was 3.9 ± 1.9. When compared to Preop levels, no significant differences were noted on POD 1 or 3, however, significantly elevated mean plasma levels were noted on POD 7-13 (5.7 ± 2.5, *P* ≤ 0.0001), POD 14-20 (5.9 ± 2.5, *P* ≤ 0.0001), POD 21-27 (6.1 ± 3.6, *P* = 0.002) and on POD 28-34 (6.8 ± 3.3, *P* = 0.0006) when compared to Preop levels. Furthermore, when the postop results of the rectal and colon cancer subgroups were compared, no significant differences were noted for either protein. Likewise, the choice of surgical method (laparoscopic *vs* hand-assisted laparoscopic) did not significantly influence the postoperative plasma levels of these 2 proteins.

***Research conclusions***

This study reports plasma MMP-2 levels are elevated for 5 wk and MMP-7 levels elevated for weeks 2-6 after minimally invasive CRC for cancer pathology. Mean MMP-2 levels were found to be significantly elevated during weeks 1 through 5 after surgery (change from mean baseline varied from 22% to 43%). This study revealed that MMP-2, therefore, fits the pattern noted for almost all of the other blood proteins (such as VEGF, PlGF, ANG2, sVCAM-1, MCP1, CHI3L1, MMP-3, IL-8) noted to have long duration elevations, namely both early and late postop increases. MMP-7 is unique because although its levels are significantly increased during weeks 2-5 (change from mean baseline varied from 41%-46%), during the first 3 d after surgery plasma levels were not significantly altered. The MMP-7 results support the concept that, perhaps, that the etiology of the early and late protein elevations are different. The etiology of these short lived blood protein elevations is likely to include anesthesia, surgical trauma, and the acute inflammatory response. The etiology of the later postop plasma changes is unclear, however, there is evidence that at least 1 source of the added proteins are the healing wounds. It is postulated that the notably increased levels of these proteins in the wounds are the result of healing related angiogenesis; as a result of diffusion along concentration gradients, blood levels of these proteins subsequently increase.  The persistent wound fluid elevations of these proteins also confirms that angiogenesis plays a prominent role in wound healing. It is the authors’ position that the first month after MICR (or any major operation) may be a dangerous period for cancer patients with residual disease due to elevated levels blood levels of MMP-2 and MMP-7, which play roles in both wound healing and tumor growth.

***Research perspectives***

Plasma MMP-2 and MMP-7, which play important roles in both wound healing and tumor growth, are elevated after surgery for over 1 mo. The findings of this study will add 2 more angiogenic proteins to the growing list of proangiogenic proteins which includes VEGF, PlGF, ANG2, sVCAM-1, MCP1, CHI3L1, MMP-3 and IL-8 that shown to be elevated post MICR for up to 5 wk. The results of this study add further evidence and support for the concept that the first month after MICR (or any major operation) may be a dangerous period for cancer patients with residual disease. All of these proteins have proangiogenic effects and plasma from the 2nd and 3rd postop weeks has been shown to stimulate Endothelial Cell invasion, migration, and proliferation which are critical steps in neovascularization. Additionally, previous study showed that simultaneously measured perioperative levels of 8 proangiogenic proteins in both the blood and fluid from surgical wounds for up to 3 wk after MICR, it was noted that wound fluid protein levels were 3-40 times higher than plasma levels which, in turn, were significantly elevated from preop plasma baseline levels. It is postulated that the notably increased levels of these proteins in the wounds are the result of healing related angiogenesis; as a result of diffusion along concentration gradients, blood levels of these proteins subsequently increase. The persistent wound fluid elevations of these proteins also confirms that angiogenesis plays a prominent role in wound healing. These findings raise the possibility that the elevated proangiogenic postop plasma might stimulate tumor angiogenesis in residual metastases, thus stimulating tumor growth early postoperatively. This study further supports the idea of administration of anti-cancer agents during the first month after surgery. Adjuvant chemotherapy is usually started 4-8 wk after surgery. The use of standard chemotherapeutic agents is problematic since these agents may interfere with wound and anastomotic healing. Immunotherapies (vaccines, select monoclonal antibodies, immunomodulators) and other anti-cancer agents that do not interfere with wound healing, however, might be given during the first month after surgery.

**REFERENCES**

1 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]

2 **Matsuda T**, Yamashita K, Hasegawa H, Oshikiri T, Hosono M, Higashino N, Yamamoto M, Matsuda Y, Kanaji S, Nakamura T, Suzuki S, Sumi Y, Kakeji Y. Recent updates in the surgical treatment of colorectal cancer. *Ann Gastroenterol Surg* 2018; **2**: 129-136 [PMID: 29863145 DOI: 10.1002/ags3.12061]

3 **Slesser AA**, Khan F, Chau I, Khan AZ, Mudan S, Tekkis PP, Brown G, Rao S. The effect of a primary tumour resection on the progression of synchronous colorectal liver metastases: an exploratory study. *Eur J Surg Oncol* 2015; **41**: 484-492 [PMID: 25638603 DOI: 10.1016/j.ejso.2014.12.009]

4 **Lange PH**, Hekmat K, Bosl G, Kennedy BJ, Fraley EE. Acclerated growth of testicular cancer after cytoreductive surgery. *Cancer* 1980; **45**: 1498-1506 [PMID: 6153570 DOI: 10.1002/1097-0142(19800315)45:6<1498::aid-cncr2820450633>3.0.co;2-7]

5 **Kaibori M**, Iwamoto S, Ishizaki M, Matsui K, Saito T, Yoshioka K, Hamada Y, Kwon AH. Timing of resection for synchronous liver metastases from colorectal cancer. *Dig Dis Sci* 2010; **55**: 3262-3270 [PMID: 20112062 DOI: 10.1007/s10620-009-1124-6]

6 **Yoshidome H**, Kimura F, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, Mitsuhashi N, Takeuchi D, Iida A, Miyazaki M. Interval period tumor progression: does delayed hepatectomy detect occult metastases in synchronous colorectal liver metastases? *J Gastrointest Surg* 2008; **12**: 1391-1398 [PMID: 18491195 DOI: 10.1007/s11605-008-0540-9]

7 **Baum M**. Does surgery disseminate or accelerate cancer? *Lancet* 1996; **347**: 260 [PMID: 8551898 DOI: 10.1016/s0140-6736(96)90433-x]

8 **Maniwa Y**, Kanki M, Okita Y. Importance of the control of lung recurrence soon after surgery of pulmonary metastases. *Am J Surg* 2000; **179**: 122-125 [PMID: 10773147 DOI: 10.1016/s0002-9610(00)00244-0]

9 **Allendorf JD**, Bessler M, Horvath KD, Marvin MR, Laird DA, Whelan RL. Increased tumor establishment and growth after open *vs* laparoscopic surgery in mice may be related to differences in postoperative T-cell function. *Surg Endosc* 1999; **13**: 233-235 [PMID: 10064753 DOI: 10.1007/s004649900952]

10 **O'Reilly MS**, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH, Folkman J. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell* 1994; **79**: 315-328 [PMID: 7525077 DOI: 10.1016/0092-8674(94)90200-3]

11 **Belizon A**, Balik E, Horst P, Feingold D, Arnell T, Azarani T, Cekic V, Skitt R, Kumara S, Whelan RL. Persistent elevation of plasma vascular endothelial growth factor levels during the first month after minimally invasive colorectal resection. *Surg Endosc* 2008; **22**: 287-297 [PMID: 18204877 DOI: 10.1007/s00464-007-9725-7]

12 **Shantha Kumara HM**, Tohme ST, Herath SA, Yan X, Senagore AJ, Nasar A, Kalady MF, Baxter R, Whelan RL. Plasma soluble vascular adhesion molecule-1 Levels are persistently elevated during the first month after colorectal cancer resection. *Surg Endosc* 2012; **26**: 1759-1764 [PMID: 22219007 DOI: 10.1007/s00464-011-2112-4]

13 **Shantha Kumara HM**, Myers EA, Herath SA, Jang JH, Njoh L, Yan X, Kirchoff D, Cekic V, Luchtefeld M, Whelan RL. Plasma monocyte chemotactic protein-1 remains elevated after minimally invasive colorectal cancer resection. *World J Gastrointest Oncol* 2014; **6**: 413-419 [PMID: 25320658 DOI: 10.4251/wjgo.v6.i10.413]

14 **Shantha Kumara HM**, Gaita D, Miyagaki H, Yan X, Hearth SA, Njoh L, Cekic V, Whelan RL. Plasma chitinase 3-like 1 is persistently elevated during first month after minimally invasive colorectal cancer resection. *World J Gastrointest Oncol* 2016; **8**: 607-614 [PMID: 27574553 DOI: 10.4251/wjgo.v8.i8.607]

15 **Shantha Kumara HM**, Gaita DJ, Miyagaki H, Yan X, Herath SA, Cekic V, Whelan RL. Minimally invasive colorectal resection is associated with significantly elevated levels of plasma matrix metalloproteinase 3 (MMP-3) during the first month after surgery which may promote the growth of residual metastases. *Surg Endosc* 2014; **28**: 3322-3328 [PMID: 24939159 DOI: 10.1007/s00464-014-3612-9]

16 **Kumara HM**, Feingold D, Kalady M, Dujovny N, Senagore A, Hyman N, Cekic V, Whelan RL. Colorectal resection is associated with persistent proangiogenic plasma protein changes: postoperative plasma stimulates *in vitro* endothelial cell growth, migration, and invasion. *Ann Surg* 2009; **249**: 973-977 [PMID: 19474682 DOI: 10.1097/SLA.0b013e3181a6cd72]

17 **Shantha Kumara HM**, Kirchoff D, Naffouje S, Grieco M, Herath SA, Dujovny N, Kalady MF, Hyman N, Njoh L, Whelan RL. Plasma from the second and third weeks after open colorectal resection for cancer stimulates *in vitro* endothelial cell growth, migration, and invasion. *Surg Endosc* 2012; **26**: 790-795 [PMID: 22083320 DOI: 10.1007/s00464-011-1953-1]

18 **Löffek S**, Schilling O, Franzke CW. Series "matrix metalloproteinases in lung health and disease": Biological role of matrix metalloproteinases: a critical balance. *Eur Respir J* 2011; **38**: 191-208 [PMID: 21177845 DOI: 10.1183/09031936.00146510]

19 **Patterson BC**, Sang QA. Angiostatin-converting enzyme activities of human matrilysin (MMP-7) and gelatinase B/type IV collagenase (MMP-9). *J Biol Chem* 1997; **272**: 28823-28825 [PMID: 9360944 DOI: 10.1074/jbc.272.46.28823]

20 **Collier IE**, Wilhelm SM, Eisen AZ, Marmer BL, Grant GA, Seltzer JL, Kronberger A, He CS, Bauer EA, Goldberg GI. H-ras oncogene-transformed human bronchial epithelial cells (TBE-1) secrete a single metalloprotease capable of degrading basement membrane collagen. *J Biol Chem* 1988; **263**: 6579-6587 [PMID: 2834383]

21 **Chow AK**, Cena J, Schulz R. Acute actions and novel targets of matrix metalloproteinases in the heart and vasculature. *Br J Pharmacol* 2007; **152**: 189-205 [PMID: 17592511 DOI: 10.1038/sj.bjp.0707344]

22 **Dong W**, Li H, Zhang Y, Yang H, Guo M, Li L, Liu T. Matrix metalloproteinase 2 promotes cell growth and invasion in colorectal cancer. *Acta Biochim Biophys Sin (Shanghai)* 2011; **43**: 840-848 [PMID: 21968416 DOI: 10.1093/abbs/gmr085]

23 **Quintero-Fabián S**, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA, Alvarez-Sánchez ME. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. *Front Oncol* 2019; **9**: 1370 [PMID: 31921634 DOI: 10.3389/fonc.2019.01370]

24 **Page-McCaw A**, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol* 2007; **8**: 221-233 [PMID: 17318226 DOI: 10.1038/nrm2125]

25 **Bergers G**, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, Tanzawa K, Thorpe P, Itohara S, Werb Z, Hanahan D. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol* 2000; **2**: 737-744 [PMID: 11025665 DOI: 10.1038/35036374]

26 **Mott JD**, Werb Z. Regulation of matrix biology by matrix metalloproteinases. *Curr Opin Cell Biol* 2004; **16**: 558-564 [PMID: 15363807 DOI: 10.1016/j.ceb.2004.07.010]

27 **Passlick B**, Sienel W, Seen-Hibler R, Wöckel W, Thetter O, Mutschler W, Pantel K. Overexpression of matrix metalloproteinase 2 predicts unfavorable outcome in early-stage non-small cell lung cancer. *Clin Cancer Res* 2000; **6**: 3944-3948 [PMID: 11051242]

28 **Ren F**, Tang R, Zhang X, Madushi WM, Luo D, Dang Y, Li Z, Wei K, Chen G. Overexpression of MMP Family Members Functions as Prognostic Biomarker for Breast Cancer Patients: A Systematic Review and Meta-Analysis. *PLoS One* 2015; **10**: e0135544 [PMID: 26270045 DOI: 10.1371/journal.pone.0135544]

29 **Kubben FJ**, Sier CF, van Duijn W, Griffioen G, Hanemaaijer R, van de Velde CJ, van Krieken JH, Lamers CB, Verspaget HW. Matrix metalloproteinase-2 is a consistent prognostic factor in gastric cancer. *Br J Cancer* 2006; **94**: 1035-1040 [PMID: 16538217 DOI: 10.1038/sj.bjc.6603041]

30 **Azevedo Martins JM**, Rabelo-Santos SH, do Amaral Westin MC, Zeferino LC. Tumoral and stromal expression of MMP-2, MMP-9, MMP-14, TIMP-1, TIMP-2, and VEGF-A in cervical cancer patient survival: a competing risk analysis. *BMC Cancer* 2020; **20**: 660 [PMID: 32669083 DOI: 10.1186/s12885-020-07150-3]

31 **Woessner JF Jr**, Taplin CJ. Purification and properties of a small latent matrix metalloproteinase of the rat uterus. *J Biol Chem* 1988; **263**: 16918-16925 [PMID: 3182822]

32 **Miyazaki K**, Hattori Y, Umenishi F, Yasumitsu H, Umeda M. Purification and characterization of extracellular matrix-degrading metalloproteinase, matrin (pump-1), secreted from human rectal carcinoma cell line. *Cancer Res* 1990; **50**: 7758-7764 [PMID: 2253219]

33 **Mimori K**, Yamashita K, Ohta M, Yoshinaga K, Ishikawa K, Ishii H, Utsunomiya T, Barnard GF, Inoue H, Mori M. Coexpression of matrix metalloproteinase-7 (MMP-7) and epidermal growth factor (EGF) receptor in colorectal cancer: an EGF receptor tyrosine kinase inhibitor is effective against MMP-7-expressing cancer cells. *Clin Cancer Res* 2004; **10**: 8243-8249 [PMID: 15623600 DOI: 10.1158/1078-0432.CCR-04-0849]

34 **Yu WH**, Woessner JF Jr, McNeish JD, Stamenkovic I. CD44 anchors the assembly of matrilysin/MMP-7 with heparin-binding epidermal growth factor precursor and ErbB4 and regulates female reproductive organ remodeling. *Genes Dev* 2002; **16**: 307-323 [PMID: 11825873 DOI: 10.1101/gad.925702]

35 **Powell WC**, Fingleton B, Wilson CL, Boothby M, Matrisian LM. The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis. *Curr Biol* 1999; **9**: 1441-1447 [PMID: 10607586 DOI: 10.1016/s0960-9822(00)80113-x]

36 **Vargo-Gogola T**, Crawford HC, Fingleton B, Matrisian LM. Identification of novel matrix metalloproteinase-7 (matrilysin) cleavage sites in murine and human Fas ligand. *Arch Biochem Biophys* 2002; **408**: 155-161 [PMID: 12464266 DOI: 10.1016/s0003-9861(02)00525-8]

37 **Noë V**, Fingleton B, Jacobs K, Crawford HC, Vermeulen S, Steelant W, Bruyneel E, Matrisian LM, Mareel M. Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. *J Cell Sci* 2001; **114**: 111-118 [PMID: 11112695]

38 **Szarvas T**, Becker M, vom Dorp F, Gethmann C, Tötsch M, Bánkfalvi A, Schmid KW, Romics I, Rübben H, Ergün S. Matrix metalloproteinase-7 as a marker of metastasis and predictor of poor survival in bladder cancer. *Cancer Sci* 2010; **101**: 1300-1308 [PMID: 20180812 DOI: 10.1111/j.1349-7006.2010.01506.x]

39 **Wang K,** Sun XJ, Li SG, Shang WH, Jia PB, Feng HA. Expressions of matrix metalloproteinase 2 and carbohydrate antigen 50 in colorectal carcinoma, transitional mucosa and normal colorectal mucosa and its clinical significance. *Zhongguo Puwai Jichu Yu Linchuang Zazhi* 2006; **13**: 417-420

40 **Mori M**, Barnard GF, Mimori K, Ueo H, Akiyoshi T, Sugimachi K. Overexpression of matrix metalloproteinase-7 mRNA in human colon carcinomas. *Cancer* 1995; **75**: 1516-1519 [PMID: 7889484 DOI: 10.1002/1097-0142(19950315)75:6+<1516::aid-cncr2820751522>3.0.co;2-7]

41 **Polistena A**, Cucina A, Dinicola S, Stene C, Cavallaro G, Ciardi A, Orlando G, Arena R, D'Ermo G, Cavallaro A, Johnson LB, De Toma G. MMP7 expression in colorectal tumours of different stages. *In Vivo* 2014; **28**: 105-110 [PMID: 24425843]

42 **Maurel J**, Nadal C, Garcia-Albeniz X, Gallego R, Carcereny E, Almendro V, Mármol M, Gallardo E, Maria Augé J, Longarón R, Martínez-Fernandez A, Molina R, Castells A, Gascón P. Serum matrix metalloproteinase 7 Levels identifies poor prognosis advanced colorectal cancer patients. *Int J Cancer* 2007; **121**: 1066-1071 [PMID: 17487834 DOI: 10.1002/ijc.22799]

43 **Luca M**, Huang S, Gershenwald JE, Singh RK, Reich R, Bar-Eli M. Expression of interleukin-8 by human melanoma cells up-regulates MMP-2 activity and increases tumor growth and metastasis. *Am J Pathol* 1997; **151**: 1105-1113 [PMID: 9327744]

44 **Elkin M**, Ariel I, Miao HQ, Nagler A, Pines M, de-Groot N, Hochberg A, Vlodavsky I. Inhibition of bladder carcinoma angiogenesis, stromal support, and tumor growth by halofuginone. *Cancer Res* 1999; **59**: 4111-4118 [PMID: 10463616]

45 **Partyka R**, Gonciarz M, Jałowiecki P, Kokocińska D, Byrczek T. VEGF and metalloproteinase 2 (MMP 2) expression in gastric cancer tissue. *Med Sci Monit* 2012; **18**: BR130-BR134 [PMID: 22460086 DOI: 10.12659/msm.882614]

46 **Asha Nair S**, Karunagaran D, Nair MB, Sudhakaran PR. Changes in matrix metalloproteinases and their endogenous inhibitors during tumor progression in the uterine cervix. *J Cancer Res Clin Oncol* 2003; **129**: 123-131 [PMID: 12669237 DOI: 10.1007/s00432-002-0411-9]

47 **Yuan S**, Lin LS, Gan RH, Huang L, Wu XT, Zhao Y, Su BH, Zheng D, Lu YG. Elevated matrix metalloproteinase 7 expression promotes the proliferation, motility and metastasis of tongue squamous cell carcinoma. *BMC Cancer* 2020; **20**: 33 [PMID: 31937294 DOI: 10.1186/s12885-020-6521-4]

48 **Jawa RS**, Anillo S, Huntoon K, Baumann H, Kulaylat M. Interleukin-6 in surgery, trauma, and critical care part II: clinical implications. *J Intensive Care Med* 2011; **26**: 73-87 [PMID: 21464062 DOI: 10.1177/0885066610384188]

49 **Shantha Kumara H**, Yan XH, Pettke E, Cekic V, Gandhi ND, Bellini GA, Whelan RL. Plasma and wound fluid levels of eight proangiogenic proteins are elevated after colorectal resection. *World J Gastrointest Oncol* 2019; **11**: 470-488 [PMID: 31236198 DOI: 10.4251/wjgo.v11.i6.470]

50 **Masson V**, de la Ballina LR, Munaut C, Wielockx B, Jost M, Maillard C, Blacher S, Bajou K, Itoh T, Itohara S, Werb Z, Libert C, Foidart JM, Noël A. Contribution of host MMP-2 and MMP-9 to promote tumor vascularization and invasion of malignant keratinocytes. *FASEB J* 2005; **19**: 234-236 [PMID: 15550552 DOI: 10.1096/fj.04-2140fje]

51 **Yu Q**, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. *Genes Dev* 2000; **14**: 163-176 [PMID: 10652271]

52 **Webb AH**, Gao BT, Goldsmith ZK, Irvine AS, Saleh N, Lee RP, Lendermon JB, Bheemreddy R, Zhang Q, Brennan RC, Johnson D, Steinle JJ, Wilson MW, Morales-Tirado VM. Inhibition of MMP-2 and MMP-9 decreases cellular migration, and angiogenesis in *in vitro* models of retinoblastoma. *BMC Cancer* 2017; **17**: 434 [PMID: 28633655 DOI: 10.1186/s12885-017-3418-y]

53 **Costache MI**, Ioana M, Iordache S, Ene D, Costache CA, Săftoiu A. VEGF Expression in Pancreatic Cancer and Other Malignancies: A Review of the Literature. *Rom J Intern Med* 2015; **53**: 199-208 [PMID: 26710495 DOI: 10.1515/rjim-2015-0027]

54 **Kim KJ**, Cho CS, Kim WU. Role of placenta growth factor in cancer and inflammation. *Exp Mol Med* 2012; **44**: 10-19 [PMID: 22217448 DOI: 10.3858/emm.2012.44.1.023]

55 **Ding YB**, Chen GY, Xia JG, Zang XW, Yang HY, Yang L. Association of VCAM-1 overexpression with oncogenesis, tumor angiogenesis and metastasis of gastric carcinoma. *World J Gastroenterol* 2003; **9**: 1409-1414 [PMID: 12854131 DOI: 10.3748/wjg.v9.i7.1409]

56 **Dutta P**, Sarkissyan M, Paico K, Wu Y, Vadgama JV. MCP-1 is overexpressed in triple-negative breast cancers and drives cancer invasiveness and metastasis. *Breast Cancer Res Treat* 2018; **170**: 477-486 [PMID: 29594759 DOI: 10.1007/s10549-018-4760-8]

57 **Zhao T**, Su Z, Li Y, Zhang X, You Q. Chitinase-3 Like-protein-1 function and its role in diseases. *Signal Transduct Target Ther* 2020; **5**: 201 [PMID: 32929074 DOI: 10.1038/s41392-020-00303-7]

58 **Mehner C**, Miller E, Nassar A, Bamlet WR, Radisky ES, Radisky DC. Tumor cell expression of MMP3 as a prognostic factor for poor survival in pancreatic, pulmonary, and mammary carcinoma. *Genes Cancer* 2015; **6**: 480-489 [PMID: 26807201 DOI: 10.18632/genesandcancer.90]

59 **Waugh DJ**, Wilson C. The interleukin-8 pathway in cancer. *Clin Cancer Res* 2008; **14**: 6735-6741 [PMID: 18980965 DOI: 10.1158/1078-0432.CCR-07-4843]

60 **Ichikawa Y**, Ishikawa T, Momiyama N, Yamaguchi S, Masui H, Hasegawa S, Chishima T, Takimoto A, Kitamura H, Akitaya T, Hosokawa T, Mitsuhashi M, Shimada H. Detection of regional lymph node metastases in colon cancer by using RT-PCR for matrix metalloproteinase 7, matrilysin. *Clin Exp Metastasis* 1998; **16**: 3-8 [PMID: 9502072 DOI: 10.1023/a:1006576032722]

61 **Miyata Y**, Iwata T, Ohba K, Kanda S, Nishikido M, Kanetake H. Expression of matrix metalloproteinase-7 on cancer cells and tissue endothelial cells in renal cell carcinoma: prognostic implications and clinical significance for invasion and metastasis. *Clin Cancer Res* 2006; **12**: 6998-7003 [PMID: 17145820 DOI: 10.1158/1078-0432.CCR-06-1626]

62 **DeClerck YA**, Perez N, Shimada H, Boone TC, Langley KE, Taylor SM. Inhibition of invasion and metastasis in cells transfected with an inhibitor of metalloproteinases. *Cancer Res* 1992; **52**: 701-708 [PMID: 1732058]

63 **Leppä S**, Saarto T, Vehmanen L, Blomqvist C, Elomaa I. A high serum matrix metalloproteinase-2 Level is associated with an adverse prognosis in node-positive breast carcinoma. *Clin Cancer Res* 2004; **10**: 1057-1063 [PMID: 14871985 DOI: 10.1158/1078-0432.ccr-03-0047]

64 **Chetty C**, Lakka SS, Bhoopathi P, Rao JS. MMP-2 alters VEGF expression *via* alphaVbeta3 integrin-mediated PI3K/AKT signaling in A549 Lung cancer cells. *Int J Cancer* 2010; **127**: 1081-1095 [PMID: 20027628 DOI: 10.1002/ijc.25134]

65 **Zhou J**, Gan N, Zhang W, Lu W, Xie X. Proliferation suppression and apoptosis of ovarian carcinoma cells induced by small interfering RNA against vascular endothelial growth factor. *J Obstet Gynaecol Res* 2010; **36**: 232-238 [PMID: 20492371 DOI: 10.1111/j.1447-0756.2010.01196.x]

66 **Wu M**, Shi Y, Xi L, Li Q, Liao GN, Han ZQ, Lu YP, Ma D. Construction of antisense MT1-MMP vector and its inhibitory effects on invasion of human ovarian cancer cells. *J Huazhong Univ Sci Technolog Med Sci* 2005; **25**: 715-717 [PMID: 16696335 DOI: 10.1007/BF02896180]

67 **Hingorani DV**, Lippert CN, Crisp JL, Savariar EN, Hasselmann JPC, Kuo C, Nguyen QT, Tsien RY, Whitney MA, Ellies LG. Impact of MMP-2 and MMP-9 enzyme activity on wound healing, tumor growth and RACPP cleavage. *PLoS One* 2018; **13**: e0198464 [PMID: 30248101 DOI: 10.1371/journal.pone.0198464]

68 **Karim RB**, Brito BL, Dutrieux RP, Lassance FP, Hage JJ. MMP-2 assessment as an indicator of wound healing: A feasibility study. *Adv Skin Wound Care* 2006; **19**: 324-327 [PMID: 16885646 DOI: 10.1097/00129334-200607000-00011]

69 **Masaki T**, Matsuoka H, Sugiyama M, Abe N, Goto A, Sakamoto A, Atomi Y. Matrilysin (MMP-7) as a significant determinant of malignant potential of early invasive colorectal carcinomas. *Br J Cancer* 2001; **84**: 1317-1321 [PMID: 11355941 DOI: 10.1054/bjoc.2001.1790]

70 **Ting WC**, Chen LM, Pao JB, Yang YP, You BJ, Chang TY, Lan YH, Lee HZ, Bao BY. Genetic polymorphisms of matrix metalloproteinases and clinical outcomes in colorectal cancer patients. *Int J Med Sci* 2013; **10**: 1022-1027 [PMID: 23801889 DOI: 10.7150/ijms.6686]

71 **Zucker S**, Hymowitz M, Conner C, Zarrabi HM, Hurewitz AN, Matrisian L, Boyd D, Nicolson G, Montana S. Measurement of matrix metalloproteinases and tissue inhibitors of metalloproteinases in blood and tissues. Clinical and experimental applications. *Ann N Y Acad Sci* 1999; **878**: 212-227 [PMID: 10415733 DOI: 10.1111/j.1749-6632.1999.tb07687.x]

72 **Klupp F**, Neumann L, Kahlert C, Diers J, Halama N, Franz C, Schmidt T, Koch M, Weitz J, Schneider M, Ulrich A. Serum MMP7, MMP10 and MMP12 Level as negative prognostic markers in colon cancer patients. *BMC Cancer* 2016; **16**: 494 [PMID: 27431388 DOI: 10.1186/s12885-016-2515-7]

73 **Wilson CL**, Heppner KJ, Labosky PA, Hogan BL, Matrisian LM. Intestinal tumorigenesis is suppressed in mice lacking the metalloproteinase matrilysin. *Proc Natl Acad Sci U S A* 1997; **94**: 1402-1407 [PMID: 9037065 DOI: 10.1073/pnas.94.4.1402]

74 **Guillen-Ahlers H**, Buechler SA, Suckow MA, Castellino FJ, Ploplis VA. Sulindac treatment alters collagen and matrilysin expression in adenomas of ApcMin/+ mice. *Carcinogenesis* 2008; **29**: 1421-1427 [PMID: 18499699 DOI: 10.1093/carcin/bgn123]

75 **Witty JP**, McDonnell S, Newell KJ, Cannon P, Navre M, Tressler RJ, Matrisian LM. Modulation of matrilysin levels in colon carcinoma cell lines affects tumorigenicity in vivo. *Cancer Res* 1994; **54**: 4805-4812 [PMID: 8062282]

76 **Zeng ZS**, Shu WP, Cohen AM, Guillem JG. Matrix metalloproteinase-7 expression in colorectal cancer liver metastases: evidence for involvement of MMP-7 activation in human cancer metastases. *Clin Cancer Res* 2002; **8**: 144-148 [PMID: 11801551]

77 **Hasegawa S**, Koshikawa N, Momiyama N, Moriyama K, Ichikawa Y, Ishikawa T, Mitsuhashi M, Shimada H, Miyazaki K. Matrilysin-specific antisense oligonucleotide inhibits liver metastasis of human colon cancer cells in a nude mouse model. *Int J Cancer* 1998; **76**: 812-816 [PMID: 9626346 DOI: 10.1002/(sici)1097-0215(19980610)76:6<812::aid-ijc8>3.0.co;2-0]

78 **Adachi Y**, Yamamoto H, Itoh F, Hinoda Y, Okada Y, Imai K. Contribution of matrilysin (MMP-7) to the metastatic pathway of human colorectal cancers. *Gut* 1999; **45**: 252-258 [PMID: 10403738 DOI: 10.1136/gut.45.2.252]

79 **Huo N**, Ichikawa Y, Kamiyama M, Ishikawa T, Hamaguchi Y, Hasegawa S, Nagashima Y, Miyazaki K, Shimada H. MMP-7 (matrilysin) accelerated growth of human umbilical vein endothelial cells. *Cancer Lett* 2002; **177**: 95-100 [PMID: 11809536 DOI: 10.1016/s0304-3835(01)00772-8]

80 **Coffey JC**, Wang JH, Smith MJ, Bouchier-Hayes D, Cotter TG, Redmond HP. Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol* 2003; **4**: 760-768 [PMID: 14662433 DOI: 10.1016/s1470-2045(03)01282-8]

81 **Allendorf JD**, Bessler M, Kayton ML, Oesterling SD, Treat MR, Nowygrod R, Whelan RL. Increased tumor establishment and growth after laparotomy *vs* laparoscopy in a murine model. *Arch Surg* 1995; **130**: 649-653 [PMID: 7763175 DOI: 10.1001/archsurg.1995.01430060087016]

82 **Tohme S**, Simmons RL, Tsung A. Surgery for Cancer: A Trigger for Metastases. *Cancer Res* 2017; **77**: 1548-1552 [PMID: 28330928 DOI: 10.1158/0008-5472.CAN-16-1536]

**Footnotes**

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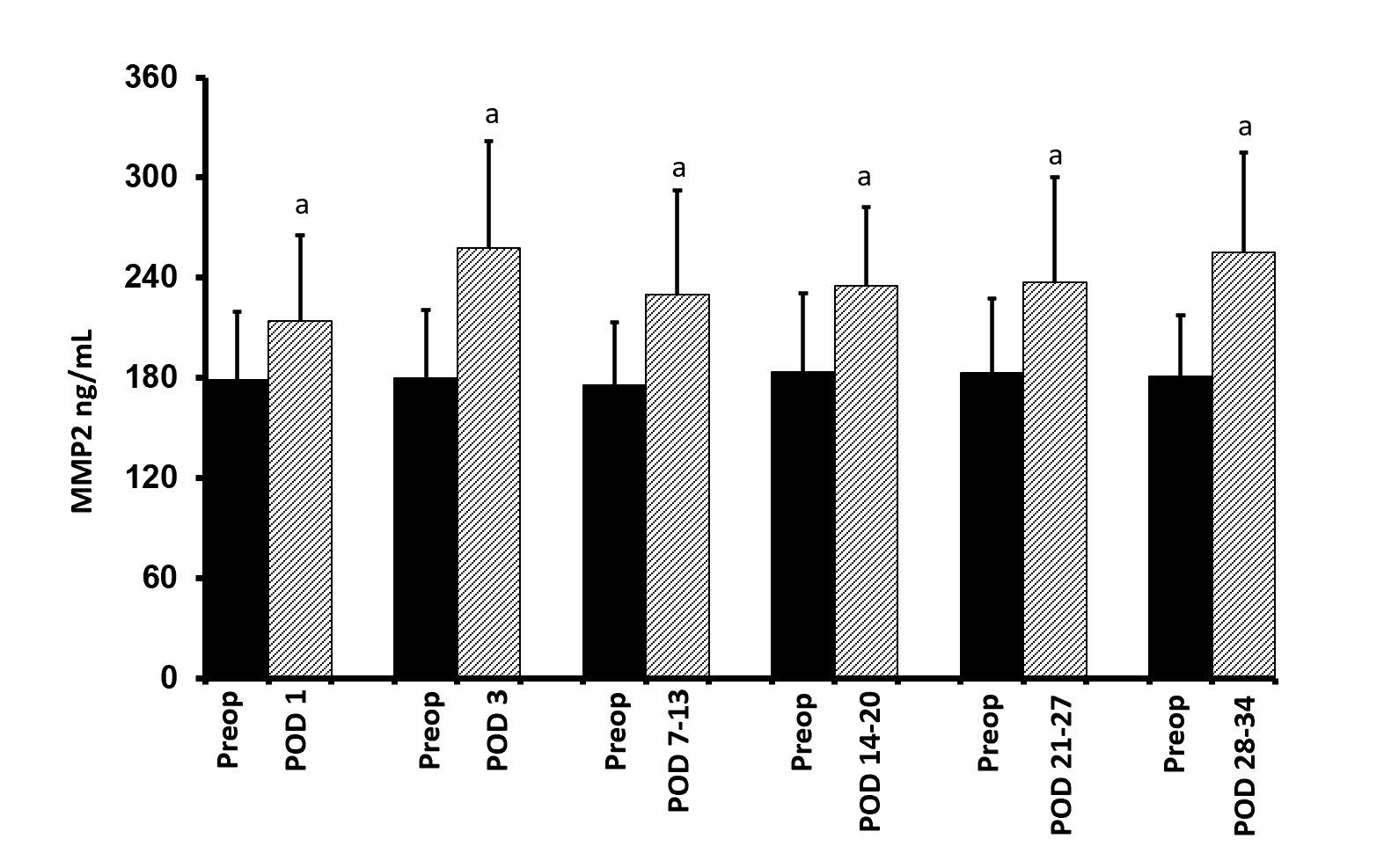
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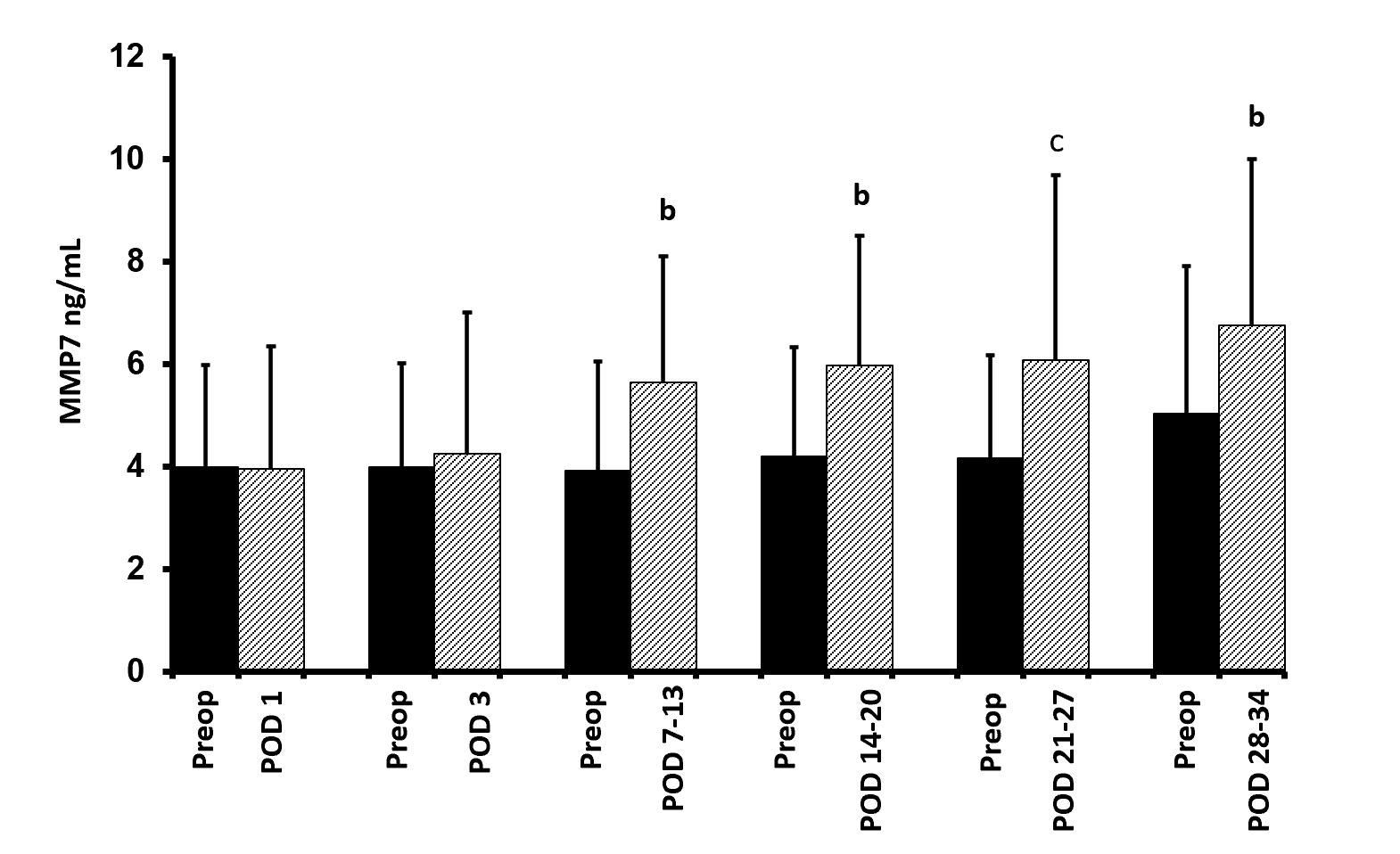
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**Figure Legends**



**Figure 1 Enzyme-linked immunosorbent assay determined preoperative and postoperative plasma MMP-2 levels of colorectal cancer patients.** MMP-2 levels are expressed as mean ± SD [preoperative (Preop) *vs* post-operative day (POD) 1 (*n* = 87, a*P* < 0.001); Preop *vs* POD 3 (*n* = 80, a*P* < 0.001); Preop *vs* POD 7-13(*n* = 65, a*P* < 0.001); Preop *vs* POD 14 -20 (*n* = 25, a*P* < 0.001); Preop *vs* POD 21-27(n = 17, a*P* < 0.001); POD 28-34 time point (*n* = 15, a*P* < 0.001)]. Statistical significance is expressed as a*P* < 0.001. POD: Post-operative day; Preop: Preoperative.



**Figure 2 Enzyme-linked immunosorbent assay determined preoperative and postoperative plasma MMP-7 levels of colorectal cancer patients.** MMP-7 levels are expressed as mean ± SD. [preoperative (Preop) *vs* post-operative day (POD) 1 (*n* = 87); Preop *vs* POD 3 (*n* = 80); Preop *vs* POD 7-13 (*n* = 65; b*P* < 0.001); Preop *vs* POD 14-20 (*n* = 25, b*P* < 0.001); Preop *vs* POD 21-27(n-17, c*P* = 0.002); POD 28-34 time point (*n* = 15, b*P* < 0.001). Statistical significance is expressed as b*P* < 0.001, c*P* < 0.01. POD: Post-operative day; Preop: Preoperative.

**Table 1 Demographic and clinical characteristics of the study population**

|  |  |
| --- | --- |
| **Characteristics** |  |
| Age, yr (mean ± SD) | 66.3 ± 12.8 |
| Sex, *n* (%) |  |
| Male | 44 (50.0) |
| Female | 44 (50.0) |
| Incision length (entire patient population), cm (mean ± SD) | 8.3 ± 4.2 |
| Incision length (lap procedure group), cm (mean ± SD) | 7.3 ± 3.7 |
| Incision length (hand procedure group), cm (mean ± SD) | 10.8 ± 4.3 |
| Operative time, min (mean ± SD) | 306.6 ± 120.5 |
| Length of stay, d (mean ± SD) | 6.8 ± 4.1 |
| Type of resection, *n* (%) |  |
| Right | 34 (37.0) |
| LAR/AR (12/1) | 13 (18.0) |
| Sigmoid/recto-sigmoid (17/6) | 23 (24.0) |
| Total/sub total (5/1) | 6 (7.0) |
| Transverse | 7 (8.0) |
| Left | 4 (5.0) |
| APR | 1 (1.0) |
| Surgical method, *n* (%) |  |
| Laparoscopic-assisted | 58 (62.0) |
| Hand-assisted/hybrid laparoscopic | 30 (38.0) |

LAR: Low anterior resection; AR: Anterior resection; APR: Abdominal perineal resection.



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