MONTH-LONG PLASMA ELEVATIONS OF 7 PROANGIOGENIC PROTEINS, BOTH EARLY AND LATE PEAKING, WERE NOTED FOLLOWING MINIMALLY INVASIVE COLORECTAL CANCER RESECTION; THESE SYSTEMIC CHANGES HAVE THE POTENTIAL TO FACILITATE THE GROWTH OF RESIDUAL TUMOR DEPOSITS

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Introduction

Prior research demonstrates that minimally invasive colorectal resection (MICR) in colorectal cancer (CRC) patients induces sustained elevations in 15 plasma proteins with proangiogenic effects that persist for 3-5 weeks postoperatively (1-11). In the past in vitro studies, plasma from weeks 2 and 3 post-MICR promoted endothelial cell proliferation, migration, and invasion when compared to results with preoperative (preop) plasma; these changes may facilitate residual tumor growth after MICR (12-14). We have also demonstrated that the plasma and wound fluid concentrations of eight proteins (Angiopoietin-2, VEGF, PLGF, MMP2, MMP3, Osteopontin, CHI3L1, and MCP-1) were significantly increased compared to preop levels following colorectal cancer (CRC) surgery. Furthermore, the wound levels of all eight proteins were found to be 3 to 106 times greater than the plasma levels. These proteins are likely to be involved in the process of wound healing (15,16). Recent investigations have identified 7 additional proangiogenic proteins (PAI-1, TIM-3, PD-L1, ET-1, MMP-8, eCIRP, Activin-A) showing similar sustained postop plasma levels in CRC patients after MICR. This study's aim was to characterize and identify the elevation patterns of these 7 proteins and to assess their potential impact.

Methods

Patients with CRC undergoing MICR were enrolled in a multicenter, IRB-approved plasma bank. Clinical and pathological data were prospectively collected. Blood samples taken preop and at multiple postop time points were processed by centrifugation at 450 G for 10 minutes and stored at -80C. Eligible patients with adequate plasma samples available were included in multiple separate plasma protein assays. Late plasma samples were grouped into 7-day blocks. The 7 proteins (plasminogen activator inhibitor-1 (PAI-1), T cell immunoglobulin and mucin-domain containing protein 3 (TIM-3), programmed death-ligand 1 (PD-L1), endothelin-1 (ET-1), matrix metalloproteinase-8 (MMP-8), extracellular cold-inducible RNA-binding protein (eCIRP), and Activin A) were assessed by ELISA in separate assays, in duplicate. The time points were Preop, POD1, POD3, POD7-13, POD14-20, POD21-27, POD28-41. The "n" per time point varied based on plasma availability. Levels were expressed as mean ± SD (pg/mL or ng/mL) For each protein the n was between 83 and 102 patients. Statistical analysis was performed using the Wilcoxon signed-rank test ($p < 0.05$).

Parameter	Result
Demographic & Operative Data	N = 222 patients
Age, years (mean ± SD)	65.70± 13.12
Sex: Male	114 (51%)
Female	108 (49%)
Incision size (cm) : Lap procedure (mean ± SD)	6.9 ± 4.1
Hand assisted procedure	9.9 ± 2.8
Length of stay, days (mean ± SD)	6.8 ± 4.9
Operative time, minutes (mean ± SD)	321.4± 120.9

Figure 1: Surgical procedure

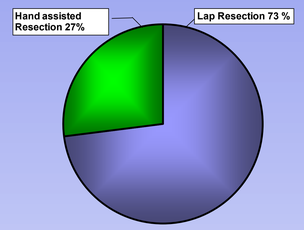

Figure 2: Types of Resection

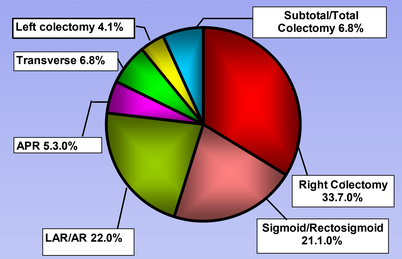

Table 2: Percent increase (%) of mean plasma levels from PreOP plasma levels

Group		POD1	POD3	POD7-13	POD14-20	POD21-27	Pod28-41	No of time point significant (%)
A	CIRP	30.1(*)	106.0 (*)	99.9 (*)	76.7(*)	130.8(*)	24.3	83
A	MMP-8	216.3 (*)	194.5(*)	176.6(*)	90.6(*)	94.6(*)	(0)	83
A	Endothelin	87.8(*)	54.8(*)	27.8(*)	26.6(*)	1.3	13.3	66
A	B7H1	25.7(*)	31.5(*)	33.6(*)	20.6(*)	68.6(*)	19.1(*)	100
A	Activin A	27.2(*)	39.1(*)	39.8(*)	32.9(*)	34.1(*)	28.6(*)	100
B	PAI-1	8.4(*)	10.6(*)	43.6(*)	66.3(*)	30.8(*)	40.5(*)	100
B	TIM3	108.1(*)	131.9(*)	169.7(*)	158.2(*)	167.3(*)	142.5 (*)	100

Results

A total of 222 CRC patients who underwent MICR met inclusion criteria (51% male/49 % female, mean age 65.7 ± 13.1 years; 29% rectal/71% colon); mean incision length 7.7± 3.9cm. (table:1) Laparoscopic surgery was performed 73% (mean incision length: 6.9±4.1cm) and 27% had hand assisted surgery (mean incision length: 9.9±2.8cm) (Figure 1). The majority of patients underwent right colectomy (33.7%), whereas 21.0% underwent sigmoid /rectosigmoid resection(Figure 2). The mean length of stay was 6.8 ± 4.9 days. The final cancer staging breakdown was; Stage I, 40%, Stage II, 30%, stage III, 33% and stage IV, 5%. The "n" for each of the 7 ELISA's varied from 83-102. Significant elevations in plasma levels from preop results were noted at 6/6 postop time points for 4 proteins and at 4-5/6 time points for the other 3 proteins. The peak elevation was noted in the first PostOp Week (POW) for 4 proteins and in the 2nd or 3rd POW for 3 proteins (CIRP, B7H1, TIM3) (Table 2).

Conclusion

Significant plasma elevations were noted for all proteins at week 3 and for 6/7 proteins at week 4. Four peaked in week 1 (Group A), while 3 peaked during weeks 2–3 (Group B). Surgery induced inflammation may account for the early peaks whereas mid- to late-phase peak elevations likely relate to wound healing. These month long increases may support residual tumor growth underscoring the need for further investigation.

References

1. Belizon A et al, n. Surg Endosc. 2008 Feb;22(2):287-97
2.Shantha Kumara HM et al., Surg Endosc. 2011 Jul;25(7):2153-8
3. Shantha Kumara HM et al., Surg Endosc. 2012 Jun;26(6):1759-64
4.Shantha Kumara HM et al., Surg Endosc. 2012 Oct;26(10):2751-7
5..Shantha Kumara HM et al., Surg Endosc. 2014 Dec;28(12):3322-8
6.Shantha Kumara HM et al World J Gastrointest Oncol. 2014 Oct 15;6(10):413-9
7.Shantha Kumara HM et alWorld J Gastrointest Oncol. 2016 Aug 15;8(8):607-14
8.Shantha Kumara HMC et al., Mol Clin Oncol. 2018 Mar;8(3):471-476
9.Shantha Kumara HMC et al., World J Surg Oncol. 2018 Jul 7;16(1):132
10. Shantha Kumara H et al., World J Gastrointest Oncol. 2021 Aug 15;13(8):879-892
11. Shantha Kumara HMC et al., Front Surg. 2021 Nov 8;8:745875
12. Kumara HM et al., Ann Surg. 2009 Jun;249(6):973-7
13.Shantha Kumara HM et al., Surg Endosc. 2012 Mar;26(3):790-5
14. Shantha Kumara HM et al., Dis Colon Rectum. 2014 Jun;57(6):740-6
15. Shantha Kumara H et al., J Gastrointest Oncol. 2024 Oct 31;15(5):2157-2165
16.Shantha Kumara H et al., World J Gastrointest Oncol. 2019 Jun 15;11(6):470-48816