MATRIX METALLOPROTEINASES 9 LEVELS ARE SIGNIFICANTLY ELEVATED IN BOTH THE PLASMA AND WOUND FLUID FOR TWO WEEKS AFTER COLORECTAL CANCER RESECTION

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Introduction

Matrix metalloproteinase 9 (MMP9), also referred to as gelatinase B, plays a key role in extracellular matrix (ECM) remodeling and production of bioactive molecules in subcellular environments that impact many physiological processes(1-3). MMP9 can cleaves many collagen sub types, elastin, Nidogen-1, and Vitronectin and also a variety of chemokines and growth factors (2,3). TNF-alpha, IL-8 , VEGF, and FGF2 stimulate MMP9 production in endothelial cells (EC) that regulates proteolytic tissue remodeling and impacts both physiologic and pathologic angiogenic restructuring (4,5). MMP9 supports tumor metastasis but also plays a role in wound healing and keratinocyte migration (6). MMP9 is produced by WBC's, ECs, and other cell types (7). Plasma MMP9 levels are elevated in colorectal cancer (CRC) patients (8). Further, plasma MMP9 elevations lasting for 1 month after CRC resection have been noted. The etiology of this postop change is unclear; a possible source is the healing wounds. The purpose of this study was to simultaneously measure the levels of MMP-9 in the plasma and fluid from the surgical wounds perioperatively in CRC patients undergoing resection.

Methods

Consenting CRC patients undergoing elective resection enrolled in an IRB approved tissue/data bank for whom there was adequate volumes of plasma and wound fluid (WF, from intra-abdominal Jackson Pratt drains) were eligible. Demographic, clinical and pathologic data were reviewed. Preoperative (preop) and post-operative (postop) blood and postop WF samples were simultaneously obtained on postop day (POD) 1, POD3 and a late time point between POD 7-13 (provided the JP drain remained). Late samples (POD 7-13) were bundled into a 7 day block and considered as a single time point. Blood was centrifuged (450 G) & plasma samples frozen; JP drain WF was centrifuged (16000G x 10 min) & the supernatant frozen (-80^{0}C). MMP9 levels were determined in duplicate via ELISA. The Wilcoxon and Mann and Whitney test were used for analysis (sig. p<0.05).

Parameter	Result
Demographic & Operative Data	N =29 patients
Age, years (mean ± SD)	66.2± 12.3
Sex: Male	12 (41.0%)
Female	17 (59.0%)
Incision size :cm (mean ±SD) LAP/Hand Open procedures	9.3±3.7 23.8±7.8
Surgery time, min (mean ± SD)	459.8± 108.1
Length of stay, days (mean ± SD)	9.2± 6.3

Table 1: MMP9 levels in preop and post op Plasma vs. postop Wound fluids

Time	Plasma (ng/ml)	(n)	Wound fluids (ng/ml)	(n)	*p*
PreOp	85.80; 95% CI: 50.32- 140.12	29	N/A	N/A	N/A
POD1	206.6;95%CI: 141.12- 329.44	29	3169.0; 95% CI: 2072.0- 4534.4	29	< 0.001
POD3	200.5;95%CI: 118.44- 296.68	27	812.0;95% CI: 440.0- 1837.6	25	< 0.001
POD 7-13	205.1;95%CI: 103.16- 289.72	17	1435.0;95% CI: 426.4- 4213.2	17	< 0.001

Figure 1: Surgical procedure

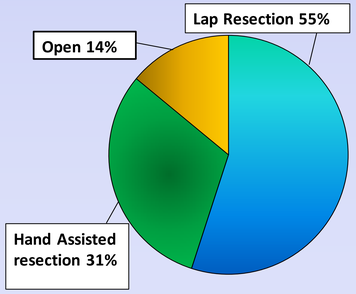
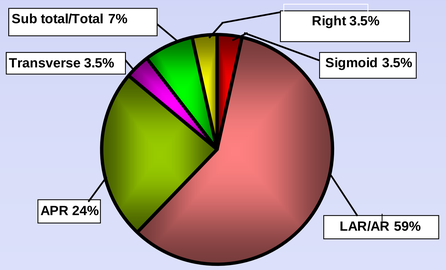


Figure 2: Types of Resection



Results

Blood and wound fluid samples from 29 CRC pts (male: 12, female: 17; colon 5, rectal 24; mean age 66.20± 12.3 years) were studied. Minimally invasive procedures were done in 25 patients (Laparoscopic (16 pts), hand assisted (9 pts) (mean incision length: 8.3±3.5,11.5±3.6) and open surgery in 4 pts (mean incision length 23.8±7.8). The mean length of stay was 9.2 ± 6.3days. The majority of patients underwent LAR/AR colectomy (59%) followed by APR resection (24%)(Figure 2).Versus preop levels, plasma MMP9 levels were 2-2.42 times elevated on postop day (POD)1, 3 and 7-13(P<0.001). Wound fluid MMP9 levels were 4-15 time higher than the corresponding plasma levels at all postop time points (p<0.0001) (Table 1).

Conclusion

Median postop plasma MMP 9 levels were found to be 2-2.42 times higher than preop. Of note, wound fluid MMP9 levels were 4-15 times higher than corresponding plasma levels. Elevated wound MMP9 levels likely account, in part, for the increased plasma levels noted late postoperatively. Elevated plasma MMP9 may promote the growth of residual tumor deposits after surgery. Further study with a larger patient group is warranted as are studies to determine the impact of these and similar surgery related plasma changes.

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