



T CELL IMMUNOGLOBULIN AND MUCIN DOMAIN-3 (TIM-3) LEVELS ARE SIGNIFICANTLY ELEVATED IN PLASMA AND WOUND FLUID FOR TWO WEEKS AFTER COLORECTAL CANCER (CRC) RESECTION.

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Introduction

TIM-3 (T cell immunoglobulin and mucin domain-3) is a type I transmembrane glycoprotein expressed on CD4+ T helper 1 (Th1) and CD8+ T cytotoxic 1 (Tc1) T cells, macrophages and endothelial cells (1-2). When bound to its ligands, Galectin-9 (Gal-9) or high mobility group protein B1 (HMGB1) , TIM-3 induces a range of immunosuppressive functions which enhance immune tolerance and inhibit anti-tumor immunity(3-5). TIM-3 contributes to suppression of the nucleic acid-mediated innate immune responses of tumor-infiltrating dendritic cells (6). Co-expression of TIM-3 and PD-1 together is associated with enhanced dysfunctionality of tumor toxic CD8+ T cells when compared to the effects of PD-1 alone (7). The combination of TIM-3 /Gal 9 pathway blockade with PD-1 /PDL1 pathways intervening therapy may reverse tumor toxic T cell exhaustion/dysfunction and improve response(8). Over expression of Tim-3 has been reported to promote oncogenic activity of many cancers including CRC(9,10) Elevated TIM-3 levels promotes tumor cell proliferation and invasion does dependent manner(10). Persistently elevated postoperative plasma and wound fluid (WL) PDL1 levels and TMP3 plasma levels after CRC resection have been reported (11,12). This study’s purpose is to determine perioperative TIM-3 levels in blood and WF taken after CRC resection.

Methods

Patients (pts) in an IRB approved data/plasma bank who underwent elective CRC resection in whom an intra-abdominal Jackson Pratt (JP) drain had been placed were studied. Demographic and clinical data were collected. Besides preoperative (preop) blood samples, postoperative blood and WF samples were simultaneously collected on postoperative day (POD) 1 and POD3; a 3rd sample set was taken in most cases between POD7-13. Samples collected pod 7-13 were bundled and considered as a single time point. Plasma was isolated via centrifugation at 450 G and clear WFS samples were collected via centrifugation at 16,000G for 10 min at 6°C. WFS and plasma were stored as aliquots at -80°C until further analysis.TIM-3 levels were determined in duplicate via ELISA. Mann Whitney and Wilcoxon signed rank tests were used for analysis (Significance p<0.05).

Parameter	Result
Demographic & Operative Data	N =23 patients
Age, years (mean ± SD)	65.2± 11.7
Sex: Male	13 (57.0%)
Female	10 (43.0%)
Incision size :cm (mean ±SD) LAP/Hand Open procedures	8.4±4.2 25.0±8.8
Surgery time, min (mean ± SD)	473.5± 109.7
Length of stay, days (mean ± SD)	8.9± 5.3

Table 1: Tim-3protein levels in preop and post op Plasma vs. postop Wound fluids

Time	Plasma (pg/ml)	(n)	Wound fluids (pg/ml)	(n)	<i>p</i>
PreOp	2176 ± 736.6	23	N/A	N/A	N/A
POD1	2645 ± 1200	23	8452 ± 6748	22	< 0.001
POD3	3491 ± 2078	20	9358 ± 2945	19	< 0.001
POD 7-13	3424 ± 1877	16	18256 ± 21681	17	< 0.001

Figure 1: procedure

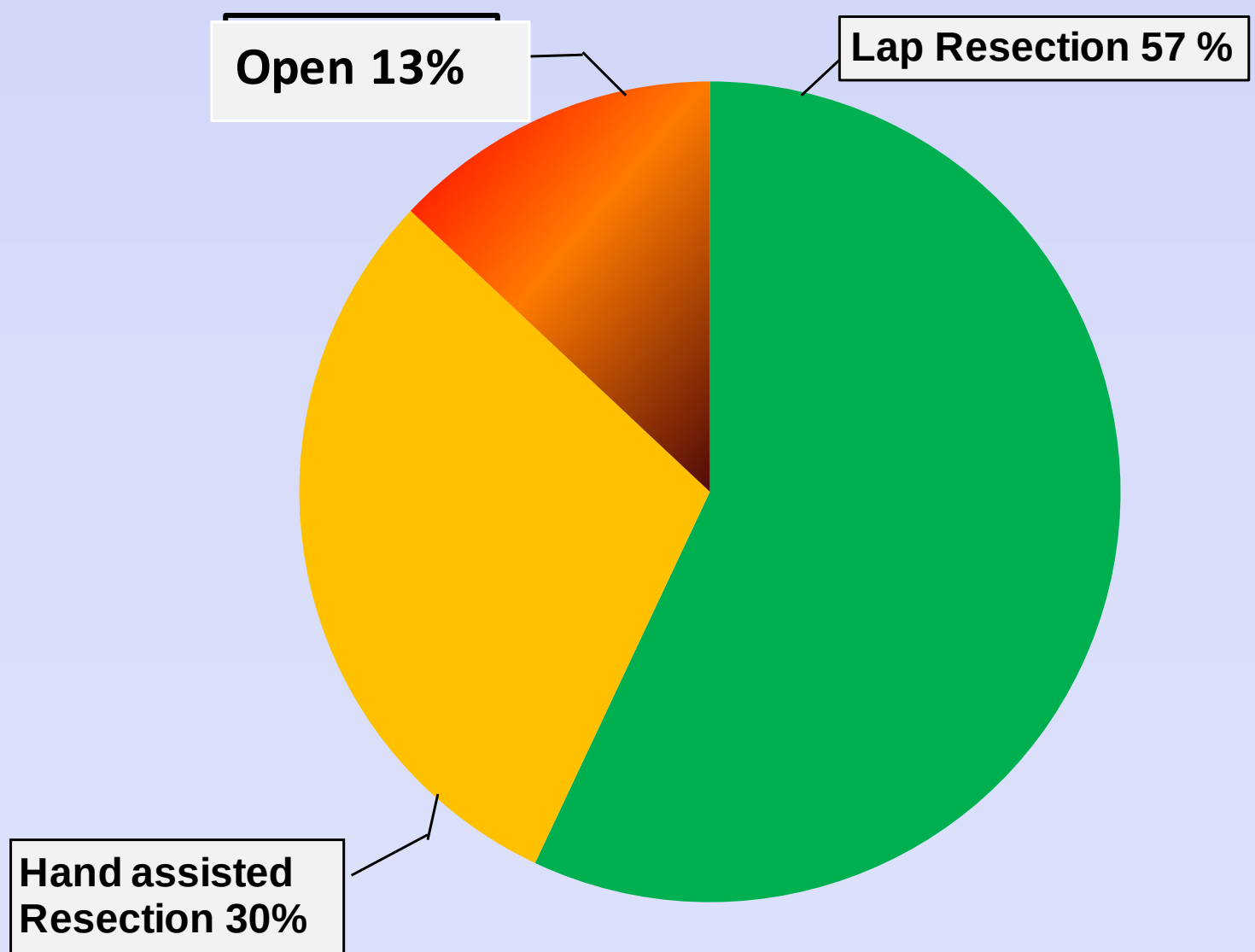
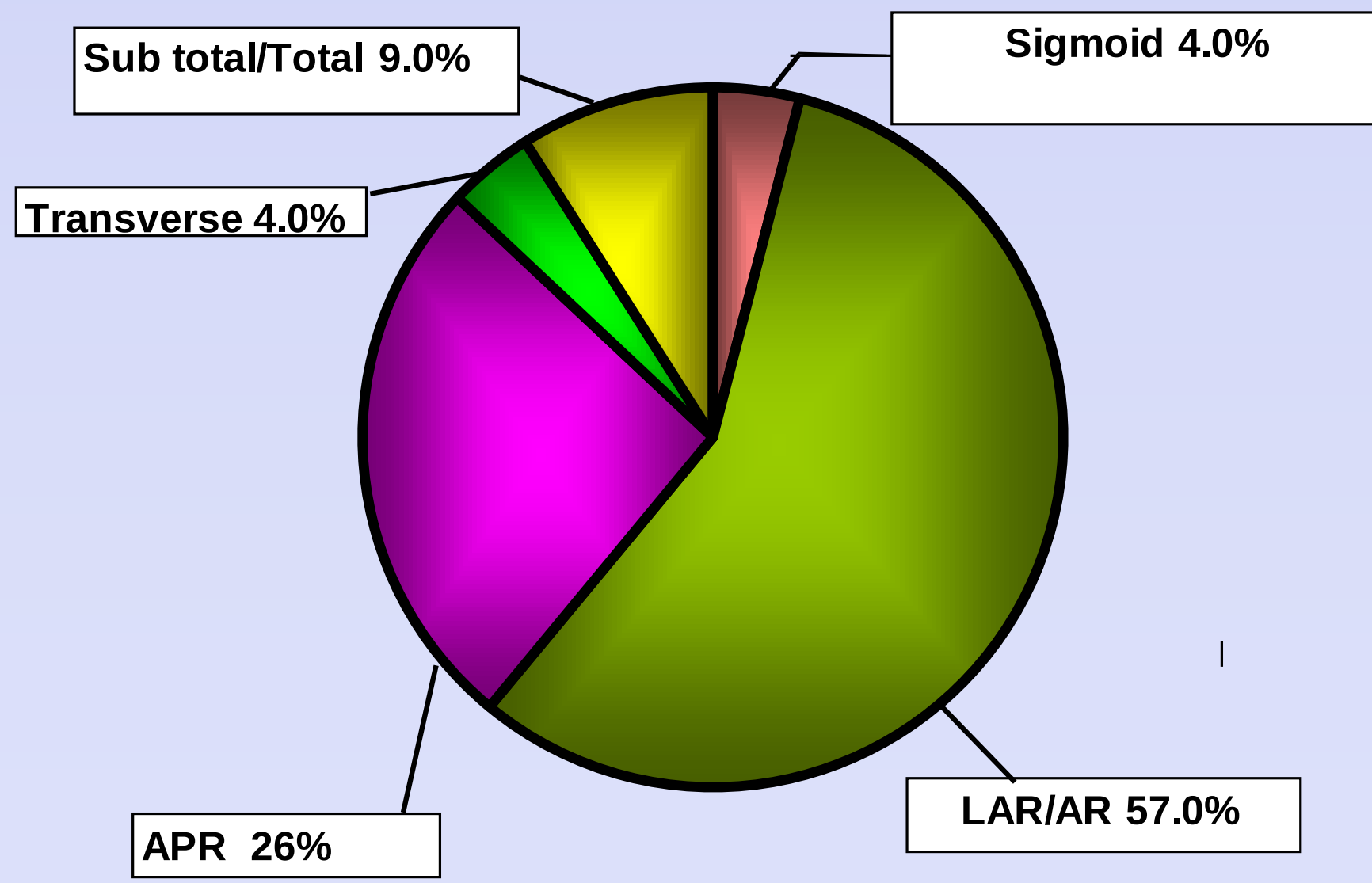


Figure 2: Types of Resection



Results

Plasma and WF samples from 23 CRC pts (male:13,female10; colon 4,rectal 19; mean age 65.2±11.4years) were studied; surgical methods used were laparoscopic (13pts); hand assisted MIS (7pts), and open (3pts)(Figure 1). Mean incision length (cm) for MIS and open pts was 8.4±4.2 and 25.0±8.8. The majority of patients underwent LAR/AR colectomy (57%) followed by APR resection (26%) and subtotal/total resection(9%) (Figure 2).The mean length of stay was 8.9±5.3 days. Plasma TIM-3 levels on postop day (POD)1, 3, and 7-13 (bundled sample time point) were 20-60% higher than preop levels (p<0.03). WF TIM-3 levels on 7-13 were significantly higher than POD1 WF levels (p<0.01). WF TIM-3 levels were 3-5 higher than the corresponding plasma levels at all postop time points (p<0.001)(Table 1).

Conclusion

Postop plasma TIM-3 levels were 20-60% higher than Preop levels(p<0.03). Mean postop WF TIM-3 levels were 3-5 x higher than paired plasma levels for 2 weeks (p<0.001). The highest WF level was noted for the POD7-13 bundled time point. The healing wounds may be the source of the added TIM-3 ,and the levels may associate with the induction of pro- inflammatory cytokines. Elevated plasma TIM-3 levels may exhaust tumor infiltrating T-cells which may facilitate the growth of residual tumor. Further investigation is warranted.

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