Commentary

Surgical intervention and circulating tumor cell count: a commentary

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Surgical resection of tumors is a common practice in breast, lung, melanoma, and many other cancers, and is known to extend life expectancy significantly. However, recurrence and metastasis are still frequently seen post-resection. Distant metastasis occurs when cells from the primary tumor enter the bloodstream, adhere to the endothelium, infiltrate a distant site and proliferate. The number of circulating tumor cells (CTCs) in the vasculature has been shown to correlate with patient survival and prognosis (1). CTC count perioperatively has been under investigation to determine whether surgical procedures introduce additional CTCs into the bloodstream. While this postsurgical CTC increase has been observed for various cancer types, many studies have shown that CTC counts normalize and often decrease after surgery (2). Still, the long-term effects on progression and survival of surgical release of CTCs have not been definitively determined. In this commentary, we discuss the prospect of minimizing surgical CTC increases using less invasive techniques as well as the need for more aggressive perioperative targeting of CTCs.

While the first CTCs were observed in the 1800s (3), the importance of CTC presence in cancer and its potential impact in cancer treatment have only recently been recognized. Early CTC research focused primarily on the isolation and enumeration of CTCs in different cancer types. Currently, studies have expanded to include the exploration of the use of CTCs in early diagnostic tests (4) as well as the development of anti-metastatic therapeutics (5-7).

One area of research that may have far reaching implications in cancer treatment is the relationship between surgical technique and CTC count. Many studies have shown that common methods used for diagnosis (biopsy) and treatment (resection) of cancer can lead to bloodborne tumor cell dissemination. In one study, The Zharov lab showed that while mechanical palpation of breast tumors did not increase CTC counts in mice, tumor biopsy and resection did (8). Moreover, lung resection was shown to increase CTC count, where the presence of CTC clusters correlated with worse prognosis (9). Bayarria-Lara *et al.* found that CTC counts decrease 1 month after lung resection, though the presence of CTC after surgery was associated with early recurrence (10).

In a recent study published in *Investigative Urology* (11), Kauffman and associates investigated whether robotic assisted laparoscopic radical prostatectomy (RALRP) reduced CTC introduction in comparison to past studies conducted on open prostatectomy. They showed that RALRP did not significantly increase CTC numbers in patients, whereas past studies of open prostatectomy based on RT-PCR amplification of epithelial markers in blood were consistent with CTC increases. In the study, blood samples were drawn from 25 patients preoperatively as well as intraoperatively. Using EpCAM-positive selection, 48% of patients were shown to be CTC-positive preoperatively while 52% of patients were CTC-positive after surgery (11). Perioperative increases and decreases in CTC count were observed at the same frequency, and increases were found to never exceed 1 CTC per 8 mL blood (11). It is suggested that RALRP may hold an advantage to open prostatectomy due to the lack of CTC introduction (11).

Similar results have been obtained in studies focused on other cancer types. In esophageal cancer, minimally invasive esophagectomy showed lower intra- and post-operative CTC counts than open esophagectomy (12). Video-assisted lobectomy also yielded fewer CTCs than open thoracic surgery for the resection of lung cancer (13). However, the impact of the additional CTCs introduced is debated. Several reports have demonstrated a correlation between increased CTC numbers postoperatively and worse prognosis in lung, colon, and stomach cancers (14-16), while one study in pancreatic cancer found no such relationship (17). In fact, reports show that the increase of CTC after surgical procedures normalizes over time, sometimes resulting in lower CTC counts than preoperatively (2,8,10,18). The eventual fate of these observed CTCs is of course unknown. Reports of this nature compel the need for further analysis of the correlation between surgical technique and cancer progression. In addition, methods to decrease CTC frequency during surgery should be investigated, including therapeutic agents to target CTCs.

Most methods for cancer treatment focus on the eradication and shrinking the primary tumor, even though 90% of cancer fatalities arise from metastasis. Recently, our group developed a therapeutic approach that directly targets CTCs (19). This nanomedicine construct is comprised of phosphatidylcholine liposomes conjugated with E-selectin, a natural endothelial cell adhesion molecule, as well as TNF-related apoptosis-inducing ligand (TRAIL), a pro-apoptotic ligand whose receptors are upregulated on many cancer cells. The drug acts by adhering to leukocytes within a patient's blood. These cells then interact with CTCs, inducing apoptosis through TRAIL signaling (19). In pre-clinical studies, E-selectin/TRAIL liposomes were shown to significantly reduce CTC number in colon and prostate cancer models. When introduced into the bloodstream of mice containing colon cancer cells, the TRAIL liposomes decreased CTC count by over 90% (19). In an orthotopic prostate cancer model, CTC counts were found to be 94% lower in mice treated with ES/TRAIL liposomes compared to control mice (7). A therapeutic of this type could hold great promise as an adjuvant treatment when used perioperatively, by preventing the operative increase of CTCs and therefore any adverse downstream effects.

While CTC count surrounding surgical procedures has not been directly implicated in metastasis, it is hypothesized that the introduction of CTCs during surgery may promote cancer progression. This motivates further research to elucidate the correlation between type and timing of surgical intervention, and cancer progression. Moreover, since over 90% of cancer fatalities result from metastasis, a greater emphasis on treatments that target CTCs or disseminated tumor cells is also warranted. It is possible that by minimizing the surgically-induced CTC burst through minimally invasive surgical techniques, as well as by targeting CTCs perioperatively, we may one day decrease the occurrence of metastasis and achieve improved patient outcomes.

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