Official Title of the Study: The ex vivo localization of sentinel nodes in colorectal cancer using Tc99m-tilmanocept as compared to vital blue dye

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Research Protocol:

The ex vivo localization of sentinel nodes in colorectal cancer using Tc99m-tilmanocept as compared to vital blue dye.

Background: Sentinel lymph node biopsy is a proven diagnostic, surgery-limiting technique for staging solid tumors. Technetium Tc99m tilmanocept is CD206-targeted agent for lymphatic mapping, with high soluble molecular nature and high target specificity.

Objective: This trial will seek to test the ex vivo performance of technetium Tc99m tilmanocept in sentinel lymph node biopsy in resected human bowel segments to evaluate timanocept localization in sentinel lymph nodes.

Materials and Methods: This study is a single center, open-label, within patient's tissue ex vivo comparative study of Lymphoseek (Lymphoseek (Technetium Tc 99m Tilmanocept) is a radiotracer that accumulates in lymphatic tissue by binding to a mannose binding receptor that resides on the surface of dendritic cells and macrophages. Lymphoseek has a diameter of about 5 nm, which is substantially smaller than current radiolabeled agents used for targeting lymphoid tissue. Lymphoseek's small diameter permits enhanced diffusion into lymph nodes and blood capillaries, resulting in a rapid injection site clearance. Upon entry into the blood, the agent binds to receptors in the liver or is filtered by the kidney and accumulates in the bladder.)and vital blue dye (Patent Bleu V) in the detection of excised lymph nodes in patients with known cancer of the colon.

The colon segment with tumor and the anticipated involved nodal bed will be removed intact. After the surgical procedure is completed, the specimen is instantly taken to an extra table in the operating room. It is performed just after the specimen is taken out. The colonic specimen is incised longitudinally on the antimesenteric side.

Lymphatic mapping is employed on the specimen by using first injection Lymphoseek (50 μg/2 mCi) in 0.1-1.0 ml, followed in 15-30 min by 1 ml 1% blue dye, each injected subserosally and submucosally around the tumor (peritumoral sites employed) by using tuberculin syringe. After 5-7 minutes of massage with little circulatory movements on the lesion, the marking agents are moved into the lymphatic paths to the sentinel lymph nodes(SLN)in the mesentery.

By low level diathermy, sharp dissection of lymphatic path(s) to the SLN(s) may be existent.

Blue nodes shall be removed first by visual inspection. This inspection and dissection shall last not longer than 20 minutes. Each blue node will then be assessed for counts as well as color and the "hot" rule (3σ) applied as described below.

Following blue node removal, each sentinel lymph node can be removed from the basin and marked before the specimen is submitted for pathologic appraisal.

The Lymphoseek-designated (localized) lymph nodes are defined as lymph nodes that have a gamma detector count greater than the sum of 3 square roots of the mean background count (i.e., standard deviation) added to the mean background count. This is referred to hereafter as the "3σ rule" and as the "threshold criteria". If the gamma detector used cannot obtain gamma counts in three 2-second intervals, then one 10-second count may be used to detect gamma counts. Any lymph node count not meeting this threshold criterion will be considered a negative (non-localized) finding. The background count may be obtained by taking the 2-second counts or the 10 second counts with the handheld gamma probe extended at least 100 cm away from the injection site and the probe pointed away from anyLymphoseek source (syringes, injection site, isotope-contaminated materials).

Probing of the area will be complete when all selected node counts are negative by use of the threshold criteria. The surgeon will continue with visualization and palpation according to local practice to ensure that no grossly positive lymph nodes remain at the site of resection. To confirm the in vivo procedure, assessment of presence of a blue hue and a set of three 2-second counts or one 10-second count will be recorded for the excised lymph nodes. The mean count of the ex vivo lymph nodes will be compared to the mean of room background counts, and the same threshold criteria used to determine a positive finding for the in vivo nodes will be applied to the ex vivo specimens.

All removed lymph nodes will be sent to pathology for further evaluation. All lymph nodes will undergo enhanced pathological evaluation including serial sectioning with H&E staining as well as immunohistochemical (IHC) markers

Statistical Analyses Plan:

The data will be summarized by the use of descriptive statistics, using percentages for all categorical variables and using means with standard deviations or medians with lower and upper ranges for all continuous variables. Bivariate analyses will be used for comparison between and within the groups. Multivariate linear regression analyses will be used when the outcome is continuous and multivariate logistic regression analysis will be used when the outcome is dichotomous. Ninety-five percent confidence intervals around the odds ratios will be calculated for the multivariate logistic regression analyses. All multivariate analyses will be adjusted for all demographic variables and all other key (confounding) variables. Levels of significance will be tested at $P<0.05$ and 95% Confidence Interval.