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Promising blood test fails to yield clues about strategies for bladder cancer treatment

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A blood test that has shown promise in predicting how cancer will progress and what treatments will be most effective for a given patient may not be reliable for either, according to a new Penn Medicine study published this week in *Cancer*, a peer-reviewed journal of the American Cancer Society.

Investigators have been looking for a biomarker in bladder cancer, and one emerging candidate is the neutrophil-to-lymphocyte ratio (NLR). Previous studies have linked an elevated NLR with worse overall survival after radical cystectomy, a surgery in which the entire bladder and nearby lymph nodes are removed. Other studies suggest NLR correlates with the amount of cancer found during surgery, meaning the blood test might predict which patients will benefit from pre-surgery chemotherapy to shrink their tumors.

But new research led by Eric Ojerholm, MD, a resident physician in the department of Radiation Oncology in the Perelman School of Medicine at the University of Pennsylvania, raises doubts about NLR as a biomarker. In contrast to previous studies, Dr. Ojerholm's team found NLR is not effective at predicting the overall survival of patients with muscle-invasive bladder cancer. Further, they found NLR was not helpful in determining which patients would benefit from chemotherapy before surgery.

Ojerholm said the discrepancy between the findings of this study and previous work comes in the methodology.

"Dozens of earlier studies reported NLR as a biomarker for bladder cancer, and we hoped that this would be true," Ojerholm said. "Yet extraordinary claims require extraordinary evidence. And all prior studies relied on observational datasets. Many also used statistical methods that can lead to false positive results. So we decided to rigorously put NLR to the test."

Ojerholm's team analyzed data that was collected in real-time during a prospective clinical trial, making this the first study of NLR in bladder cancer not to rely on observational data.

The study analyzed SWOG 8710, which was a randomized Phase III trial of 317 patients with muscle-invasive bladder cancer. All patients were treated with radical cystectomies. Half had pre-surgery chemotherapy, while the other half did not.

"The trial we used has a few big advantages to study NLR," Ojerholm said. "First, baseline blood samples were collected as part of the trial protocol. Second, the study's long-term follow-up gave us adequate 'statistical power,' meaning that if NLR really was a biomarker, then we should be able to detect it. Third, the trial randomly assigned some patients to receive pre-surgery chemotherapy. This allowed us to test NLR both as a prognostic and predictive biomarker."

Of the 317 total patients, Ojerholm and his team identified 230 for a prognostic analysis to see if NLR could serve as a predictor of how long patients would live after curative treatment. They identified 263 others for a predictive analysis to see if NLR could tell which patients would respond to chemotherapy. There was a median follow-up of 18.6 years.

For the prognostic analysis, NLR was not a significant factor in overall survival. The important factors were age and whether the patient received pre-surgery chemotherapy. For the predictive analysis, NLR did

not predict which patients benefitted from chemotherapy.

On the question of why most previous publications supported NLR as a biomarker, Ojerholm pointed to several factors beyond methodology and statistical design.

"There's also the problem of publication bias," Ojerholm explained. "Sometimes authors won't submit negative results, and sometimes journals won't accept them. That could be a real issue as NLR research continues."

Ojerholm stressed that no single study is definitive, and doctors must weigh results from the entire literature.

"Yet this study does raise questions about NLR for bladder cancer," Ojerholm added, "and we need more evidence before using this biomarker in clinical practice."

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