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ctDNA-Guided Bladder Preservation in Muscle-Invasive Bladder Cancer

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Natera. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to share key findings from the integrated analysis of the phase 2 RETAIN trials, which evaluated ctDNA response-adapted bladder preservation in muscle-invasive bladder cancer, is lead author Dr. Pooja Ghatalia. She's an Associate Professor in the Department of Hematology and Oncology at Fox Chase Cancer Center at Temple University Hospital in Philadelphia. She also presented this research at the 2026 ASCO Genitourinary Cancers Symposium. Dr. Ghatalia, welcome to the program.

Dr. Ghatalia:
Thank you so much for having me.

Dr. Turck:
Now before we dive into the RETAIN data, Dr. Ghatalia, could you briefly explain why bladder preservation strategies are such an important area of research in muscle-invasive bladder cancer?

Dr. Ghatalia:
Absolutely. So as you know, muscle-invasive bladder cancer has historically been treated with neoadjuvant therapy, which has previously been chemotherapy and then chemoimmunotherapy as perioperative therapy. And now, we are looking at enfortumab-vedotin and pembrolizumab in the neoadjuvant setting. But ultimately, the standard of care is to receive cystectomy or definitive chemoradiation. But radical cystectomy is a life-altering operation for our patients which not only affects their quality of life, but the procedure itself is associated with significant morbidity.

Additionally, since we have better neoadjuvant therapies now with a pathologic complete response of almost 60 percent with enfortumab-vedotin in the neoadjuvant setting, patients often ask us if they could potentially avoid immediate cystectomy. And therefore, there is a real need to understand how response-adapted bladder preservation strategies could be developed going forward.

Dr. Turck:
So then let's turn the RETAIN-2 trial, which evaluated a response-adapted strategy in patients with muscle-invasive bladder cancer by combining platinum-based chemotherapy with nivolumab. Based on data from 71 patients, the estimated two-year metastasis free survival was about 80 percent both in the intent-to-treat group and among those who underwent active surveillance. With that context in mind, what stands out to you most about these outcomes when we think about bladder preservation strategies today?

Dr. Ghatalia:
I think the key message is that based on these results, response-adapted bladder preservation is feasible. We did meet our primary endpoint in our RETAIN-2 clinical trial. About 68 percent of patients were able to keep their bladders intact without requiring any salvage cystectomy or salvage chemoradiation, and they were metastasis-free at the two year follow-up. But these results are not perfect because we still had patients who had metastases. There were patients who had local recurrence. But these two-year MFS rates are comparable, and they support the ongoing strategies to investigate response-adapted bladder preservation.

Dr. Turck:
And if we look more closely at the 22 patients who entered active surveillance, 36 percent experienced bladder recurrence, 18 percent

developed metastases, and 73 percent ultimately remained metastasis-free with an intact bladder. So how should clinicians think about that balance between local recurrence risk and metastatic control when considering bladder preservation?

Dr. Ghatalia:
Local recurrence is something that is likely going to happen in some patients with these bladder preservation strategies. But several of these patients with local recurrence could be managed with either BCG therapy or salvage cystectomy; therefore, avoiding immediate cystectomy does not put patients at a significantly higher risk of metastasis.

Having said that, how we should detect local recurrence can potentially be developed upon more. In our study, we primarily used cystoscopic surveillance and urine cytology to detect local recurrence. So these will likely be incorporated in future trials to detect local recurrence sooner so as to avoid development of metastasis in these patients and to potentially offer salvage therapies.

Dr. Turck:
Now, across both of the RETAIN trials, 274 ctDNA timepoints from 111 patients were analyzed using a tumor-informed assay. Based on the findings, baseline ctDNA positivity was 42.2 percent and dropped to 13.6 percent post-treatment, with nearly 73 percent of baseline-positive patients clearing ctDNA. From your perspective, what might these clearance patterns tell us about treatment response and the presence of residual disease in this setting?

Dr. Ghatalia:
So these results are sort of expected, and they are in line with what we have seen with the NIAGARA data where perioperative gemcitabine/cisplatin durvalumab was used as well as with the data from the HCRN trial that also had gemcitabine/cisplatin nivolumab that was recently published. I will say that our baseline ctDNA positivity rate was a little bit lower than the NIAGARA data, which could be representative of patients who were primarily clinical T2–T3 as opposed to also having T4 patients or higher-risk patients who may not have gone forward with a bladder preservation approach. But I believe these clearance rates may be higher once we start having more effective neoadjuvant therapies.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Pooja Ghatalia about her recent research on ctDNA response-adapted bladder preservation in muscle-invasive bladder cancer.

So another key finding from the integrated analysis across both trials was that patients who were ctDNA-negative post-treatment—or who cleared ctDNA from baseline—had substantially lower recurrence rates compared with those who remained ctDNA-positive or did not clear; we saw recurrence rates around 35 to 44 percent versus 86 to 92 percent.

With that being said, Dr. Ghatalia, to what extent do these findings suggest a potential role for ctDNA in informing bladder preservation strategies?

Dr. Ghatalia:
You know, one of the key results of our study was that ctDNA is extremely prognostic for systemic recurrence. In fact, patients who remained ctDNA-negative at baseline and post-neoadjuvant therapy were the best performers. Patients who were ctDNA-positive at baseline who then became ctDNA-negative post-neoadjuvant therapy did a little bit worse than the patients who were persistently ctDNA-negative. But patients who remained ctDNA-positive at baseline and post-neoadjuvant therapy had the worst outcomes. I think this information is really important as we design bladder preservation trials as I think we should incorporate both baseline and post-neoadjuvant ctDNA in decision-making.

But how do we go forward? Patients who are persistently ctDNA-positive should likely not be offered approaches such as active surveillance. They probably need intensification of treatment, some surgical procedure, or some local therapy. That is one argument. Another possible way of looking at it is that if a patient is persistently ctDNA-positive, they're likely going to recur. And if the patient in front of you is a patient who is relatively frail or is not hoping to be too heroic in their treatment approaches, then offering them chemoradiation is maybe a better approach as opposed to radical cystectomy.

Dr. Turck:
Now, among patients undergoing active surveillance who were ctDNA-negative post-treatment, 12- and 24-month metastasis-free survival were 97.1 percent and 82.4 percent, respectively—suggesting strong prediction of metastatic control. However, recurrence-free survival was lower—largely driven by local recurrences—and 19 of 22 patients who recurred were ctDNA-negative. So what does this divergence tell us about the biological and technical limitations of plasma ctDNA in detecting residual bladder-confined disease?

Dr. Ghatalia:
While ctDNA is excellent at predicting metastatic disease control, it is not great at predicting the residual disease in the bladder in

patients undergoing cystectomy, nor is it a good predictor of development of local recurrence in patients who forego immediate cystectomy and go on to active surveillance.

So you mentioned the results of the patients on RETAIN trials who went on to active surveillance, and as you indicated, most of the patients who developed local recurrence going forward did not have ctDNA positivity as an indicator. And similar results were also seen in the cystectomy patients where among the patients who are ctDNA-negative, we saw that about 60 percent of patients had muscle-invasive disease, so T2 or above disease at the time of cystectomy. And this information has also been shown in the NIAGARA as well as in the HCRN data.

And so consistency is seen across these trials, which again brings home the point that ctDNA cannot be looked at in isolation. We have to use ctDNA in combination with clinical restaging as well as other biomarkers, such as urinary tumor DNA, to make decisions about patients who are on active surveillance and monitoring those patients while they are on active surveillance.

Dr. Turck:
Taking all of this together before we close, Dr. Ghatalia, post-treatment ctDNA negativity appears to predict metastatic control but not local recurrence. How do you see multimodal molecular surveillance evolving in bladder preservation protocols, and what next steps would be needed for this approach to become standard practice?

Dr. Ghatalia:
So I would say that if a patient is ctDNA-negative at baseline and post-neoadjuvant therapy and if clinical staging is negative, I think those patients may be really good candidates for active surveillance. I do think that based on our RETAIN data, the incorporation of the molecular biomarker that we had is likely not going to be developed further because we found that several patients went on to cystectomy just because they were mutation-negative based on the design of the study. But those patients were ypT0 and potentially could have gone on to active surveillance. So that biomarker is likely not to be developed further in future bladder preservation trials.

And for patients who are ctDNA-positive at post-neoadjuvant therapy, what to do for those patients is not completely clear based on our study. We only had 10 patients who were persistently ctDNA-positive in our study, and clearly those patients did poorly. What local therapy to offer those patients or if treatment intensification is needed is still an open question that will need to be developed further in future trials.

And I think monitoring patients on active surveillance in more aggressive ways is definitely going to become important. I mentioned urinary tumor DNA. Now, utDNA is great, but there are some problems with utDNA as well because utDNA is sometimes associated with higher false-positive rates just because of the fact that even normal urothelium could potentially shed DNA that could be picked up as abnormal by the utDNA assays. Therefore, we need to be careful even when we incorporate utDNA and when trying to determine which patients truly have local recurrence, who should be offered salvage therapies.

Dr. Turck:
As those forward-looking comments bring us to the end of today's program, I want to thank my guest, Dr. Pooja Ghatalia, for joining me to share data from the RETAIN trials on ctDNA response-adapted bladder preservation in muscle-invasive bladder cancer. Dr. Ghatalia, it was great speaking with you today.

Dr. Ghatalia:
Same here, and thank you for this opportunity.

Announcer:
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