Transcript Details
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Refining Multimodal Therapy for Mesothelioma: Clinical Impact of SMART Sequencing

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, Dr. John Cho will discuss the rationale behind the SMART treatment approach for mesothelioma, which he spoke about at the 2025 World Conference on Lung Cancer. Dr. Cho is a radiation oncologist at Princess Margaret Cancer Centre and an Associate Professor in the Department of Radiation Oncology at the University of Toronto. Let's hear from him now.

Dr. Cho:
So mesothelioma is actually a very rare malignancy that unfortunately affects patients who have been exposed to asbestos. The reason why we developed the SMART therapy was basically because the treatment for mesothelioma is, despite many decades of effort, still lacking. And what I mean by that is I would say since the 1960s-70s when significant, serious efforts have been made to try to improve the outcomes of meso, despite these many decades of effort, we still actually don't have a cure for meso. It's not for lack of trying. Part of the issue is that meso is a very, very tough malignancy to deal with.

So the original treatment for mesothelioma is what was commonly called trimodality therapy because it included three disciplines, so we would treat these meso patients if they were considered surgically resectable with induction or neoadjuvant chemotherapy in the hopes of trying to downstage the tumor—typically two cycles—and then the patient would go ahead with surgery called extrapleural pneumonectomy, which is a bit of a tongue twister, but basically, that refers to a pneumonectomy which is removing the entire lung from the patient, but the extrapleural part refers to the lining around the lungs. So it's removed on block at the same time, so it's actually a major operation.

And the issue was that with an EPP, or extrapleural pneumonectomy, by itself is it hasn't been shown to be very helpful. First of all, it's quite toxic because it's quite morbid. Some patients don't survive the operation. And secondly, it wasn't very effective. So if you just did the surgery, in 60–80 percent of the patients, the meso would just grow back in the affected lungs, so it was toxic and wasn't very effective, so surgery really didn't take off until about 2001.

There was a paper that was published by a big cancer group in New York, Memorial Sloan Kettering, which basically was the first group to demonstrate that if you added adjuvant radiation following EPP, you could actually improve local control. So they basically gave between 50–60 Gray, 25, 30 fractions over five to six weeks, and they were able to demonstrate that you could actually improve local control from a failure rate of say 60–80 percent down to less than 10 percent, so it made a huge difference in terms of local control.

And one of the original hypotheses that we wanted to test—which was the actual original genesis for the SMART study—was to see if switching the order of the treatment would make a difference. So instead of doing chemo, surgery, and the radiation, our idea was to swap the radiation and then do the surgery plus or minus chemo. So SMART is actually an acronym for surgery for mesothelioma after radiation therapy, so that's how we came up with that acronym. And our biggest concern when we first came up with this idea was whether we could do it safely or not because no one up to that time has ever tried doing this big operation EPP with this big radiation.

So the original SMART study, which took more than 10 years to accrue because, like I said, meso is fairly rare, we were able to actually show that indeed we could do it safely. And then when we looked at the patterns of failure, we were able to identify one subgroup of patients that did particularly well, and these were the patients that had epithelioid mesothelioma. So again, for those of you who are not familiar with meso, meso comes in several different histological subtypes, the most common being epithelioid, which is probably 60–80 percent of patients, and then the remainder would be nonepithelioid, which is a bit of a grab bag. We have sarcomatoid, and then we

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have biphasic, which is a mix of sarcomatoid and epithelioid together. And the sarcomatoid component, if you were to have that, these meso patients often would have much worse outcomes.

So we were able to identify that if you had epithelioid mesothelioma and if the lymph nodes in the middle of your chest were not involved in two nodes in the TNM staging, these patients did particularly well. So in this particular study, we were able to demonstrate a median survival of about 65 months or about 5.5 years, which for mesothelioma is extraordinarily good. So that was the SMART study.

Announcer:
That was Dr. John Cho talking about the rationale of SMART therapy for mesothelioma, a topic he presented at the 2025 World Conference on Lung Cancer. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

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