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Circulating thrombospondin-2 enhances prediction of malignant intraductal papillary mucinous neoplasm☆

DR. JEFFREY HARDACRE (Cleveland, Ohio): The group in Indiana remains at the forefront of study in pancreatic cystic disease. In this study you have shown that serum levels of thrombospondin-2 enhance our ability to predict the degree of dysplasia in IPMN's. The level is most useful when combined with 19–9 and other radiographic and clinical features. These data and future studies will help us get to that sweet spot of predicting which lesions harbor high grade dysplasia and, therefore, mandate resection as compared to ongoing surveillance. I have a few questions.

How are you using Thrombospondin-2 clinically in your clinical decision making? How do you act on disparate data? That is to say, what would you do for a 1.5 cm branch duct lesion with no worrisome features or high risk stigmata by consensus guidelines but with a markedly elevated Thrombospondin-2? Alternatively, what would you do for a 1.5 cm mixed type lesion with a small nodule on the wall and a duct diameter of 6 mm but a very low Thrombospondin-2? Are you using sequential Thrombospondin-2 levels as part of your surveillance protocol? And, finally, your study is focused on the use of serum Thrombospondin-2 in predicting the degree of dysplasia in these lesions. Have you studied cyst fluid levels of that compound?

DR. SIMPSON: How are we using Thrombospondin-2 currently? We feel this is pretty preliminary data considering this is the first study of Thrombospondin-2 in IPMN specifically, so we're not using it for clinical decision making just yet. If we were, if we were in a case with disparate data, your example a very benign appearing cyst but markedly elevated Thrombospondin-2, if you can remember from our scatter plots, only highgrade and invasive lesions had Thrombospondin-2 levels much above 40. So while I don't think we would pull the trigger on surgery just based on that data point alone, we would certainly be more concerned about that patient and increase our surveillance, recommend endoscopy and further evaluation.

In the converse, if someone has worrisome features or high risk stigmata but a more moderate or low Thrombospondin level, I think we would be better suited to go with the consensus guidelines, because, again, if you look at our scatter plots, there's a lot of overlap in that low 20–30 ng per milliliter range, so I don't think I would hold back surgery based on a lower Thrombospondin level.

And that's a nice segue into your next question about longitudinal collection. Like I said before, I think this might be a test better suited for longitudinally following the trend in patients over time, and this is something we're actually planning to do in our clinic.

Now, we haven't talked about testing Thrombospondin-2 in cyst fluid, but this is something else to consider to make sure it correlates and to see if, you know, locally in the pancreas Thrombospondin-2 levels increase as well as circulating levels.

DR. SUKAMAL SAHA (Flint, Michigan): May I ask you, your clinical judgment today at your institution, would you give us one, two, three criteria you are using, who to go to, follow-up, ERCP or CAT scan followed by who do you take a survey. Will you give us just a brief answer for that, please.

DR. SIMPSON: There's a lot of things to consider, so surgical candidacy and willingness of the patient to go to surgery, are they having symptoms, regardless of what their cyst or main pancreatic duct looks like, largely because of disparate risk in malignant progression. Of course, a dilated duct, especially when it gets into that 7–8-mm range, we start to get more worried about a more aggressive main duct involved IPMN.

The side branch lesions largely are followed, unless they have something like an enhancing mural nodule, they're growing exponentially again causing symptoms. We heavily use endoscopy. We have great endoscopists at Indiana University. We're very lucky, so we use this fluid analysis quite a lot, and all of these factors go into our decision making for deciding surgery versus surveillance.

DR. SAHA: So looking back, the people who you have done surgery and this blood test, have you correlated anything at all of the people that you have done surgery?

DR. SIMPSON: These all – I don't think I understand your question. These all are patients that have gone to surgery.

DR. SAHA: So level of that correspond to your pathologic diagnosis, does it really match really well or somewhat or –

DR. SIMPSON: Somewhat, so if you remember from our graphs, so the very high levels of Thrombospondin only seem to occur in the high grade and invasive lesions. There's this kind of middle group in the 20 to 30 range where there's a lot of overlap, so I don't know that it would be all that helpful. It would be – what we're planning to do, again, is follow longitudinally and see if a persistent increase in trend correlates with patients that end up going to surgery have high grade or invasive lesion, if that's something that can better predict what their pathology would look.

DR. ANNA LEDGERWOOD (Detroit, Michigan): Does it go down postoperatively, have you looked at that? And the second thing is, have you looked at it in any other pancreatic diseases, such as pancreatitis?

DR. SIMPSON: Both of your questions, so, number one, have we looked at it postoperatively, no. I'm not exactly sure what the half life of Thrombospondin-2 is, but that would be interesting to look at because, you know, CA 19–9, we expect to drop and then we follow it postoperatively for pancreatic cancer. It would be interesting to see if Thrombospondin-2 follows that same pattern. And, no, we haven't looked at it in other pancreatic diseases like benign pancreatitis.

☆ (Presentation given by Rachel Simpson, M.D.)

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