Discussion of 2021-1753

CLINICAL FACTORS PREDICTIVE OF LYMPH NODE METASTASIS IN THYROID CANCER PATIENTS: A MULTIVARIATE ANALYSIS

**DR HERBERT CHEN** (Birmingham, AL): The favorite topic of debate amongst endocrine surgeons is the extent of surgery for well-differentiated thyroid cancer.  Although this debate has been going on for the last few decades, I suspect this debate will continue for the next few decades.  For those of you who do not do this every day, options now include total thyroidectomy, lobectomy, prophylactic unilateral vs bilateral central neck dissection vs no neck dissection at all.  Even more recently, no surgery at all for papillary thyroid cancer.  Just observation of papillary thyroid cancer is now an option.  Studies like this provide us more information to help make this decision and more fodder for our continuing debate.

Dr Rosen and colleagues from the MedStar Washington Hospital Center performed a 7‑year review of their records.  In reviewing over 900 patients in their final analysis, they found that age, tumor size, extrathyroidal tumor extension, and lymphovascular invasion were independent predictors of significant lymph node metastases.

I did not see in the manuscript the description of your institutional practice regarding prophylactic lymph node dissection.  I recognize you did a couple of models deploying it and not deploying it, but just wondering if prophylactic lymph node dissections are routinely performed.  If this is the case, this may lead to an increasing number of patients who have clinically insignificant micrometastases.  Could you comment about the percent of patients who had prophylactic lymph node dissection in your group?

How many of the 28% of patients who had lymph node metastases had clinically significant macrometastatic disease?

Did the presence of positive lymph node metastases in your patients lead to either a higher mortality or higher rate of recurrence?

**DR JOE SHARMA** (Atlanta, GA): As a new member, this is really an honor, and this is supposed to be Dr Nancy Perrier. I am going to invoke my Dr Perrier this morning, but I do not have the drawl.

This paper provides a robust experience in thyroid cancer. As Dr Chen alluded, it is an ongoing debate that is not going to be settled by this paper. The ability to do a randomized controlled trial in this has been calculated, and it will require roughly 6,000 patients, and we are not there yet.

I have more of a philosophical question for the team: why are lymph nodes involved important? When we looked at the paper from *American Surgeon*, we did see a difference. But if we change our staging system to not the TNM 1, but others, we start losing that difference between lymph node positivity and lymph node negativity. I would appreciate some comments about that.

Factors are often identified that are predictive, but how many are truly identified preoperatively? Even extracapsular invasion is something that can be detected often on ultrasound, but it may not be. Are these factors truly preoperatively seen with lymphovascular involvement? That is obviously a postoperative issue.

Did you follow the patients with no lymph node metastases and what happened to them? Do you have any sense of whether their biology with positive thyroglobulins or follow‑up ultrasounds were positive?

Lastly, here is a little bit of a critique. Overall, 41% of your patients underwent a neck dissection. You did speak about the intentionality of a neck dissection. However, your decision-making for a prophylactic lymph node is not clear, and if you could define that. What do you mean by that?

Some of us do separate out central lymph nodes from lateral lymph nodes. I do not know if biology supports that, but the operative approach supports it. Should you separate out that lymph node data with that stratifier?

I do not know if we can make a conclusion, although you were very careful in how you stated it is not statistically significant. But at the same time, if it is not statistically significant, should we make conclusions toward ethnicity and smoking?

**DR BRENESSA LINDEMAN** (Birmingham, AL): My question is related to the finding of margin status and that this was not associated with lymph node metastases. I was curious if this was associated with recurrence. Given your ability to go back very discreetly through the operative reports and the pathology, if you were able to identify something that I believe has vexed endocrine surgeons for much of time, that there is a difference between anterior margin positivity vs posterior margin positivity specifically related to recurrence.

**DR JOHN HANKS** (Charlottesville, VA): As a long‑term or original District of Columbia native, I have held Dr Wartofsky and Dr Burman in great respect for years. I know that Dr Rosen is truly standing on the shoulders of giants. I have great respect for that group.

One short question, and maybe I missed it. You never mentioned a previous history of radiation, and that has been associated with some of these thyroid malignancies. Do you have that data? If not, why not?

**DR HUI ZHENG** (Washington, DC): First, to address Dr Chen's questions regarding our institutional practice, there are four full‑time fellowship trained attending surgeons.  The routine practice is that all patients with biopsy‑proven papillary thyroid cancer before surgery will undergo cervical lymph node mapping by ultrasound.  Any of the worrisome findings will be biopsied.

Patients with confirmed metastases will undergo total thyroidectomy with neck dissection, and patients whose lymph node mapping is negative but still have suspicious features will also undergo intraoperative neck evaluation.

Otherwise, patients who just undergo total thyroidectomy and patients who have preoperative indeterminate biopsy results, namely Bethesda 3 to 5 categories, may undergo lymph node mapping based on providers such as endocrinologists and especially if they undergo genetic testing with *BRAF* gene mutations.  For the last group of patients, they will be selected for central neck evaluation at the time of surgery.

Otherwise, for Bethesda 2 nodules, they are unlikely to have any preoperative central neck evaluation , and a central neck dissection will not be performed unless an unexpected result was encountered in the operating room.  With that said, about 32% of the patients did undergo prophylactic lymph node dissection, meaning there is no lymph node metastases pre‑op and about 9% underwent therapeutic dissection.

Regarding whether all the lymph node metastases are macromets, it is difficult in our institution to ascertain the size of all the lymph node metastases due to the ununiform reporting standards.  This is especially true for cases that happened before the 2015 guideline update by the American Thyroid Association.  With that said, about 6% of them did have the reported data, and out of that 6%, 98% of them were over 0.2 cm, which is the most commonly defined threshold for macrometastases.  Furthermore, 72% were over 1 centimeter and 12% were over 3 centimeter of the limited data we have on this.

I know a lot of you have commented or asked about association with mortality or recurrence rate, and in our area, there is an abundance of endocrinologists who are interested in treating thyroid cancer.  Most of them are outside of our network.  Also, because of Washington DC being a national seat of government, there is a large population that is migratory.  They come to work and will move out in a few years.  Therefore, it has been challenging to collect this data, but we are currently working on it.  Of the four surgeons, Dr Rosen follows her patients throughout their course.  Anecdotally, none of her patients have died from their disease.

Regarding Dr Perrier's questions delivered by Dr Sharma, why is lymph node metastases important?  I think it is important for tailoring the surgical management at the time of diagnosis.  I do understand that lymph node metastases does not necessarily translate into mortality or even recurrence, and we are currently working on validating that in our data set.

Regarding the question about whether these are truly preoperative factors, it is true that some of these factors are not known preoperatively, but the findings that we have, such as age and extrathyroidal extension, can be incorporated in at least up to the surgery.  If we do find gross extrathyroidal extension, we can decide still at that point to perform a central neck dissection.

Regarding whether these patients without lymph node metastases are followed, the same issue still applies that a lot of our patients are treated by an outside endocrinologist and some of them might move away, so we lose a significant amount of them.  But I am still in the process of ascertaining that as well.

The intention of incorporating the two variables of whether neck dissection was performed or whether lymph node was extracted from surgical pathology was meant to adjust for the clinical judgment that could have gone into the decision to perform the extensive surgery.  But it turns out these two variables pretty much filtered out most of the preoperative findings.  It is definitely an exercise in learning, designing a multivariate analysis, and we will keep that for future references.

Regarding whether the location of the lymph node matters, I do not think we can know from this study, and part of the reason we had those subsequent two tables is precisely for that reason.  We wanted to see what variables are important for each of these outcomes.

Biologically or anatomically, when there is data that shows upper pole lesions can spread to lateral neck more easily, that probably pertains to the pattern of drainage by the lymph node change.  Again, our study was not designed to answer these questions.

Regarding ethnicity and smoking, I think that is a curiosity point for us because, unfortunately, we only have about 50 Hispanic patients and over 95% of our patients are nonsmokers reportedly.  Despite this, there is a significant odds ratio and a p value that is fairly close to significance, so that is what intrigued us, and we want to spur further investigation into this area.

Regarding Dr Lindeman's question, again, I cannot comment on the long‑term outcomes because we do not really have that data.

Regarding Dr Hanks' question, we do have that data of history of radiation.  Again, approximately 99% of them deny having any radiation exposure in their past, and that is why I decided not to incorporate that part of the data into the analysis.