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Commentary: pT3N2 non–small cell lung cancer: A heterogenous disease treated with homogenous therapy

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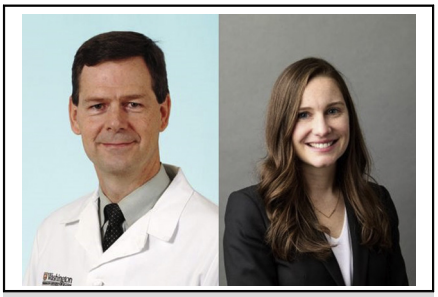

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CENTRAL MESSAGE

The biology of T3N2 non–small cell lung cancer is heterogenous. Currently, all are treated similarly with adjuvant chemotherapy. Should we be doing more to personalize treatment for these tumors?

Current guidelines recommend adjuvant therapy for patients with T3 non–small cell lung cancer (NSCLC) who receive surgery as the initial therapy and are found, surprisingly, to have pathologic N2 disease.[1] For these patients, survival ranges widely from 10% to 40%. That variability reflects the heterogeneity of these tumors, which may in turn be related to the various qualifiers associated with T3 classification: tumor size (5-7 cm), chest wall invasion, and/or multiple tumor nodules in the same lobe.[2-4]

In a recent publication in *JTCVS Open*, Wang and colleagues[3] probe the National Cancer Database to take a deep dive into the care provided and outcomes observed for this group of patients. They found that the 5-year overall survival was quite different among the various T3 qualifier cohorts: from 19.8% (chest wall invasion) to 31.7% (intralobar metastasis). They also found important differences among these T3 subsets in the degree of improvement of survival associated with the addition of adjuvant chemotherapy. In Table 2 of their article, the authors describe the hazard ratios for death associated with the lack of adjuvant therapy for the different subgroups. They found that patients with multiple T3 qualifiers had a 3.36 hazard ratio for death without chemotherapy versus those given adjuvant chemotherapy. This was followed by patients with chest wall invasion who had a hazard ratio of 2.91 for death for surgery alone compared with surgery with adjuvant chemo. Patients declared T3 by tumor size faced a hazard ratio of 2.6 in the absence of chemotherapy, and those T3 by multiple tumor nodules had a hazard ratio of 1.6 for death if they did not receive chemotherapy after surgery. These apparent differences in risk of death without chemotherapy may reflect the different biology of these tumors and response to chemotherapy.

Readers will realize these are nuanced results, given the selection bias and the small number of patients who did not receive chemotherapy, yet despite the tumor heterogeneity, we seem to be saddled with a homogenous adjuvant therapy recommendation: standard chemotherapy. When patients miss an opportunity for upfront chemotherapy due to surprise N2 disease, more options may be useful, but high-quality trials specifying indications and ideal patient populations lag behind the current clinical gap demonstrated by this manuscript. Immunotherapy is currently recommended for patients with pT3N2 who have already had adjuvant chemotherapy.[1] In 2018, Forde and colleagues[5] demonstrated that neoadjuvant nivolumab created a dramatic major pathologic response in 45% of resected stage I-IIIA NSCLC in both PD-L1–positive and PD-L1–negative tumors. Since then, multiple ongoing trials are evaluating the effect of immunotherapy for resectable NSCLC.[6-8] These ongoing trials may broaden the indications for adjuvant immunotherapy to additional patients with different biologies, for example, if tumor characteristics other than PD-L1 positivity are shown

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to be associated with a favorable response to immunotherapy. So-called "targeted therapy" has also been shown to dramatically improve outcomes in those with targetable driver mutations.[9,10] However, routine initial use for targeted agents is not well-established for resectable disease. Understanding the molecular genomics behind tumor behavior is increasingly studied and may help us understand how to choose ideal therapies.[11,12] Additional mechanistic studies demonstrating how different genomic alterations affect tumor growth, propensity for metastasis, and response to systemic therapies will likely help guide indications for treatment.

Overall, this paper in *JTCVS Open* reinforces the current recommendation for adjuvant chemotherapy: it certainly is associated with improved survival. It also provides a glimpse at the notable heterogeneity of T3 disease. These findings highlight our lack of understanding about how to choose appropriate treatments in a personalized manner. Current and future ongoing studies will likely shape how we treat advanced disease in a more personalized and less homogenous manner.

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