Editorial

Visiting an old foe: distant recurrence following R0 lobectomy for pathological N0 lung adenocarcinoma

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Lung cancer remains the leading cause of cancer-related death worldwide, with estimated 5-year survival rates for patients with pathological N0 (pN0) non-small cell lung cancer (NSCLC) as low as 56% (1,2). Although these staggering low survival rates could be attributed to a multitude of patient-related and tumor-related factors, recent evidence suggests that these outcomes are most likely related to tumor recurrence and metastasis (1,3-5). In this regard, identification of clinically relevant predictors for tumor recurrence is an integral step towards improving patient prognosis, with a goal of defining a relevant patient cohort that would benefit from possible additional therapies (either induction or adjuvant therapy).

In the current era however, there still remains limited evidence regarding predictors of overall survival (OS), disease-free survival (DFS) and distant recurrence in patients in patients with early stage (N0) NSCLC. To address this knowledge gap, Brandt and colleagues provide a useful assessment of factors associated with distant recurrence following R0 lobectomy for pN0 lung adenocarcinoma in their retrospective single-center analysis of 893 patients over a median follow-up of 35 months (1). Importantly, this study highlights several findings which warrant a closer review in order to assess their overall validity and usefulness in clinical practice.

First, this study underscored the concerning fact that distant recurrence rates remain high for larger T stage tumors despite contemporary optimal surgical approaches and node-negative disease. For instance, Brandt *et al.* found a 5-year cumulative incidence of distant recurrence of 14% and on multivariable analysis, demonstrated that large tumors sizes (pT2a and pT2b/3 tumors) were associated with distance recurrence and DFS (1). This makes intuitive sense and several existing studies corroborate these findings (6-8). One study for instance, found that tumor size >2.7 cm was an independent risk factor for local recurrence (6). Similarly, Wu *et al.* have previously demonstrated that tumor size was a predictor of all recurrence in patients with stage I lung cancer, but not distant recurrence (7). The study also found large tumors (3–5 cm) had a higher risk of distant metastasis (7).

The role of adjuvant therapy in large tumors largely remains unclear. The Cancer and Leukemia Group B (CALGB) 9633 trial evaluated benefit of paclitaxel and carboplatin versus placebo for pT2N0M0 NSCLC and found no difference in DFS or OS, but post ad-hoc analysis suggested tumors >4 cm treated with adjuvant experienced improved DFS and OS versus placebo (9). The impact of induction therapy (chemoradiation) on outcomes following T3/T4 N0 NSCLC is also not well elucidated but may be reasonable in select cases (8).

As noted in the study by Brandt *et al.*, lymphovascular invasion (LVI) was also associated with distance recurrence and DFS (1). In the complete case analysis, this relationship was not evident likely due to small sample size. However, largely, these findings were consistent with other studies in the literature (10-12). For instance, Kiankhooy and colleagues demonstrated that LVI was a predictor of

any recurrence and multi-site recurrence in 532 patients with stage IA to IIA NSCLC (11). Similar findings were observed in a meta-analysis by Mollberg and colleagues of patients with stage I NSCLC (13). As per NCCN guidelines, LVI is a "high-risk factor" that may provide the basis for consideration of adjuvant therapy on a case-by-case basis, although isolated LVI is currently not an indication for adjuvant therapy (level 2A evidence) (10,11,14).

Contrary to existing studies, histologic subtype was not a significant predictor for OS and DFS in this study. This finding may be due to the sample size since solid predominant and micropapillary subtypes have been shown to be independent predictors of DFS and distance recurrence (15,16). In fact, micropapillary histologic subtype, which is more frequently seen in solid nodules on high-resolution computed tomography has also been shown to be associated with higher frequency of LVI and lymph node metastasis (16). Thus, findings of micropapillary component in adenocarcinoma, which can possibly be identified preoperatively should raise concern for likely high-grade recurrence potential.

What was interesting was that anaplastic lymphoma kinase (ALK) translocations and epidermal growth factor receptor (*EGFR*) mutations were not associated with distant recurrence, which could be explained by the loss of power in the setting of missing data. However, recent studies have demonstrated the prognostic implications of oncogenic genetic alterations which encompass the *ALK*, *EGFR*, and Kristen rat sarcoma viral oncogene homolog (*KRAS*) mutations (17-19). Although these genetic mutations in the context of NSCLC still remain relatively not well elucidated, but some studies have shown to be associated with worse prognosis, especially in younger patients (17-19). There is also emerging evidence to suggest the possible role of epithelial-mesenchymal (E-M) transition as a vehicle for cancer metastasis. One study for instance, found a substantial expression levels of Twist, Snail and E-cadherin—important transition regulators involved in the E-M process—and which were significant prognostic predictors in patients with pN0 NSCLC (i.e., associated with worse recurrence free survival, and worse OS) (3).

In terms of distant recurrence, not surprisingly, several tumor features such as maximum-standardized update value (SUV max) were associated with increased rates of distance recurrence (1). This is also consistent with other studies (20,21). One study found that high positron emission tomography (PET)-SUV max (exceeding 3.3) of the primary tumor was associated with elevated risk of nodal disease in peripheral T1a N0 NSCLC patients (20). Likewise, Xie *et al.* demonstrated that positive findings at preoperative PET in the mediastinum appeared to have prognostic implications despite mediastinal lymph nodes being histologically negative, as these were associated with higher observed rates of local-regional and distant failure (21). This fact further emphasizes the role of accurate staging with mediastinoscopy and lymph node sampling.

In addition to LVI, visceral plural invasion and lymphovascular space invasion have also been implicated to play a crucial role in locoregional recurrence after surgical resection (6). In one study for instance, tumor spread through air spaces (STAS), based on histopathological evaluation, was a significant risk factor for local recurrence in early-stage lung cancer, especially after limited resection. The STAS-positive group was associated with presence of micropapillary and/or solid components in patients with adenocarcinoma and with lymphovascular and pleural invasion (22). Nonetheless, pathological and molecular significance of STAS remains to be determined in the context of pN0 disease and R0 resection.

Likewise, optimal margin distance is another area of interest with important implications on overall prognosis. For instance, according to one study, for patients undergoing sub-lobar/wedge resection for early NSCLC, increasing the margin distance ≤15 mm significantly decreased the local recurrence risk, with no evidence of additional benefit beyond 15 mm (23). Furthermore, in a pooled analysis of 138 patients with lesions less than or equal to 2 cm undergoing wedge resection over a mean follow-up of 49.6 months, increased margin distance was independently associated with longer survival (hazard ratio 0.94). Interestingly, margin distance greater than 9 mm was associated with longest recurrence-free survival and a margin distance greater than 11 mm was associated with longest OS (24).

Overall, strict adherence to National Comprehensive Cancer Network (NCCN) guidelines in terms of anatomic resection, negative margins, assessment of hilar/mediastinal lymph nodes and examination of three or more mediastinal nodal stations is essential to ensure overall improvement in survival. Current National Cancer NCCN guidelines suggest chemotherapy for patients with high-risk features, including size >4 cm (level 2A evidence) (25). However, attainment of these consensus-based "target" metrics unfortunately still remains low (14). Likewise, there exists variations in the treatment observed among NCCN institutions especially given lack of level 1 evidence in

managing stage I NSCLC. Additionally, the impact of patient and physician preference may need to be explored further.

In summary, the study by Brandt *et al.* provides a useful framework for identifying risk factors for tumor distant recurrence and metastasis. Furthermore, it adds to the growing body of literature to support use of adjuvant therapies in patients with large tumors and LVI, despite achieving R0 resection in the setting of pN0 nodal disease. This area, however, remains largely controversial with lack of randomized studies to help guide clinical judgement. Regardless, treatment decisions even in the context of early stage NSCLC should warrant a multi-disciplinary team-based treatment model in order to further improve overall surgical and oncologic efficiency of surgical resection, wherever possible.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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