



Incidence of bronchopleural fistula after pneumonectomy in an era of revolution

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Comment on: Skrzypczak P, Roszak M, Kasprzyk M, *et al.* The technique of stump closure has no impact on post-pneumonectomy bronchopleural fistula in the non-small cell lung cancer—a cross-sectional study. *J Thorac Dis* 2022;14:3343-51.

Keywords: Pneumonectomy; bronchopleural fistula (BPF); neoadjuvant therapy; immunotherapy

Submitted Oct 31, 2022. Accepted for publication Dec 30, 2022. Published online Feb 17, 2023.

doi: 10.21037/jtd-22-1545

View this article at: <https://dx.doi.org/10.21037/jtd-22-1545>

Immunotherapy is revolutionizing the field of lung cancer. With growing experience and surgical volume, more and more lung resections are being undertaken after neoadjuvant therapy, which can now include upfront immunotherapy (1-3). While it's difficult to tease out every nuance, Checkmate 816 trial suggests that neoadjuvant immunotherapy will drive the pneumonectomy rates down as the proportion of more parenchymal-preserving surgery, such as a lobectomy, will rise (1). By the same token, neoadjuvant immunotherapy may indeed render more unresectable hilar tumors resectable and may even introduce a novel concept of salvage resection for recurrence with completion of definitive therapy months to years prior. However, upfront immuno- or immuno-chemotherapy, and especially concomitant radiation, may pose a higher-risk of peri-operative complications, especially the incidence of bronchopleural fistula (BPF) (4,5). The concept of 'abscopal effect' is commonly used to justify the addition of radiation to immunotherapy, as the addition of radiotherapy to immune-checkpoint inhibitors has demonstrated a synergistic effect (6,7). The two modalities combined have an enhanced response in both local and distant (i.e., non-radiated) tumors and yields superior tumor responses that then translates into improved survival outcomes (albeit in metastatic settings) (8). This phenomenon may prove

to have value in neoadjuvant setting in years to come (9). Given that 24% of the patients can have a complete pathological response after neoadjuvant immunotherapy (1), patients treated with additional preoperative radiation may almost certainly yield even higher response rates, thus opening up a larger surgical pool than ever before. However, these patients will undoubtedly pose a greater challenge when they undergo a planned pneumonectomy or suddenly become resectable or worse if they re-surface with a recurrence and then get considered for salvage resection in the setting of fibrosis from prior radiation. Needless to say, the routine addition of immunotherapy in the neoadjuvant setting may present unique and varying challenges as we know nothing about the potential harm it can have to bronchial stumps and vascularity thereof. While this novel treatment strategy does open up a larger surgical pool, it also opens up a larger cohort of perioperative complications with BPF as the most feared of it all.

Skrzypczak *et al.* have performed an excellent review of their experience of 472 pneumonectomies and BPFs over a period of 11 years at a single institution (10). Amongst the 455 patients who underwent an R0 resection with complete mediastinal lymphadenectomy, they found that neither the hand-sewn *vs.* stapled technique nor the buttressing made a difference in the BPF rate, but

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indeed the side of the pneumonectomy (right *vs.* left) did. While the study strengthens the long-standing dogma of right sided pneumonectomies' being fraught with more complications than the left given the more vertical anatomy of the bronchus and single *vs.* dual blood supply to the stump, it was not clear from the study if they also analyzed other potential contributing factors to the incidence of the BPF. These include the use of neoadjuvant therapy especially radiation as it may have a stronger association with the incidence of BPF, when compared to immuno-chemo-radio naïve patients. It would have also been extremely important to include preoperative steroid use and preoperative smoking as well as number of days when smoking was quit prior to surgery as both have been shown to increase the risk of pulmonary complications, prolonged ventilation, risk of reintubation, and hence a higher risk of BPF formation (11,12). Historically, the teaching has been to prophylactically reinforce the stump with viable tissue especially if the surgeon felt that wound healing can be compromised in the setting of prior radiation or smoking or possibility of postoperative radiation therapy (13-15).

Since the authors chose to discuss the incidence of BPF within 30 days from surgery and not within 5–7 days peri-operatively, lots of these contributing factors, and not technique alone, could have accounted for the development of the BPF. Other confounding factors such as the use of intra-operative or postoperative pressors *vs.* inotropes and ischemia generated from staplers over hand-sewn techniques can compromise blood flow to both the stump and buttressed tissue. The authors nicely demonstrated that when patients were compared in the latter era (2013–2019) to an earlier time period (2006–2012), the primary thing that changed was the increased use of staplers and the 'lesser' use of vascularized buttressing, and yet the incidence of BPF did not change. This supported their hypothesis that technique did not impact the incidence of BPF. And so, when comparing the side of the pneumonectomy and its impact on the development of a BPF, that indeed still withstood the test of time. Despite these shortcomings listed above, the study by Skrzypczak *et al.* did affirm our clinical experience 'down to the T' and was overall meticulously designed.

Looking forward, while a randomized study to determine if the technique and buttressing really impact the incidence of postoperative BPF, the accrual will likely have to include multiple institutions and may take years to obtain a large 'n'. Albeit difficult, perhaps another review of this patient population data can be fine-tooth combed

to sift another study where a clear 1:1 propensity score matching of patients with BPF with patients who did not develop a BPF can be performed while controlling for all potential morbidities that can impact stump perfusion, such as diabetes, peripheral vascular disease suggesting compromised vascularity, preoperative smoking and/or radiation, and/or neoadjuvant therapy, amount of blood loss, use of intraoperative pressors, and prolonged *vs.* re-intubation (12,15). Such a detailed analysis will help the readers truly understand the impact of technique and buttressing on the incidence of BPF.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1545/coif>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Khaitan PG. Incidence of bronchopleural fistula after pneumonectomy in an era of revolution. *J Thorac Dis* 2023;15(2):226-228. doi: 10.21037/jtd-22-1545