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Commentary: The enemy of good: Wishing we always have randomized data

R. Taylor Ripley, MD, Bryan M. Burt, MD, and Shawn S. Groth, MD, MS

Bryan M. Burt, MD, R. Taylor Ripley, MD, and Shawn S. Groth, MD, MS

CENTRAL MESSAGE

Adjuvant chemotherapy should be considered after surgical resection for stage I and II pulmonary sarcomatoid carcinoma.

In this article, Abdallah and colleagues¹ sought to establish guidelines for adjuvant therapy after resection of pulmonary sarcomatoid carcinoma (PSC). As the authors note, this tumor is a rare variant of lung cancer, constituting <1% of all lung cancers, with minimal published evidence to guide management, including the indications for adjuvant therapy. They performed a retrospective study of the National Cancer Database (NCDB) for patients diagnosed with PSC between 2004 and 2015. They found that adjuvant chemotherapy was associated with improved overall survival for patients with stage II and III (but not stage I) PSC, consistent with treatment recommendations for other non–small cell lung cancer (NSCLC) histologies.

Randomized controlled trials have provided significant evidence to guide NSCLC treatment. Seminal trials, such as the IALT (International Adjuvant Lung Cancer Trial) and ANITA (Adjuvant Navelbine International Trialist Association) have demonstrated a significant survival benefit for cisplatin-based chemotherapy for patients with completely resected NSCLC.^{2,3} However, little is known about any specific benefit for rare NSCLC histologies, forcing clinicians who care for these patients to extrapolate treatment recommendations from the best available evidence. While a randomized controlled trial to guide all treatment recommendations may be ideal, it is often not practical. To establish a benefit of adjuvant chemotherapy,

the IALT randomized 1867 patients from 148 centers in 33 countries, and the ANITA randomized 840 patients from 101 centers in 14 countries. These trials required many years for follow-up data and large numbers of patients for adequate statistical power. Trials of this size would not be feasible for a tumor as rare as PSC.

The use of large cancer registries like the NCDB provide a unique opportunity to study rare malignancies.⁴ Nonetheless, observational studies using large administrative databases and cancer registries are not without limitations. Selection bias is a particular concern. Indeed, Abdallah and colleagues report that in the nonmatched analysis, patients who received adjuvant therapy were younger, had private insurance, a higher rate of adjuvant radiotherapy, and fewer comorbidities. When studying survival following cancer treatment, information on recurrence and disease-specific survival would be beneficial, but the NCDB does not provide this information to researchers.⁴ Furthermore, the NCDB also lacks data on functional status, recovery from surgery, and other variables critical to determining whether a particular patient is fit for adjuvant therapy. These missing variables are particularly important when using cancer registry data. Although propensity score matching is a common tool for assessing causal inference from observational data, it can have the opposite of the intended effect when there is an imbalance between unmatched variables; matching can increase the discrepancy between groups and bias in the model.

Despite the limitations of the data, Abdallah and colleagues should be commended for establishing the highest available level of evidence for this rare disease. Their conclusions will likely influence our recommendations and tumor board discussions for the foreseeable future.

From the Division of General Thoracic Surgery, The Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Tex.

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Address for reprints: R. Taylor Ripley, MD, Division of General Thoracic Surgery, Department of Surgery, Baylor College of Medicine, 7200 Cambridge St, Suite 6A, Houston, TX 77030 (E-mail: R.Taylor.Ripley@bcm.edu).

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Commentary: Resected pulmonary sarcomatoid carcinoma—a defined treatment paradigm, or just the end of the beginning of the search?

Timothy J. P. Batchelor, BSc, MBChB, MSc, FRCS(CTh)

Events at a cellular level help to explain the behavior of pulmonary sarcomatoid carcinoma (PSC). This rare tumor is a form of non-small cell lung cancer (NSCLC) characterized by a change from an epithelioid subtype to a sarcomatoid subtype. Spindle and/or giant cells are seen. At least 10% of the tumor must have undergone such sarcomatoid change for it to be classified as PSC according to the World Health Organization.¹ Because this change represents a form of high-grade tumor progression, the survival is correspondingly poor stage for stage when compared with more common forms of NSCLC.

Members of lung cancer multidisciplinary teams, including thoracic surgeons, are not often called on to

Timothy J. P. Batchelor, BSc, MBChB, MSc, FRCS(CTh)

CENTRAL MESSAGE

Adjuvant chemotherapy should be offered to patients with resected stage II and III pulmonary sarcomatoid carcinoma, but the search for more targeted therapies continues.

make management decisions regarding PSC. Attitudes about treatment and prognosis may tend toward nihilism. This is not altogether unreasonable given the poor prognosis and the lack of a firm evidence base for treatment. In unresected disease, patients often respond poorly to first-line chemotherapy.²

In an attempt to improve the lot of patients with PSC who have undergone lung resection, adjuvant chemotherapy is often recommended. Until now, there has been little evidence to back this up. This raises questions about such patients being exposed to unnecessary harm. Abdallah and colleagues³ have clearly had similar reservations and have performed a retrospective study using the National Cancer Database, identifying patients with resected PSC. Following some statistical manipulations, including propensity matching, they found that adjuvant chemotherapy appears to confer a long-term survival advantage in stage II and III disease. No such benefit is seen in stage I disease. The study has

From the Department of Thoracic Surgery, University Hospitals Bristol & Weston National Health Service Foundation Trust, Bristol Royal Infirmary, Bristol, United Kingdom.

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Address for reprints: Timothy J. P. Batchelor, BSc, MBChB, MSc, FRCS(CTh), Department of Thoracic Surgery, University Hospitals Bristol & Weston NHS Foundation Trust, Bristol Royal Infirmary, Bristol BS2 8HW, United Kingdom (E-mail: tim.batchelor@uhbw.nhs.uk).

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