

Current Evidence Does Not Warrant Frozen Section Evaluation for the Presence of Tumor Spread Through Alveolar Spaces

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• **Context.**—Tumor spread through alveolar spaces (STAS) has been correlated with unfavorable prognosis in lung adenocarcinomas treated with sublobar resection, but it is unknown whether STAS can be reliably identified in frozen section (FS) to help stratify patients for lobectomy or sublobar resection.

Objective.—To evaluate STAS in FS.

Design.—Tumor spread through alveolar spaces was evaluated in hematoxylin-eosin–stained FS, FS control slides, and all additional slides with lung tissue adjacent to tumor (AdLT) from 48 pT1–2 adenocarcinomas operated on using video-assisted thoracotomy (n = 25) or open thoracotomy (n = 23). The samples included lobectomies (n = 27) and sublobar resections (n = 21). The STAS incidences were compared by FS versus FS control versus AdLT, video-assisted thoracotomy versus open thoracotomy, and lobectomy versus sublobar resection. Sensitivity, specificity, and positive and negative predictive values of STAS⁺ findings were calculated. The literature was queried

for best evidence regarding incidence and predictive value of STAS in FS.

Results.—Tumor spread through alveolar spaces positivity was identified in 46 of 48 cases (95.8%), including 23 FS (47.9%), 32 FS control (66.7%), and 43 AdLT (89.6%). The STAS incidence was significantly higher in AdLT than in FS or FS control. Only 2 of the 25 cases that were STAS[−] in FS were true negatives. Frozen section sensitivity to detect STAS positivity was 50%, with a 100% positive predictive value and 8% negative predictive value. Systematic literature review identified no evidence regarding STAS identification in FS.

Conclusions.—The sensitivity and negative predictive value of FS for STAS detection are unacceptably low. There are insufficient data to support intraoperative detection of STAS as a useful predictive feature to help stratify patients for lobectomy or sublobar resections.

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Pathologists have generally regarded the presence of detached tumor cell clusters seen in alveolar spaces adjacent to a carcinoma as a technical artifact resulting from dislodgment of tumor cells during surgical manipulation and/or subsequent tissue processing in the laboratory, but the significance of this histopathologic finding has been controversial. An alternative hypothesis, proposed in 1995 by Colby et al,¹ suggested that the detached tumor cell clusters within alveolar spaces adjacent to a carcinoma represent in vivo tumor spread through alveolar spaces rather than a laboratory artifact. Pezzella et al^{2,3} supported this concept in 2 studies describing “an alveolar/non-angiogenic pattern” of tumor growth in 8 of 36 resected pulmonary metastases from a variety of primary carcinomas (22.2%), and in 80 of 500 resected early-stage non–small cell lung cancers (16%). Both studies described the presence of

tumor cells filling alveoli in areas showing intact lung architecture, and emphasized that the absence of neoangiogenesis, tumor-associated stroma, and tissue destruction distinguishes this pattern of tumor spread from metastasis through lymphatic and/or vascular channels. Shiono et al⁴ reported the presence of “aerogenous spreads with floating cancer cell clusters (ASFC) at least 0.5 mm from the main metastatic lesion” in 49 of 96 resected pulmonary metastases from colorectal primaries (51%) and demonstrated that the presence of a positive surgical margin and/or 10 or more aerogenous spreads with floating cancer cell clusters were each predictive for pulmonary recurrences. Interestingly, their study reported no significant difference in the number of aerogenous spreads with floating cancer cell clusters observed in lobectomy and limited resection specimens. In 2013 Nitadori et al⁵ proposed the term “tumor spread through alveolar spaces (STAS)” to describe this interesting finding, a nomenclature that is currently used in the pathology literature. The concept of STAS is based on its association with less favorable prognosis, but it remains controversial because it is difficult to completely exclude the possibility that friable tumor cells could be displaced during surgery or tissue processing within the pathology laboratory, introducing a variable that would be difficult to distinguish from “true” intra-alveolar tumor spread. Thunnissen et al⁶ recently cautioned against misdiagnosing tumor cell dis-

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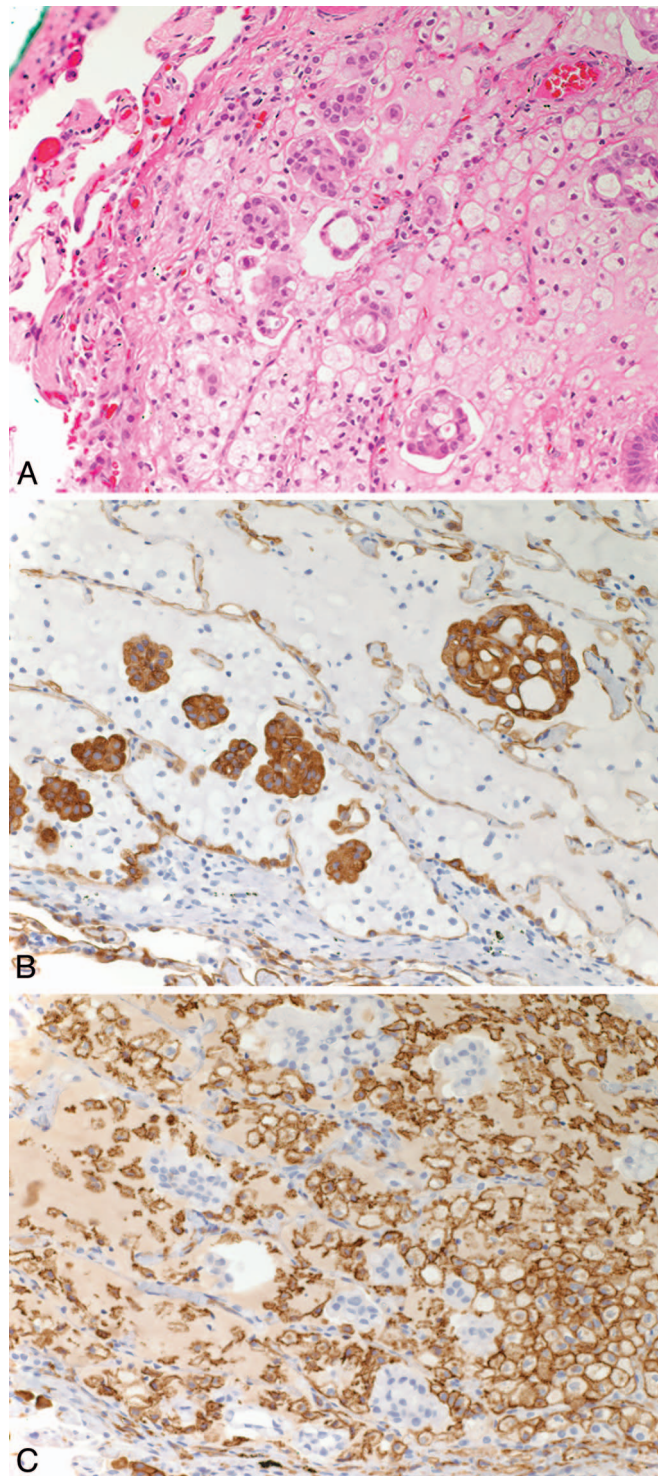
placement during sectioning—a phenomenon that they designated STAKS (“spreading through a knife surface”)—as STAS.

Tumor spread through alveolar spaces is frequently seen in lung resection specimens containing primary and metastatic tumors, and the concept that STAS is a form of aerogenous tumor spread rather than a histologic artifact is supported by several studies showing a significant correlation between STAS presence and decreased overall survival and/or increased risk of tumor recurrence in patients undergoing lung resections for primary lung adenocarcinomas. For example, Warth et al⁷ observed STAS in 288 of 569 resected primary lung adenocarcinomas at various stages (50.6%), and demonstrated that it was associated with reduced overall and disease-free survival. In other retrospective, nonrandomized studies of lung adenocarcinoma patients, Nitadori et al^{5,8} and Kadota et al⁹ also showed a significant association between STAS and an increased risk for tumor recurrence in patients who underwent sublobar resection but not in those who were treated with lobectomy. These observations raise the practical question of whether the presence of STAS should be evaluated intraoperatively with frozen sections (FSs) as a predictive feature that could be used by thoracic surgeons to stratify patients with lung cancer for lobectomy or sublobar resection.

Evidence-based pathology advocates the use of best available scientific data (evidence) from the literature and personal experience to guide the diagnosis and treatment of individual patients.^{10,11} We evaluated the presence of STAS in the FS and other available slides from cases of pulmonary adenocarcinoma operated on at our institution and queried the pathology literature for current best evidence regarding these issues.

MATERIALS AND METHODS

After approval by our Institutional Review Board, the surgical pathology database at our medical center was searched for resected pulmonary pT1–2 adenocarcinomas that had been diagnosed intraoperatively by FS and resected during the same operation. Specimens from patients with previously treated primary lung tumors, metastatic tumors, and cases in which tumor cells were observed beyond the confines of tissue sections on slide review (indicating probable contamination in the histology laboratory) were excluded. The study cohort included 2 groups of randomly selected cases: tumors resected via video-assisted thoracoscopic surgery (VATS; n = 25) and tumors resected via open thoracotomy (OT; n = 23). The 2 groups were selected to investigate whether the VATS procedure, requiring more tissue manipulation to remove a lung specimen through a considerably smaller space than via OT, resulted in a higher incidence of STAS. Seven different thoracic surgeons performed the lobectomies (n = 27) and sublobar resections (n = 21). If the results provided a suitable data set, survival data were available for analysis from our tumor registry. The adenocarcinomas were reclassified according to the 2015 World Health Organization classification, and the predominant histologic subtype was determined using the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma criteria.^{12,13} Using a double-headed microscope, 2 experienced pathologists searched for STAS on hematoxylin-eosin–stained FS slides, slides from the FS control block (FSC), and all other slides with lung tissue adjacent to tumor (AdLT). The criteria proposed by Warth et al,⁷ Kadota et al,⁹ and Ohe et al¹⁴ were used to diagnose STAS, and tumor cells that were attached to alveoli or present within lymphatic or vascular spaces or in the stroma were excluded. Immunostains for cytokeratin 7 (Leica Biosystems Inc, Buffalo Grove, Illinois) and CD163 (Leica Biosystems) were used in selected cases to



Tumor spread through alveolar spaces (STAS). A, Detached tumor cells within alveolar spaces separate from the main tumor. B, Tumor cells highlighted with immunohistochemical stain for cytokeratin 7. Alveolar macrophages are negative for cytokeratin 7. C, Alveolar macrophages highlighted with immunohistochemical stain for CD163. Tumor cells are negative for CD163 (hematoxylin-eosin, original magnification $\times 200$ [A]; original magnification $\times 200$ [B and C]).

distinguish tumor cells from clustered alveolar macrophages (Figure). The following features were recorded: presence/absence of STAS, number of detached tumor cell groups observed in alveolar spaces adjacent to the tumor (0 groups, 1–5 groups or >5 groups),

Table 1. Specific Questions Formulated to Query for the Presence of Tumor Spread Through Alveolar Spaces (STAS) in Pulmonary Resection Specimens

What is the overall incidence of STAS?
What is the incidence of STAS on frozen section slides?
What was the duration of fixation prior to tumor sectioning described?
What is the incidence of STAS on frozen section control slides?
What is the incidence of STAS in additional sections of nonneoplastic lung tissue?
What is the histologic subtype of adenocarcinoma in cases with STAS?
Was the surgery performed using video-assisted thoracoscopic surgery or open thoracotomy?
What surgical procedure was performed (lobectomy, segmentectomy, wedge resection, other)?
What clinical outcome data were available (overall survival, disease-free survival, local recurrence rate)?
Was there a significant association between STAS and prognosis by surgical procedure?

Table 2. Patient and Tumor Characteristics (N = 48)

	OT (n = 23)	VATS (n = 25)
Age, y, median (range)	67.5 (51–85)	73 (51–87)
Sex, No., female:male	12:11	11:14
Tumor size, cm, median (range)	1.5 (0.4–5.4)	1.5 (0.9–4.6)
Predominant histology, No.		
Acinar	15	10
Mucin-secreting acinar	2	3
Papillary	3	1
Micropapillary	2	4
Lepidic	0	3
Solid	1	4
Procedure, No.		
Lobectomy	18	9
Trisegmentectomy	0	4
Segmentectomy	1	7
Wedge	4	5
TNM category (all M0), No.		
T1N0	8	18
T1N1	4	0
T1N2	2	0
T1NX	3	1
T2N0	3	1
T2N1	1	0
T2N2	2	0
No. of surgeons	5	2

Abbreviations: OT, open thoracotomy; VATS, video-assisted thoracotomy.

and the maximum distance (<3 alveolar spaces or ≥3 alveolar spaces) from the tumor edge to the detached tumor cells in the FS, FSC, and AdLT slides of each case. In cases with more than 1 FS, FSC, and/or AdLT slide, the total number of STAS groups observed in slides of each type and the single greatest distance of STAS from the tumor edge were recorded per case. The STAS incidence, number of groups, and distance from the tumor edge were compared by FS versus FSC versus AdLT, VATS versus OT, and by lobectomy versus sublobar resection using 2-tailed χ^2 statistics and *P* values <.05 as significant (software available online at www.Medcalc.org; accessed March 27, 2017). Sensitivity, specificity, and positive and negative predictive values of FS and other slides to diagnose STAS were also calculated.

The specific questions shown in Table 1 were formulated to perform a systematic literature review of the English-language literature and query for the incidence of STAS on FS and its possible prognostic or predictive value, using PubMed (National Library of Medicine), Web of Science, and ScienceDirect. The following search terms were used: “STAS,” “tumor spread through air spaces,” “intra-alveolar tumor spread,” “displaced tumor,” “air space invasion,” “aerogenous tumor,” “aerogenous spread,” “tumor islands,” and “free-floating tumor cells” in conjunction with “lung” and “pulmonary.” The abstracts of all retrieved references were reviewed, and case reports, abstracts, and editorial articles were excluded from the study. The level of evidence of each study was assessed using previously published criteria.^{10,11}

RESULTS

The demographics and tumor characteristics of the patients in our study are shown in Table 2. The median age of patients in the VATS group was 5.5 years older than that of patients in the OT group. The VATS group contained a smaller proportion of lobectomies (*P* = .004) and a larger proportion of pT1–2 N0 lesions than the OT group (*P* = .001). No significant differences were observed in sex, median tumor size, distribution of predominant histologic subtypes, or STAS incidence between the 2 groups.

Tumor spread through alveolar spaces was seen in association with tumors ranging from 0.6 to 5.4 cm in diameter and from pT1N0 to pT2N2, across all histologic subtypes of adenocarcinoma, and in cases operated by each of the 7 participant thoracic surgeons. Tumor spread through alveolar spaces was identified in 46 of the 48 cases (95.8%) and was present in 23 of 48 FSs (47.9%), 32 of 48 FSCs (66.7%), and 43 AdLTs (89.6%). However, concordant presence of STAS in the FS, FSC, and AdLT from the same

case was seen in only 18 of the 46 STAS⁺ cases (39.1%). The incidence of STAS positivity was significantly higher in AdLT than in FSC (*P* = .007) and FS (*P* < .001). There was no significant difference in STAS⁺ incidence by FSC versus FS (*P* = .06), lobectomy versus sublobar resection (*P* = .11), or VATS versus OT (*P* = .17). In more than 75% of the 46 STAS⁺ cases, 5 or more tumor cell clusters were seen in alveolar spaces, and/or STAS was present more than 3 alveolar spaces from the tumor edge. No STAS was seen in 25 FSs, but only 2 of these cases were true negatives, with absence of STAS in both the corresponding FSC and AdLT.

Table 3 shows that FS yielded 50% sensitivity, 100% specificity, 100% positive predictive value, and 8% negative predictive value for the detection of STAS. Combining the FS findings with those on the corresponding FSC increased the sensitivity for the diagnosis of STAS from 50% to 76.1% (*P* < .001) and increased the negative predictive value from 8% to 15.4% (Table 3). Because all but 2 of our 48 cases were STAS⁺, the dataset was not suitable to analyze for possible prognostic or predictive value.

Table 4 shows the results of the systematic literature review. Only retrospective case series, describing fairly heterogeneous cases in terms of TNM category and other features, were found, providing only level 4 evidence. The incidence of STAS in T1 to T2 primary lung adenocarcinomas ranged from 80 of 500 cases (16%) to 155 of 411 cases (38%).^{3,9} Tumor spread through alveolar spaces was present in 288 of 569 cases (50.6%) in the study by Warth et al,⁷ which included resection specimens from patients with stages I to IV primary lung adenocarcinomas. In the study by Shiono et al,⁴ STAS was observed in 49 of 96 resected pulmonary metastases from patients with colorectal primaries (51%). Several studies as well as editorials note the potential clinical importance of reporting STAS intraoperatively at a time when it could help guide the extent of

STAS Present in	No. (%) STAS ⁺ Cases	Sensitivity, %	Specificity, %	PPV, %	NPV, %	STAS Presence in Each Data Row Compared With "Overall Presence" Row, P Value (95% CI) ^a
FS slides	23 (50)	50	100	100	8	<.001 (33.0507–65.9962)
FSC but not in FS slides	12 (26.1)	26.1	100	100	5.6	<.001 (56.9954–85.7229)
AdLT but not in FS or FSC slides	11 (23.9)	23.9	100	100	5.4	<.001 (59.3673–87.4238)
FS and/or FSC slides	35 (76.1)	76.1	100	100	15.4	<.001 (10.2028–38.7526)
"Overall presence" of STAS	46 (95.8)					

Abbreviations: AdLT, all additional slides with tumor-adjacent lung tissue; CI, confidence interval; FS, frozen section; FSC, frozen section control; NPV, negative predictive value; PPV, positive predictive value.

^a Overall presence = FS, FSC, and/or AdLT.

resection, but none provide any data regarding the incidence of STAS in FS slides or its predictive value.^{9,15–18} Indeed, Morimoto et al¹⁷ state that "it is difficult to diagnose STAS in frozen section because the lung is not sufficiently inflated," and "the diagnosis of STAS is only possible in permanent sections."

DISCUSSION

Our retrospective study demonstrates that although STAS was present in 46 of our 48 cases (95.8%), FS could identify its presence in only 23 of these 46 cases (50%). The incidence of STAS detection was higher in FSC slides and AdLT slides than in FS slides of comparable cases, suggesting that future prospective studies evaluating intraoperative FS for the presence of STAS may benefit from the selection of samples that include larger portions of nonneoplastic lung tissue adjacent to the tumor and/or microscopic examination of additional deeper levels prepared from the frozen tissue block. Because almost all cases in our study exhibited the presence of STAS, the data were not suitable for statistical analysis regarding the impact of

STAS presence on survival, recurrence rate, or other prognostic and predictive variables. Systematic literature review identified no data on the incidence of STAS in FS slides and no information supporting the intraoperative use of STAS presence as a predictive feature.

We cannot explain the substantially higher incidence of STAS observed in our cases than in previous studies (Table 4). We followed the guidelines published by Warth et al⁷ and Kadota et al⁹ to diagnose STAS and confirmed cells as either epithelial cells or alveolar macrophages with immunohistochemical stains in selected cases. Although the number of cases we studied is small, we attempted to avoid selection bias by randomly choosing cases spanning more than 2 decades that were operated on by several different surgeons who performed lobectomies and variously sized sublobar resections, which were sampled by various pathologists and pathology residents. There was no significant difference in the incidence of STAS by OT and VATS or by surgical procedure (lobectomy, wedge resection, segmentectomy, and trisegmentectomy). These results were somewhat surprising, because we had hypothesized that the

Source, y; Total Cases in Study	Cases Studied	STAS Incidence	STAS in FS slides
Pezzella et al, ³ 1997; n = 500	NSCLC pT1–2N0M0	16% of all cases	NR
Onozato et al, ²⁰ 2013; n = 261	Stages I–II lung adenoCA, including 31 MIAs 82 wedge resections 179 surgical procedure NOS	22.2% of all cases	NR
Kadota et al, ⁹ 2015; N = 411	Stage I lung adenoCA 291 lobectomies 120 limited resections	37.7% of all cases 37.5% of lobectomies 38.3% of limited resections	NR
Warth et al, ⁷ 2015; n = 569	Stages I–IV lung adenoCA 472 lobectomies 18 sublobar resections 13 bilobectomies 66 pneumonectomies	50.6% of all cases	NR
Morimoto et al, ¹⁷ 2016; n = 67	67 lung adenoCA with micropapillary component 56 lobectomies 10 sublobar resections 1 pneumonectomy	46.3% of all cases	NR
Shiono and Yanagawa, ¹⁹ 2016; n = 318	Stage I lung adenoCA, included MIA and AIS 202 lobectomies 77 segmentectomies 39 wedge resections	14.8% of all cases 15.8% of lobectomies 11.7% of segmentectomies 14.8% of wedge resections	NR
Current study, 2016; n = 48	Stages I–II lung adenoCA 27 lobectomies 21 sublobar resections	95.8% of all cases 100% of lobectomies 90.5% of sublobar resections	Yes

Abbreviations: adenoCA, adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; NOS, not otherwise specified; NR, not recorded; NSCLC, non-small cell lung cancer.

^a Only studies providing level 4 evidence are available.

VATS group would show a higher incidence of STAS resulting from the detachment of tumor cells during the manipulation required to remove the resected specimen through a smaller chest wall incision. There is limited information about the incidence of STAS by surgical approach or procedure. The surgical approach, OT versus VATS, was mentioned in a study by Shiono and Yanagawa¹⁹ but was not evaluated for its statistical significance. Their study found no significant difference in the incidence of STAS by lobectomy versus segmentectomy or other surgical procedures. Similarly, Onozato et al²⁰ found no significant difference in STAS incidence when they compared wedge resections with “anatomic” resections. More than 75% of our STAS⁺ cases showed 5 or more tumor cell clusters in alveolar spaces and/or STAS 3 or more alveolar spaces from the tumor edge. Warth et al⁷ found no significant difference in overall survival or disease-free survival when they compared patients whose tumors showed “limited” STAS (<3 alveolar spaces from the main tumor) with those whose tumors showed “extensive” STAS (>3 alveolar spaces from the main tumor).

The concept that STAS is a form of intrapulmonary tumor spread rather than an artifact secondary to tissue manipulation during surgery or processing in the pathology laboratory is supported by studies showing that patients whose resection specimens are STAS⁺ have a significantly worse prognosis than those whose specimens lack this finding. However, in the English-language literature we found only retrospective studies of relatively small patient cohorts, providing only level 4 evidence. Moreover, these studies used somewhat different criteria to define STAS⁺, evaluated assorted variables—separately and/or in different combinations (such as patient age, tumor TMN, histologic subtype, extent of STAS, distance of STAS from tumor edge, and tumor proliferation index [Ki-67]), and/or evaluated different prognostic parameters (such as overall survival, disease-free survival, risk of recurrence, and/or time to locoregional, distant, and/or any recurrence). Hence they do not provide comparable data that could be analyzed with meta-analysis. The results are also somewhat variable. For example, some studies have shown an increased risk for tumor recurrence only in patients treated with “limited” (sublobar) resection but not in those undergoing lobectomy, whereas others have shown no significant difference in incidence of recurrence by surgical procedure.^{5,8,9,19} Prognostic data regarding the presence of STAS could also have been biased by the histologic subtype(s) of the adenocarcinomas that were included in each study, particularly by the incidence of micropapillary adenocarcinoma, a tumor subtype associated with worse prognosis.^{7,8,17,20,21} Morimoto et al¹⁷ showed that in tumors with a micropapillary component, the recurrence-free survival in STAS⁺ tumors was similar to that in patients with pT3 tumors, whereas recurrence-free survival in STAS⁻ tumors was similar to that in patients with pT2 tumors.

In summary, our findings and the lack of substantial information in the literature regarding the intraoperative evaluation of STAS with FS suggest that currently there is insufficient evidence supporting the need for routine reporting of STAS in intraoperative FS. Although patholo-

gists may elect to mention the presence of this feature during intraoperative consultation in cases where STAS is seen in FS slides, they should advise thoracic surgeons that to date there are no prospective data showing that this information is useful to help stratify patients for lobectomy versus sublobar resections.

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