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STAS IS AN ARTIFACT

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STAS Limitations

STAS has several limitations with respect to the concept as well as a possible application in limited resections. In 2016 Morimoto and colleagues reported that In frozen sections, the lung is not sufficiently inflated. Therefore, it is difficult to diagnose 'free tumor clusters' in the airspace1. Subsequently, four studies were published as summarized in Table 1. Furthermore, several confounders may have an influence on the occurrence of STAS such as: i) influence of surgeons hands on the tumor cells; ii) clamping artifact during segmentectomy2; iii) removal of lobe through a small hole during video assisted thoracoscopy; iv) influence of pathologists hands on the tumor cells; v) influence of knife during cutting a combination of any of these with lymphangitic spread.

Table 1. Summary of four studies examining STAS on frozen section. N (STAS)= number of cases studied / prevalence of STAS [percentage]; Gold = golden standard; FSC = frozen section control; Personal opinion is opinion from 2 or more of the participating pathologists; Sens = sensitivity; Spec = Specificity; PPV = positive predictive value; NPV = negative predictive value;

	N; (STAS)	Gold	Sens.	Spec.	PPV	NPV	Accuracy	Kappa	Year Reference
Walts	48; (50%)	FSC/ [5)]	50%	100%	100%	8%	-	-	2018[3)]
Eguchi	698; 39%	Personal opinion[1)]	59-86%	74-100%			75%	0.67[1)]	2018[4)]
Villalba	100; 43%[6)]	Personal opinion[2)]	44.2 [7)]	91.2 [8)]	79.2		77% [3)]	0.51[4)]	2021[5)]
Zhou	163; 24%	Permanent section[9)]	55%	80%	48%	85%	74%	0.34	2021[6)]

1) Methodological flaw compared to other studies: cases with artifacts were excluded; Golden standard determined by 2 out of the 5 pathologists; Gwet's AC1 (coefficient 0.67)
2) Golden standard determined by 3 out of the 5 pathologists

3) Mean interobserver agreement after the second round on frozen section;
4) In between first and second round of reading sections was a discussion/learning session. Fleiss kappa mean after second round for STAS (standard error (SE): ± 0.03); for artifact mean kappa 0.30 ±SE 0.03.
5) Concordance presence of STAS in frozen section, frozen section control (FFPE) and adjacent sections was 39%.
6) In frozen section prevalence 43% in FSC 60%; compared to FSC in FS n= 2 out of 43 FP, 5 = FN.
7) 5 observers range first and second round: 20-44% and 28-41%, respectively; see also note 4); overall 44.2%, 95% confidence interval 29-60%.
8) Overall: 91.2%, 95% confidence interval 81-97%
9) STAS present in permanent sections (n=40), STAS also on frozen sections: n=22 (sensitivity 55%). STAS absent permanent sections (n=123), STAS also absent on the frozen sections n=99 (specificity 80%). STAS on frozen sections n=44 (PPV 48%). STAS absent on frozen sections n=117 (NPV 85%).

The concerns of STAS analysis in frozen sections are clearly expressed in the summary of the paper by Villalba and colleagues, which are pathologists with specific interest in pulmonary pathology: “As current accepted definitions for STAS and artifactual clusters are variably interpreted by pathologists, more precise criteria should be established and standardized, possibly by web-based or in-person tutorials, before the assessment of STAS can be implemented globally in the intraoperative setting to aid surgical decision making.” [5)].

1. Morimoto J, Nakajima T, Suzuki H, et al. Impact of free tumor clusters on prognosis after resection of pulmonary adenocarcinoma. *J Thorac Cardiovasc Surg*. 2016;152(1):64-72. doi:10.1016/j.jtcvs.2016.03.088

2. Thunnissen E, Blaauwgeers HJLG, de Cuba EM V., et al. Ex Vivo Artifacts and Histopathologic Pitfalls in the Lung. *Arch Pathol Lab Med*. 2016;140(3):212-220. doi:10.5858/arpa.2015-0292-OA

3. Walts AE, Marchevsky AM. Current evidence does not warrant frozen section evaluation for the presence of tumor spread through alveolar spaces. *Arch Pathol Lab Med*. 2018;142(1):59-63. doi:10.5858/arpa.2016-0635-OA

4. Eguchi T, Tan KS, Montecalvo J, et al. Lobectomy Is Associated with Better Outcomes than Sublobar Resection in Spread through Air Spaces (STAS)-Positive T1 Lung Adenocarcinoma: A Propensity Score–Matched Analysis. *J Thorac Oncol*. 2018;14(1):87-98. doi:10.1016/j.jtho.2018.09.005

5. Villalba JA, Shih AR, Sayo TMS, et al. Accuracy and Reproducibility of Intraoperative Assessment on Tumor Spread Through Air Spaces in Stage 1 Lung Adenocarcinomas. *J Thorac Oncol*. 2021;16(4):619-629. doi:10.1016/j.jtho.2020.12.005

6. Zhou F, Villalba JA, Sayo TMS, et al. Assessment of the feasibility of frozen sections for the detection of spread through air spaces (STAS) in pulmonary adenocarcinoma. *Mod Pathol*. July 2021. doi:10.1038/s41379-021-00875-x