Prognostic significance of limited resection and lobectomy and the role of adjuvant chemotherapy in Lung Adenocarcinoma with Spread Through Air Spaces

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ABSTRACT

Background: Tumor spread through air spaces (STAS) has recently been recognized as a form of tumor invasion having an unfavorable prognosis in patients with early-stage lung adenocarcinoma. But the association between STAS and procedure-specific outcomes(limited resection and lobectomy) in different clinicopathologic features and the significance of adjuvant chemotherapy have not been studied well

Methods: We retrospectively reviewed 1059 patients who underwent lobectomy (n=916) or limited resection (n=154) for lung adenocarcinoma with STAS from 2015 to 2020. 916 (773 of lobectomy and 143 of limited resection) of them were finally enrolled in the study cohort. We divided the study population into groups according to type of surgery, i.e., lobectomy vs. limited resection, and to adjuvant chemotherapy, i.e., with ACT vs. without ACT. Propensity score matching was performed to reduce confounding bias between surgical groups. Stratums were determined concomitantly by pathological T stage. Outcomes were analyzed by using Kaplan-Meier and Cox proportional hazards model.

Results: For overall survival and recurrence-free survival after propensity score matching (138 pairs), Kaplan-Meier analysis revealed that there was no significant difference between limited resection group and lobectomy group (P=0.216 and P=0.221 respectively). Univariate analysis revealed that pathologic stage was a prognostic factor in either the limited resection group or lobectomy group. For the recurrence-free survival, the presence of pleural invasion predicted poorer prognosis in both univariate and multivariate analyses (RFS hazard ratio [HR] 3.341, 95% confidence interval [CI] 1.291-8.647, P=0.013). Adjuvant chemotherapy was a significant risk factor for the lobectomy group (p=0.008) but not limited group (P=0.115). In a stratified subgroup based on with and without adjuvant chemotherapy, adjuvant chemotherapy was significantly associated with poorer outcomes for those undergoing lobectomy group among patients with stage I (3y-RFS: 93.3% vs. 79.6%).

Conclusions: Limited resection wasn't a significant prognostic factor for lung adenocarcinoma patients with STAS in the short-term follow up and adjuvant chemotherapy was not indispensable for them after surgery.

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INTRODUCTION

Spread through air spaces (STAS) was recognized as an additional invasive pattern of lung adenocarcinoma(ADC) beyond non-lepidic pattern, stroma infiltration and adjacent structure invasion.
For a long time, it has been reported that lobectomy, which is reputed to be the standard of care for the management of early-stage lung adenocarcinoma patients, was associated with better prognosis and lower local recurrence than limited resection (generally including wedge resection and segmentectomy) of resected stage I lung adenocarcinoma. But the latest phase 3 trial suggested that segmentectomy should be the standard surgical procedure for patients with small-peripheral NSCLC.
There have been some conflicting findings in literature regarding perform lobectomy when STAS is present, which has important treatment implications. Kadota et al. reported that STAS was a crucial risk factor of recurrence in stage I ADC underwent limited resection but not in those who were treated with lobectom. Many recent results chimed with this finding in early-stage tumors. However, other studies have found that prognosis after limited resection was comparable with that of lobectomy in lung ADC with STAS without increasing locoregional recurrence.
Additionally, grounded in an initial study by Donglai Chen et al. illustrated that adjuvant chemotherapy brought better outcomes for patients with stage IB ADC/STAS-positive and those with stage IA ADC/STAS-positive who underwent limited resection, we also explored the potential benefits of ACT in patients with early-stage ADC/STAS-positive who underwent limited resection in our subgroup analysis.

METHODS AND MATERIALS

The records of all patients with STAS-positive lung tumors who underwent limited resection or lobectomy at the Shanghai Chest Hospital between May 2015 and October 2020 were reviewed. Patients who received surgical treatment with pathology confirmed ADC with STAS and had complete follow-up data were included in this retrospective study. Cases with neoadjuvant therapy, multiple nodules, pneumonectomy or bilobectomy, other lung cancer surgery within the past 2 years since the surgical date, concurrent other disease progression and positive surgical margin were excluded from the study cohort. We identified a total of 916 patients according to these criteria.

In order to help to balance multiple characteristics in retrospective studies to approximate a random experiment, we use propensity-score matching (PSM) method in our study. Variables included in the model were age at surgery, gender, pathologic stage, pleural invasion (present or not), lymphatic invasion (present or not), vascular invasion (present or not), histologic subtype, CT features (nodule type, spiculated sign, vacuole sign and air bronchogram) and chemotherapy status.

RESULTS

Matching achieved a good balance without P<0.05 for all variables between the two groups.

There was no significant difference in RFS and OS between lobectomy and limited resection (P = 0.697 and P = 0.216, respectively)(Figure1)

Kaplan–Meier analysis(Figure2) revealed that patients received ACT had significantly worse RFS than those without ACT both in all patients (3-y RFS, 92.9% vs. 72.3%, P = 0.002) and lobectomy group (3-y RFS, 94.1% vs. 71.6%, P = 0.021), but not in limited group (P = 0.078)

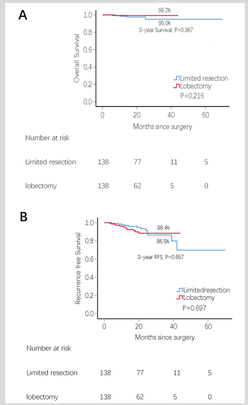


Figure 1. Kaplan-Meier analysis in groups after matching

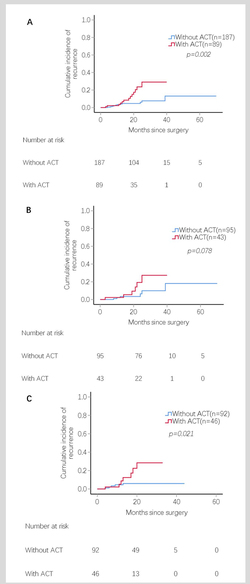


Figure 2. Cumulative incidence of recurrence between ACT+ and ACT- groups

RESULTS

Results of univariable analyses for all survival end points of interest are shown in Table 2. Poor OS and RFS were significantly associated with pleural invasion (OS, P = 0.008; RFS, P< 0.001); pathologic TNM stage and histologic subtype. Factors significantly associated with a higher risk of recurrence were solid nodule and adjuvant chemotherapy. And the univariable analysis revealed that spiculated sign was associated with OS of the patients. However, in multivariate analysis, only pleural invasion, nodule type and histologic subtype (acinar predominant and papillary predominant) remained independently associated with RFS (Table 1)

To further identify the role of ACT in STAS-positive ADC, we selected stage I patients from our primary cohort before PSM. Among patients with stage I ADC/STAS-positive, ACT was associated with worse RFS than without ACT (P < 0.001) (Figure 3), which was observed in both the subgroup of lobectomy (P < 0.001) but not limited resection(P = 0.156)

Variables	OS			RFS		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Pathologic stage						
Stage I	Ref			Ref		
Stage II	0.576	0.017-19.556	0.759	2.798	0.879-8.905	0.082
Stage III	0.897	0.074-10.845	0.932	1.119	0.327-3.829	0.858
Pleural invasion						
Absent	Ref			Ref		
Present	12.028	0.724-199.788	0.083	3.341	1.291-8.647	**0.013**
Histologic subtype						
Invasive nanconma predominant	Ref			Ref		
Acinar predominant	0.007	0.001-0.301	**0.010**	0.063	0.011-0.350	**0.002**
Papillary predominant	<0.001	/	0.940	0.035	0.004-0.307	**0.003**
Micropapillary predominant	0.023	0.001-1.190	0.061	0.191	0.029-1.232	0.082
Solid predominant	<0.001	/	0.987	0.252	0.044-1.437	0.121
Others	0.068	0.001-4.720	0.214	0.136	0.010-1.773	0.128
Nodule type						
Solid				Ref		
Part solid				0.263	0.154-0.649	**0.006**
Spiculated sign						
Absent	Ref			Ref		
Present	12.036	0.883-164.058	0.062	1.685	0.674-4.211	0.265
Adjuvant chemotherapy						
Absent				Ref		
Present				2.713	1.172-6.280	**0.020**

Significant *P*-values are shown in bold

Table1 Multivariate analysis of factors associated with OS and RFS based on univariate analysis

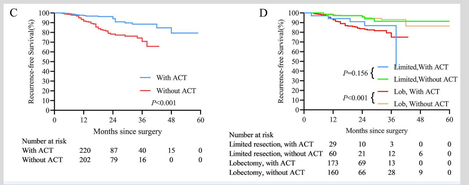


Figure3. RFS survival of patients with ACT and without ACT in stage I patients

DISCUSSION

Many studies supported that STAS is an important predictor of worse clinical outcome (recurrence and survival) in patients with early-stage lung ADC that have undergone limited surgical resection. But to date, the necessity to perform lobectomy for early-stage STAS-positive ADC still remains controversial since data shown prognosis after segmentectomy for patients with STAS-positive lung adenocarcinoma was comparable with that of patients undergoing lobectomy
In our study, we have demonstrated the prognosis of patients who underwent limited resection for STAS-positive lung ADC was comparable with that of patients who underwent lobectomy. Results from our study seemed to be contrary to the conclusions of many previous studies. This difference could be due to the fact that we included larger tumors (>3 cm), which would lead to lower RFS in lobectomy group.
Decisions on optimal surgical procedure in daily clinical practice are mainly grounded on clinicopathologic characteristics, especially findings on CT or PET-CT. So, it's more necessary to build a precise prognostic model considering findings of preoperative CT and PET-CT for limited resection. Definition of STAS implies it's a post-excision diagnosis, which is also difficult to predict intraoperatively.
In this study, we initially found patients received ACT were associated with higher proportion of pleural invasion, vascular invasion, solid nodules and most of them received lobectomy. Risk factors above could effectively predict recurrence and mortality in a prognostic model built for invasive ADC by Liu et al. It may be reasonable that ACT not only didn't bring additional survival benefits in our cohort, but also associated with lower RFS, especially in lobectomy group.

CONCLUSIONS

In conclusion, we have demonstrated that limited resection could achieve comparable survival outcome with lobectomy in STAS-positive ADC in short-term follow-up. ACT bring no prognosis advantage in stage I ADC with STAS either in patients underwent lobectomy or limited resection. But the efficacy of our conclusions should be investigated further by a large-scale, prospective, multicenter study.

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