Original Article

Prognosis and status of lymph node involvement in patients with adenocarcinoma in situ and minimally invasive adenocarcinoma—a systematic literature review and pooled-data analysis

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Background: Adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) have been brought up that substitute for bronchioloalveolar carcinoma (BAC), according to the new classification of lung adenocarcinoma. There has been increasing opinions that argues for the adjustment of lymph node disposition in patients with such early stage tumors. Therefore, we sought to overview the prognosis and status of lymph node involvement in AIS/MIA patients.

Methods: PubMed, Springer and Ovid databases were searched for relevant studies. Data was extracted and results summarized to demonstrate the disposition of lymph nodes in AIS/MIA.

Results: Twenty-three studies consisting of 6,137 lung adenocarcinoma were included. AIS/MIA accounted for 821 of the total 6,137. All included patients received curative surgery. After a review of the summarized data we found that only one patient (with MIA) had N1 node metastasis, N2 disease was not found in any of the included patients. In concordance with this, studies that reported 5-year disease free survival (5-year DFS) have almost 100% rate.

Conclusions: Our findings indicated that patients with AIS/MIA have good survival prognosis after surgical resection, and that recurrence and lymph node metastasis in these patients is rare. Therefore, we strongly encouraged further studies to determine the role of different lymph node disposition strategies.

Keywords: Adenocarcinoma in situ (AIS); minimally invasive adenocarcinoma (MIA); lymph node involvement

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Introduction

Lung cancer is the leading course of cancer-related mortality worldwide, and lung adenocarcinoma represents the most common histological subtype of lung cancer (1). In the past decade, numerous advances have taken place within various fields for lung adenocarcinoma, particularly in molecular biology with the discovery that EGFR and ALK biomarkers are responsive to targeted drugs. However, surgical resection is still the best option for patients with localized non-small cell lung cancer (NSCLC).

With the development of imaging procedures, such as high resolution computed tomography (HRCT), numerous small-sized lung cancers can be detected. Patients in which such small lesions are detected, generally have earlier disease stages at diagnosis, as a result, improved survival (2). Lobectomy with systematic lymph node dissection (SLND) is still the standard surgical treatment for complete resection (3); but, SLND remains controversial especially in the very-early stage NSCLC. Proponents argue that the removal of lymph nodes is important for survival as well as for staging. On the other hand, opponents consider that lymph node removal does not contribute to prognosis and may increase the morbidity and mortality after surgery. Therefore, the predictive factors of lymph node status are important for avoiding excessive surgery.

Recently, a new classification of adenocarcinoma was raised by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/ European Respiratory Society (ERS) (4). The previous definition of BAC is no longer used and is instead called adenocarcinoma in situ (AIS) which is described as small (≤3 cm) solitary adenocarcinomas with pure lepidic growth lacking invasion. A related entity, sometimes previously referred to as minimally invasive BAC, is introduced in the new classification and called minimally invasive adenocarcinoma (MIA). MIA is described as small (≤3 cm) lepidic predominant tumors with ≤0.5 cm of invasion. A number of previous studies showed good survival prognosis for these two categories (5-7). Therefore, we hypothesized limited surgery that avoids excessive lymph node dissection might be appropriate for patients with AIS and MIA.

We performed a systematic literature review and pooled data analysis focusing on the lymph node status and survival prognosis after curative surgery for patients with AIS and MIA and describe our results here.

Methods

Literature search

Medline by PubMed, Springer and Ovid databases were used to search for relevant studies from the date of inception to April 2015. The language was limited to English. We used "adenocarcinoma in situ", "minimally invasive adenocarcinoma", "bronchioloalveolar carcinoma" and "lung adenocarcinoma" in different combinations in all fields. Reference lists of relevant publications were subsequently searched as a supplement.

Study selection

All studies containing patients with AIS or MIA were selected. Because the new classification of lung adenocarcinoma by IASLC/ATS/ERS was only implemented in 2011, we also included the former pure-BAC with tumor ≤3 cm and Noguchi classification (8) of localized BAC (less than 2 cm in diameter) without active fibroblastic proliferation (types A and B) for analysis.

Included studies met the following criteria: (I) studies included patients with AIS or MIA or pure-BAC ≤3 cm or Noguchi type A and type B adenocarcinoma; (II) all patients should underwent curative surgical treatment; (III) included patients did not receive adjuvant chemotherapy and radiotherapy before or after surgery; (IV) the surgical procedure and the situation of lymph node metastasis were clearly stated; (V) studies were limited to human subjects. Studies that included only pathologic-N0 patients were excluded. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded.

Outcome measures

Primary outcome was the number of included patients with lymph node metastasis; 5-year disease free survival (5-year DFS) rates were also assessed.

Data extraction and quality assessment

The full-text articles were reviewed and data were extracted by two independent authors. Any discrepancies were resolved by discussion and came to consensus with a third author. Extracted data included: publication details, study period, median follow-up time, number of included patients, surgical procedure, 5-year DFS rates. The quality of observational studies was modified by criteria suggested by the Newcastle-Ottawa quality assessment tool (9).

Results

Literature search

A total of 1,722 articles were found after the initial literature search. After implementing inclusion and exclusion criteria, and removal of duplicate publications, review articles, case reports, conference presentations, editorials and chapters of books, a total of twenty-three studies were eligible for further analysis (5,7,8,10-29) (*Figure 1*). Between the 23 articles, there were 6,137 lung

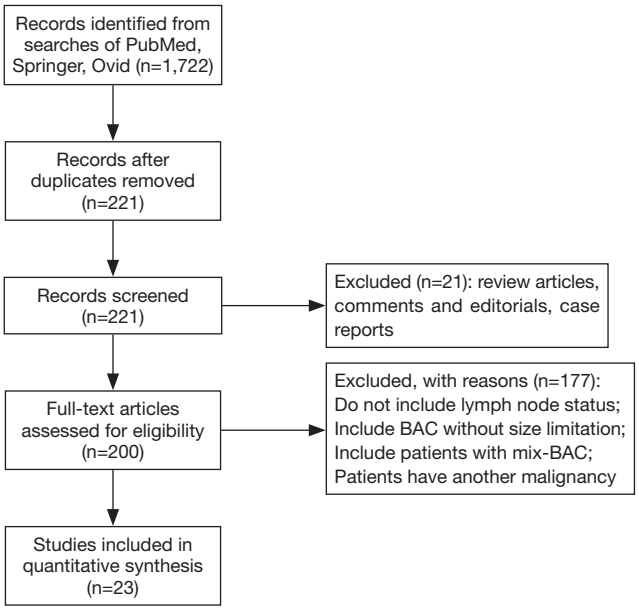

Figure 1 Flow chart of the literature search. BAC, bronchioloalveolar carcinoma.

adenocarcinomas, of which AIS/MIA accounted for 821. All included patients received curative surgical resection. None of the included patients received adjuvant chemotherapy or radiotherapy before or after surgery. Details are listed in *Table 1*.

Detection of N disease, 5-year DFS

Patients with AIS/MIA underwent lobectomy, sublobectomy or wedge resection in combination with either lymph node sampling or SLND in these studies. After a review of the lymph node status, only one N1 metastasis was found in MIA, and no cases of N2 disease were found. Studies that reported 5-year DFS have almost 100% DFS rate (*Table 1*). We therefore propose that patients with AIS/MIA have extremely low rates of metastasis and recurrence.

Discussion

To the best of our knowledge, the present study is the first and largest analysis in regard to lymph node status in patients with AIS and MIA. In the new classification of lung cancer (4), the definition of BAC is no longer used and instead divided into five major categories: (I) AIS; (II) MIA; (III) lepidic predominant adenocarcinoma (nonmucinous); (IV) other invasive adenocarcinomas with lepidic component; (V) invasive mucinous adenocarcinoma. In our study we analyzed two kinds of low grade adenocarcinoma: AIS, which is a localized small (≤3 cm) adenocarcinoma with growth restricted to neoplastic cells along preexisting alveolar structures (lepidic growth), lacking invasion; and MIA, which is a small, solitary adenocarcinoma (≤3 cm), with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension in any one focus. Patients defined under the classification of lung adenocarcinoma by Noguchi and associates (8) (less than 2 cm in diameter), localized BAC without active fibroblastic proliferation classified as types A and B, were also analyzed in the present study.

The combination of all 23 studies held 6,137 lung adenocarcinoma cases, of which the AIS/MIA accounted for 821. Because some studies only included patients with adenocarcinoma 2 cm or less (8,14,17,19,20), the percentage of AIS/MIA reached 14% in our research. All patients with AIS/MIA received curative surgery combined with either lymph node sampling or SLND. From the results we found that only one patient with MIA had N1 lymph node metastasis, no cases of N2 disease were found. Although overall survival is the most common survival analysis method utilized in lung cancer studies, DFS more accurately reflects the biological behavior of the tumor in low grade tumor populations such as our series of AIS/MIA, where there is a high percentage of overall survival. Studies that reported 5-year DFS have almost 100% DFS rate; the recurrence of AIS/MIA was extremely low.

With the application of HRCT screening, an increasing number of early-stage lung cancers have been detected, most of which are AIS/MIA. AIS is also known to correspond to pure ground-glass nodule (GGN), MIA was more commonly referred to as mix-GGN (14,30). Forecasting lymph node metastasis is very important in determining the treatment strategy. The definition of complete resection, proposed by the IASLC, mandates that: a negative microscopic margin is obtained and SLND should be performed (3). However, previous studies demonstrated that survival of lymph node sampling was acceptable and was no worse than that after SLND (31,32). The American College of Surgery Oncology Group Z0030 trial (33) showed no difference in both survival and DFS between SLND and sampling group. Meanwhile, there was a significantly longer mean duration of surgery and a higher drain secretion in the SLND group compared with that in the sampling group (34,35). For patients with no risk or with ultralow risk of recurrence, excessive surgery

Table 1 The characteristics of included studies and our institute

Author, year	Period	Median follow-up (month)	Adenocarcinoma	AIS	MIA	BAC ≤3 cm, Noguchi type A and type B adenocarcinoma	Lymph node metastasis		Surgical procedure	5-year DFS rate
							N1	N2		
IASLC/ATS/ERS classification										
Russell, 2011	1996-2009	NR	210	1	7	–	0	0	Lobectomy with SLND was performed in the case of AIS and 6 of 7 cases of MIA	100%
Yoshizawa, 2011	1995.1-2005.11	NR	514	1	8	–	0	0	Lobectomy with SLND	100%
Zhang, 2012	2008.4-2011.10	NR	215	5	7	–	0	0	SLND	NR
Xu, 2012	2007-2010	NR	87	3	8	–	0	0	NR	100%
Tsuta, 2013	1998.1-2002.12	98.4	904	69	33	–	0	0	NR	100%
Imai, 2013	2004.1-2011.12	NR	453 (T)	22	23	–	1	0	Complete resection	NR
Gu, 2013	2005-2008	44	292	1	14	–	0	0	Complete resection	100%
Zhang, 2014	2011.9-2013.1	NR	140	68	60	–	0	0	NR	NR
Yanagawa, 2014	2002-2012	40.5	562	41	45	–	0	0	Lobectomy and sublobectomy with SLND was performed in 42 and 44 cases of AIS/MIA, respectively	100%
2004 WHO classification										
Noguchi, 1995	1962-1993	NR	236	–	–	34	0	0	NR	NR
Watanabe, 2001	1973-1998	NR	170	–	–	24	0	0	Lobectomy combined with SLND	NR
Watanabe, 2002	1996.7-2001.6	32	NR	–	–	17	0	0	Wedge resection: 14; segmentectomy: 2	100%
Ishiwa, 2003	1991-1999	NR	71	–	–	13	0	0	Lobectomy combined with SLND	NR
Sakurai, 2004	1985-2002	61.2	108	–	–	25	0	0	Complete resection	100%
Sakurai, 2004	1993.1-2000.12	–	1045	–	–	85	0	0	Complete resection	100%
Yamada, 2004	2000.1-2002.2	29.3	62 (lesions)	–	–	44	0	0	Wedge resection as primary treatment	100%
Yoshida, 2005	1998.8-2002.10	50	50	–	–	25	0	0	Wedge resection: 22; segmentectomy: 3	100%
Yim, 2007	1992-2004	NR	141	–	–	29	0	0	Complete resection	NR
Borczuk, 2009	1997-2000	NR	178	–	–	8	0	0	NR	NR
Koike, 2009	1999.4-2007.9	51	118 (BAC)	–	–	46	0	0	Wedge resection: 44; segmentectomy: 2	93%
Vazquez, 2009	1993-2007	NR	279	–	–	20	0	0	NR	100%
Anami, 2009	1993.12-2000.12	83.5	139	–	–	27	0	0	Complete resection	NR
Oka, 2010	1999-2008	39.6	163(BAC)	–	–	8	0	0	Complete resection	100%

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; DFS, disease free survival; BAC, bronchioloalveolar carcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; SLND, systematic lymph node dissection; NR, not reported.

or unnecessary therapy may be avoided. Based on these data and analysis, we believe that limited surgical resection without systemic lymph node sampling or dissection is adequate surgical treatment for the treatment of pathologic AIS/MIA NSCLC.

However, the results regarding AIS/MIA as very favorable prognostic categories have largely been based on nonmucinous tumors, as mucinous and mixed mucinous/nonmucinous AIS/MIA are extremely rare. Kadota *et al*. (36) and Noguchi *et al*. (8) reported mucinous AIS and MIA that had 100% 5-year DFS. Oka *et al*. (29) found that patients with mucinous AIS/MIA showed excellent prognosis after surgical resection, none of the patients had lymph node metastases or lymphovascular invasion. Hence, recent results showed no difference of survival benefits between mucinous and nonmucinous AIS/MIA.

Recently, in a report presented by Yeh *et al*. (37), frozen section was found to have a specificity of 80% in identifying lepidic predominant adenocarcinomas. In cases of AIS, all pathologists made accurate interpretations using frozen sections. In cases of MIA, 6.7% of frozen section diagnoses were AIS, 41.3% were MIA, and 52% were invasive adenocarcinoma. Also the inflation method, as described by Myung *et al*. (38) and Xu *et al*. (39) has been shown to be able to expand the alveolar spaces in frozen section slides. It did show a promise of frozen section in classifying lung adenocarcinoma subtypes. We believe that multiple frozen sections to classify lung adenocarcinoma subtypes intraoperatively would increase the concordance rate.

A number of limitations should be noted. First, because the new classification was brought up in 2011, some patients might have been missed as we only included pure-BAC with tumor ≤3 cm and Noguchi type A and B; second, the lymph node disposition was not unanimous among the included studies; third, all results came from postoperative pathological analysis; forth, not all included studies reported 5-year DFS rate and median follow-up; fifth, the number of harvested lymph node is not reported in all included papers. They only tell whether SLND is used. We listed this information together with surgical procedure in the table.

Conclusions

These results indicated that patients with AIS/MIA have good survival prognosis after surgical treatment. Because of the rare recurrence and lymph node metastasis rates, patients with these very-early stage NSCLCs could be nominated for limited surgical resection that SLND or sampling might be avoided.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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