Review

TNM Classification for Lung Cancer

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The international tumor-node-metastasis (TNM) staging system is the "international language" in cancer diagnosis and treatment. Six revisions of the TNM staging system for lung cancer have been repeated over the past 35 years after the beginning of UICC-TNM classification in 1968. The 1997 revision for lung cancer has undergone an extensive correction for many deficiencies of the old staging system. As a result, the new staging system appears to be a great improvement over previous editions. There are, however, still some controversies and proposals for revising, even when the new staging system is applied in daily diagnoses and treatment for lung cancer. In the present paper, these problems are presented and discussed. Main subjects for discussions are as follows: (1) Since the 2nd revision, T1 and T2 lesions were divided at the border of a 3 cm tumor size. Is 3 cm diameter an appropriate cut-off point for dividing T1 and T2 lesions? (2) Is it valid to subdivide T1 and T2 lesions into each A and B? (3) Is it appropriate to down-stage all of T3N0M0 to stage IIB, because there exists heterogeneity of T3? (4) Definitions of T4 lesion. (5) Controversies in three kinds of lymph node maps. Especially, where there is a boundary between N1 and N2 station in each map? (6) How to classify separate tumor nodules (STN) in the same lobe, and in the non-primary lobe. (7) Controversy exists concerning the validity of present stage grouping, because there are no significant difference of survivals between IB and IIA, IIA and IIB in most reports and also between T3N0M0 and T3N1M0 in some reports. (Ann Thorac Cardiovasc Surg 2003; 9: 343–50)

Key words: lung cancer, TNM staging system, tumor size, lymph node map, separate tumor nodule

Introduction

The international tumor-node-metastasis (TNM) classification proposed by the Union Internationale Contre le Cancer (UICC) has been widely used in the investigation and treatment of cancers of various organs. The UICC believes the TNM staging system serves a number of related objectives, namely (1) to aid the clinician in the planning of treatment, (2) to give some indication of prognosis, (3) to assist in evaluation of the results of treatment, (4) to facilitate the exchange of information between treatment centers, and (5) to contribute to the continuing investigation of human cancer.[1)]

Historically, the TNM system for the classification of malignant tumors was developed by Denoix (France) between 1942 and 1952. He recommended classifying malignant tumors according to TNM descriptions. In 1950, the UICC appointed a "Committee on Tumour Nomenclature and Statistics" and adopted general definitions of local extension of malignant tumors. In 1958, the Committee published the first recommendation regarding cancers of the breast and larynx. Between 1960 and 1967, the Committee published nine brochures describing proposals for classification of 23 sites. It was recommended that the classification proposals for each site be subjected to prospective or retrospective trials over a five-year period. In 1968, these brochures were combined into a booklet outlining the staging for lung cancer, and this was actually the first edition of the UICC-TNM Classification of Malignant Tumours which was subse-

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Table 1. Evolutions of TNM staging system (UICC)

Second ed. (1974)		Third ed. (1978)		Fourth ed. (1987)		Fifth ed. (1997)	
Occult ca.	TXN0M0	Occult ca.	TXN0M0	Occult ca. Stage 0	TXN0M0 TisN0M0	Occult ca. Stage 0	TXN0M0 TisN0M0
Stage I	T1N0M0 T1N1M0 T2N0M0	Stage Ia Stage Ib	T1N0M0 T2N0M0 T1N1M0	Stage I	T1N0M0 T2N0M0	Stage IA Stage IB	T1N0M0 T2N0M0
Stage II	T2N1M0	Stage II	T2N1M0	Stage II	T1N1M0 T2N1M0	Stage IIA Stage IIB	T1N1M0 T2N1M0 T3N0M0
Stage III	T3anyN/M N2anyT/M M1anyT/N	Stage III	T3N0/1M0 anyTN2M0	Stage IIIA Stage IIIB	T1N2M0 T2N2M0 T3N0/1/2M0 anyTN3M0 T4anyNM0	Stage IIIA Stage IIIB	T1N2M0 T2N2M0 T3N1/2M0 anyTN3M0 T4anyNM0
		Stage IV	anyTanyNM1	Stage IV	anyTanyNM1	Stage IV	anyTanyNM1
Major revision		Divide Stage Ia & Ib M1→Stage IV		T1N1N0→Stage II N3 & T4→Stage IIIB		Divide Stage IA & IB Stage IIA & IIB T3N0M0→Stage IIB	

quently translated into 11 languages.[2] Modern TNM classification began with the 2nd edition.[3] As a result of the Task Force on Lung Cancer of the American Joint Committee on Cancer Staging (AJCC) which was held in 1973, Mountain et al. reported a new criteria for clinical staging of non small cell lung cancer (NSCLC) after an evaluation of more than 300 curves and survival tables for 2,155 patients treated in the previous four years.[4] The new staging system for lung cancer was presented in the 2nd edition.[3]

Revision of the TNM classification was repeated at four to 10 year intervals, i.e. 1974 (2nd edition), 1978 (3rd edition), 1987 (4th edition), 1997 (5th edition), and 2002 (6th edition; minor revision of the 5th edition) (Table 1). In the 5th edition,[1] the following new features of the revised staging system were presented: (1) the division of stage I into IA and IB, (2) the division of stage II into IIA and IIB and the assignment of T3N0M0 to stage IIB, (3) designation of tumors with satellite nodules in the same lobe as T4, and (4) the assignment of a primary tumor with one or more synchronous lesions within different lobes of the same lung as M1. As a result, the 1997 staging system appears to be a great improvement over previous editions. There are, however, some remaining controversies and debate arising in daily diagnoses and treatment of lung cancer patients, even when the new staging system is applied. In fact, since the revision of the 5th edition in 1997, there were 57 English publications regarding validity, controversy, and proposals for the new TNM staging system, and 16 of these were published by Japanese authors. In addition, there were 12 articles in Japanese journals with English abstracts.

"T1" and "T2" Category

In the first edition of the UICC-TNM Classification of Malignant Tumour published in 1968, T1 was defined as "a tumor confined to segmental bronchus or to a segment of one lobe", T2 as "a tumor confined to lobar bronchus or to one lobe", T3 as "a tumor invading the main bronchus or more than one lobe", and T4 as "a tumor extending beyond the lung".[2] However, Mountain et al. reported that T2 should be divided at the border of a 3 cm tumor size as the result of the Task Force on Lung Cancer of AJCC.[4] The 2nd edition of UICC-TNM classification first applied this classification to lung cancer.[3] Thereafter, 3 cm has been regarded as the only tumor size used to establish a prognostic threshold in the staging of lung cancer. Even though the staging system has been revised repeatedly, criteria for tumor size have remained unchanged for the past 30 years. In the old classification, both T1N0M0 and T2N0M0 were classified as stage I. However, by the 1997 revision of the TNM staging system,[4] stage I was divided into stages IA (T1N0M0) and IB (T2N0M0), because there was a significant difference in survival rates between the two groups in many reports.[5-7]

On multivariate analysis, tumor size was the most significant factor among eight parameters contributing to the

prognoses of patients in stage I.[7] Thus, the prognostic value of tumor size has been discussed for many years. However, controversy concerning the relation between tumor size and patient prognosis persists, and the appropriate cut-off for tumor size, i.e. 2, 3, 4, 5 or 7 cm to classify T1 and T2 diseases continues to be debated. We reported a significant difference in five-year survival rate between T1N0M0 and T2N0M0 disease. In addition, we observed a further significant drop in survival rate for patients with a tumor size more than 5 cm compared to that of those with tumors measuring 3 to 5 cm (46% vs. 61%). From these data, we proposed to subdivide T diseases further by size of tumor.[7] Carbone et al. proposed that T2 lesions more than 5 cm should be upgraded to T3, because this group showed significantly poorer prognosis than with T2 less than 5 cm.[8] As one of the important issues addressed by a consensus report from International Association for the Study of Lung Cancer (IASLC) Staging Committee held in June 1996, the prognostic independence of the T2 size (3 vs. 4 vs. 5 cm) was confirmed.[9] In October 1996, The IASLC sponsored an International Workshop on Intrathoracic Staging.[10] Concerning the relation between tumor size and stage, there was evidence in the literature that either 4 or 5 cm was a better cut-off point between T1 and T2 tumors with regard to ultimate prognosis and survival. It was recommended that this cut-off point be revised. The Spanish group (GCCB-S) studied clinical tumor size and prognosis in lung cancer. Survivals were compared 0-2, 2.1-4, 4.1-7, and more than 7 cm. In this study, although 3 cm was not a cut-off value for tumor size between prognostic categories, there were significant differences between the four groups.[11] In 2002, this group again reported a study on the prognosis of stage IA-IB lung cancer. There were significant differences in the survival rate between each group. They confirmed that 3 cm was not a prognostic threshold of stage I lung cancer.[12] Harpole et al. compared the five-year survival rates of groups with a tumor size less than 2 cm, 2-4 cm and with a tumor measuring 4 cm or more. There were significant differences between each group.[13] Ginsberg reported that, at present, T1 and T2 tumors are considered well defined, but recent analyses suggest that survival is much worse for patients with tumors larger than 5 cm than for those with tumors smaller than 5 cm, and it appears that this 5-cm parameter has greater prognostic value than the current 3-cm cut-off for T1 tumors. A prospective analysis should therefore address whether the definition of T1 tumor should retain its less than 3 cm cut-off or should be changed to include a 4- or 5-cm lesion, with a tumor larger than 5 cm being reclassified, creating a higher cut-off for T2 status.[14]

On the other hand, in recent years, there have been moderate numbers of NSCLC less than 1 or 2 cm showing most favorable surgical outcomes. It seems reasonable that T classification of lung cancer should be further subdivided in accordance to the size of the tumor as already has been done in the present TNM classification of tumors such as lip and oral cavity, pharynx, salivary gland, thyroid gland, anal canal, and breast tumor (T1a, less than 0.5 cm; T1b, 0.5-1 cm; T1c, 1-2 cm; T2, 2-5 cm; T3, more than 5 cm).[1] Boyd et al. proposed that the advent of screening mammography resulted in the detection of mm-sized breast cancers and led to a subdivision of T1 (less than 2 cm) into T1a-c. Therefore they suggested subdividing T1 lesions of lung cancer.[15] Ishida,[16] Read,[17] Warren,[18] and Padilla[19] and their colleagues similarly noted significant differences in survivals between patients with tumors less than 2 cm and those with tumors measuring 2.1-3.0 cm.

On the contrary, Patz et al. classified tumors less than 3 cm into 4 quartiles. However, the Cox model did not show a significant relationship between tumor size and survival.[20] Yanagi et al. reported that the survival rate of patients with lesions measuring 2 cm or less was better than that with a lesion diameter more than 2 cm, but there was no significant difference in survival rates between the two groups. They concluded that it was not justifiable to subclassify stage IA NSCLC based on 2 cm.[21] Koike et al. compared the survival of cT1N0M0 patients with a lesion measuring less than 2 cm and that of those with lesions measuring 2.1 to 3 cm. The former group showed a significantly better survival rate than the latter. However, by multivariate analysis, tumor size was not a significant prognostic factor.[22]

"T3" and "T4" Category

T3N0M0 was down-graded to IIB in the present classification, but heterogeneity of T3 was pointed out in many reports.[14,23-27] Ginsberg raised the question whether all T3 can be grouped in one stage.[14] Riquet proposed that, as the pathologic character of each pT3 subgroup seems different, further research is warranted to explore the pathologic and biological factors influencing prognosis for each pT3 subgroup.[26]

Green and Lilenbaum,[24] reviewed three large series (Naruke et al.,[28] Mountain,[29] and Watanabe et al.[30]), and concluded that T3N0-1 disease should be separated from

patients with N2 disease and grouped in stage IIB.[26] However, according to Detterbeck et al.[23] this perception is primarily regarding the survival of T3N0-1 patients who have chest wall involvement. The T3 classification also includes tumors that involve mediastinal structures, the main stem bronchus less than 2 cm from the carina, and the Pancoast tumors. They compared survival for each of these four T3 categories by a reviewing the literature, making the question of reclassifying all T3 categories a complex issue. The available data show that patients with T3N0-1 tumors involving the chest wall have a good prognosis after resection, whereas patients with central T3N0-1 tumors (mediastinal or main stem bronchial involvement) have a prognosis similar to that of patients with resected IIIA (N2) tumors. They concluded that classifying T3 chest wall tumors as stage IIB may be justified; however, classifying central T3 tumors as stage IIB may not be justified.[23]

Oda et al. analyzed the surgical results of 53 T3N0M0 patients with chest wall invasion. The five-year survival rates of patients with invasion of the parietal pleural layer, with invasion of the soft part layer, and with rib destruction were 39%, 47% and 9%, respectively. They concluded that T3N0M0 with bone destruction should remain in stage IIIA or be categorized as T4.[31]

Ginsberg reported that a tumor invading only the parietal pleura has a much more optimistic prognosis than that invading through the endothoracic fascia, chest wall musculature, or rib. He proposed that minimal invasion (pleura only) should be classified as T2, since five-year survival rate following complete resection of such lesion is 50% or greater. Deeper invasion should retain its T3 classification. A tumor invading the mediastinum and superior sulcus tumor, now classified as T3, does not have the same prognosis as stage II lesions and could thus remain as T3, with these T3 tumors reverting to stage IIIA disease once again.[14]

Yokoi et al. collected 63 patients who underwent resection of T3 lung cancer invading the diaphragm at 31 institutions of the Japan Lung Cancer Study Group. Complete resection was performed in 55 patients and their five-year survival rate was 22.6%. The five-year survival rate of patients with shallow invasion (parietal pleura of subpleural tissue involvement) was 33.0%, whereas that of patients with deep invasion (muscle or peritoneal infiltration) was 14.3% (P=0.036). From these data, they concluded that diaphragmatic invasion, especially invasion of the muscle layer or deeper tissue, are not considered to be T3 lesions, because these cancers are generally technically resectable but oncologically almost incurable.[32] Inoue et al. proposed that diaphragm invasion should be T4 disease.[33]

The difference between mediastinal pleural invasion (designated as T3) and mediastinum (designated as T4) is not clear. Ginsberg proposed that, although the T4 category has been reasonably well described, tumors invading the phrenic nerve or vagus nerve in the aortic or subaortic region, now classified as T3, have extremely poor prognoses and probably should be upgraded to a T4 designation. More precise definitions to identify the T status of the superior sulcus tumor (T3 vs. T4) are required. For example, the presence of Horner's syndrome, motor (vs. sensory) dysfunction of the lower brachial plexus (C8 involvement), or involvement of the subclavian vessels in all likelihood should designate this tumor as T4.[14]

"N" Category

To date, there are three kinds of maps, i.e. Japan Lung Cancer Society (JLCS) map (so-called Naruke-map).[34] American Thoracic Society (ATS) map,[35] and the recently proposed Mountain-map.[36] There are some differences in the characters of these three maps. JLCS-map is based on the bronchial tree, thoracotomy findings and resected specimen. ATS-map is based on major anatomic structures and mediastinoscopic identification. The Mountain-map is based on mediastinal pleura and mediastinoscopic identification.

After proposal of the Mountain-map, there was great confusion regarding N category, especially concerning the boundary between #7 (subcarinal) and #10 (hilar) lymph nodes. In the JLCS-map, the #7 lymph node is defined as the lymph node in contact with the subcarina. However, the Mountain-map defines all subcarinal area nodes within the pleural reflection as #7 nodes, including part of the nodes designated as #10 nodes on the JLCS-map. Lymph node metastasis to the #7 lymph node is an N2 lesion, whereas metastasis to #10 is an N1 lesion. This confusion is exacerbated by the difference in survival rates between N1 and N2 lesions.

Where is the boundary between N1 and N2 stations in lung cancer? Asamura et al. retrospectively analyzed the pattern of lymphatic involvement and prognosis in 180 N1 patients. The prognosis was compared between N1 without #10 involvement ($N1^-$, n=145), N1 with #10 involvement ($N1^+$, n=35), and N2 (n=166). Their five-year survival rate was 70%, 54%, and 37%, respectively. A significant difference was observed between $N1^+$ and N2,

but not observed between $N1^-$ and $N1^+$. However, survival curves of single-node N2 (n=66) and $N1^+$ were superimposed. They concluded that, in terms of prognosis, the pleural reflection does not seem an appropriate anatomical boundary between N1 and N2 stations in lung cancer.[37)]

There are also differences in nomenclature for nodal stations of nodes #3, #7, and #1 between the JLCS-map and the ATS-map. In the ATS-map nodal involvements is divided strictly at the midline, while #7 node involvement is bilateral. Furthermore the ATS-map includes #3 node with #2 (paratracheal), #4 (tracheobronchial), #6 (paraaortic), and node #3p with node #8. Accordingly, where lymphadenopathy in these node groups extends beyond the midline, it is defined as bilateral nodal involvement (N3 lesion). Consequently, there is great confusion as well as some controversy over the definitions of N2 and N3 disease, which may lead to difficulties in interpreting results for such patients. If metastases to nodes #3, #3p and #3a are included in N3 disease, the survival of stage IIIA patients is moderately improved; furthermore, if the involvement of node #7 is excluded from N2 disease, survival in stage IIIA is even more markedly improved. Ginsberg pointed out that the definition of N3 disease within the mediastinum is quite vague and depends on the nodal map used. The lymphatic drainage of the various lobes to the superior mediastinum should be considered in designating N3 disease. Left-sided tumors, for example, drain ipsilaterally in the superior mediastinum, along only the left tracheoesophageal groove. Any lymph node drainage to the right of the left paratracheal border should be considered contralateral or N3 disease for these left-sided tumors. In contrast, right-sided disease drains to lymph nodes in the superior mediastinum, anterior to the trachea as far as the left tracheal border. These should all be considered ipsilateral (right) paratracheal lymph nodes. Because of these anatomic features, the left anterior border of the trachea and not the midline of the trachea should be designated as the dividing point between ispilateral and contralateral. By this definition, contralateral N3 nodes from a right-sided tumor would include only those lymph nodes along the left tracheoesophageal groove and along the lateral border of the left mainstem bronchus. According to this new definition, normal lymphatic drainage of the hemithoraces rather than the midline would define a lymph node as left or right paratracheal (level 4 and 2).[14)] He also pointed out that controversy persists regarding what constitutes subcarinal (N2) versus contralateral (N3) nodes in the subcarinal space. Many Japanese surgeons identify subcarinal nodes along the medial border of the contralateral mainstem bronchus as contralateral N3 lymph nodes. In contrast, most surgeons in North America consider lymph nodes anywhere within the subcarinal space as ipsilateral. A universally acceptable definition is needed.[14)]

As the survival rate of patients having cN2 disease shows a poor prognosis, there are some reports that this group should be categorized into stage IIIB.[25,38,39)]

Separate Tumor Nodule

The greatest controversy regarding the definition of M1 disease arises when ipsilateral satellite lesions (separate tumor nodule, STN) are present.[7,40-45)] In the 5th edition, STN in the same lobe is defined as T4 and STN in a different lobe is M1.

STN in the primary lobe may behave more favorably than patients with other subgroup of T4 stage IIIB disease. As a result, patients with stages IIIB show favorable prognoses because a moderate number of patients with STN of T4 are included. From these facts, there are some proposals (including ours), that STN in the primary lobe should be T3. Urschel et al.[40)] retrieved 11 articles and their data were pooled for analysis. Of 568 resected patients with satellite nodules, actuarial five-year survival rate was 20%. Five articles gave separate survival data for STN in primary versus ipsilateral non-primary lobes. All five articles showed better survival for STN in a primary lobe. STN in a primary lobe have a better prognosis than those in the ipsilateral non-primary lobe. Survival for resected lung cancer with STN in a primary lobe is better than that usually observed for T4 (IIIB) disease. From these results, they concluded that the 1997 staging revisions may unduly upstage patients with STN in a primary cancer lobe. The previous classification shown in UICC-TNM supplement 1993,[46)] in which, upgrading T designation by one level (T1 to T2, T2 to T3, and T3 to T4) for same lobe STN, may have been appropriate. Alternatively, the recommendations of Deslauriers and coworkers,[41)] to stage these STN as T3, seem to be acceptable as well. On the contrary, STN in ipsilateral non-primary lobes share metastatic mechanisms and have survival results consistent with M1 stage disease. Their 1997 M1 designation may be appropriate.[40)]

Yano et al. analyzed cases of intrapulmonary satellite nodules and reported the validity of the1997 staging system. However, if all PM1 (STN in the non-primary lobe) with any T and N factor are included in T4, it may im-

prove the survival rate of T4 compared to than that of T4 by the former classification.[42] Okada et al. evaluated patients with ipsilateral STN by applying the1997 classification. They concluded that the new TNM staging system for STN reclassified in 1997 was less acceptable for surgical-pathologic staging than the revision in 1992.[43] On the contrary, Okumura et al. reported that STN within the same lobe of the primary tumor was comparable with T4 and that in a different lobe was comparable with M1. In terms of postoperative prognosis, the revised TNM classification for intrapulmonary metastasis seems to be appropriate.[44]

Staging

The 1997 international staging system for lung cancer proposed in the 5th edition has been evaluated by many authors.[5,6,25,33,47-55] Most of them reported that it is acceptable, but, there are still some controversies in the staging of patients among them.

There are no objections to dividing stage I into IA and IB. However, most reports indicate that there are no differences between stage IB and IIA in post-surgical staging.[5,6,25,33,47-50,52,53] Padilla et al. analyzed 637 cases with stage IB disease and concluded that stage IB did not succeed in configuring a group of patients with a homogenous prognosis, as there was a wide variety in a five-year survival rate. The estimation of prognosis derived from a multivariable analysis could obviate the limitations of the actual staging system for NSCLC.[54] Inoue et al. proposed combining T2N0M0 with T1N1M0 together.[33]

Furthermore, there are several reports that there is no difference in survival between stage IIA and IIB.[14,25,48,49,52,53] This may be caused by the fact that there are generally few patients with T1N1M0 in each series.[48,49,52,53]

In the 1997 revision, T3N0M0 was staged to IIB from IIIA, because survival of patients in this stage greatly exceeds that of patients with stage IIIA (N2) lung cancer. However, as already indicated, there are some reports that T3N1M0 also should be classified as stage IIB in selected situations, because this group of patients shows a survival rate similar to that of T3N0M0.[23,24,33]

In the present classification, it has often been reported that there was no difference observed between prognoses of patients with stage IIIA and IIIB disease,[25,27,56] Kameyama et al. observed that there was no difference in survivals between patients with T3 disease and this seemed to affect the prognoses of patients with stage IIIA and IIIB disease. With reclassification based on surgical curability, difference between their prognoses became evident. Kameyama et al. therefore proposed their own definition of T3 and T4 disease for future revision of the TNM classification.[56]

Saito et al.[25] and Inoue et al.[33] proposed that, as T3N2M0 shows a poor prognosis, it may be appropriate to classify such cases as IIIB.

The heterogeneity of the stage IIIB has been pointed out and a new revision of the staging system has been proposed. Grunenwald and Le Chevalier proposed the following modification of the staging system: 1) subdivision of N2 disease into two categories–mN2 (clinical N2), clinically considered N0-1 but pN2 postoperatively; and cN2 (clinical N2), histologically proven at the first pretreatment staging; 2) subdivision of T4 disease into two subcategories–$T4_1$, including invasion of superior vena cava, left atrium, carina, trachea, great arteries (considered potentially respectable in selected cases); and $T4_2$, including invasion of the heart (except left atrium), esophagus, vertebrae, malignant pleural or pericardial effusion (considered definitively unresectable; and 3) subdivision of stage III into subcategories–IIIA, including T3N1, T3-T3 mN2; IIIB, including T1-T3cN2, $T4_1$ N0-N2; and IIIC, including $T4_2$; any N, any TN3.[39]

Future Revision

The international TNM staging system is the "international language" of cancer diagnosis and treatment. The rationale for dividing cancer patients into groups according to the so-called T (tumor), N (node) and M (metastasis) stages was based on the finding that survival rates are higher for patients with localized disease compared to those in patients with tumors extending beyond the organ of origin. Six revisions of the TNM staging system have been adopted over the past 35 years. The next revision of UICC-TNM staging classification will probably take place in 2007 and, in preparation for those discussions, the International Staging Committee of the IASLC chaired by Goldstraw is collecting a worldwide database. The UICC deadline for the next revision and their request for submissions is January 2005. This would mean that any proposals would have to be presented to the board of the IASLC towards the end of 2004.[57]

Addendum

At the IASLC International Staging Committee which

was held August 9, 2003 at Vancouver, it was reported that the enacted next revision in 2007 was amended to 2009. Hence all schedules will be postponed two years, which means that the UICC deadline for the next revision and their request for submissions will be January 2007. This will mean that any proposals would have to be presented to the board of the IASLC towards the end of 2006.

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