Cytological Diagnosis of Lung Cancer in Chiang Mai, Thailand : Cyto-Histological Correlation and Comparison of Sensitivity of Various Methods

SAMREUNG RANGDAENG, M.D.*,
JONGKOLNEE SETTAKORN, M.D.*,
CHAICHARN BHOTHIRAT, M.D.**,
APINUN ARAMRATANA, M.D., Ph.D.****
CHARIN YA-IN, M.D.*,
BENJAPORN CHAIWUN, M.D.*,
CHUSAK SIRIVANICHAI, M.D.***,

Abstract

To evaluate the role of cytology of sputum, bronchial brushing (BB), bronchial washing (BW), bronchoalveolar lavage (BAL) and fine needle aspiration cytology (FNA) in the diagnosis of lung cancer using histological material as a gold standard, a retrospective study was performed on cytological materials obtained from 243 patients with possible lung cancer. Of these, 160 had been confirmed histologically to have lung cancer. Cytological materials included in the study were 31 sputa, 123 BWs, 11 BBs and 36 BALs. Meanwhile, FNAs and concurrent gun biopsies (GBs) were performed on 23 patients clinically and histologically proved to have lung cancer. The overall sensitivity of sputum, BW and BAL was 0.222, 0.455 and 0.361, respectively. BB provided a significantly far superior sensitivity (0.800) than those of three former methods with $p<0.05$ by Fisher's exact test. FNA and GB seemed to provide greater sensitivity of 0.913 and 0.783, respectively. Although the complimentary role of various conventional cytological techniques is well recognized, bronchial brushing is the only single technique that significantly improved diagnostic yield. FNA and GB techniques should be encouraged due to their superior sensitivity.

Key word : Lung Cancer, Cytology, Cyto-Histological Correlation

RANGDAENG S, YA-IN C, SETTAKORN J, et al
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* Department of Pathology,
** Department of Internal Medicine,
*** Department of Radiology,
**** Department of Family Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

Lung carcinoma has been well recognized as the most common cause of cancer death in most industrialized countries[1]. Its incidence in Chiang Mai, located in the northern part of Thailand, has also been comparably high over the past 12 years compared to other parts of the country. According to data obtained from Chiang Mai Cancer registry in 1995, the age standardized incidence was 42.5 per cent for males and 29.7 per cent for females and ranked first among all cancers in both sexes[2]. Recently, adenocarcinoma has emerged as the leading cell type encountered. More than 65 per cent of lung cancer patients come for medical attention in the advanced stage including metastasis to either regional lymph nodes or distant organs. Thus, five year survival rates are still very low. It has been generally accepted that the main reason for this tragic situation is the lack of the implementation of an early cancer detection program.

Diagnosis of lung cancer by cytological methods including sputum, brush, washing and fine needle aspiration is time-honored, reliable and cost-effective[3]. However, cytological methods accounted for only 5 per cent of total primary diagnosis of lung cancer from 1983 to 1995 in Chiang Mai (Srisukho S. - Personal communication). To promote cytological methods as a tool for early lung cancer detection, its performance in the detection of cancer must be evaluated. In this present study, the authors retrospectively evaluated the diagnostic efficacy of each method from January 1996 to October 1998.

MATERIAL AND METHOD

Cytologic cases of the lung that were performed for possible lung mass at Chiang Mai University Hospital from January 1996 to October 1998 were retrieved from the departmental files. Using histology as the final diagnostic outcome, 162 of 243 patients had been verified to have lung cancer including 149 fiberoptic bronchial biopsies, 23 lobectomies (13 patients had had a biopsy and subsequent resection) and 3 pleural biopsies from patients with massive pleural effusion and biopsies which failed to obtain diagnostic materials.

The tumor types were classified according to the World Health Organization as squamous cell carcinomas, adenocarcinomas, small cell carcinomas and large cell carcinomas[4]. Cytologic criteria for each tumor type have been published elsewhere[5,6]. Demographic data concerning age, sex and stage of disease were obtained from the medical records. TNM system for tumor staging was used for non small cell carcinoma[7,8], whereas, limited and extended-disease category were applied for small cell carcinoma[9,10].

All cytologic materials from confirmed cases were reviewed by four pathologists and included 31 sputum samples from 20 patients, 123 bronchial washings from 121 patients, 36 bronchioloalveolar lavages (BAL) and 11 bronchial brushings. BAL and bronchial brushing were performed only once in each individual patient. In the case of discordance between diagnosis made by cytology and by histology, all materials were simultaneously observed by all pathologists under a multi-head microscope.

Meanwhile, fine needle aspiration (FNA) and gun needle biopsies (GB) have been recently introduced in our institution. Only 23 cases were performed on peripheral lung lesions that were subsequently proved to be lung cancer. Only three patients had conventional cytological materials available before performing FNA or GB. Thus, valid comparison between FNA or GB and conventional methods could not be made.

Diagnostic sensitivity and agreement of diagnoses between histology and cytology from various methods were calculated. For simplicity, cytological diagnosis was divided into three categories as follows: *Unsatisfactory* (no cells from deeper airways was included), *Negative* (no tumor cells detectable), and *Positive* (presence of atypical cells, so called "suspicious or doubtful" or presence of unequivocal malignant cells). The first unsatisfactory group was excluded from analysis. The statistical difference was evaluated by Fisher's exact test using EpiInfo program version 6.

RESULTS

Of 162 patients in the present study, the various cell types of lung cancer included 80 squamous cell carcinomas (49.4%), 50 adenocarcinomas (30.8%), 10 large cell carcinomas (6.2%), 18 small cell carcinomas (11.1%) and 4 non-small cell carcinomas not otherwise specified (2.5%).

Information concerning the stage of disease was available from the medical records of 119 of 162 cases. Using the TNM staging system for non small cell carcinoma, 13 patients (12.1%) were classified as having stage I disease, 6 (5.6%) had stage II, 56 (52.3%) had stage III and 32 (30.0%) had stage IV. Of 18 small cell carcinomas, 5 patients had limited disease, whereas, 7 individuals had extensive disease.

Table 1. Distribution of tumor *versus* stage.

Tumor Type	I	II	III	IV	NA*
Non small cell carcinoma					
Squamous cell carcinoma	9	3	32	17	19
Adenocarcinoma	3	1	17	12	17
Large cell carcinoma	1	0	6	2	1
Non small cell NOS**	0	2	1	1	0
Subtotal	13	6	56	32	37
Small cell carcinoma					
Limited disease		5			
Extended disease		7			
NA*		6			

* NA = Information on stage not available.
** NOS = Non small cell not otherwise specified.

Table 2. Sensitivity obtained by various cytologic methods.

Technique	Sensitivity*
Sputum	0.222 (4/18)
Bronchial washing	0.455 (51/112)
Bronchoalveolar lavage (BAL)	0.361 (13/36)
Bronchial brushing	0.800 (8/10)

* Sensitivity was calculated after cases that belonging to the unsatisfactory group were excluded. Each individual patient was counted as a single case regardless of how many times the same cytologic method was performed.

No information was available in 37 non-small cell and 6 small cell carcinomas. Data concerning tumor cell type and stage is summarized in Table 1.

Overall sensitivity of various cytological methods

Upon excluding unsatisfactory material, the sensitivity of sputum, bronchial washing, bronchoalveolar lavage and bronchial brushing cytology was 0.222, 0.455, 0.361 and 0.800, respectively when considering that each patient was positively identified as having lung cancer by cytology regardless of how many specimens were obtained from the same patient. (Table 2) There was no significant difference between the sensitivity of sputum, bronchial washing and bronchoalveolar lavage by statistical analysis. The sensitivity of bronchial brushing was far superior to that of other non brushing methods either calculated from separated or combined data ($p<0.05$) under Fisher's exact test.

Influence of tumor type on cytologic sensitivity

Taking tumor cell type into consideration, the difference between brushing and non-brushing cytology was attributable to tumor cell type particularly squamous cell carcinoma ($p<0.05$). The histologic and cytologic findings of squamous cell carcinoma, adenocarcinoma and small cell carcinoma are shown in Fig. 1 to 3. Diagnostic sensitivity concerning other tumor types showed no significant difference. Table 3 demonstrates the respective p-value calculated from difference of the sensitivity between brushing and non-brushing methods compared with those obtained from squamous cell carcinoma and adenocarcinoma. The total number of other tumor types was too small to make a reliable analysis.

Among those positive cytology cases, overall concordance rate for tumor type between cytology of all methods and histology was 48.6 per cent for complete agreement (exact same tumor type), 43.2 per cent for partial agreement (belonged to non-small cell group but different type) and 8.1 per cent disagreement. Moreover, there was no significant difference of such cyto-histologic agreement between the brushing and non brushing methods as shown in Table 4.

Influence of tumor stage on cytologic sensitivity

Table 5 demonstrates the possible effect of tumor stage on sensitivity of cytological detection. Although no statistical assumption of their difference was unveiled, data showed a tendency that brushing cytology was more efficient in limited disease-stage (stage I or II in non-small cell and limited disease

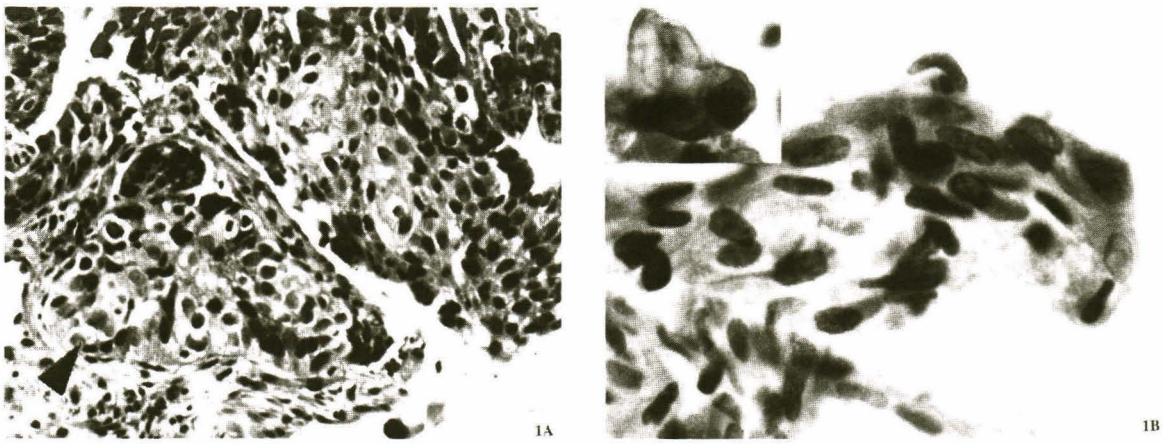

Fig. 1. (A) The histologic picture of squamous cell carcinama taken from bronchial biopsy shows invasive nests of malignant squamous epithelial cells (arrow), H&E x200. (B) The smear from bronchial washing of the same patient reveals a syncytial sheet of rather spindle shape, malignant squamous epithaelial cells and keratinized malignant cells (inset), Papanicolaou x 400.

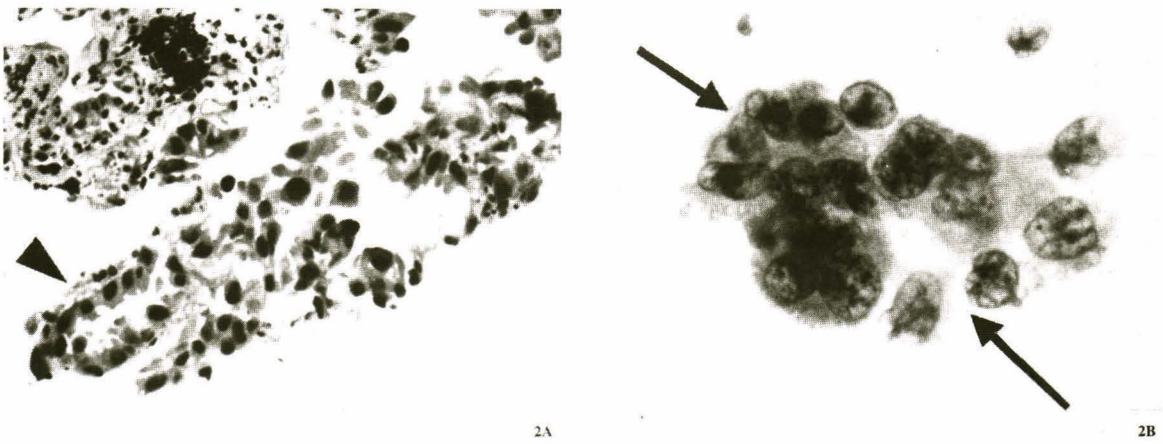

Fig. 2. (A) Tissue from bronchial biopsy demonstrates discohesive fragments of malignant epithelial cells with glandular formation (arrow) which are the features of adenocarcinoma, H&E x200. (B) The smear from bronchial washing of the same patient shows a cluster of large sized, malignant epithelial cells with well formed glandular lumens (arrow), Papanicolaou x 400.

in small cell carcinoma) while it was less useful in advanced disease-stage (Stage III or IV in non-small cell and extensive disease in small cell carcinoma).

Fine needle aspiration *vs* gun needle biopsy

Of 23 lung cancer patients, 22 were successfully diagnosed by either fine needle aspiration (FNA) or gun needle biopsy (GB). Of 22 positive cases, 17 were identified by both methods, 4 by FNA only and 1 by GB only. A single case was found in which both FNA and GB failed to obtain diagnostic materials. The sensitivity of FNA and GB was 0.913 and 0.783, respectively. The sensitivity was slightly increased to 0.956 when both methods were combined. (Table 6).

DISCUSSION

To decrease the mortality rate from lung cancer, reliable diagnostic methods to detect early lung cancer are essential. Sputum cytology provides

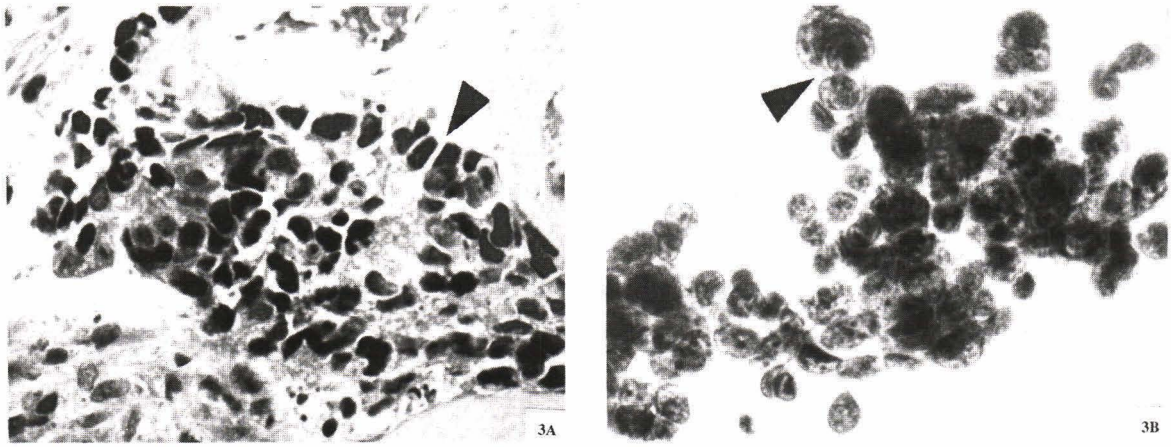

Fig. 3. **(A) Histogic specimen from bronchial biopsy reveals a group of small size, malignant epithelial cells with high nuclear cytoplasmic ratio and focal necrosis H&E x400. (B) The smear from bronchial washing of the same patient exhibits the corresponding features. Internuclear articulations (arrow) are observed in both specimens, Papanicolaou x 400.**

Table 3. Sensitivity of brush and non-brush methods according to tumor type.*

Tumor Type	Technique		P-value
	Brush	Non Brush	
Squamous cell carcinoma	1.000 (4/4)	0.452 (38/84)	0.0479
ADC	0.600 (3/5)	0.340 (16/47)	0.3418

* Number of other cells too small to calculate.

the most cost effective and most convenient way to screen for lung cancer. This is particularly true when applied to groups of high risk individuals[11,12]. Although sensitivity was relatively low compared with other cytologic methods, the ease of obtaining specimens has superseded its weak point. From the authors' experience, sensitivity of sputum cytology was rather low compared to that published in the literature[13-24] as shown in Table 7. Further work needs to be done to explore the causes of the relatively inferior sensitivity of sputum cytology.

In the present study, not only did sputum cytology provide a relatively low sensitivity but fluid based procedures such as bronchial washing also gave relatively inferior sensitivity in comparison with that shown in the literature in which the sensitivity varied from 61 to 76 per cent[13,15,21,25,26]. One possible reason could be different case selection criteria, as malignant cells would be easier to obtain from centrally located or exophytic tumors than periphery located or submucal ones. From the authors' experience, bronchial washing usually obtains a large amount of blood that eventually dilutes the diagnostic cellular material. The same impression was shared with Sing et al[24], Dasgupta et al[27], Reichenberger et al[28], and Jones et al[29] in which bronchial washing usually obtained low yields for sufficient diagnostic materials (46% *vs* 50%, 48%, 27% and 26%, respectively).

The only promising cytologic method experienced by the authors was bronchial brushing in which the sensitivity was comparable to that done elsewhere[13-24,27-29]. (Table 7) Unfortunately, for unknown reasons, this technique was not popular among pulmunologists in our institution. The procedure might be difficult to perform in cases that the bronchial lumens are completely obstructed in patients with advanced stage cancer while it is much easier to do a biopsy or to do a washing. Indeed, the majority of the patients in the present study belonged

Table 4. Cyto-histologic concordance of tumor type.

Histologic diagnosis	Cytological diagnosis				
	Adenocarcinoma	Large cell carcinoma	Squamous cell carcinoma	Small cell carcinoma	Non small cell NOS
Brushing mehods					
Adenocarcinoma	0	0	2	0	1
Large cell carcinoma	0	0	0	0	0
Squamous cell carcinoma	0	0	3	1	0
Non small cell NOS	0	1	0	0	0
Small cell carcinoma	0	0	0	0	0
Non brushing methods					
Adenocarcinoma	8	0	2	0	7
Large cell carcinoma	1	1	1	0	0
Squamous cell carcinoma	7	0	21	1	9
Non small cell NOS	0	1	0	0	0
Small cell carcinoma	1	0	0	3	3

Table 5. Influence of stage on the sensitivity of brush and non-brush methods.

Stage	Brush	Non-brush	Significance*
I	1.000 (1/1)	0.350 (7/20)	NS
II	1.000 (1/1)	0.333 (3/9)	NS
III	0.333 (1/3)	0.356 (21/59)	NS
IV	1.000 (3/3)	0.514 (18/35)	NS

* Not statistically significant.

Table 6. Fine needle aspiration and gun needle biopsy.*

Result	FNA	GB	FNA + GB
Positive	21	18	22
Negative	2	5	1

* FNA = Fine needle aspiration cytology
GB = Gun needle biopsy
FNA + GB = Combined results of FNA and GB.

Sensitivity of FNA	0.913 (21/23)
Sensitivity of GB	0.783 (18/23)
Sensitivity of FNA + GB	0.956 (22/23)

Table 7. Comparison of sputum and brush cytology in the literature.

Authors	Year	Sputum	Brush
Bibbo et al[13]	1973	0.169 (27/160)	0.701 (157/224)
Skitarelic et al[14]	1974	0.719 (23/32)	0.900 (18/20)
Bedrossian et al[15]	1976	0.560 (28/50)	0.760 (38/50)
Chopra et al[16]	1977	0.471 (24/51)	0.863 (44/51)
Chaudhary et al[17]	1978	0.246 (28/114)	0.491 (56/114)
Jay et al[18]	1980	0.500 (29/58)	0.591 (29/49)
Lundgren et al[19]	1983	0.635 (33/52)	0.650 (39/60)
Tanaka et al[20]	1985	0.310 (27/87)	0.764 (107/140)
Truong et al[21]	1985	0.600 (60/100)	0.760 (76/100)
Liang[22]	1989	0.733 (118/161)	0.400 (2/5)
Fraire et al[23]	1991	0.275 (14/51)	0.372 (29/78)
Sing et al[24]	1997	0.403 (93/231)	0.500 (107/214)
Dasgupta et al[27]	2000	-	0.545 (30/55)
Reichenberger et al[28]	2000	-	0.379 (22/58)
Jones et al[29]	2001	-	0.718 (369/514)
Average from literature		0.439 (504/1147)	0.648 (1123/1732)
Present study		0.222 (4/18)	0.800 (8/10)

to the advanced-stage group. The findings in the present study may encourage pulmunologists to perform brushing instead of fluid based procedures such as washings.

Comparing stage-by-stage, the sensitivity of brushing and non brushing methods have become less significantly different. Non brushing methods seem to have gained more sensitivity in stage IV disease. However, in the present study the numbers for each method except bronchial washing were too low to make a reliable statistical analysis. It is noteworthy that, in this study, brushing cytology was more useful in stage I and II disease. Sing et al suggested that sputum cytology was more sensitive than brushing in their T1 patients(24). In the present study, for sputum cytology, one out of four stage I patients and two out of seven stage II-IV patients had positive results. The results in the present study are similar to others in that there was no influence of stage on the sensitivity of sputum cytology(30,31).

Fine needle aspiration, as experienced by the authors has given encouraging results. Although the number of cases is still low for lung mass, preliminary data has suggested the complimentary role of gun needle biopsy to fine needle aspiration cytology. The sensitivity of both procedures was much higher than that of conventional methods. The present results are in agreement with Blumenfeld et al (32) who recommended fine needle aspiration as the initial diagnostic modality in lung mass especially those located in the periphery.

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การวินิจฉัยโรคมะเร็งปอดโดยใช้การตรวจทางเซลล์วิทยา ในประเทศไทย

สำเริง รางแดง, พ.บ., ชรินทร์ ยาอินทร์, พ.บ.*,*
จงกลณี เศรษฐกร, พ.บ., เบญจพร ไชยวรรณ์, พ.บ.*,*
*ชายชาญ โพธิรัตน์, พ.บ.**, ชูศักดิ์ สิริวณิชชัย, พ.บ.***, อภินันท์ อร่ามรัตน์, พ.บ.*****

เพื่อที่จะประเมินบทบาทของการตรวจวินิจฉัยทางเซลล์วิทยาจากสิ่งส่งตรวจ อันได้แก่ sputum, bronchial brushing (BB), bronchial washing (BW), bronchoalveolar lavage (BAL) และ fine needle aspiration cytology (FNA) ในการวินิจฉัยโรคมะเร็งปอด โดยใช้การวินิจฉัยโรคจากชิ้นเนื้อของผู้ป่วยเป็นมาตรฐาน ได้ทำการศึกษาย้อนหลังจากสิ่งส่งตรวจทางเซลล์วิทยาของผู้ป่วยที่สงสัยว่าเป็นมะเร็งปอด 243 ราย ในจำนวนนี้ 160 ราย ได้มีการยืนยันการวินิจฉัยโรคจากชิ้นเนื้อว่าเป็นมะเร็งปอดจริง สิ่งส่งตรวจในการศึกษานี้ ได้แก่ 31 sputa, 123 BWs, 11 BBs, 36 BALs, 23 FNAs และ gun biopsies (GBs) ความไวของการตรวจ sputum, BW และ BAL ในการวินิจฉัยโรคมะเร็งปอด เท่ากับ 0.222, 0.455 และ 0.361 ตามลำดับ ในขณะที่ BB มีความไวในการวินิจฉัยโรคมะเร็งปอด เท่ากับ 0.800 ซึ่งมากกว่าสามวิธีข้างต้นอย่างมีนัยสำคัญ ($p<0.05$) FNA และ GB มีความไวในการวินิจฉัยโรคมะเร็งปอด เท่ากับ 0.913 และ 0.783 ตามลำดับ จึงสรุปได้ว่า BB และ FNA เป็นสิ่งส่งตรวจทางเซลล์วิทยาที่มีความไวในการวินิจฉัยโรคมะเร็งปอด มากกว่าวิธีอื่น

คำสำคัญ : มะเร็งปอด, เซลล์วิทยา, cyto-histological correlation

สำเริง รางแดง, ชรินทร์ ยาอินทร์, จงกลณี เศรษฐกร, และคณะ
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 953-961

* ภาควิชาพยาธิวิทยา,
** ภาควิชาอายุรศาสตร์,
*** ภาควิชารังสีวิทยา,
**** ภาควิชาเวชศาสตร์ครอบครัว, คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่, เชียงใหม่ 50200