Croat Med J 2005;46(3):449-457

Three Years of Experience with Routine Use of Telepathology in Assessment of Excisional and Aspirate Biopsies of Breast Lesions

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Aim To examine the applicability of routine telepathology to accurately diagnose breast lesions.

Methods During a 36 month period, a dynamic telepathology system was used to assess 315 excisional biopsies and 209 fine needle aspirates of breast lesions submitted by surgeons located 20 km from the hospital. The results of the gross and microscopic telepathology diagnoses were compared with final microscopic diagnoses.

Results No frozen sections were obtained in 120 of 315 cases submitted for frozen section due to lack of gross lesion (73/120), a papillary lesion or a lesion smaller than 1 cm (22/120), or a gross-only diagnosis of a benign process was given (23/120). For frozen sections, the microscopic telepathology diagnoses had a sensitivity of 81.6%, specificity of 100.0%, and diagnostic accuracy of 95.3%. For malignant tumors, the positive predictive value was 100.0% and the negative predictive value was 94.0%. For the fine needle aspirates, microscopic telepathology diagnoses agreed with conventional cytology in 163 of 209 cases. Tissue pathology was available for 109 of the fine needle aspirate specimens. For these 109 cases, telepathology diagnosis of malignancy was shown to have a sensitivity of 91.2% and specificity of 100.0%. Malignancy was identified in 8 of 16 cases with an atypia microscopic telepathology diagnosis and in 18 of 21 suspicious microscopic telepathology diagnoses.

Conclusion This long term study demonstrates that the routine use of telepathology compares well with conventional microscopy in the assessment of both frozen sections and fine needle aspirates of breast lesions.

Telepathology is the acquisition, transmission, and interpretation of images of both gross pathology specimens and microscopic slides. As such, telepathology is routinely used throughout the world for assessment of frozen sections, cytology specimens, and consultation cases (1). However, despite numerous feasibility studies of its applicability for routine use, telepathology in the United States has not found widespread acceptance, except in the Department of Veterans Affairs and the Department of Defense Facilities and at occasional academic centers (1-13).

A problem facing many pathology practices is the increasing demand for pathology services at one or more secondary locations. As a case-in-point, a free-standing breast disease center was established 11 miles (20 km) from the Ohio State University Medical Center. The major goal of the breast cancer center is to provide patients with a same-day diagnosis of their disease process, so the location of the center required full-time pathologist support in place for immediate assessment of frozen sections and surgeon-obtained fine needle aspirates of breast lesions. Considering the small

number of cases actually examined there, having a full-time pathologist at this location proved to be not only staffing prohibitive but also not cost effective. Problem solving to meet the needs of the patients, surgeons, and also the Department of Pathology at this location, resulted in the establishment of a telepathology service linking this center to the main Pathology resources. This article examines the first 36 months of our experience with the routine use of dynamic telepathology to provide gross and microscopic assessments of routine breast biopsy specimens for frozen sections and for the initial assessment of surgeon-obtained fine needle aspirates of breast lesions.

Patients and Methods

Patients

Frozen section cases. During the first 36 months of the telepathology service, a total of 329 biopsy samples, obtained in an outpatient setting, were submitted for telepathology assessment. These specimens were obtained from 317 different patients, including 6 men and 311 women. Of these 329 specimens, 315 (95.7%) came from the breast, 6 from the chest wall, 6 from the axilla, and 2 from the skin or subcutaneous soft tissue. This paper focuses on the 315 breast specimens that were obtained from 5 men and 310 women. Twelve of these women had two separate biopsy samples. Most specimens (311 of 329 or 94.5%) were excisional biopsies, whereas 18 of 329 (5.5%) were core biopsies.

Fine needle aspiration cases. During this same period, a total of 251 cytology specimens were submitted for telepathology assessment. These specimens were obtained from 251 patients, including 6 men and 245 women. The organ/tissue sites sampled were identified as being from the breast (n = 210), lymph node (n = 20), skin/chest wall (n = 5), soft tissue (n = 6), thyroid (n = 5), neck (n = 4), and mandible (n = 1). Of those obtained from the breast, 209 were fine needle aspirations and one represented nipple fluid discharge; 4 were from men and 205 from women.

Surgeons

Utilization of the telepathology service varied with the surgeon. A total of 7 different surgical oncologists submitted at least one breast biopsy (range from 1 to 224). This compared to 17 different physicians, including a gynecologist, who submitted at least one cytology specimen (range 1-107) for telecytology assessment. In only one case, a surgical oncologist uniformly utilized telepathology to assess both types of samples.

Telepathology System

The components of the dynamic telepathology system (MedMicro, Trestle Corporation, Irvine, CA, USA) include an Olympus BX50 microscope (MedMicro), with 2×, 4×, 10×, 20×, and 60× Plan ACH objectives mounted on a motorized nosepiece. The microscope is equipped with an x,y,z motorized stage (Prior Scientific, Rockland, MA, USA), and a Panasonic GP-KS 1000 (Panasonic Corp, Secaucus, NJ, USA) and an Olympus PMTV camera. The cameras are linked to a digitizer (Coreco, Billerica, MA, USA) mounted within the server. The gross features of the biopsy specimens are assessed using a VZ-7D video presenter with a NTSX to RGBS decoder (Wolfvision, Duluth, GA, USA) linked to the server. The server is a Gateway EA E5200-600 equipped with a Pentium III 600 MHz processor with 256 MB RAM, a 32 MB graphics card, and a 40 GB hard drive, running Windows 2000. Signals reach the computers on each of the pathologists' desktops via a dedicated T3 line. A local area network distributed the MedMicro software (MedMicro) to each pathologist's desktop computer. The software interface provides the pathologist with a 600×395 pixel diagnostic image as well as an overview image. The system provides complete control of the microscope, as well as anautomatic focus, step-through focus, and adjustment of brightness and contrast of the image.

Specimen Assessment by Telepathology

Specimen handling protocols. Each breast biopsy specimen is received and processed by a cytotechnologist trained to process tissue specimens for frozen sectioning and staining, as well as to operate the telepathology system. The cytotechnologist contacts the pathologist "on call" for frozen sections when a biopsy specimen is received. The gross specimen is viewed on the pathologist's desktop computer using the gross working station (ie video presenter). The pathologist decides on whether or not a frozen section should be obtained from the selected area based on the transmitted gross features and the physical characteristics of the lesion, as noted by the technologist.

Based on published criteria, a frozen section is not obtained in the following cases: where there is no apparent lesion, where the lesion is less than 1 cm in size, if the lesion is papillary, or if the diagnosis of fibroadenoma could be made, based on gross features (14-17).

In the cases involving cytology specimens, the surgeon submits multiple air-dried smears. Slides are stained with DiffQuik and a Papanicolaou stain for rehydrated slides. Each stained slide is screened and dotted by the on-site cytotechnologist. One or more slides containing representative material was used for telepathology assessment.

Telepathology assessment protocols. The dynamic nature of the telepathology system allows the pathologist to review the entire slide by moving the microscope stage, adjusting the magnification, and then focusing. The slide overview feature of the software continuously updates the pathologist as to the areas of the slide that had been reviewed. The pathologist's subsequent telepathology diagnosis is transferred to the surgeon so that he or she can discuss the initial gross or microscopic diagnosis with the patient prior their leaving the outpatient center. No attempt is made to alter the diagnostic criteria used by the pathologist to make the diagnosis using the telepathology system. In the cases where the diagnosis is in question, the telepathologist is able to consult another pathologist to simultaneously look at the slide(s) on their own desktop computer without leaving their offices.

The distributed nature of the dynamic telepathology system allowed 17 different surgical pathologists to review the frozen sections at their own desk. The number of frozen section cases reviewed by telepathology varied from 1 to 65 for any single pathologist. Although the telepathology system is designed for rapid processing of cases among pathologists, the variability in number of cases assessed by telepathology was due to differences in scheduling. As it happened, in many cases the same pathologist was scheduled for frozen sections on the day(s) of the week when the surgeons scheduled their cases. Fifteen surgical pathologists rendered the final pathology diagnosis, whereas 2 of them had not. Each frozen section is reviewed in conjunction with the permanent sections taken from the frozen section block and other samplings from the biopsy. Each of the DiffQuik and the Papanicolaou stained slides, in addition to any hematoxylin and eosin stained slides from a cell block, is reviewed by the cytopathologist on service on any particular day. Six board-certified cytopathologists rendered from 4 to 130 separate microscopic telepathology diagnoses on the breast fine needle aspirates and nipple discharge specimens. The cytologic diagnoses were categorized as unsatisfactory, benign, atypical, suspicious, or malignant, according to National Cancer Institute Guidelines (18).

Results

This study examined the concordance between the telepathology diagnosis and the final diagnosis as it pertains to both frozen sections and fine needle aspiration diagnoses of breast lesions. In addition, the study examined concordance of the microscopic telepathology diagnoses for fine needle aspirate specimens with the final tissue histopathologic diagnosis.

Gross-only Assessment by Telepathology

Table 1 presents the final tissue diagnoses for those breast biopsy specimens where no frozen section was obtained after an initial gross assessment by telepathology. A frozen section was

Table 1. Final diagnosis of gross-only telepathology assessment of breast lesions*

Final diagnosis	Gross-only telepathology assessment				
	NOS	gross-only diagnosis	no distinct lesion	<1 cm lesion	total
Benign	1	1	11	1	14
FCC/PBD	0	1	48	10	59
Papilloma	0	1	3	3	7
Fibroadenoma	1	20	7	4	32
Malignant:					
ductal carcinoma *in situ*	0	0	1	1	2
lobular carcinoma *in situ*	0	0	1	0	1
infiltrating ductal carcinoma	0	0	2	2	4
infiltrating lobular carcinoma	1	0	0	0	1
Total	3	23	73	21	120

*Abbreviations: NOS – not otherwise specified; FCC/PBD – fibrocystic change/proliferative breast disease.

not obtained in 120 of the 315 specimens (38.1%), based on the telepathology assessment of the gross specimen. In 2 cases, the report was not specific as to why a frozen section was not obtained, but the final microscopic diagnosis was benign in each case, and a malfunction of the cryostat precluded a frozen section from being obtained in a single case that was subsequently shown to be an infiltrating lobular carcinoma. A gross-only diagnosis of a benign process, based solely on the gross features of the lesion, was rendered in 23 of the 120 (19.2%) cases. There was a 100% concordance between the microscopic telepathology diagnoses and the final microscopic diagnoses for these 23 cases; 21 were diagnosed as a "benign tumor" or a fibroadenoma, 1 was shown to be an abscess, and 1 was shown to be fibrocystic change. Following standard protocols, the telepathologist did not obtain a frozen section for 73 of 120 (60.8%) specimens that lacked a discrete lesion or for 22 of 120 (18.3%) lesions containing a discrete lesion that was either papillary and/or was less than 1 cm in size. Malignant lesions, including 1 ductal carcinoma in-situ (DCIS), 1 lobular carcinoma in-situ (LCIS), and 2 infiltrating ductal carcinomas, were identified in the permanent sections in 4 of the 73 specimens lacking a distinct lesion. Similarly, 1 DCIS and 2 infiltrating ductal carcinomas were identified in 3 of 20 specimens where the lesion was less than 1 cm in size.

Frozen Section Assessment by Telepathology

A frozen section was obtained in 195 of 315 (61.9%) tissue specimens submitted for possible frozen section diagnosis by telepathology. In Table 2, the final microscopic diagnoses are compared with the microscopic telepathology diagnoses for these breast biopsy specimens. In 5 of 195 cases (2.6%), the microscopic telepathology diagnosis was deferred by the pathologist, based on their uncertainty of the diagnosis. In no case was there a correlation between the experience of the pathologist and either telepathology or making a frozen section diagnosis of a breast lesion.

This study did not dictate the terminology for making either microscopic telepathology diagnoses or final microscopic diagnoses; therefore the diagnostic categories in Table 2 combine several diagnoses. The "benign" category included gynecomastia, inflammation, fibrosis, and fat necrosis. The cases categorized as "FCC/PBD" include fibrocystic change, proliferative breast disease, and sclerosing adenosis. The category of "benign tumor" includes papillomas and fibroadenomas. A malignant diagnosis was used for cases of DCIS, LCIS, and invasive carcinoma.

A benign microscopic telepathology diagnosis was made in 139 cases (71.3%), with concordance with the final microscopic diagnosis in all but two cases (1.4%). Each case was reviewed. A sampling error accounts for the fact that in one case the frozen section lacked the tumor cells noted in other sections taken from the specimen. The second case represented a misdiagnosis of DCIS. A microscopic telepathology diagnoses of "atypical cells" was made for 11 specimens. The final microscopic diagnosis in these cases included 4 cases of infiltrating ductal carcinoma, 1 case of infiltrating lobular carcinoma, 1 case of DCIS, 1 case of Rosai-Dorfman disease, 1 case of lymphoid hyperplasia, 1 case of atypical ductal hyperplasia, 1 case of fibrocystic change, and 1 case of fibroadenoma. The microscopic telepathology diagnoses were 100% accurate in the cases where a malignancy was identified. These included carcinoma *in situ* (DCIS, n=2; LCIS, n=1) and invasive carcinoma (ductal, n=36; lobular, n=1). Excluding the cases deferred by the pathologist, these results demonstrated an overall sensitivity of 81.6% and a specificity of 100%, as well as a diagnostic accuracy of 95.3%. For malignant tumors, the positive predictive value was 100% and the negative predictive value was 94%.

Table 2. Breast lesion frozen section telepathology diagnosis vs final diagnosis

Final diagnosis	Telepathology diagnosis						
	deferred	benign	FCC/PBD	atypical cells	benign tumor	malignant	total
Benign	0	9	0	2	1	0	12
FCC/PBD*	1	19	25	2	2	0	49
Benign tumor	3	17	5	1	59	0	85
Malignant	1	0	2	6	0	40	49
Total	5	45	32	11	62	40	195

*FCC/PBD – fibrocystic change/proliferative breast disease.

Cytologic Assessment by Telepathology

Tissue was obtained in 109 of the 209 (52.1%) cases. Table 3 demonstrates the concordance between the tissue histopathology diagnoses and microscopic telepathology diagnoses in these cases. Malignancy was identified in 6 (27.3%) of 22 of insufficient microscopic telepathology diagnosis samples, which is indicative of a sampling error in at least 5 of the cases. Malignant findings were made in 3 (15.8%) of 19 benign microscopic telepathology diagnoses with subsequent tissue confirmation. Of 16 cases with an atypia microscopic telepathology diagnosis, the final tissue diagnosis of breast carcinoma was made in 8 cases. This compares with 18 of the 21 cases with a suspicious microscopic telepathology diagnosis. There were no false positive microscopic telepathology diagnoses of malignancy in the 31 cases with tissue follow-up. The most malignant diagnosis was Infiltrating ductal carcinoma (61 out of 66 cases; 92.4%), followed by infiltrating lobular carcinoma in 4 of 66 cases (6.1%), and a single case of metastatic renal cell carcinoma (1.5%).

In Table 4, the final diagnoses is compared with the telepathology diagnoses for breast-derived cytologic specimens that included 208 fine needle aspirates and a nipple discharge specimen. This table does not include one microscopic telepathology diagnosis that was deferred due to an equipment failure. The cytopathologic diagnoses are categorized as insufficient, benign, atypical, suspicious, and malignant (18). An insufficient microscopic telepathology diagnosis or final microscopic diagnosis was assigned to cytologic specimens that had too few ductal cells alone or in combination with mature adipose tissue, blood, or inflammation. "Benign" microscopic telepathology diagnoses and/or final microscopic diagnoses were associated with a benign process (e.g., hyperplasia, fibrocystic change) which included fibroadenoma. Although somewhat equivocal, atypical cells and cells suspicious for malignancy were divided into two separate categories. The latter category included the diagnosis "atypical cells, cannot rule out cancer". Cytologically, malignant cells were classified as malignant.

Significant discordance between the cytologic microscopic telepathology diagnoses and the cytologic final microscopic diagnoses was considered to be a change in more than one diagnostic category, either up or down in malignancy. Using this criterion, a total of 8 cases (3.8%) were significantly discordant upon review – 5 microscopic telepathology diagnosis cases upgraded and 3 microscopic telepathology diagnosis cases downgraded. The single microscopic telepathology diagnosis of insufficient that was upgraded to atypia was shown to be malignant on an immediate follow-up biopsy. A tissue diagnosis of a fibroadenoma was made for both of the benign microscopic telepathology diagnoses cases that were upgraded to suspicious. Four cases with a microscopic telepathology diagnosis of atypia were

Table 3. Telepathology diagnosis vs final tissue diagnosis

Tissue biopsy results	Final diagnosis					
	insufficient	benign	atypia	suspicious	malignant	total
Benign	16	16	8	3	0	43
FCC/PBD*	8	6	3	2	0	
Fibroadenoma	4	8	0	0	0	
Other	4	2	5	1	0	
Malignant:	6	3	8	18	31	66
ductal carcinoma	6	2	6	16	31	
lobular carcinoma	0	1	2	1	0	
metastatic	0	0	0	1	0	
Total	22	19	16	21	31	109

*FCC/PBD – fibrocystic change/proliferative breast disease.

Table 4. Breast cytology telepathology diagnosis vs final diagnosis

Final diagnosis	Telepathology diagnosis					
	insufficient	benign	atypia	suspicious	malignant	total
Insufficient	79	3	2	0	0	84
Benign	0	32	6	1	0	39
Atypia	1	4	7	4	0	16
Suspicious	0	2	8	6	2	18
Malignant	0	0	2	14	36	52
Total	80	41	25	25	38	209

changed – 2 upgraded to malignancy and 2 downgraded to insufficient quality. For the two cases that were downgraded, one was shown to be due to inflammation, whereas the other was diagnosed as infiltrating ductal carcinoma. Infiltrating ductal carcinoma was identified in the two cases that were upgraded from atypia to malignancy. These results suggest a false negative rate 0.5% (1 case in 209) of for cytologic microscopic telepathology diagnoses. However, these results also indicate a systemic error in the protocols that we are currently using. The examination of only a single slide for a given case may well have contributed to the upgrading of 5 of the diagnoses made by telepathology.

Discussion

The literature contains a growing list of articles detailing the use of telepathology diagnosis of frozen sections, cytologic specimens, routine surgical pathology, and expert consultation (1). We have more than three years of experience with the routine use of telepathology to examine breast lesions that fall into each of these categories. Our experiences with dynamic (live robotic) telepathology over the first 36 months of this period are unique, due to the limited nature of the tissue being examined and the fact that this technology is incorporated into the department's normal workflow. Our results demonstrated that telepathology is as effective as conventional microscopy in gross and microscopic diagnosis of biopsies and fine needle aspirates of breast lesions.

Our protocol for using telepathology in the diagnosis of frozen sections requires an initial gross evaluation of the specimen. Not all tissue specimens are submitted for frozen section. Published guidelines recommend that frozen sections should not be performed on breast specimens which lack a detectable lesion or contain a lesion that is less than 1 cm or is papillary (14). The diagnostic accuracy of the frozen section decreases from 96% to 92% when these guidelines are not followed (15,17). The routine use of, but not the efficacy of, telepathology to assess the gross specimens has been reported (10,19). Of our 315 specimens, 120 (38.1%) were not submitted for frozen section. The resolution of the gross station camera allowed the pathologist to make a gross diagnosis of "benign lesion, benign tumor, or fibroadenoma" with confidence for 23 of the 120 specimens (19.2%). The accuracy of this gross-only microscopic telepathology diagnosis was 100%. A malignant process was identified on permanent sections in 7 of the remaining 97 specimens. The fact that these lesions were small indicates that there was a likelihood of a false negative microscopic telepathology diagnoses if the frozen section was obtained. These data have indicated for the first time that telepathology can be used with confidence for critical decision making about whether or not a frozen section needs to be made, and if so where the lesion should be sampled.

Our protocol requires the use of a live robotic telepathology system. Commercial telepathology systems, available from several vendors, as well as various home grown systems, have expanded telepathology from its beginnings in remote corners of Norway to numerous institutions around the world, including Croatia (1,21,22). Dynamic (live robotic) telepathology, as used here, overcomes the problem of image quality and image-sampling error commonly associated with the decreased diagnostic accuracy of static telepathology (24). This decrease in diagnostic accuracy is the main reason why dynamic pathology should be considered as the equipment standard for frozen section diagnosis. Our results, and those of others, support this conclusion (3,10-12,20,26).

How do our results compare with others? The sensitivity and specificity of conventional frozen section diagnosis of breast lesions ranges from 0.77 to 0.92 and 0.92 to 1.0, respectively, whereas the diagnostic accuracy varies from 0.857 to 1.0 (3,15,17,20). Our results demonstrated an overall sensitivity of 81.6%, specificity of 100.0% and a diagnostic accuracy of 95.3%. Our results are well within the published range for conventional frozen section diagnosis. The reduced sensitivity reflects the fact that two specimens should not have been submitted for frozen section. One was a core biopsy, where sampling error accounted for the discrepancy, and the other was a small papillary lesion that contained carcinoma *in situ*. Both cases were difficult to diagnose and required peer evaluation, prior to issuing the final diagnosis. There are always difficult-to-diagnose cases. Our protocols call for peer evaluation of such cases prior to issuing final diagnosis. It is important to note that the microscopic telepathology diagnosis does not dictate whether or not the patient

undergoes definitive surgery. This is only done after the final biopsy diagnosis is reported.

When we compared the microscopic telepathology diagnoses with the tissue diagnoses, the sensitivity and specificity for microscopic telepathology diagnoses of malignant cells was 91.2% and 100.0%, respectively. There were 3 false negatives and no false positive results. Malignancy was identified in 8 of 16 cases with a microscopic telepathology diagnoses of atypia and in 18 of 21 cases with a microscopic telepathology diagnoses of suspicious. These results compare well with those published using conventional cytology (36-40) and are better than those reported using static telepathology protocols (30,32).

The high rate of 38.3% of cases with a microscopic telepathology diagnosis of insufficient cells (Table 4) reflects the fact that no pathologist obtained the breast fine needle aspirates at this multidisciplinary breast disease clinic. One would expect that our unsatisfactory rate as well as our false negative rate, 6 of 22 cases with tissue confirmation (Table 3), would have been lower if the specimens had been obtained by a pathologist as has been previously reported (35-37). Of interest is the fact that immediate tissue follow-up was obtained only in 31 cases, and that only 2 were malignant. Thus the surgeons did not see telecytology as a tool for determining sample adequacy.

The overall diagnostic concordance between the microscopic telepathology diagnoses and the final microscopic diagnoses derived by conventional microscopy was 78.0% (163 of 209). Almost identical results were reported by Singh et al, using a dynamic telepathology system to assess 47 breast fine needle aspirates immediately after conventional cytology (34). A microscopic telepathology diagnoses of atypia or of suspicious was the largest source of discordance. As previously reported by Galvez et al, the source of this disagreement is the lack of standardized diagnostic criteria used by the cytopathologists (31). In contrast, microscopic telepathology diagnoses and final microscopic diagnoses agreed in 36 of 38 cases when a microscopic telepathology diagnosis of malignant cells was made. The two discordant cases were later shown to be malignant upon the resection of the lesions.

Despite published concerns, we found that both telecytology and telepathology integrated well into our daily workflow (41). There is no argument that telepathology takes more time than normal frozen sections or fine needle aspirates evaluation. However, our decision to employ a dynamic telepathology saved us time – driving time to the site and time from the site to the lab when we tried a courier system – and money. This makes it a cost effective decision. The distributive nature of our system reduces the time needed to diagnose difficult cases – multiple pathologists can view the case simultaneously. During the initial studies prior to going live, we found that the time to make a diagnosis varied with the difficulty of the case and with the pathologist's level of self confidence in making a microscopic telepathology diagnoses. Over time, the latter problem decreased with increasing experience. Similar results have been noted by others (10). We did find that the time to make a diagnosis once the slide was scanned approached the prolonged times, 20 minutes or more, reported by some authors (1,2,34). In our hands, the mean time for diagnosis ranged from a mean of 4.9 ± 4.2 minutes down to 1.9 ± 1.9 minutes. Similar results have also been reported (12,42).

It is important to realize that our routine use of telepathology for the primary diagnosis of breast frozen sections and for the initial assessment of breast fine needle aspirates specimens is a unique application of this technology. However, our results do agree with the published data on the sensitivity and specificity of telepathology for a wide range of specimens including frozen sections and fine needle aspirations. We continue to utilize this technology on a day-to-day basis, using the protocols as reported here.

Acknowledgments

The authors have no commercial affiliations with the companies mentioned in this article.

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Received: March 21, 2005
Accepted: March 31, 2005

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