# Double Check Up of Malignancy Biopsy Specimens for Patient Safety

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***Background:*** *The diagnostic of malignancy in biopsy specimens is very important because it guides to selected treatment option and prognostic prediction. However, biopsy specimens usually have small pieces leading to variations of the interpretation by anatomical pathologists.*
***Objective:*** *To detect and correct the errors or the significant discrepancies in the diagnosis of biopsy specimens before sign-out and to determine the frequency of anatomic pathology significant discrepancies.*
***Design:*** *The application of the mutually agreed work instructions (record) for the detection of errors or the significant discrepancies and their process of sign-out. The record of biopsy specimen that received a secondary check (1,959 cases, 2005-2007) was analyzed.*
***Results:*** *After a secondary check, 53 cases of non-malignancy for any reason by a second pathologist were included. However, when using our definition on significant discrepancies, only 37 cases were considered. Another seven cases with the opinions with malignancy that were of different cell types that do harm to the patients were added. Therefore, 44 cases (2.25%) had truly significant discrepancies.*
***Conclusion:*** *The truly significant discrepancy frequency was 2.25% during the process of pre-sign-out secondary check of malignancy of biopsy specimens. The project has been applied as a routine daily work. It can be an innovative safety program for patient in Thailand.*

***Keywords:*** *Patient safety, Quality improvement, Quality assurance, Surgical pathology, Malignancy*

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The routine works for diagnostic anatomical pathology in the department of pathology, Ramathibodi hospital had some discrepancies. The discrepancies were detected by clinician, intradepartmental and interdepartmental conference, or incidental double check up (previously related surgical specimen). These discrepancies were not systematically recorded. Furthermore, the discrepancies created various degrees of patients' harms and the patients were not always informed.

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The diagnosis of malignancy has many effects on the patients such as psychological and familial. Furthermore, the diagnosis affects the treatments and how it is going to be carried-out. Thus, the diagnoses of malignancy cannot be missed for any single case. However, the diagnosis is based on a small specimen (biopsy) that may have many problems thus, could lead to errors of diagnosis. The department of pathology set-up a project to try to solve the problems called the pre-sign-off secondary diagnostic check of biopsy specimen project.

## Material and Method

The present project ran since March 2004 as a routine daily work with the cooperation of all anatomical pathologists in the department. The mutually agreed

work instructions are demonstrated in Fig. 1. The process started with the diagnostic of any biopsy specimen that was sent to the secretary of the surgical pathology report unit for record. Then the specimen was delivered to a second pathologist for diagnosis and the record was updated (Fig. 2). Consistent diagnosis would be sent back to the secretary for the record and to the first pathologist to be sign-off.

Any discrepant diagnosis was recorded, including the reasons and the suggestions. Discrepant diagnosis would also be sent to the first pathologist. If the first pathologist agreed with the second pathologist, then the suitable report would be sign-off. If the first pathologist did not agree with the second pathologist, then an authorized consultant or a departmental conference would be used. The consultant's opinion would be considered and then the appropriate diagnosis would be made by the first pathologist and sign-off. The first pathologist may refer the case to another pathologist. Then, the pathologist who received the referred case would have the authority to sign-off the diagnosis. In any case, the opinion from the departmental conference/ consultant must be attached to the report, whether agreed or not.

The discrepancies included cell type, differentiation, and any reason for the different result. The significant discrepancies were confined to the results of non-malignancy and malignancy thus, differences of cell type, which were considered harmful, play an important role in treatment selection.

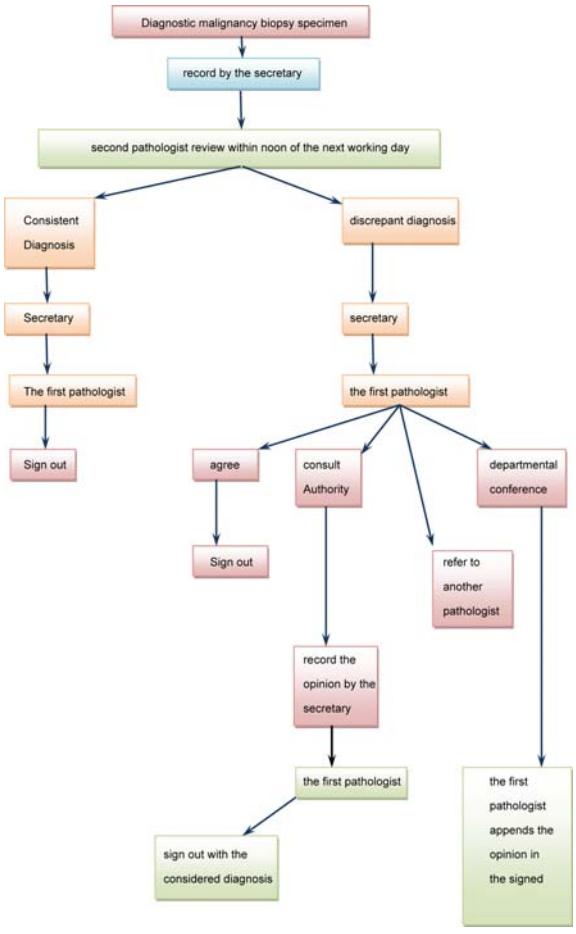


**Fig. 1**

## Results

After running the present project for about nine months, the annually consecutive data between 2005 and 2007 were collected. The results are shown in Table 1 including total number of biopsy specimens (n = 41,994), number of malignancy biopsy specimens that had a secondary check (n = 1,959), number of cases with significant discrepancies (n = 60), and number of cases that had agreed diagnoses but needed opinions (n = 179).

The cases with significant discrepancies can be divided into benign, atypia, highly suggestive/ suggestive of malignancy, and different cell type with harm (Table 2) according to the information from a record form (Fig. 2). The types of significant discrepancies with their instructed processes (Fig. 1) of signed diagnosis are demonstrated in Table 3. The differences of cell type that harm the patients have a variation of processes and the suitable presentation is displayed with individual cases.

The added opinions of the cases with agreed diagnoses can be classified as the same cell type but with disagreed differentiation, additional histologic finding except cell differentiation, giving more or different detail of diagnosis except cell differentiation and additional histologic finding, partially agreed diagnosis (consistent main diagnosis but disagreed with the other parts of diagnosis), and suggestive of additional study for confirmation of the diagnosis (Table 4).

## Discussion

After the recognition of the discrepancies in the diagnosis and the mutually agreed work instruction, a record form (Fig. 2) was introduced based on the concept of "two-step discrepancy is an error"[1]. Raab defined an error as an instance where the diagnoses of

| Case | Surgical Number | Result | | | | Cell type | | Differentiation | | Additional suggestion | Pending process | Final diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Benign | Atypical | Highly suggestive/ suggestive | Malignant | discrepant | consistent | discrepant | consistent | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**Fig. 2** A record of the second review of malignancy biopsy specimen

**Table 1.**

| Total biopsy number | Cases of malignancy biopsy specimen with secondary check (% of total biopsy) | Significant discrepancies/agreed (cases) | Agreed with additional opinions (cases) |
|---|---|---|---|
| 2005 13,151 | 699 (5.32%) | 20/679 | 57 |
| 2006 13,917 | 625 (4.49%) | 19/606 | 56 |
| 2007 14,926 | 635 (4.25%) | 21/614 | 66 |
| Total 41,994 | 1,959 (4.67%) | 60/1,899 | 179 |

**Table 2.** Significant discrepancies (60 cases or 3.06% of total malignancy biopsy with secondary check

| | |
|---|---|
| Benign | 14 cases |
| Atypia | 23 cases |
| Highly suggestive/suggestive of malignancy | 16 cases |
| Different cell type with harm | 7 cases |

the cytologic specimen and the histologic specimen are different by two or more steps. The step differences were classified as benign, atypical, suspicious of malignancy, and malignant. For example, the distance between suspicious of malignancy and benign lesion is an error but atypical lesion and benign lesion is not.

The results of non-malignancy of any reason after the secondary check (n = 53) are no longer truly significant discrepancies according to the two-step concept. If the truly significant discrepancies are the distance from the diagnosis with malignancy by the first pathologist, they should be benign lesions and atypical lesions after the secondary check and the summary of these groups is only 37 cases.

Because patient safety is defined as freedom from accidental injury in the delivery of health care[2], the truly significant discrepancies are not confined only to benign or atypical lesion with secondary check. Therefore, the additional concept that a discrepancy that resulted in patient harm[3] must also be considered. This is classified as different cell type that do harm to the patient even if the second pathologist gave an opinion with malignancy. For example, nasopharyngeal carcinoma vs. lymphoma and bronchogenic carcinoma of small vs. non-small cell subtype are all malignancies but have different treatment and prognosis of the particular organs. The seven cases of this group are added in the truly significant discrepancies.

The total number of truly significant discrepancies is 44 cases or 2.25% of total malignancy biopsy with secondary check. Raab declared anatomic pathology errors with 1% to 43% of all anatomic pathology specimens. This wide range depends on the method of detection and the definition of errors. Mean anatomic pathology error frequency ranged from 1% to 5%, based on single-institution data[3]. Nakhleh identified that many studies had the discrepancies in the 40% of cases but the significant error rates were 0.26% to 1.7%[2]. There is no established acceptable error rate in anatomic pathology. The six sigma standard for manufacturing is 3.4 defects per million, so this should be applied in the factories not pathologists because the anatomic pathology works have a long way to meet the six sigma standard.

**Table 3.** Types of significant discrepancies based on second pathologists' opinions and their processes of signed diagnoses

| | |
|---|---|
| Benign (14 cases) | |
| The first pathologist signed malignancy | 1 case |
| The first pathologist signed benign | 3 cases |
| The first pathologist signed atypia | 3 cases |
| The first pathologist signed highly suggestive/suggestive of malignancy | 4 cases |
| Consultant agreed with the first pathologist and the first pathologist signed malignancy | 2 cases |
| Consultant gave an opinion with atypia and the first pathologist signed atypia | 1 case |
| Atypia (23 cases) | |
| The first pathologist signed malignancy | 5 cases |
| The first pathologist signed atypia | 6 cases |
| The first pathologist signed highly suggestive/suggestive of malignancy | 1 case |
| Consultant agreed with the first pathologist and the first pathologist signed malignancy | 5 cases |
| Consultant gave an opinion with atypia and the first pathologist signed atypia | 1 case |
| Consultant gave an opinion with highly suggestive/suggestive of malignancy and the first pathologist signed highly suggestive/suggestive | 1 case |
| Consultant gave an opinion with malignancy but the first pathologist signed atypia | 1 case |
| Refer to another pathologist and then signed malignancy (the same as the first pathologist) | 1 case |
| Refer to another pathologist and then signed atypia | 1 case |
| Departmental conference concluded with malignancy and the first pathologist signed malignancy | 1 case |
| Highly suggestive/suggestive of malignancy (16 cases) | |
| The first pathologist signed malignancy | 3 cases |
| The first pathologist signed highly suggestive/suggestive of malignancy | 6 cases |
| The first pathologist signed atypia | 3 cases |
| Consultant agreed with the first pathologist and the first pathologist signed malignancy | 1 case |
| Refer to another pathologist and then signed highly suggestive/suggestive of malignancy | 1 case |
| Departmental conference concluded with malignancy and the first pathologist signed malignancy | 2 cases |
| Different cell type with harm (7 cases) | |
| 1. The second pathologist gave an opinion with small cell carcinoma vs non-small cell carcinoma according to a very small received tissue and the first pathologist still signed non-small cell carcinoma. | |
| 2. The second pathologist had a hesitation of malignancy then the first pathologist signed suggestive of squamous cell carcinoma. | |
| 3. The second pathologist prefered undifferentiated carcinoma not lymphoma and then the first pathologist changed to sign undifferentiated small cell carcinoma. | |
| 4. The second pathologist prefered squamous cell carcinoma not small cell carcinoma and the first pathologist changed to sign poorly differentiated carcinoma. | |
| 5. The second pathologist could not exclude small cell carcinoma from inconclusive lymphoma and the first pathologist changed to sign compatible with small cell carcinoma. | |
| 6. The consultant agreed with the first pathologist that it should be AML not ALL and the first pathologist signed AML. | |
| 7. The second pathologist gave an opinion with adenocarcinoma (primary vs. metastasis) not hepatocellular carcinoma and the first pathologist refered to another pathologist. The final diagnosis was combined hepatocellular and cholangiocarcinoma. | |

The approval processes of all types of discrepancies (Table 3) are categorized by workflow instruction (Fig. 1). The truly significant discrepancies with benign or atypical lesions have the process of approval as demonstrated. The following events are not shown in the table because of the wide range of variations and they cannot be grouped. For example, presence or absence of following specimens, presence of following specimens but with larger or smaller size, presence of following specimens but with only metastatic site, presence of following specimens but after the specific treatment, presence of following specimens but with the more accurate site of biopsy by different procedures, etc.

The signed diagnosis after the processes in the work instruction of the cases with highly suggestive/suggestive of malignancy (n = 16) by secondary check may still have truly significant discrepancies. Even though 13 cases are signed with malignancy or highly suggestive/suggestive of

**Table 4.** Agreed with opinion (179 cases or 9.14% of total malignancy biopsy with secondary check)

| | |
|---|---|
| Differentiation in the same cell type | 40 cases |
| Additional histologic finding | 23 cases |
| Giving more or different detail of diagnosis | 62 cases |
| Partially agreed (consistent main diagnosis) | 36 cases |
| Additional study for confirmation | 18 cases |

malignancy, the other three cases are signed with atypical lesions that are two steps from the diagnosis of malignancy mentioned by the first pathologist. Unlike the cases with malignancy by the first pathologist with benign or atypical lesions diagnosis by the second pathologist, all cases that are recognized as two steps away from malignancy, which are truly significant discrepancies, should be carefully managed. The cases with highly suggestive/suggestive of malignancy by the second pathologist are also very important and should be managed in the same way. This is because the final report (n = 3) is atypical lesion even if the diagnoses by the second pathologist is not two steps away from the malignancy by the first pathologist.

The meaning of the error in the present study may be not completely similar to Raab's definition[1]. One pathologist who diagnosed two steps away from the diagnosis of another may be right or wrong. Theoretically, the specimens may provide more tissue leading to the correct diagnosis thus, the error of one pathologist can be proven. On the other hand, most of the received second-specimens in the study did not provide more tissue from the same lesion. For example, specimens can be received from metastatic site or after a period of treatment. If the same lesion is repeatedly probed, less tissue but more accurate site depends on clinician techniques or experience. Therefore, this may give the correct diagnosis. However, more tissue but not from the diagnostic site may give the incorrect diagnosis. In any case, most of the cases diagnosed with benign or atypia by the second pathologist had no additional specimen.

Particular specimens that had secondary check may have been diagnosed two steps away from original diagnostic by different pathologists but they may not be concluded with error because differently reasonable diagnoses may be accepted by the different pathologists.

The category of the differences of cell type that harm the patients can be diverse as demonstrated with the seven cases in Table 3. Only three cases had an additional specimen (case 4, 5, and 6). Case 4 and 5 were diagnosed with small cell carcinoma and case 6 was diagnosed with myeloid cell tumor. This result shows two correct diagnoses by the first pathologist and one correct diagnosis by the second pathologist but the error cannot be concluded for any one. The discussion about error should be concentrated with the same biopsy specimens not to compare with additional specimens.

The opinions for the biopsy specimens in particular cases may have different diagnosis, not only by the second pathologist but also with the other pathologists, and all of the reasons can be accepted. At this point, discussion with other experts such as surgeons or radiologists may be helpful and the word "error" may finally be applied. The only true gold standard for diagnoses is long-term follow-up and response to therapy but it is impractical[4].

The added opinions by the second pathologists (Table 4) were considered even if the main diagnoses were consistent. These results support the variation of the differently acceptable opinions among the specialty in the field of anatomic pathology. The opinions in Table 4 do no harm to the patients so they are separately categorized.

From the project beginning (March 2004) until now, the work instructions are applied as a routine work with good cooperation of all anatomical pathologists in the department. This work meets both quality assurance and quality improvement as recommended by the association of directors of anatomic and surgical pathology (ADASP)[4]. The fulfilled criteria are systemic monitoring, quality committee, internal second review of every diagnosed biopsy specimens (quality assurance case reviews), defining error or discrepancy types, and error or discrepancy correction. Nakhleh described error-reduction strategies with the design for errors[5]. A system should be designed with timely secondary checks for error detection and correction before final sign-off. This strategy is also familiar with the department's project. Even though the second review prior to case sign-off is the most common method used to prevent diagnostic errors, most of them are selected organs (breast, prostate gland, etc) or selected diagnoses (melanoma, gastrointestinal malignancies, etc)[2]. Unlike this project, every single case of malignant biopsy specimens must follow the work instructions for detection and correction of the errors or discrepancies before sign-off. It can be called

innovation because there is no other systematic control for the quality assurance as a routine work in the other institutions in Thailand.

## Conclusion

The truly significant discrepancy frequency is 2.25% during the process of pre-sign-off secondary check of diagnosing biopsy specimens. This rate is within the wide range of discrepancies of many studies. The effort should be recognized by pathologists as an attempt to reduce discrepancy. The project has been applied routinely in the daily work, and has the cooperation of all anatomical pathologists in the department. It is truly innovation for patient safety in Thailand.


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# การตรวจซ้ำชิ้นเนื้อเล็กที่ได้รับการวินิจฉัยว่าเป็นมะเร็ง เพื่อความปลอดภัยของผู้ป่วย

**พัฒนา ศรมยุรา, ยิ่งลักษม์ วิเศษศิริ, มานะ โรจนวุฒนนท์, วรชัย ศิริกุลชยานนท์, รังสิมา อรุณโรจน์, วาสนา กนกศิลป์, นพดล ลาภเจริญทรัพย์, ศันสนีย์ วงศ์ไวศยวรรณ, ยุวดี เลี่ยวไพรัตน์, พนัส เฉลิมแสนยากร, สุชิน วรวิชชวงษ์, นิรมล ฉันท์พลากร, ไพศาล ลีละชัยกุล, อัจฉราพร พงษ์ทิพพันธ์**

***ภูมิหลัง:*** *การวินิจฉัยมะเร็งจากชิ้นเนื้อ biopsy มีความสำคัญมากเพราะนำไปสู่ทางเลือกในการรักษา และยังเป็นตัวชี้บ่งการดำเนินโรค อย่างไรก็ดีเนื่องจากชิ้นเนื้อที่ได้มักมีขนาดเล็ก ซึ่งอาจมีข้อจำกัดในการอ่านแปลผลแตกต่างกันไปในพยาธิแพทย์แต่ละท่าน*

***วัตถุประสงค์:*** *เพื่อค้นหาและแก้ไขการวินิจฉัยที่ผิดพลาด หรือแตกต่างกันอย่างมีนัยสำคัญในชิ้นเนื้อ biopsy ก่อนที่จะมีการรายงานผลและประเมินว่าความแตกต่างในการวินิจฉัยดังกล่าวมีความถี่มากน้อยเพียงใด*

***วัสดุและวิธีการ:*** *ใช้วิธีการปฏิบัติงานซึ่งได้รับความเห็นชอบจากพยาธิแพทย์ทุกท่าน เพื่อค้นหาการวินิจฉัยที่ผิดพลาด หรือ แตกต่างกันอย่างมีนัยสำคัญ รวมทั้งกระบวนการดำเนินงานต่าง ๆ เพื่อที่จะรายงานผลโดยวิเคราะห์จากแบบบันทึกการอ่านผลชิ้นเนื้อ biopsy ที่วินิจฉัยว่าเป็นมะเร็งและได้รับการตรวจซ้ำในช่วงปี พ.ศ. 2548 ถึง พ.ศ. 2550 จำนวน 1,959 ราย*

***ผลการศึกษา:*** *ภายหลังที่มีการตรวจซ้ำชิ้นเนื้อ biopsy ที่วินิจฉัยโดยพยาธิแพทย์ท่านแรกว่าเป็นมะเร็งพบว่ามีจำนวน 53 ราย ซึ่งพยาธิแพทย์อีกท่านหนึ่งเห็นว่าไม่ใช่มะเร็งด้วยเหตุผลต่าง ๆ กัน อย่างไรก็ดีเมื่อตัดความเห็นที่กล่าวว่าเป็นเพียง highly suggestive/suggestive of malignancy ออกไป เนื่องด้วยไม่ใช่ความแตกต่างในการวินิจฉัยอย่างมีนัยสำคัญที่แท้จริงก็จะเหลือเพียง 37 ราย เท่านั้นนอกจากนี้ยังพบว่ามีอีก 7 ราย ซึ่งแม้พยาธิแพทย์อีกท่านหนึ่งจะเห็นด้วยว่าเป็นมะเร็ง แต่เห็นว่าเป็นเซลล์คนละชนิดกันกับพยาธิแพทย์ท่านแรก ซึ่งอาจทำให้ผู้ป่วยได้รับอันตรายได้ โดยสรุปแล้วจึงมีทั้งสิ้น 44 ราย (2.25%) ซึ่งมีการวินิจฉัยที่แตกต่างกันอย่างมีนัยสำคัญที่แท้จริง*

***สรุป:*** *การวินิจฉัยที่แตกต่างกันอย่างมีนัยสำคัญที่แท้จริงมีความถี่ 2.25% เมื่อตรวจสอบโดยใช้กระบวนการตรวจซ้ำชิ้นเนื้อ biopsy ที่ได้รับการวินิจฉัยว่าเป็นมะเร็ง โครงงานนี้ได้นำมาใช้เป็นงานประจำนับเป็นนวัตกรรมเพื่อความปลอดภัยของผู้ป่วยในประเทศไทย*