COMPARATIVE STUDY OF DIAGNOSTIC ACCURACY BETWEEN CLOSE NEEDLE BIOPSY AND OPEN INCISIONAL BIOPSY IN MUSCULOSKELETAL SARCOMA

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science Program in Health Development

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การศึกษาเปรียบเทียบความถูกต้องแม่นยำในการวินิจฉัยทางพยาธิวิทยาของมะเร็งชนิดปฐมภูมิกระดูกและเนื้อเยื่อเกี่ยวพันระหว่างวิธีการเจาะตรวจแบบปิดและวิธีผ่าตัดแบบเปิด

พันเอก พฤษพงศ์ ศรีสวัสดิ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
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Thesis Title	COMPARATIVE STUDY OF DIAGNOSTIC ACCURACY BETWEEN CLOSE NEEDLE BIOPSY AND OPEN INCISIONAL BIOPSY IN MUSCULOSKELETAL SARCOMAS
By	Colonel. Phutsapong Srisawat
Field of Study	Health Development
Thesis Advisor	Associate Professor, Taweechai Tejapongvorachai M.D., M.sc.

Accepted by the Faculty of Medicine Chulalongkorn University in Partial Fulfillment of the Requirements of the Master's Degree

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พฤษพงศ์ ศรีสวัสดิ์: การศึกษาเปรียบเทียบความถูกต้องแม่นยำในการวินิจฉัยทางพยาธิวิทยาของมะเร็งชนิดปฐมภูมิกระดูกและเนื้อเยื่อเกี่ยวพัน ระหว่างวิธีการเจาะตรวจแบบปิดและวิธีผ่าตัดแบบเปิด (COMPARATIVE STUDY OF DIAGNOSTIC ACCURACY BETWEEN CLOSE NEEDLE BIOPSY AND OPEN INCISIONAL BIOPSY IN MUSCULOSKELETAL SARCOMA) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: รศ.นพ.ทวีชัย เตชะพงศ์วรชัย, 23 หน้า.

วัตถุประสงค์: เพื่อเปรียบเทียบความถูกต้องแม่นยำและความสามารถในการให้ผลวินิจฉัยทางพยาธิวิทยา, ความผิดพลาดและภาวะแทรกซ้อนในการวินิจฉัยทางพยาธิวิทยาของของมะเร็งชนิดปฐมภูมิของกระดูกและระบบเนื้อเยื่อเกี่ยวพันโดยเปรียบเทียบ2วิธี ระหว่างวิธีการเจาะตรวจแบบปิดที่ห้องตรวจโรคผู้ป่วยนอกและวิธีผ่าตัดแบบเปิดที่ห้องผ่าตัด

รูปแบบการวิจัย: เชิงพรรณาเปรียบเทียบในด้านการวินิจฉัยโรค (Descriptive study, diagnostic aspect)

สถานที่ทำการวิจัย: กองออร์โธปิดิกส์ โรงพยาบาลพระมงกุฎเกล้า และ สถาบันพยาธิวิทยา กรมแพทย์ทหารบก

ระเบียบวิธีวิจัย: เก็บรวบรวมข้อมูลโดยการทบทวนย้อนหลังจากฐานข้อมูลเวชระเบียนผู้ป่วยและฐานข้อมูลทางพยาธิวิทยาเลือกประชากรตัวอย่างผู้ป่วยมะเร็งชนิดปฐมภูมิกระดูกและระบบเนื้อเยื่อเกี่ยวพันที่มารับการรักษาระยะเวลา10ปีย้อนหลัง(พศ. 2545-2554) โดยแบ่งประชากรตัวอย่างเป็น2กลุ่ม ได้แก่ กลุ่มมะเร็งปฐมภูมิที่วินิจฉัยโดยใช้วิธีการเจาะตรวจแบบปิดโดยที่ไม่มีเครื่องมือทางรังสีวินิจฉัยช่วยขณะทำหัตถการ ณ ห้องตรวจโรคผู้ป่วยนอก และ กลุ่มมะเร็งปฐมภูมิที่วินิจฉัยโดยใช้วิธีการผ่าตัดแบบเปิดที่ห้องผ่าตัด นำมาเปรียบเทียบความแม่นยำในการวินิจฉัยทางพยาธิวิทยาโดยละเอียด4ด้าน ได้แก่ ธรรมชาติของก้อนเนื้องอก ชื่อโรคมะเร็ง ชนิดของโรคมะเร็ง ความรุนแรงของโรคมะเร็ง โดยใช้ผลพยาธิของก้อนโรคมะเร็งขณะทำการผ่าตัดรักษาตอนสุดท้ายเป็นมาตรฐานหลัก และยังทำการเก็บข้อมูลอื่นเปรียบเทียบด้วย ได้แก่ ความสามารถในการวินิจฉัยของแต่ละวิธี ความผิดพลาดที่เกิดจากการวินิจฉัย (ผิดพลาดรุนแรง;วินิจฉัยผิดจากมะเร็งเป็นเนื้องอกธรรมดา, ผิดพลาดเล็กน้อย;วินิจฉัยผิดในส่วนอื่น) ภาวะแทรกซ้อนที่เกิดจากการทำหัตถการ

ผลการศึกษา: จากผู้ป่วยมะเร็งปฐมภูมิของกระดูกและระบบเนื้อเยื่อเกี่ยวพันจำนวนทั้งสิ้น200ราย แบ่งเป็นจากกลุ่มมะเร็งปฐมภูมิที่วินิจฉัยโดยใช้วิธีการผ่าตัดแบบเปิด 105ราย กลุ่มมะเร็งปฐมภูมิที่วินิจฉัยโดยใช้วิธีการเจาะตรวจแบบปิด 95ราย ความแม่นยำในการวินิจฉัยทางพยาธิวิทยาโดยวิธีการผ่าตัดแบบเปิด ได้แก่ 97.14% สำหรับธรรมชาติของก้อนเนื้องอก, 89.52% สำหรับชื่อโรคมะเร็ง, 89.52%สำหรับชนิดของโรคมะเร็ง, 88.57%สำหรับความรุนแรงของโรคมะเร็ง ความแม่นยำในการวินิจฉัยทางพยาธิวิทยาโดยวิธีการผ่าตัดแบบปิดได้แก่ 96.84%, 89.47%, 88.42%, 86.32% เรียงตามลำดับ เมื่อเปรียบเทียบโดยใช้วิธีทางสถิติพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญ (ธรรมชาติของก้อนเนื้องอก; P-value = 0.901 95%CI = -0.432 ถึง 0.380, ชื่อโรคมะเร็ง; P-value = 0.991 95%CI = -0.227 ถึง 0.224, ชนิดของโรคมะเร็งP- value = 0.803 95%CI = -0.250 ถึง 0.193,ความรุนแรงของโรคมะเร็ง; P-value = 0.63 95%CI = -0.261 ถึง 0.15) อีกทั้งไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติสำหรับความสามารถในการวินิจฉัยของแต่ละวิธี 98.13%โดยวิธีการผ่าตัดแบบเปิด, 97.94%โดยวิธีการเจาะตรวจแบบปิด. (P-value = 0.919 95%CI = -0.469 ถึง 0.520) พบว่ามีความผิดพลาดรุนแรงทั้งหมดที่เกิดจากการวินิจฉัยจำนวน 6 ราย (3%), 3 ราย (2.86%) โดยวิธีการผ่าตัดแบบเปิด และ 3 ราย (3.16%) โดยวิธีการผ่าตัดแบบปิด พบว่ามีความผิดพลาดเล็กน้อยทั้งหมด 18 ราย (9%), 9 ราย (8.57%) โดยวิธีการผ่าตัดแบบเปิด 9 ราย (9.47%) โดยวิธีการเจาะตรวจแบบปิด ไม่มีภาวะแทรกซ้อนที่เกิดจากตรวจวินิจฉัยทั้งสองวิธี

สรุป: ความถูกต้องแม่นยำและความสามารถในการให้ผลวินิจฉัยทางพยาธิวิทยาโดยวิธีการเจาะตรวจแบบปิดโดยที่ไม่มีเครื่องมือทางรังสีวินิจฉัยช่วยขณะทำหัตถการ ณ ห้องตรวจโรคผู้ป่วยนอก ให้ผลที่ไม่แตกต่างกับวิธีการผ่าตัดแบบเปิดที่ห้องผ่าตัดในผู้ป่วยมะเร็งปฐมภูมิของกระดูกและระบบเนื้อเยื่อเกี่ยวพัน

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

ปีการศึกษา 2555 ลายมือชื่อ อ. ที่ปรึกษาวิทยานิพนธ์หลัก .....

#547 49152 30: MAJOR HEALTH DEVELOPMENT

KEYWORDS: DIAGNOSTIC ACCURACY/ CLOSE NEEDLE BIOPSY/ SARCOMA

PHUTSAPONG SRISAWAT: COMPARATIVE STUDY OF DIAGNOSTIC ACCURACY BETWEEN CLOSE NEEDLE BIOPSY AND OPEN INCISIONAL BIOPSY IN MUSCULOSKELETAL SARCOMAS. ADVISOR: ASSOC PROF. TAWEECHAI TEJAPONGVORACHAI, M.D., M.Sc., 23 pp.

Objective: In this study, we purpose to study the diagnostic accuracy and other diagnostic values (diagnostic yield, error, complication) of CNB without real-time image-guidance in out-patient clinic by comparing with open incisional biopsy in musculoskeletal sarcoma patients.

Methods: We retrospectively reviewed the biopsy cases of sarcoma patients since 2002-2011 from medical records and histopathology database. The diagnostic accuracy in 4 aspects of histopathology: nature (benign or malignant), specific diagnosis, histological type, and histological grade between 2 methods were compared statistically, the gold standard were the histopathology from resected specimens while definite surgery and information of clinicoradiographic/laboratory by clinical course. The other diagnostic values (diagnostic yield, error, complication) were also compared between both methods.

Results: There were 200 cases (open incisional biopsy 105 cases and CNB 95 cases). The diagnostic accuracies of open incisional biopsy were 97.14% for nature, 89.52% for specific diagnosis, 89.52% for histological type, 88.57% for histological grade and the diagnostic accuracies of CNB were 96.84%, 89.47%, 88.42%, 86.32% respectively. There were no statistically significant different between 2 methods in all histological aspects (nature; P-value = 0.901 95%CI = -0.432 to 0.380, specific diagnosis; P-value = 0.991 95%CI = -0.227 to 0.224, histological type P- value = 0.803 95%CI = -0.250 to 0.193, and histological grade; P-value = 0.63 95%CI = -0.261 to 0.158). The diagnostic yields of both methods were 98.13% for open incisional biopsy, 97.94% for CNB. It was no statistically significant different also as shown in table 6 (P-value = 0.919 95%CI = -0.469 to 0.520). There were 6 cases (3%) for overall major errors, 3 cases (2.86%) for open incisional biopsy and 3 cases (3.16%) for CNB. There were 18 cases (9%) for minor errors, 9 cases (8.57%) for open incisional biopsy and 9 cases (9.47%) for CNB. There was no related biopsy complication in both methods**.**

Conclusion: The office-based CNB for diagnosis musculoskeletal sarcoma can achieve the acceptable high diagnostic accuracy rates comparing with the open incisional biopsy.

Field of Study: Health Development Student's Signature: .....

Academic Year: 2012 Advisor's Signature: .....

ACNKOWLEDGEMENTS

I would like to express my gratitude to Associate Professor Taweechai Tejapongvorachai, my advisor for the helpful advice and comments until this study accomplished. I also wish to thank Professor John J. Kavanagh and Dr.Cameron Hurst for their kindness and valuable advice. I also appreciate my teachers and colleagues (Dr.Puwadol Veeraphun, Associate Professor Thipachart Punyaratabandhu, Associate Professor Supichai Chareonvareekul, Associate Professor Thawee Songpattanasilpa, Assistant Professor Pipat Sritanabutr, General Sahachart Pipithkul) at Musculoskeletal Oncology unit, Department of Orthopedic Surgery, Phramongkutklao Hospital and College of Medicine for their sharing the information of patients' care. We would like to express our gratitude to all staff of the Clinical Epidemiology Unit, Faculty of Medicine, Chulalongkorn University for their support.

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Chapter I

Introduction

Background and Rationale

The biopsy is simple procedure but a critical and important step in the diagnosis of neoplasm, inflammatory, infectious, and reactive lesions of the musculoskeletal system. Although an open, incisional technique traditionally has been considered the gold standard, it requires an incision, an operative room facility, cost, and general or regional anesthesia. The overall diagnostic accuracy of open biopsies ranges from 91% to 96%. *(1-4)* Complications of open biopsy include seroma, hematoma, infection, wound dehiscence with tumor fungation, local recurrence, and fracture were reported. *(2,3,4,6)* As an alternative to open biopsy, percutaneous techniques, including close core needle biopsy has been developed. These techniques can be performed in the out-patient clinic under local anesthesia when the pertinent landmarks of lesions are palpable or in the radiology suite using imaging guided; fluoroscopy, CT, MRI, or ultrasound.*(7-17)*Advantages of close core needle biopsy over open incisional biopsy include less invasive, smaller incisions, time saving, no need hospitalization, lower cost, avoidance general or regional anesthesia, lower wound complication rates, less obstacle of biopsy scar to definitive surgery and earlier commencement to chemotherapy or radiation, ability to perform in difficult accessible locations(spine, pelvis), and easy to perform multiple sites in same time. Potential disadvantages may include decreased diagnostic accuracy and tumor sampling error. There were many studies that reported about diagnostic accuracy of close percutaneous needle biopsy for musculoskeletal tumors with various techniques, namely conventional close needle biopsy without image-guide, with image-guide (fluoroscopy-guide, ultrasound-guide, CT-guide, MRI-guide, various devices with different core diameter. The overall diagnostic accuracy of close needle biopsy ranges from 68% to 100 %. Most of these literatures were the retrospective studies without comparative statistic analysis between 2 methods; open incisional biopsy (gold standard) and close needle biopsy. Some studies excluded inadequate or non-diagnostic biopsies from their statistical analysis, which may falsely elevate accuracy rates. There were a few studies of close needle biopsy performing in office-based or out-patient clinic setting without image-guide. Adams SC. and et al *(5)* reported high acceptable diagnostic accuracy rate. They performed the close needle biopsy at out-patient clinic setting without image-guide. The close needle biopsy with image-guide yields the diagnostic accuracy more than close needle biopsy without real-time image guide logically because of accurate targeting directly. However the image-guide biopsy increases the time schedule, cost for procedure, risk of radiation exposure while performing biopsy and need for radiological facilities. In this study, we purpose to study the diagnostic accuracy of close percutaneous needle biopsy without real-time image-guiding in out-patient clinic setting by comparing with standard open incisional biopsy in musculoskeletal sarcoma patients.

Chapter II

Literature review

Through “PUBMED” and “Google scholar” medical database searching engine, the keyword (Biopsy [ALL Fields] And diagnostic accuracy [All Fields] and musculoskeletal tumor [All Fields] were searched. The articles which seemed to be well matched or related to the clinical question were selected and reviewed as followed.

Many published papers *(14, 18, 19, 20, 21)* of closed needle biopsy reported diagnostic accuracy but most of them combined the results of conventional close needle biopsy at out-patient clinic with image guide technique. Some studies *(22, 23, 24*) excluded inadequate or nondiagnostic biopsies from their accuracy analysis which may increase false accuracy rate.

There were a few reports which compare diagnostic accuracy between 2 different biopsy methods Skrzynski MC and et al *(2)* reported diagnostic accuracy comparing between out-patient core needle biopsy with open biopsy in of musculoskeletal tumors. The study design was ambidirectional, prospective study in 62 patients performed with close core needle biopsy compared with retrospective study in 50 patients performed with open biopsy in same institution. The diagnostic accuracy of close needle biopsy was 84 per cent and the diagnostic accuracy of open biopsy was 96 per cent. There was not comparative by statistic analysis.

Adams SC. and et al *(5)* reported the retrospective review study of 234 patients with 252 core needle biopsies of malignant bone and soft tissue tumors. The diagnostic accuracy was 91%. They performed the close needle biopsy at out-patient clinic; office-based setting without image-guide, which is different from many recent studies with imaging-guided technique. However their patients included only in bone and soft-tissue malignancies. So there was no overall diagnostic accuracy of all tumors including benign lesions.

Thipachart and et al. *(25)* reported in Thai, the prospective comparative study between close needle biopsy and open incisional biopsy in 52 patients. The diagnostic accuracy of close biopsy was 90.38% and open biopsy was 98.37%. However the patient subjects were included only in the soft tissue tumors and compare between 2 methods in one patient simultaneously and performed in the operating room setting. No study follow-up in other aspects, namely errors, complications and cost analysis, were performed.

Chapter III

Research design and Methodology

1. **Research Question**

Primary question: Is the diagnostic accuracy of close needle biopsy without image-guide at out-patient clinic setting similar to open incisional biopsy in musculoskeletal sarcomas?

Secondary question: Are the other aspects of diagnostic values (diagnostic yield, errors, and complications) of close needle biopsy at out-patient clinic similar to open incisional biopsy in musculoskeletal sarcomas?

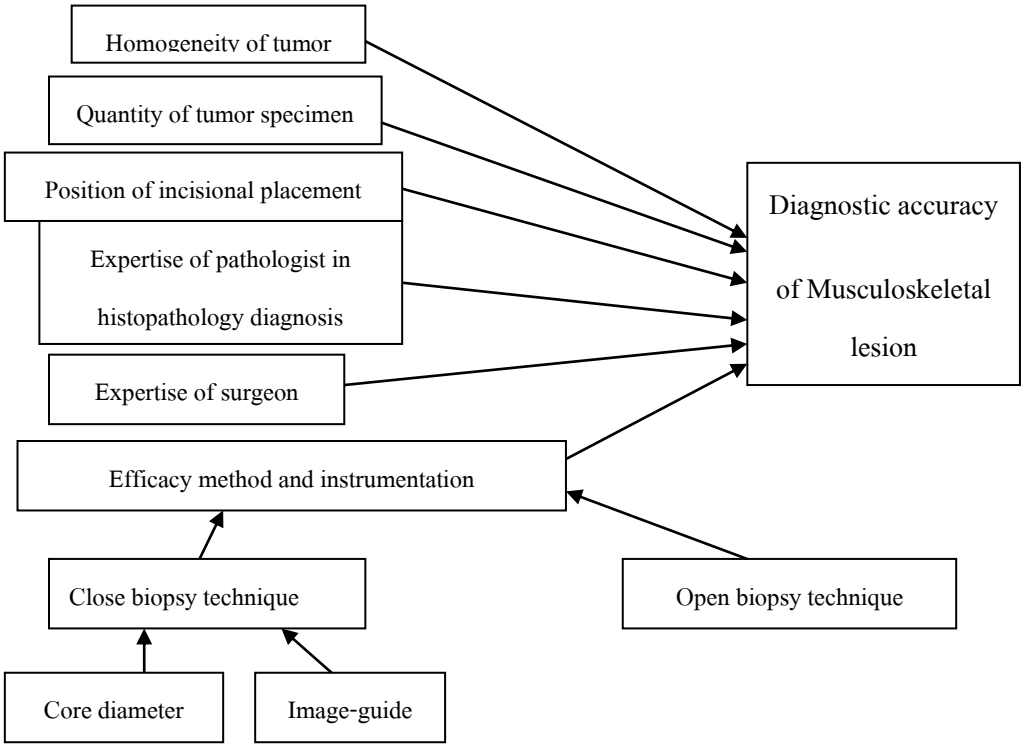
2. **Objective**

- Primary Objective: To compare and determine association between the diagnostic accuracy of close needle biopsy without image-guide at out-patient clinic and open incisional biopsy in musculoskeletal sarcoma patients.
- Secondary Objective: To study diagnostic values **(**diagnostic yield, error, complication**)** of close needle biopsy in out-patient clinic comparing with open incision biopsy in musculoskeletal sarcoma patients.

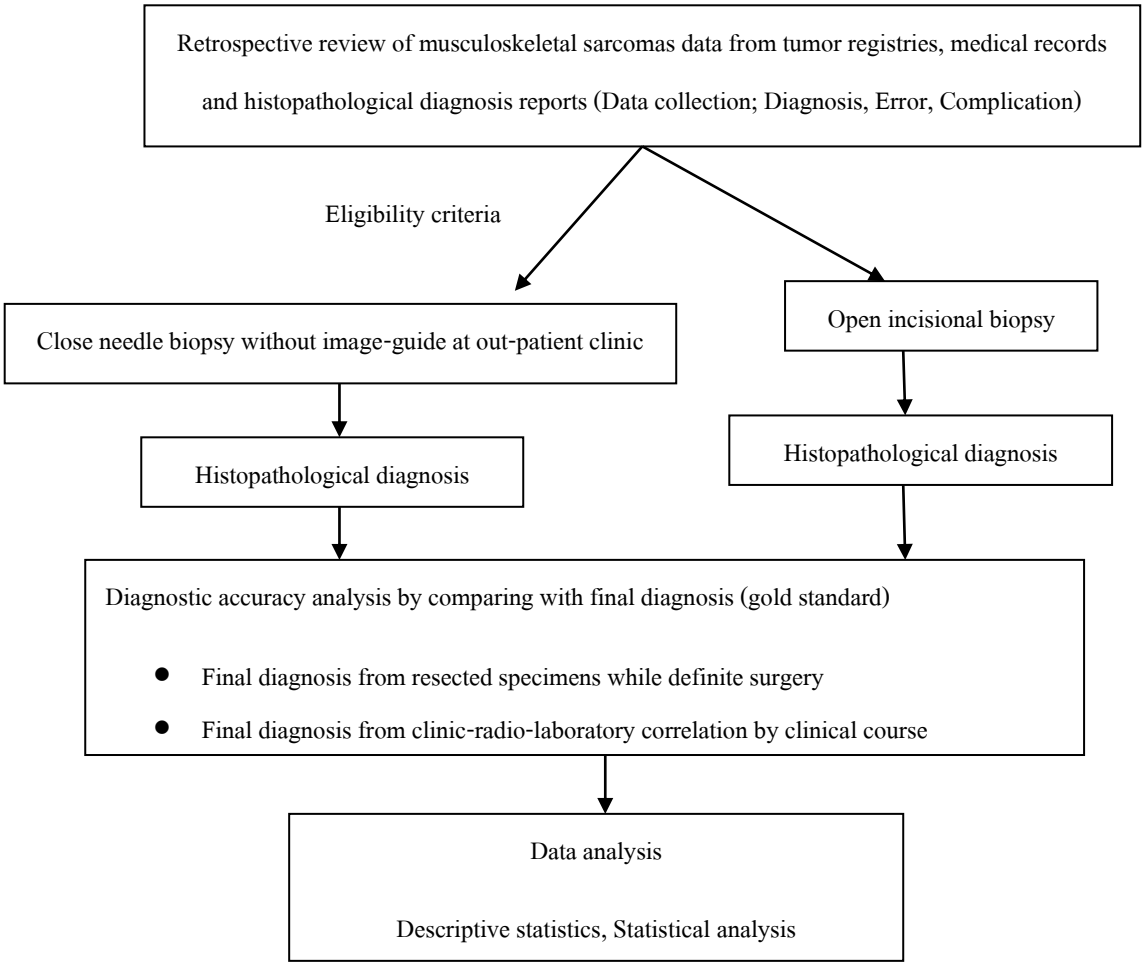
3. **Hypothesis**

The diagnostic accuracy of close percutaneous needle biopsy is not different to diagnostic accuracy of open incisional biopsy in musculoskeletal sarcoma patients.

4. **Conceptual Framework**



FLOW diagram



5. Domains

In situation: the musculoskeletal sarcoma patients had been treated at musculoskeletal oncology clinic, Department of Orthopedics, Phramongkutklao hospital and college of medicine.

6. **Keywords** : close needle biopsy, open incisional biopsy, diagnostic accuracy, musculoskeletal sarcoma

7. Operation Definition

- Diagnostic accuracy = true positive + true negative / all results (comparing gold standard)
- Diagnostic yield = number of effective of biopsies (diagnostic result) / total number of biopsies
- Error (false positive & false negative):

  Major = misdiagnosis malignant as benign (False negative)

  Minor = misdiagnosis in histological type or grade

- Complications = detecting duration after procedure within 2 weeks.

8. Research Design

Descriptive study, comparative, diagnostic aspect

9. Research Methodology

Population and sample

- Target population

  Musculoskeletal sarcoma patients

- Study population

  Musculoskeletal sarcoma patients at Phramongkutklao hospital and college of medicine

- Recruit sample Setting; Musculoskeletal tumor patients on service at musculoskeletal oncology clinic, Phramongkutklao Hospital since year 2002-2011 and start study after approval by ethic committee and director of hospital.

Eligibility criteria

Inclusion criteria

- Musculoskeletal sarcoma patients

  Soft tissue sarcomas

  Bone sarcomas with soft-tissue extension

- Extremity and trunk location
- Available the histopathology from resected specimens while definite surgery
- Available information of clinicoradiographic/laboratory and clinical course

Exclusion criteria

-Close needle biopsy with other imaged guide technique (fluoroscopy, ultrasound, CT)

Sample size calculation

The outcome variable data are categorical data (nominal, dichotomous) for comparing two independent groups. So we used the software PS Power and Sample Size Calculations Version 3.0, January 2009 and nQuery advisor 6.01 to calculate the sample size.

Formula of sample size calculation: $N = \frac{[\ Z_{\alpha/2}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}\ ]^2}{(P_1-p_2)^2}$

- Previous diagnostic accuracy of open Incisional biopsy from review published literature (2) is 96%
- Previous diagnostic accuracy of close percutaneous needle biopsy from review published literature (2) is 84%
- 2-sided, type I error of 0.05 and 80% power

Sample size = 97 cases per group or total sample size is 194 cases

(Total ~200 cases, each 100 cases per group)

Maneuver

This study was approved by our institutional research ethics board before starting; the informed consent was waived due to observational retrospective nature of the study. We retrospectively reviewed all 200 patients from our single institution between January 2002 to December 2011 by searching the data from electronic-database of tumor registry of musculoskeletal oncology unit, Department of Orthopedics and histopathological reports from electronic-database of Department of Pathology**.** The inclusion criteria were musculoskeletal sarcoma patients with clinical pertinent mass (soft tissue sarcomas or bone sarcomas with soft-tissue extension), located at the extremity or trunk, and available information of the histopathology from resected specimens while definite surgery and clinicoradiographic/laboratory or clinical course. We excluded the CNB with other imaged guide technique (fluoroscopy, ultrasound, CT), unplanned excision cases, and recurrent sarcoma. The following data were collected:

1. Patient demographics: age, gender
2. Locations of tumor
3. Tissue origins: Bone sarcoma or soft tissue sarcoma
4. Provisional diagnosis from histological results which obtained by CNB and open incisional biopsy separately in 4 aspects: Nature (Benign & Malignant), Specific diagnosis (Name of tumor), Histological type, and Histological grade.
5. Numbers of biopsy in each method
6. Final diagnosis was obtained by histopathology reports of resected specimen while definite surgery and compatible with clinicoradiographic/laboratory or clinical course at follow up period.
7. Majors error and minor errors
8. Biopsy related complication

All procedures of CNB and open incisional biopsy had been performed by 5 orthopedic oncologists with fellowship training of the orthopedic oncology in the same hospital. All cases had been performed the biopsy after complete investigations (laboratory, MRI, CT, Bone scan). The standard of procedures of biopsy was similar and strict in the same principle all cases. The open incisional biopsy was performed in the operating theater under general or regional or local anesthesia depending on individual condition of patients. The patients usually stayed overnight in the hospital for postoperative 1 day to aware the acute complications. Regarding CNB, the needle devices were Tru-Cut® needle (14GX15cm, Allegiance, Illinois, USA) in all cases. After clinical examination, laboratory inspection, and radiographic imaging review, the risks/benefits and alternatives

of biopsy were discussed with the patients then formally consented before any procedure. We performed the CNB in the procedure room at out-patient clinic and discharge the patients at the same day. We prepared and draped the area in sterile technique followed by infiltration of 1% lidocaine for local anesthesia then the needle was advanced into the mass. The location of needle entry and depth with direction of needle was guided carefully by the MRI of lesion by same principle of open incisional biopsy. We attempted for obtaining multiple specimens (at least 4 pieces) with single entry but coaxial (*15*). The quality and amount of core specimen was inspected in each time. The core specimens were handled meticulously to avoid crush artifact when histopathological diagnosis. The specimens were sent for bacterial culture or staining if infection were suspected. The wounds were closed by the compressive dressing to stop bleeding and the patients were observed for at least 30 minutes to ensure the absence of immediate complications, such as hemorrhage or neurovascular injury. All patients received the prescription for pain relief. The biopsy core specimens were fixed in formalin and routinely processed for hematoxylin and eosin staining for permanent histopathology. Special staining and immunohistochemical studies were performed in selected cases to confirm diagnosis. Each histopathological diagnosis had been reported the final diagnosis by musculoskeletal pathologists with well-experienced in orthopedic oncology field based on WHO classification of bone and soft-tissue tumors 2002(*18*). The weekly pathological slide review had been performed by both orthopedists and pathologists for confirm the diagnosis. The monthly inter-department tumor conference by multidisciplinary musculoskeletal tumor specialist team (orthopedist, oncologist, pathologist, and radiologist) had been performed for review and discussion to confirm definitive diagnosis and plan for treatment in each case.

We measured the primary outcome, diagnostic accuracy and the secondary outcome **(**diagnostic yield, error, complication) by comparing between 2 methods. Regarding diagnostic accuracy, we had evaluated the diagnostic accuracy in 4 aspects of histopathology, namely; Nature (Benign & Malignant), Specific diagnosis (Name of tumor), Histological type, and Histological grade. Each sample had been evaluated and interpreted by definitions following**.** The correct results meant the results of histopathology report compatible with final diagnosis which obtained by histopathology reports of resected specimen while definite surgery and compatible with final diagnosis which correlated with clinicoradiographic/laboratory or clinical course. The incorrect results meant the histopathology report from any biopsy incompatible with final diagnosis which obtained by histopathology reports of resected specimen while definite surgery, inconclusive or requiring repeat biopsy. Then the diagnostic accuracy and diagnostic yield was calculated by outcome definition as followings, the diagnostic accuracy was defined the sum of true positive and true negative results divided by total number of biopsies performed. The diagnostic yield was numbers of effective of biopsies (diagnostic result) dived by total numbers of biopsies. The errors (false positive & false negative) were divided 2 types, major and minor errors. The major error meant misdiagnosis in nature of tumor, diagnose malignant tumor as benign tumor, the minor error meant misdiagnosis in specific name of sarcoma, histological type or histological grade. The related

biopsy complication such as seroma, hematoma, infection, wound dehiscence with tumor fungation was detecting duration after procedure within 2 weeks.

Outcome Measurement

Primary outcome: Diagnostic accuracy

Secondary outcome: Diagnostic yield, Error ;(major & minor), Complication, Cost analysis

Diagnostic accuracy Measurement

I plan to evaluate the diagnostic accuracy in 4 aspects of Pathology.

Nature (Benign & Malignant) Specific diagnosis (Name of tumor)

Histological type Histological grade (for malignancy)

Definition of outcome terminology; Correct/Incorrect/Not applicable

C=correct I=incorrect NA=not applicable

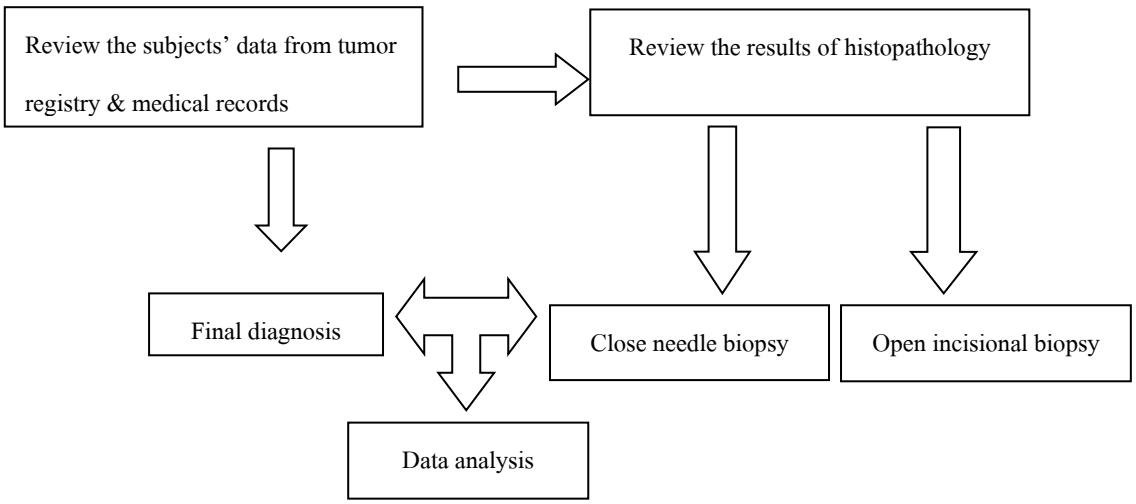
Correct = Compatible with final diagnosis which obtained by histopathology reports of resected specimen while definite surgery or compatible with final diagnosis which correlated with clinicoradiographic/laboratory or clinical course.

Incorrect =Incompatible, Inconclusive, Requiring repeat biopsy

Not applicable= unable to report in some pathological aspects namely histological grade for benign tumors

The diagnostic accuracy and diagnostic yield will be calculated by outcome definition.

10. Data Collection



11. Data Analysis

Regarding statistical analysis, the descriptive statistics were used for demographic data, diagnostic accuracy and diagnostic yield. We used the Chi-square (or Fisher's exact) test and Bonferroni's correction when necessary to determine of association and compare proportions between two biopsy methods by STATA/ MP12. We considered the statistical significant different when p-value was less than 0.05. All p-value are two-tailed.

12. Ethical Considerations

- This study needs to review medical records, report of histopathology results in human subjects for protecting patient's confidentiality. Therefore, the research proposal must be approved by the ethics committee and ask for permission from hospital director before starting the study.
- There are personal data, so all data will be kept in a personal computer belongs to the investigator. The entrance to the data will need a specific code. Result of study will be presented in general, not as individual data.

13. Obstacle

Retrospective study, Selection bias

14. Limitation

- Retrospective study
- Selection bias
- Not cover all types of other close needle biopsy technique, such as image-guide or different needle devices with various core diameters.
- Not including all of musculoskeletal lesions.

Chapter IV

Results

Patients' characteristics and Outcome of Treatment

There were 200 cases included into the study, 105 cases for open incisional biopsy and 95 cases for CNB, male 109 cases (54.5%) and female 91 cases (45.5%). The mean age of the patients was 34.88± 20 years, (30.81±18.89 years for open incisional biopsy and 39.37±20.34 years for CNB). There were 119 cases (59.5%) of bone sarcoma and 81 cases (41.5%) of soft-tissue sarcoma. The demographic data of patients and distribution of lesions were shown in table 1 and 2. The final histopathogical diagnoses of lesions by biopsy from both methods were shown in table 3 and 4. The diagnostic accuracies in each aspect comparing both methods were shown in table 5. The diagnostic accuracies of open incisional biopsy were 97.14% for nature, 89.52% for specific diagnosis, 89.52% for histological type, 88.57% for histological grade and the diagnostic accuracies of CNB were 96.84% for nature, 89.47% for specific diagnosis, 88.42% for histological type, 86.32% for histological grade respectively. There were no statistically significant different between 2 methods in all histological aspects (nature; P-value = 0.901 95%CI = -0.432 to 0.380, specific diagnosis; P-value = 0.991 95%CI = -0.227 to 0.224, histological type P- value = 0.803 95%CI = -0.250 to 0.193, and histological grade; P-value = 0.63 95%CI = -0.261 to 0.158). The diagnostic yields of both methods were 98.13% for open incisional biopsy, 97.94% for CNB. It was no statistically significant different also as shown in table 6 (P-value = 0.919 95%CI = -0.469 to 0.520). There were 6 cases (3%) for overall major errors, 3 cases (2.86%) for open incisional biopsy and 3 cases (3.16%) for CNB. There were 18 cases (9%) for minor errors, 9 cases (8.57%) for open incisional biopsy and 9 cases (9.47%) for CNB. Major errors by CNB were misdiagnosis from malignant as benign namely; epithelioid sarcoma as fibromatosis, osteosarcoma as giant cell tumor and chondrosarcoma as chondroma. Although misdiagnosis, all cases were treated properly, 1 case was repeated by open incisional biopsy and the other 2 case were not performed the repeated biopsy but had been treated as sarcoma by wide local excision with or without chemotherapy. Because we diagnose the musculoskeletal tumor by multidisciplinary approach, clinic-radio-pathological diagnostic principle, not only histopathological result is one modality to confirm the diagnosis but clinical and radiological information must to compatible with it. Major errors by open incisional biopsy were misdiagnosis of fibrosarcoma as fibromatosis, epithelioid sarcoma as fibromatosis and osteosarcoma as giant cell tumor. Minor errors by CNB were misdiagnosis in histological grade 1 case, histological grade with histological type 1 case, and histological grade with histological type with specific diagnosis 7 cases. Minor errors by open incisional biopsy were misdiagnosis in histological grade 1 case, histological grade with histological type 1 case, and histological grade with histological type with specific diagnosis 7 cases. There was no complication related biopsy in both methods.

Table 1 Demographic data of the patients

	Open incisional biopsy	Close needle biopsy
Gender		
• Male	56 (53.3%)	53 (55.8%)
• Female	49 (46.7%)	42 (44.2%)
Age (years)	30.81±18.89	39.37±20.34
Tissue origin		
• Bone sarcoma	77 (73.3%)	42 (44.2%)
• Soft-tissue sarcoma	28 (26.7%)	53 (55.8%)

Table2 Distribution of the lesions

Location	Open incisional biopsy	Close needle biopsy
Neck	-	3(3.2%)
Shoulder	4(3.81%)	4(4.2%)
Arm	3(2.86%)	2(2.1%)
Elbow	1(0.95%)	-
Forearm	3(2.86%)	3(3.2%)
Wrist & Hand	-	-
Back	5(4.76%)	4(4.2%)
Pelvis & Hip	12(11.43%)	11(11.6%)
Thigh	16(15.24%)	28(29.5%)
Knee	49(46.67%)	29(30.5%)
Leg	11(10.48%)	9(9.5%)
Foot & Ankle	1(0.95%)	2(2.1%)
Total	105	95

Table3 Final histopathology results for open incisional biopsy

Soft tissue sarcoma	
• Malignant fibrous histiocytoma	8
• Synovial sarcoma	7
• Myxoid fibrosarcoma	3
• Leiomyosarcoma	3
• Epithelioid sarcoma	2
• Fibrosarcoma	2
• Liposarcoma	1
• Malignant Peripheral nerve sheath tumor	2
Bone sarcoma	
• Osteosarcoma	55
• Ewing's sarcoma	10
• Chondrosarcoma	9
• Chordoma	2
• Adamantinoma	1
Total	105

Table 4 Final histopathology results for Close needle biopsy

• Soft tissue sarcoma	
Malignant fibrous histiocytoma	15
Liposarcoma	9
Synovial sarcoma	8
Leiomyosarcoma	7
Myxoid fibrosarcoma	6
Epithelioid sarcoma	3
Rhabdomyosarcoma	3
Hemangiopericytoma	1
Malignant Peripheral nerve sheath tumor	1
• Bone sarcoma	
Osteosarcoma	32
Chondrosarcoma	7
Ewing's sarcoma	3
Total	95

Table 5 Comparison of diagnostic accuracy by open incisional biopsy & close needle biopsy

Biopsy method	Accuracy rate %			
	Nature	Specific diagnosis	Histological type	Histological grade
Open incisional biopsy	97.14%	89.52%	89.52%	88.57%
Close needle biopsy	96.84%	89.47%	88.42%	86.32%
P-value	0.901	0.991	0.803	0.630
95% CI	-0.432 to 0.380	-0.227 to 0.224	-0.250 to 0.193	-0.261 to 0.158

Table 6 Comparison of diagnostic yield by open incisional biopsy & close needle biopsy

Biopsy method	Number of effective biopsies (diagnostic cases)	Total number of biopsies	Diagnostic yield (%)	P-value	95%CI
Open incisional biopsy	105	107	98.13%	0.919	- 0.469 to 0.520
Close needle biopsy	95	97	97.94%		

Chapter V

Discussion

The appropriate technique of biopsy for musculoskeletal sarcoma remains still controversial and often selected by the preference of individual operating surgeons. Although the CNB has become more generally used in present, There were many studies that reported about diagnostic accuracy of CNB for musculoskeletal tumors with various techniques, namely conventional CNB without image-guide, with image-guide (fluoroscopy-guide, ultrasound-guide, CT-guide, MRI-guide, various devices with different core diameter. The overall diagnostic accuracy of CNB ranges from 68% to 100 % *(6-17, 19-22)*. Most of these literatures included the CNB with image-guide and were the retrospective studies without comparative statistic analysis between 2 methods. Some studies excluded inadequate or non-diagnostic biopsies from their statistical analysis, which may falsely elevate accuracy rates *(23, 24, 25)*. The CNB with image-guide yields the diagnostic accuracy more than CNB without real-time image guide logically because of accurate targeting directly. However the image-guide biopsy increases the time schedule, cost for procedure, risk of radiation exposure while performing biopsy and need for radiological facilities. There were a few studies of CNB performing in office-based or out-patient clinic setting without image-guide and few reports which compare diagnostic accuracy between 2 different biopsy methods. Skrzynski MC*(2)* reported diagnostic accuracy comparing between out-patient core needle biopsy with open biopsy in of musculoskeletal tumors. The study design was ambidirectional, prospective study in 62 patients performed with CNB compared with retrospective study in 50 patients performed with open incisional biopsy in same institution. The diagnostic accuracy of CNB was 84% and the diagnostic accuracy of open incisional biopsy was 96%. The subjects included all musculoskeletal lesions, benign and malignant. There was not comparative by statistic analysis and no subgroup analysis in histopathological aspects. Adams SC.*(6)* reported the descriptive study of high diagnostic accuracy rate by the CNB at out-patient clinic setting without image-guide, however the subjects included all malignancy, primary and secondary and no comparison of the diagnostic accuracy with open incisional biopsy by statistic analysis. Thipachart*(26*) reported the prospective comparative study between CNB and open incisional biopsy in 52 patients. The diagnostic accuracy of CNB was 90.38% and open incisional biopsy was 98.37%. However the patient subjects were included only in the soft tissue tumors, including both benign and malignant lesions and compare between 2 methods in same patient simultaneously and performed in the operating room setting. They did not study in subgroup of other histological aspects.

Our results of diagnostic accuracy of CNB are similar high when comparing with the previous studies. In the subgroup analysis of 4 histological aspects, the diagnostic accuracy was reasonably reduced in subgroups respectively from nature, specific diagnosis, histological type and histological grade. This result compared favorably with the success rates for open incisional biopsy. It seems to be high diagnostic accuracy for CNB because we selected the subjected which only the sarcoma patients not include the other musculoskeletal lesions

and we cautiously performed the biopsy in these patients based on clinical-radiological information. Our study has some limitations. First our study was retrospective study, so the patients had been selected to perform any method without randomized allocation. The best study comparing the outcomes of both methods should be a prospective, randomized controlled trial which the only variable is the type of biopsy performed. Nevertheless, the both groups of patients were comparable because the same criteria had been used for inclusion in the study, all patients were sarcomas with similar clinical presentation, both methods of biopsy were performed in a contemporary period by the same group of experienced orthopedic oncologists, same institution and the results were reviewed by the same group of experience musculoskeletal pathologists. Second limitation of our subjects was only the primary malignancy of bone and soft-tissue (sarcoma), not included benign, tumor-like lesion, infection, or metastases. So the diagnostic accuracy of our study did not represent the overall accuracy of musculoskeletal lesions. Third limitation, we performed the CNB in all patients by only one type instrument, Tru-Cut® needle and unable to perform same number of specimens in every case. It seems to be high variability in number of biopsy core specimens. However we attempted to obtain the at least 4 core specimens in each biopsy by consideration of diagnostic yield *(15)* and all cases were performed the biopsy of same group of orthopedic oncologists in same institution. So our study maybe did not represent the results from other needle type. Another limitation, we studied in the sarcoma treatment center with multidisciplinary team approach, many experienced specialists involved in each step of the treatment process from beginning including biopsy, so our results may not be generalized to other practice. Despite these limitations, this study provides important and clinically relevant information.

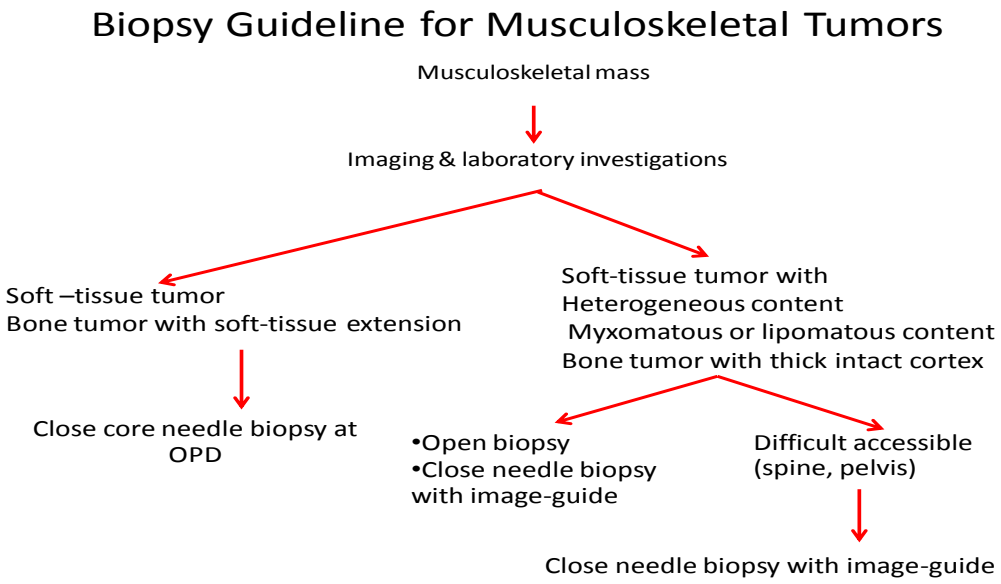
To initiate the treatment of musculoskeletal tumors, the correct diagnosis is important, so the following crucial factors are required; large enough amounts of the sample, appropriate portion of the lesion and correct histopathological interpretation by experienced pathologist for definitive diagnosis. The errors from biopsy can occur by depending on these factors sometimes. Some lesions in which the histological malignancy could not be determined was well-differentiated liposarcoma from benign lipoma or myxomatous tumor even by an open biopsy. Occasionally sarcoma has histological heterogeneity, the CNB is limited in amount of sample specimen, so most representative area may be missed. Such situation can cause the different provisional diagnosis from biopsy and definitive diagnosis from resected specimen. It recommends that meticulous examination of whole specimens is mandatory to make final diagnosis. Multiple samples from different depths of the lesions under imaging information may minimize the risk of misdiagnosis in such cases. Besides the histopathological findings, our principle for musculoskeletal tumor diagnosis is clinical and radiographic approach. Image findings from radiographic procedures (plain radiographs, computed tomography, magnetic resonance imaging, etc.) can provide useful information about the nature of the tumors. This approach composed with multidisciplinary specialists' team, orthopedic oncologist, radiologist, and pathologist. The pathologist usually must be informed about this information to differential diagnosis before examining the slides. Closed

communication among the team is important to confirm the correct diagnosis of the musculoskeletal lesions. To achieve the cooperation of the specialists, it is recommended to perform the close needle biopsy at medical center where is experienced in the treatment of musculoskeletal lesions. We did not specifically perform about cost analysis of CNB in this study, however there are some reports about a saving of CNB versus open incisional biopsy*(2,26)* which we hypothesize our study same situation.

Chapter VI
Conclusion

In conclusion the CNB without real-time image guidance at outpatient clinic can achieved the acceptable high diagnostic accuracy to diagnose musculoskeletal sarcomas similar comparing with the open incisional biopsy. It can be reliable method to diagnose the musculoskeletal sarcoma. However the multidisciplinary team approach by clinic-radio-pathology diagnostic principle should be performed to diagnose the musculoskeletal sarcoma cautiously. Our institute has been used this method in our clinical practice as shown in following strategic guideline (figure1).

Figure 1 Guideline for Biopsy in Musculoskeletal tumors



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APPENDIX

Appendix

Case record form

Case Number	Sex/age	Site	Close needle biopsy diagnosis	Pathological aspect of close biopsy diagnosis N S T G	Final diagnosis
1 …… …… 100					

Case Number	Sex/age	Site	Open biopsy diagnosis	Pathological aspect of open biopsy diagnosis N S T G	Final diagnosis
1 …… …… 100					

N=Nature S=Specific diagnosis T=Type G=Grade C=Correct I=Incorrect

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